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Local Consolidation Therapy in Patients with EGFR Mutated Non-Small Cell Lung Cancer (NSCLC) Receiving Frontline Osimertinib, A Real-World Experience

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SUMMARY

Objective: This retrospective study aims to evaluate the impact of Local Consolidation Therapy (LCT) on progression-free survival (PFS) and overall survival (OS) in patients with stage IV EGFR-mutated non-small cell lung cancer (NSCLC) receiving frontline osimertinib treatment.

Methods: We conducted a chart review of patients diagnosed with stage IV EGFR-mutated NSCLC between January 2021 and May 2023, treated with osimertinib as frontline therapy. The study included 48 patients, 15 receiving LCT through either consolidation surgery or radiation. Kaplan-Meier methodology and log-rank tests were utilized to analyze PFS and OS, comparing outcomes between patients who received LCT and those who did not.

Results: The median PFS for patients receiving LCT was 22.5 months, compared to 9.3 months in the non-LCT group. Similarly, the median OS was significantly improved in the LCT group, with the median OS not reached, compared to 11.9 months in the non-LCT group. No significant differences were observed between early and late consolidation radiation therapy regarding its impact on PFS and OS.

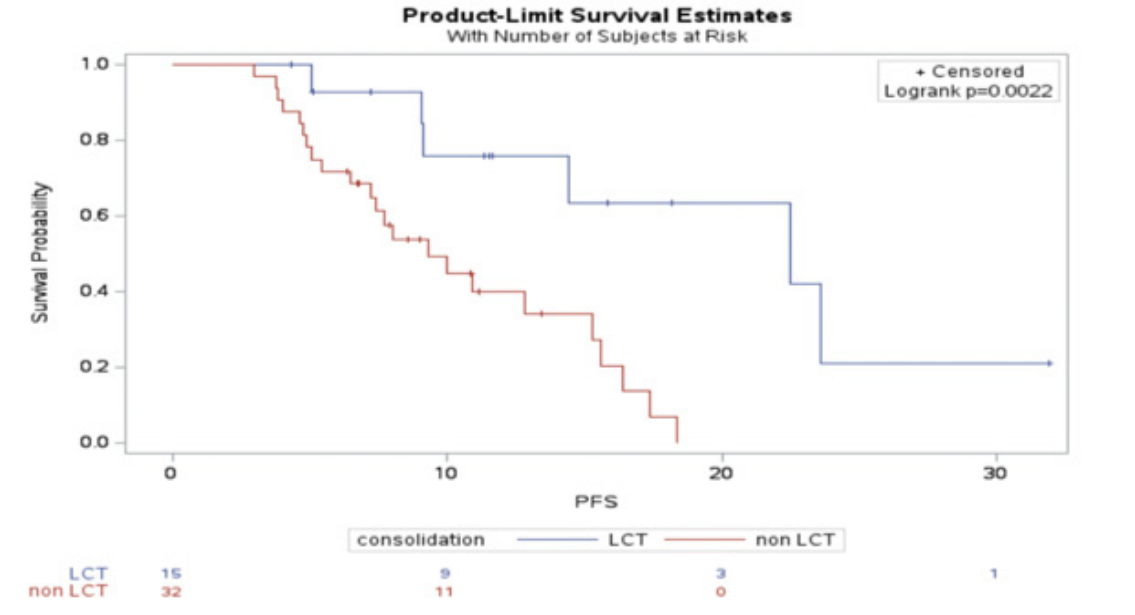
Conclusion: When combined with frontline osimertinib, LCT significantly improves PFS and OS in patients with advanced EGFR-mutated NSCLC. These findings suggest that LCT is a viable and effective strategy for enhancing the outcomes of patients undergoing treatment for this challenging condition. The safety of LCT was also confirmed, with no reported complications related to the therapy. This study contributes valuable insights into the evolving treatment landscape for advanced EGFR NSCLC, highlighting the potential of LCT to augment the efficacy of systemic therapies.

Abbreviations: OS: Overall Survival; LCT: Local Consolidation Therapy; PFS: Progression-Free Survival; NSCLC: Non-Small Cell Lung Cancer; TKIs: Tyrosine Kinase Inhibitors

Introduction

Front-line osimertinib has been a breakthrough in treating advanced EGFR NSCLC due to its efficacy and good tolerance [1]. Unfortunately, most patients develop resistance mechanisms and disease progression. Many strategies have been deployed to overcome or delay the development of resistance with little success, for example, the addition of selective MET tyrosine kinase inhibitors (TKIs) [2,3], anti-angiogenesis agents [4], and immunotherapy [5], among others. Local consolidation therapy (LCT) is a therapeutic option with proven benefits in non-oncogene drives NSCLC. Randomized phase 2 data in the biomarker unselected NSCLC space showed statistically significant improvement in progression-free survival (PFS) by adding local consolidation radiation to patients who received front-line therapy and did not experience disease progression [6]. A meta-analysis of local consolidation therapy (radiation/surgery) of 7 studies, including 693 patients, showed improvement in PFS and overall survival (OS) [7]. More recently, a body of literature has emerged utilizing local consolidation radiation in advanced EGFR-mutated NSCLC [8]. The site of initial involvement appears to be a common

culprit for disease progression following front-line therapy [9]. In the era of earlier generation TKIs, adding LCT to EGFR TKI improved both PS and OS (retrospective data) [10,11]. This approach improved PFS and OS even in an elderly cohort (above 80 years old) [12], which suggests this approach is safe and well tolerated. A study evaluating LCT to all metastatic sites after front-line EGFR TKI also showed improved PFS and OS compared to LCT to partial sites or observation [13]. In the osimertinib era, a study including 25 patients treated with first-line Osimertinib found that LCT significantly improved PFS [14]. We plan to expand on this dataset and hypothesize that LCT improved progression-free survival and overall survival in patients with advanced EGFR mutated NSCLC receiving frontline Osimertinib (Figure 1).



Note: Overall log-rank test p=0.0022

Non-LCT median PFS 9.3 months, 95% CI (6.5, 15.27)

LCT median PFS 22.5 months, 95% CI (9.13,.)

Figure 1: Progression-free survival curves of LCT cohort and non-LCT cohort.

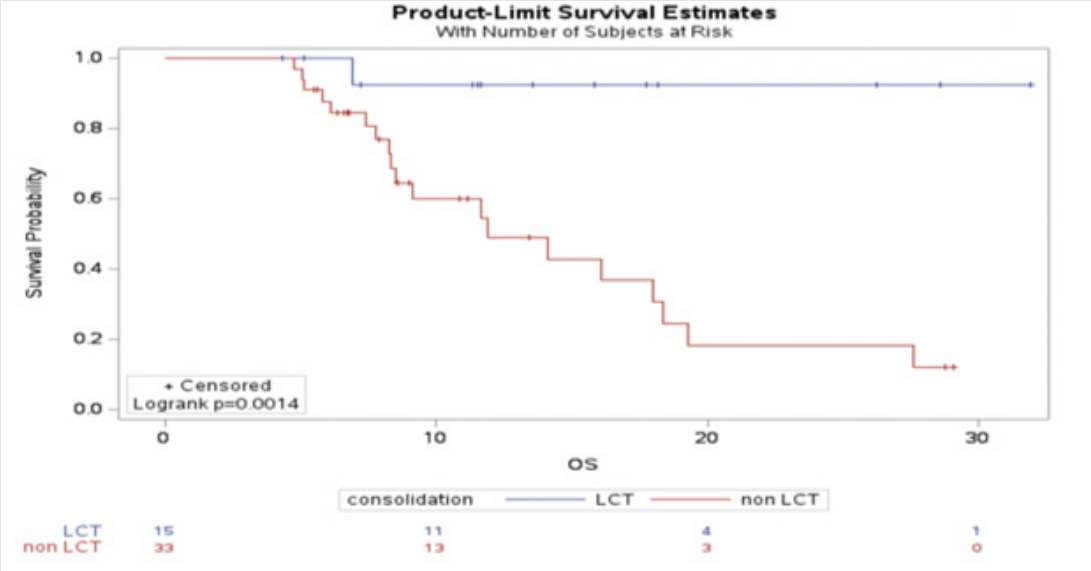
Methods

We conducted a single institution retrospective chart review of patients initially diagnosed with stage IV EGFR-mutated NSCLC between January 2021 and May 2023. Inclusion criteria were 1) diagnosed with stage IV EGFR mutated NSCLC (common and uncommon mutations were included) and 2) received osimertinib as frontline treatment. The time of data cut-off was October 15th, 2023. Restaging CT scans were performed in 2-3 month intervals, and brain MRIs were obtained at the treating physician's discretion (mandatory per national guidelines at baseline). Local consolidation therapy took the form of either consolidation surgery or consolidation radiation. Radiation was performed at the site of residual disease after frontline osimertinib (early local consolidation RT) or at the site of oligo progression (late consolidation RT) after a multidisciplinary review. Our objective was to correlate local consolidation therapy with progression-free survival (PFS) and overall survival (OS). Kaplan-Meier methodology was used to analyze PFS and OS. A log-rank test was used to compare PFS and OS between LCT vs. non-LCT patients.

Results

48 patients with advanced EGFR mutated NSCLC were included in the analysis (Table 1). Fifteen patients (31%) received LCT. Of these, 6 patients (40%) underwent consolidation surgery on the primary mass in the lung (Figure 2). Nine patients (60%) underwent local consolidation radiation, 5 of which underwent early consolidation RT to the site of residual disease (all lung). The median age was the same in both groups (non-LCT and LCT). Both groups had a female predominance in (75.8% and 60% in non-LCT and LCT, respectively). Most patients had adenocarcinoma histology (90.6% and 93.3% in non-LCT and LCT, respectively). The majority of patients in both

groups were TP53 co-mutated. The median follow-up was 273 days. At the time of data cut-off, 20 patients (41%) had expired. Of the 28 live patients, 10 experienced disease progression. The median PFS in the non-LCT group was 9.3 months, 95% CI (6.5, 15.27). The median PFS in the LCT group was PFS 22.5 months, 95% CI (9.13,.). The median OS in the non-LCT group was OS=11.9 months, 95% CI (8.33, 18.37). The median in the LCT group was not reached. There was no difference in impact on PFS and OS between early and late consolidation RT.



Note: Overall log-rank test p=0.0014

Non-LCT: median OS=11.9 months, 95% CI (8.33, 18.37)

LCT: median not reached

Figure 2: Overall survival curves of LCT cohort and non-LCT cohort.

Table 1: Baseline characteristic table by LCT and non-LCT.

	Consolidation			
	No (N=33)	**Yes (N=15)**	**Total (N=48)**	**P-value**
Age at diagnosis				0.7737[1]
N	33	15	48	
Mean (SD)	63.0 (11.52)	62.0 (10.09)	62.7 (11.00)	
Median	63	63	63	
Range	42.0, 83.0	43.0, 78.0	42.0, 83.0	
Gender, n (%)				0.3153[2]
Female	25 (75.8%)	9 (60.0%)	34 (70.8%)	
Male	8 (24.2%)	6 (40.0%)	14 (29.2%)	
Histology, n (%)				1.0000[2]
Adenocarcinoma	29 (90.6%)	14 (93.3%)	43 (91.5%)	
Squamous cell carcinoma	2 (6.3%)	1 (6.7%)	3 (6.4%)	
Other	1 (3.1%)	0 (0.0%)	1 (2.1%)	

Missing	1	0	1	
EGFR type, n (%)				0.5030[2]
Exon 19 deletion	15 (45.5%)	9 (64.3%)	24 (51.1%)	
Exon 21 L858R	13 (39.4%)	3 (21.4%)	16 (34.0%)	
Compound EGFR mutations	2 (6.0%)	1 (7.1%)	3 (6.3%)	
Uncommon EGFR mutations	3 (9.1%)	1 (7.1%)	4 (8.5%)	
Missing	0	1	1	
TP53 co-mutated, n (%)				1.0000[2]
No	10 (30.3%)	4 (26.7%)	14 (29.2%)	
Yes	23 (69.7%)	11 (73.3%)	34 (70.8%)	
Brain metastasis at diagnosis, n (%)				0.5419[2]
No	17 (51.5%)	6 (40.0%)	23 (47.9%)	
Yes	16 (48.5%)	9 (60.0%)	25 (52.1%)	
Intrathoracic disease only, n (%)				0.7204[2]
No	26 (78.8%)	11 (73.3%)	37 (77.1%)	
Yes	7 (21.2%)	4 (26.7%)	11 (22.9%)	
Liver metastases, n (%)				1.0000[2]
No	28 (84.8%)	13 (86.7%)	41 (85.4%)	
Yes	5 (15.2%)	2 (13.3%)	7 (14.6%)	

Note: [1]Equal variance two sample t-test; [2]Fisher Exact p-value.

Discussion

In our retrospective cohort, adding local consolation treatment in radiation or surgery significantly improved PFS and OS. Eligibility for local consolidation therapy requires a significant treatment response which could introduce a selection bias; patients eligible for LCT might have more favorable disease biology. Comparing non-LCT vs. LCT in patients with oligo-residual disease could address this bias. Our cohort would not have been powered to answer this question. In our cohort, however, both groups were well balanced in the presence of brain and liver metastases, and TP53-comutation, factors usually associated with worse outcomes [15-17]. During cancer treatment, there is a constant change in the clonal composition of the tumor. One of the resistance mechanisms is the clonal dominance of a smaller subset of subclones [18]; in the case of EGFR NSCLC on osimertinib, these would be osimertinib-resistant clones. Therefore, LCT could potentially eradicate these resistant clones and potentially explain the antineoplastic effect of LCT. The administration of LCT has been safe. None of the 15 patients who received LCT had complications related to LCT. The treatment of advanced EGFR NSCLC is evolving, with novel agents soon to be introduced to the clinic, such as the EGFR MET antibody amivantamab in combination with the EGFR TKI lazertinib, or the combination of cytotoxic chemotherapy with osimertinib. Given the non-curative nature of these systemic therapies, LCT will continue to be a promising option to prolong response and survival.

Conclusion

This study has demonstrated that the integration of Local Consolidation Therapy (LCT) with frontline osimertinib treatment in patients with advanced EGFR mutated non-small cell lung cancer significantly enhances both progression-free survival (PFS) and overall survival (OS). The substantial extension of median PFS from 9.3 months in the non-LCT group to 22.5 months in the LCT group underscores the efficacy of LCT in prolonging the duration of disease control. Moreover, the median OS in the LCT cohort has notably not been reached, suggesting a potentially profound impact on patient survival. This finding is significant given the historical challenges in treating this patient population, where resistance to frontline therapies often leads to rapid disease progression. Furthermore, the study also highlights the need for careful patient selection and acknowledges the possibility of selection bias, as those eligible for LCT may inherently have more favorable disease biology. However, the balanced representation of brain and liver metastases, as well as TP53 co-mutation status in both cohorts, provides confidence in the comparability of the groups. The safety profile of LCT, as evidenced by the absence of LCT-related complications in the study, further supports its integration into the treatment paradigm for advanced EGFR NSCLC. As the landscape of NSCLC treatment continues to evolve with emerging therapies, the role of LCT as a valuable adjunct to systemic therapies becomes increasingly significant, offering a

promising avenue to enhance both the quality and duration of life for patients afflicted with this challenging disease.

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