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Long-term Follow-up of Resected EGFR-mutated Non-small Cell Lung Cancer: A Real-world Study in a Portuguese Centre

Seguimento a Longo Prazo de Carcinoma Pulmonar Não-pequenas Células EGFR-mutado Ressecado: Um Estudo de Vida Real num Centro Português

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ABSTRACT

Surgically resected epidermal growth factor receptor-mutated non-small cell lung cancer continues to carry a substantial risk of recurrence. The aim of this retrospective, single-center study, conducted at a Portuguese tertiary hospital was to evaluate the clinical course of these patients, diagnosed between 2016 and 2020, with the final clinical data review in November, 2024. A total of 48 patients were included, predominantly female (72.9%) and non-smokers (70.8%), most presenting exon 21 *L858R* or exon 19 deletion mutations. Mutations were identified by Sanger sequencing or next-generation sequencing. Programmed death-ligand 1 expression was < 1% in 58.3% of cases. At a median follow-up of 73.6 months, 31.3% of patients experienced relapse, all progressing to stage IV disease. The five-year disease-free survival and overall survival rates were 70% and 81%, respectively. Staging significantly influenced prognosis, with five-year disease-free survival ranging from 84% in stage IB to 20% in stage III. No significant differences were observed between epidermal growth factor receptor mutation subtypes. These findings are consistent with previous real-world studies and the placebo arm of the ADAURA trial, supporting the use of adjuvant osimertinib to reduce recurrence and improve long-term outcomes, while also emphasizing the need for improved perioperative risk assessment – including staging, histopathologic features, and molecular and genetic profiling – to guide personalized treatment.
Keywords: Carcinoma, Non-Small-Cell Lung/surgery; ErbB Receptors/genetics; Mutation; Neoplasm Staging

RESUMO

O carcinoma pulmonar de não pequenas células com mutação no recetor do fator de crescimento epidérmico ressecado cirurgicamente mantém um risco elevado de recidiva. Este estudo retrospetivo, realizado num hospital terciário português, avaliou 48 doentes diagnosticados entre 2016 e 2020, com revisão final dos dados em novembro de 2024. A maioria dos doentes era do sexo feminino (72,9%), não fumadores (70,8%) e apresentava sobretudo mutações no exão 21 (*L858R*) ou deleções no exão 19. As mutações foram identificadas por sequenciação de Sanger ou de nova geração. Em 58,3% dos casos, a expressão do ligando associado à morte celular programada foi inferior a 1%. Após um seguimento mediano de 73,6 meses, 31,3% dos doentes apresentaram recidiva, todos evoluindo para estádio IV. As taxas de sobrevivência livre de doença e global aos cinco anos foram de 70% e 81%, respetivamente. O estadiamento inicial influenciou significativamente o prognóstico, com a sobrevivência livre de doença a cinco anos a variar entre 84% (estádio IB) e 20% (estádio III). Não se observaram diferenças significativas entre os subtipos de mutação. Estes resultados são consistentes com estudos prévios e com o braço placebo do estudo ADAURA, apoiando a integração do osimertinib adjuvante na prática clínica para reduzir a recidiva e melhorar a sobrevivência a longo prazo, bem como enfatizando a necessidade de uma avaliação perioperatória mais abrangente – incluindo estadiamento, características histopatológicas e perfil genético e molecular – para orientar estratégias terapêuticas personalizadas.
Palavras-chave: Carcinoma do Pulmão de Não-pequenas Células; Estadiamento de Neoplasia; Mutação; Receptor ErbB/genética

INTRODUCTION

Lung cancer remains a major health burden, with non-small cell lung cancer (NSCLC) comprising 85% of cases.[1] Epidermal growth factor receptor (EGFR) mutations in NSCLC represent 12.8% of cases in Europe and 49.1% in Asia.[2] In early stages, surgical resection provides the best outcomes.[3] Traditionally, adjuvant chemotherapy was recommended for stages II–III and for stage IB tumors > 4 cm, offering a modest 4% - 5% survival benefit at five years.[4]

In the phase 3 ADAURA trial, adjuvant osimertinib significantly improved 4-year disease-free survival (DFS) compared with placebo in resected stage IB–IIIA EGFR-mutated NSCLC, establishing a new standard of care.[5] Further real-world evidence, however, is still limited. The aim of this study was to describe the clinicopathological features, recurrence patterns, and survival outcomes of patients with resected EGFR-mutated NSCLC at a Portuguese tertiary center.

STUDY DESIGN

This retrospective study at the Department of Pulmonary Oncology of Unidade Local de Saúde de Santa Maria, in Lisbon, included patients ≥ 18 years, ECOG performance status 0 - 1, and resected EGFR-mutated NSCLC (staged I–IIIB, TNM 8th edition),[6] diagnosed between January, 2016,

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and June, 2020, with data extracted from medical records up to November, 2024. Synchronous neoplasms were excluded. Epidermal growth factor receptor mutations were identified by Sanger or next-generation sequencing.

The primary endpoints were DFS (time from surgery to recurrence), and OS (time from surgery to death).

We used SPSS Statistics®, version 29. A *p*-value < 0.05 was considered significant. Descriptive statistics included medians for continuous variables and percentages for categorical variables. Median follow-up was calculated using the reverse Kaplan-Meier method. Disease-free survival and OS were analyzed with Kaplan-Meier curves, and Cox regression was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs).

MAIN FINDINGS

Of 48 patients (Table 1), most were female (72.9%), non-smokers (70.8%), ECOG performance status 0 (75.0%), and a median age of 67 years (range 44 - 85). All had adenocarcinoma histology; 58.3% had negative programmed death ligand-1 (PD-L1) expression. The most frequent mutations were exon 21 *L858R* (41.7%) and exon 19 deletion (27.1%). Five had exon 18 (10.4%) and one had an exon 20 (2.1%) mutation.

Patients underwent lobectomy with lymph node dissection and 93.8% achieved R0 resection. A minority were staged according to the 7th TNM edition, with staging unchanged according to the 8th edition.[6,7] Postoperative stages included 10 patients (20.8%) with stage IA, 25 (52.1%) with IB, 8 (16.7%) with II and 5 (10.4%) with III.

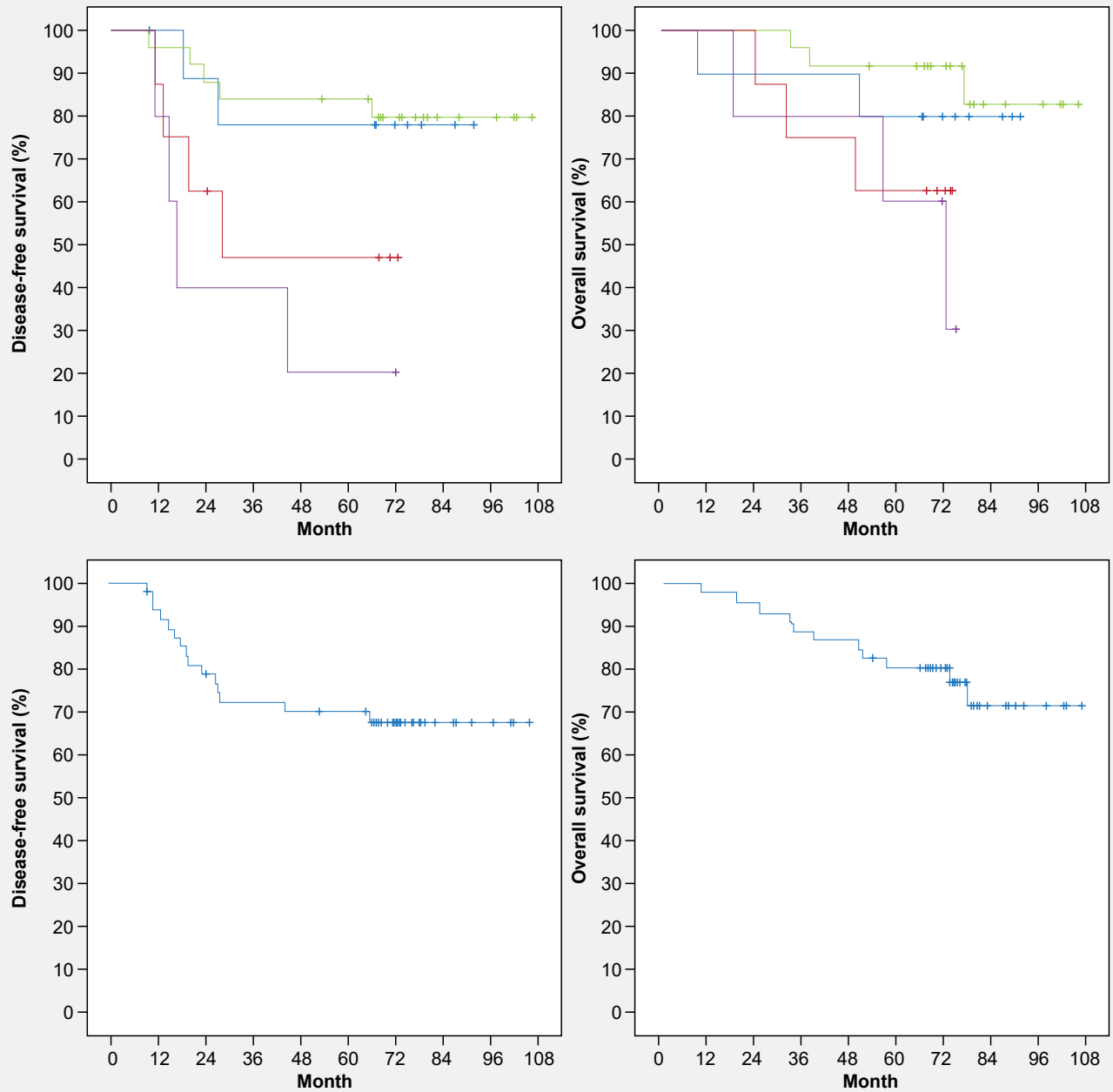
A total of 34 patients (70.8%) received adjuvant treatment: 54.1% chemotherapy and 16,9% chemoradiotherapy. With a median follow-up of 73.6 months (95% CI: 71.0 - 76.2), 15 patients (31.3%) relapsed, all with stage IV disease. Relapses occurred in all stages except IIA: 2 of 10 patients in IA, 5 of 25 (IB), 4 of 7 (IIB), 3 of 4 (IIIA), and the only patient staged IIIB. Most relapses were extra-thoracic (n = 8, 53.3%), involving the lung (53.3%), pleura (26.7%), brain (20.0%) and bone (20.0%). All relapsed patients received a TKI (osimertinib 73.3%, afatinib 20.0% and erlotinib 6.7%). Of the 15 relapses, 11 patients died, nine from disease progression (1 IA, 3 IB, 2 IIB, 2 IIIA, and 1 IIIB). Three received second-line systemic therapy and one received a third-line regimen. Median survival post-relapse was 43.80 months, and 36.37 months in patients with central nervous system (CNS) metastases. Four maintain osimertinib at follow-up.

Median DFS and OS were not reached (Fig. 1). Five-year DFS and OS were 70% and 81%, respectively. By stage, the 5-year DFS was 78% for IA, 84% for IB, 49% for II, and 20% in stage III. Patients with postoperative staging I had significantly longer DFS (HR 0.22, 95% CI: 0.08 - 0.61, $p = 0.004$) and OS (HR 0.20, 95% CI: 0.06 - 0.73, $p = 0.014$)

Table 1 – Baseline patient and disease characteristics of total population and patients with relapse. Reported variables include age, gender, ECOG PS, smoking status, TNM stage, EGFR mutation, PD-L1 expression, surgery performed, resection margins and adjuvant treatment.

Characteristics	Total (n = 48) n (%)	With relapse (n = 15) n (%)
Age		
Median [range]	67 [44 - 85]	64 [44 - 73]
≥ 65 years	29 (59.1)	7 (46.7)
Sex		
Male	13 (27.1)	6 (40.0)
Female	35 (72.9)	9 (60.0)
Performance status		
0	36 (75.0)	11 (73.3)
1	12 (25.0)	4 (26.7)
Smoking status		
Never	34 (70.8)	11 (73.3)
Current or former	14 (29.2)	4 (26.7)
TNM staging		
IA	10 (20.8)	2 (13.3)
IB	25 (52.1)	5 (33.3)
IIA	1 (2.1)	0 (0.0)
IIB	7 (14.6)	4 (26.7)
IIIA	4 (8.3)	3 (20.0)
IIIB	1 (2.1)	1 (6.7)
EGFR exons identified		
18	5 (10.4)	2 (13.3)
19	20 (41.7)	6 (40.0)
20	1 (2.1)	0 (0.0)
21	22 (45.8)	7 (46.7)
EGFR status*		
Exon 21 *L858R*	20 (41.7)	7 (46.7)
Exon 19 deletion	13 (27.1)	2 (13.3)
Other	12 (25.0)	6 (40.0)
PD-L1 status		
< 1%	28 (58.3)	7 (46.7)
1 - 49%	13 (27.1)	6 (40.0)
> 49%	0 (0.0)	0 (0.0)
Unknown	7 (14.6)	2 (13.3)
Location of lobectomy		
Upper right lobe	15 (31.3)	5 (33.3)
Medium lobe	2 (4.2)	1 (6.7)
Lower right lobe	9 (18.7)	2 (13.3)
Upper left lobe	10 (20.8)	4 (26.7)
Lower left lobe	12 (25.0)	3 (20.0)
Surgical outcome		
R0	45 (93.8)	13 (86.7)
R1	3 (6.2)	2 (13.3)
Adjuvant treatment		
Chemotherapy	26 (54.1)	8 (53.3)
Chemoradiotherapy	8 (16.7)	5 (33.3)
No adjuvant treatment	14 (29.2)	2 (13.3)

* EGFR mutation testing was performed on tumor tissue obtained at surgery using Sanger sequencing (12/48, 25.0%) or next-generation sequencing (36/48, 75.0%). NGS included institutional level 1 (n = 28), level 2 (n = 2), and standard (n = 6) panels.



No. at risk	48	44	37	33	32	31	20	7	4	0
No. at risk by stage										
IA	10	9	8	7	7	7	4	2	0	0
IB	25	24	22	21	21	20	15	5	4	0
II	8	7	5	3	3	3	1	0	0	0
III	5	4	2	2	1	1	0	0	0	0

48	47	46	43	43	42	37	26	8	4	0
10	9	9	9	9	8	5	3	0	0	0
25	25	25	24	23	21	16	5	4	0	0
8	8	8	6	6	5	3	0	0	0	0
5	5	4	4	4	3	2	0	0	0	0

Figure 1 – Kaplan-Meier curves of disease-free survival (DFS) and overall survival (OS) for the overall population (n = 48) and stratified by postoperative stage (IA–III, TNM 8th edition).[6] Numbers at risk are shown below each curve.

compared with stage II-III. No statistically significant differences in DFS or OS were found between stages IA and IB or between EGFR mutation subtypes.

CLINICAL IMPLICATIONS

The clinical characteristics of our patients were consistent with the literature on EGFR-mutated NSCLC, with predominance of women, non-smokers, median age, exon 19 deletions and exon 21 *L858R* mutations, and mostly negative PD-L1 expression. One patient carried a rare exon 20 indel (p.Ser768_Val769delinsIleLeu), distinct from classical insertions, and has remained relapse-free.

All relapses occurred as stage IV disease, and, notably, two of 10 stage IA patients also relapsed, highlighting that recurrence risk persists in early stages. This aligns with French (n = 171) and Canadian (n = 156) cohorts, which reported early relapse rates of around 20% in stage IA–IB.[8,9]

Staging significantly influenced DFS and OS, in line with other real-world series. In our cohort, the five-year DFS was 84% (stage IB), 49% for stage II, and 20% for stage III, illustrating the prognostic impact of stage at diagnosis. Although ADAURA excluded stage IA and IIIB, our DFS and OS results were similar to its placebo arm, with a four-year DFS of 73%, 56%, and 32% for IB, II, and IIIA, respectively; OS was also comparable: 92% (IB), 63% (II), 60% (III) in our cohort versus 91%, 85%, and 66% in ADAURA.[5] In contrast, ADAURA patients treated with osimertinib achieved far superior four-year DFS (90% IB, 91% II, 88% IIIA) and OS (94% *vs* 73%), supporting adjuvant osimertinib as the current standard of care.

Relapse patterns are also relevant. Osimertinib's superior CNS penetration reduces brain metastases and improves intracranial control, which is critical given the high rate of CNS relapse, also observed in our study.[5]

Prognostic factors reported in other real-world cohorts also deserve consideration. In Singapore (n = 389), five-year DFS without adjuvant TKI was 37.2%, and adverse features included nonacinar or nonlepidic histology, sublobar resection, positive margins, and lymphovascular invasion,[10] while Canadian data linked uncommon EGFR mutations to worse four-year survival (56% *vs* 73% - 82%).[9] Beyond clinicopathologic factors, genomic, transcriptomic, and proteomic profiling may aid risk stratification and enable individualized adjuvant strategies.[11,12]

The retrospective design, single-center setting, small sample size, and absence of co-mutation or control group constitute the main limitations of this study. Nevertheless, it adds meaningful long-term real-world evidence from a Portuguese cohort, complementing the existing data from Western populations.

CONCLUSION

This real-world study highlights that relapse is common in resected EGFR-mutated NSCLC, even at early stages, and often involves extrathoracic spread associated with poor prognosis. Enhanced perioperative risk assessment and personalized adjuvant treatment strategies are promising to improve long-term outcomes.

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The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

IS, MC, ASV: Study design, data collection and analysis, writing of the manuscript.

MA: Data collection.

FF, ALM, DH, PA: Critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

FF received payment or honoraria from AstraZeneca for lectures, presentations, speakers' bureaus, manuscript writing or educational events; received support for attending meetings and/or travel from Takeda and Pharmamar.

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