Salvage Surgery in Non-Small Cell Lung Cancer

Methods

1. NCDB
2. NSCLC (Stage I - IV)
3. Definitive Therapy
4. Salvage Surgery > 5 Months after Therapy Start

Salvage surgery after definitive immunotherapy: n = 164
Salvage surgery after definitive chemoradiation: n = 445

Results

- **Overall Survival**: Salve surgery after immunotherapy and chemoradiation.
- **Resection Type**:
  - Wedge Resection: 11.6% (CR: 4.6%)
  - Segmentectomy: 5.5% (CR: 2.6%)
  - Lobectomy: 73.8% (CR: 73.9%)
  - Pneumonectomy: 9.2% (CR: 16.7%)

Implications

- **Feasibility**
  - In the majority of cases, lobar and sublobar resections achieve R0 resection.

- **Safety**
  - Salvage surgery, even after a prolonged period from initiation of definitive nonsurgical therapy, is associated with low mortality and low readmission rates.
Salvage Lung Resection after Immunotherapy is Feasible and Safe

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Article Word Count: 3,774 words
Glossary

ICI = Immune checkpoint inhibitors

NCDB = National Cancer Database

NSCLC = Non-small cell lung cancer

TKI = Tyrosine kinase inhibitor
Central Picture

Overall survival: salvage surgery after immunotherapy.

Central Message

Salvage lung resections are feasible and safe for patients with non-small cell lung cancer who have residual or recurrent tumors after immunotherapy and is associated with durable survival.

Perspective Statement

Immunotherapy is being increasingly used to treat non-small cell lung cancer. However, over half of patients who initially respond will progress within 7 months. For those patients with oligo-progression, surgery may be a viable option for eliminating residual or recurrent disease. Our NCDB study suggests that surgery can be a feasible and safe local therapy option in this setting.

Structured Abstract

Objectives: Patients with non-small cell lung cancer (NSCLC) treated with immunotherapy and modern chemoradiation regimens show improved progression-free and overall survival. However, patients with limited oligo-progression represent a potential population in which local therapy such as surgery may have a potential role as salvage treatment. The objectives of our study were to evaluate the feasibility and safety of salvage lung resection after immunotherapy in patients with NSCLC.
**Methods:** The National Cancer Database (NCDB) was queried for patients diagnosed and treated for NSCLC stage I-IV, from 2013 to 2020. Patients who underwent surgery as salvage after immunotherapy were defined as undergoing surgery >5 months from the initiation of immunotherapy. As a sensitivity analysis, patients who underwent surgery as salvage after chemoradiation were also analyzed in a similar fashion. Surgical outcomes such as type of surgery, complete resection (R0) rates, and complete pathologic response (cPR) rates were determined for feasibility. Length of stay (LOS), 30-day readmission rates, and 30-day mortality rates were determined and overall survivals were estimated with Kaplan-Meier analysis to evaluate for safety.

**Results:** Of the 934,093 patients diagnosed with NSCLC stage I-IV from 2013-2020, 164 patients received immunotherapy and after 5mo underwent surgery. Lobectomy was the most commonly performed operation (74%) and pneumonectomy was required in 9% (n=15). R0 resection was achieved in 89% (n=146) and of these patients, 23% (n=37) had cPR. Median LOS was 4 days, 30-day readmission was 5%, and 30-day mortality was 0.6%. In our sensitivity analysis of chemoradiation patients (n=445), the above data were similar to previously reported cohort studies of patients undergoing chemoradiation and subsequently salvage surgery.

**Conclusion:** Lung resection after immunotherapy appears to be a feasible salvage treatment option, with lobectomy being most common and with high R0 resection rates. Low patient morbidity and mortality rates also suggest the safety of this approach. Salvage surgery may be considered in patients who have oligo-progression after immunotherapy within the context of a comprehensive multidisciplinary treatment plan.

**Keywords**

Lung cancer, Immunotherapy, Chemotherapy, Radiation, Lobectomy, Pneumonectomy
Introduction
Immunotherapy has fundamentally transformed the management of locally-advanced non-small cell lung cancer (NSCLC) with improved effectiveness of drug therapies, such as immune checkpoint inhibitors (ICI). The addition of immunotherapy to platinum-based chemotherapy provides an even superior pathological response and survival benefit over chemotherapy alone. Despite advances in multimodal therapies, many patients with locally-advanced NSCLC experience local disease recurrence or local progression after definitive non-surgical treatment. Cohort studies have suggested salvage surgery after chemoradiation as a potential curative treatment option for these select patients, improving overall survival and quality of life. However, salvage surgery is also often associated with higher morbidity and mortality rates compared to primary surgery.

This study aimed to investigate the feasibility and safety of salvage lung resection in patients with non-small cell lung cancer who received immunotherapy or definitive chemoradiation. The purpose of this study was to determine whether salvage lung resection could be a viable treatment option for this patient population given the potential benefits and risks associated with this procedure.

Materials and Methods
The National Cancer Database (NCDB) was queried for adult patients diagnosed with NSCLC from 2013 to 2020, stages I-IV, treated with immunotherapy or chemoradiation, who subsequently underwent surgery. To exclude patients treated with neoadjuvant strategies, surgery as salvage was defined as surgery occurring at least 5 months after the initial immunotherapy treatment or initial chemoradiation treatment.
Data were obtained from the NCDB, a large-scale registry that captures information on cancer cases from over 1,500 Commission on Cancer Centers in the United States and Puerto Rico. The NCDB is maintained in collaboration with the American Cancer Society and the American College of Surgeons and is estimated to capture approximately 70% of newly diagnosed cases of cancer in the United States of America. Certified independent tumor registrars used standardized coding guidelines to ensure the quality and accuracy of the data captured in the NCDB. The NCDB provides extensive clinical and demographic information on patients treated at the Commission on Cancer-approved hospitals, including diagnosis, stage of diagnosis, primary treatment, follow-up information, and other relevant data. It captures 72% of all newly diagnosed malignancies in the US annually. Overall coverage of cancer cases in the NCDB has remained relatively stable with a slight increase from 67% observed in 2004–2006. Case coverage also increased slightly between 2012 and 2014, as did the number of Commission on Cancer-accredited facilities, which increased from 1455 to 1475 and represents approximately 25% of acute-care facilities. Data captured in the NCDB were recorded using the American Joint Committee on Cancer's seventh edition TNM classification.

It is important to note that the analytical or statistical methods used as well as the conclusions drawn from the data obtained from the NCDB have not been verified by the American College of Surgeons or the Commission on Cancer; therefore, they are not accountable for them. This study, utilizing de-identified data from the NCDB, was reviewed by the Institutional Review Board of Yale University and was exempt from informed consent requirements, as the data were fully de-identified.

Patient Selection
This study aimed to evaluate the clinical outcomes of adult patients diagnosed with NSCLC in the NCDB between 2013 and 2020. Our study was a retrospective analysis of data obtained from the NCDB, focusing on the demographic, clinical, and pathological characteristics of the study cohort.

The inclusion criteria for the study were adults aged ≥18 years with a diagnosis of NSCLC, while the exclusion criteria were patients who underwent primary surgery, those who never underwent surgery, or if survival data were unknown. Additional exclusions were made for cases in which information on the surgical procedure was missing or in which ablative procedures were performed.

Variables such as age, sex, ethnicity, comorbidities (represented by the Charlson/Deyo score), primary tumor site, clinical stage, histology, grade, definitive therapy, and procedure type were extracted from the NCDB. The study used the seventh edition of the American Joint Committee on Cancer Tumor, Node, and Metastasis staging criteria to report the clinical and pathological stages. Histology was simplified into two categories, adenocarcinoma and non-adenocarcinoma, as classified by the International Classification of Disease for Oncology third edition.

The treatment sequence of surgery and chemotherapy was defined using the NCDB variables, with the extent of surgery documented as sublobar resection (wedge resection or segmentectomy), lobectomy, or pneumonectomy. We defined definitive surgery as noted by the NCDB PUF data dictionary to be the most invasive surgical procedure for the primary site. Immunotherapy was defined as first course treatment using biological or chemical agents that alter the immune system or change the host's response to tumor cells. Therapy was grouped
into immunotherapy with or without chemoradiation, and chemoradiation without immunotherapy. Definitive chemoradiation was characterized by the combination of multiagent chemotherapy and radiation therapy. Our study design intentionally did not aim for a direct comparison between the immunotherapy and chemoradiation groups, recognizing the absence of a traditional control group. This approach was chosen to focus on evaluating the outcomes and feasibility within each treatment modality independently. Complete pathologic response was defined as pathologic stage pT0N0. All other categories, including no pathologic response or partial pathologic response, were classified as not pT0N0.

To address the potential for neoadjuvant therapy bias, we utilized a conditional landmark analysis, setting the surgery time point to at least five months after the initiation of immunotherapy, chemotherapy, and radiotherapy. The primary outcome of the study was 3-year overall survival, with secondary outcomes including 30-day and 90-day mortality, hospital length of stay, 30-day readmission rate, R0 resection, and extent of surgery. These secondary outcomes were examined as potential surrogate markers for postoperative morbidity and feasibility of surgical therapy, which were not recorded in the NCDB.

Statistical Analysis

Prior to the analysis, the normality of the data was evaluated using the Shapiro-Wilk test. Continuous variables were expressed as medians (interquartile range [IQR]), while categorical variables were presented as absolute numbers and percentages. To compare continuous variables between groups, Mann-Whitney U test was utilized, while categorical variables were assessed using chi-square test. For the construction of survival curves, the Kaplan-Meier method was employed, and their comparability was assessed using the log-rank test. To model the relationship between surgery type and timing and mortality, logistic regression analysis was
executed. The statistical models used in this study were not adjusted for the covariates. All statistical analyses were performed using SAS (version 9.4) manufactured by Statistical Analysis System (SAS) Institute based in Cary, North Carolina.

Results
A total of 609 patients with stage I - IV NSCLC who underwent salvage surgery after immunotherapy (N=164) or definitive chemoradiation therapy (N=445) were identified in the NCDB from 2013 to 2020. Patient characteristics are presented in Table 1. There was no statistically significant difference in the sex distribution between the two groups. Specifically, 45.1% of patients in the immunotherapy group were male compared to 54.9% female, whereas 53.4% of patients in the chemoradiation group were male compared to 46.6% female. The median age was 61 years (interquartile range [IQR], 56-68) in the immunotherapy group and 62 years (IQR, 55-69) in the chemoradiation group. Most patients in the immunotherapy group had stage III (39.6%) and IV (34.2%) disease, whereas most patients in the chemoradiation group had stage II (22.7%) and III (68.1%) disease. Data were missing for 6.1% of the patients in the immunotherapy group and 1.1% of the patients in the chemoradiation group. Most patients in the immunotherapy group had adenocarcinoma (70.1%), whereas in the chemoradiation group, there was an even distribution of adenocarcinoma (47.0%) and non-adenocarcinoma (53.0%). Comorbidity, measured using the Charlson Comorbidity score, was similar between the two groups. In the immunotherapy group, 67.7% of patients had a score of 1 and 23.2% had a score of 2. In the chemoradiation group, 58.4% of patients had a score of 1 and 27.4% had a score of 2.

Table 1: Baseline characteristics and post-surgical outcomes among patients who underwent salvage surgery after immunotherapy or chemoradiation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Immunotherapy</th>
<th>Chemoradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (%) n=164</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (%) n=445</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>61 (56-68)</td>
<td>62 (55-69)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74 (45.1)</td>
<td>243 (53.4)</td>
</tr>
<tr>
<td>Female</td>
<td>90 (54.9)</td>
<td>212 (46.6)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>15 (9.2)</td>
<td>46 (10.1)</td>
</tr>
<tr>
<td>White</td>
<td>134 (87.7)</td>
<td>384 (84.4)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (9.2)</td>
<td>25 (5.5)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>115 (70.1)</td>
<td>214 (47.0)</td>
</tr>
<tr>
<td>Squamous</td>
<td>38 (23.2)</td>
<td>199 (44.7)</td>
</tr>
<tr>
<td>Large Cell</td>
<td>0 (0.0)</td>
<td>9 (2.0)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (4.3)</td>
<td>23 (5.2)</td>
</tr>
<tr>
<td>BAC</td>
<td>4 (2.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16 (9.8)</td>
<td>20 (5.5)</td>
</tr>
<tr>
<td>2</td>
<td>17 (10.4)</td>
<td>101 (22.7)</td>
</tr>
<tr>
<td>3</td>
<td>65 (39.6)</td>
<td>303 (68.1)</td>
</tr>
<tr>
<td>4</td>
<td>56 (34.2)</td>
<td>16 (3.6)</td>
</tr>
<tr>
<td>Missing</td>
<td>10 (6.1)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Surgical Procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedge Resection</td>
<td>19 (11.6)</td>
<td>21 (4.6)</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>9 (5.5)</td>
<td>12 (2.6)</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>121 (73.8)</td>
<td>336 (73.9)</td>
</tr>
<tr>
<td>Pneumonecetomy</td>
<td>15 (9.2)</td>
<td>76 (16.7)</td>
</tr>
<tr>
<td>R0 Resection</td>
<td>146 (89.0)</td>
<td>399 (89.7)</td>
</tr>
<tr>
<td>Complete pathologic response pT0N0</td>
<td>37 (22.6)</td>
<td>117 (26.3)</td>
</tr>
<tr>
<td>Not complete pathologic response</td>
<td>146 (89.0)</td>
<td>399 (89.7)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>148 (90.3)</td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>63 (38.4)</td>
<td></td>
</tr>
<tr>
<td>Time of Surgery after immunotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-6 months</td>
<td>51 (31.1)</td>
<td>211 (46.4)</td>
</tr>
<tr>
<td>6-7 months</td>
<td>41 (25.0)</td>
<td>121 (26.6)</td>
</tr>
<tr>
<td>7-9 months</td>
<td>42 (25.6)</td>
<td>86 (18.9)</td>
</tr>
<tr>
<td>&gt;9 months</td>
<td>30 (18.3)</td>
<td>37 (8.1)</td>
</tr>
<tr>
<td>Charlson Comorbidity Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>111 (67.7)</td>
<td>260 (58.4)</td>
</tr>
<tr>
<td>2</td>
<td>38 (23.2)</td>
<td>122 (27.4)</td>
</tr>
<tr>
<td>3</td>
<td>11 (6.7)</td>
<td>40 (9.0)</td>
</tr>
<tr>
<td>4</td>
<td>4 (2.4)</td>
<td>23 (5.2)</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>1 (0.6)</td>
<td>17 (3.8)</td>
</tr>
</tbody>
</table>
Additionally, we evaluated the 30-day mortality rate, unplanned readmissions to the hospital, and length of hospital stay in both groups. In the immunotherapy group, the 30-day mortality rate was 0.6%, and the rate of unplanned hospital readmissions within 30 days was 4.9%. The median length of stay was 4 days (IQR, 2.0 - 6.0). In contrast, the 30-day mortality rate in the chemoradiation group was 3.8%, and the rate for unplanned hospital readmissions within the same period was 4.0%. The median length of stay was 5 days (3.0 - 7.0). The overall survival (OS) of both groups was compared using Kaplan-Meier curves, and the results are presented in Figure 3. Figure 3A and 3B show the OS of the immunotherapy and chemoradiation groups, respectively.

Among the patients in the immunotherapy group, the majority (31.1%) underwent surgery 5-6 months after the beginning of immunotherapy. One-quarter of the patients (25.0%) underwent surgery 6-7 months after the start of immunotherapy, 25.6% underwent surgery in the 7-8 month range, and 18.3% underwent surgery more than 9 months later. Most patients (46.4%) underwent surgery 5-6 months after the start of chemoradiation treatment. Of the remaining patients, 26.6% underwent surgery after 6-7 months, 18.9% underwent surgery in the 7-9 month range, and 8.1% underwent surgery more than 9 months after starting treatment.

We performed logistic regression analysis to investigate the relationship between the timing of surgery after the initiation of therapy and 90-day mortality in our study population. The reference group comprised patients who underwent surgery between five and six months after the start of chemoradiation treatment. Logistic regression analysis showed that patients who underwent surgery 6-7 months after therapy initiation had an odds ratio of 1.650 (p=0.823) for 90-day mortality. Similarly, those who underwent surgery 7-8 months later had an odds ratio...
of 1.603 (p=0.916), while those who underwent surgery nine months or later had the highest odds ratio of 2.192 (p=0.369) for 90-day mortality. In a separate analysis, we investigated the relationship between the timing of surgery and the 90-day mortality in the immunotherapy group. Logistic regression analysis revealed that patients who underwent surgery 6-7 months after initiating immunotherapy had an odds ratio of 0.621 (p=0.917) for 90-day mortality, whereas those who underwent surgery between 7-9 months had an odds ratio of 0.742 (p=0.763). Additionally, patients who underwent surgery nine months or later after the initiation of immunotherapy had the lowest odds ratio for 90-day mortality, with a value of 0.391 (p=0.383).

Table 2: Logistic regression model of the timing of surgery after immunotherapy and chemoradiation with the 90-day mortality outcome

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95 % CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Timing of surgery after immunotherapy (reference = 5-6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6-7 months</td>
<td>0.621</td>
<td>0.175</td>
<td>2.204</td>
</tr>
<tr>
<td>&gt;7-9 months</td>
<td>0.742</td>
<td>0.223</td>
<td>2.472</td>
</tr>
<tr>
<td>&gt;9 months</td>
<td>0.391</td>
<td>0.077</td>
<td>1.988</td>
</tr>
<tr>
<td>Timing of surgery after chemoradiation (reference = 5-6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6-7 months</td>
<td>1.650</td>
<td>0.758</td>
<td>3.590</td>
</tr>
<tr>
<td>&gt;7-9 months</td>
<td>1.603</td>
<td>0.671</td>
<td>3.830</td>
</tr>
<tr>
<td>&gt;9 months</td>
<td>2.192</td>
<td>0.744</td>
<td>6.460</td>
</tr>
</tbody>
</table>

CI, Confidence Interval

Type of Surgery

The most common surgical procedure in the immunotherapy group was lobectomy (73.8%), followed by wedge resection (11.6%), pneumonectomy (9.2%) and segmentectomy (5.5%).
Similarly, in the chemoradiation group, lobectomy was performed in 73.9% of the patients, followed by pneumonectomy (16.2%), wedge resection (4.6%), and segmentectomy (2.6%). Regarding surgical margins, 89.0% of patients in the immunotherapy group and 89.7% of patients in the chemoradiation group underwent R0 resection. Subgroup analysis of both groups showed that 22.6% of R0-resected patients in the immunotherapy group had pathological T0 stage, whereas in the chemoradiation group, 26.3% had pathological T0 stage.

Chemotherapy and Radiation

In the immunotherapy cohort, 84% of the patients underwent multi-agent chemotherapy, with 39% receiving radiotherapy, primarily at the tumor site (71%). Conversely, all patients in the chemoradiation group received both treatments, with the vast majority (98.9%) receiving radiation at the primary site. The remaining 1.1% of patients received radiation directed at other sites, including the spine, vertebral bodies, soft tissue, or brain.

Table 3: Logistic regression model of type of surgery after immunotherapy and chemoradiation with the outcome 90-day mortality.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95 % CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Type of surgery after immunotherapy (reference = lobectomy)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedge</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&gt;999.999</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>0.82</td>
<td>0.09</td>
<td>7.39</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>1.77</td>
<td>0.45</td>
<td>6.92</td>
</tr>
<tr>
<td>[Type of surgery after chemoradiation (reference = lobectomy)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedge</td>
<td>1.09</td>
<td>0.24</td>
<td>4.96</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&gt;999.999</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>1.76</td>
<td>0.84</td>
<td>371</td>
</tr>
</tbody>
</table>
Our patient population was subjected to logistic regression analysis to investigate the impact of the type of surgery and extent of resection on 90-day mortality. Lobectomy was the preferred surgical technique and was used as the reference group. In the immunotherapy group, we discovered that patients who underwent wedge resection had an odds ratio of <0.001 (p=0.947) for 90-day mortality, whereas those who underwent segmentectomy had an odds ratio of 0.82 (p=0.953). Pneumonectomy had an odds ratio of 1.77 (p=0.939) for 90-day mortality compared to the reference group. The lobectomy group was used as the reference group. Patients who underwent wedge resection had an odds ratio of 1.09 (p=0.964) for the 90-day mortality. In contrast, segmentectomy had a negligible odds ratio of less than 0.001 (p=0.962), indicating a significantly lower risk of 90-day mortality than the reference group. Pneumonectomy had an odds ratio of 1.76 (p=0.957) for 90-day mortality.

**Discussion**

Salvage surgery emerges as a promising treatment modality for NSCLC patients post-unsuccessful definitive nonsurgical treatments, aiming not just at local tumor control but at improving survival rates. Yet, its broader application remains tempered by concerns over morbidity and the nuanced efficacy observed across patient subsets.12 Does the survival advantage suggested by existing literature for salvage surgery, amidst its complexities, hold a consistent promise across diverse NSCLC scenarios? This study seeks to examine the feasibility and results of salvage surgery in the area where definitive treatments have failed. Available studies suggest that salvage surgery may confer some survival advantage for selected NSCLC patients after various modalities of chemoradiation, tyrosine kinase inhibitors, and immune checkpoint inhibitors who have a good performance status, localized disease, favorable histology, complete resection, and no major complications.6,13–16 However, these
studies were primarily retrospective and observational, with small sample sizes and potential bias. Consequently, the efficacy and safety of salvage surgery in patients with NSCLC remain unclear, and more extensive, well-designed prospective studies are necessary to establish its usefulness. The selection criteria for patients eligible for salvage surgery after immunotherapy or chemoradiation are not well defined. Studies suggest that salvage surgery may be feasible and beneficial in selected patients who achieve a good response or stable disease after systemic or local treatment, and who have resectable tumors with no distant metastasis.17–20

Salvage lung resection can be performed by either lobectomy or sublobar resection, with the extent of surgery being a crucial factor in determining the feasibility of salvage surgery. It is widely believed that most patients with locally advanced NSCLC require lobectomy or pneumonectomy to achieve adequate resection margins.21 Our study found that the most common procedure in both the immunotherapy and chemoradiation groups was lobectomy, accounting for 73.8% and 73.9% of the cases, respectively. Sublobar resections were performed in 17.1% of patients in the immunotherapy group, while pneumonectomy was performed in 16.7% of patients in the chemoradiation group. Complete resection was achieved in 89.0% of patients in the immunotherapy group and 89.7% of patients in the chemoradiation group. A review of salvage surgery resection after chemoradiation by Hamada et al. showed a mean pneumonectomy rate of 28%, with lobectomy performed in 63% of the cases.21 Even higher rates of lobectomy were observed in smaller studies of salvage surgery after immunotherapy or targeted therapy (78 - 100%).19,22,23 Given the perioperative morbidity and mortality associated with pneumonectomies, it appears that performing a lobectomy or sublobar resection and achieving adequate negative margins is a feasible surgical management approach. To compare the procedures in terms of overall survival (OS), we performed logistic regression with lobectomy as the reference in both groups. In the chemoradiation group, the
odds ratio (OR) for pneumonectomy was 1.76 (p = 0.957). In the immunotherapy group, the OR for pneumonectomy was 1.77 (p value = 0.939). While our study does not establish a significant survival difference between surgical procedures, it prompts a reevaluation of surgical strategies in NSCLC treatment, encouraging further research into how parenchymal-sparing procedures might influence long-term outcomes. Nonetheless, the odds ratio (OR) suggests that patients in which lobectomy and sublobar resection can be performed, may have a potential advantage regarding OS over patients undergoing pneumonectomy. The observed trends, despite statistical caution due to a small patient cohort and heterogeneity, underline the necessity for larger, more controlled studies to explore the potential benefits of different surgical approaches. Our data indicate that lobectomy is not inferior to pneumonectomy in terms of survival outcome. The lower perioperative morbidity and mortality associated with lobectomy not only reinforce its feasibility but also suggest a paradigm shift in selecting surgical options, highlighting the importance of personalized patient care in NSCLC treatment.

In this study, a high rate of complete resection (R0) in both immunotherapy and chemoradiation groups were seen (89.0 % and 89.7 %, respectively). These findings align with those reported in the literature, where complete resection rates span from 81-100%, irrespective of the initial treatment approach. \cite{7,8,16,21–23} Notably, a significant segment of our cohort achieving complete resection also presented with pathologic T0 (pT0) stage—22.6% in the immunotherapy group and 26.3% in the chemoradiation group. In contrast, previous studies reported much lower pT0 stages, ranging from 6-27%, or did not report it at all.\cite{7,16,22}

Figure 4 showcases a pivotal comparison of OS among patients who underwent complete resection with or without pT0. Patients who underwent immunotherapy prior to salvage surgery and reached pT0 stage showcased an OS rate of 100%, significantly surpassing the survival
rate of 67.2% observed in patients with viable tumor resections. Similarly, in the chemoradiation group, patients with pT0 had a significantly better survival rate than those with resected viable tumors.

To assess the safety of salvage surgery, we analyzed the length of hospital stay, readmission rate, and mortality within the first 30 days after discharge. Patients who received immunotherapy had an average hospital stay of 4.0 days (IQR, 2.0 - 6.0), contrasting with 5.0 days (IQR, 3.0 - 7.0) for those undergoing chemoradiation. Early readmission rates were comparably low, at 4.9% in the immunotherapy group and 4.0% in the chemoradiation group. Post-surgery mortality rates were minimal, at 0.6% and 3.8% in the immunotherapy and chemoradiation groups, respectively, underscoring the procedure's safety within the initial postoperative period.

The length of hospital stay reported in our study, which varied from 4 to 9 days, is within the range reported in the literature. The 30-day mortality rate in the literature also varies widely, ranging from 0 to 11% and putting our study in the lower end of it. Salvage surgery is commonly associated with an increased incidence of perioperative complications. This is due to data from neoadjuvant chemoradiation therapies, which demonstrate fibrotic changes in hilar structures. Moreover, these patients usually have a greater tumor burden or are initially deemed inoperable. Another safety factor for patients is the extent of surgery, where an increased incidence of complications is associated with a higher rate of pneumonectomies. Our data regarding length of hospital stay, readmission rate, mortality, and the higher rate of lobar and sublobar resection indicate that salvage surgery may be a safer option than previously believed.
The optimal timing of salvage surgery remains uncertain. Our findings highlight a pivotal insight into the timing of salvage surgery following initial therapy for NSCLC, suggesting a nuanced interplay between early and late surgical interventions. Specifically, the data reveal that late salvage surgery after chemoradiation may be influenced by hilar fibrosis, while surgeries performed late after immunotherapy may benefit from its immunoalteration effects. This distinction underscores the need for future research to delve deeper into the biological impacts of timing on salvage surgery outcomes, potentially guiding more personalized and effective treatment strategies for NSCLC patients. We categorized patients into four groups based on when they underwent salvage surgery following their initial therapy. This division enabled a closer look at the effects of timing on surgical outcomes post-immunotherapy. Our goal was to enhance the study's consistency and minimize bias through this approach. Recognizing how these timing nuances affect outcomes is crucial for refining surgical schedules to improve patient results. Most of the patients in both the immunotherapy and chemoradiation groups underwent salvage surgery 5-7 months after the start of initial therapy. We chose 5 months as the cutoff point for salvage surgery due to the lack of data on the time frame between the start of initial therapy and surgery and to exclude patients who did not meet our criteria. Interestingly, our data showed that a longer time frame between the initial therapy and salvage surgery was prognostically better in patients who received immunotherapy, with an odds ratio (OR) of 0.391 for surgery > 9 months after the start of immunotherapy. However, for patients who received chemoradiation, the opposite was observed, with an OR of 2.192 for surgery > 9 months after the start of chemoradiation, although the results were not significant. Although longer intervals may increase the intraoperative risk, they can also confirm the absence of distant recurrences. Another important consideration is the possibility of developing drug resistance during the extended interval, which could affect the effectiveness of salvage surgery.
Limitations

The findings of this study should be interpreted with caution due to several important limitations. First, the sample size was insufficient for subgroup analysis, particularly in the immunotherapy group, although larger than other published studies. Second, the patients had diverse clinical stages and tumor histology, which limited the ability to compare therapy strategies in detail. Third, we lack data on the exact timing of initial treatment and salvage surgery. We used 5 months or later as a time point for salvage surgery, which could have resulted in selection bias and misclassification. For example, some patients in our cohort might have received neoadjuvant treatment, or there may be cases of patients who underwent salvage surgery earlier than 5 months that were not captured in our dataset. Fourth, we were unable to determine the specific immunotherapy regime; the dataset we used from the National Cancer Database (NCDB) includes a range of agents under the “immunotherapy” variable, such as immune checkpoint inhibitors, tumor vaccines, and other immunomodulatory drugs. Therefore, drugs such as TKI could have been classified as immunotherapy in the NCDB dataset. Finally, our study lacked specific details regarding the indication for salvage surgery, including whether it was for persistent disease, recurrence, or whether wedge resections were performed for diagnostic purposes. Furthermore, our dataset revealed the inclusion of early-stage lung cancer patients undergoing immunotherapy. This subset predominantly comprised individuals initially deemed inoperable or those participating in clinical trials. Due to the limitations of our data source, specific details regarding the rationale for choosing immunotherapy in these early-stage cases were not available. This aspect represents a notable limitation in our analysis, as it precludes a comprehensive understanding of the decision-making processes underlying the treatment choices for these patients.
Conclusions
In this study, we analyzed the outcomes of salvage surgery in patients who had previously received definitive therapy strategies, such as immunotherapy or chemoradiation, for lung cancer using data from the NCDB. We found that salvage surgery was feasible and safe, with high rates of complete resection, short hospital stays, low 30-day mortality and unplanned readmission rates. These results are encouraging and suggest that salvage surgery may offer a potential benefit for highly selected patients who have residual or recurrent disease after definitive therapy. Prospective randomized trials are needed to confirm the efficacy and optimal timing of salvage surgery in this patient population.

References


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Figure 1: Graphical Abstract

Figure 2: Patient Selection

NSCLC, Non-Small Cell Lung Cancer

Figure 3A: Overall survival of patients with NSCLC (stages I-IV) who underwent salvage surgery after immunotherapy.

3-year overall survival: 73.4%. Stratum specific 95% confidence intervals are presented by the shaded region.
Figure 3B: Overall survival of patients with NSCLC (stages I-IV) who underwent salvage surgery after chemoradiation.

3-year overall survival: 69.8%. Stratum specific 95% confidence intervals are presented by the shaded region.

Figure 4A: Overall survival of patients with NSCLC (stages I-IV) who underwent salvage surgery and R0 resection after immunotherapy.

3-year overall survival: pT0N0 (100%), not pT0N0 (67.2%). Stratum specific 95% confidence intervals are presented by the shaded region.

Figure 4B: Overall survival of patients with NSCLC (stages I-IV) who underwent salvage surgery and R0 resection after chemoradiation.

3-year overall survival: pT0N0 (77.5%), not pT0N0 (66.7%). Stratum specific 95% confidence intervals are presented by the shaded region.

Supplemental Figure 1A: Overall survival of patients with NSCLC (stages I-IV) who underwent salvage surgery with different extents of resection after immunotherapy.

3-year overall survival: Lobectomy (72.5%), Pneumonectomy (92.9%), Segmentectomy (74.1%), Wedge (69.0%). Stratum specific 95% confidence intervals are presented by the shaded region.

Supplemental Figure 1B: Overall survival of patients with NSCLC (stages I-IV) who underwent salvage surgery with different extents of resection after immunotherapy.
3-year overall survival: Lobectomy (72.3%), Pneumonectomy (64.7%), Segmentectomy (58.3%), Wedge (42.9%). Stratum specific 95% confidence intervals are presented by the shaded region.
Overall Survival: Salvage Surgery after Immunotherapy

Survival Percentage

Time (years)

Number at risk

Strata

All

Time (years)

Strata

All

0 1 2 3

0.5 1 1.5 2 2.5 3

164 164 147 127 100 74 58
Salvage Surgery in Non-Small Cell Lung Cancer

Methods:
- NCDB
  - NSCLC (Stage I - IV)
  - Definitive Therapy
  - Salvage Surgery > 5 Months after Therapy Start

Salvage surgery after definitive immunotherapy: \( n = 164 \)
Salvage surgery after definitive chemoradiation: \( n = 445 \)

Results:
- Resection Type
  - Wedge Resection: 11.6% CR: 4.6%
  - Segmentectomy: 5.5% CR: 2.6%
  - Lobectomy: 73.8% CR: 73.9%
  - Pneumonectomy: 9.2% CR: 16.7%

- Resection Margins
  - Complete Resect. pT0N0: 89.0% CR 89.7%
  - pT0N0: 22.6% CR 26.3%

- Outcome
  - Mortality: 0.6% CR 3.8%
  - Readmission Rate: 4.9% CR 4.0%

Implications:
- Feasibility
  - In the majority of cases, lobar and sublobar resections achieve R0 resection.

- Safety
  - Salvage surgery, even after a prolonged period from initiation of definitive nonsurgical therapy, is associated with low mortality and low readmission rates.
Survival Percentage

Time (years)

Number at risk

Strata Not pT0N0 pT0N0

Time 0 0.5 1 1.5 2 2.5 3

Not pT0N0 328 328 285 240 214 189 162

pT0N0 117 117 109 103 90 78 69

p = 0.01
Salvage Lung Resection After Immunotherapy in Lung Cancer is Feasible and Safe