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Primary Lung Cancer in Non-Smoking Women: A Retrospective Analysis at CHU Hassan II, Fez

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Abstract

Background: Lung cancer among female never-smokers constitutes a distinct clinicopathological entity with rising incidence. This study aims to characterize the epidemiological, histopathological, therapeutic, and outcome features of primary lung cancer in non-smoking women treated at CHU Hassan II, Fez.

Methods: A retrospective review was conducted of medical records of female never-smokers diagnosed with primary lung cancer between [insert study period]. Variables analyzed included age, histology, stage (according to the 8th edition TNM), treatment modalities, EGFR mutation status, and clinical outcomes.

Results: Mean age at diagnosis was 58 years (range: 28–82). Adenocarcinoma was predominant. At presentation, 62.9 % had metastatic disease, with brain involvement most common. Only 2.9 % had surgical resection; 22.9 % received curative chemoradiotherapy; 44.1 % received palliative radiotherapy. EGFR testing was conducted in 7 patients; 5 (71.4 %) were positive, and 3 received EGFR-targeted therapy. At median follow-up of 42 months: complete remission (2.9 %), partial remission (11.4 %), stable disease (17.1 %), progression (34.3 %), metastatic relapse (16 %), and 3-year mortality of 74.3 %.

Conclusion: Adenocarcinoma predominance and high EGFR mutation frequency corroborate global trends in never-smoking women with lung cancer. These findings highlight the need for molecular diagnostics, tailored therapy, and public health interventions for this demographic.

Keywords: Lung cancer; Never-smoker; Women; EGFR; Brain metastases; Radiotherapy; Morocco.

1. Introduction

Lung cancer in never-smokers (LCINS) represents a clinically distinct entity, more frequent in women and typically adenocarcinoma. [1,2] Recent population data show a substantial share of newly diagnosed lung cancers occur in never-smokers, particularly among women. [3] Established risks in never-smokers include secondhand smoke, indoor air pollution (e.g., cooking oil fumes), and radon. [4–6] Biologically, oncogenic drivers are common; EGFR mutations are enriched in female never-smokers with adenocarcinoma. [7] Modern EGFR-TKIs markedly improve systemic and intracranial control, yet access and testing gaps persist in many regions. [8,9,10] We describe the clinicopathologic features, management, and outcomes of female never-smokers treated for primary lung cancer at our institution, and contextualize findings with current evidence.

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2. Methods

Design and setting. Retrospective cohort from a single tertiary radiotherapy department. Consecutive *female* patients with primary lung cancer and **never-smoker** status (lifetime <100 cigarettes) were included. Data were abstracted from charts, radiology, radiotherapy plans, and multidisciplinary notes.

Data collected. Age, histology, stage at presentation, sites of metastases (notably brain), treatment intent and modalities (chemotherapy, radiotherapy details, surgery), molecular testing (EGFR), response, relapse, and survival status at ~3 years.

Definitions. Staging followed the **8th edition TNM** classification. [11] "Curative-intent chemoradiotherapy (CRT)" denotes thoracic external-beam radiotherapy (RT) with concurrent chemotherapy for stage III disease; "palliative RT" denotes symptom-directed RT (e.g., bone, brain, thoracic airway/hemoptysis). Radiological response categories reflect standard clinical practice (complete/partial response, stable/progressive disease).

Ethics. Study used de-identified retrospective data consistent with local oversight requirements.

3. Results

3.1. Patient characteristics

Thirty-five women met criteria (mean age 58 years; range 28–82). Adenocarcinoma predominated. At diagnosis, **22/35 (62.9%)** had de-novo metastatic (stage IV) disease; **13/35 (37.1%)** had non-metastatic disease. Brain was the most frequent metastatic site among stage IV cases (Figure 1).

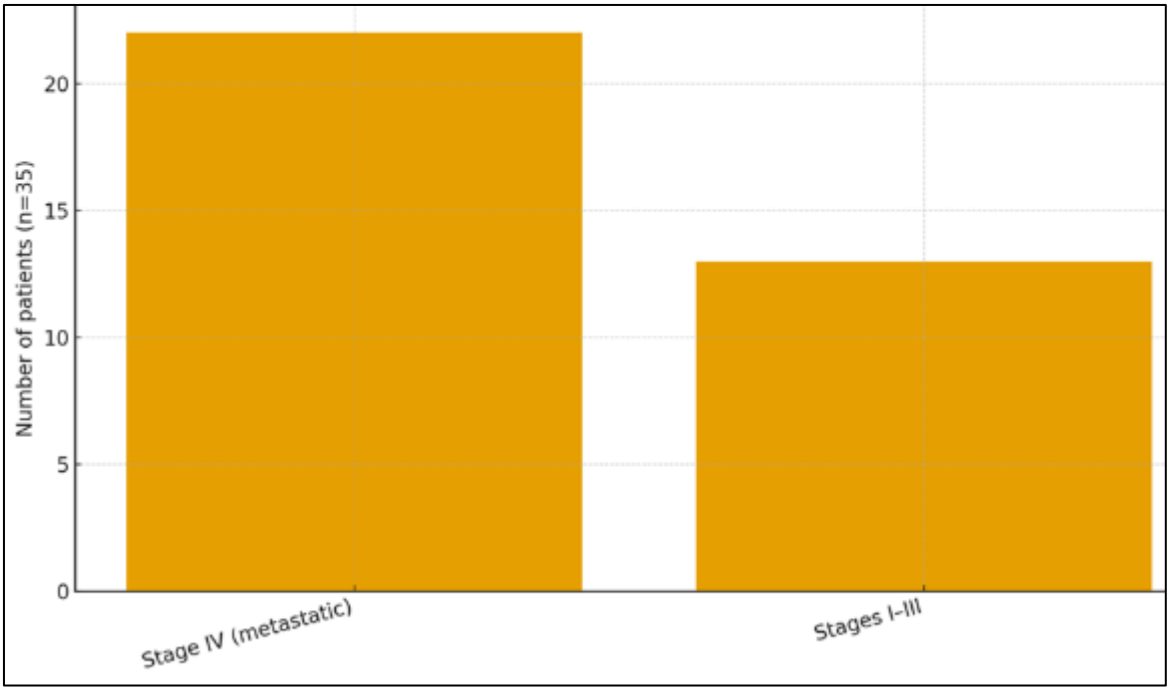

Figure 1 Baseline stage distribution (n=35); the X-axis represents cancer stage, and the Y-axis represents the number of patients.

3.2. Treatment patterns (Figure 2)

Management was heterogeneous and often multimodal:

- **Chemotherapy only: ~19/35 (55%)** received systemic therapy without RT.
- **Palliative RT: ~15/35 (44.1%)** received RT for symptom control (modalities included cranial and extracranial sites).

- **Curative-intent CRT (thoracic): 8/35 (22.9%)** treated definitively.
- **Surgery: 1/35 (2.9%)** underwent resection.

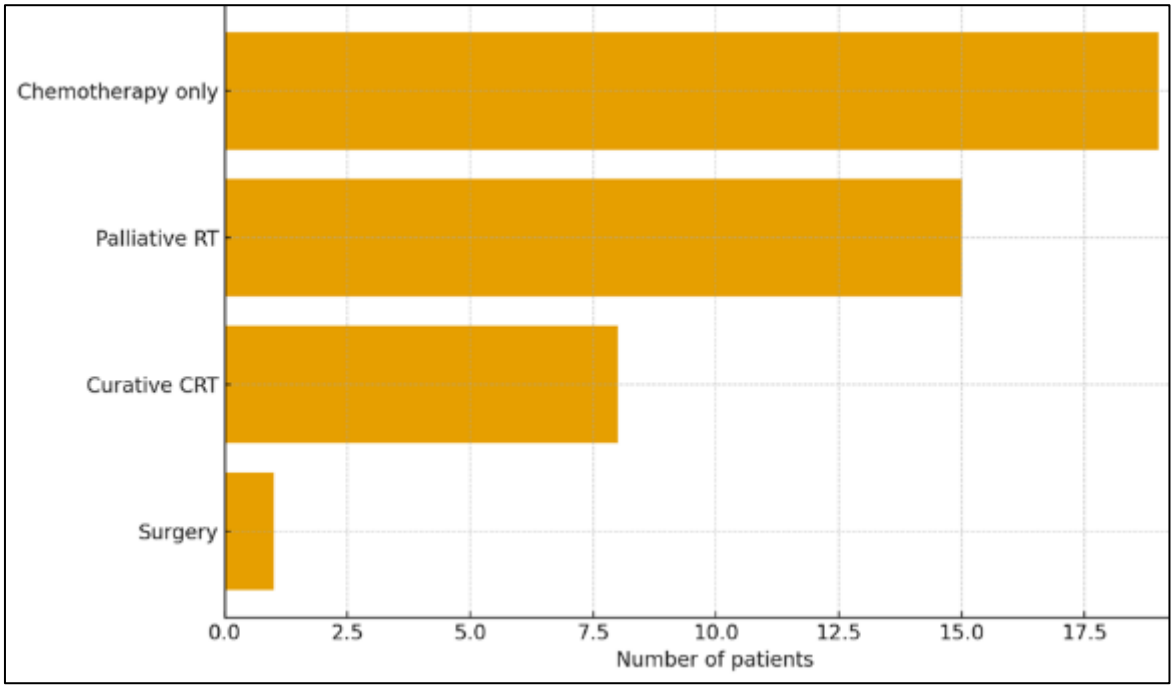

Figure 2 Treatment modalities. The X-axis represents the number of patients and the Y-axis represents the treatment modality.

3.3. Molecular testing and targeted therapy

EGFR testing was performed in **7/35** (20%); **5/7** (71%) were mutation-positive. **Three** EGFR-positive patients received TKIs (Figure 3A & 3B).

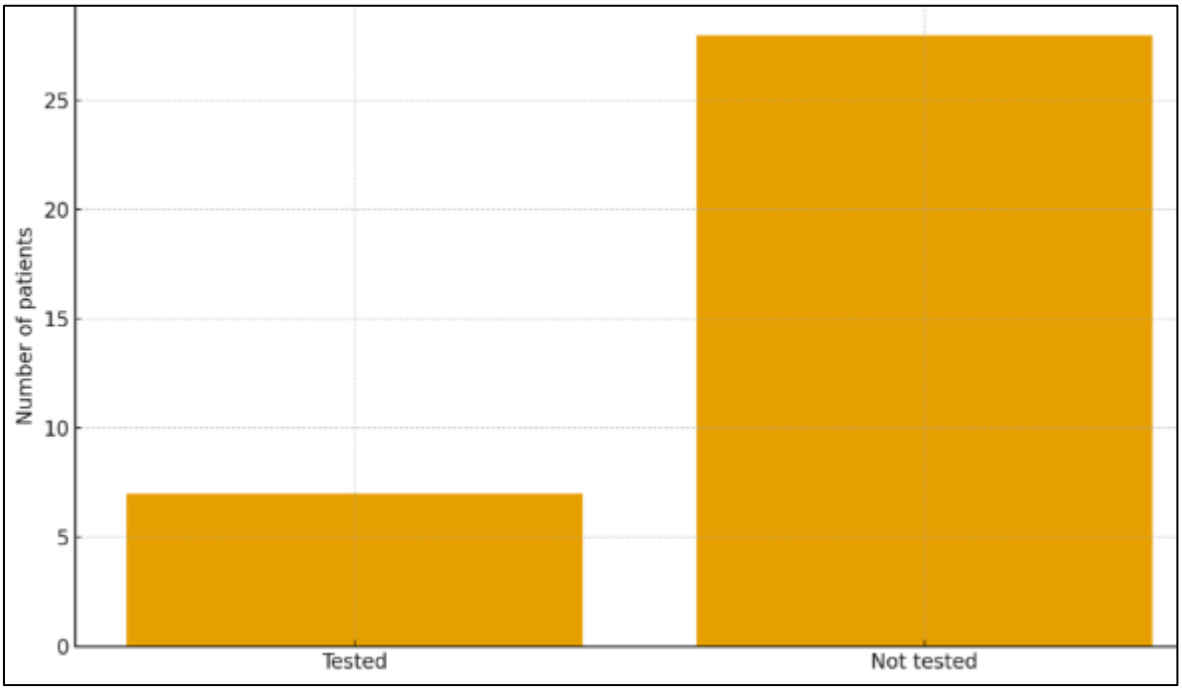

Figure 3A EGFR testing uptake

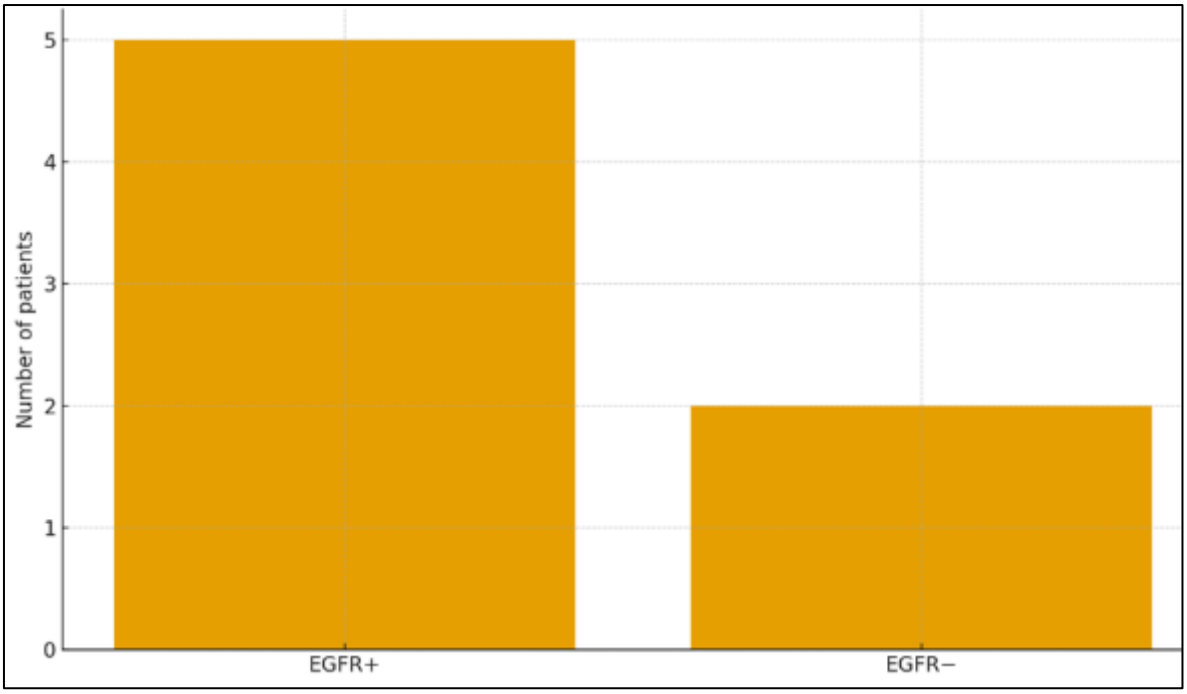

Figure 3B EGFR mutation results

3.4. Response and outcomes

Best radiologic response across the cohort: complete response 1/35 (2.9%), partial response 4/35 (11.4%), stable disease 6/35 (17.1%), progressive disease 12/35 (34.3%). Metastatic relapse occurred in ~6/35 (16%) during follow-up (mean 42 months). Three-year mortality was 26/35 (74.3%) (Figure 4).

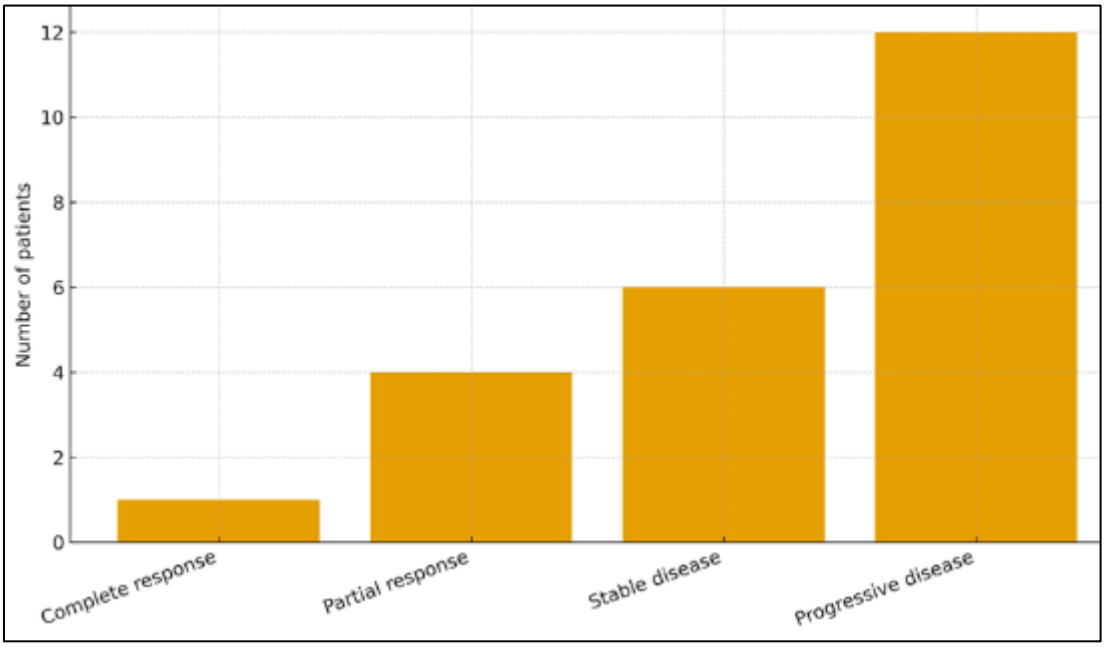

Figure 4 Best radiologic response

4. Discussion

Our cohort illustrates hallmark features of LCINS in women: adenocarcinoma histology, advanced stage at diagnosis, frequent cerebral metastases, and under-utilization of EGFR testing despite high positivity when performed. These observations are concordant with prior reviews that frame LCINS as a distinct entity with female predominance and adenocarcinoma pathology [1,2]. Population-level analyses likewise confirm a meaningful burden of lung cancer among never-smokers—particularly women—highlighting the limitations of relying solely on smoking history to prompt screening and clinical suspicion [3].

Environmental exposures plausibly contribute to disease risk in never-smokers, and several factors are especially relevant in many domestic and occupational settings. A recent systematic review and meta-analysis from 2024 associates secondhand smoke exposure with an elevated risk of lung cancer in never-smokers [4]. In parallel, cooking oil fumes—an exposure common in poorly ventilated kitchens—have been repeatedly linked to increased risk among women [5]. Residential radon remains another established risk, with a clear dose–response relationship demonstrated even in never-smokers [6]. Collectively, these data reinforce the need for public-health measures—improved ventilation, clean-cooking strategies, and radon mitigation—alongside heightened clinical vigilance.

Molecular profiling is essential for optimal care. In our series, only 20% of patients underwent EGFR testing, yet 71% of those tested were positive, mirroring meta-analytic estimates that EGFR mutations are enriched among never-smokers and women with adenocarcinoma [7]. Given the transformative impact of osimertinib (FLAURA) on progression-free and overall survival, including superior CNS control, systematic upfront genotyping and reliable access to TKIs are critical quality-of-care levers [8]. Importantly, clinical selection (never-smoker, female sex, adenocarcinoma histology) can enrich pretest probability but cannot substitute for genotyping; the IPASS trial underscores the hazards of treating by clinical phenotype alone rather than by molecular status [9].

Brain metastases were common at presentation in our stage IV cases, aligning with literature that oncogene-driven NSCLC (e.g., EGFR/ALK) exhibits a higher propensity for CNS involvement [10]. For patients with poor prognosis who are unsuited to focal therapy, the QUARTZ randomized trial showed no survival or quality-of-life benefit from adding whole-brain radiotherapy (WBRT) to optimal supportive care, supporting a selective approach to WBRT [12]. When WBRT is indicated, memantine reduces cognitive decline and should be used when feasible [13]. In parallel, targeted agents with robust CNS activity—such as osimertinib—should be prioritized and integrated with focal radiotherapy as needed, rather than defaulting to WBRT [10,12,13].

Finally, the implications for our setting are clear. The combination of late presentation, limited molecular testing, and constrained access to TKIs likely contributed to modest response rates and high three-year mortality [7–10]. Pragmatic improvements—reflex testing for EGFR (and ALK/ROS1 where possible), streamlined tissue acquisition and reporting pathways, and assured availability of CNS-active TKIs—could meaningfully improve outcomes in resource-constrained environments [12,13].

4.1. Limitations

Retrospective single-centre design; small sample; incomplete granularity for some variables; potential overlap across treatment categories (e.g., palliative RT and chemotherapy). Nonetheless, the data reflect “real-world” practice and highlight actionable gaps.

5. Conclusion

Female never-smokers with lung cancer in our cohort frequently presented with metastatic disease—often to the brain—and experienced poor survival. EGFR testing was under-utilized despite a high positivity rate among those tested. Systematic molecular profiling and access to modern TKIs (with CNS activity) should be core components of care, alongside selective and neurocognitively mindful radiotherapy strategies.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest.

Statement of informed consent

This retrospective study was approved by the institutional review board of Hassan II University Hospital, which waived the requirement for informed consent due to anonymized data collection. The study adhered to the principles of the Declaration of Helsinki.

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