

Recurrence-Free Survival in Patients With Surgically Resected Non-Small Cell Lung Cancer

A Systematic Literature Review and Meta-Analysis



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BACKGROUND: Standard treatment for early-stage or locoregionally advanced non-small cell lung cancer (NSCLC) includes surgical resection. Recurrence after surgery is commonly reported, but a summary estimate for postsurgical recurrence-free survival (RFS) in patients with NSCLC is lacking.

RESEARCH QUESTION: What is the RFS after surgery in patients with stage I-III NSCLC at different time points, and what factors are associated with RFS?

STUDY DESIGN AND METHODS: A systematic search was performed in MEDLINE, EMBASE, and Cochrane databases between January 2011 and June 2021. The primary outcome was RFS at 1, 2, 3, and 5 years postresection. Single-arm, random-effects meta-analyses were done to calculate effect estimates and 95% CIs. Analyses were stratified by stage/substage as per the *AJCC Cancer Staging Manual*, and RFS was estimated (1) after pooling studies, using seventh or eighth edition staging criteria; and (2) among studies using only the eighth edition. Meta-regressions were performed to assess associations between RFS and patient demographic/clinical characteristics of interest.

RESULTS: Data from 471 studies comprising 1,060 surgical study arms were extracted. RFS estimates from 60,695 patients staged with the seventh or eighth edition were analyzed. RFS ranged from 96% at 1 year postresection to 82% at 5 years for stage I, and from 68% at 1 year to 34% at 5 years for stage III. Estimates for patients staged using only eighth edition criteria were slightly higher. Older age, higher percentage of male patients, advancing stage, larger tumor size, and geographic region (North America/Europe vs Asia) were significantly associated with worse RFS.

INTERPRETATION: This study presents a comprehensive assessment of reported RFS from published clinical literature, offering estimates at multiple postsurgical time points and by geographic region. Findings can inform treatment decisions, clinical trial design, and future research to improve outcomes among patients with NSCLC.

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KEY WORDS: meta-analysis; non-small cell lung cancer; recurrence; recurrence-free survival; surgery; surgical resection; systematic review

ABBREVIATIONS: AJCC = American Joint Commission on Cancer; DFS = disease-free survival; LPFS = local progression-free survival; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; RFS = recurrence-free survival

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Take-home Points

Study Questions: What are the recurrence-free survival (RFS) estimates after surgery in patients with clinical stage I-III NSCLC at various time points, and what factors are associated with RFS?

Results: For patients staged with the *AJCC Cancer Staging Manual* seventh or eighth edition, RFS ranged from 95% at 1 year postresection to 81% at 5 years for stage I, and from 68% at 1 year to 34% at 5 years for stage III, with slightly higher estimates for patients staged using only the eighth edition criteria. Older age, higher percentage of male patients, advancing stage, larger tumor size, and geographic region (North America or Europe vs Asia) were significantly associated with worse RFS.

Interpretation: This study presents a comprehensive assessment of reported RFS from published clinical literature that can inform treatment decisions, clinical trial design, and future research to improve outcomes among patients with non-small cell lung cancer.

Lung cancer is the second most common cancer worldwide and the leading cause of cancer-related death.¹ The two primary histologic subtypes are non-small cell lung cancer (NSCLC) and small-cell lung cancer.² Surgical resection is part of the standard

treatment for early-stage or locoregionally advanced NSCLC in patients fit enough to tolerate an operation; however, postoperative recurrence is common and ranges from 30% to 75%.^{3,4} These estimates are derived from a few studies, most published more than 20 years ago. Two more systematic reviews included six studies⁵ and 11 studies,⁶ respectively, and neither published a summary estimate for recurrence-free survival (RFS). Compared with recurrence rates, RFS is reported at fixed time points, making it easier to meta-analyze than recurrence rates, which are often presented as the total number of events that occurred during study follow-up, with variable durations. RFS also captures deaths, which makes it a potential surrogate end point for overall survival (OS).

With the implementation of the eighth edition of the American Joint Commission on Cancer (AJCC) TNM staging system as the standard classification for lung cancers in the United States in January 2018,⁷ comparisons between studies may be impacted.⁸ A contemporary and comprehensive review of recurrence outcomes in patients with surgically resected NSCLC is lacking. The aim of this systematic literature review and meta-analysis was to summarize and analyze RFS and recurrence rates after surgery in patients with NSCLC over time by stage, incorporating different staging classifications (seventh and eighth edition), and to examine factors associated with RFS.

Study Design and Methods

Search Strategy and PICOS

Institutional review board approval was not required for this work because no participants were recruited. A systematic literature review protocol was not registered, but the review followed predefined screening and extraction criteria.

This systematic literature review and meta-analysis were conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines.⁹ A systematic search was conducted by an information specialist and peer-reviewed by a second information specialist, using Peer Review of Electronic Search Strategies

guidelines.¹⁰ The detailed search strategy is presented in e-Tables 1 and 2. Example search terms used included key words and MeSH terms such as: “lung cancer,” “cancer recurrence,” “surgery,” and “survival analysis.” MEDLINE, EMBASE, and Cochrane databases were searched for English language studies conducted between January 2011 and June 2021, based on predefined PICOS (population, intervention, comparator, outcomes, and study design) criteria (e-Table 3).

Eligibility Criteria

Studies enrolling adults with clinical stage I-III NSCLC who underwent lung surgery alone or in combination with other therapies (neoadjuvant or adjuvant) were eligible for inclusion.

Resections of interest were wedge, segmentectomy, lobectomy, and pneumonectomy, with inclusion of all surgical approaches (video-assisted thoracoscopic surgery, robot-assisted thoracoscopic surgery, and thoracotomy). Eligible studies could be either single- or multiarm studies comparing distinct treatment methods. Studies that included a mix of surgery types were also included. Only studies including surgeries for primary lung cancer were included. Studies enrolling patients undergoing surgery for recurrent tumors or diagnostic purposes were excluded.

Eligible studies must have reported one or more of the following recurrence outcomes: local, locoregional, regional, distant recurrence,

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local tumor recurrence, or RFS. Studies that reported disease-free survival (DFS) or progression-free survival (PFS) instead of RFS were also included, as these outcomes are often used interchangeably in practice.

Included studies were single-arm, comparative observational studies, or randomized trials, whereas case reports, narrative reviews, and preclinical studies were excluded. Observational studies were included to capture all available evidence on surgery in patients with NSCLC. Studies focused on evaluating risk factors and predictors of recurrence outcomes were excluded. For a detailed list of inclusion and exclusion criteria, refer to [e-Table 3](#). The search strategy was supplemented with manual screening of published reviews and meta-analysis reference lists for relevant publications to ensure completeness. To increase precision, included studies were restricted to those with a sample size of at least 100 surgically treated patients, or at least 50 in each arm if the study included multiple surgery arms. Studies with duplicate data were excluded if they overlapped with another publication.

Screening and Data Extraction

Screening of identified records was performed by two independent reviewers, using the DistillerSR platform (DistillerSR),¹¹ with discrepancies resolved by a third reviewer. Records were screened for title and abstract eligibility, after which eligible studies were sought for retrieval. Records that could be retrieved and fit the PICOS criteria were then assessed for full-text eligibility.

Only studies reporting staging data according to the seventh or eighth AJCC TNM classification were included in the meta-analysis summary RFS estimate. RFS was estimated from date of surgery to the date of recurrence or death from any cause at 1, 2, 3, and 5 years postresection, loss to follow-up, or end of study, whichever occurred first. Studies that censored non-cancer-related or all-cause death from RFS were not included in the meta-analysis, due to competing risk, which can occur for survival analysis of RFS if death is excluded as an event and instead censored. Censoring death in an RFS analysis is informative censoring, which may cause bias in the estimated RFS when using the Kaplan-Meier method because it violates the assumption of noninformative censoring (ie, a patient who is censored is representative of patients who remain uncensored).^{12,13} Studies in which the methods were unclear about

handling competing risk were extracted and included in the meta-analysis.

Extraction of key baseline characteristics (ie, geographic region, number of male patients, average follow-up duration, tumor stage) and outcome data (ie, RFS/DFS/PFS, local progression-free survival [LPFS]; and locoregional, distant, and overall recurrence rates) from identified studies was performed in Excel (Microsoft). Recurrence data from Kaplan-Meier or cumulative incidence curves were digitized with Digitizelt software (version 2.5.3; Bormisoft) to accurately estimate outcome rates at time points of interest.

Data Analyses and Statistics

All analyses were performed with the meta package in R (version 3.6.1; R Foundation). Single-arm random-effects meta-analyses were conducted by multiplying the proportion of surviving patients without recurrence at each time point by the initial population sample size. Inverse variance 95% CIs were calculated. Study weighting in the meta-analyses was based on the initial population because complete censoring data were not available for all studies. Study arms were the unit of analysis, and studies could contribute multiple arms with distinct resection types. Results from the single-arm meta-analyses are presented as column graphs categorized by stage and time postresection. Heterogeneity was assessed with I^2 values, and variability in study-level patient baseline characteristics was addressed by the use of multivariable meta-regressions.

Meta-regressions were conducted to examine associations between RFS estimates and study-level patient age (1-year intervals), proportion of male patients, stages II and III vs stage I, average tumor size (1-cm intervals), study region (Asia, Europe, and North America), surgery type (lobectomy, sublobar resection, pneumonectomy, and mixed or unspecified surgical procedures), and use of adjuvant or neoadjuvant chemotherapy. Results for each meta-regression are reported as ORs with 95% CI, with OR < 1 indicating worse RFS and OR > 1 indicating better RFS. P values ≤ 0.05 were considered statistically significant. A summary of all meta-regression results by covariate and time intervals is presented as forest plots.

Subgroup analyses, sensitivity analyses, and quality assessment of included studies were conducted to ensure robustness of the results ([e-Table 4](#)). Publication bias was also assessed. Refer to [e-Appendix 1](#) for a detailed description of these analyses.

Results

Study and Patient Characteristics

The search identified 8,871 unique records, of which 771 were assessed for full-text eligibility. Data from 471 studies encompassing 1,060 surgical study arms were extracted ([Fig 1](#)). Included studies were conducted primarily in Asia (70%), followed by North America (18%) and Europe (10%). Most studies were retrospective (87%) and were conducted in single-center settings (75%).

More than two-thirds (69%) of study arms included between 50 and 250 patients. The average follow-up duration was 31 to 50 months in 41% ($n = 437$) of the study arms and not reported in 16% ($n = 171$). RFS data

from these study arms were included in the meta-analyses and meta-regressions.

The average mean age was 64 years across all study arms. There were 523 and 255 study arms that used the seventh and eighth edition AJCC TNM classification, respectively. The most frequently reported disease stage was stage I, accounting for 32% (168 of 523) and 38% (97 of 255) of the seventh and eighth edition study arms, respectively. Few eighth edition study arms ($n = 15$) reported recurrence rates for clinical substages IA1, IA2, and IA3. Only pathologic staging was reported in 42% of seventh edition and 24% of eighth edition study arms, which were not included in this analysis. No staging information was reported in 7% of seventh edition study arms and 8% of eighth edition study arms.

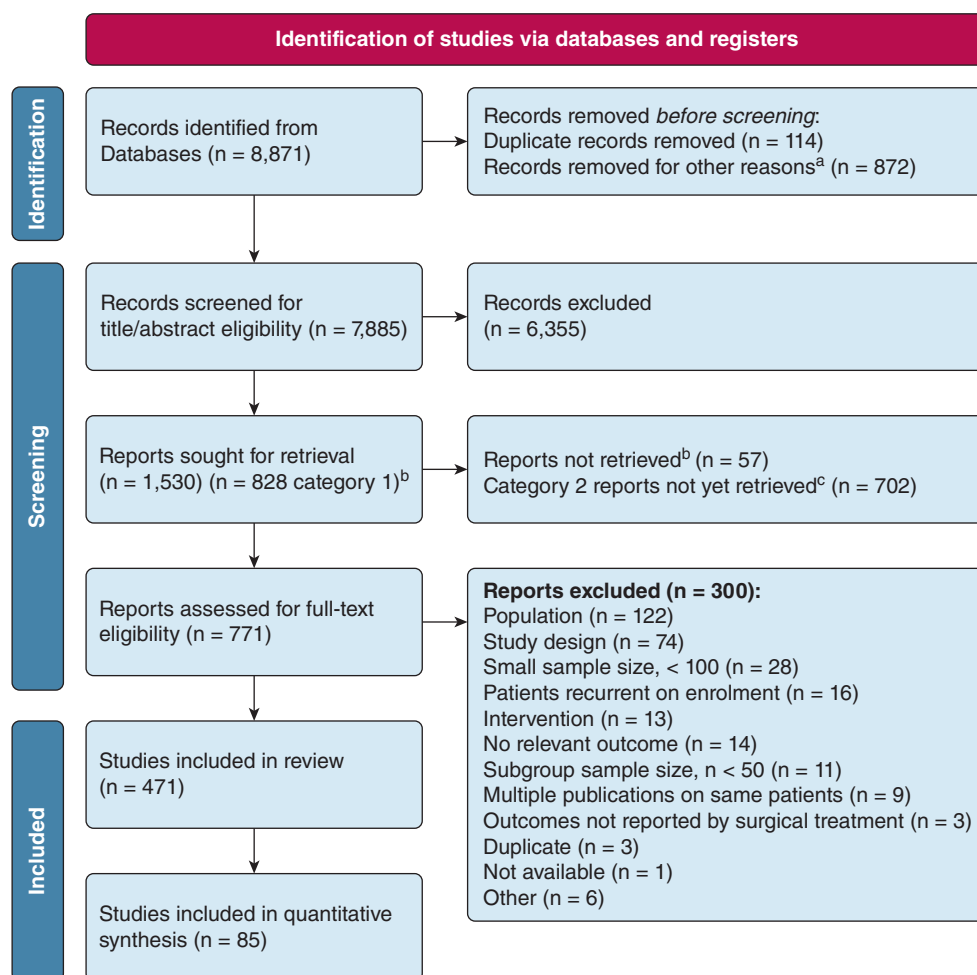


Figure 1 – 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. ^aThese records were removed after applying an English language filter after deduplication. ^bStudies were grouped into nonprognostic (category 1) and prognostic (category 2) categories. Prognostic studies refer to those evaluating the following as predictors of outcomes: genetic factors, patient and tumor baseline characteristics, imaging, comorbidities, and tumor biopsy. Category 1 studies included those that evaluated the efficacy of surgery in the general stage I-III NSCLC population. ^cThe reasons were that they were determined to be duplicates (4), non-English (1), or conference abstracts (52) during the retrieval process. NSCLC = non-small cell lung cancer.

RFS Results

RFS estimates from 60,695 patients (n = 161 study arms) staged with AJCC seventh or eighth edition were analyzed, with patients with stage I disease representing 79% of the sample. Death was included as an event in one-half of the study arms, while another 38% had unclear methods. Results for 3- and 5-year RFS are shown in Figure 2. RFS declined sharply with advancing stage at both the 3-year (87% for stage I, 58% for stage II, and 38% for stage III) and 5-year time points (81% for stage I, 50% for stage II, and 34% for stage III). A similar trend was observed at 1- and 2-year follow-ups (e-Fig 1). The highest RFS during follow-up was observed for stage IA (96% at 1 year and 86% at 5 years), whereas only 34% of patients with stage III disease were alive without disease recurrence at 5 years

(see forest plots in e-Figs 2-6). The unadjusted single-arm meta-analyses demonstrated high I^2 values indicative of significant heterogeneity, and thus meta-regressions were performed to control for differences in study-level patient baseline characteristics.

RFS estimates at 3- and 5-year follow-ups for eighth-edition-only study arms were similar for stage IA patients and overall stage I patients but higher for patients with stage III disease than were pooled seventh and eighth edition results (Fig 3). This finding was also observed at 1- and 2-year follow-ups (e-Fig 7).

Descriptive RFS and Recurrence Outcomes

Only six study arms reported RFS data for clinical substages IA1, IA2, and IA3; the small sample sizes precluded performing meta-analyses (Table 1,

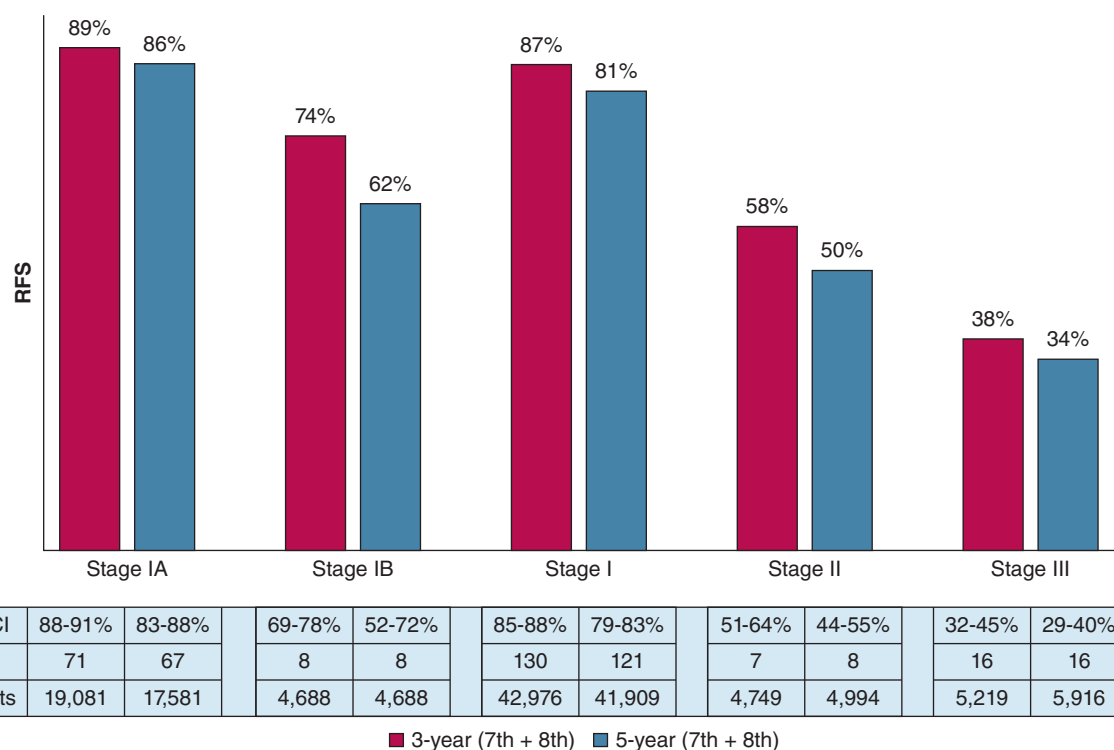


Figure 2 – Overview of RFS results: data from study arms that staged patients using seventh or eighth American Joint Commission on Cancer edition. Note: Stage I includes patients with stage IA and stage IB disease. RFS = recurrence-free survival.

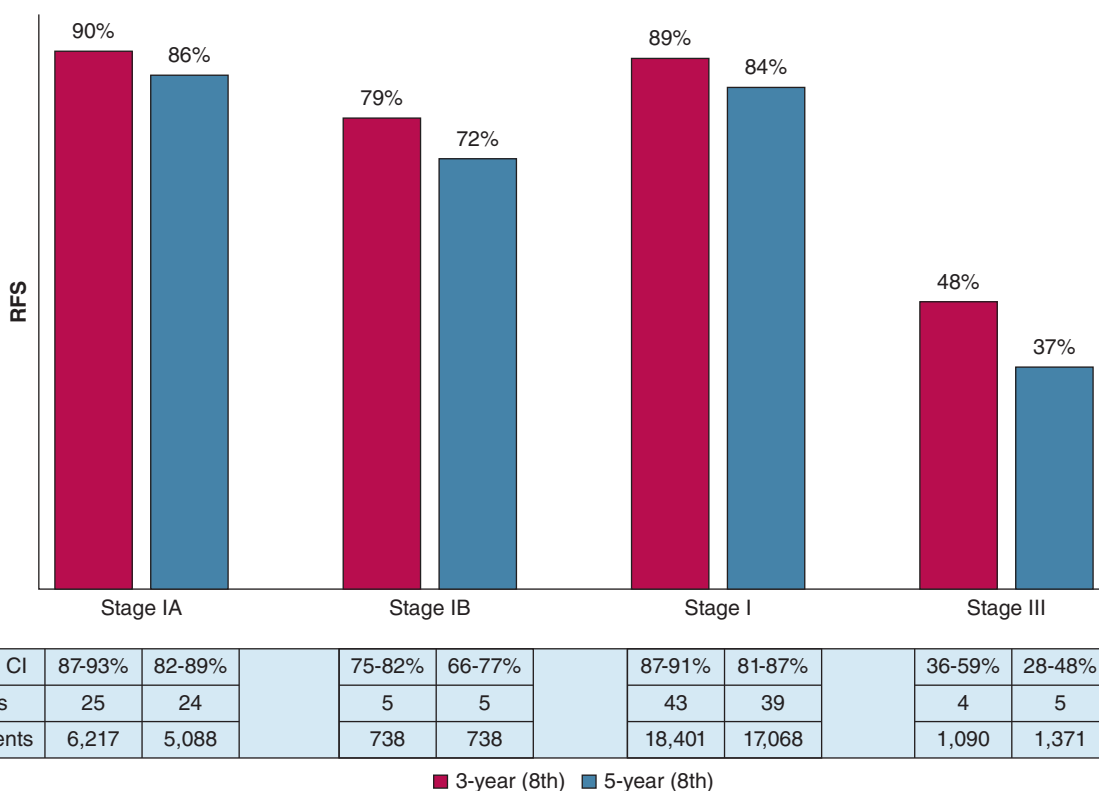


Figure 3 – Overview of RFS results: data from study arms that staged patients using eighth American Joint Commission on Cancer edition. Notes: (1) Stage I includes patients with stage IA and stage IB disease; (2) no data for patients with stage II disease. RFS = recurrence-free survival.

TABLE 1] Recurrence-Free Survival by Time for Clinical Substages IA1, IA2, and IA3

Clinical Stage	3-Year RFS			5-Year RFS		
	Study Arms	Patients	RFS Range (%)	Study Arms	Patients	RFS Range (%)
IA1	4	556	94.9-100	4	556	81.7-100
IA2	5	626	75.8-100	5	626	62.5-97.9
IA3	3	474	66.8-74.9	3	474	53.6-61.8

RFS = recurrence-free survival.

e-Table 5). Whereas RFS ranges for stage IA3 were lower than expected relative to stage IA1 and comparable to the single-arm meta-analysis results for stage IB, the median of the mean patient age in stage IA3 study arms was 67.8 years, compared with 58.4 years in the stage IA1 study arms and 64.4 years in the stage IB study arms.

Locoregional, distant, and overall recurrence ranges are shown in Table 2. Recurrence rates ranged widely, but summary estimates were not computed because rates were seldom reported by time point. Although distant recurrence is generally higher than locoregional recurrence, recurrence rate ranges should be interpreted with caution because of lack of time-standardized reporting.

Time-specific LPFS at 5 years was extracted for 56 study arms, but all but two study arms (96%) did not report results by stage, making estimates difficult to interpret. Therefore, meta-analyses of RFS by recurrence type were not computed.

Meta-Regression Results

In the multivariable meta-regressions (Figs 4A, 4B), statistically significant worse odds of RFS were observed with increasing age, increasing tumor size, and North

American/European study arms (vs Asian) at 5-year follow-up. The odds of RFS at 5 years from North America/Europe were 62% and 59% lower ($P \leq .001$ and $P = .03$), respectively, compared with Asian arms. Similar findings were observed at 3-year follow-up, at which time an increased proportion of male patients and more advanced stage (stages II and III vs stage I) were additionally associated with worse RFS, whereas the OR estimate for European study arms (vs Asian) remained less than 1 but was not significant. Study arms treating patients with mixed approaches (vs lobectomy) at 5-year follow-up were associated with better RFS. Advancing stage was associated with 59% worse odds of RFS at 3 years and 46% worse odds of RFS at 5 years, and increasing tumor size was associated with 40% and 54% worse odds of RFS at the same time points. Similar findings on advancing stage and increasing tumor size associated with worse RFS were observed at earlier time points (e-Fig 8).

Subgroup analyses demonstrated that RFS estimates across all time points for patients with stage IA and I disease were consistently higher in Asian vs North American/European study arms (year 5: 87% vs 60% and 83% vs 71%, respectively; see e-Appendix 2 and e-Fig 9 for more information). Compared with the primary analysis, RFS point estimates in sensitivity analyses that included only study arms with no competing risk were

TABLE 2] Proportion of Recurrence by Recurrence Type

Clinical Stage (Staging Edition)	Locoregional Recurrence			Distant Recurrence			Overall Recurrence		
	Study Arms	Patients	Recurrence Range (%)	Study Arms	Patients	Recurrence Range (%)	Study Arms	Patients	Recurrence Range (%)
IA (seventh + eighth)	29	5,230	1-12.2	37	9,940	0-13.8	46	12,343	0-26.3
IB (seventh + eighth)	2	307	10.2-12.9	2	307	2-6.3	6	925	12.7-34.5
I (seventh + eighth)	74	17,249	0-27.5	88	24,195	0-31	114	29,152	0-56.4
II (seventh + eighth)	1	122	35.2	2	367	28-46	1	122	44.3
III (seventh + eighth)	6	1,386	8.4-47.9	7	2,096	30-62.8	12	3,652	32-65.4

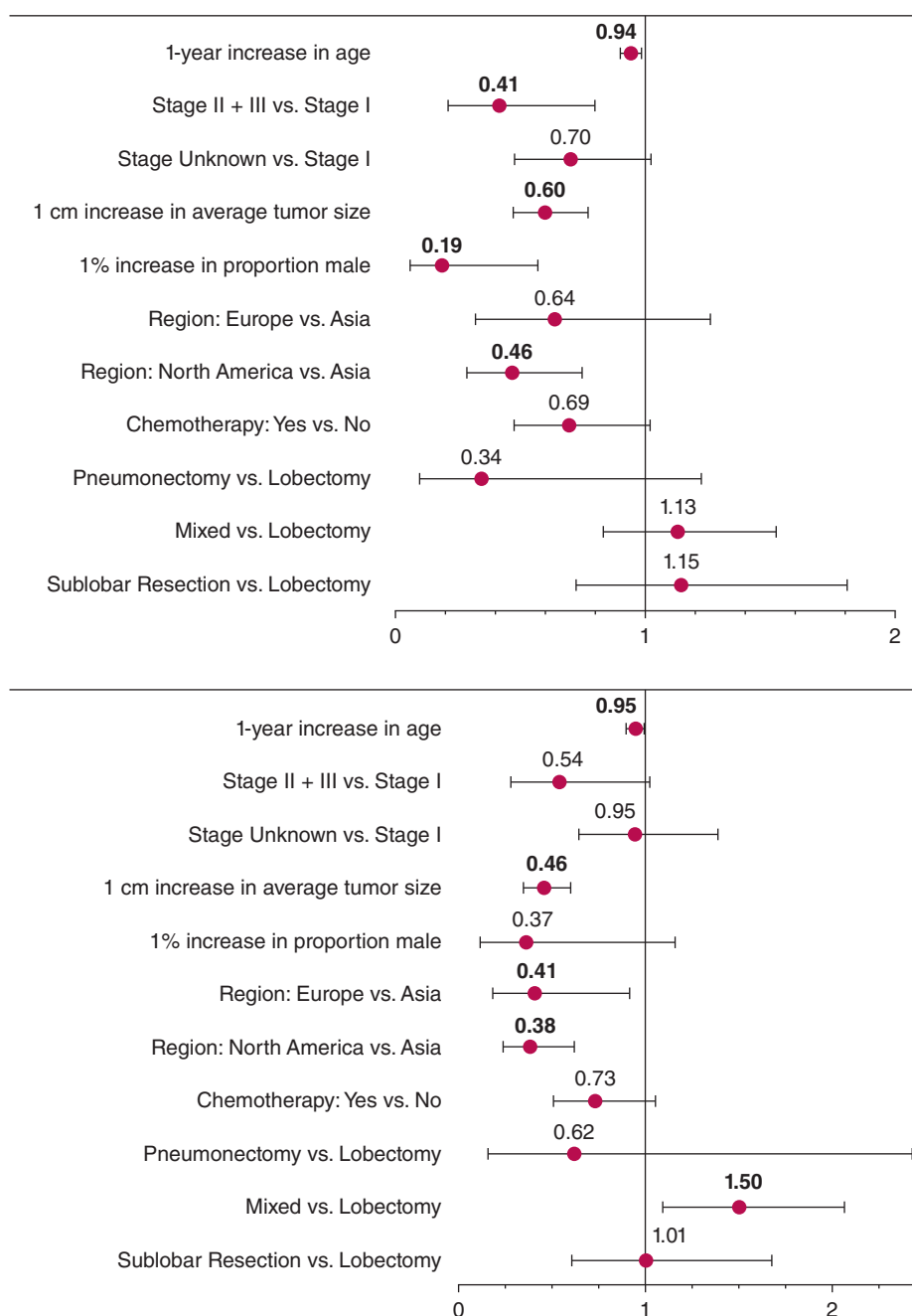


Figure 4 – Overview of meta-regression results for patients staged according to seventh or eighth American Joint Commission on Cancer staging edition (A) 3-year and (B) 5-year RFS. Notes: OR > 1 = better odds of RFS; OR < 1 = worse odds of RFS; bolded OR indicates that the P value is statistically significant; chemotherapy includes both adjuvant and neoadjuvant chemotherapy; mixed signifies studies that used a combination of surgical techniques; sublobar resection includes segmentectomy and wedge resection. RFS = recurrence-free survival.

slightly lower for each stage at each corresponding time point (e-Figs 10, 11). RFS point estimates from analyses of studies (n = 61) scoring ≥ 9 , using the methodological index for non-randomized studies instrument, were comparable to the primary analysis for most stages and time points (e-Fig 12, e-Table 6). Publication bias was detected in analyses of stage IA and I study arms, and there was a high level of agreement between the Egger test

and LFK index for most time points (e-Figs 13-16, e-Table 7). Refer to the online article for additional details on the subgroup, sensitivity, quality assessment, and publication bias analyses.

Discussion

To date, this is the largest systematic literature review and meta-analysis analyzing RFS estimates after surgery

in patients with NSCLC with early-stage or locoregionally advanced disease. This comprehensive assessment of RFS included 85 studies and recurrence data, extracted from published clinical literature, of more than 60,000 surgically treated patients with NSCLC. Overall, the 5-year RFS was 86% for stage IA, 62% for stage IB, 81% for stage I, 50% for stage II, and 34% for stage III patients. As expected, we observed a steep decline in RFS between stage I and stage III disease at all time points of interest.

Several reviews have published summary estimates for the rate of postsurgical recurrence, but a summary estimate of RFS is lacking. Uramoto and Tanaka³ reported that 30% to 55% of patients with NSCLC develop recurrence and die of their disease despite curative resection. Sasaki et al⁴ and Stirling et al⁵ presented broader recurrence ranges of 30% to 75% and 17.8% to 71%, respectively. The decision to focus on RFS in this study instead of overall recurrence was due to a lack of published studies meta-analyzing RFS, which is of interest to physicians and patients. Furthermore, US Food and Drug Administration guidance has recommended the assessment of RFS as a clinical trial end point in certain contexts, stating it may serve as a surrogate end point for traditional/accelerated approval.¹⁴ Although disease recurrence is a simpler outcome that does not include non-cancer-related deaths and is less affected by the competing risk issues impacting RFS, the cumulative incidence of recurrence is infrequently reported in the NSCLC literature. In addition, studies that do report recurrence usually state the total number of recurrences during the follow-up period. Reporting in this way makes comparisons between studies and meta-analytic synthesis of data challenging because of variable or unknown follow-up durations. These limitations suggest that recurrence is less suitable than RFS for comparing treatment efficacy in the surgically treated NSCLC population. Similar to reporting of RFS, there should be an effort to standardize reporting of recurrence rates by time, as this information would be of high utility to both clinicians and patients.

This systematic literature review presents a robust summary of contemporary recurrence data, as represented by analyses of eighth edition-staged patients from more than 50 study arms. Patients classified using the eighth edition only had similar, but slightly higher RFS estimates compared with pooled seventh and eighth edition results, directionally aligning with the expected difference in disease severity. This may be explained by some seventh edition patients with more advanced stage

IB disease being reclassified into eighth edition stage IIA, thus “decreasing” the overall disease severity of eighth edition stage I and IB cohorts.¹⁵ Similarly, patients with more advanced stage IIB disease based on the seventh edition classification would be upstaged to eighth edition stage IIIA.¹⁵

Multivariable meta-regressions indicated that increasing age, more advanced disease stage, and increasing tumor size were independently associated with worse RFS at all time points, consistent with previous studies.¹⁶⁻²¹

Although study arms treating patients with mixed surgical approaches (vs lobectomy) were associated with better RFS at 5-year follow-up, the association was not significantly different at any other time point and therefore must be interpreted with caution. Most of the meta-regression data were from the Asian literature, representing 80% to 82% of included studies. Asian studies consistently reported higher RFS estimates at all time points compared with North American/European studies in our analyses and in the literature. For example, a Japanese trial (JCOG0802) enrolling 1,106 patients with peripheral stage IA disease reported a 5-year DFS of 88% (87% in our analysis).²² However, a North American/Australian trial (CALGB 140503) reported 5-year relapse-free survival of 63.6% and 64.1% after sublobar and lobar resection, respectively, in more than 1,000 patients with clinical stage IA disease (60% in our analysis).²³ Our analysis is aligned with these studies and others that demonstrated higher RFS estimates across all time points for patients with stage I disease in Asian study arms. Improved RFS and relapse outcomes in Asian patients may be due to the higher prevalence of those who never smoked,²⁴ younger age at diagnosis,²⁵ and higher incidence of ground-glass opacities,²⁶ which are associated with better prognosis and lower recurrence rates than are pure solid tumors.^{22,27-29} Our systematic review revealed that patients with stage I and stage IA disease enrolled in Asian studies were younger than their North American/European counterparts, but smoking status and incidence of ground-glass opacities could not be controlled in the meta-regressions.

To our knowledge, our study is the most comprehensive and robust summary of postsurgical recurrence outcomes in patients with NSCLC presented to date. The systematic literature review followed prespecified PICOS criteria and was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. Summaries of RFS at different time points allow clinicians and patients to

better understand how disease prognosis changes over time and provide a standardized measurement of recurrence to inform future research. In addition, presentation of separate analyses of pooled seventh and eighth edition results and more contemporary eighth edition results may inform how changes in staging edition can influence recurrence estimates. The analyses were further reinforced by using multivariable meta-regressions to control for confounding factors, by using inclusion criteria that considered issues of competing risk, and by conducting quality assessment and publication bias analysis of included studies. We excluded studies that used pathologic staging alone because treatment decisions are based on clinical staging. In addition, clinical trials typically enroll patients based on clinical staging before randomization.

The limited number of eighth edition study arms resulted in seventh edition results being substantially better represented in the pooled seventh and eighth edition analyses. It was not possible to reclassify all patients staged using seventh edition criteria to the corresponding eighth edition classification, as few studies provided patient-level data. Specifically, the proportion of patients who were classified as having stage IB or IIB disease, using seventh edition criteria, and subsequently upstaged to eighth edition stage IIA or IIIA, could not be calculated. Consequently, the cohort of patients included in the pooled seventh and eighth edition analyses is not completely representative of the overall population with disease categorized according to eighth edition staging.

One aim of this study was to summarize locoregional, distant, and overall recurrence rates, but interpretation of the reported ranges is limited by most studies reporting recurrence rates over the course of follow-up. Standardizing the reporting of recurrence rates by time would allow robust summarization of recurrence estimates. In addition, we were unable to summarize LPFS because most of the studies did not report this outcome by stage. The sample sizes for some of the stage II and III analyses were small, which led to relatively wide RFS CIs. The analyses presented here highlight the need for more studies reporting multimodal treatments to improve RFS in those with locoregionally advanced NSCLC.

Advancements in perioperative therapies such as immune-checkpoint inhibitors and molecular targeted therapies have been assessed in several pivotal practice-changing trials.³⁰⁻³³ We expect that the increased

availability of these drugs in routine clinical practice will enable more personalized treatment plans tailored to patient-specific disease markers. It is hoped that this will lead to both reduced recurrence rates and higher RFS, particularly in later-stage patients.

Competing risk was mitigated by excluding studies in which death was explicitly censored. Not accounting for competing risk in Kaplan-Meier analysis may introduce bias and overestimate the cumulative incidence of an event in the presence of competing events³⁴; in this study, the results would have been biased toward reporting higher RFS. As expected, in a sensitivity analysis that included only study arms clearly defining both recurrence and death as RFS events, RFS estimates were slightly lower at each corresponding time point and stage, compared with the primary analysis. Although it was beyond the scope of this study, assessing the correlation between RFS and OS to determine whether RFS serves as a good surrogate end point for OS is an important topic as it may reduce the time and cost of treatment development.³⁵ Previous studies have shown that depending on the cancer type and treatment, RFS correlates relatively strongly with OS.³⁵⁻³⁸

Interpretation

Our systematic literature review and meta-analysis presents a contemporary and thorough assessment of RFS and recurrence outcomes from the published clinical literature, providing estimates at multiple time points after surgery by stage and geographic region. RFS estimates for Asian study populations were better than for North American and European populations, consistent with previous findings from regional studies. The study also reveals the inconsistency in reporting of recurrence rates by time, highlighting a need for more standardized outcome reporting practices. These findings can inform treatment decisions, clinical trial design, and future research to improve outcomes among patients with NSCLC.

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Additional information: The e-Appendixes, e-Figures, and e-Tables are available online under “Supplementary Data.”

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