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EFFICACY OF ADJUVANT CHEMORADIOTHERAPY IN PATIENTS WITH MACROSCOPIC RESIDUAL OR RECURRENT NON-SMALL CELL LUNG CANCER AFTER SURGERY

*Ngo Dang Huong, Vu Hong Nam, Nguyen Thi Thu Thao, Huynh Duc Tin, Le Thi Yen Oanh, Nguyen Thi Nhu An, Nguyen Thanh Cong**

Military Hospital 175 - Ho Chi Minh City, Vietnam

ABSTRACT

Objective: To evaluate the clinicopathological characteristics of patients with non-small cell lung cancer (NSCLC) presenting with macroscopic residual nodal disease or post-operative recurrence, and to assess the efficacy of adjuvant chemoradiotherapy in these patient groups.

Patients and Methods: Patients diagnosed with non-small cell lung cancer who underwent surgical resection and were subsequently assessed for residual disease or post-operative recurrence.

Results: A total of 37 patients had post-operative recurrence and 31 patients had residual tumor. Lymph node stations 4R and 7 accounted for the highest rates of nodal metastasis (36% and 51.4%, respectively). Median overall survival was 18.6 months in the recurrence group and 25.4 months in the residual disease group.

Keywords: *Lung cancer, macroscopic residual, postoperative radiation.*

1. INTRODUCTION

Non-small cell lung cancer ranks second in both incidence and mortality among both sexes in Vietnam.

Radical surgery remains the cornerstone of treatment, particularly in early-stage disease. However, the surgical approach as well as the standards for lymph node dissection remain controversial and challenging. Several studies have concluded that the rate of residual lymph node or tumor disease ranges from 5–15% among all radical surgical cases [1]. This represents a risk factor leading to early recurrence and metastasis. In patients who achieve negative surgical margins and adequate lymph node dissection, the Lung-ART study has shown that pN2 patients derive no survival benefit from postoperative adjuvant chemoradiotherapy.

For cases with microscopic or macroscopic residual tumor or nodal disease, adjuvant chemoradiotherapy is indicated according to NCCN and ASTRO guidelines [5] [6]. In cases of local or regional tumor recurrence after surgery, adjuvant chemoradiotherapy remains the preferred treatment indication.

Study objectives:

To investigate the clinical and paraclinical characteristics of non-small cell lung cancer patients with residual tumor or nodal disease after surgery and patients with post-operative recurrence

To evaluate the efficacy of postoperative adjuvant chemoradiotherapy in the two patient groups described above

2. SUBJECTS AND METHODS

2.1.Study Subjects

Patients diagnosed with non-small cell lung cancer who underwent tumor resection and mediastinal lymph node dissection, and were assessed for macroscopic residual disease or recurrence after surgery.

Inclusion criteria:

- Patients with macroscopic residual tumor or lymph nodes after surgery, as assessed on contrast-enhanced CT scan performed 2 weeks postoperatively.

- Patients with postoperative locoregional recurrence: those with negative surgical margins and adequate mediastinal lymph node dissection (in both number and nodal stations), as documented in the operative report, and with a contrast-enhanced chest CT scan performed 2 weeks postoperatively demonstrating no residual disease. Recurrence was defined as a newly detected lesion at the surgical bed / bronchial stump, ipsilateral hilum, or a mediastinal–hilar nodal station on serial contrast-enhanced CT (RECIST 1.1), reviewed and adjudicated by the multidisciplinary tumor board, and identified before the initiation of adjuvant chemoradiotherapy (within 6 months of surgery). Patients whose first site of treatment failure was distant metastasis were not included in this cohort.

- Histopathologic characterization: In the macroscopic residual disease (R2) group, gross residual tumor or positive surgical margin was confirmed by the operative report together with the postoperative pathology report. In the recurrence group, the new lesion was characterized radiologically (RECIST 1.1) and adjudicated by the multidisciplinary tumor board; percutaneous or endobronchial biopsy was obtained whenever the lesion was safely accessible. Histologic subtype was recorded in all patients; tumor differentiation

Military Hospital 175 - Ho Chi Minh City, Vietnam
**Corresponding author: Nguyen Thanh Cong*
Email: bscongthanhnguyenbv175@gmail.com - Tel: 0982249818
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grade, lymphovascular invasion and visceral pleural invasion are additionally reported in Table 1 where available.

Exclusion criteria:

Postoperative patients without adequate surgical margin assessment, those without lymph node dissection, or with insufficient number of nodes or nodal stations dissected.

2.2 Study Methods

Retrospective and prospective descriptive case series study; data were analyzed using statistical algorithms with SPSS 22.0 software, with statistical significance set at $p < 0.05$. Non-parametric tests were used for non-normal distributions, while Chi-square and t-tests were used for normal distributions.

- Definition of survival time: Overall survival (OS) and progression-free survival (PFS) were defined separately for each subgroup. In the macroscopic residual disease (R2) group, OS and PFS were calculated from the date of surgery to the date of death from any cause (for OS) or the date of documented disease progression on imaging/death (for PFS). In the recurrence group, OS and PFS were calculated from the date of recurrence diagnosis on CT scan to the date of death or subsequent disease progression. Patients alive at the data cut-off date (April 1, 2026) or lost to follow-up were censored at the last clinic visit. OS and PFS were estimated using the Kaplan-Meier method, and comparisons between the two groups were performed using the log-rank test.

3. RESULTS

A total of 68 patients with non-small cell lung cancer assessed for residual tumor/lymph nodes or recurrence after surgery received external beam radiotherapy and adjuvant chemotherapy between January 1, 2023 and April 1, 2026 at Military Hospital 175.

- Epidemiology: Median age in both groups was 64 years; the cohort included 53 male and 15 female patients.

Table 1. Clinical and treatment characteristics of the two patient groups

Characteristics	Recurrence group (n=37)	Residual group (n=31)
Histopathology, n (%)		
Adenocarcinoma	26 (70.2)	24 (77.4)
Squamous cell carcinoma	10 (27.0)	7 (22.6)
Adenosquamous carcinoma	1 (3.2)	0 (0.0)
Primary tumor location, n (%)		
Right	25 (67.6)	22 (71.0)
Left	12 (32.4)	9 (29.0)
Postoperative stage, n (%)		
I	6 (16.2)	11 (35.5)
II	20 (54.1)	9 (29.0)
IIIA	4 (10.8)	5 (16.1)
IIIB	7 (18.9)	6 (19.4)
Surgical approach, n (%)		
Wedge resection	8 (21.6)	12 (38.7)
Segmentectomy	12 (32.4)	16 (51.6)
Lobectomy	17 (45.9)	3 (9.7)
Total radiotherapy dose, n (%)		
54 Gy	2 (5.4)	5 (16.1)
60 Gy	13 (35.1)	15 (48.4)
66 Gy	22 (59.5)	11 (35.5)
Chemotherapy, n (%)		
Concurrent	15 (40.5)	19 (61.3)
Sequential	22 (59.5)	12 (38.7)

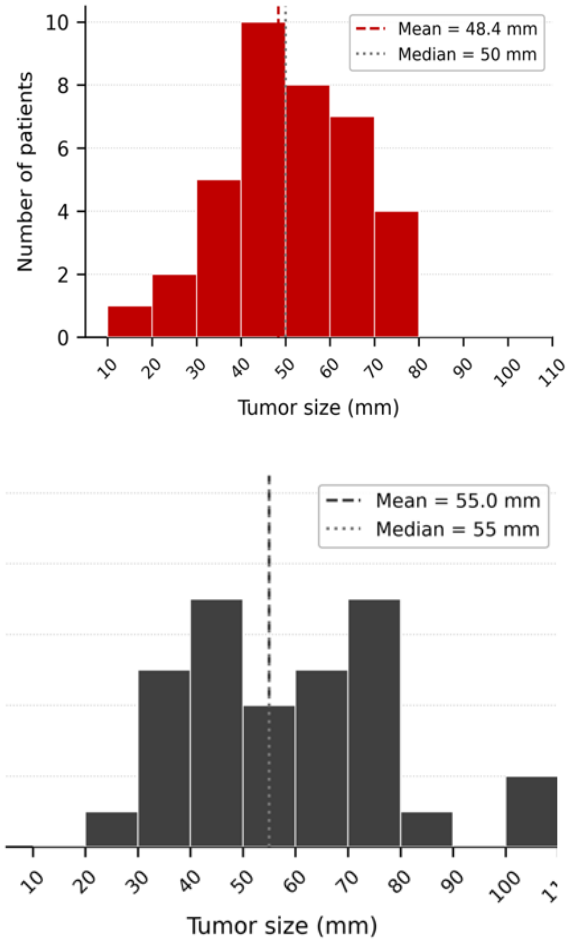

Figure 1. Distribution of primary tumor size in the two patient groups

Characteristics: the mean primary tumor size was 48.4 mm in the residual group and 55 mm in the recurrence group. Large tumor size and central location are also obstacles for surgeons attempting to achieve negative surgical margins.

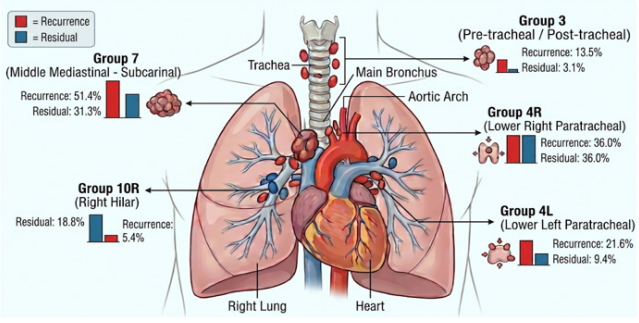

Figure 2. Characteristics of lymph node stations in the two patient groups

Comments:

Station 7 (subcarina) was the lymph node station with the highest rate of metastasis in both subgroups, particularly in the recurrence group (51.4%) compared with the residual group (31.3%). Station 4R ranked second, just after station 7, with comparable rates between the two groups (~36%).

Stations 4L and 3 appeared more frequently in the recurrence group (21.6% vs 9.4%; 13.5% vs 3.1%).

Station 10R was three times higher in the residual group than in the recurrence group (18.8% vs 5.4%).

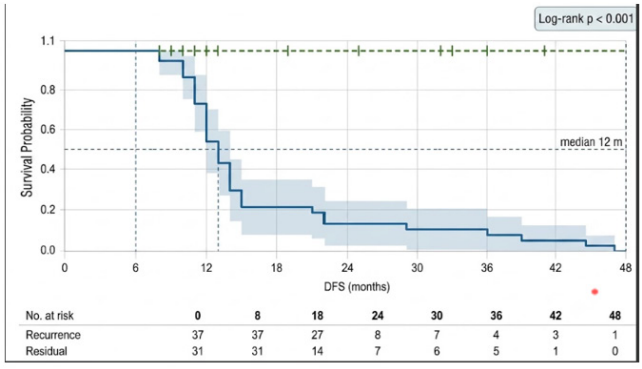

Figure 3. Kaplan-Meier curve of progression-free survival (PFS) in the two patient groups

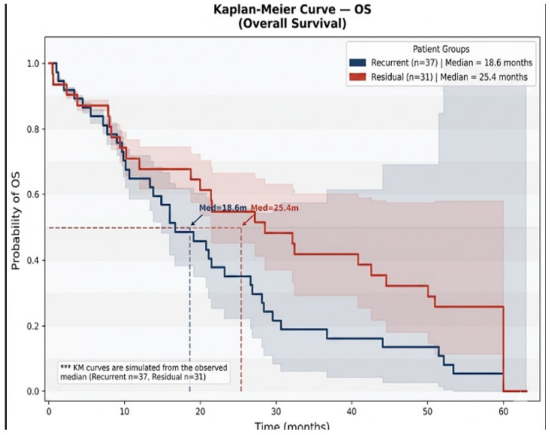

Figure 4. Kaplan-Meier curve of overall survival (OS) in the two patient groups

Comments: With a median follow-up of 24 months (range, 6–48 months), survival outcomes differed markedly between the two subgroups.

In the recurrence group (n=37), median progression-free survival (PFS) was 12.8 months and median overall survival (OS) was 18.6 months. The Kaplan-Meier curve showed that the rate of disease progression increased rapidly within the first 12 months after initiation of adjuvant chemotherapy, reflecting the poorly differentiated histological features of patients with early recurrence after radical surgery.

In the postoperative macroscopic residual disease group (n=31), median overall survival reached 25.4 months (range, 8–41 months), significantly higher than in the recurrence group (18.6 months). This result suggests that early initiation of chemoradiotherapy immediately after surgery in the R2 group — before the development of distant metastases — still provides a clinically meaningful survival benefit, despite the incomplete removal of residual tumor/lymph nodes.

4. DISCUSSION

Mediastinal lymph node stations 7 and 4 had the highest rates of residual disease and recurrence in our study. This finding is consistent with reports from the American Association for Thoracic Surgery and the European Society of Thoracic Surgeons (ESTS). Several authors have attributed this to the complex anatomical relationships of these two nodal stations with adjacent structures — including the main bronchus, pulmonary artery, and esophagus — which render complete resection technically demanding. The adoption of robotic-assisted thoracic surgery has provided surgeons with greater confidence in margin control and mediastinal lymphadenectomy in complex cases. Nevertheless, a multicenter analysis by the Society of Thoracic Surgeons (STS) concluded that robotic surgery did not reduce the rates of positive surgical margins or residual mediastinal nodal disease compared with video-assisted thoracoscopic surgery (VATS)[3][4].

A notable finding of our study was that the gross residual disease group (R2) achieved a median overall survival (mOS) of 25.4 months, which was superior to that of the recurrence group (18.6 months), despite the fact that the primary tumor or involved lymph nodes had not been completely resected. This paradoxical observation may be explained by three factors. First, tumor biology: the recurrence group had a larger mean tumor size (55 mm vs. 48.4 mm) and a higher proportion of stage II disease (54.1%), suggesting an aggressive early-relapse phenotype characterized by rapid proliferation following curative-intent resection. Second, timing of treatment initiation: the R2 group received concurrent chemoradiotherapy within 4–6 weeks postoperatively, at a point when micrometastatic burden remained minimal and the post-surgical tumor microenvironment was still treatment-responsive; in contrast, the recurrence group had an interval of 6–24 months during which resistant subclones could be selected and established. Third, treatment intensity: a higher proportion of the recurrence group received 66 Gy (59.5% vs. 35.5%), consistent with the principle of dose escalation for gross disease — yet overall survival remained inferior to the R2 group, underscoring the limitations of radiotherapy dose escalation alone once the biological characteristics of the tumor have shifted. These observations support a strategy of early and aggressive intervention for R2 disease in the immediate postoperative setting, rather than deferring treatment until clinical recurrence.

The Lung-ART trial, conducted in patients with pathologically confirmed pN2 disease and complete resection (R0), demonstrated no overall survival benefit from adjuvant postoperative radiotherapy (PORT), while documenting a significant increase in cardiopulmonary toxicity. However, subgroup analyses revealed that PORT reduced the locoregional recurrence rate from

46.1% to 25.0%. [3] In our study, the median progression-free survival (mPFS) of 12.8 months in the recurrence group was

With respect to surgical approach, a notable difference was observed between the two groups: lobectomy was performed in only 9.7% of the R2 group compared with 45.9% of the recurrence group; conversely, wedge resection and segmentectomy accounted for 90.3% of procedures in the R2 group. This suggests that sublobar resection is an important risk factor for gross residual disease, consistent with recommendations from the ESTS and the CALGB 140503 trial, which affirm that lobectomy remains the standard of care for tumors >2 cm or when N1/N2 nodal involvement is suspected. The ESTS standard for systematic nodal dissection requires a minimum of 6 lymph nodes (3 N2 + 3 N1) from at least 3 distinct nodal stations — a benchmark for assessing the adequacy of initial resection and stratifying residual disease risk. For tumors >5 cm, centrally located lesions, or cases with clinical suspicion of N2 disease on preoperative staging, multidisciplinary team (MDT) discussion should be undertaken to evaluate neoadjuvant chemo-immunotherapy (per the CheckMate 816 protocol) prior to surgical decision-making, with the goal of minimizing the risk of gross residual disease and optimizing conditions for achieving a negative surgical margin (R0 resection).

In comparison, Hancock et al. (2015), in a study of more than 3,400 patients evaluating both R1 and R2 resections, reported a median overall survival of 17.6 months with radiotherapy alone and 35.6 months with concurrent chemoradiotherapy. [1] The median overall survival of 25.4 months observed in our R2 cohort reflects the differences in sample size and the fact that our study population was restricted exclusively to patients with gross residual disease, who are inherently at higher risk for early disease progression and distant metastasis. Nevertheless, both studies provide compelling evidence supporting the benefit of concurrent chemoradiotherapy in patients with microscopically positive surgical margins (R1) and, to an even greater clinical challenge, in those with gross residual disease (R2). Furthermore, in the R2 setting, chemoradiotherapy should no longer be regarded merely as adjuvant therapy, but must be approached as a definitive treatment strategy employing higher radiation doses (>60 Gy) to compensate for unresected gross disease, given that re-resection is only rarely feasible in lung cancer patients.

Limitations: This study has several limitations. First, it is a retrospective, single-center analysis with a modest sample size. Second, the time-zero for survival analysis differed between the two subgroups (date of surgery for the R2 group vs. date of recurrence diagnosis on CT for the recurrence group), which introduces a lead-time effect; the two overall-survival estimates should therefore be interpreted as within-group descriptors rather than a direct head-to-head comparison. Third, histopathologic characterization in this analysis was restricted to subtype and stage; a systematic assessment of tumor differentiation grade, lymphovascular invasion and visceral pleural invasion is being compiled and will strengthen the biological interpretation in a subsequent report. Prospective, multicenter validation is warranted to confirm the observed patterns of nodal failure and the survival benefit of early definitive chemoradiotherapy in the R2 setting.

5. CONCLUSION

In this cohort of 68 non-small cell lung cancer patients with either macroscopic residual disease (R2) or postoperative locoregional recurrence, nodal failure clustered at station 7 (51.4% and 31.3%) and station 4R (~36%). Adjuvant / definitive chemoradiotherapy achieved a median overall survival of 25.4 months in the R2 group and 18.6 months in the recurrence group. Based on these findings we recommend: (1) in R2

disease, chemoradiotherapy should be initiated early (within 4–6 weeks of surgery) and delivered at a definitive dose (≥60 Gy) rather than as conventional low-dose adjuvant therapy; (2) the indication for postoperative radiotherapy and the total dose should be individualized according to the number and station of involved lymph nodes, the presence of extracapsular extension and nodal size, rather than a uniform extrapolation of the Lung-ART result to all pN2 patients; and (3) for tumors >5 cm, centrally located lesions, or with clinical suspicion of N2 involvement, multidisciplinary discussion should be undertaken to consider neoadjuvant chemo-immunotherapy prior to surgery, so as to minimize the risk of R2 resection. Prospective, multicenter studies are needed to confirm these findings.

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