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Does Location Matter? Impact of Tumor Location (Peripheral vs Central) on Surgical Outcomes of Segmentectomy in Early Stage NSCLC: A Meta-Analysis

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ABSTRACT

Introduction: Recent studies recommend segmentectomy for early-stage peripheral NSCLC due to better lung parenchyma preservation; however, its role in early-stage central NSCLC remains debated. This study aims to analyze the impact of tumor location (peripheral vs central) on segmentectomy outcomes in early-stage NSCLC.
Methods: Only studies comparing segmentectomy outcomes by tumor location (peripheral vs central) in early-stage (T1a–cN0M0) NSCLC will be included. Studies involving lobectomy, wedge resection, or more advanced stages will be excluded. We registered the study protocol on PROSPERO (CRD420251127645). Article searches will be conducted in PubMed, Scopus, and Web of Science. All databases were last searched on 16 August 2025. Risk of bias will be assessed using the Newcastle–Ottawa Scale. Data will be analyzed with RevMan 5.4 and presented as forest plots.
Result: Five cohort studies were included, comprising a total 2,134 participants (1,499 peripheral and 635 central tumours) were included. The meta-analysis findings indicated that there were no significant differences between peripheral and central tumor locations regarding 5-year overall survival, recurrence-free survival, recurrence patterns, or intraoperative blood loss. However, segmentectomy performed for peripheral tumors resulted in a significantly shorter operative duration compared with procedures for central tumors (SMD −0.20; 95% CI −0.30 to −0.10; $p < 0.0001$).
Conclusion: This study has limitations due to the small sample size and study design, which affect its generalizability. Nevertheless, the analysis results indicate that segmentectomy is also a choice of treatment for early-stage central NSCLC.

Keyword: Central; Non-Small Cell Lung Cancer; Peripheral; Segmentectomy

INTRODUCTION

Pulmonary carcinoma represents the premier malignancy internationally and the primary driver of oncology-based mortality globally, reaching roughly 2,480,675 diagnoses and triggering 1,817,469 fatalities worldwide[1]. The frequency of emerging lung tumors persists in climbing yearly, with a projected 4.62 million fresh incidents and 3.55 million casualties by 2050[2]. Universally, lung cancer produces a total of diminished prosperity worth United States Dollar (USD) 167.36 billion[3]. Within every pulmonary malignancy, non-small cell lung cancer (NSCLC) remains most dominant, accounting for 75–78% of patients[4].

The 5-year general survival probability for lung malignancy fluctuates between the regional phase and the systemic stage, spanning from 70.6% to 9.3%. This represents a major factor behind the

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extreme lethality of lung cancer, since nearly 50% of pulmonary tumors are identified at a late phase[5]. Nevertheless, the adoption of low-dose computed tomography (LDCT) imaging programs has been documented to improve the discovery of early-phase NSCLC and decrease fatalities by 20%[6].

With the increasing detection of early-stage NSCLC, the role of surgical therapy has become increasingly important. Current clinical trials, such as JCOG0802/WJOG4607L and CALGB 140503, have reported that segmentectomy is non-inferior or even superior to lobectomy in early-stage peripheral NSCLC[7,8]. However, the outcomes of segmentectomy in early-stage central NSCLC have shown variable results[9–13].

Given the conflicting evidence, a systematic review and meta-analysis are required to synthesize the available data on the impact of tumor location (peripheral vs central) on segmentectomy outcomes in small-sized, early-stage NSCLC. The aim of this study is to provide the best available evidence to determine whether segmentectomy is a feasible curative option for central NSCLC and to support clinicians in making informed surgical decisions.

METHOD

Protocol Registration

Comprehensive evaluation and meta-analysis for this research were performed following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 framework, which is available at https://www.prisma-statement.org/. Complete PRISMA checklists are presented in Supplementary Data 4. The protocol of this study has been registered and accepted by the International Prospective Register of Systematic Reviews (PROSPERO), with identification number [CRD420251127645].

Eligibility Criteria

The eligibility criteria for this study was based on the PICOS framework, with additional inclusion and exclusion criteria. PICOS framework comprises following elements: [P]atients, patients with Early Stage NSCLC (cT1a–cN0M0); [I]ntervention, Segmentectomy on peripheral tumour; [C]omparator, Segmentectomy on central tumour; [O]utcome, survival outcome (5-year survival rate dan recurrence free survival), Recurrence Outcome (local recurrence, regional recurrence, distal recurrence, total recurrence) dan Intraoperative outcome (operative time dan blood loss). Inclusion criteria as: (1) Study that compare tumour location (peripheral vs central), (2) NSCLC clinical stage T1a-cN0M0. Exclusion criteria as: (1) Lobectomy, (2) Wedge Resection, (3) NSCLC Clinical Stage >T1a-cN0M0. A centrally located tumour is defined as a tumour located within the inner two-thirds of the lung parenchyma on axial, coronal, and sagittal CT scan imaging[9]. A peripherally located tumour is defined as a tumour located within the outer one-third of the lung parenchyma, measured from the visceral pleura toward the hilum. The location was determined based on axial, coronal, and sagittal CT scan imaging[9]. Other terms such as *deep*, *inner*, and *non-peripheral* were considered to meet the above definition and, based on CT scan findings, were classified as centrally located tumours.

Information sources and search strategy

Four authors (MIB, MA, BM, and MDH) systematically searched the literature in PubMed, Scopus, and the Web of Science Core Collection using the keywords “Non-small-cell lung cancer,” “peripheral,” and “central”. The search covered publications from January 1990 to 16 August 2025 (final search date). For articles that met the eligibility criteria, reference lists were further screened to identify additional literature. The search strategy for each database is provided in Supplementary Data 1.

Selection Process

Duplicates were removed using Rayyan AI; subsequently, title/abstract and full-text screening of studies was conducted by Four independent reviewers (MIB, MA, BM, MDH). Disagreements were discussed until consensus was reached. The complete literature search procedure is illustrated in Fig. 1.

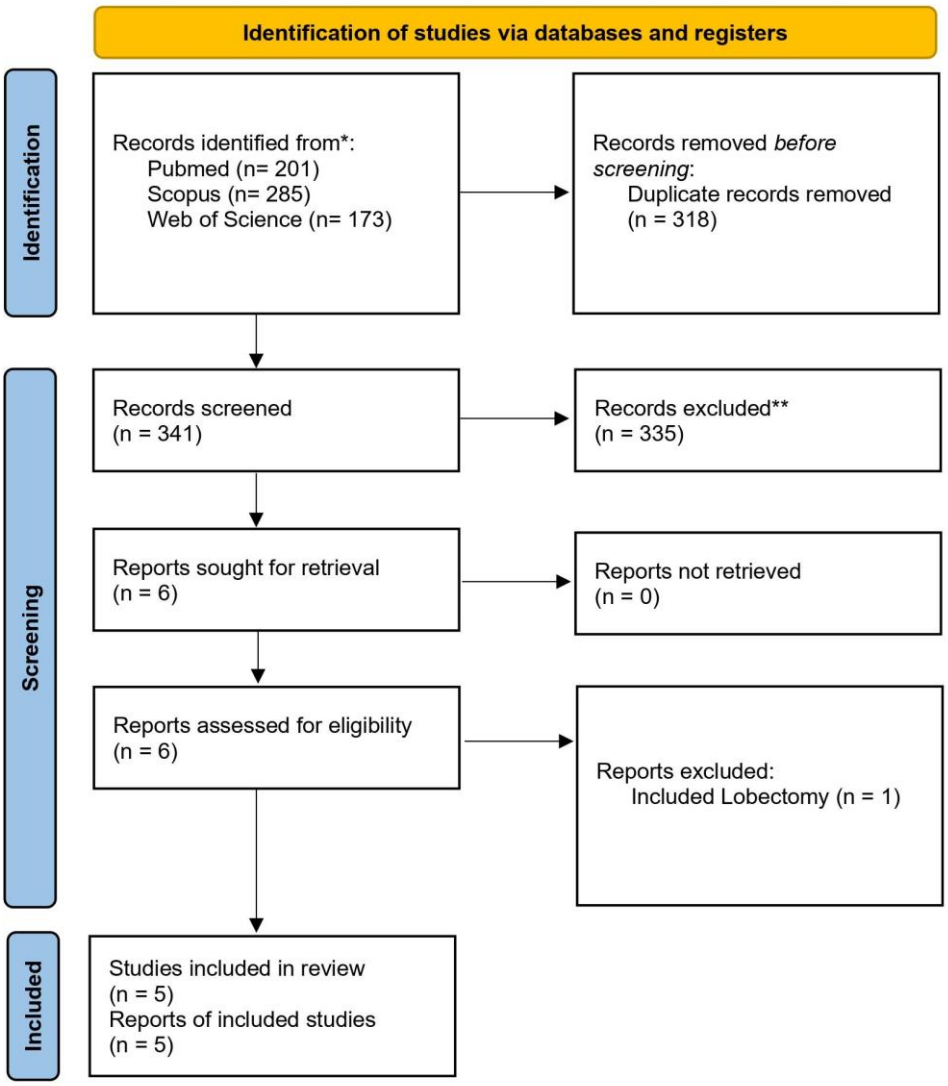

Figure 1. PRISMA Flow Diagram

Data Collection Process and Data Items

Data extraction was performed by four independent investigators (MIB, MRA, BM, MDH) and afterward debated until a mutual agreement was achieved. The gathered information comprised: researcher and release date; research site; participant attributes (age, sex, lesion size); and results. The specifications of the research results are more extensively detailed in Table 1.

Study risk of bias assessment, reporting bias assessment and certainty assessment

Our team evaluated the possibility of prejudice within our cohort utilizing the Newcastle Ottawa scale (NOS). This appraisal was conducted based on the findings of the *Agency for Healthcare Research* and Quality (AHRQ) (Supplementary Data 2). Dissemination bias was gauged through funnel plot visualization, with Egger's regression afterward utilized to determine the existence of likely reporting

bias if over ten researches were accessible for every category, following the suggestions of the Cochrane Handbook. Quality assessment for the result will be assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Supplementary Data 3).

Table 1. Outcome Definition

Outcome	Definition
5-Year overall survival rate	5-year overall survival refers to the proportion of patients who remain alive five years following surgery, irrespective of the cause of death[12].
Recurrence Free Survival	Recurrence-Free Survival (RFS) refers to the time interval from surgery to cancer recurrence or death from any cause[12].
Local recurrence	Local recurrence is defined as the reappearance of the tumor at the resected margin of the lung or bronchus[12].
Regional Recurrence	Regional recurrence signifies malignancy reappearance inside the identical chest area, encompassing the remaining pulmonary lobe, same-side lobe, or the hilar and mediastinal lymphatic glands[12].
Distal Recurrence	Distant recurrence occurs when the tumor reappears in the contralateral lung, other organs, or as diffuse pleural disease[12].
Total Recurrence	Total recurrence represents the overall incidence of cancer recurrence after surgery, comprising the sum of local, regional, and distant recurrences[12].
Operative Time	Duration spanning from the instant the individual enters the Operating Theatre (OT) until the point when the individual departs the OT [14].
Blood Loss	Volume of blood loss during surgical procedure[9].

Effect Measure and Synthesis Methods

Researches fulfilling the PICO standards were categorized according to study attributes and results, encompassing survival metrics (5-year survival probability and recurrence-free survival), relapse metrics (local relapse, regional relapse, distant relapse, and total relapse), and surgical metrics (procedural duration and hemorrhage). Researches which failed to offer retrievable or equivalent information for a particular result were omitted from that integration but stayed qualified for alternative pertinent evaluations.

Data conversion was performed to enable synthesis of the study results. Conversion of median (Q1–Q3) data to mean ± standard deviation (SD) was conducted using the formulas proposed by Luo et al. (2018)[15] and Wan et al. (2014)[16] when no data skewness was present. When data skewness was detected using the formula by Shi et al. (2023)[17] conversion was performed using the method described by Cai et al. (2021)[18].

Findings from information integration were displayed as forest plots created through Review Manager software (RevMan v5.4). Combined projections were computed as risk ratios (RR) for binary information and standardized mean differences (SMD) for linear information, including 95% confidence intervals (CI). Numerical diversity was appraised utilizing the I^2 statistic, where an I^2 figure of 0–40% signified a minimal degree of variance. A fixed-effect framework was utilized for meta-analyses of researches with minimal diversity, whereas a random-effects framework was utilized for researches with significant variance. Regarding integration findings with significant diversity, sensitivity testing was executed utilizing Duval and Tweedie's trim-and-fill technique.

RESULT

Search results and study selection

The initial search yielded 659 studies obtained from PubMed (201), Scopus (285), and Web of Science (173). The process of duplicate removal and title and abstract screening ultimately resulted in 6 studies for eligibility assessment. The article by Tsubokawa et al[19]. was excluded because it did not meet the population criteria, as it included a lobectomy group. Ultimately, 5 studies were included in our review (Fig. 1).

Study Characteristic

In total, this study included 2,134 patients, consisting of 1,499 patients with peripherally located tumors and 635 patients with central-located tumors. The study locations were primarily centered in Japan, with one study originating from China. The operational definitions of the study outcomes have been described in the Methods section. The study characteristics and outcomes of the included studies are presented in Table 2.

Study risk of bias assessment and certainty assessment

Assessment using the NOS showed that five studies had AHRQ Good ratings, and the details of the assessment are presented in Supplementary Data 2. The GRADE assessment showed that the effect of tumor location on the survival outcomes (5-year survival rate and recurrence-free survival) recurrence outcomes (local recurrence, regional recurrence, distant recurrence, and total recurrence), and intraoperative parameters (operative time and blood loss) had high certainty of evidence. Supplementary Data 3 presents the details of the GRADE assessment.

Survival Outcome

The analysis of the 5-year overall survival rate included three studies, with a total of 1,594 patients (Peripheral: 1,116; central: 478). These three studies had good-quality AHRQ ratings. The analysis showed an RR of 1.02 (95% CI 1.00–1.05; $p = 0.08$), indicating no significant difference between peripheral and central tumor locations with respect to the 5-year overall survival rate (Fig. 2). The level of heterogeneity was low ($I^2 = 0\%$).

The synthesis of recurrence-free survival included four studies, with a total of 1,796 patients (Peripheral: 1,243; central: 553). These four studies had good-quality AHRQ ratings. The analysis showed an RR of 1.01 (95% CI 0.98–1.04; $p = 0.67$), indicating no significant difference between peripheral and central tumor locations with respect to RFS (Fig. 3). The level of heterogeneity was low ($I^2 = 0\%$).

Tabel. 2. Study Characteristic

Author, Year	Location	Sample		Age		Gender		Tumour Diameter	
		Peripheral	Central	Peripheral	Central	Peripheral (M/F)	Central (M/F)	Peripheral	Central
Matsui, T. et al. (2024)[9]	Japan	256	82	72 (66–77)	69 (62–73)	119/137	35/47	18 (13-23)	16 (12-23)
Takamori, et al. (2020)[10]	Japan	64	21	64.5 (59.2-72.7)	62 (55-71)	30/34	6/15	14 (11-16)	13 (11-17)
Tane, et al. (2022)[11]	Japan	127	75	69.6 ± 7.3	69.6 ± 8.6	82/45	42/33	14.6 ± 0.3	14.4 ± 0.4
Yang, et al. (2025)[12]	China	576	274	61 (54-67)	60 (53-66)	336/240	151/123	13.4 (10.4-17)	13.4 (10-16)
Yano, eta l. (2024)[13]	Japan	476	183	70 (62-75)	68 (63-75.5)	204/272	85/98	17 (14-22)	17 (13-20.5)

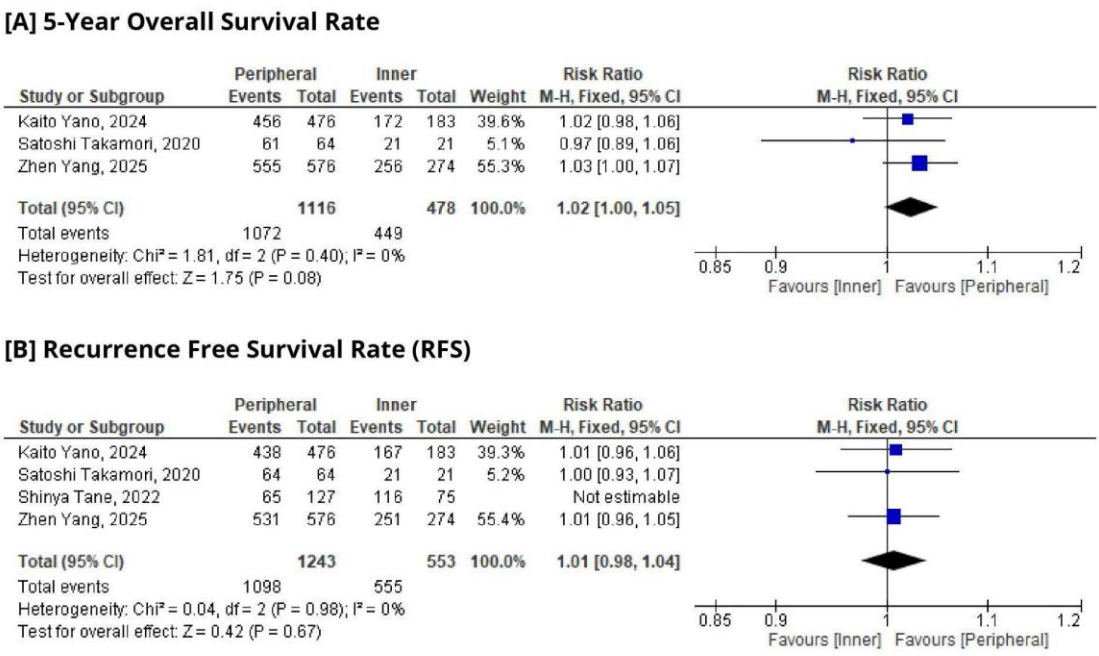

Figure 2. [A] Forest Plot of 5-Year Overall Survival Rate, [B] Forest Plot of RFS

Recurrence Outcome

The synthesis of local recurrence included four studies, with a total of 2,049 patients (Peripheral: 1,435; Central: 614). These four studies had good-quality AHRQ ratings. The analysis showed an RR of 0.63 (95% CI 0.32–1.26; p = 0.19), indicating no significant difference between peripheral and central tumor locations with respect to the incidence of local recurrence (Fig. 3). The level of heterogeneity was low (I^2 = 28%).

The synthesis of regional recurrence included three studies, with a total of 1,711 patients (Peripheral: 1,179; Central: 532). These three studies had good-quality AHRQ ratings. The analysis showed an RR of 1.19 (95% CI 0.60–2.37; p = 0.62), indicating no significant difference between peripheral and central tumor locations with respect to the incidence of regional recurrence (Fig. 3). The level of heterogeneity was low (I^2 = 0%).

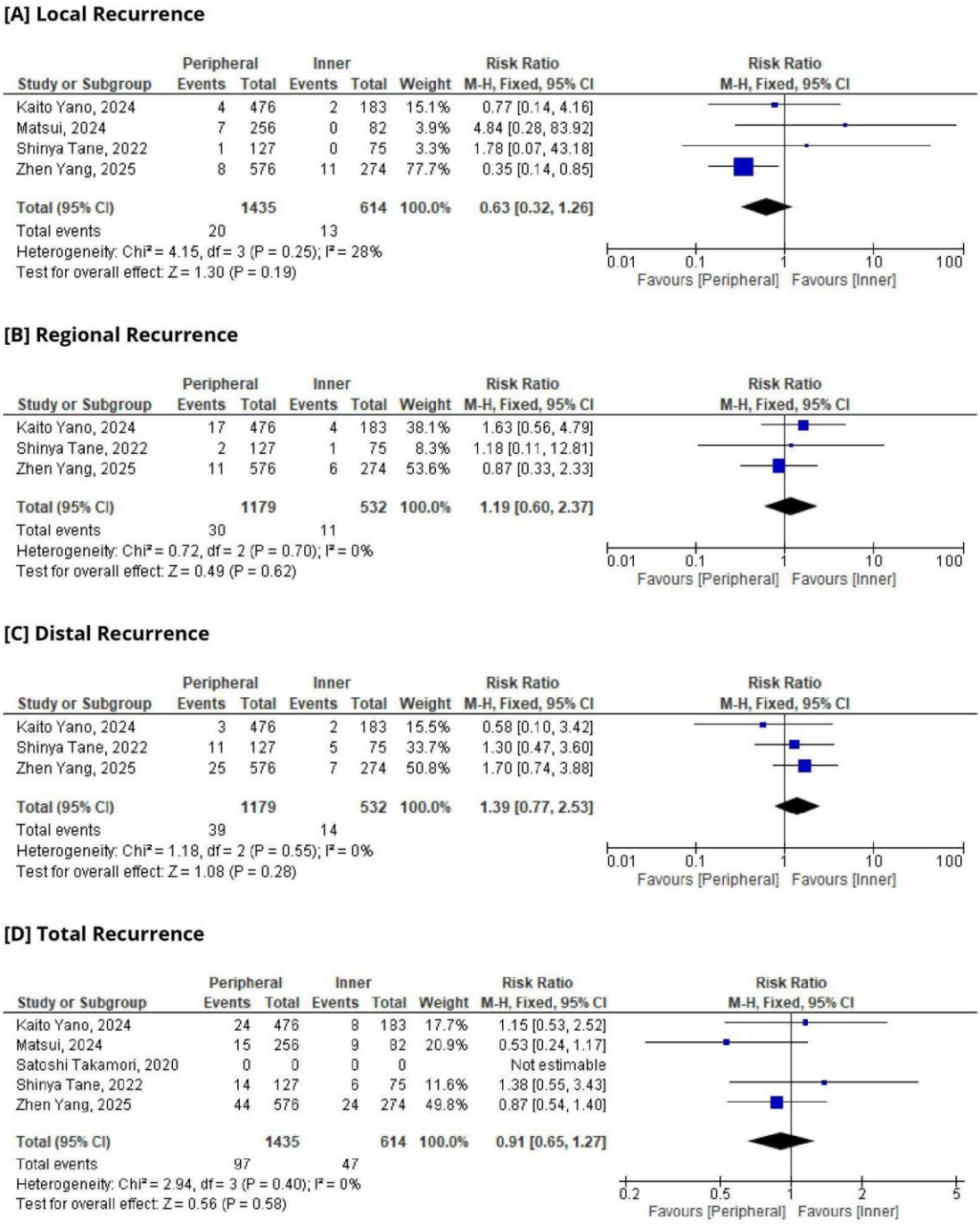

Figure 3. [A] Forest Plot of Local Recurrence, [B] Forest Plot of Regional Recurrence, [C] Forest Plot of Distal Recurrence, [D] Forest Plot of Total Recurrence

The synthesis of distant recurrence included three studies, with a total of 1,711 patients (Peripheral: 1,179; Central: 532). These three studies had good-quality AHRQ ratings. The analysis showed an RR of 1.39 (95% CI 0.77–2.53; p = 0.28), indicating no significant difference between peripheral and central tumor locations with respect to the incidence of distant recurrence (Fig. 3). The level of heterogeneity was low (I^2 = 0%).

The synthesis of total recurrence included four studies, with a total of 2,049 patients (Peripheral: 1,435; Central: 614). These four studies had good-quality AHRQ ratings. The analysis showed an RR of 0.91 (95% CI 0.65–1.27; p = 0.58), indicating no significant difference between peripheral and central tumor locations with respect to the incidence of total recurrence (Fig. 3). The level of heterogeneity was low (I^2 = 0%).

Intraoperative Outcome

The synthesis of operative time included four studies, with a total of 1,932 patients (Peripheral: 1,372; Central: 560). These four studies had good-quality AHRQ ratings. The analysis showed a standardized mean difference (SMD) of −0.20 (95% CI −0.30 to −0.10; p < 0.0001), indicating a significant difference between peripheral and central tumor locations with respect to operative time, with the peripheral group tending to have a shorter operative time (Fig. 4). The level of heterogeneity was low (I^2 = 0%).

The synthesis of blood loss included four studies, with a total of 1,932 patients (Peripheral: 1,372; Central: 560). These four studies had good-quality AHRQ ratings. The analysis showed a standardized mean difference (SMD) of −0.04 (95% CI −0.14 to 0.06; p = 0.46), indicating no significant difference between peripheral and central tumor locations with respect to blood loss (Fig. 4). The level of heterogeneity was low (I^2 = 0%).

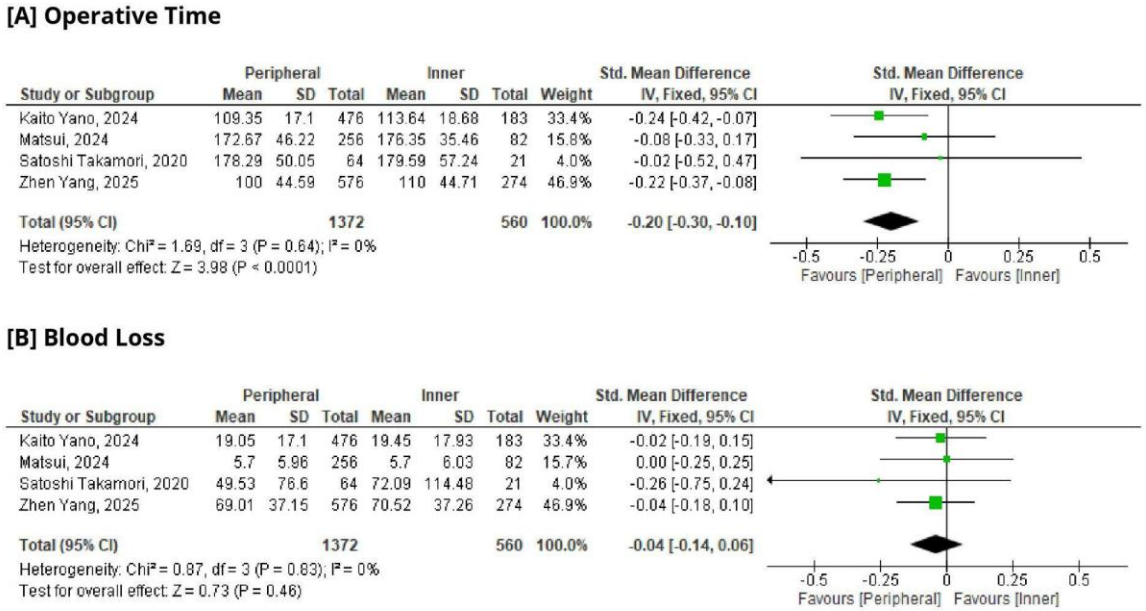

Figure 4. [A] Forest Plot of Operative Time, [B] Forest Plot of Blood Loss

DISCUSSION

Currently, segmentectomy has become the main treatment of choice for early-stage peripheral NSCLC, as compared with lobectomy, segmentectomy preserves more lung parenchyma, allowing patients to retain better physiological reserve[20]. However, segmentectomy for central NSCLC is still

often avoided due to the difficulty in achieving adequate surgical margins compared with peripheral NSCLC, which may increase the risk of local recurrence[9].

This meta-analysis provides a new perspective by synthesizing several studies that included groups with varying surgical margins, ranging from >2 mm to <2 mm[9–13]. Outcomes from this meta-analysis demonstrated that lesion site (peripheral against central) lacked a meaningful influence on survival metrics (5-year survival probability and recurrence-free survival), relapse metrics (local relapse, regional relapse, distant relapse, and total relapse), or hemorrhage volume during segmentectomy. This finding may be explained by the study by Donlagic et al. (2025),[21] which stated that as long as an R0 resection is achieved, a resection margin of <2 mm may still be acceptable because it yields comparable survival and local recurrence outcomes. These findings also support the notion that, compared with tumor location, tumor invasiveness plays a greater role in determining recurrence outcomes[22].

Findings from this meta-analysis indicated that lesion site exerted a meaningful influence on surgical duration. The longer operative time in the central group is presumed to be due to the more complex surgical technique compared with the peripheral group. Tumors located in the central area are close to the hilum; therefore, surgeons need to perform more meticulous dissection than in the peripheral area to protect important structures such as major vessels and segmental bronchi[9,13].

This study has several limitations related to the characteristics of the studies included in this meta-analysis. The first limitation is the absence of secondary outcomes such as postoperative pulmonary function, which makes considerations regarding the application of segmentectomy for central-located tumors less comprehensive. Another constraint involves the fact that every research incorporated into this meta-analysis was a retrospective cohort study, which poses the danger of selection prejudice and hidden variables. A concluding drawback is that the majority of investigations in this meta-analysis originated from Japan, with negligible participation from other nations, which restricts the external validity of the results to groups with diverse patient profiles.

This study also has methodological limitations. Although this study followed the PRISMA 2020 guidelines and was registered in PROSPERO, the total number of included studies was small. This reduces the strength of the pooled effect estimates. The small number of studies also meant that funnel plots and Egger's test were not performed, and therefore publication bias could not be evaluated. The final limitation is related to data conversion; although data conversion was performed using validated methods, it still has the potential to affect precision.

Given some limitations in this study, further studies such as prospective, multicenter studies and randomized controlled trials are needed to validate the findings of this study. Future research should also focus on long-term functional outcomes by assessing postoperative lung function.

Overall, the results of this study indicate that segmentectomy is a therapy that can be considered even for early-stage NSCLC with tumors located in the central area. Therefore, tumor location alone should not be considered a contraindication for segmentectomy.

REGISTRATION AND PROTOCOL

This study protocol was registered and approved in the PROSPERO database under the registration number [CRD420251127645]. The PROSPERO PDF was provided in Supplementary Data 5.

SUPPORT

The researchers obtained no monetary assistance for the investigation, writing, and/or dissemination of this manuscript.

CONFLICT OF INTEREST

There is no conflict of interest.

AVAILABILITY OF DATA AND MATERIAL

The datasets generated and analyzed in this study are available in the Zenodo repository, (https://zenodo.org/doi) (https://doi.org/10.5281/zenodo.18015326)

CONCLUSION

Overall, the results of this study indicate that segmentectomy is a therapy that can be considered even for early-stage NSCLC with tumors located in the central area. Therefore, tumor location alone should not be considered a contraindication for segmentectomy.

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