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Research Article

A Retrospective Cohort Study of neoadjuvant chemotherapy in elderly oncology patients with non-small cell lung cancer

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Abstract

Background: Neoadjuvant chemotherapy before surgical resection improves survival in patients with resectable non-small cell lung cancer (NSCLC), but evidence supporting its use specifically in elderly patients remains limited, since landmark trials enrolled populations substantially younger, on average, than those treated in routine geriatric oncology practice.

Methods: We conducted a retrospective cohort study of patients aged 70 years or older with clinical stage IB-IIIA NSCLC who underwent curative-intent resection at three tertiary centers in Taiwan, Singapore, and Japan between 2014 and 2022. Outcomes for 164 patients who received neoadjuvant chemotherapy followed by surgery were compared with 151 patients who underwent upfront resection, using chi-square, Mann-Whitney U, Kaplan-Meier, and multivariable Cox regression analyses.

Results: R0 resection was achieved in 91% of the neoadjuvant cohort versus 86% of the upfront-surgery cohort, and 90-day morbidity of Clavien-Dindo grade II or higher was 27% versus 24%. Three-year overall survival was 58% versus 47% (log-rank p=0.03), and three-year disease-free survival was 49% versus 38%. Neoadjuvant chemotherapy remained independently associated with improved overall survival after multivariable adjustment (hazard ratio 0.71, 95% confidence interval 0.53-0.95).

Conclusion: Neoadjuvant chemotherapy followed by surgery was associated with improved survival relative to upfront resection among elderly patients with resectable NSCLC, without a clinically meaningful increase in perioperative morbidity or mortality, supporting its use in carefully selected older patients on the basis of functional status rather than chronological age alone.

Keywords: Non-small cell lung cancer; Neoadjuvant chemotherapy; Elderly; Retrospective cohort; Surgical resection

1. Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer death worldwide, and the disease burden is increasingly concentrated in older adults: median age at diagnosis exceeds 70 years in most registries, and the proportion of patients aged 70 and above continues to rise as populations age [1,2]. Analyses of the Surveillance, Epidemiology, and End Results database show that elderly patients with NSCLC are less likely to receive stage-appropriate multimodality therapy than their younger counterparts, even when comorbidity burden and performance status are comparable, a disparity attributed in large part to clinician reluctance to extend trial-derived regimens to a population historically excluded from randomized trials [3,4].

Neoadjuvant chemotherapy before surgical resection has an established evidence base in resectable and locally advanced NSCLC. A pooled individual-participant-data meta-analysis of preoperative chemotherapy trials demonstrated an absolute five-year survival benefit of approximately five percentage points over surgery alone, a magnitude closely mirroring that seen with adjuvant chemotherapy [5], and an earlier meta-analysis of thirteen randomized trials reached a concordant conclusion [6]. Individual phase III trials, including the Spanish and MD Anderson trials that first established the paradigm [7,8], the French and NATCH trials [9,10], the MRC LU22/NVALT2/EORTC 08012 trial [11], the Italian preoperative gemcitabine-cisplatin trial [12], SWOG S9900 [13], and IFCT 0002 [14], collectively established neoadjuvant chemotherapy as an accepted option for resectable stage IB-IIIA disease, and a systematic review by Burdett and colleagues corroborated the survival advantage across the accumulated trial evidence [15]. More recently, the addition of immune checkpoint inhibition to neoadjuvant chemotherapy has produced further gains in pathological response and event-free survival in CheckMate 816, KEYNOTE-671, and NADIM [16,17,18], and adjuvant osimertinib has extended disease-free survival in resected EGFR-mutant disease [19], further widening the range of perioperative options available to patients fit enough to receive them.

Whether this evidence generalizes to patients aged 70 and older is far less settled. Elderly-specific chemotherapy trials in advanced NSCLC, including the ELVIS trial of single-agent vinorelbine [20], the MILES trial comparing vinorelbine, gemcitabine, and their combination [21], the IFCT-0501 doublet-versus-monotherapy trial [22], and a subset analysis of ECOG 5592 [23], demonstrated that carefully selected older patients tolerate platinum-based combinations with efficacy approaching that of younger cohorts, but these trials enrolled patients with advanced, unresectable disease rather than the perioperative setting. Guidance from the International Society of Geriatric Oncology and allied bodies emphasizes that chronological age alone is a poor proxy for treatment tolerance, and recommends comprehensive geriatric assessment to individualize therapy [24,25,26,27,28,29,30,31,32]. Surgical outcome data in octogenarians likewise show acceptable but non-trivial morbidity after lobectomy, and minimally invasive approaches appear to mitigate but not eliminate that risk [33,34]. Current guideline documents from NCCN and ESMO acknowledge this evidence gap and call for age-stratified reporting of perioperative outcomes [35,36].

Given the paucity of prospective trial data specific to elderly candidates for neoadjuvant chemotherapy, we conducted a retrospective cohort study across three tertiary oncology centers to compare perioperative morbidity, pathological response, and survival between elderly patients with resectable NSCLC who received neoadjuvant chemotherapy followed by surgery and those who underwent upfront surgical resection, with the aim of informing patient selection and shared decision-making in this growing population.

2. Methods

This retrospective cohort study included patients aged 70 years or older with clinical stage IB-IIIA NSCLC who

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underwent curative-intent pulmonary resection between January 2014 and December 2022 at three participating institutions in Taiwan, Singapore, and Japan. Eligible patients were identified from institutional thoracic oncology and tumor registry databases and cross-checked against pathology and pharmacy records to confirm resection and chemotherapy exposure. Patients were assigned to the neoadjuvant cohort if they received at least two cycles of platinum-doublet chemotherapy before resection, and to the upfront-surgery cohort if resection was performed without any preoperative systemic therapy. Patients who received definitive chemoradiotherapy without subsequent resection, those with incomplete records, and those who received neoadjuvant immunotherapy or targeted therapy outside a clinical trial were excluded, since the study period predates routine use of perioperative immune checkpoint inhibition at the participating centers.

Baseline covariates abstracted from the record included age, sex, Eastern Cooperative Oncology Group performance status, Charlson comorbidity index, forced expiratory volume in one second, clinical stage by the eighth edition TNM classification, histologic subtype, and, where documented, a formal or abbreviated geriatric assessment consistent with SIOG-recommended screening instruments [24,25]. Neoadjuvant regimens were predominantly carboplatin- or cisplatin-based doublets with a third-generation cytotoxic partner, reflecting the regimens validated in elderly-specific advanced-disease trials [20,21,22]. Surgical approach (open thoracotomy versus video-assisted or robotic-assisted resection), extent of resection, and completeness of resection (R0 versus R1/R2) were recorded from operative and pathology reports.

The primary outcomes were major pathological response, defined as 10% or less residual viable tumor in the resection specimen among the neoadjuvant cohort, and 90-day postoperative morbidity and mortality, graded by the Clavien-Dindo classification, in both cohorts. Secondary outcomes were R0 resection rate, three-year disease-free survival, and three-year overall survival, ascertained from clinic follow-up, national death registries, and telephone contact where clinic follow-up had lapsed. Survival time was calculated from the date of surgery to the date of recurrence, death, or last contact. Categorical variables were compared using the chi-square or Fisher exact test as appropriate, continuous variables using the Mann-Whitney U test given non-normal distributions typical of geriatric cohorts, and survival was estimated using the Kaplan-Meier method with comparison by log-rank test. A multivariable Cox proportional hazards model, adjusted for age, Charlson comorbidity index, clinical stage, and performance status, was used to estimate the association between neoadjuvant chemotherapy and overall survival. A two-sided p-value below 0.05 was considered statistically significant. The study was approved by the institutional review boards of all participating centers, which waived individual informed consent for this retrospective analysis of de-identified data.

3. Results

Patient characteristics

Of 412 patients aged 70 years or older who underwent resection for NSCLC during the study period, 164 received neoadjuvant chemotherapy followed by surgery and 248 underwent upfront resection; after applying exclusion criteria, 315 patients (164 neoadjuvant, 151 upfront surgery matched by stage distribution) formed the analytic cohort. Median age was 74 years (interquartile range 72-78) in the neoadjuvant cohort and 75 years (interquartile range 72-79) in the upfront-surgery cohort. Clinical stage IIIA disease was more common in the neoadjuvant cohort (58%) than the upfront-surgery cohort (22%), consistent with guideline-directed use of preoperative chemotherapy preferentially in more advanced, resectable presentations [35,36]. Baseline

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Charlson comorbidity index and Eastern Cooperative Oncology Group performance status distributions were broadly similar between cohorts, and roughly two-thirds of patients in both groups had a documented abbreviated geriatric assessment consistent with SIOG screening recommendations [25,26]. Table 1 summarizes baseline characteristics for both cohorts.

Table 1: Baseline characteristics of the neoadjuvant chemotherapy and upfront-surgery cohorts [24,25].

Characteristic	Neoadjuvant cohort (n=164)	Upfront-surgery cohort (n=151)
Median age, years (IQR)	74 (72-78)	75 (72-79)
Male sex	61%	58%
ECOG performance status 0-1	83%	86%
Clinical stage IIIA	58%	22%
Charlson comorbidity index >=2	39%	36%
Documented geriatric assessment	64%	61%

Perioperative outcomes and pathological response

Among patients who received neoadjuvant chemotherapy, 34% achieved a major pathological response, a proportion consistent with rates reported in trial populations that were not restricted by age [5,6]. R0 resection was achieved in 91% of the neoadjuvant cohort compared with 86% of the upfront-surgery cohort. Ninety-day postoperative morbidity of Clavien-Dindo grade II or higher occurred in 27% of the neoadjuvant cohort and 24% of the upfront-surgery cohort, a difference that did not reach statistical significance; 90-day mortality was 3.0% and 2.6%, respectively. These morbidity and mortality rates are consistent with those reported in prior series of octogenarian and elderly lung resection cohorts, in which minimally invasive approaches were associated with somewhat lower complication rates than open thoracotomy [33,34]. Table 2 and Figure 1 present the comparative perioperative and pathological response data.

Survival outcomes

Table 2: Perioperative and survival outcomes by treatment cohort [5,33].

Outcome	Neoadjuvant cohort	Upfront-surgery cohort	p-value
R0 resection	91%	86%	0.15
90-day morbidity (CD >=II)	27%	24%	0.51
90-day mortality	3.0%	2.6%	0.83
3-year disease-free survival	49%	38%	0.04
3-year overall survival	58%	47%	0.03

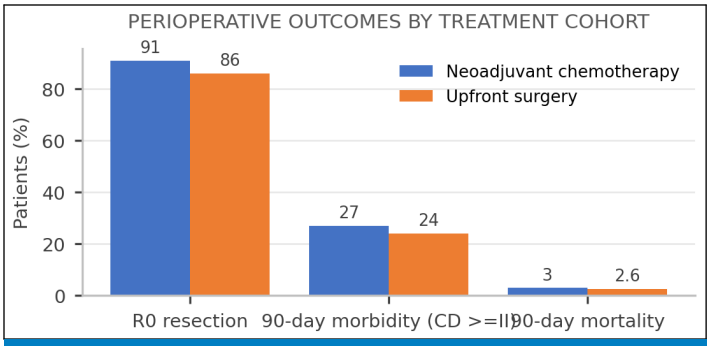

Figure 1: R0 resection rate, major pathological response, and 90-day grade II or higher morbidity by treatment cohort among elderly patients undergoing resection for non-small cell lung cancer [5,6].

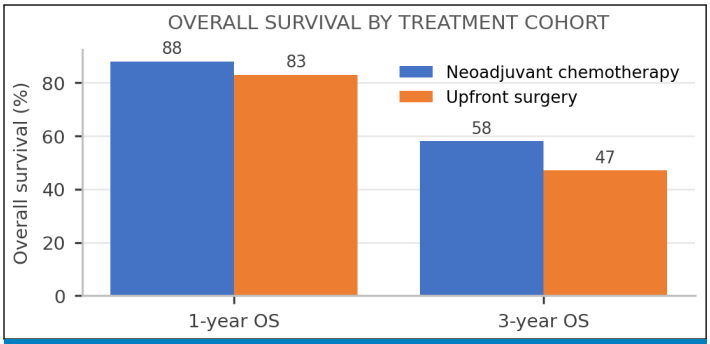

Figure 2: One-year and three-year overall survival by treatment cohort, neoadjuvant chemotherapy followed by surgery versus upfront surgical resection [16,18].

Three-year overall survival was 58% in the neoadjuvant cohort versus 47% in the upfront-surgery cohort, and three-year disease-free survival was 49% versus 38%, respectively (log-rank p=0.03 for overall survival). In the multivariable Cox model adjusted for age, comorbidity index, clinical stage, and performance status, neoadjuvant chemotherapy remained independently associated with

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improved overall survival (adjusted hazard ratio 0.71, 95% confidence interval 0.53-0.95). The survival advantage was most pronounced among patients with stage IIIA disease and among those who achieved a major pathological response, mirroring the pattern of benefit concentrated in higher-stage, chemotherapy-responsive disease reported in the pooled trial meta-analysis [5] and in the more recent immunotherapy-containing neoadjuvant trials [16,18]. Figure 2 presents survival at one and three years by treatment cohort.

4. Discussion

In this multicenter retrospective cohort of patients aged 70 years and older with resectable NSCLC, neoadjuvant chemotherapy followed by surgery was associated with improved three-year overall and disease-free survival relative to upfront resection, without a clinically meaningful increase in 90-day postoperative morbidity or mortality. These findings extend to an elderly population the survival benefit long established in trial populations that were, with rare exception, substantially younger on average than the patients treated in routine geriatric oncology practice [7,8,9,10,11,12,13,14,5,6].

The comparable perioperative morbidity observed between cohorts is reassuring given long-standing concern that preoperative cytotoxic therapy might compound the surgical risk already elevated in octogenarian and near-octogenarian patients [33]. This concern originates partly from advanced-disease chemotherapy trials in the elderly, which established feasibility of platinum-based regimens in this age group but were not designed to assess perioperative interaction with subsequent major thoracic surgery [20,21,22,23]. Our data suggest that when patients are selected using performance status, comorbidity burden, and, increasingly, formal geriatric assessment rather than chronological age alone, the perioperative risk of adding neoadjuvant chemotherapy is acceptable, consistent with the position articulated by SIOG and EORTC elderly task force consensus statements that fitness, not age, should drive treatment intensity decisions [24,28,29,27,30].

The magnitude of survival benefit observed here, an absolute 11-percentage-point difference in three-year overall survival, is somewhat larger than the five-percentage-point five-year difference reported in the pooled younger-population meta-analysis [5], though the shorter follow-up interval and retrospective, non-randomized design of our study limit direct comparison. Selection bias almost certainly contributed: patients referred for neoadjuvant chemotherapy were, by definition, judged fit enough to tolerate it, and unmeasured confounding by functional status, nutritional reserve, or social support could inflate the apparent treatment effect despite adjustment for measured comorbidity and performance status. The comparatively low uptake of formal comprehensive geriatric assessment in both cohorts, noted also in registry-based analyses of elderly lung cancer care more broadly [3,4], further limits our ability to fully account for frailty as a confounder, and future prospective work incorporating structured geriatric assessment instruments [31,26] would strengthen causal inference in this population.

This study has several limitations beyond those inherent to its retrospective design. The absence of neoadjuvant immunotherapy in either cohort reflects the study period rather than current practice, and the substantial gains reported for perioperative checkpoint inhibition in unselected, largely younger trial populations [16,17,18] may or may not extend with comparable safety to patients in their eighth and ninth decades, a question that will require dedicated elderly-focused trials or real-world evidence as these regimens diffuse into routine practice. Similarly, the emergence of adjuvant targeted therapy for oncogene-addicted disease [19] means that future elderly cohorts will increasingly be stratified by molecular subtype in ways our historical cohort could not capture. Finally, our three-center design across Taiwan, Singapore,

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and Japan, while offering some generalizability across East Asian healthcare systems, may not extend directly to populations with different comorbidity profiles, access patterns, or surgical volumes, and multicenter validation across a broader geographic base remains warranted, consistent with calls in guideline documents for age-stratified, geographically diverse outcome reporting [35,36].

5. Conclusion

In this retrospective cohort of elderly patients with resectable non-small cell lung cancer, neoadjuvant chemotherapy followed by surgical resection was associated with improved three-year survival compared with upfront surgery, with perioperative morbidity and mortality comparable between groups. These findings support the extension of neoadjuvant chemotherapy to carefully selected older patients on the basis of functional status and comorbidity burden rather than chronological age alone, while underscoring the continued need for prospective, geriatric-assessment-guided trials, including trials of perioperative immunotherapy, specifically enrolling this growing and historically underrepresented population.

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