國立臺灣大學公共衛生學院環境與職業健康科學研究所

博士論文

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Doctoral Dissertation

早期肺癌手術選擇之最佳化：基於腫瘤特徵的肺葉切除術、肺節切除術與楔狀切除術比較分析

Optimizing Surgical Selection for Early-Staged Lung Cancer: A Comparative Analysis of Lobectomy, Segmentectomy and Wedge Resection Based on Tumor Characteristics.

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早期肺癌手術選擇之最佳化：基於腫瘤特徵的肺葉切除術、肺節切除術與楔狀切除術比較分析

Optimizing Surgical Selection for Early-Staged Lung Cancer: A Comparative Analysis of Lobectomy, Segmentectomy and Wedge Resection Based on Tumor Characteristics.

本論文係江旺恒君（學號 D09852005）在國立臺灣大學公共衛生學院環境與職業健康科學研究所完成之博士學位論文，於民國 114 年 7 月 8 日承下列考試委員審查通過及口試及格，特此證明

口試委員：

陳保中 （簽名）

（指導教授）

誌謝

博士班的畢業標誌著我人生中一個階段的結束以及另一個階段的開始。

傳統上，撥往左邊的帽穗代表獨立研究的能力、領導團隊的視野，以及探索未知、突破疆界的勇氣等等。但說實話，此刻我就單單想大聲喊一句「我是博士了！」說來可笑，小時候常常跟爸爸媽媽應承下許多浮誇不實的願望：「媽~我以後要當總統！」、「爸~我長大要成為愛因斯坦第二」、「媽~我以後要賺很多錢帶你去環遊世界！」……對爸媽很抱歉的是多數的願望跟承諾隨著慢慢長大都一一跳票了，差一點，「我長大要當博士！」的願望也要跳票，但很高興現在我可以在完成厚厚的博士論文後寫這一篇短短的致謝給我爸媽、我的家人、我的師長和我自己，宣告我終於將這小時候許下的最小的一個願望實現了！

攻讀博班的這五年剛好也是晉升主治醫師的頭五年，除了新身分的適應之外，面對未來也是徬徨無措。第一年在台大雲林分院擔任主治醫師，至今猶記每週四清晨搭著搖搖晃晃的電動公車，帶著昏昏沉沉的睡意搭上高鐵，去台北上課 meeting，高鐵站的摩斯漢堡早餐跟八卦台地的晨曦是最鮮明的記憶；第二年之後調任回總院擔任教學型主治醫師，這時原以為不用再搭高鐵通勤上課可以有更多時間投入博士研究，但恰恰相反，教學、行政、臨床事務紛沓而來，來自師長、同儕跟自己的壓力四面而至，手忙腳亂、左支右絀、捉襟見肘……都不足以形容這幾年間窘迫。幸而指導教授陳保中老師從不疾言厲色數落我那慘不忍睹的研究進度，非但沒有成為壓垮駱駝的稻草，反而讓我覺得博班 meeting 是一個溫暖的避風港。

這五年間除了博班研究跟職涯探索之外，還討到了老婆，雖然跟我同樣是胸腔外科醫師，但外向活潑的個性和我有很大的不同，常常能跟我互補，也為生活帶來許多歡聲笑語，她的支持鼓勵不僅讓我獲得了穩定的力量，也讓我們在磨合中吸收了彼此的不同特質，變得更加完整圓融。爸爸媽媽則是一如既往地堅定地、盲目地支持自己兒子，不論是跟他們抱怨壓力、抱怨環境、抱怨人，最後都得到同樣一個結論：「兒子是最棒的！」雖然多數時候這個結論並不完全正確，但這樣的全方位護持對於在臨床和學業中深陷掙扎的我就是最重要最寶貴的，也沒可能有其他人可以如此無條件地贊同我了。從爸爸媽媽而來的，還有一部分是信仰的力量，我雖然來自基督徒家庭，但有時覺得上教會聽道理有那麼一點遙遠縹緲，但透過爸媽對我的疼愛，我願意相信聖靈是屬實的，正藉由爸爸媽媽一點一滴地按抹在我頭上。

完成學位後，我希望未來能帶著更開闊的眼界，對自己有更高的期許，同時也能腳踏實地耕耘努力；更重要的，在老婆跟爸媽對我的支持下可以既勇敢又戰戰兢兢、既自信又如履薄冰地實現自我目標，期許自己能為改善社會現況及科學研究貢獻一份綿薄之力。

2025.07

中文摘要

背景： 早期非小細胞肺癌（NSCLC），特別是肺腺癌的手術治療方式正在演進。傳統的肺葉切除術雖為標準，但亞肺葉切除術（SLR，包含肺節切除術與楔狀切除術）因早期篩檢的普及與保留肺功能的需求而日益受到重視。然而，最佳的手術範圍，特別是在不同亞肺葉切除技術的選擇以及處理具有臟層肋膜侵犯（VPI）等不良特徵的腫瘤方面，仍存在爭議。本論文旨在基於腫瘤特徵比較肺葉切除術、肺節切除術與楔狀切除術，以優化早期肺腺癌的手術選擇。

方法： 本研究包含四個系列研究，運用國立臺灣大學醫學院附設醫院之機構資料庫以及臺灣癌症登記中心之全國性數據（2011-2018 年）。比較分析針對臨床第一期或病理 T2a 期（腫瘤≤3 公分合併 VPI）N0M0 之非小細胞肺癌患者。研究中一致採用傾向評分匹配（PSM）以平衡觀察性研究中各手術組（SLR vs. 肺葉切除；肺節 vs. 楔狀切除）的基線共變量，比較其總體存活期（OS）、無病存活期（DFS）及肺癌特異性存活期（LCSS）。分析根據關鍵腫瘤特徵（如大小、實質比例（C/T ratio）、VPI 狀態）進行分層。使用 Cox 比例風險模型確定獨立預後因子。

結果： 經 PSM 校正後，對於 cT1N0 肺腺癌，SLR 的 OS 與 DFS 與肺葉切除術相當。比較兩種 SLR 術式於 IA 期肺腺癌，全國性數據分析顯示肺節切除術的 OS 優於楔狀切除術，此差異主要由>2 公分的腫瘤驅動；對於≤2 公分的腫瘤，兩者預後相當。單機構數據分析進一步指出，僅在腫瘤>2 公分且 C/T ratio >50%的亞組中，肺節切除術的 DFS 顯著優於楔狀切除術。針對 pT2a(≤3cm+VPI)N0M0 的特定亞組，SLR 的 LCSS 與肺葉切除術在嚴謹匹配校正後相當。腫瘤大小、實質成分/C/T 比、淋巴血管侵犯（LVI）及 VPI 程度（PL2 vs PL1）是重要的獨立預後因子，而手術範圍本身在校正這些因子後的影響相對較小。

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結論：早期肺腺癌手術的最佳化需要基於腫瘤特徵的個人化策略。SLR 是經選擇的 cT1N0 病例的可行選項。肺節切除術主要適用於>2 公分或具較高侵襲性影像特徵的腫瘤；楔狀切除術則適用於≤2 公分的低風險腫瘤。即使存在 VPI（於≤3 公分 N0 腫瘤），SLR 亦可能提供與肺葉切除術相當的癌症特異性存活。本研究結果支持根據腫瘤大小、影像學特徵及 VPI、LVI 等病理風險因子綜合評估，以制定最適切的手術決策。

中文關鍵字：

早期肺癌（Early-Staged Lung Cancer）

亞肺葉切除術 (Sublobar Resection)

肺節切除術 (Segmentectomy)

肺葉切除術 (Lobectomy)

術式選擇 (Surgical Selection)

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Abstract

Background: The surgical management of early-stage non-small cell lung cancer (NSCLC), particularly adenocarcinoma, is evolving. While lobectomy remains a standard, sublobar resections (SLR), including segmentectomy and wedge resection, are increasingly utilized, driven by enhanced early detection and the desire for parenchyma-sparing surgery. However, the optimal surgical extent, especially concerning the choice between different SLR techniques and the management of tumors with adverse features like visceral pleural invasion (VPI), remains debated. This thesis aimed to optimize surgical selection by comparing lobectomy, segmentectomy, and wedge resection based on tumor characteristics in early-stage lung adenocarcinoma.

Methods: This research comprised a series of four studies utilizing institutional data from National Taiwan University Hospital and nationwide population-based data from the Taiwan Cancer Registry Database (2011-2018). Comparative analyses focused on patients with clinical stage I or pathological T2a (≤3cm with VPI) N0M0 lung adenocarcinoma. Propensity score matching (PSM) was consistently employed to balance baseline covariates in observational comparisons of overall survival (OS), disease-free survival (DFS), and lung cancer-specific survival (LCSS) between surgical groups (SLR vs. Lobectomy; Segmentectomy vs. Wedge Resection). Analyses were stratified by key tumor characteristics, including size, consolidation-to-tumor (C/T) ratio, and VPI status. Cox proportional hazards models identified independent prognostic factors.

Results: After PSM, SLR demonstrated comparable OS and DFS to lobectomy for cT1N0 lung adenocarcinoma. Comparing SLR types for stage IA adenocarcinoma, segmentectomy showed superior OS compared to wedge resection in the population-based analysis, primarily driven by tumors >2cm; outcomes were comparable for tumors ≤2cm. Institutional data analysis further refined this, showing segmentectomy yielded better DFS only when both tumor size >2cm and C/T ratio >50% were present. For the specific subgroup of pT2a(≤3cm+VPI)N0M0 NSCLC, SLR

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provided comparable LCSS to lobectomy after rigorous PSM adjustment. Across analyses, tumor size, solid component/C/T ratio, LVI, and degree of VPI (PL2 vs PL1) emerged as significant prognostic factors, while surgical extent often was not an independent predictor after accounting for these characteristics in matched N0 cohorts.

Conclusion: Optimizing surgical selection for early-stage lung adenocarcinoma requires a personalized approach integrating tumor characteristics. SLR is oncologically comparable to lobectomy for selected cT1N0 cases. Segmentectomy appears superior to wedge resection primarily for tumors >2cm or those exhibiting higher radiological invasiveness. Even in the presence of VPI (in ≤3cm N0 tumors), SLR may offer comparable cancer-specific survival to lobectomy. These findings support tailoring surgical extent based on a comprehensive assessment of tumor size, radiological features, and pathological risk factors like VPI and LVI.

Keywords:

Early-Staged Lung Cancer

Sublobar Resection

Segmentectomy

Lobectomy

Surgical Selection

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Introduction

1. The Landscape of Lung Cancer and the Imperative for Early Detection

Lung cancer remains a formidable global health challenge, consistently ranking among the leading causes of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) accounts for the vast majority of cases, with adenocarcinoma emerging as the predominant histological subtype, particularly in East Asia and globally over recent decades. Historically, the prognosis for lung cancer patients has been poor, largely due to diagnosis at advanced stages where curative treatment options are limited. However, the landscape is evolving, driven significantly by advancements in screening and early detection methodologies.

The implementation of low-dose computed tomography (LDCT) screening programs, validated by large-scale trials such as the National Lung Screening Trial (NLST) in the United States and the NELSON trial in Europe, has demonstrated a significant reduction in lung cancer mortality. These programs have led to a notable stage shift, with an increasing proportion of lung cancers being detected at earlier, potentially curable stages. This paradigm shift towards early detection underscores the critical need to refine and optimize treatment strategies for early-stage NSCLC, ensuring maximal oncological efficacy while minimizing treatment-related morbidity and preserving long-term quality of life. Adenocarcinoma, being the most frequent histotype identified in these early stages, particularly manifests as small nodules or ground-glass opacities (GGOs), further necessitating tailored surgical approaches.

2. The Historical Gold Standard: Lobectomy

For decades, anatomical lobectomy, the surgical removal of an entire lobe of the lung containing the tumor, coupled with systematic mediastinal lymph node dissection or sampling, has

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been the undisputed gold standard for the treatment of early-stage NSCLC. This standard was largely cemented by the findings of a pivotal randomized controlled trial (RCT) conducted by the Lung Cancer Study Group (LCSG) published in 1995[1]. The LCSG trial compared lobectomy with more limited resections (predominantly non-anatomical wedge resections, but also segmentectomies) for patients with T1N0 NSCLC. The results indicated that limited resection was associated with a significantly higher rate of locoregional recurrence and a trend towards poorer overall survival (OS) compared to lobectomy. Consequently, lobectomy was established as the procedure providing the best balance between complete tumor removal, adequate lymph node assessment for staging, and long-term oncological control for patients fit enough to tolerate the procedure.

Despite its proven oncological efficacy, lobectomy involves the removal of a substantial amount of functional lung parenchyma, which can lead to a significant and permanent reduction in pulmonary function. This loss of lung function can impact postoperative recovery, exercise tolerance, and overall quality of life, particularly in patients with pre-existing pulmonary comorbidities (such as chronic obstructive pulmonary disease, COPD) or limited cardiopulmonary reserve. Furthermore, lobectomy carries inherent risks of perioperative morbidity and, albeit low, mortality. These limitations highlighted the need for less invasive, parenchyma-sparing surgical options, especially given the increasing detection of very small, early-stage tumors through screening[2-5].

3. The Emergence of Sublobar Resection (SLR)

The drive towards minimizing surgical trauma and preserving lung function, combined with the changing epidemiology of lung cancer presentation due to screening, fueled renewed interest in sublobar resection (SLR) techniques. SLR encompasses two main procedures: anatomical segmentectomy and non-anatomical wedge resection[6-8].

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Segmentectomy: Involves the removal of a specific bronchopulmonary segment (or segments) containing the tumor, following anatomical planes. This requires meticulous dissection and division of the segmental bronchus, artery, and vein. It is considered an anatomical resection, aiming to achieve oncological clearance similar to lobectomy but for a smaller unit of the lung.

Wedge Resection: A non-anatomical procedure involving the removal of a wedge-shaped piece of lung tissue containing the tumor, typically secured with surgical staples. It does not follow specific segmental boundaries and is generally technically simpler than segmentectomy.

The primary theoretical advantage of SLR over lobectomy is the preservation of a greater volume of functional lung tissue, potentially leading to better postoperative pulmonary function, reduced perioperative complications, and improved tolerance for future treatments should recurrence or a second primary lung cancer occur. Initial concerns, rooted in the LCSG trial, centered on whether these less extensive resections could provide equivalent oncological outcomes, particularly regarding local control and long-term survival. Numerous retrospective studies emerged throughout the 2000s and 2010s comparing SLR and lobectomy, often yielding conflicting results but suggesting potential equivalence for smaller tumors (e.g., ≤2 cm or even ≤1 cm)[9-13]. These studies, however, were often limited by selection bias, heterogeneity in patient populations, and variations in surgical techniques.

4. Landmark Trials Affirming SLR for Small Tumors: JCOG0802 and CALGB 140503

The debate surrounding the oncological adequacy of SLR for early-stage NSCLC prompted the initiation of large-scale, prospective, randomized controlled trials. Two such landmark trials, JCOG0802 from Japan[14] and CALGB 140503 from North America (later Alliance) [15], have recently reported their pivotal findings, significantly impacting clinical practice.

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* JCOG0802: This trial randomized patients with peripheral NSCLC tumors ≤2 cm and a consolidation-to-tumor (C/T) ratio >0.5 to either lobectomy or segmentectomy. The results, published in 2022, demonstrated that segmentectomy was superior to lobectomy in terms of 5-year OS (primary endpoint). However, segmentectomy showed non-inferiority, not superiority, for relapse-free survival (RFS) and was associated with a higher rate of locoregional recurrence compared to lobectomy (10.5% vs. 5.4%). The OS benefit in the segmentectomy arm was partly attributed to more deaths from other causes in the lobectomy arm.

* CALGB 140503 (Alliance): This international trial randomized patients with peripheral NSCLC tumors ≤2 cm (confirmed N0 intraoperatively) to either lobectomy or sublobar resection (which included both segmentectomy and wedge resection, though segmentectomy was preferred). Published in 2023, the trial found that SLR was non-inferior to lobectomy regarding 5-year disease-free survival (DFS, primary endpoint). OS was also similar between the groups, and while locoregional recurrence rates were numerically slightly higher after SLR, the difference was not substantial. Postoperative pulmonary function showed a small but statistically significant advantage for the SLR group.

Collectively, these trials established that for carefully selected patients with small (≤2 cm), peripheral, node-negative NSCLC, SLR (particularly anatomical segmentectomy) can achieve oncological outcomes comparable to lobectomy, often with better preservation of lung function. However, these trials also highlighted critical nuances. The JCOG trial specifically assessed segmentectomy, while CALGB allowed both segmentectomy and wedge resection, lacking the statistical power for a direct, adequately powered comparison between the two SLR techniques. Therefore, while validating SLR as an option, these trials left a significant question unanswered:

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within the spectrum of SLR, when is segmentectomy necessary, and when might a simpler wedge resection suffice?

5. The Ongoing Debate: Segmentectomy versus Wedge Resection

The choice between segmentectomy and wedge resection represents the next frontier in optimizing surgical management for early-stage NSCLC, and current evidence remains conflicting and debated.

Arguments favoring segmentectomy often center on its nature as an anatomical resection. Proponents suggest it allows for a more thorough removal of the tumor along with its associated lymphatic drainage pathways within the segment, potentially leading to lower recurrence rates compared to wedge resection. It may also facilitate more extensive lymph node sampling or dissection within the segment and hilum compared to wedge resection. Achieving adequate resection margins, especially for deeper or larger tumors within the size limit, might also be more reliably accomplished with segmentectomy.

Conversely, wedge resection is technically less demanding, generally faster, and potentially associated with lower perioperative morbidity compared to the more complex dissection required for segmentectomy. For very small, peripheral, and non-invasive or minimally invasive tumors (e.g., pure GGOs or tumors ≤1 cm), wedge resection might provide sufficient oncological control while maximizing parenchymal preservation and minimizing surgical risk[16-20].

Observational studies comparing the two techniques have yielded mixed results. Several database analyses (using SEER, NCDB, or national registries like the TCR) and meta-analyses have reported varying conclusions[21-29]:

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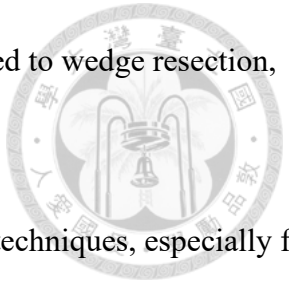

- Some suggest segmentectomy offers superior OS or DFS compared to wedge resection, particularly for tumors larger than 1 cm or ≤2 cm.
- Others find comparable survival outcomes between the two SLR techniques, especially for the smallest tumors (≤1 cm) or GGO-predominant lesions.
- One meta-analysis concluded wedge resection was associated with poorer prognosis overall compared to lobectomy, while segmentectomy yielded similar outcomes to lobectomy, though wedge might be reasonable in the elderly.
- The studies from our own study group, largely from the same research group using institutional and national Taiwanese data, consistently suggest segmentectomy is preferable for tumors >2cm (potentially in combination with C/T ratio >50%), while outcomes are comparable for tumors ≤2cm.

This lack of definitive consensus highlights the likelihood that the optimal SLR approach is not uniform but depends heavily on specific tumor and patient characteristics. Methodological rigor, particularly the use of propensity score matching (PSM) to mitigate selection bias in observational studies, is crucial when interpreting these comparisons[31-40].

6. The Central Role of Tumor Characteristics in Surgical Decision-Making

Given the conflicting data and the lack of high-level evidence definitively favoring one SLR technique over the other universally, the focus shifts towards personalized surgical strategies. Optimizing surgical selection requires a nuanced understanding of how specific tumor characteristics influence prognosis and potentially modify the relative effectiveness of lobectomy, segmentectomy, and wedge resection. The title of this thesis reflects this central theme. Key

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characteristics include:

* Tumor Size: Size is a fundamental prognostic factor in NSCLC, incorporated into TNM staging. As discussed, many studies stratify outcomes based on size thresholds (e.g., ≤1 cm, 1-2 cm, >2 cm, ≤3 cm). The provided studies suggest a potential size threshold around 2 cm where the benefit of segmentectomy over wedge resection becomes apparent for adenocarcinomas[41].

* Radiological Appearance (C/T Ratio): The proportion of solid component versus GGO on CT, often quantified by the C/T ratio, is a powerful predictor of tumor invasiveness and prognosis. GGO-predominant lesions (low C/T ratio, e.g., ≤0.5) are often associated with less aggressive histologies (like adenocarcinoma in situ or minimally invasive adenocarcinoma) and excellent prognosis, making them strong candidates for SLR, potentially even wedge resection. Conversely, solid-predominant tumors (high C/T ratio), even if small, may harbor more aggressive features, potentially warranting more extensive resection (segmentectomy or lobectomy). One of the provided studies specifically found segmentectomy advantageous over wedge only when both tumor size >2cm and C/T ratio >50% were present. The solid component diameter itself is also an independent predictor of recurrence[42].

* Visceral Pleural Invasion (VPI): As defined by tumor extension beyond the pleural elastic layer (PL1: invasion beyond elastic layer; PL2: invasion to pleural surface), VPI is a recognized adverse prognostic factor, leading to upstaging to pT2a even for tumors ≤3cm in the 8th edition AJCC staging. Its presence signifies a potentially more aggressive tumor phenotype with increased risk of recurrence, particularly distant metastasis. This creates a significant clinical dilemma: does the negative implication of VPI mandate lobectomy, or can SLR suffice for small, VPI-positive tumors without lymph node involvement?

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Evidence is conflicting: some database studies favor lobectomy, while others, including meta-analyses and the specific manuscript provided comparing SLR vs. lobectomy for pT2a(≤3cm+VPI)N0M0 NSCLC using TCR data, suggest comparable LCSS after adjusting for confounders. Some studies suggest SLR outcomes are comparable to lobectomy specifically for small (≤2cm) VPI+ tumors or when segmentectomy is performed. The degree of invasion (PL1 vs. PL2) may also matter, with PL2 potentially indicating worse prognosis.

* Lymphovascular Invasion (LVI): The presence of tumor cells within lymphatic or blood vessels is consistently identified as a strong, independent predictor of recurrence and poorer survival across various stages of NSCLC, including early stages. Its prognostic significance might outweigh the choice between SLR and lobectomy in node-negative disease, suggesting a higher systemic risk.

* Histology and Differentiation: While this thesis focuses on adenocarcinoma, specific subtypes (e.g., micropapillary, solid) are known to be more aggressive than others (e.g., lepidic). Poor differentiation is also a well-established negative prognostic factor. These features may influence the perceived need for more extensive resection or adjuvant therapy consideration.

* Other Factors: Preoperative serum Carcinoembryonic Antigen (CEA) levels have been shown to be an independent risk factor for recurrence. Emerging factors like Spread Through Air Spaces (STAS) are also being recognized as indicators of higher recurrence risk, particularly after SLR[43-46].

7. Summary of Backgrounds

The surgical management of early-stage lung adenocarcinoma is undergoing a significant

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evolution. Lobectomy, the long-standing standard, is increasingly challenged by less invasive sublobar resections, validated for small tumors by recent landmark trials. However, the optimal extent of resection, particularly the choice between segmentectomy and wedge resection, and the appropriate application of SLR in the presence of adverse tumor features like VPI or larger size within the early-stage definition, remain critical areas of uncertainty and represent significant knowledge gaps. This thesis endeavors to contribute to resolving these controversies by rigorously analyzing the comparative effectiveness of lobectomy, segmentectomy, and wedge resection, stratified by prognostically important tumor characteristics. By leveraging data primarily from the provided studies, supplemented by the broader literature, this work aims to generate evidence that can inform more personalized and optimized surgical decision-making for patients with early-stage lung adenocarcinoma, ultimately striving to improve long-term outcomes[47-51].

8. Rationale and Objectives of the Thesis

The current body of evidence presents a complex picture. While SLR is now accepted as a standard option for small, peripheral NSCLC based on RCTs, the optimal type of SLR (segmentectomy vs. wedge resection) remains unclear. Furthermore, the applicability of SLR, and the choice between its subtypes, becomes significantly more controversial when adverse features like larger size (>2cm), solid appearance (high C/T ratio), or visceral pleural invasion are present, even in clinically node-negative disease. Most comparative studies rely on retrospective data, necessitating careful adjustment for confounding using methods like PSM, as demonstrated in the provided papers[52-57].

There is a clear need for evidence-based guidance to help clinicians tailor surgical approaches for early-stage lung adenocarcinoma by integrating multiple tumor characteristics simultaneously, moving beyond single-factor considerations. This thesis aims to address this gap by performing a comparative analysis of lobectomy, segmentectomy, and wedge resection for early-stage

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(specifically clinical T1 or pathological T2a due to VPI, N0M0) lung adenocarcinoma, explicitly focusing on how outcomes differ based on key tumor characteristics such as size, C/T ratio, VPI status, and potentially others like LVI or histological subtype.

The primary objectives are:

* To compare the survival outcomes (such as OS, DFS, or LCSS) associated with lobectomy, segmentectomy, and wedge resection in specific subgroups of early-stage lung adenocarcinoma defined by tumor size and other relevant characteristics (e.g., C/T ratio, VPI).

* To identify which tumor characteristics significantly predict recurrence and survival following different surgical extents.

* To synthesize the findings to provide insights that can contribute to a more refined, evidence-based framework for optimizing surgical selection in this patient population.

Methods and Materials

This thesis integrates the findings from a series of four distinct but interrelated studies investigating the optimal surgical management of early-stage lung cancer (Figure 1). For presenting a comprehensive and cohesive discussion in this dissertation, the results from a series of four interrelated studies are included. It is pertinent to note that one of these studies was completed and published[58] before the author's matriculation into the doctoral program. The methodologies employed in each study are detailed sequentially in the following sections, corresponding to the core publications that form the basis of this dissertation. While each study addressed specific comparative questions—sublobar resection versus lobectomy, wedge resection versus

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segmentectomy, and the impact of visceral pleural invasion—they collectively contribute to the overarching goal of optimizing surgical selection based on tumor characteristics by utilizing both institutional and nationwide population-based data resources from Taiwan. Rigorous statistical methods, particularly propensity score matching, were consistently applied across the studies to mitigate selection bias inherent in observational research.

Part 1: Comparative Analysis of Sublobar Resection and Lobectomy for Clinical T1N0 Lung Adenocarcinoma (Based on Chiang et al., 2020) [58]

1. Study Design and Objective

This initial study was designed as a retrospective cohort analysis aiming to evaluate the differences in clinical outcomes, specifically overall survival (OS) and disease-free survival (DFS), between patients undergoing sublobar resection (SLR, encompassing wedge resection and segmentectomy) and those undergoing standard lobectomy for clinical T1N0 (cT1N0) lung adenocarcinoma. Recognizing the potential for significant selection bias in the choice of surgical procedure, a propensity score-matched (PSM) analysis was employed as the primary analytical strategy to compare outcomes between balanced patient groups.

2. Data Source and Study Population

Data for this study were sourced from a prospectively collected lung cancer database maintained at the National Taiwan University Hospital (NTUH), a major tertiary referral center in Taiwan. The database encompasses detailed clinical, pathological, surgical, and follow-up information. The study cohort was derived from consecutive patients with NSCLC who underwent pulmonary resection performed by a single, specialized thoracic surgical team between January 2011 and December 2016. This approach using a single-team data set aimed to minimize variability

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related to surgical technique, perioperative care protocols, and follow-up standards.

3. Patient Selection: Inclusion and Exclusion Criteria

From an initial pool of 1911 NSCLC patients undergoing surgery during the study period, a rigorous selection process was applied (detailed in Figure 2). The primary inclusion criterion was a diagnosis of solitary, clinical T1N0 lung adenocarcinoma, with tumor size defined as ≤3 cm based on the solid component diameter on preoperative imaging. Exclusion criteria were implemented to ensure a homogenous cohort focused on early-stage disease amenable to potentially curative resection: patients with histological types other than adenocarcinoma, those presenting with synchronous multiple lung cancers, evidence of distant metastasis (M1 disease), clinically positive lymph node metastasis (cN+), receipt of neoadjuvant therapy (chemotherapy or radiotherapy prior to surgery), and tumors larger than the specified T1 criteria were excluded. After applying these criteria, the final study cohort comprised 1035 patients. (Figure 2)

4. Ethical Considerations

The study protocol received approval from the Research Ethics Committee of National Taiwan University Hospital (Approval Number 201803041RINC). Due to the retrospective nature of the analysis using de-identified data from the existing database, the requirement for obtaining individual patient informed consent was formally waived by the ethics committee. Patient confidentiality was maintained throughout the study.

5. Preoperative Evaluation and Staging

All patients included in the cohort underwent a standardized comprehensive preoperative evaluation within two months prior to surgery. This typically included:

* Imaging: Chest radiography, contrast-enhanced computed tomography (CT) of the chest

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and upper abdomen, brain CT or magnetic resonance imaging (MRI), and either whole-body bone scintigraphy or positron emission tomography/computed tomography (PET/CT) scanning for staging.

* Laboratory Tests: Routine blood chemistry analyses and measurement of serum carcinoembryonic antigen (CEA) levels.

* Functional Assessment: Pulmonary function tests (PFTs) including forced vital capacity (FVC) and forced expiratory volume in one second (FEV1).

Clinical lymph node status (cN-stage) was primarily determined by imaging. Lymph nodes were considered potentially positive if they exhibited hypermetabolic activity on PET scan or measured ≥1 cm in the short-axis diameter on CT. Suspicious nodes were further investigated and confirmed pathologically whenever clinically feasible and necessary, using techniques such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), mediastinoscopy, or video-assisted thoracoscopic surgical (VATS) biopsy. Clinical staging was performed according to the 8th Edition of the American Joint Committee on Cancer (AJCC) TNM staging system.

Key imaging characteristics were carefully reviewed and measured on a standard picture archiving and communication system (PACS) by two experienced thoracic surgeons, with consensus reached for all measurements. These included the total tumor diameter, the diameter of the solid component, and the consolidation-to-tumor (C/T) ratio. The C/T ratio was calculated as the maximum diameter of the consolidation divided by the maximum total tumor diameter, following the JCOG0201 definition (pure GGO C/T=0, solid tumor C/T=1). Tumor depth was defined as the shortest distance from the tumor edge to the visceral pleura.

6. Surgical Procedures and Intraoperative Management

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Patients were categorized into two groups based on the surgical procedure received: SLR (including wedge resection and segmentectomy) or lobectomy (n=431). The choice of surgical procedure was determined at the discretion of the attending surgeon, often guided by institutional tendencies and discussed within a weekly multidisciplinary lung cancer conference. General guidelines considered lobectomy standard, particularly for tumors >20 mm or with a C/T ratio >50%. SLR was preferentially considered for patients with smaller or less invasive-appearing tumors, peripheral location suitable for wedge resection, compromised pulmonary function, advanced age, or significant comorbidities rendering them higher risk for lobectomy.

Intraoperative frozen section pathological analysis was routinely performed for all patients to confirm malignancy. If malignancy was confirmed, the adequacy of the resection margin was assessed. For SLR, if the margin was deemed insufficient (defined as <20 mm or less than the tumor diameter), immediate conversion to a larger anatomical resection (segmentectomy or lobectomy) was typically performed. The majority of procedures were performed via VATS, although conversions to thoracotomy occurred in a small number of cases. Lymph node dissection or sampling was performed according to the surgeon's standard practice, typically involving hilar and mediastinal stations relevant to the tumor location.

7. Pathological Evaluation

All resected specimens underwent formal pathological examination. Histopathological diagnosis of adenocarcinoma was confirmed postoperatively. Tumor specimens were formalin-fixed and paraffin-embedded. The microscopic examination was performed by experienced pulmonary pathologists. Histological subtyping was conducted according to the 2015 World Health Organization (WHO) classification of lung tumors, identifying the predominant pattern (e.g., lepidic, acinar, papillary, micropapillary, solid). Pathological reports were retrospectively reviewed to extract key features, including final pathological tumor size, histological differentiation grade,

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presence or absence of visceral pleural invasion (VPI) and lymphovascular invasion (LVI), final pathological T, N, and overall stage (8th AJCC edition), status of resection margins (positive or negative), total number of lymph nodes dissected, and number of lymph node stations dissected. Any missing information was obtained through re-examination of slides by a dedicated thoracic pathologist.

8. Postoperative Follow-up and Recurrence Definition

After discharge, patients were followed up systematically in the outpatient clinic. The standard protocol involved physical examinations, serum CEA level monitoring, and chest CT scans every 6 months for the initial 2 years post-surgery. Subsequently, follow-up intervals were extended to every 6 to 12 months based on physician assessment. Additional imaging (e.g., brain MRI/CT, PET/CT, bone scan) or procedures (e.g., bronchoscopy, biopsies) were performed if signs or symptoms suggestive of recurrence emerged.

Tumor recurrence was categorized based on location:

* Local Recurrence: Defined as tumor reappearance at the surgical margin (staple line, bronchial stump, or intersegmental plane).

* Regional Recurrence: Included new ipsilateral lung lesions, recurrence in ipsilateral hilar or mediastinal lymph nodes, malignant pleural effusion, or pleural nodules. Lymph node recurrence was typically confirmed by PET avidity or size criteria (≥1 cm short axis) on CT.

* Distant Metastasis: Defined as metastatic spread to the contralateral thorax or any extrathoracic organ.

Recurrence diagnoses were confirmed pathologically whenever clinically feasible and safe,

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using methods like image-guided needle biopsy, surgical biopsy, or cytological analysis of pleural fluid.

9. Statistical Analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided p-value < 0.05 was considered statistically significant.

- Descriptive Statistics:** Continuous variables were presented as mean ± standard deviation (SD), and categorical variables as number (percentage).
- Unmatched Comparisons: Before matching, baseline characteristics and perioperative outcomes between the SLR and lobectomy groups were compared using the Student's t-test for continuous variables and the Chi-squared test or Fisher's exact test for categorical variables.
- Survival Analysis: OS and DFS curves were generated using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test.
- Multivariable Analysis: Cox proportional hazards regression models were used to identify independent predictors of DFS, adjusting for significant variables identified in univariable analysis.
- Propensity Score Matching (PSM): To minimize confounding by indication, a propensity score representing the probability of receiving SLR versus lobectomy was calculated for each patient using a multivariable logistic regression model. The model included baseline covariates deemed clinically relevant to the choice of surgery: Eastern Cooperative Oncology Group (ECOG) performance status, total tumor diameter, solid component diameter, and C/T ratio. Patients in the lobectomy group were matched 1:1 to patients in

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the SLR group using a nearest-neighbor algorithm with a caliper restriction set at 0.25 standard deviations of the logit of the propensity score.

* Matched Comparisons: After matching, baseline characteristics and outcomes were compared between the paired groups using McNemar's test or Bowker's test of symmetry for categorical variables and the paired t-test for continuous variables. Kaplan-Meier survival analysis and log-rank tests were repeated on the matched cohorts.

Part 2: Comparative Analysis of Wedge Resection versus Segmentectomy for Clinical T1N0 Lung Adenocarcinoma (Based on Chiang et al., 2021)[59]

1. Study Design and Objective

Building upon the previous findings supporting SLR, this second study focused specifically on comparing the two main types of SLR: non-anatomical wedge resection versus anatomical segmentectomy. This retrospective cohort study aimed to evaluate perioperative outcomes and long-term survival (OS and DFS) between these two techniques for patients diagnosed with cT1N0 lung adenocarcinoma, again utilizing PSM to control for baseline differences.

2. Data Source and Study Population

The study drew upon the same prospectively collected database at NTUH and involved the same single surgical team as Part 1, extending the inclusion period to December 2017. This allowed for a larger cohort and potentially longer follow-up for some patients.

3. Patient Selection: Inclusion and Exclusion Criteria

From an initial pool of 2725 NSCLC patients operated on between January 2011 and December 2017, selection criteria were applied to isolate the target population (Figure 3). Eligible patients

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were those diagnosed with solitary cT1N0 lung adenocarcinoma who underwent curative-intent SLR (wedge resection or segmentectomy). Exclusion criteria mirrored those in Part 1, specifically removing patients with non-adenocarcinoma histology, multiple tumors, distant metastasis, solid tumor component >3 cm, clinically positive nodes, or those who underwent lobectomy or more extensive resections. This process yielded a final cohort of 1002 patients who underwent SLR (810 wedge resections, 192 segmentectomies). (Figure 3.)

4. Ethical Considerations

The study protocol was approved by the NTUH Research Ethics Committee (Project Approval No. 202003087RIND), and the requirement for individual patient informed consent was waived.

5. Preoperative Evaluation and Staging

The preoperative workup was consistent with that described in Part 1, including PFTs, serum CEA levels, and comprehensive imaging (chest/abdomen CT, brain CT/MRI, bone scan, PET/CT) completed within two months before surgery. For patients older than 70 or with significant comorbidities, echocardiography was additionally performed. Clinical node staging criteria (PET avidity or CT size >1 cm) and methods for pathological confirmation (EBUS, surgical biopsy) remained the same. Imaging parameters, including tumor depth (shortest distance to pleura), solid component definition (opacity obscuring vessels/bronchi), and C/T ratio (maximum solid diameter / maximum total diameter), were measured consistently by two surgeons with consensus review. Pathological staging followed the 8th edition AJCC TNM classification.

6. Surgical Procedures and Intraoperative Management

The institutional criteria favoring SLR (tumor ≤2 cm, C/T ratio ≤50%, cN0M0, or compromised patients) were applied. The decision between wedge resection and segmentectomy

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was primarily based on the ability to achieve an adequate resection margin, defined as >2 cm or greater than the tumor diameter. Wedge resection was considered if this margin could be achieved; otherwise, segmentectomy was performed. The specific plan was discussed in the multidisciplinary meeting. Intraoperative frozen section was used to confirm malignancy and assess margins, with conversion to larger resection (additional margin or lobectomy) if margins were inadequate.

VATS was the standard approach, with details on non-intubated and uniportal techniques referenced from prior publications by the group. Standard patient positioning and nerve blocks were employed. Specific staplers were used for vessels, parenchyma, and bronchi. For segmentectomies, preoperative 3D CT reconstruction (using Synapse 3D) was utilized to plan the division of segmental bronchi and vessels. The intersegmental plane was identified intraoperatively using either the inflation-deflation technique or near-infrared fluorescence imaging with intravenous indocyanine green (ICG) after dividing the target structure. For wedge resections, the lesion was elevated to ensure sufficient stapled margins. Following resection, mediastinal lymph node sampling was performed based on tumor location for staging.

7. Pathological Evaluation

Methods for pathological analysis were consistent with Part 1. Histological classification used the 2015 WHO criteria, and staging was based on the 8th edition AJCC system. Data extraction and re-review processes remained the same.

8. Postoperative Follow-up and Outcome Measurement

Postoperative management protocols, including follow-up schedules (physical exam, CEA, chest CT every 6 months for 2 years, then 6-12 monthly) and management of positive margins or nodal disease, were consistent with Part 1. Prolonged air leak was defined as leakage persisting for ≥3 days. Recurrence assessment involved imaging (CT, PET, MRI) and pathological confirmation

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via biopsy or cytology when possible. Recurrence patterns were classified as local, regional, or distant using the same definitions as in Part 1.

9. Statistical Analysis

Statistical analyses were conducted using SAS version 9.4 and SPSS with an R add-on for PSM. A p-value < 0.05 indicated significance.

- Data Distribution & Comparisons:Normality of continuous data was assessed using the Kolmogorov-Smirnov test. Appropriate tests (Student's t-test or Mann-Whitney U test for continuous; Chi-squared or Fisher's exact test for categorical) were used for group comparisons before matching.

- Survival Analysis:Kaplan-Meier method with log-rank tests was used for OS and DFS comparisons.

- Multivariable Analysis: Cox proportional hazards regression was used to identify independent predictors of DFS.

- Propensity Score Matching (PSM): Logistic regression was used to calculate propensity scores for receiving segmentectomy versus wedge resection. Covariates included in the model were selected based on clinical judgment: age, tumor depth, total tumor size, solid tumor size, baseline FVC, and family history of lung cancer. Matching was performed 1:1 using a nearest-neighbor algorithm with a caliper defined by a standardized mean difference of <0.2 for balanced covariates. Balance diagnostics were performed (details in supplementary materials of the original paper).

- Subgroup Analysis: Post-matching, subgroup survival analyses (DFS) were performed based on clinically significant risk factors identified in the multivariate analysis (tumor

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diameter >2 cm and C/T ratio >50%).

Part 3: Population-Based Comparison of Segmentectomy versus Wedge Resection for Stage IA Lung Adenocarcinoma (Based on Chiang et al., 2025)[60]

1. Study Design and Objective

This third study broadened the scope by utilizing a nationwide, population-based dataset to compare segmentectomy versus wedge resection. The primary objective was to assess differences in OS between these two SLR techniques for patients diagnosed with clinical stage IA lung adenocarcinoma in a real-world setting across Taiwan, again employing PSM to enhance comparability. Subgroup analyses based on tumor size were planned.

2. Data Source and Study Population

This study leveraged two major Taiwanese national databases: the Taiwan Cancer Registry (TCR) and the National Health Insurance Research Database (NHIRD).

- TCR: A comprehensive, population-based registry collecting mandatory reports on newly diagnosed cancer cases from hospitals nationwide since 1979, including demographics, tumor characteristics (histology, stage), treatment details, and follow-up status. Data quality is rigorously maintained.

- NHIRD: Contains administrative and health claims data from Taiwan's universal National Health Insurance program, providing information on healthcare utilization, procedures, and diagnoses. Linkage between TCR and NHIRD, as well as the national death registry, was performed using scrambled unique identifiers to obtain comprehensive treatment and survival information.

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The study period encompassed patients diagnosed between January 1, 2011, and December 31, 2018.

3. Patient Selection: Inclusion and Exclusion Criteria

Patients were initially identified from the TCR based on a diagnosis of clinical stage IA lung adenocarcinoma using specific ICD-O-3 morphology codes (primarily 8140-8149, 8250-8269, etc.). Key exclusion criteria included: histology other than adenocarcinoma (e.g., squamous cell, large cell, carcinoid specified by codes), diagnosis outside the study period, clinical stage beyond IA (T2+, N1+, M1), history of other primary cancers, lack of surgical intervention, surgical margins positive for malignancy, or incomplete/duplicate records. Only patients who underwent either segmentectomy or wedge resection with negative margins were included in the final analytic cohort. This resulted in 6598 patients (2061 segmentectomy, 4537 wedge resection). The selection process is illustrated in Figure 4 of the original paper.

4. Ethical Considerations

The study involved secondary analysis of de-identified data obtained from the TCR and NHIRD. Ethical approval was obtained from the Institutional Review Board of National Taiwan University Hospital (202010026RINA), and the requirement for individual patient consent was waived due to the nature of the de-identified database analysis.

5. Exposure, Outcome, and Covariate Definitions

* Exposure: The primary exposure was the type of SLR performed, categorized as segmentectomy or wedge resection. This was determined based on procedure codes and information within the linked TCR and NHIRD datasets, with physician review for validation.

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* Outcome: The primary endpoint was Overall Survival (OS), defined as the time interval from the date of surgery to the date of death from any cause. Survival status and date of death were ascertained through linkage with the official Taiwan death registry via the TCR/NHIRD infrastructure. Lung cancer-specific survival (LCSS) was also assessed as a secondary endpoint.

* Covariates/Confounders: Potential confounders were identified through literature review, expert consultation (senior epidemiologists and chest surgeons using a modified Delphi method), and directed acyclic graph (DAG) analysis. Variables included in the analyses and matching procedures were: patient age (continuous and categorized as ≤75 vs. >75 years), sex, self-reported smoking history (never, quit, current), tumor differentiation grade (well, moderate, poor/undifferentiated), pathological T stage, pathological N stage, tumor size (continuous and categorized: <1 cm, 1-2 cm, 2-3 cm, >3 cm), histological subtype (lepidic, acinar, papillary, micropapillary, solid), presence of lymphovascular invasion (LVI), and presence of visceral pleural invasion (VPI, categorized by PL stage 0, 1, 2, 3). Information on adjuvant therapy received (chemotherapy, radiotherapy, targeted therapy) and number of lymph nodes examined were also collected.

6. Statistical Analysis

Analyses were conducted for both the entire cohort and the PS-matched subpopulation.

* Descriptive Statistics: Continuous variables were summarized using means and standard deviations (SD); categorical variables using frequencies and percentages. Group comparisons used ANOVA (or likely t-tests) and Chi-squared tests.

* Propensity Score Matching (PSM): A PSM approach was implemented to balance baseline characteristics between the segmentectomy and wedge resection groups. Propensity scores

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were generated via logistic regression using the covariates listed above (age, size, pT, pN, LVI, VPI, sex, histology, smoking). A 1:1 greedy nearest-neighbor matching algorithm was employed with a caliper width set at 0.01 standard deviations of the logit of the propensity score. Exact matching was not explicitly enforced for specific variables in this iteration, but covariates like age and tumor size were included in both continuous and categorical forms to prioritize balance. The quality of matching was assessed using model diagnostics (Hosmer-Lemeshow test, c-statistic) and visual inspection of propensity score distributions before and after matching (Supplementary Figure S1 in the original paper).

* Survival Analysis: Kaplan-Meier curves were constructed to visualize OS for segmentectomy versus wedge resection groups, both before and after matching. Log-rank tests were used to compare survival distributions. Subgroup analyses were performed based on tumor size categories (<1 cm, 1-2 cm, >2 cm). Similar analyses were conducted for LCSS.

* Cox Regression: Cox proportional hazards models were employed to estimate crude and adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for the association between surgical type (wedge vs. segmentectomy as reference) and OS. The multivariable model adjusted for significant confounders identified (smoking status, age >75, sex, differentiation, tumor size, pathological N stage, VPI, LVI). Baseline hazard stratification was applied across different tumor size categories in the Cox models to accommodate potential non-proportional hazards. Statistical significance was set at $p < 0.05$.

Part 4: Comparative Analysis of Sublobar Resection versus Lobectomy for Small (≤3cm) NSCLC with Visceral Pleural Invasion (Based on Chiang et al., 2025)[61]

1. Study Design and Objective

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This final study specifically addressed the controversial subgroup of patients with small NSCLC tumors (≤3 cm) exhibiting visceral pleural invasion (VPI). It was designed as a population-based, retrospective cohort study using the TCR database to compare the effectiveness, primarily in terms of lung cancer-specific survival (LCSS), of SLR versus standard lobectomy in patients diagnosed with pathological stage T2a (defined by tumor ≤3cm plus VPI) N0M0 NSCLC. PSM was utilized to minimize confounding.

2. Data Source and Study Population

The study again utilized the validated, nationwide TCR database. The study period covered patients diagnosed between January 1, 2011, and December 31, 2018.

3. Patient Selection: Inclusion and Exclusion Criteria

An initial cohort of 36,560 NSCLC patients was identified from the TCR. A sequential exclusion algorithm (Figure 1 in the manuscript) was applied. Crucially, this study focused on patients with pathologically confirmed T2aN0M0 NSCLC, where the T2a designation was specifically due to the presence of VPI (tumor ≤3 cm with PL1 or PL2 invasion). Patients were excluded if they did not undergo surgery, had tumors >3 cm, lacked VPI (PL0) or had extensive pleural involvement (PL3, classified as T3), had pathologically confirmed nodal (N+) or distant metastasis (M1), had positive surgical margins, or had duplicate/incomplete records. This resulted in a final analytical cohort of 2,460 patients meeting these specific criteria, comprising 624 who underwent SLR and 1,836 who underwent lobectomy. (Figure 5)

4. Ethical Considerations

The study protocol, involving secondary analysis of de-identified TCR data, received approval from the Institutional Review Board of National Taiwan University Hospital (202311023W). The

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requirement for individual patient consent was waived.

5. Exposure, Outcome, and Covariate Definitions

- Exposure: The type of curative-intent, complete (margin-negative) pulmonary resection performed, categorized as SLR or Lobectomy based on TCR documentation.

- Outcome: The primary endpoint was Lung Cancer-Specific Survival (LCSS). LCSS was calculated as the time from the date of definitive surgery to the date of death attributed specifically to lung cancer. Patients dying from other causes were censored at the time of death. Survival status and cause of death were ascertained via linkage to the official Taiwanese national death registry.

- Covariates: Key baseline demographic and clinicopathological variables extracted from the TCR included: patient age, sex, self-reported smoking history, tumor size (continuous and categorical), pathological T stage details (implicitly defined by size ≤3cm + VPI), histological type (adenocarcinoma, squamous cell carcinoma, others), tumor differentiation grade, presence of LVI, and the extent of VPI (PL1 vs. PL2). Information on adjuvant therapy and number of lymph nodes examined was also collected.

6. Statistical Analysis

All statistical analyses were performed using R version 4.5.0. A two-sided p-value < 0.05 was considered significant.

- Descriptive Statistics: Baseline characteristics were summarized for the overall and matched cohorts using means ± SD for continuous variables and frequencies (n) and percentages (%) for categorical variables. Comparisons between SLR and lobectomy groups used Student's t-tests or Mann-Whitney U tests for continuous data, and

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Chi-squared tests for categorical data.

* Propensity Score Matching (PSM): To balance observed covariates between the SLR and lobectomy groups, 1:1 PSM was performed. Propensity scores were estimated using a multivariable logistic regression model including age, sex, smoking history, tumor size, pathological T stage (implicitly linked to size/VPI), histological type, differentiation grade, LVI presence, and VPI status (PL1/PL2). Matching employed a greedy nearest-neighbor algorithm without replacement, using a caliper width of 0.01 standard deviations of the logit of the propensity score. Balance assessment included comparing baseline characteristics post-matching and evaluating propensity score distributions (Supplementary Figure S1 in the manuscript).

* Survival Analysis: LCSS was estimated using the Kaplan-Meier method, and survival curves were generated for SLR versus lobectomy groups, both before and after matching. Log-rank tests were used for comparisons. Stratified analyses based on VPI extent (PL1 vs. PL2) were also performed.

* Cox Regression: Cox proportional hazards models were used to assess the association between surgical type and LCSS, calculating unadjusted and multivariable-adjusted hazard ratios (HRs) with 95% CIs. The multivariable model adjusted for age, sex, smoking, laterality, differentiation, tumor size category, histology, VPI status (PL2 vs PL1), LVI, and lymph node dissection number (<6 vs ≥6).

Results

This section details the principal findings derived from the four distinct studies that constitute the core of this dissertation. Each part corresponds chronologically to the studies outlined in the

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Materials and Methods section, presenting results from the institutional comparison of sublobar resection (SLR) versus lobectomy, the comparison of wedge resection versus segmentectomy, a population-based validation of the wedge versus segmentectomy comparison, and finally, a population-based analysis focusing on the challenging subgroup of patients with small, visceral pleura-invading NSCLC.

Part 1: Comparative Analysis of Sublobar Resection and Lobectomy for Clinical T1N0 Lung Adenocarcinoma (Based on Chiang et al., 2020)[58]

1. Baseline Characteristics of the Unmatched Cohort

The initial study cohort comprised 1035 patients diagnosed with cT1N0 lung adenocarcinoma between 2011 and 2016 at NTUH, of whom 604 (58.4%) underwent SLR (470 wedge resections, 134 segmentectomies) and 431 (41.6%) underwent lobectomy. The overall cohort had a mean age of 59.5 ± 11.1 years, was predominantly female (66.1%), and consisted largely of never-smokers (87.1%) (Table 1).

Significant differences in baseline clinical and pathological characteristics existed between the groups prior to matching, reflecting selection biases inherent in clinical practice. Patients undergoing SLR typically presented with less aggressive features: they had significantly smaller mean total tumor diameters, smaller mean solid component diameters, lower mean consolidation-to-tumor (C/T) ratios, better ECOG performance status (more likely to be status 0), and shallower mean tumor depth compared to the lobectomy group (all $p<0.001$).

Pathologically, tumors resected via lobectomy were significantly larger and exhibited more adverse features. Visceral pleural invasion (VPI) was present in 21.8% of lobectomy cases versus 6.0% of SLR cases ($p<0.001$), and lymphovascular invasion (LVI) was found in 16.7% versus 5.8% ($p<0.001$). Lobectomy specimens were more likely to show moderate or poor differentiation (72.4%

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vs 45.5%, p<0.001) and less likely to have a lepidic-predominant histological subtype (7.4% vs 36.8%, p<0.001). Pathological lymph node involvement was also more frequent in the lobectomy group, with higher rates of both pN1 (5.8% vs 0.1%) and pN2 (7.0% vs 0.9%) disease (p<0.001). Interestingly, despite the more extensive resection, positive microscopic resection margins were more frequent in the lobectomy group (2.6%) compared to the SLR group (0.4%, p=0.002).

2. Perioperative Outcomes (Unmatched Cohort)

SLR was associated with significantly more favorable perioperative outcomes compared to lobectomy. Mean operative time (97.2 ± 39.7 min vs 152.2 ± 49.4 min, p<0.001), estimated blood loss (8.0 ± 45.8 mL vs 37.2 ± 107.9 mL, p<0.001), chest tube duration (1.7 ± 1.5 days vs 2.9 ± 2.4 days, p<0.001), and postoperative hospital stay (3.8 ± 2.6 days vs 5.9 ± 5.1 days, p<0.001) were all significantly shorter for the SLR group. There was no 30-day mortality in either group. The rate of conversion from VATS to open thoracotomy was low overall (0.5%) and not significantly different between groups. Consistent with the surgical extent, significantly more lymph nodes were dissected during lobectomy (mean 14.1 ± 7.6) compared to SLR (mean 6.0 ± 5.4; p<0.001), with more nodes recovered from both N1 and N2 stations. The overall postoperative morbidity rate was 3.8% for the entire cohort, with no significant difference between the lobectomy (5.3%) and SLR (2.6%) groups (p=0.203). Prolonged air leak (>5 days) was the most frequent complication.

3. Survival Outcomes (Unmatched Cohort)

The median follow-up duration for the cohort was 38.0 ± 16.2 months. In the unmatched analysis, the 3-year OS rate was high overall (98.9%) and did not differ significantly between the SLR and lobectomy groups (p=0.149, log-rank test). However, the 3-year DFS rate was significantly better for patients who underwent SLR (95.1%) compared to those who underwent lobectomy (83.5%; p<0.001, log-rank test). This finding likely reflected the baseline differences,

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with the SLR group having inherently less aggressive tumors (Figure 6).

4. Recurrence Patterns and Risk Factors (Unmatched Cohort)

Overall, 105 patients (10.1%) experienced tumor recurrence during follow-up. The recurrence rate was substantially lower in the SLR group (4.5%, 27/604) compared to the lobectomy group (18.1%, 78/431). Distant metastasis was the most common pattern of failure overall (57/105 recurrences, 54.3%). Notably, among patients who experienced recurrence, the proportion of local recurrences (at the resection margin/staple line) was higher in the SLR group (8/27, 29.6%) than in the lobectomy group (8/78, 10.3%).

Univariable analysis identified numerous clinical and pathological factors associated with worse DFS, including older age, elevated serum CEA, larger tumor size (total and solid diameter), higher C/T ratio, lobectomy procedure, non-uniportal VATS approach, intubated anesthesia, larger pathological tumor size, poorer differentiation, non-lepidic subtype, presence of VPI, presence of LVI, positive resection margin, and pathological N1 or N2 stage (all $p<0.05$). However, in the multivariable Cox regression analysis adjusting for baseline clinical factors (age, CEA, total size, solid size, C/T ratio, VATS approach, anesthesia method, surgical method), only two factors emerged as independent predictors of poorer DFS: elevated preoperative serum CEA level (HR 5.06, 95% CI 3.10-8.25, $p<0.001$) and larger solid component diameter on CT (HR 3.50 for 1-2cm vs 0-1cm, $p=0.018$; HR 7.77 for 2-3cm vs 0-1cm, $p=0.001$). The choice of surgical method (SLR vs lobectomy) was not an independent predictor of DFS in this adjusted model (HR for SLR 0.67, 95% CI 0.39-1.15, $p=0.148$) (Table 2).

5. Propensity Score Matched Analysis

PSM successfully created 284 matched pairs of patients undergoing SLR and lobectomy. After matching, the groups were well-balanced on the included baseline covariates (ECOG PS, total

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tumor size, solid component size, C/T ratio). However, some differences persisted: mean tumor depth remained shallower in the matched SLR group (0.8 ± 0.9 cm vs 1.3 ± 1.3 cm, p<0.001), and pathological differences noted before matching (larger size, more non-lepidic subtypes, higher N stage, trend towards worse differentiation in lobectomy group) remained, suggesting residual confounding. The number of dissected lymph nodes remained significantly higher in the matched lobectomy group (mean 13.4 ± 6.8 vs 6.5 ± 5.8, p<0.001). The perioperative advantages of SLR (shorter operative time, less blood loss, shorter hospital stay) were maintained in the matched comparison.

Crucially, in the matched cohort analysis, there was no longer a statistically significant difference in survival outcomes between the two surgical approaches. The Kaplan-Meier curves for OS (p=0.424) and DFS (p=0.296) were similar for the matched SLR and lobectomy groups.

Part 2: Comparative Analysis of Wedge Resection versus Segmentectomy for Clinical T1N0 Lung Adenocarcinoma (Based on Chiang et al., 2021)[59]

1. Baseline Characteristics of the Unmatched Cohort

This study included 1002 patients with cT1N0 lung adenocarcinoma undergoing SLR (810 wedge resections, 192 segmentectomies) at NTUH between 2011 and 2017. The mean age was 59.6 ± 11.8 years, 67.8% were female, and 87.8% were never-smokers. Before matching, patients undergoing wedge resection were significantly younger (mean 58.8 vs 62.9 years, p<0.001), had shallower mean tumor depth (0.8 ± 0.8 cm vs 1.0 ± 1.1 cm, p=0.001), smaller mean total tumor diameters, and smaller mean solid component diameters compared to the segmentectomy group (p<0.001). Pathologically, the segmentectomy group exhibited more aggressive tumor features, including significantly higher rates of moderate/poor differentiation (58.3% vs 47.6%, p=0.007), LVI (9.9% vs 5.2%, p=0.014), non-lepidic predominant subtype (71.4% vs 54.1%, p<0.001), larger

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pathological tumor size, higher pathological T stage (p<0.001), and more frequent nodal upstaging (pN+ rate 4.2% vs 1.0%, p<0.001) (Table 3).

2. Perioperative Outcomes (Unmatched Cohort)

All procedures were performed via VATS, with high rates of uniportal (61.4%) and non-intubated (44.7%) approaches. Conversion to thoracotomy was rare (0.2%), and no 30-day mortality occurred. Wedge resection demonstrated significantly better perioperative outcomes, including shorter mean operative time (82.3 ± 36.5 min vs 127.5 ± 42.8 min, p<0.001), less mean operative bleeding (3.4 ± 28.1 mL vs 17.7 ± 62.6 mL, p=0.002), shorter mean chest tube duration (1.5 ± 1.5 days vs 2.0 ± 1.3 days, p<0.001), and shorter mean postoperative hospital stay (3.6 ± 3.1 days vs 4.8 ± 5.4 days, p<0.001). Segmentectomy involved significantly more extensive lymph node assessment, with higher mean numbers of total dissected nodes (8.2 ± 5.8 vs 4.6 ± 4.4, p<0.001), N1 nodes (2.0 ± 2.5 vs 0.2 ± 0.1, p<0.001), N2 nodes (6.3 ± 5.0 vs 4.5 ± 4.3, p<0.001), and total dissected stations (3.6 ± 1.3 vs 2.3 ± 1.0, p<0.001). Postoperative morbidity was higher after segmentectomy, primarily driven by a higher rate of prolonged air leak (20.5% vs 11.1%, p<0.001).

3. Survival Outcomes (Unmatched Cohort)

With a median follow-up of 3.6 years, there was no significant difference in OS (p=0.824) or 5-year DFS (wedge 94.3% vs segmentectomy 92.7%, p=0.584) between the two SLR groups in the unmatched analysis.

4. Recurrence Patterns and Risk Factors (Unmatched Cohort)

The overall recurrence rate was low at 4.7% (47/1002). The recurrence rate was 4.3% (35/810) in the wedge group and 6.3% (12/192) in the segmentectomy group. Recurrence patterns were

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broadly similar between groups, with distant metastasis being the most common site. Univariable analysis identified several factors associated with poorer DFS. Multivariable Cox regression analysis revealed that elevated preoperative serum CEA level (HR 2.51, 95% CI 1.17-5.37, p=0.018), total tumor diameter >2 cm (HR 2.66, 95% CI 1.23-5.75, p=0.012), and C/T ratio >50% (HR 3.58, 95% CI 1.70-7.54, p<0.001) were independent predictors of worse DFS. Notably, the type of sublobar resection (wedge vs segmentectomy) was not independently associated with DFS in the multivariable model (HR 1.20, 95% CI 0.62-2.33, p=0.585) (Table 4).

5. Propensity Score Matched Analysis

PSM yielded 168 matched pairs of patients undergoing wedge resection and segmentectomy. The matching successfully balanced baseline demographic and clinical characteristics, including age, sex, comorbidities, PFTs, tumor depth, total size, solid size, and C/T ratio. However, pathological T stage remained significantly higher in the segmentectomy group even after matching (p=0.045), indicating persistent differences in underlying tumor biology not fully captured by clinical variables. Post-matching, wedge resection maintained advantages in operative time, blood loss, and uniportal approach rates, while segmentectomy still involved significantly more lymph node dissection. Differences in hospital stay and chest tube duration were no longer significant after matching.

In the matched cohort, Kaplan-Meier analysis revealed no statistically significant difference in OS (p=0.078) or DFS (p=0.111) between wedge resection and segmentectomy, although a non-significant trend towards better DFS was observed for segmentectomy (Figure 7).

6. Matched Subgroup Survival Analysis (DFS)

Given the trend in DFS and the identification of tumor size >2cm and C/T ratio >50% as risk factors, a predefined subgroup analysis was performed on the matched cohort.

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- High-Risk Subgroup (Size >2cm AND C/T >50%): In this subgroup (n=57 matched pairs), segmentectomy was associated with significantly better 5-year DFS compared to wedge resection (74.7% vs 33.6%; p=0.039, log-rank test).

- Lower-Risk Subgroup (Size ≤2cm OR C/T ≤50%): In the remaining patients (n=279 matched pairs), there was no significant difference in 5-year DFS between segmentectomy and wedge resection (96.7% vs 94.2%; p=0.446, log-rank test).

Part 3: Population-Based Comparison of Segmentectomy versus Wedge Resection for Stage IA Lung Adenocarcinoma (Based on Chiang et al., 2025)[60]

1. Baseline Characteristics of the Unmatched Cohort

This population-based study utilizing the TCR and NHIRD included 6598 patients with clinical stage IA lung adenocarcinoma undergoing SLR between 2011 and 2018 (2061 segmentectomy, 4537 wedge resection). The cohort characteristics reflected the broader Taiwanese population with this diagnosis: mean age 60.3 ± 11.7 years, 66.2% female, and 81.5% never-smokers (Figure 4).

Before matching, significant differences indicative of selection bias were observed. Patients undergoing wedge resection had significantly smaller tumors (mean 1.1 ± 0.7 cm vs 1.3 ± 0.8 cm for segmentectomy, p<0.001), with a much higher proportion of tumors <1 cm (53.1% vs 34.3%). The wedge group also had lower rates of pathological nodal metastasis (pN+: 1.0% vs 2.0%, p<0.001), better tumor differentiation (well-differentiated: 42.8% vs 39.6%), a higher proportion of lepidic-predominant histology (50.3% vs 43.1%), less frequent LVI (0.6% vs 1.2%), less frequent VPI (sum of PL1/2/3: 8.0% vs 9.1%), and fewer lymph nodes examined (mean 6.3 ± 7.0 vs 12.8 ± 9.2) (all p<0.01) (Table 5).

2. Survival Outcomes (Unmatched Cohort)

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In the unmatched population-based cohort, Kaplan-Meier analysis demonstrated significantly superior OS for patients undergoing segmentectomy compared to wedge resection ($p<0.0001$). Unmatched subgroup analysis by tumor size showed:

- Tumors <1 cm: No statistically significant difference in OS ($p=0.051$).
- Tumors 1-2 cm: Segmentectomy associated with significantly better OS ($p<0.0001$).
- Tumors >2 cm: Segmentectomy associated with significantly better OS ($p<0.0001$).

3. Propensity Score Matched Analysis

PSM resulted in 1499 well-matched pairs of patients undergoing segmentectomy and wedge resection. Baseline characteristics, including age, sex, BMI, smoking status, tumor size categories, pathological T/N stages, differentiation, histology subtype, LVI, and VPI, were successfully balanced between the groups after matching (all $p>0.05$).

In the matched cohort, segmentectomy remained associated with significantly better OS compared to wedge resection overall ($p=0.019$, log-rank test). Matched subgroup analysis by tumor size revealed:

- Tumors <1 cm: No significant difference in OS ($p=0.31$).
- Tumors 1-2 cm: No significant difference in OS ($p=0.38$).
- Tumors >2 cm: Segmentectomy maintained a significant OS advantage ($p=0.038$). When tumors ≤2 cm were analyzed together post-matching, OS was comparable between segmentectomy and wedge resection ($p=0.200$). Analysis of LCSS demonstrated consistent findings (Figure 8).

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4. Cox Proportional Hazards Models for Overall Survival

Multivariable Cox regression analysis performed on the entire cohort (n=6598), adjusting for potential confounders, confirmed that undergoing wedge resection was independently associated with significantly worse OS compared to segmentectomy (adjusted Hazard Ratio [aHR] 2.16, 95% CI 1.44–3.24, p<0.001). Other independent predictors of poorer OS included smoking history (aHR 1.92), age >75 years (aHR 2.10), moderate differentiation (aHR 1.88) or poor differentiation (aHR 3.11) compared to well-differentiated, larger tumor size categories (aHR 3.90 for 1-2cm, 8.23 for 2-3cm, 10.61 for >3cm, all vs <1cm), and pathological N2 stage (aHR 4.91 vs N0) (all p<0.05). In this model, sex, VPI status, and LVI status were not found to be independent predictors of OS.

Part 4: Comparative Analysis of Sublobar Resection versus Lobectomy for Small (≤3cm) NSCLC with Visceral Pleural Invasion (Based on Chiang et al., 2025)[61]

1. Baseline Characteristics of the Unmatched Cohort

This study focused on 2460 patients from the TCR (2011-2018) diagnosed with pT2a(≤3cm+VPI) N0M0 NSCLC, including 624 who received SLR and 1836 who received lobectomy. The cohort characteristics were mean age 63.7 ± 10.4 years, 57.5% female, 72.8% never-smokers, and approximately 90% adenocarcinoma histology. VPI was classified as PL1 in 76.1% and PL2 in 23.9%.

Before matching, significant differences existed. Patients undergoing SLR were notably older (mean 68.0 vs 62.3 years, p<0.001), less likely to be female (53.0% vs 59.0%), more likely to be ever-smokers (31.9% vs 25.6%), had a smaller proportion of tumors in the 2-3 cm range (40.7% vs 63.1%), had significantly fewer lymph nodes examined (mean 12.7 ± 10.2 vs 19.2 ± 11.2, p<0.001), had a higher proportion of PL1 VPI (80.0% vs 74.8%), and received less adjuvant chemotherapy (26.3% vs 36.3%) compared to the lobectomy group (all p<0.05). Locoregional recurrence was

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noted in 3.0% and distant recurrence in 14.9% of the overall cohort (Table 6).

2. Survival Outcomes (Unmatched Cohort)

In the unmatched analysis, patients who underwent lobectomy demonstrated significantly better LCSS compared to those who received SLR (p=0.01, log-rank test). Stratified analysis showed this advantage held true for the PL1 VPI subgroup (p=0.009) but not for the PL2 VPI subgroup, where LCSS was similar between surgical approaches (p=0.14).

3. Propensity Score Matched Analysis

PSM generated 523 well-matched pairs of SLR and lobectomy patients. Post-matching, the groups were balanced regarding age, sex, BMI, smoking status, tumor size category, histological type, differentiation grade, LVI presence, and VPI status (PL1/PL2) (all p>0.05). The number of examined lymph nodes remained significantly higher in the matched lobectomy group (mean 19.3 ± 11.2 vs 13.0 ± 10.4, p<0.001).

In the crucial matched cohort analysis, there was no statistically significant difference in LCSS between SLR and lobectomy, both overall (p=0.21) and when stratified by VPI extent (PL1 subgroup: p=0.11; PL2 subgroup: p=0.94) (Figure 9).

4. Cox Proportional Hazards Models for Lung Cancer-Specific Survival (Matched Cohort)

While univariable Cox analysis in the matched cohort still showed a trend favoring lobectomy (HR 0.66, 95% CI 0.47–0.91, p=0.011), this association disappeared after multivariable adjustment. In the final multivariable Cox model performed on the matched pairs, the type of surgical procedure (SLR vs lobectomy) was not found to be an independent predictor of LCSS (aHR for Lobectomy 0.75, 95% CI 0.52–1.08, p=0.124). Significant independent predictors of worse LCSS in this specific pT2a(≤3cm+VPI)N0M0 cohort were: age >75 years (aHR 1.97, 95% CI 1.40–2.77,

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p<0.001), presence of PL2 VPI compared to PL1 (aHR 2.04, 95% CI 1.50–2.77, p<0.001), and the presence of LVI (aHR 5.21, 95% CI 2.84–9.57, p<0.001).

Discussion

The surgical treatment paradigm for early-stage non-small cell lung cancer (NSCLC), particularly the increasingly prevalent adenocarcinoma subtype, is undergoing a profound transformation. Driven by the success of lung cancer screening programs leading to the detection of smaller, earlier lesions, and facilitated by advancements in minimally invasive surgical techniques, the historical dogma favoring lobectomy as the universal standard is being rigorously challenged. Sublobar resection (SLR), encompassing anatomical segmentectomy and non-anatomical wedge resection, has emerged as a critical alternative, promising preservation of pulmonary function and potentially reduced perioperative impact without compromising oncological efficacy in appropriately selected patients[62-66]. This dissertation aimed to contribute significantly to this evolving field by systematically comparing lobectomy, segmentectomy, and wedge resection across diverse clinical scenarios relevant to early-stage lung adenocarcinoma (≤3cm), utilizing both detailed institutional data and large-scale, population-based evidence from Taiwan. The core focus was to elucidate how specific tumor characteristics, including size, radiological appearance, visceral pleural invasion (VPI), and lymphovascular invasion (LVI)—influence outcomes and should guide the choice of surgical extent. The collective findings from the four constituent studies strongly advocate for a personalized surgical strategy, moving beyond simplistic size-based algorithms towards a more integrated assessment of tumor biology and patient factors.

1. Consolidating the Role of Sublobar Resection in the Modern Era

The foundational question addressed was whether SLR provides comparable oncological outcomes to the traditional standard of lobectomy for early-stage disease. The first study within this

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thesis directly compared SLR (wedge and segmentectomy combined) with lobectomy for clinical T1N0 lung adenocarcinoma at a single high-volume institution. While initial unadjusted analyses suggested better disease-free survival (DFS) for SLR, this was attributed to selection bias favoring SLR for less aggressive tumors. Crucially, after rigorous propensity score matching (PSM) to balance baseline characteristics, both overall survival (OS) and DFS were found to be statistically comparable between the SLR and lobectomy groups[67-68]. This finding provides strong, real-world validation within a specific adenocarcinoma cohort for the landmark conclusions drawn from the JCOG0802 and CALGB 140503 randomized controlled trials (RCTs). These RCTs established the non-inferiority of SLR (specifically segmentectomy in JCOG0802, and SLR generally in CALGB 140503) for selected patients with small (≤2cm), peripheral, node-negative NSCLC. Our results extend this evidence, suggesting that even within the slightly broader cT1N0 definition used, carefully selected patients undergoing SLR for adenocarcinoma can expect long-term survival outcomes equivalent to those achieved with lobectomy[69-75].

The potential advantages of SLR extend beyond oncological equivalence. Preservation of pulmonary function is a primary driver for considering less extensive resection. Although detailed long-term pulmonary function test (PFT) data were not systematically collected across all studies in this thesis, the consistently observed perioperative benefits of SLR in Part 1—significantly shorter operative times, reduced blood loss, shorter chest tube duration, and abbreviated hospital stays compared to lobectomy, even after matching—support the notion of reduced physiological impact. External studies focusing on long-term function generally confirm that SLR, particularly segmentectomy, leads to better preservation of postoperative FEV1 and FVC compared to lobectomy. Furthermore, recent systematic reviews focusing on quality of life (QoL) suggest that SLR often results in better outcomes in physical and respiratory function domains, faster recovery, and potentially less long-term fatigue or distress compared to lobectomy, especially when

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performed using minimally invasive techniques like video-assisted thoracoscopic surgery (VATS). These functional and QoL benefits significantly strengthen the rationale for choosing SLR when oncologically appropriate, particularly for patients with limited baseline respiratory reserve or those highly valuing functional preservation[76-83].

A necessary trade-off with SLR, however, is the extent of lymph node assessment. The studies within this thesis consistently demonstrated that SLR yields fewer dissected lymph nodes and sampled stations compared to lobectomy, and specifically, that wedge resection yields fewer nodes than segmentectomy. This difference persisted even after PSM. While concerning from a traditional oncological perspective emphasizing comprehensive staging, the clinical relevance of this difference in the context of contemporary early-stage, predominantly node-negative disease warrants critical evaluation. The ACOSOG Z0030 trial showed no survival benefit for complete mediastinal lymphadenectomy over systematic sampling in N0/N1 (non-hilar) NSCLC. Other studies have also failed to consistently demonstrate a survival advantage correlating directly with the number of lymph nodes removed in stage I disease, provided key stations are appropriately sampled and found negative. Given the high accuracy of modern preoperative staging with PET/CT and the extremely low rates of occult nodal positivity observed in the highly selected cN0 cohorts undergoing SLR in our studies (e.g., pN+ rates <2% in Part 3 SLR group, <5% in Part 2 segmentectomy group), it is plausible that the reduced nodal yield with well-performed SLR does not significantly impact staging accuracy or survival outcomes for the vast majority of these patients. The focus should perhaps be on adequate sampling of key hilar and mediastinal stations relevant to the tumor's location to confidently confirm N0 status, rather than maximizing the absolute node count, especially when balancing against the potential morbidity of more extensive dissection[84-88].

2. Navigating the Sublobar Spectrum: Segmentectomy versus Wedge Resection

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With SLR established as a valid option, the critical question becomes when to choose anatomical segmentectomy versus non-anatomical wedge resection. This was the focus of the second and third studies in this dissertation, providing complementary institutional and population-based perspectives. The institutional study (Part 2) found comparable OS and DFS overall between wedge and segmentectomy after matching but importantly identified a high-risk subgroup (tumor size >2cm and C/T ratio >50%) where segmentectomy offered significantly better DFS. For lower-risk patients (≤2cm or C/T ≤50%), outcomes were similar. This hinted at a threshold effect based on combined size and invasiveness features[89,90].

The large population-based study (Part 3) using the TCR/NHIRD dataset provided robust confirmation and refinement. After PSM, segmentectomy demonstrated a significant OS advantage over wedge resection for the overall stage IA adenocarcinoma cohort. However, the subgroup analysis was revealing: this advantage was driven entirely by tumors larger than 2cm. For tumors ≤2cm (both <1cm and 1-2cm subgroups), OS was comparable between segmentectomy and wedge resection after matching. This large-scale evidence strongly supports a size threshold of approximately 2cm for stage IA lung adenocarcinoma, above which anatomical segmentectomy should be preferred over wedge resection to optimize long-term survival. This aligns with findings from several external meta-analyses and database studies suggesting segmentectomy's superiority emerges for tumors >1cm or >2cm, while outcomes converge for smaller lesions.

The rationale for segmentectomy's superiority in larger (>2cm) tumors likely lies in its adherence to anatomical principles. By removing the entire segment, it potentially provides wider parenchymal margins in all dimensions, reducing the risk of local recurrence from microscopic extensions or multifocal growth within the segment, which may become more probable as tumor size increases. Furthermore, segmentectomy inherently includes the segmental bronchus, vessels, and associated intrapulmonary/hilar lymphatics, allowing for a more complete regional oncological

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resection and better assessment of N1 nodes compared to a simple wedge. The significantly higher lymph node yield consistently observed with segmentectomy versus wedge resection in our studies supports this[91-95].

Conversely, for small tumors (≤2cm), especially those <1cm or with favorable radiological features (GGO-dominant/low C/T ratio), the biological potential for local infiltration or lymphatic spread is often substantially lower. In this context, the advantages of anatomical resection may diminish. A well-executed wedge resection achieving clear margins might provide equivalent oncological control. Given the demonstrated perioperative advantages of wedge resection in the institutional setting (shorter operative time, less blood loss) and its technical simplicity, it remains a highly attractive option for these select low-risk tumors, maximizing parenchymal preservation. However, it is crucial that wedge resection achieves adequate margins, as suboptimal margins are a known risk factor for recurrence. Techniques like preoperative localization for deep or small nodules and careful intraoperative assessment are essential when performing wedge resection.

Perioperative complication profiles between wedge and segmentectomy warrants consideration. While our institutional study (Part 2) suggested higher morbidity (mainly prolonged air leak) with segmentectomy before matching, other studies present conflicting results. Some report comparable safety profiles, while others suggest segmentectomy might carry higher risks of severe complications (Grade ≥III) compared to wedge resection, potentially due to the more complex dissection involved. This highlights the importance of surgical expertise and patient selection when choosing segmentectomy.

3. Integrating Tumor Characteristics for Personalized Surgical Strategy

The core contribution of this thesis lies in demonstrating the necessity of integrating multiple tumor characteristics beyond just size to guide surgical selection.

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Size and Radiological Invasiveness (C/T Ratio): The results consistently highlight the synergy between tumor size and radiological markers of invasiveness. The finding in Part 2 that segmentectomy's advantage over wedge was most pronounced when both size >2cm and C/T >50% were present is particularly informative. It suggests that a large tumor with significant GGO might still be amenable to potentially less aggressive approaches than a similarly sized solid tumor. Conversely, a smaller solid tumor might warrant more caution (favoring segmentectomy over wedge) than a small GGO. The solid component size itself was also identified as an independent predictor of recurrence in Part 1, aligning with the AJCC 8th edition's emphasis on the invasive component size for T staging in part-solid nodules. These findings strongly advocate for incorporating quantitative assessment of tumor density/consolidation alongside size in preoperative decision-making algorithms[96-99].

Visceral Pleural Invasion (VPI): The presence of VPI in small (≤3cm), node-negative NSCLC poses a significant clinical dilemma. VPI is an established adverse prognostic factor associated with increased recurrence risk and warrants upstaging to pT2a. The central question addressed in Part 4 was whether this increased risk mandates lobectomy over SLR. Our population-based PSM analysis provided a perhaps surprising result: after rigorous adjustment for confounders, SLR achieved comparable LCSS to lobectomy in this specific pT2a(≤3cm+VPI) N0M0 cohort. This contrasts sharply with some SEER database studies that reported superior survival with lobectomy for VPI+ tumors, even those ≤2cm. However, our finding aligns with other meta-analyses and database studies suggesting potential equivalence, particularly when segmentectomy is the SLR modality or for tumors ≤2cm[100-106].

Why might SLR suffice despite VPI? One hypothesis is that in truly localized (N0M0) disease, VPI, while indicating aggressive biology, primarily increases the risk of systemic relapse (micrometastases) rather than mandating wider local parenchymal resection beyond what achieves

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clear margins. If complete R0 resection is achieved, the difference between removing a segment versus a lobe might not significantly alter the systemic risk profile dictated by the tumor's inherent biology (reflected partly by VPI and LVI). In our matched VPI+ cohort (Part 4), factors independently predicting worse LCSS were age, LVI, and importantly, the degree of pleural invasion (PL2 worse than PL1), while surgical extent (SLR vs Lobe) was not significant. This suggests that while VPI matters, especially the depth (PL2), it might influence prognosis more profoundly than it dictates the necessity of lobectomy over well-performed SLR in node-negative small tumors. However, given the conflicting literature and the inherent risks, segmentectomy should likely be the preferred SLR approach over wedge resection when VPI is known or suspected, to maximize the chances of achieving adequate deep margins and regional control. The increased risk associated with VPI (especially PL2) and LVI also underscores the importance of discussing potential benefits of adjuvant therapy, even in this nominally 'early' stage.

Lymphovascular Invasion (LVI): LVI was consistently identified as a powerful independent predictor of worse outcomes (DFS in Part 1, LCSS in Part 4). This aligns with extensive literature confirming LVI as a marker of aggressive behavior and increased metastatic potential, often proposed as a high-risk feature warranting consideration for adjuvant chemotherapy even in stage I disease. The presence of LVI likely diminishes the relative importance of local surgical extent (SLR vs Lobe) on long-term survival, shifting the focus towards addressing the heightened systemic risk. Accurate pathological identification and reporting of LVI are therefore crucial for prognostication and treatment planning.

Spread Through Air Spaces (STAS): Although not systematically assessed in the core studies of this thesis due to limitations in registry data or standard reporting during the study period, STAS has emerged as a significant prognostic factor and pattern of invasion in lung adenocarcinoma. Defined as tumor cells spreading within airspaces beyond the main tumor edge, STAS is strongly

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associated with increased recurrence rates (particularly locoregional) and worse survival, especially following limited resection. Its presence raises concerns about achieving adequate margins with SLR, particularly wedge resection, as tumor cells may extend considerably beyond the radiologically or grossly apparent tumor border. Some institutions now consider STAS found on frozen section an indication for converting SLR to lobectomy. Future studies comparing surgical outcomes must incorporate STAS status, and reliable intraoperative detection methods are needed. The potential impact of STAS may further argue for anatomical segmentectomy over wedge resection, or even lobectomy, in tumors deemed likely to be STAS-positive based on radiological or other predictive features.

4. Towards an Integrated Framework for Surgical Selection

Based on the synthesis of findings from this dissertation and contextualizing literature, a more nuanced, integrated approach to surgical selection for early-stage (≤3cm, cN0) lung adenocarcinoma can be proposed:

Initial Assessment (Size, Radiology, Location):

- ≤1cm, Peripheral, GGO-dominant: Wedge resection is a strong candidate, offering maximal lung preservation with likely equivalent oncological outcomes to segmentectomy.
- >1cm to ≤2cm, Peripheral: If GGO-dominant or easily amenable to wide wedge margins, wedge resection remains an option. If solid-dominant or margins are questionable with wedge, segmentectomy is preferred.
- >2cm to ≤3cm: Segmentectomy should be the preferred SLR approach due to superior survival compared to wedge in this size range. Lobectomy remains a standard alternative.

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Incorporate High-Risk Features (VPI, LVI, STAS if assessable):

- VPI Present (≤3cm, N0): SLR (preferentially segmentectomy) appears oncologically non-inferior to lobectomy based on LCSS. However, VPI signifies higher risk; consider closer follow-up and potential adjuvant therapy discussion, especially for PL2.

- LVI Present: Indicates high systemic risk. Ensure R0 resection (via appropriate SLR or lobectomy) and strongly consider adjuvant therapy.

- STAS Suspected/Confirmed: May argue for wider margins, favouring segmentectomy over wedge, or potentially conversion to lobectomy, though high-level evidence is still evolving.

- Patient Factors: Always integrate patient age, comorbidities, pulmonary function, frailty, and preferences into the final decision, especially when oncological outcomes between options appear comparable (e.g., Seg vs Wedge for ≤2cm tumors).

5. Strengths and Limitations of the Dissertation Research

The body of work presented in this thesis holds several significant strengths. It leverages both detailed institutional data allowing for granular clinical insights and large, nationwide population-based data (TCR/NHIRD) providing real-world applicability and statistical power, particularly important for analyzing specific subgroups like VPI-positive tumors. The focus on adenocarcinoma, the most common NSCLC subtype, enhances clinical relevance. A major methodological strength is the consistent and rigorous application of propensity score matching across all comparative studies, which substantially mitigates the inherent selection biases in observational surgical research, allowing for more reliable comparisons between treatment groups. Furthermore, the research tackles clinically pertinent and often controversial questions regarding the

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limits of SLR and the optimal choice between segmentectomy and wedge resection, providing direct evidence to inform practice. The use of specific endpoints like LCSS, particularly when analyzing the VPI cohort, appropriately addresses the issue of competing risks in population studies[107-111].

Despite these strengths, limitations inherent to the methodologies and data sources must be acknowledged. All studies are retrospective observational analyses; thus, despite PSM, the potential for residual confounding from unmeasured variables remains. Factors such as detailed baseline pulmonary function beyond FVC/FEV1, precise intra-parenchymal tumor location influencing margin achievability with SLR, granular comorbidity scores (e.g., Charlson Comorbidity Index), socioeconomic factors, variations in specific surgical techniques (e.g., VATS vs. robotic, uniportal vs. multiportal, specific methods for margin assessment or intersegmental plane identification), and subtle differences in surgeon experience could not be fully accounted for, particularly in the registry-based studies. The absence of randomization is the fundamental limitation preventing definitive causal inference. Heterogeneity exists within the SLR groups (variable proportions of wedge vs segmentectomy in Part 1 and 4). Detailed perioperative complication data, margin distance quantification, and long-term QoL metrics were not available in the population databases. Information on emerging factors like STAS was not systematically available for the study periods. Finally, the findings are primarily derived from a Taiwanese population and healthcare context; while biologically plausible, direct generalizability to other populations with potentially different genetic backgrounds, environmental exposures, or healthcare systems warrants confirmation through international collaborative research[112-117].

6. Clinical Implications and Future Directions

Notwithstanding the limitations, the research presented in this dissertation has significant clinical implications. It provides robust evidence supporting the judicious expansion of SLR for

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early-stage lung adenocarcinoma, moving beyond restrictive criteria solely based on tumor size <2cm. It offers critical data to guide the often-difficult choice between segmentectomy and wedge resection, strongly suggesting a size threshold around 2cm, modulated by radiological appearance, above which segmentectomy is preferred. Perhaps most impactfully, it challenges the notion that VPI in small, node-negative tumors automatically necessitates lobectomy, suggesting SLR can achieve comparable cancer-specific survival, although these patients remain at higher risk overall. This necessitates a shift towards highly personalized surgical planning informed by a comprehensive assessment of tumor characteristics and patient factors, facilitated by multidisciplinary team discussions.

Looking forward, several avenues for research are apparent. Prospective, multi-centre RCTs remain the ultimate goal, particularly for directly comparing segmentectomy versus wedge resection, ideally stratified by key characteristics like size, C/T ratio, and potentially STAS status. Incorporating long-term PFTs and patient-reported QoL outcomes as primary or key secondary endpoints in such trials is essential. Further research is needed on optimizing intraoperative assessment, including reliable frozen section analysis for STAS and potentially advanced imaging or molecular techniques for margin evaluation during SLR. The integration of radiomics and genomics holds promise for developing non-invasive prediction models to better estimate tumor invasiveness (including VPI, LVI, STAS risk) and lymph node metastasis probability preoperatively, thereby refining patient selection for different surgical approaches. Understanding the differential response to adjuvant therapies based on specific high-risk features (VPI, LVI, STAS, micropapillary components) identified in potentially curative SLR or lobectomy specimens is another critical area requiring dedicated trials. Continued long-term follow-up and detailed subgroup analyses from the completed JCOG and Alliance trials will also yield valuable data. Finally, international collaborations are needed to validate these findings across diverse populations

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and healthcare settings.

7. Overall Conclusion

The surgical treatment of early-stage lung adenocarcinoma is rapidly evolving towards less invasive, function-preserving strategies. This dissertation contributes substantially to this evolution by demonstrating that sublobar resection, when appropriately selected, can achieve oncological outcomes comparable to lobectomy for a significant proportion of patients with tumors ≤3cm, including selected cases with visceral pleural invasion but without nodal metastasis. Furthermore, it provides strong evidence that within the sublobar spectrum, anatomical segmentectomy offers superior long-term survival compared to wedge resection for larger (>2cm) stage IA adenocarcinomas, while outcomes are comparable for smaller lesions (≤2cm). Optimizing surgical selection demands a personalized approach, meticulously integrating tumor size, radiological indicators of invasiveness like the C/T ratio, and critical pathological features such as VPI and LVI. By providing robust institutional and population-based evidence from Taiwan, this research offers a valuable framework to guide clinicians in making more informed, individualized decisions, ultimately aiming to improve survival while preserving quality of life for patients diagnosed in the early stages of this common malignancy.

References

1. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for TI NO non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg. 1995;60(3):615-22; discussion 622-3.
2. Speicher PJ, Gu L, Gulack BC, et al. Sublobar resection for clinical stage IA non-small-cell lung cancer in the United States. Clin Lung Cancer. 2016;17(1):47-55.
3. Kates M, Swanson S, Wisnivesky JP. Survival following lobectomy and limited resection for the treatment of stage I non-small cell lung cancer ≤ 1 cm in size: a review of SEER data. Chest. 2011;139(3):491-6.
4. Whitson BA, Groth SS, Andrade RS, Maddaus MA, Habermann EB, D'Cunha J. Invasive adenocarcinoma with bronchoalveolar features: a population-based evaluation of the extent of

doi:10.6342/NTU202501946

resection in bronchoalveolar cell carcinoma. J Thorac Cardiovasc Surg. 2012;143(3):591-600.e1.
5. Yendamuri S, Sharma R, Demmy M, Groman A, Hennon M, Dexter E, et al. Temporal trends in outcomes following sublobar and lobar resections for small (≤2 cm) non-small cell lung cancers: a surveillance epidemiology end results database analysis. J Surg Res. 2013;183(1):27-32.
6. Harada H, Okada M, Sakamoto T, Matsuoka H, Tsubota N. Functional advantage after radical segmentectomy versus lobectomy for lung cancer. Ann Thorac Surg. 2005;80(6):2041-5.
7. McMurry TL, Shah PM, Samson P, et al. Treatment of stage I non-small cell lung cancer: what's trending? J Thorac Cardiovasc Surg. 2017;154(3):1080-7.
8. Hu SY, Hsieh MS, Hsu HH, et al. Correlation of tumor spread through air spaces and clinicopathological characteristics in surgically resected lung adenocarcinomas. Lung Cancer. 2018;126:189-93.
9. Lin MW, Huang YL, Yang CY, et al. The differences in clinicopathologic and prognostic characteristics between surgically resected peripheral and central lung squamous cell carcinoma. Ann Surg Oncol. 2019;26(1):217-29.
10. Bai JH, Hsieh MS, Liao HC, et al. Prediction of pleural invasion using different imaging tools in non-small cell lung cancer. Ann Transl Med. 2019;7(3):33.
11. Lee PN, Forey BA, Coombs KJ. Time trends in never smokers in the relative frequency of the different histological types of lung cancer, in particular adenocarcinoma. Regul Toxicol Pharmacol. 2016;74:12-22.
12. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer-major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(2):138-55.
13. Suzuki K, Koike T, Asakawa T, et al. A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). J Thorac Oncol. 2011;6(4):751-6.
14. Saji H, Okada M, Tsuboi M, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. Lancet. 2022;399(10335):1607-1617.
15. Altorki N, Wang X, Kozono D, et al. Lobar or Sublobar Resection for Peripheral Stage IA Non-Small-Cell Lung Cancer. N Engl J Med. 2023;388(6):489-498.
16. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol. 2015;10(9):1243-60.
17. Hung WT, Hung MH, Wang ML, Cheng YJ, Hsu HH, Chen JS. Nonintubated thoracoscopic surgery for lung tumor: seven years' experience with 1,025 cases. Ann Thorac Surg. 2019;107(6):1607-12.
18. Fiorelli A, Caronia FP, Daddi N, et al. Sublobar resection versus lobectomy for stage I non-small cell lung cancer: an appropriate choice in elderly patients? Surg Today. 2016;46(12):1370-82.

doi:10.6342/NTU202501946

19. Gu C, Wang R, Pan X, et al. Sublobar resection versus lobectomy in patients aged ≤35 years with stage IA non-small cell lung cancer: a SEER database analysis. J Cancer Res Clin Oncol. 2017;143(11):2375-82.
20. Khullar OV, Liu Y, Gillespie T, et al. Survival after sublobar resection versus lobectomy for clinical stage IA lung cancer: an analysis from the national cancer data base. J Thorac Oncol. 2015;10(11):1625-33.
21. Kodama K, Higashiyama M, Okami J, et al. Oncologic outcomes of segmentectomy versus lobectomy for clinical T1a N0 M0 non-small cell lung cancer. Ann Thorac Surg. 2016;101(2):504-11.
22. Koike T, Kitahara A, Sato S, et al. Lobectomy versus segmentectomy in radiologically pure solid small-sized non-small cell lung cancer. Ann Thorac Surg. 2016;101(4):1354-60.
23. Tsutani Y, Miyata Y, Nakayama H, et al. Oncologic outcomes of segmentectomy compared with lobectomy for clinical stage IA lung adenocarcinoma: propensity score-matched analysis in a multicenter study. J Thorac Cardiovasc Surg. 2013;146(2):358-64.
24. Dziedzic DA, Rudzinski P, Langfort R, et al. Risk factors for local and distant recurrence after surgical treatment in patients with non-small-cell lung cancer. Clin Lung Cancer. 2016;17(5):e157-e67.
25. Mery CM, Pappas AN, Bueno R, et al. Similar long-term survival of elderly patients with non-small cell lung cancer treated with lobectomy or wedge resection within the surveillance, epidemiology, and end results database. Chest. 2005;128(1):237-45.
26. Tsutani Y, Mimura T, Kai Y, et al. Outcomes after lobar versus sublobar resection for clinical stage I non-small cell lung cancer in patients with interstitial lung disease. J Thorac Cardiovasc Surg. 2017;154(3):1089-96.
27. Wisnivesky JP, Henschke CI, Swanson S, et al. Limited resection for the treatment of patients with stage IA lung cancer. Ann Surg. 2010;251(3):550-4.
28. Koike T, Yamato Y, Yoshiya K, et al. Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer. J Thorac Cardiovasc Surg. 2003;125(4):924-8.
29. Warren WH, Faber LP. Segmentectomy versus lobectomy in patients with stage I pulmonary carcinoma. Five-year survival and patterns of intrathoracic recurrence. J Thorac Cardiovasc Surg. 1994;107(4):1087-93; discussion 1093-4.
30. Keenan RJ, Landreneau RJ, Maley RH Jr, et al. Segmental resection spares pulmonary function in patients with stage I lung cancer. Ann Thorac Surg. 2004;78(1):228-33; discussion 228-33.
31. Kodama K, Doi O, Higashiyama M, Yokouchi H. Intentional limited resection for selected patients with T1 N0 M0 non-small-cell lung cancer: a single-institution study. J Thorac Cardiovasc Surg. 1997;114(3):347-53.
32. Subramanian M, McMurry T, Meyers BF, et al. Long-term results for clinical stage IA lung cancer-comparing lobectomy and sublobar resection. Ann Thorac Surg. 2018;106(2):375-81.
33. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol. 2010;28(6):928-35.
34. Wolf AS, Swanson SJ, Yip R, et al. The impact of margins on outcomes after wedge resection for stage I non-small cell lung cancer. Ann Thorac Surg. 2017;104(4):1171-8.

doi:10.6342/NTU202501946

35. Passlick B, Kubuschock B, Sienel W, et al. Mediastinal lymphadenectomy in non-small cell lung cancer: effectiveness in patients with or without nodal micrometastases results of a preliminary study. Eur J Cardiothorac Surg. 2002;21(3):520-6.
36. Keller SM, Adak S, Wagner H, Johnson DH; Eastern Cooperative Oncology Group. Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer. Ann Thorac Surg. 2000;70(2):358-65; discussion 365-6.
37. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg. 2011;141(3):662-70.
38. Flores RM, Nicastri D, Bauer T, et al. Computed tomography screening for lung cancer: mediastinal lymph node resection in stage IA nonsmall cell lung cancer manifesting as subsolid and solid nodules. Ann Surg. 2017;265(5):1025-33.
39. Yendamuri S, Dhillon SS, Groman A, et al. Effect of the number of lymph nodes examined on the survival of patients with stage I non-small cell lung cancer who undergo sublobar resection. J Thorac Cardiovasc Surg. 2018;156(1):394-402.
40. Huang X, Wang J, Chen Q, Jiang J. Mediastinal lymph node dissection versus mediastinal lymph node sampling for early stage non-small cell lung cancer: a systematic review and meta-analysis. PLoS One. 2014;9(10):e109979.
41. Saji H, Matsubayashi J, Akata S, et al. Correlation between whole tumor size and solid component size on high-resolution computed tomography in the prediction of the degree of pathologic malignancy and the prognostic outcome in primary lung adenocarcinoma. Acta Radiol. 2015;56(10):1187-95.
42. Kamiya S, Iwano S, Umakoshi H, et al. Computer-aided volumetry of part-solid lung cancers by using CT: solid component size predicts prognosis. Radiology. 2018;287(3):1030-40.
43. Maeda R, Yoshida J, Ishii G, et al. Risk factors for tumor recurrence in patients with early-stage (stage I and II) non-small cell lung cancer: patient selection criteria for adjuvant chemotherapy according to the seventh edition TNM classification. Chest. 2011;140(6):1494-502.
44. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC cancer staging manual: esophagus and esophagogastric junction. Ann Surg Oncol. 2010;17(7):1721-4.
45. Wang S, Zhang B, Qian J, et al. Proposal on incorporating lymphovascular invasion as a T-descriptor for stage I lung cancer. Lung Cancer. 2018;125:245-52.
46. Nakagawa K, Watanabe SI, Kunitoh H, et al. The Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group: past activities, current status and future direction. Jpn J Clin Oncol. 2017;47(3):194-9.
47. Kent MS, Mandrekar SJ, Landreneau R, et al. A Nomogram to predict recurrence and survival of high-risk patients undergoing sublobar resection for lung cancer: an analysis of a multicenter prospective study (ACOSOG Z4032). Ann Thorac Surg. 2016;102(1):239-46.
48. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med. 2020;382(6):503-13.
49. Aberle DR, Adams AM, Berg CD, et al.; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409.

doi:10.6342/NTU202501946

50. Razi SS, Nguyen D, Villamizar N. Lobectomy does not confer survival advantage over segmentectomy for non-small cell lung cancer with unsuspected nodal disease. J Thorac Cardiovasc Surg. 2020;159(6):2469-2483.e5.
51. Nakamura K, Saji H, Nakajima R, et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607L). Jpn J Clin Oncol. 2010;40(3):271-4.
52. Altorki NK, Wang X, Wigle D, et al. Perioperative mortality and morbidity after sublobar versus lobar resection for early-stage non-small cell lung cancer: post-hoc analysis of an international, randomised, phase 3 trial (CALGB/Alliance 140503). Lancet Respir Med. 2018;6(12):915-24.
53. Zhao M, Lu T, Huang Y, et al. Survival and Long-Term Cause-Specific Mortality Associated With Stage IA Lung Adenocarcinoma After Wedge Resection vs Segmentectomy: A Population-Based Propensity Score-Matching and Competing Risk Analysis. Front Oncol. 2019;9:593.
54. Cao J, Yuan P, Wang Y, et al. Survival Rates After Lobectomy, Segmentectomy, and Wedge Resection for Non–Small Cell Lung Cancer. Ann Thorac Surg. 2018;105(5):1483-91.
55. Dai C, Shen J, Ren Y, et al. Choice of Surgical Procedure for Patients With Non–Small-Cell Lung Cancer ≤ 1 cm or >1 to 2 cm Among Lobectomy, Segmentectomy, and Wedge Resection: A Population-Based Study. J Clin Oncol. 2016;34(26):3175-82.
56. Razi SS, John MM, Sainathan S, Stavropoulos C. Sublobar resection is equivalent to lobectomy for T1a non-small cell lung cancer in the elderly: a Surveillance, Epidemiology, and End Results database analysis. J Surg Res. 2016;200(2):683-9.
57. Zhang Y, Sun Y, Chen H. A propensity score-matching analysis of survival following segmentectomy or wedge resection in early-stage lung invasive adenocarcinoma or squamous cell carcinoma. Oncotarget. 2016;7(13):13880-5.
58. Chiang XH, Hsu HH, Hsieh MS, et al. Propensity-Matched Analysis Comparing Survival After Sublobar Resection and Lobectomy for cT1N0 Lung Adenocarcinoma. Ann Surg Oncol. 2020;27(3):703-715.
59. Chiang XH, Lu TP, Hsieh MS, et al. Thoracoscopic Wedge Resection Versus Segmentectomy for cT1N0 Lung Adenocarcinoma. Ann Surg Oncol. 2021;28(13):8398-8411.
60. Chiang XH, Wei CF, Lin CC, et al. Segmentectomy Versus Wedge Resection for Stage IA Lung Adenocarcinoma-A Population-Based Study. Cancers (Basel). 2025;17(6):936. Published 2025 Mar 10.
61. Chiang XH, Chen CJ, Wei CF, et al. Sublobar Resection Versus Lobectomy for Small (≤3 cm) NSCLC with Visceral Pleural Invasion: A Propensity-Score-Matched Survival Analysis from a Nationwide Cohort. Cancers (Basel). 2025;17(12):1990. Published 2025 Jun 14.
62. Goldstraw P, Chansky K, Crowley J, et al.; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(1):39-51.
63. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The Eighth Edition Lung Cancer Stage Classification. Chest. 2017;151(1):193-203.

doi:10.6342/NTU202501946

64. Austin JH, Müller NL, Friedman PJ, et al. Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society. Radiology. 1996;200(2):327-31.
65. Lin MW, Tseng YH, Lee YF, Hsieh MS, Lin CH, Chen JS. Computed tomography-guided patent blue vital dye localization of pulmonary nodules in uniportal thoracoscopy. J Thorac Cardiovasc Surg. 2016;152(2):535-44.e2.
66. Brunelli A, Cassivi SD, Salati M, et al. Digital measurements of air leak flow and intrapleural pressures in the immediate postoperative period predict risk of prolonged air leak after pulmonary lobectomy. Eur J Cardiothorac Surg. 2011;39(4):584-8.
67. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011;10(2):150-61.
68. Grose E, Wilson S, Barkun J, et al. Use of Propensity Score Methodology in Contemporary High-Impact Surgical Literature. J Am Coll Surg. 2020;230(1):101-112.e1.
69. Yoshimura M. Radical segmentectomy and wedge resection for good-risk patients with peripheral ct1an0m0 lung cancer radical segmentectomy and wedge resection for good-risk patients with peripheral ct1an0m0 lung cancer. Nihon Geka Gakkai Zasshi. 2016;117(4):278-82. [Article in Japanese]
70. Filosso PL, Guerrera F, Falco NR, et al. Anatomical resections are superior to wedge resections for overall survival in patients with stage 1 typical carcinoids. Eur J Cardiothorac Surg. 2019;55(2):273-9.
71. Ha KJ, Yun JK, Lee GD, et al. Surgical Outcomes of Radiographically Noninvasive Lung Adenocarcinoma According to Surgical Strategy: Wedge Resection, Segmentectomy, and Lobectomy. Korean J Thorac Cardiovasc Surg. 2018;51(6):376-83.
72. Zhong C, Sakurai H, Wei S, Fang W, Asamura H. Sublobar resections for small-sized stage Ia lung adenocarcinoma: a Sino-Japanese multicenter study. J Thorac Dis. 2018;10(2):991-8.
73. Altorki NK, Kamel MK, Narula N, et al. Anatomical Segmentectomy and Wedge Resections Are Associated with Comparable Outcomes for Patients with Small cT1N0 Non-Small Cell Lung Cancer. J Thorac Oncol. 2016;11(11):1984-92.
74. National Comprehensive Cancer Network. Non-small cell lung cancer (Version 1.2021). Accessed Dec 20, 2020. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
75. Okada M, Koike T, Higashiyama M, Yamato Y, Kodama K, Tsubota N. Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study. J Thorac Cardiovasc Surg. 2006;132(4):769-75.
76. Aokage K, Saji H, Suzuki K, et al. A non-randomized confirmatory trial of segmentectomy for clinical T1N0 lung cancer with dominant ground glass opacity based on thin-section computed tomography (JCOG1211). Gen Thorac Cardiovasc Surg. 2017;65(5):267-72.
77. Kent M, Landreneau R, Mandrekar S, et al. Segmentectomy versus wedge resection for non-small cell lung cancer in high-risk operable patients. Ann Thorac Surg. 2013;96(5):1747-54; discussion 1754-5.
78. Moon Y, Lee KY, Park JK. Margin Width of Resected Lepidic Lung Cancer Does Not Affect Recurrence After Sublobar Resection. World J Surg. 2018;42(5):1449-57.

doi:10.6342/NTU202501946

79. Wolf AMD, Oeffinger KC, Shih TY, et al. Screening for lung cancer: 2023 guideline update from the American Cancer Society. CA Cancer J Clin. 2024;74(1):50-81.
80. Li T, He W, Zhang X, et al. Survival outcomes of segmentectomy and lobectomy for early stage non-small cell lung cancer: A systematic review and meta-analysis. J Cardiothorac Surg. 2024;19(1):353.
81. Tsutani Y, Handa Y, Shimada Y, Ito H, Ikeda N, Nakayama H, et al. Comparison of cancer control between segmentectomy and wedge resection in patients with clinical stage IA non-small cell lung cancer. J Thorac Cardiovasc Surg. 2021;162(4):1244-1252.e1.
82. Hanna WC. Commentary: Wedge versus segmentectomy—It is best to err on the side of caution. J Thorac Cardiovasc Surg. 2021;162(4):1254.
83. Akamine T, Yotsukura M, Yoshida Y, Nakagawa K, Yatabe Y, Watanabe S-I. Feasibility and effectiveness of segmentectomy versus wedge resection for clinical stage I non-small-cell lung cancer. Eur J Cardiothorac Surg. 2023;63(2):ezad018.
84. Wang P, Wang S, Liu Z, Sui X, Wang X, Li X, Qiu M, Yang F. Segmentectomy and Wedge Resection for Elderly Patients with Stage I Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 2022;11(2):294.
85. Saji H, Okada M, Tsuboi M, et al.; West Japan Oncology Group and the Japanese Clinical Oncology Group. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. Lancet. 2022;399(10335):1607-1617.
86. Rusch VW. Wedge Resection vs Segmentectomy for Clinical Stage IA Non–small Cell Lung Cancer: Are They Truly Oncologically Equivalent? Ann Thorac Surg. 2024;118(3):548-549.
87. Brunelli A. Wedge or Segmentectomy for Early-Stage Non–Small Cell Lung Cancer? The Dilemma Remains Unresolved. Ann Surg Oncol. 2025;32(2):639-640.
88. Shi Y, Wu S, Ma S, Lyu Y, Xu H, Deng L, Chen X. Comparison Between Wedge Resection and Lobectomy/Segmentectomy for Early-Stage Non-small Cell Lung Cancer: A Bayesian Meta-analysis and Systematic Review. Ann Surg Oncol. 2022;29(3):1868-1879.
89. Chen CL, Hsu JS, Shen YW, et al. Changes in Staging and Management of Non-Small Cell Lung Cancer (NSCLC) Patients Following the Implementation of Low-Dose Chest Computed Tomography (LDCT) Screening at Kaohsiung Medical University Hospital. Cancers (Basel). 2024;16(20):3727.
90. Yang SM, Chung WY, Ko HJ, et al. Single-stage augmented fluoroscopic bronchoscopy localization and thoracoscopic resection of small pulmonary nodules in a hybrid operating room. Eur J Cardiothorac Surg. 2023;63(1):ezac541.
91. Hamatake D, Yoshida Y, Miyahara S, Yamashita SI, Shiraishi T, Iwasaki A. Surgical outcomes of lung cancer measuring less than 1 cm in diameter. Interact Cardiovasc Thorac Surg. 2012;15(5):854-8.
92. Towe CW, Grau-Sepulveda MV, Hartwig MG, et al.; Society of Thoracic Surgeons Database Analysis. The Society of Thoracic Surgeons Database Analysis: Comparing Sublobar Techniques in Stage IA Lung Cancer. Ann Thorac Surg. 2024;118(4):665-671.
93. Thomas PA, Seguin-Givelet A, Pages PB, et al.; EPITHOR Group. Real-world outcomes of lobectomy, segmentectomy and wedge resection for the treatment of stage c-IA lung carcinoma. Eur J Cardiothorac Surg. 2024;66(4):ezae251.

doi:10.6342/NTU202501946

94. Okereke IC, Bates MF, Jankowich MD, Rounds SI, Kimble BA, Baptiste JV, et al. Effects of Implementation of Lung Cancer Screening at One Veterans Affairs Medical Center. Chest. 2016;150(5):1023-1029.
95. Altorki N, Wang X, Damman B, et al.; Alliance/CALGB investigators. Lobectomy, segmentectomy, or wedge resection for peripheral clinical T1aN0 non-small cell lung cancer: A post hoc analysis of CALGB 140503 (Alliance). J Thorac Cardiovasc Surg. 2024;167(1):338-347.e1.
96. Karch A, Krumkamp R, Kreuels B. Randomized, placebo-controlled trial or post hoc subgroup analysis: the importance of standardized and comprehensive reporting. J Infect Dis. 2014;210(1):158-9.
97. Granholm A, Alhazzani W, Derde LPG, et al. Randomised clinical trials in critical care: past, present and future. Intensive Care Med. 2022;48(2):164-178.
98. Lin LY, Warren-Gash C, Smeeth L, Chen PC. Data resource profile: the National Health Insurance Research Database (NHIRD). Epidemiol Health. 2018;40:e2018062.
99. Wang W, Liu H, Li G. What's the difference between lung adenocarcinoma and lung squamous cell carcinoma? Evidence from a retrospective analysis in a cohort of Chinese patients. Front Endocrinol (Lausanne). 2022;13:947443.
100. Choi YL, Sun JM, Cho J, et al. EGFR mutation testing in patients with advanced non-small cell lung cancer: a comprehensive evaluation of real-world practice in an East Asian tertiary hospital. PLoS One. 2013;8(2):e56011.
101. Lei X, Zhou N, Zhang H, et al. Lobe-Specific Analysis of Sublobar Lung Resection for NSCLC Patients with Tumors <2 cm. Cancers (Basel). 2022;14(13):3265.
102. Hattori A, Takamochi K, Oh S, Suzuki K. Prognostic impact of a ground-glass opacity component in the clinical T classification of the eighth edition of the TNM classification of lung cancer. J Thorac Cardiovasc Surg. 2021;161(4):1469-1480.e1.
103. Yoshida J, Nagai K, Asamura H, et al.; Japanese Joint Committee for Lung Cancer Registration. Visceral pleura invasion impact on non-small cell lung cancer patient survival: its implications for the forthcoming TNM staging based on a large-scale nation-wide database. J Thorac Oncol. 2009;4(8):959-963.
104. Liu QX, Deng XF, Zhou D, Li JM, Min JX, Dai JG. Visceral pleural invasion impacts the prognosis of non-small cell lung cancer: A meta-analysis. Eur J Surg Oncol. 2016;42(11):1707-1713.
105. Dai ZY, Shen C, Wang X, Wang FQ, Wang Y. Could less be enough: sublobar resection vs lobectomy for clinical stage IA non-small cell lung cancer patients with visceral pleural invasion or spread through air spaces. Transl Lung Cancer Res. 2025;14(3):459-470.
106. Mathey-Andrews C, Abruzzo AR, Venkateswaran S, et al. Segmentectomy vs Lobectomy for Early Non-Small Cell Lung Cancer With Visceral Pleural Invasion. Ann Thorac Surg. 2024;117(4):1007-1014.
107. Wang Y, Lyu D, Fan L, Liu S. Research progress in predicting visceral pleural invasion of lung cancer: a narrative review. Transl Cancer Res. 2024;13(2):1137-1147.
108. Chiang CJ, You SL, Chen CJ, et al. Quality assessment and improvement of nationwide cancer registration system in Taiwan: a review. Jpn J Clin Oncol. 2015;45(3):291-296.

doi:10.6342/NTU202501946

109. Chiang CJ, Lo WC, Yang YW, You SL, Chen CJ, Lai MS. Incidence and survival of adult cancer patients in Taiwan, 2002-2012. J Formos Med Assoc. 2016;115(12):1076-1088.
110. Dignam JJ, Zhang Q, Kocherginsky M. The use and interpretation of competing risks regression models. J Clin Oncol. 2012;30(10):e1129-35.
111. Howlader N, Ries LAG, Mariotto AB, Reichman ME, Ruhl J, Cronin KA. Improved estimates of cancer-specific survival rates from population-based data. J Natl Cancer Inst. 2010;102(20):1584-1598.
112. Sakurai H, Asamura H. Sublobar resection for early-stage lung cancer. Transl Lung Cancer Res. 2014;3(3):164-172.
113. Lula Lukadi J, Mariolo AV, Ozgur EG, et al. Upstaged from cT1a-c to pT2a lung cancer, related to visceral pleural invasion patients, after segmentectomy: is it an indication to complete resection to lobectomy? Interact Cardiovasc Thorac Surg. 2023;37(3):ivad102.
114. Ding C, Jia Q, Wu Z, Zhang Y, Hu Y, Wang J, Wei D. Efficacy of thoracoscopic segmentectomy versus lobectomy in the treatment of early invasive lung adenocarcinoma: a propensity score matching study. Front Oncol. 2023;13:1186991.
115. Huang W, Deng HY, Lin MY, et al. Treatment Modality for Stage IB Peripheral Non-Small Cell Lung Cancer With Visceral Pleural Invasion and ≤3 cm in Size. Front Oncol. 2022;12:830470.
116. Hattori A, Suzuki K, Matsunaga T, Takamochi K, Oh S. Visceral pleural invasion is not a significant prognostic factor in patients with a part-solid lung cancer. Ann Thorac Surg. 2014;98(2):433-8.
117. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424.

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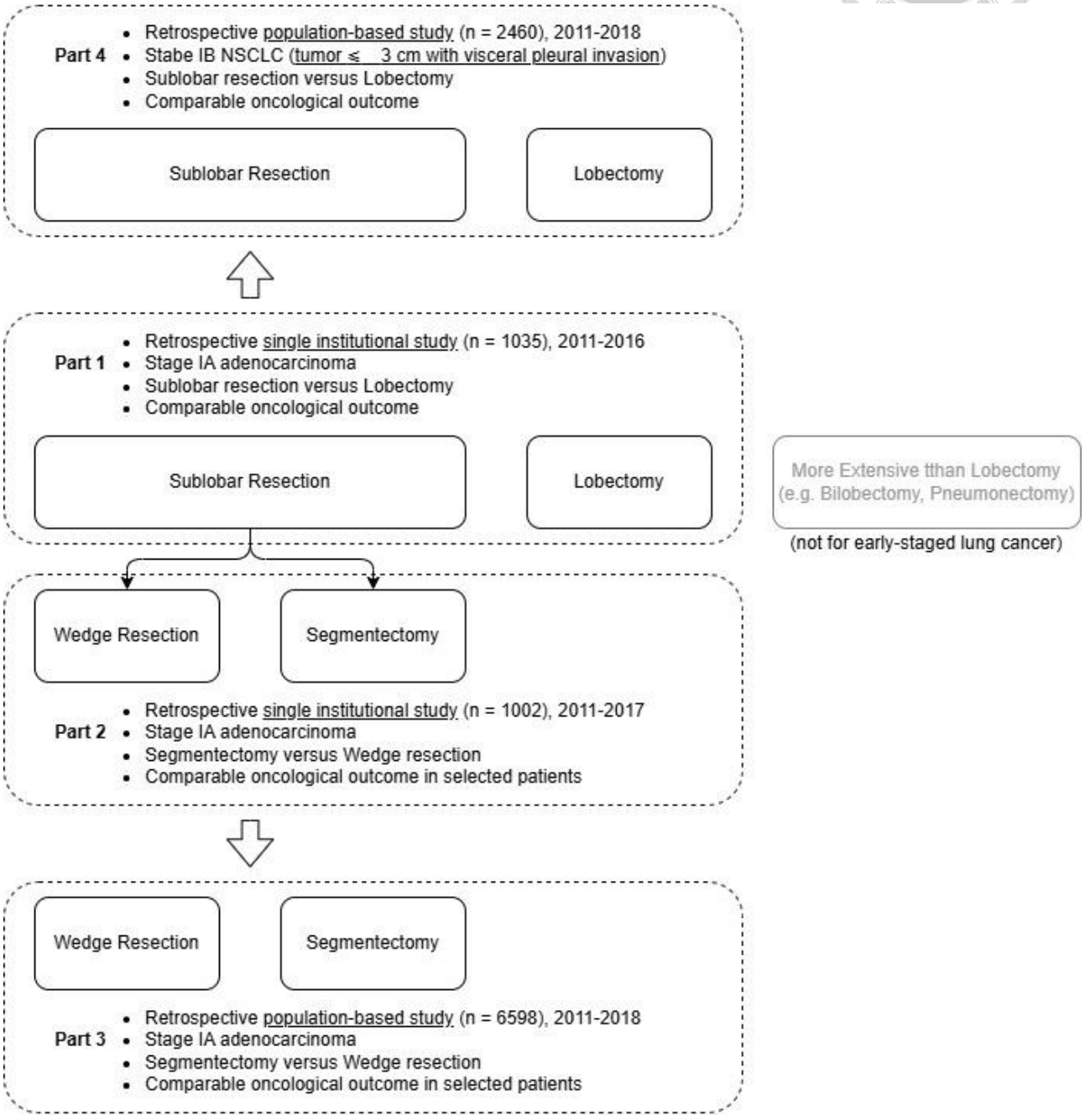
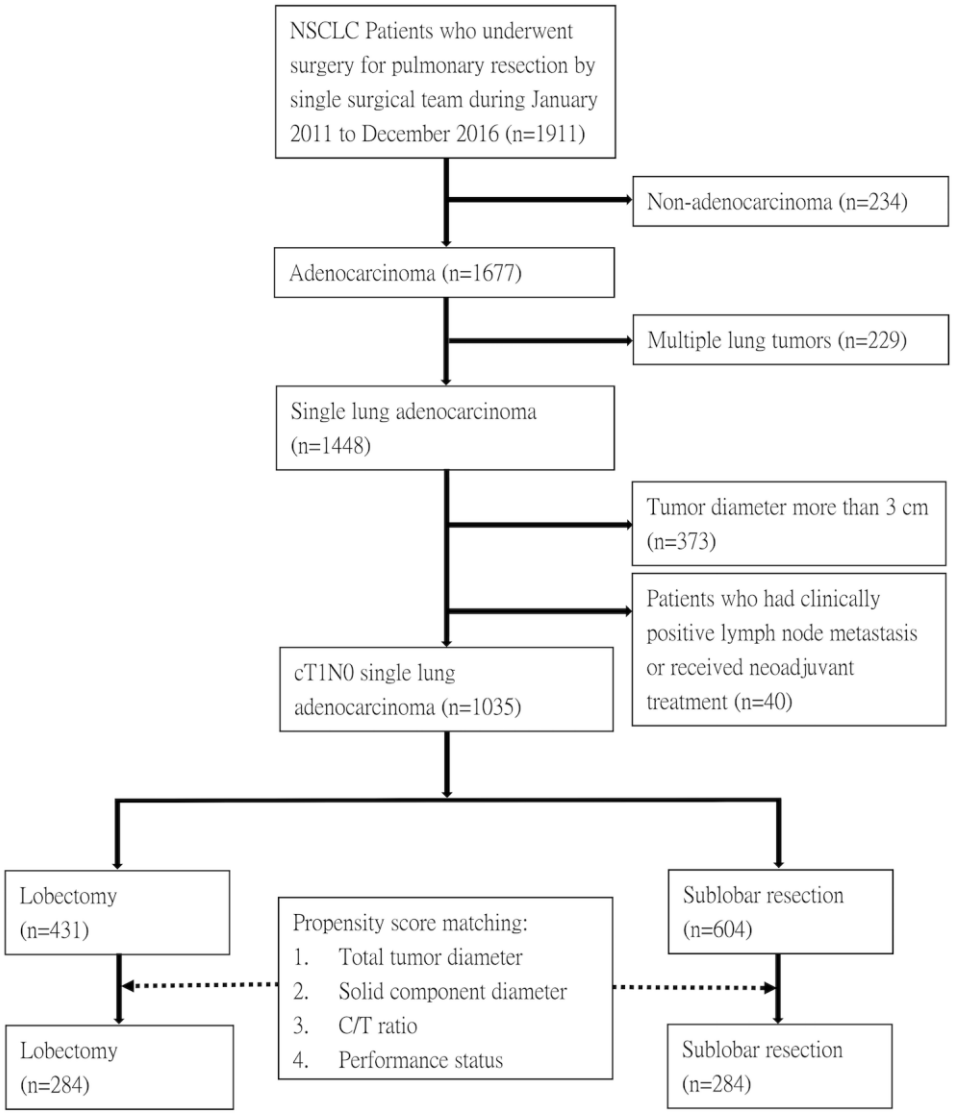
Figures

Figure 1. Framework Diagram of the Series of Studies in This Doctoral Dissertation



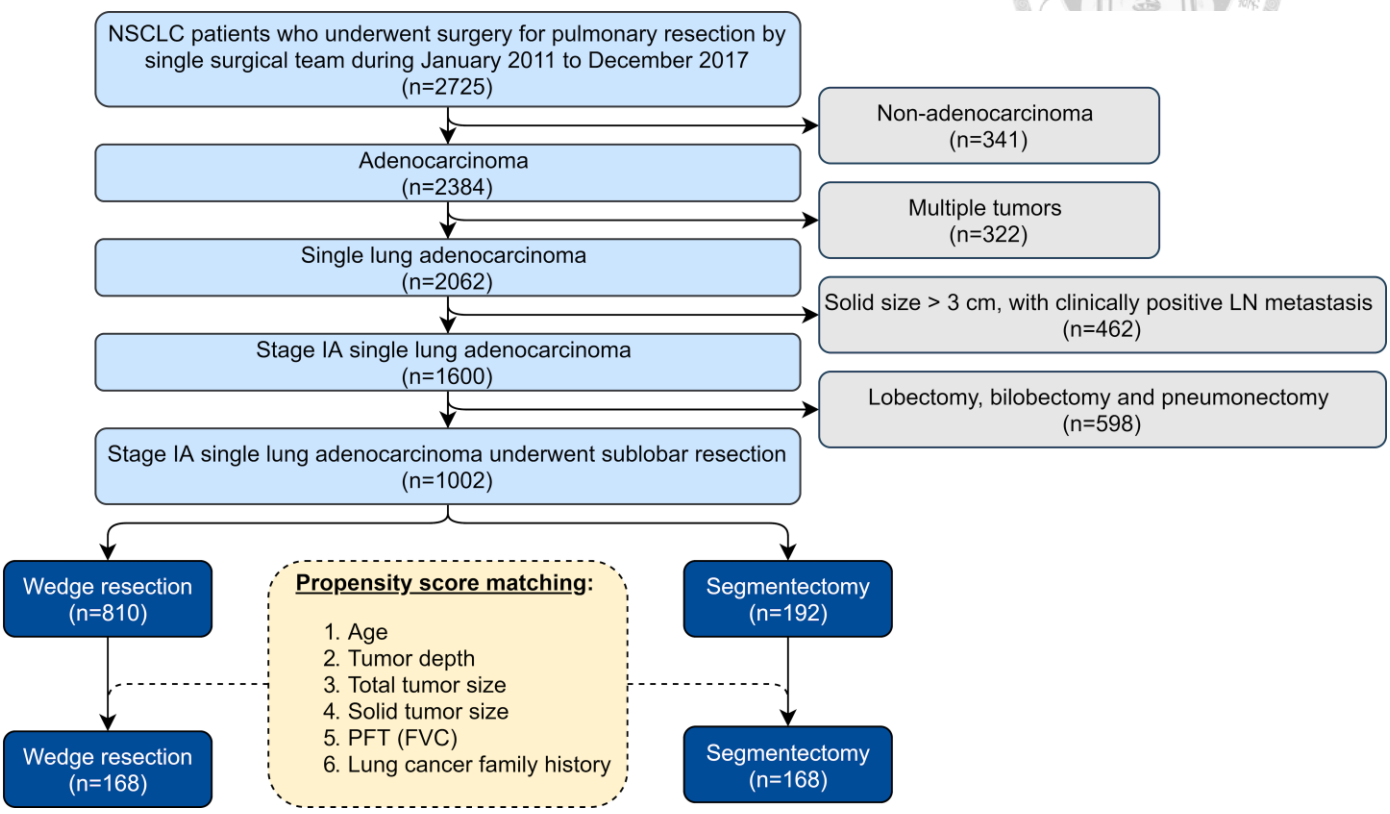
doi:10.6342/NTU202501946

Figure 2. Algorithm for patient selection for propensity-matched analysis comparing survival after sublobar resection and lobectomy for cT1N0 lung adenocarcinoma



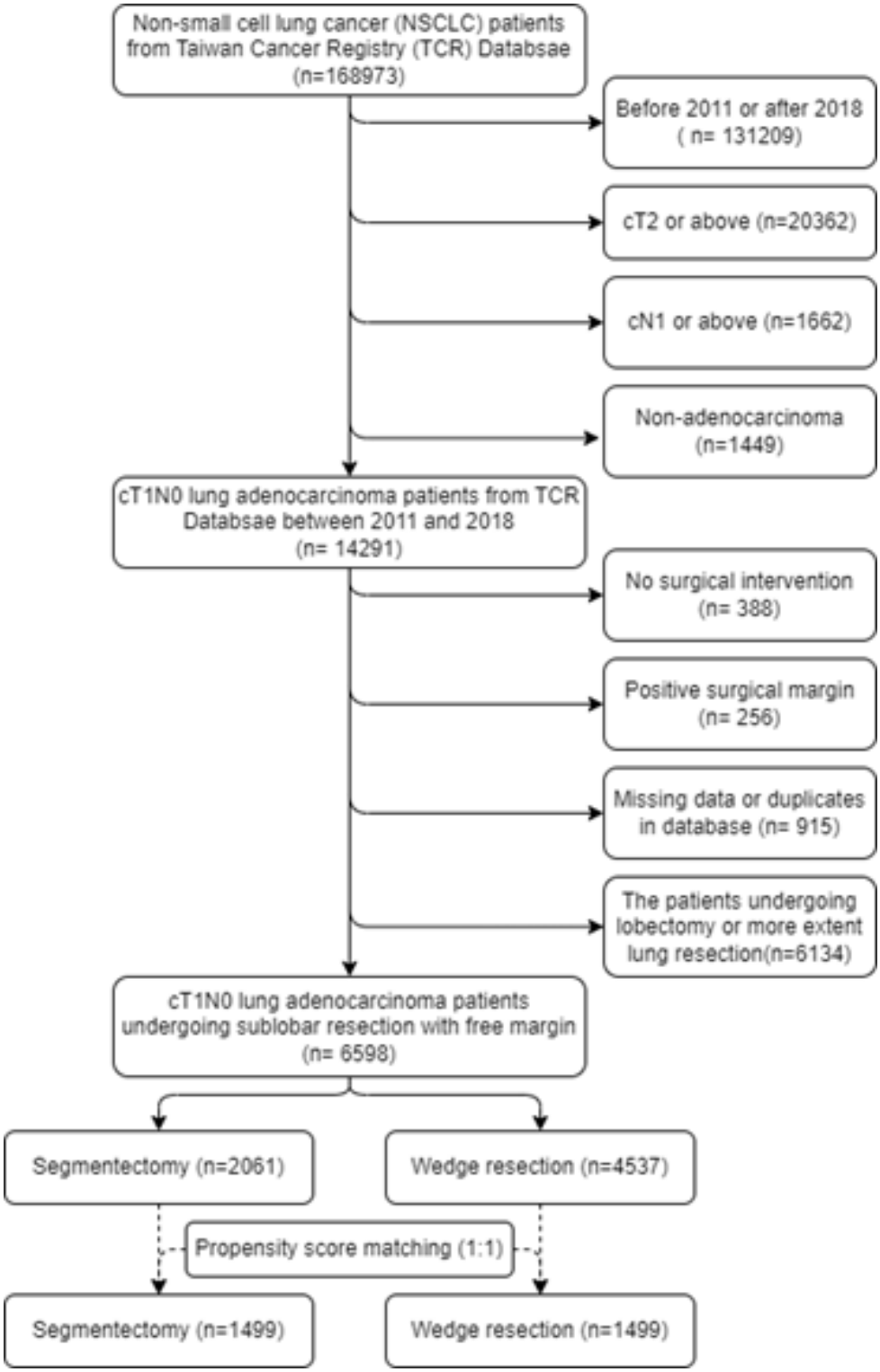
doi:10.6342/NTU202501946

Figure 3. Algorithm of the patient selection comparing wedge resection and segmentectomy for cT1N0 lung adenocarcinoma



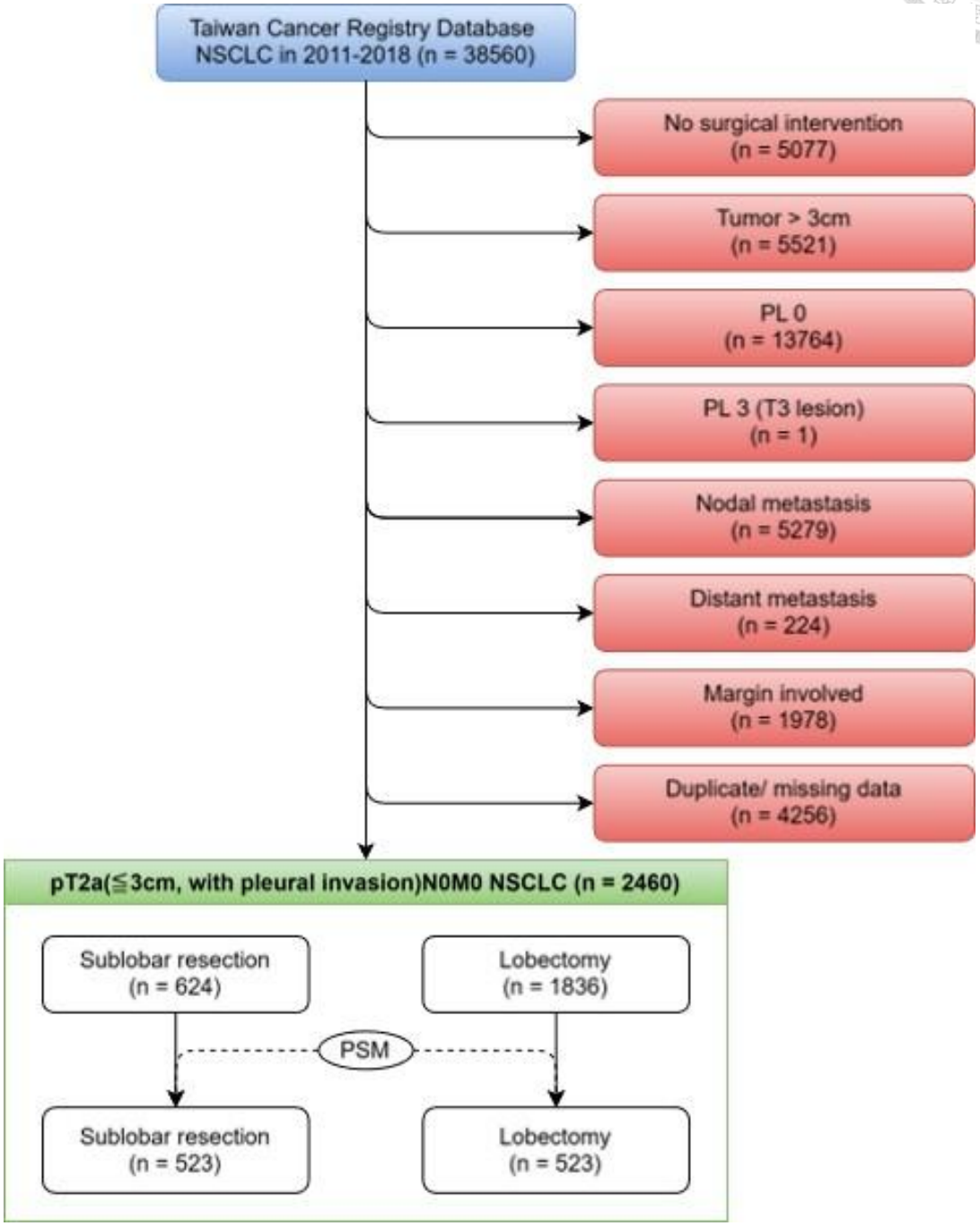
doi:10.6342/NTU202501946

Figure 4. Selection algorithm for population-based study comparing segmentectomy and wedge resection in stage IA lung adenocarcinoma



doi:10.6342/NTU202501946

Figure 5. Selection algorithm for nation-wide study comparing sublobar resection versus lobectomy for small (≤3cm) NSCLC with visceral pleural invasion



doi:10.6342/NTU202501946

Figure 6. Kaplan–Meier survival curves for (a) overall survival before propensity matching; (b) disease-free survival before propensity matching; (c) overall survival after propensity matching; and (d) disease-free survival after propensity matching

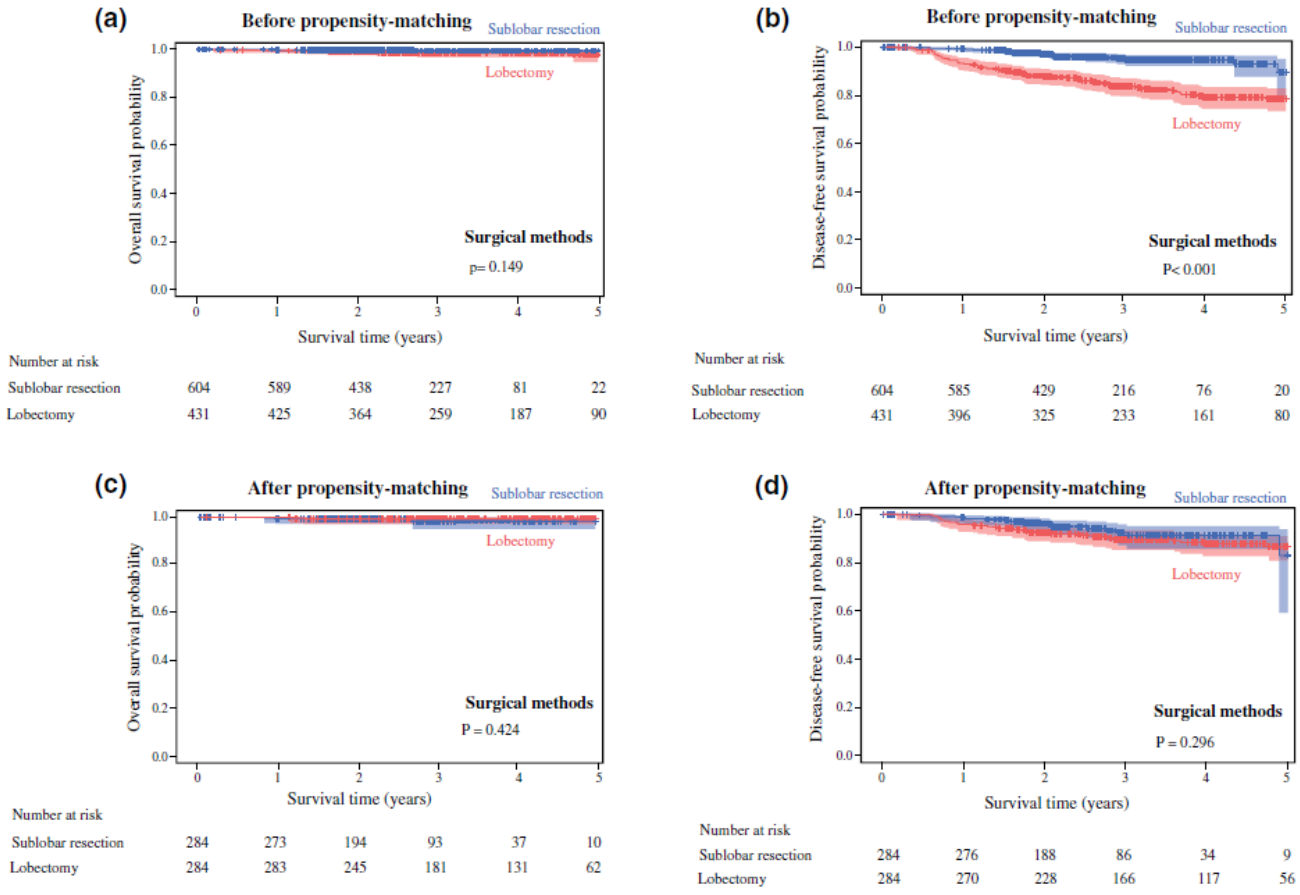


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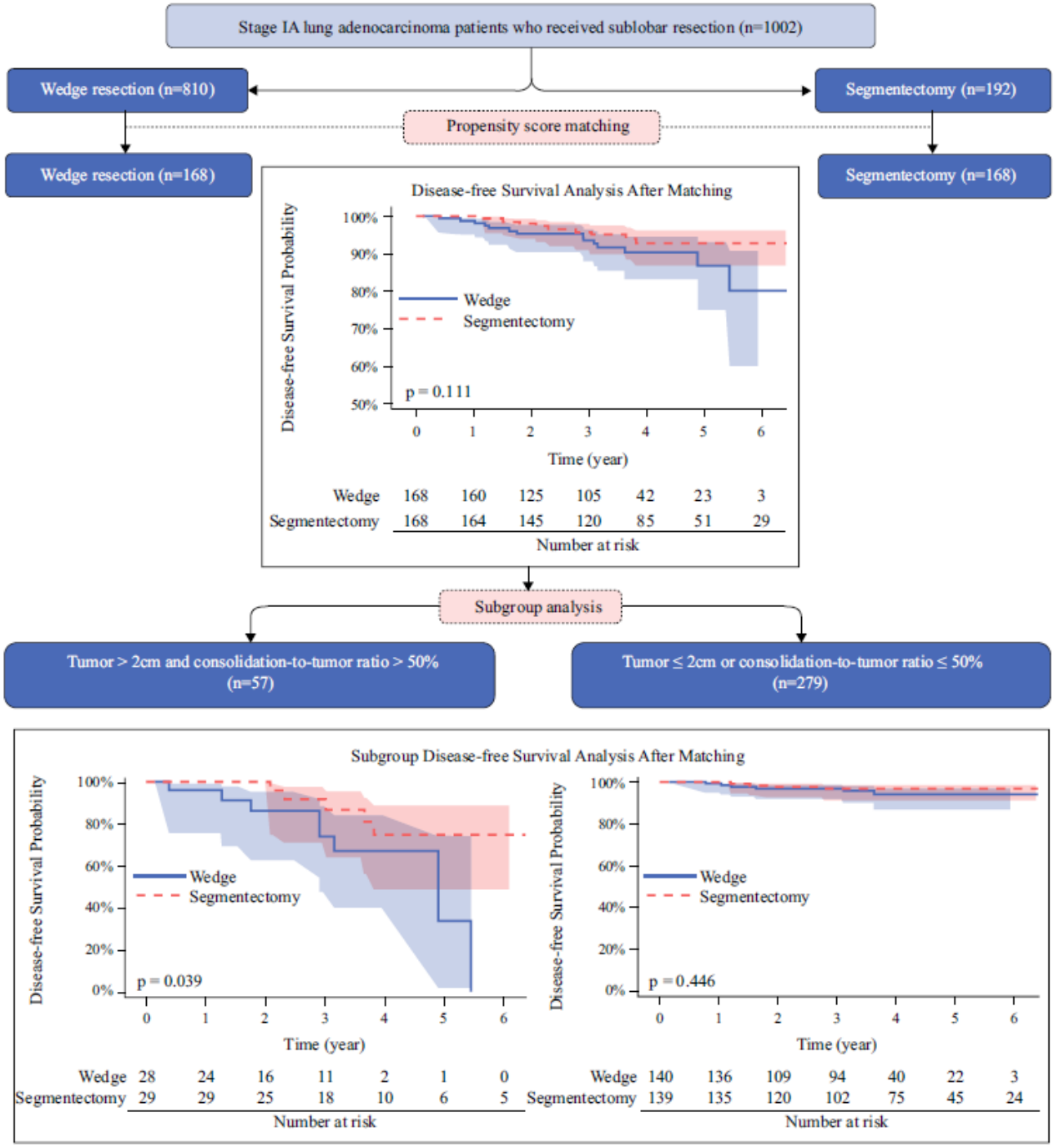
Figure 7. Subgroup analysis showed that segmentectomy correlated with better disease-free survival (DFS) than wedge resection for the patients with a tumor diameter greater than 2 cm and a C/T ratio higher than 50%. Besides, no DFS difference between the two sublobar resection groups for the remaining patients with stage IA lung adenocarcinoma was observed.



doi:10.6342/NTU202501946

Figure 8. Overall survival analysis after matching; (A) for total included patients; (B) for tumor size 0–1 cm; (C) for tumor size 1–2 cm; (D) for tumor size > 2 cm

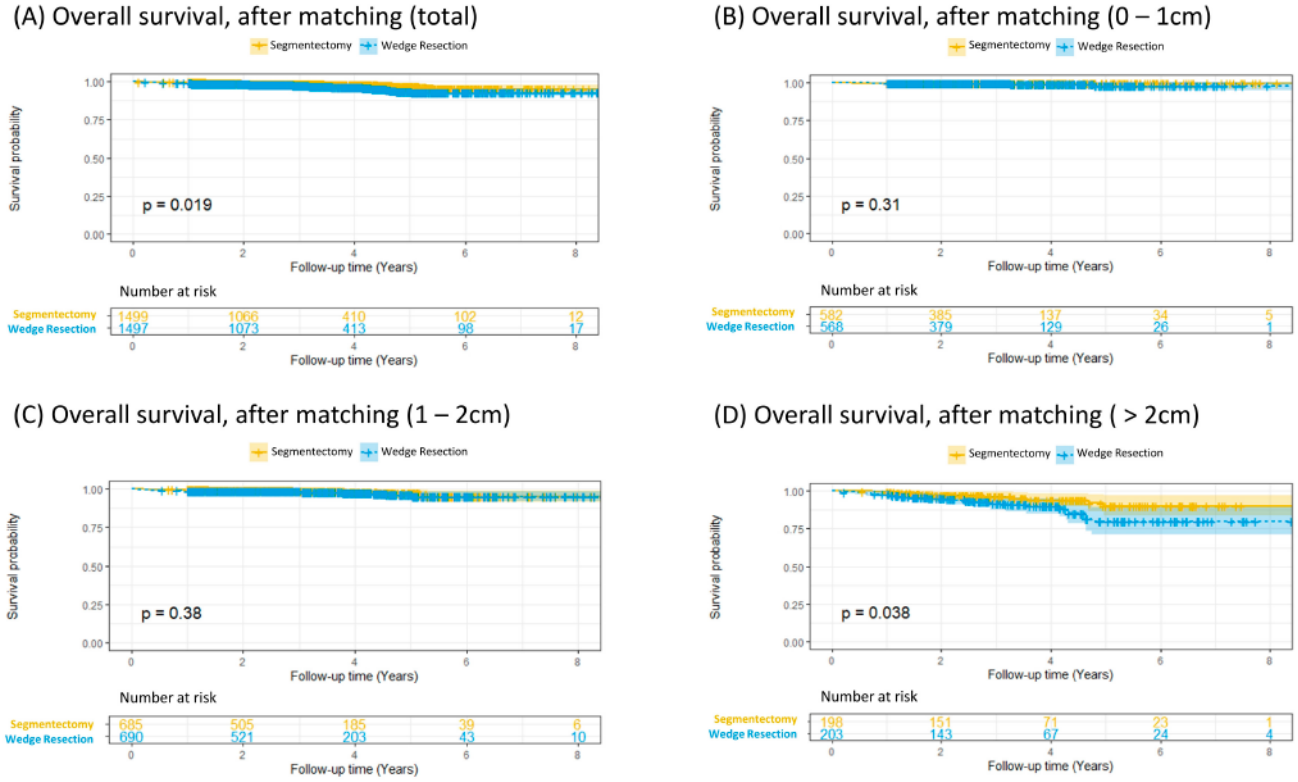


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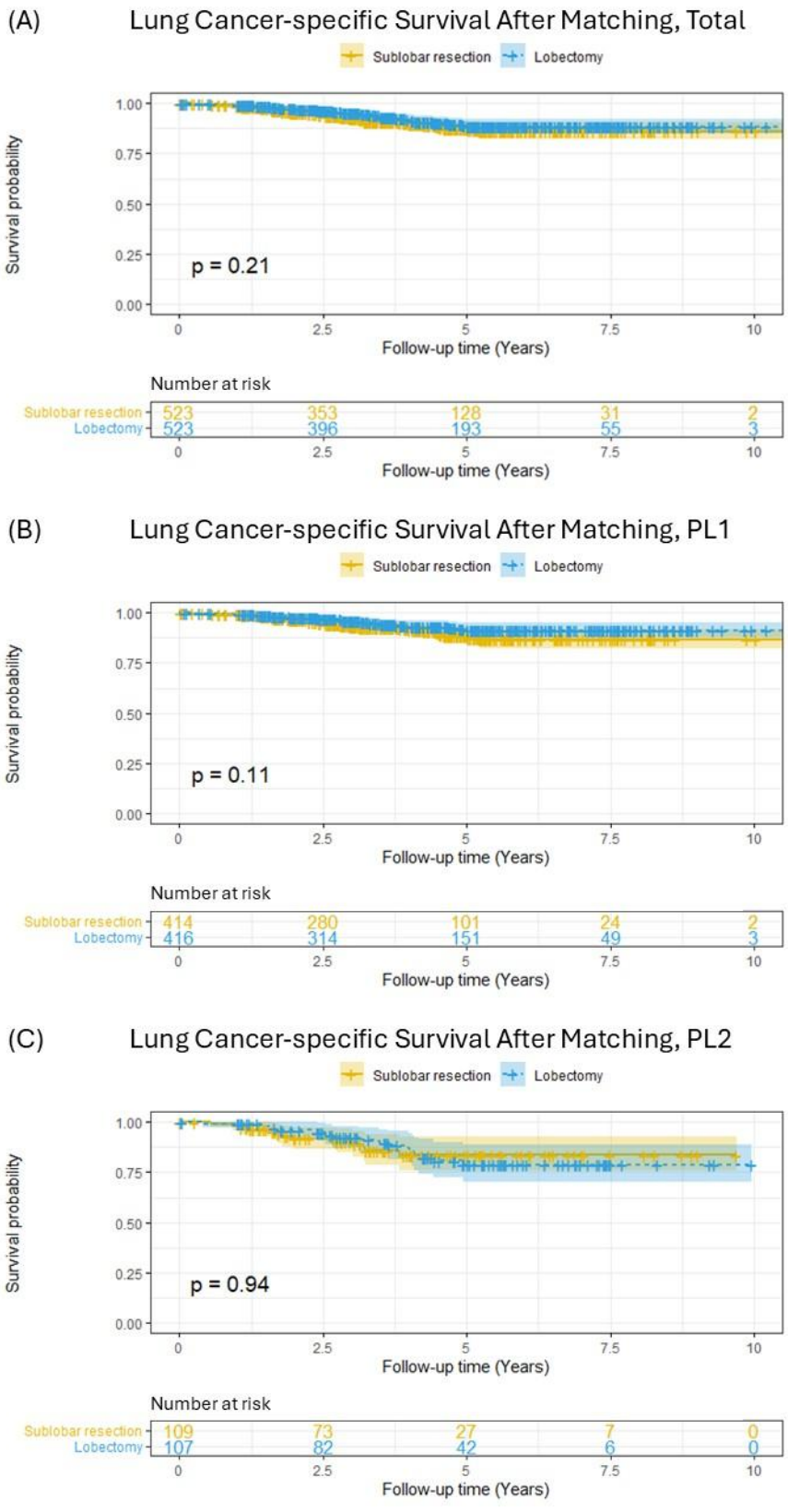
Figure 9. Lung cancer-specific survival in pT2aN0M0 (tumor ≦ 3cm) non-small cell lung cancer patients after matching (A) Total included patients, (B) PL1 patients, (C) PL2 patients



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Tables

Table 1. Demographic and clinical features of cT1N0 lung adenocarcinoma patients undergoing sublobar resection or lobectomy

	Before matching				After matching			
	All 1035	Sublobar 604	Lobectomy 431	*p* value	All 568	Sublobar 284	Lobectomy 284	*p* value
Age (years)	59.5 ± 11.1	59.7 ± 11.9	59.1 ± 10.7	0.375	60.6 ± 11.2	60.9 ± 12.4	60.1 ± 9.9	0.42
Male	351 (33.9)	197 (32.6)	154 (35.7)	0.297	216 (38.0)	107 (37.7)	109 (38.4)	0.862
ECOG PS				< 0.001				0.596
0	815 (78.7)	507 (83.9)	308 (71.4)		457 (80.5)	231 (81.3)	226 (79.6)	
≥ 1	220 (21.2)	97 (16.1)	123 (28.5)		111 (19.5)	53 (18.7)	58 (20.4)	
PFT								
FVC (%)	111.6 ± 59.1	113.3 ± 76.5	109.1 ± 14.7	0.203	111.0 ± 53.8	112.3 ± 75.3	109.7 ± 14.2	0.582
FEV1 (%)	109.1 ± 18.3	108.7 ± 18.8	109.7 ± 17.4	0.376	109.9 ± 18.7	109.1 ± 20.2	110.8 ± 17.1	0.286
Smoking status				0.045				0.726
Smoker	133 (12.9)	67 (11.1)	66 (15.3)		87 (15.3)	42 (14.8)	45 (15.9)	
Non-smoker	902 (87.1)	537 (88.9)	365 (84.7)		481 (84.7)	242 (85.2)	239 (84.2)	
Family history				0.244				0.836
Yes	205 (19.8)	127 (21.0)	78 (18.1)		118 (20.8)	60 (21.1)	58 (20.4)	
No	830 (80.2)	477 (79.0)	353 (81.9)		450 (79.2)	224 (78.9)	226 (79.6)	
Comorbidities								
DM	96 (9.3)	54 (8.9)	42 (9.7)	0.660	58 (10.2)	31 (10.9)	27 (9.5)	0.579
HTN	284 (27.4)	165 (27.3)	119 (27.6)	0.917	175 (30.8)	90 (31.7)	85 (29.9)	0.649
ESRD	14 (1.4)	6 (1.0)	8 (1.9)	0.236	10 (1.8)	4 (1.4)	6 (2.1)	0.523
Other malignancies	118 (11.4)	69 (11.4)	49 (11.4)	0.978	58 (10.2)	30 (10.6)	28 (9.9)	0.781
CEA (ng/mL)				0.112				0.347
≥ 5	58 (5.6)	28 (4.6)	30 (7.0)		35 (6.1)	20 (7.3)	15 (5.4)	
< 5	951 (91.9)	560 (92.7)	391 (90.7)		517 (91.0)	253 (92.7)	264 (94.6)	
NA	26 (2.5)	16 (2.6)	10 (2.3)		16 (2.8)	11 (3.9)	5 (1.8)	
Depth (cm)	0.9 ± 1.0	0.8 ± 0.9	1.1 ± 1.2	< 0.001	1.0 ± 1.1	0.8 ± 0.9	1.3 ± 1.3	< 0.001
Total tumor diameter (cm)				< 0.001				0.078
0–1	242 (23.4)	208 (34.4)	34 (7.9)		90 (15.9)	56 (19.7)	34 (12.0)	
1–2	428 (41.4)	284 (47.0)	144 (33.4)		259 (45.6)	123 (43.3)	136 (47.9)	
2–3	273 (26.4)	98 (16.2)	175 (40.6)		193 (34.0)	91 (32.0)	102 (35.9)	
≥ 3	92 (8.9)	14 (2.3)	78 (18.1)		26 (4.6)	14 (4.9)	12 (4.2)	
Solid component diameter (cm)				< 0.001				0.349
0–1	657 (63.5)	483 (80.0)	174 (40.4)		335 (59.0)	176 (62.0)	159 (56.0)	
1–2	231 (22.3)	89 (14.7)	142 (32.9)		164 (28.9)	76 (26.8)	88 (31.0)	
2–3	147 (14.2)	32 (5.3)	115 (26.7)		69 (12.2)	32 (11.3)	37 (13.0)	
C/T ratio (%)	37.8 ± 36.0	27.5 ± 33.7	52.3 ± 34.0	<0.001	42.6 ± 36.0	40.2 ± 36.0	45.1 ± 35.9	0.114
0–25	462 (44.6)	354 (58.6)	108 (25.1)		215 (37.9)	119 (41.9)	96 (33.8)	
25–50	166 (16.0)	84 (13.9)	82 (19.0)		104 (18.3)	46 (16.2)	58 (20.4)	
≥ 50	407 (39.3)	166 (27.5)	241 (55.9)		249 (43.8)	119 (41.9)	130 (45.8)	

Data are expressed as mean ± SD or *n* (%)

CEA carcinoembryonic antigen, *C/T* consolidation-to-tumor, *DM* diabetes mellitus, *ECOG PS* Eastern Cooperative Oncology Group performance status, *ESRD* end-stage renal disease, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *HTN* hypertension, *NA* not available, *PFT* pulmonary function test, *SD* standard deviation

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Table 2. Multivariable analyses of correlations between clinicopathological features and DFS of cT1N0 lung adenocarcinoma patients

Variables	Recurrence		
	HR	95% CI	*p* value
Age (years)			
≥ 65	1		
< 65	1.217	0.785–1.888	0.380
CEA (ng/mL)			
< 5	1		
≥ 5	5.055	3.099–8.246	< 0.001
Total tumor diameter (cm)			
0–1	1		
1–2	1.941	0.402–9.363	0.409
2–3	2.225	0.423–11.700	0.345
> 3	2.376	0.427–13.219	0.323
Solid component diameter, cm			
0–1	1		
1–2	3.499	1.238–9.888	0.018
2–3	7.766	2.235–26.984	0.001
C/T ratio (%)			
0–25	1		
25–50	1.910	0.578–6.315	0.289
50–100	2.257	0.628–8.110	0.212
Uniportal VATS			
Yes	1		
No	1.056	0.436–2.561	0.904
Anesthesia method			
Intubated	1		
Non-intubated	0.888	0.562–1.401	0.608
Surgical method			
Lobectomy	1		
Sublobar resection	0.670	0.389–1.152	0.148

CEA carcinoembryonic antigen, *CI* confidence interval, *C/T* consolidation-to-tumor, *HR* hazard ratio, *VATS* video-assisted thoracoscopic surgery

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Table 3. Demographic and clinical features of cT1N0 lung adenocarcinoma patients who underwent sublobar resectiona

Clinical features	Before matching				After matching			
	All (n = 1002) n (%)	Wedge (n = 810) n (%)	Segmentectomy (n = 192) n (%)	p Value	All (n = 336) n (%)	Wedge (n = 168) n (%)	Segmentectomy (n = 168) n (%)	p Value
Mean age (years)	59.6 ± 11.8	58.8 ± 11.8	62.9 ± 11.1	<0.001	61.8 ± 11.3	61.6 ± 11.8	62.0 ± 10.9	0.754
Male	323 (32.2)	257 (31.7)	66 (34.4)	0.480	116 (34.5)	62 (36.9)	54 (32.1)	0.358
ECOG				0.164				0.766
0	869 (86.9)	708 (87.6)	161 (83.9)		282 (83.9)	142 84.5)	140 (83.3)	
≥ 1	131 (13.1)	100 (12.4)	31 (16.2)		54 (16.1)	26 (15.5)	28 (16.7)	
Mean PFT								
FVC, %	113.1 ± 68.7	109.2 ± 15.2	106.9 ± 16.6	0.067	107.9 ± 15.6	108.5 ± 15.3	107.4 ± 15.8	0.513
FEV1, %	109.0 ± 18.6	108.9 ± 18.4	109.1 ± 19.0	0.874	109.0 ± 17.8	109.1 ± 18.4	108.8 ± 17.3	0.886
Smoking status				0.171				0.178
Smoker	122 (12.2)	93 (11.5)	29 (15.1)		53 (15.8)	31 (18.5)	22 (13.1)	
Non-smoker	878 (87.8)	715 (88.5)	163 (84.9)		283 (84.2)	137 (81.6)	146 (86.9)	
Family history				0.336				0.229
Yes	219 (21.9)	172 (21.3)	47 (24.5)		71 (21.1)	31 (18.5)	40 (23.8)	
No	781 (78.1)	636 (78.7)	145 (75.5)		265 (78.9)	137 (81.6)	128 (76.2)	
Comorbidities								
DM	246 (24.6)	204 (25.2)	42 (21.9)	0.338	83 (24.7)	48 (28.6)	35 (20.8)	0.100
HTN	272 (27.2)	208 (25.7)	64 (33.3)	0.032	102 (30.4)	48 (28.6)	54 (32.1)	0.476
ESRD	12 (1.2)	11 (1.4)	1 (0.5)	0.337	5 (1.5)	4 (2.4)	1 (0.6)	0.176
Cardiac diseases	145 (14.5)	112 (13.8)	33 (17.2)	0.234	60 (17.9)	34 (20.2)	26 (15.5)	0.254
Other malignancies	94 (9.4)	75 (9.3)	19 (9.9)	0.785	29 (8.6)	11 (6.6)	18 (10.7)	0.173
CEA (ng/mL)				0.511				0.184
≥ 5	53 (5.5)	41 (5.3)	12 (6.5)		20 (6.2)	13 (7.9)	7 (4.4)	
< 5	906 (94.5)	734 (94.7)	172 (93.5)		304 (93.8)	151 (92.1)	153 (95.6)	
N/A	43 (4.3)	35 (4.3)	8 (4.2)		12 (3.6)	4 (2.4)	8 (4.8)	
Mean depth (cm)	0.8 ± 0.8	0.8 ± 0.8	1.0 ± 1.1	0.001	1.0 ± 1.0	1.0 ± 0.9	1.0 ± 1.0	0.918
Total tumor diameter (cm)				< 0.001				0.860
0–1	371 (37.0)	338 (41.7)	33 (17.2)		64 (19.1)	32 (19.1)	32 (19.1)	
1–2	453 (45.2)	372 (45.9)	81 (42.2)		158 (47.0)	82 (48.8)	76 (45.2)	
2–3	146 (14.6)	90 (11.1)	56 (29.2)		93 (27.7)	45 (26.8)	48 (28.6)	
> 3	32 (3.2)	10 (1.2)	22 (11.5)		21 (6.3)	9 (5.4)	12 (7.1)	
Solid component diameter (cm)				< 0.001				0.839
0–1	788 (78.6)	669 (82.6)	119 (62.0)		225 (67.0)	115 (68.5)	110 (65.5)	
1–2	157 (15.7)	113 (14.0)	44 (22.9)		76 (22.6)	36 (21.4)	40 (23.8)	
2–3	57 (5.7)	28 (3.5)	29 (15.1)		35 (10.4)	17 (10.1)	18 (10.7)	
C/T ratio				0.274				0.266
0–25	520 (51.9)	427 (52.7)	93 (48.4)		163 (48.5)	75 (44.6)	88 (52.4)	
25–50	150 (15.0)	124 (15.3)	26 (13.5)		55 (16.4)	32 (19.1)	23 (13.7)	
> 50	332 (33.1)	259 (32.0)	73 (38.0)		118 (35.1)	61 (36.3)	57 (33.9)	

CEA, carcinoembryonic antigen; C/T ratio, consolidation-to-tumor ratio; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group performance status; ESRD, end-stage renal disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HTN, hypertension; N/A, not available; PFT, pulmonary function test

[a]All the enrolled patients were Asian.

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Table 4. Multivariable analysis of correlations between clinical features and DFS for patients with cT1N0 lung adenocarcinoma who underwent sublobar resection

Variables	Recurrence		
	HR	95% CI	*p* Value
Age (years)			
< 65	1		
≥ 65	1.659	0.825–3.335	0.155
CEA (ng/mL)[a]			
< 5	1		
≥ 5	2.506	1.169–5.369	0.018
Total tumor diameter (cm)			
≤ 2	1		
> 2	2.659	1.230–5.746	0.012
Solid component diameter (cm)			
≤ 2	1		
> 2	1.156	0.503–2.655	0.733
C/T ratio (%)			
≤ 50	1		
> 50	3.575	1.696–7.538	< 0.001
Uniportal VATS			
Yes	1		
No	0.736	0.348–1.554	0.421
Anesthesia method			
Intubated	1		
Non-intubated	0.674	0.322–1.410	0.294
FEV1 (%)			
≥ 80	1		
< 80	1.398	0.330–5.927	0.649

CEA, carcinoembryonic antigen; CI, confidence interval; C/T ratio, consolidation-to-tumor ratio; DFS, disease-free survival; FEV1, forced expiratory volume in 1 s; HR, hazard ratio; VATS, video-assisted thoracoscopic surgery.

[a]There were 43 patients who lacked the data of preoperative serum CEA level.

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Table 5. Demographic and clinical features of clinical stage IA lung adenocarcinoma patients undergoing sublobar lung resection.

	Before Matching				After Matching			
	All	Segmentectomy	Wedge	*p* Value	All	Segmentectomy	Wedge	*p* Value
	n = 6598	n = 2061	n = 4537		n = 2998	n = 1499	n = 1499	
Age, yr	60.3 (11.7)	60.9 (11.0)	60.1 (12.0)	0.012	61.01 (11.54)	60.77 (11.25)	61.26 (11.83)	0.248
Female	4371 (66.2)	1348 (65.4)	3023 (66.6)	0.344	1957 (65.3)	987 (65.8)	970 (64.7)	0.539
BMI	24.1 (3.7)	24.2 (3.5)	24.0 (3.8)	0.136	24.07 (3.58)	24.12 (3.50)	24.01 (3.66)	0.403
Smoking status				0.412				0.739
Never smoked	5375 (81.5)	1676 (81.3)	3699 (81.5)		2462 (82.1)	1227 (81.9)	1235 (82.4)	
Smoked	1203 (18.2)	376 (18.2)	827 (18.2)		536 (17.9)	272 (18.1)	264 (17.6)	
Tmor size (cm)				<0.001				0.955
0–1	3114 (47.2)	707 (34.3)	2407 (53.1)		1150 (38.4)	582 (38.8)	568 (37.9)	
1–2	2617 (39.7)	981 (47.6)	1636 (36.1)		1377 (45.9)	685 (45.7)	692 (46.2)	
2–3	741 (11.2)	321 (15.6)	420 (9.3)		401 (13.4)	198 (13.2)	203 (13.5)	
≥3	126 (1.9)	52 (2.5)	74 (1.6)		70 (2.3)	34 (2.3)	36 (2.4)	
Differentiation *				<0.001				0.814
Well	2757 (41.8)	816 (39.6)	1941 (42.8)		1220 (40.7)	617 (41.2)	603 (40.2)	
Moderate	2919 (44.2)	1023 (49.6)	1896 (41.8)		1452 (48.4)	716 (47.8)	736 (49.1)	
Poor	296 (4.5)	96 (4.7)	200 (4.4)		145 (4.8)	71 (4.7)	74 (4.9)	
Histology subtype				<0.001				0.660
Lepidic	3170 (48.0)	888 (43.1)	2282 (50.3)		1351 (45.1)	669 (44.6)	682 (45.5)	
Acinar	1797 (27.2)	697 (33.8)	1100 (24.2)		939 (31.3)	487 (32.5)	452 (30.2)	
Papillary	304 (4.6)	102 (4.9)	202 (4.5)		157 (5.2)	74 (4.9)	83 (5.5)	
Micropapillary	67 (1.0)	28 (1.4)	39 (0.9)		39 (1.3)	21 (1.4)	18 (1.2)	
Solid	1260 (19.1)	346 (16.8)	914 (20.1)		512 (17.1)	248 (16.5)	264 (17.6)	
Lymphovascular invasion *	54 (0.8)	25 (1.2)	29 (0.6)	0.005	29 (1.0)	13 (0.9)	16 (1.1)	0.709
Visceral pleural invasion *				0.007				0.931
PL0	6049 (91.7)	1874 (90.9)	4175 (92.0)		2729 (91.0)	1368 (91.3)	1361 (90.8)	
PL1	364 (5.5)	140 (6.8)	224 (4.9)		189 (6.3)	93 (6.2)	96 (6.4)	
PL2	125 (1.9)	33 (1.6)	92 (2.0)		55 (1.8)	27 (1.8)	28 (1.9)	
PL3	60 (0.9)	14 (0.7)	46 (1.0)		25 (0.8)	11 (0.7)	14 (0.9)	
pT stage				<0.001				0.838
T1a	3354 (50.8)	789 (38.3)	2565 (56.5)		1242 (41.4)	633 (42.2)	609 (40.6)	
T1b	2224 (33.7)	853 (41.4)	1371 (30.2)		1207 (40.3)	597 (39.8)	610 (40.7)	
T1c	447 (6.8)	217 (10.5)	230 (5.1)		263 (8.8)	128 (8.5)	135 (9.0)	
T2 and above	571 (8.7)	202 (9.8)	369 (8.1)		286 (9.5)	141 (9.4)	145 (9.7)	
pN stage *				<0.001				0.612
N0	5557 (84.2)	1971 (95.6)	3586 (79.0)		2862 (95.5)	1435 (95.7)	1427 (95.2)	
N1	20 (0.3)	14 (0.7)	6 (0.1)		8 (0.3)	5 (0.3)	3 (0.2)	
N2	67 (1.0)	26 (1.3)	41 (0.9)		32 (1.1)	13 (0.9)	19 (1.3)	
Nx	954 (14.5)	50 (2.4)	904 (19.9)		96 (3.2)	46 (3.1)	50 (3.3)	
Adjuvant therapy				0.002				0.770
CCRT	18 (0.3)	0 (0.0)	18 (0.4)		0			
Chemotherapy	286 (4.3)	99 (4.8)	187 (4.1)		148 (4.9)	73 (4.9)	75 (5.0)	
Radiotherapy	23 (0.3)	2 (0.1)	21 (0.5)		4 (0.1)	2 (0.1)	2 (0.1)	
Target therapy	73 (1.1)	18 (0.9)	55 (1.2)		23 (0.8)	9 (0.6)	14 (0.9)	
Lymphnode dissection								
Nodes examined	8.30 (8.32)	12.78 (9.15)	6.27 (7.03)	<0.001	10.55 (7.60)	10.47 (7.48)	10.62 (7.72)	0.599

Data are presented as mean ± SD (range) or number (%). * The categories of differentiation, lymphovascular invasion, visceral pleural invasion, and pathological stage are lacking some data. CCRT, concurrent chemoradiotherapy; ICU, intensive care unit; LN, lymph node.

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Table 6. Demographic and clinical features of patients with pT2a (≤3 cm, with pleural invasion) N0M0 NSCLC that underwent sublobar resection or lobectomy.

	Before Matching				After Matching			
	Total	Sublobar Resection	Lobectomy	*p* Value	Total	Sublobar Resection	Lobectomy	*p* Value
	(n = 2460)	(n = 624)	(n = 1836)		(n = 1046)	(n = 523)	(n = 523)	
Age, yrs	63.7 (10.4)	68.0 (10.6)	62.3 (9.9)	<0.001	66.86 (9.85)	66.94 (9.97)	66.77 (9.75)	0.775
Female	1415 (57.5%)	331 (53.0%)	1084 (59.0%)	0.010	573 (54.8%)	283 (54.1%)	290 (55.4%)	0.709
BMI, kg/m^2	24.3 (3.6)	24.6 (3.7)	24.2 (3.5)	0.034	24.41 (3.62)	24.59 (3.79)	24.23 (3.42)	0.113
Smoking status				0.003				0.893
Never smoker	1791 (72.8%)	425 (68.1%)	1366 (74.4%)		727 (69.5%)	362 (69.2%)	365 (69.8%)	
Ever smoker	669 (27.2%)	199 (31.9%)	470 (25.6%)		319 (30.5%)	161 (30.8%)	158 (30.2%)	
Laterality				<0.001				<0.001
Right	1525 (62.0%)	338 (54.2%)	1187 (64.7%)		621 (59.4%)	277 (53.0%)	344 (65.8%)	
Left	935 (38.0%)	286 (45.8%)	649 (35.3%)		425 (40.6%)	246 (47.0%)	179 (34.2%)	
Tumor size, cm				<0.001				0.683
0–1	124 (5.0%)	65 (10.4%)	59 (3.2%)		76 (7.3%)	37 (7.1%)	39 (7.5%)	
1–2	924 (37.6%)	305 (48.9%)	619 (33.7%)		516 (49.3%)	252 (48.2%)	264 (50.5%)	
2–3	1412 (57.4%)	254 (40.7%)	1158 (63.1%)		454 (43.4%)	234 (44.7%)	220 (42.1%)	
Differentiation *				0.217				0.933
Well	240 (9.8%)	71 (11.4%)	169 (9.2%)		115 (11.0%)	57 (10.9%)	58 (11.1%)	
Moderate	1572 (63.9%)	397 (63.6%)	1175 (64.0%)		664 (63.5%)	336 (64.2%)	328 (62.7%)	
Poor	585 (23.8%)	145 (23.2%)	440 (24.0%)		254 (24.3%)	123 (23.5%)	131 (25.0%)	
N/A	63 (2.6%)	11 (1.8%)	52 (2.8%)		13 (1.2%)	7 (1.3%)	6 (1.1%)	
Histology				0.001				0.615
Adenocarcinoma	2204 (89.6%)	534 (85.6%)	1670 (91.0%)		906 (86.6%)	449 (85.9%)	457 (87.4%)	
SCC	107 (4.3%)	40 (6.4%)	67 (3.6%)		55 (5.3%)	31 (5.9%)	24 (4.6%)	
Others	149 (6.1%)	50 (8.0%)	99 (5.4%)		85 (8.1%)	43 (8.2%)	42 (8.0%)	
Lymphovascular invasion	94 (3.8%)	25 (4.0%)	69 (3.8%)	0.874	39 (3.7%)	19 (3.6%)	20 (3.8%)	1.000
Visceral pleural invasion				0.011				0.939
PL1	1873 (76.1%)	499 (80.0%)	1374 (74.8%)		830 (79.3%)	414 (79.2%)	416 (79.5%)	
PL2	587 (23.9%)	125 (20.0%)	462 (25.2)		216 (20.7%)	109 (20.8%)	107 (20.5%)	
Lymph nodes examined number	17.52 (11.30)	12.70 (10.20)	19.16 (11.19)	<0.001	16.14 (11.24)	12.99 (10.39)	19.29 (11.18)	<0.001
Recurrence *				0.061				0.249
In situ	0				0			
Locoregional	73 (3.0%)	23 (3.7%)	50 (2.7%)		38 (3.6%)	20 (3.8%)	18 (3.4%)	
Distant	366 (14.9%)	80 (12.8%)	286 (15.6%)		141 (13.5%)	74 (14.1%)	67 (12.8%)	
N/A	105 (4.3%)	35 (5.6%)	70 (3.8%)		46 (4.4%)	29 (5.5%)	17 (3.3%)	

Data are presented as mean ± SD (range) or number (%). * Missing data for differentiation and recurrence are indicated by N/A. BMI, body mass index; CCRT, concurrent chemoradiotherapy; NSCLC, non-small-cell lung cancer; SCC, squamous cell carcinoma; TKI, tyrosine kinase inhibitor.

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