Original Article

Impact of radiological follow-up frequency on resected lung cancer: a propensity score matching analysis

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Background: Despite advances in lung cancer treatment and the subsequent improvement in oncological outcomes, the optimal frequency of radiological follow-up remains unclear. Current recommendations lack consensus and do not consider individual patient characteristics and tumor factors. This study aimed to examine the impact of radiological follow-up frequency on oncological outcomes following lung cancer resection.

Methods: A prospective multicenter study, involving patients who underwent anatomical lung resection in the GEVATS database between December 2016 and March 2018. The relationship between surveillance frequency and oncological outcomes was evaluated. Two groups were established based on follow-up frequency: low frequency (LF) and high frequency (HF). Subgroup analyses were performed based on tumor stage, histology, lymphadenectomy, and adjuvant therapy. Propensity score matching (PSM) was applied to balance the groups.

Results: A total of 1,916 patients were included in the study, LF 444 (23.17%), HF 1,472 (76.83%). Factors associated with HF surveillance included higher stage, adjuvant chemotherapy and adjuvant radiotherapy. Subanalyses were performed after PSM for various factors, revealing significant differences between LF and HF groups in cancer-specific survival among who received adjuvant therapy {LF 53.021 months [95% confidence interval (CI): 48.622–57.421] *vs.* HF 58.836 months (95% CI: 55.343–62.330); HR 0.453, 95% CI: 0.242–0.849; P=0.013}, as well as overall survival for patients with squamous cell carcinoma [LF 54.394 months (95% CI: 51.424–57.364) *vs.* HF 61.578 months (95% CI: 59.091–64.065); HR 0.491, 95% CI: 0.299–0.806; P=0.005] and those who received adjuvant therapy LF 50.176 months [95% CI: 45.609–54.742) *vs.* HF 57.189 months (95% CI: 53.599–60.778); HR 0.503, 95% CI: 0.293–0.865; P=0.013].

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*, the Spanish Video-Assisted Thoracic Surgery Group (GEVATS) (available at https://cdn.amegroups.cn/static/public/JTD-23-1973-Supplementary.pdf).

Conclusions: Findings suggest that high-frequency surveillance only improves survival outcomes in lung cancer patients who received adjuvant treatment or had squamous cell carcinoma. Therefore, future guidelines for lung cancer follow-up should consider individualizing the frequency of radiological surveillance based on patients' risk profiles.

Keywords: Lung cancer; radiological surveillance; oncological outcomes; follow-up

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Introduction

Surgical resection remains the standard treatment for early-stage lung cancer in patients with good cardiopulmonary functional status, often accompanied by systemic therapies and/or radiotherapy depending on tumor stage (1).

Despite curative-intent treatment, the five-year survival rate for these patients' post-surgical resection varies from 41% to 90% according to pathological stage (1). Indeed, it exists a high risk of recurrent disease development, up to 40% in locally advanced stages (2) and a cumulative risk of up to 20% at 10 years for the development of a second primary lung cancer (3).

Globally, the increasing prevalence of lung cancer survivors and other malignancies incurs substantial economic costs, with projections showing an ongoing escalation of these expenses (4). However, not all cancer survivors require the same medical care or oncological follow-up, as this depends on multiple factors such as the specific type of malignancy, age at diagnosis, previous comorbidity, types, and duration of treatment received, genetic factors, and lifestyle behaviors. In recent years, leading organizations such as the American Cancer Society (ACS) and the American Society of Clinical Oncology (ASCO) have suggested the gradual development of personalized oncological follow-up recommendations that take into account the individual needs of the patient (5-7). This personalized approach could not only improve oncological outcomes for patients but also optimize the use of healthcare resources.

Specifically, the oncological follow-up of patients with resected lung cancer is fundamentally clinical and radiological because, despite the described utility of blood biomarker determination in other solid tumors, in lung cancer there is not enough evidence to support its routine use as a method of oncological follow-up (8,9).

Concerning radiological imaging tests, computed tomography (CT) has become the standard radiological test in the oncological follow-up of patients surgically treated for lung cancer, given the need to diagnose early cases of recurrence or the appearance of a second primary lung cancer to establish early treatment and thus increase the survival rate (10).

However, there are multiple recommendations for radiological follow-up frequency for these types of patients depending on the institution or society involved, but not on the individual characteristics of the patient and the tumor, most of them based on low-level evidence (11). The American College of Chest Physicians (CHEST), European Society of Medical Oncology (ESMO), National

Highlight box

Key findings

- This study examines the impact of radiological follow-up frequency on oncological outcomes after lung cancer resection. No significant differences in oncological outcomes were found between high-frequency and low-frequency follow-up groups overall. However, subgroups of patients who benefited from close radiological follow-up were identified.

What is known and what is new?

- Current recommendations for radiological follow-up in lung cancer patients vary widely, but there's limited evidence on the optimal frequency.
- This study adds novel insights by suggesting that intensive radiological surveillance might not be necessary for most surgically treated lung cancer patients.

What is the implication, and what should change now?

- Individualized surveillance regimens based on patient risk profiles should be considered to optimize oncological outcomes and reduce healthcare costs.
- Further research is needed to confirm these findings and develop evidence-based follow-up strategies tailored to each patient's needs.

Comprehensive Cancer Network (NCCN), ASCO, or the Spanish Society of Thoracic Surgery (SECT) recommend different surveillance intensities that vary from quarterly to annually (12-16). This follow-up frequency is maintained during the first 2 or 3 years after resection, during which the risk of recurrence is higher; and generally adopting annual surveillance as the subsequent follow-up frequency; which seems to be sufficient in intensity and similar to the recommended frequency for detecting second primary lung neoplasms in high-risk patients, as shown by the results of the National Lung Screening Trial (17).

Furthermore, we must balance the benefits of close long-term CT monitoring with the inherent drawbacks of an excessive frequency of follow-up, such as the appearance of false positives, unjustified invasive procedures, psychological stress, cumulative radiation risks, and increased healthcare costs (18).

Recent studies suggest that more frequent postoperative radiological surveillance using CT after lung cancer resection is not associated with improved oncological outcomes in patients in early stages (19-21). In our study, we hypothesize that closer radiological surveillance is not associated with better oncological outcomes after surgical resection for lung cancer globally, but rather these favorable outcomes from close radiological follow-up will depend on factors related to the patient and the tumor. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1973/rc).

Methods

GEVATS (22) database was designed as a multicenter cohort study to record all anatomical lung resections performed within each participating (33 Spanish thoracic surgery departments) over 15 months (12/20/2016-03/20/2018) and their oncological follow-up, with completion on 09/15/2022. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Clinical Research Ethics Committee of University Clinical Hospital of Valladolid (No. CASVE-PS-16-273). All participating hospitals/institutions were informed and agreed the study. Informed consent was obtained from the recruited patients to use their clinical data for scientific purposes.

The information was stored in a database that included 283 variables structured across the following five blocks: baseline characteristics, staging and pathological diagnosis, surgical procedure, postoperative morbimortality and oncological follow-up. All variables were adapted according to the standards published by the Society of Thoracic Surgeons (STS) and the European Society of Thoracic Surgeons (ESTS) (23).

The inclusion criteria were undergoing complete surgical resection of non-small cell lung cancer and participating in the follow-up program. Clinical and pathological stages were defined in accordance with the American Joint Committee on Cancer staging manual (24). Surgical treatment included parenchymal resection and mediastinal lymphadenectomy. Adjuvant treatments were indicated at the discretion of each center tumor board. Oncological follow-up using CT was reported at 3-month intervals until completing a 4-year follow-up or until the patient experienced relapse or death. The radiological follow-up provided to each patient was directly dependent on the specific follow-up protocols of each participating hospital center and on the physician responsible for such follow-up (oncologists, general practitioners, pulmonologists or thoracic surgeons). Dates of local or distant recurrence, disease-free intervals, and specific or overall mortality were reported.

Bilateral surgical procedures and those performed on patients younger than 18 years old were excluded. Patients for whom there were no data on the type of lung resection, patient discharge status, no surveillance testing, or those who had histology different from lung cancer, had residual tumor, recurred or died within the first 90 days, or those lost to follow up were excluded. The quality of the collected data was established through an internal audit by the members of the Scientific Committee of GEVATS (22).

We evaluated the relationship between surveillance frequency (quantifying the number of computed tomography scans and their density over time) and disease-free interval (DFI), overall and cancer-specific survival. A binary classification of oncological follow-up frequencies using CT has been adopted: low (LF) and high frequency (HF) groups. This methodological decision is based on the lack of an international consensus concerning the optimal frequency of radiological follow-up. Grouping follow-up frequencies into two general categories of HF and LF has allowed for a more structured comparison of data, facilitating analysis and the identification of patterns among different frequency groups while aligning with clinical practice and the recommendations of leading societies.

- LF group:
  - Patients who did not receive a CT scan every six

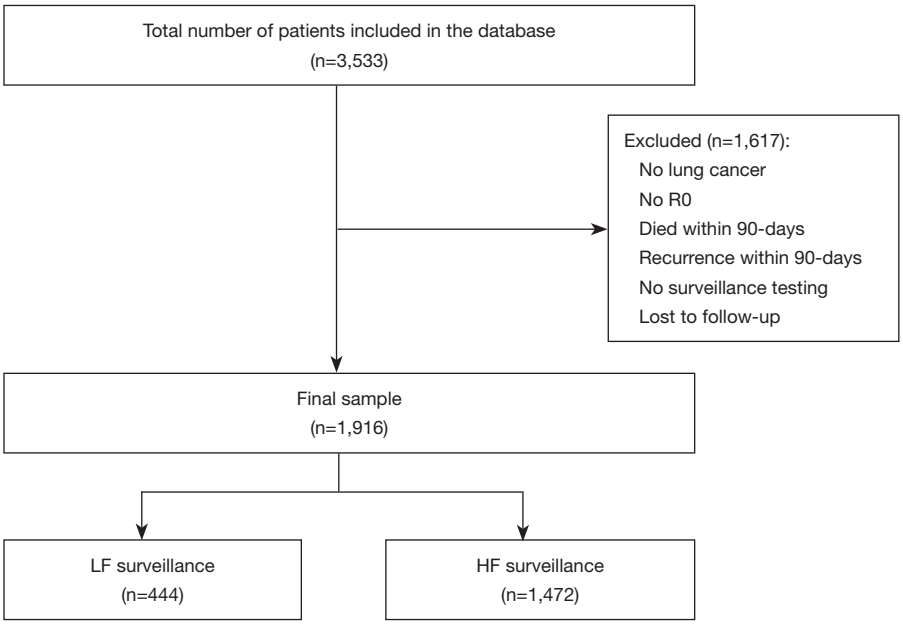

Figure 1 Flowchart of patient selection for the analysis of the total number of patients in the GEVATS database. HF, high frequency; LF, low frequency; GEVATS, Spanish Video-Assisted Thoracic Surgery Group.

months in the first two years.
- Patients who did not have an annual CT scan in the subsequent two years.

❖ HF group:
- Patients who received one or more CT scans every six months in the first two years.
- Patients who had at least one CT scan annually in the subsequent two years.

Analysis of disease-free interval and specific and overall survival were performed by subgroups: Stages, histology, lymphadenectomy (defined as obtaining a representative sample of lymph node from three or more stations during surgery, always including station 7) and adjuvant therapy. Sub-analysis of disease-free interval and specific and overall survival were performed after matching both LF and HF groups for the variables: stage, histology, and adjuvant therapy.

Statistical analysis

Categorical variables were presented as absolute and relative frequency, while continuous variables were presented as mean and standard deviation. Statistical analysis included Pearson's chi-square test, Student's T-test for independent samples, Kaplan-Meier survival analysis, Log-rank test, and Cox regression. Propensity score analysis was conducted using the "matchit" function with "method=nearest". IBM SPSS Statistics 24.0 (Chicago, IL, USA) and R Studio software were used for analysis., considering P values <0.05 significant.

Results

A total of 3,533 anatomical lung resections were recruited between December 2016 and March 2018.

A total of 1,916 patients who met the inclusion criteria were identified. Of these patients, 444 (23.17%) belonged to the LF follow-up group, and 1,472 (76.83%) belonged to the HF follow-up group (*Figure 1*).

Demographic, clinical, and therapeutic characteristics, as well as univariate analysis on their influence on closer follow-up, can be found in *Table 1*. Univariate analysis revealed that patients with a more advanced tumor stage (P=0.03) and those who received adjuvant treatment (P=0.001), specifically chemotherapy (P=0.001) and radiotherapy (P=0.001), were more likely to have closer follow-up.

Using multivariate models, no statistically significant differences were found between the two groups regarding disease-free interval {LF 51.434 months [95% confidence interval (CI): 49.413–53.445] *vs.* HF 49.474 months (95% CI: 48.139–50.809); HR 1.116, 95% CI: 0.926–1.344;

Table 1 Univariate analysis of demographic, clinical, and therapeutic characteristics between the LF and HF groups

Characteristics	Global	LF group	HF group	P value
Age (years)	65.46±9.84	65.45±9.59	65.47±9.92	0.97
Gender				0.98
Male	1,328 (69.31)	308 (69.37)	1,020 (69.29)	
Female	588 (30.69)	136 (30.63)	452 (30.71)	
BMI (kg/m^2)	26.99±4.71	27.04±4.42	26.97±4.8	0.79
Tobacco habit				0.92
Never	248 (12.94)	61 (13.74)	187 (12.7)	
Ex-smoker 1–12 months	808 (42.17)	187 (42.12)	621 (42.19)	
Ex-smoker >12 months	270 (14.09)	65 (14.64)	205 (13.93)	
Current smoker	568 (29.65)	127 (28.6)	441 (29.96)	
Unknown	22 (1.15)	4 (0.9)	18 (1.22)	
High blood pressure (yes)	890 (46.5)	218 (49.1)	672 (45.71)	0.21
Heart failure (yes)	48 (2.51)	11 (2.48)	37 (2.51)	0.97
Ischemic heart disease (yes)	178 (9.29)	50 (11.26)	128 (8.7)	0.10
Arrhythmia (yes)	163 (8.51)	36 (8.13)	127 (8.63)	0.74
Stroke (yes)	96 (5.01)	18 (4.05)	78 (5.3)	0.29
Diabetes mellitus (yes)	375 (19.58)	94 (21.17)	281 (19.1)	0.34
FEV1 (%)	87.83±19.96	87.23±19.71	88±20.04	0.48
DLCO (%)	81.83±20.62	81.13±21.17	82.04±20.46	0.46
ASA classification				0.48
1	45 (2.36)	8 (1.8)	37 (2.52)	
2	842 (44.08)	186 (41.89)	656 (44.75)	
3	989 (51.78)	243 (54.73)	746 (50.89)	
4	34 (1.78)	7 (1.58)	27 (1.84)	
Chemotherapy induction (yes)	124 (6.47)	29 (6.53)	95 (6.45)	0.95
Tumour histology				0.86
ADC	1,065 (55.79)	245 (55.68)	820 (55.82)	
SCC	586 (30.7)	137 (31.14)	449 (30.57)	
TC	105 (5.5)	23 (5.23)	82 (5.58)	
AC	23 (1.2)	3 (0.68)	20 (1.36)	
LCNEC	52 (2.72)	11 (2.5)	41 (2.79)	
SCLC	14 (0.73)	4 (0.91)	10 (0.68)	
Undifferentiated	31 (1.62)	10 (2.27)	21 (1.43)	
Others	33 (1.73)	7 (1.59)	26 (1.77)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Global	LF group	HF group	P value
Tumour size				0.15
T1a	177 (9.4)	38 (8.82)	139 (9.57)	
T1b	435 (23.1)	110 (25.52)	325 (22.38)	
T1c	263 (13.97)	74 (17.17)	189 (13.02)	
T2a	512 (27.19)	104 (24.13)	408 (28.1)	
T2b	156 (8.28)	33 (7.66)	123 (8.47)	
T3	230 (12.21)	48 (11.14)	182 (12.53)	
T4	103 (5.47)	21 (4.87)	82 (5.65)	
Tis	3 (0.16)	2 (0.46)	1 (0.07)	
Tx	4 (0.21)	1 (0.23)	3 (0.21)	
Lymph node involvement				0.059
N0	1,467 (77.91)	327 (75.87)	1,140 (78.51)	
N1	223 (11.84)	50 (11.6)	173 (11.91)	
N2	191 (10.14)	52 (12.06)	139 (9.57)	
N3	1 (0.05)	1 (0.23)	0 (0)	
Nx	1 (0.05)	1 (0.23)	0 (0)	
Lymphadenectomy (yes)	1,343 (70.09)	309 (69.59)	1,034 (70.24)	0.79
Tumor stage				0.03
Carcinoma *in situ*	3 (0.16)	0 (0)	3 (0.21)	
IA1	156 (8.33)	33 (7.73)	123 (8.51)	
IA2	378 (20.18)	100 (23.42)	278 (19.23)	
IA3	225 (12.01)	61 (14.29)	164 (11.34)	
IB	381 (20.34)	71 (16.63)	310 (21.44)	
IIA	108 (5.77)	22 (5.15)	86 (5.95)	
IIB	311 (16.6)	65 (15.22)	246 (17.01)	
IIIA	253 (13.51)	54 (12.65)	199 (13.76)	
IIIB	58 (3.1)	21 (4.92)	37 (2.56)	
Adjuvant chemotherapy (yes)	629 (32.83)	82 (18.47)	547 (37.16)	<0.001
Adjuvant targeted therapy (yes)	41 (2.14)	6 (1.35)	35 (2.38)	0.19
Adjuvant radiotherapy (yes)	191 (9.97)	23 (5.18)	168 (11.41)	<0.001
Adjuvant treatment (yes)	678 (35.5)	89 (20.09)	589 (40.15)	<0.001
Recurrence (yes)	663 (33.9)	144 (31.6)	519 (34.7)	0.22
Recurrence type				0.76
Distant	267 (40.3)	58 (40.6)	209 (40.3)	
Loco-regional	309 (46.7)	69 (48.3)	240 (46.2)	
Mixed	86 (13.0)	16 (11.2)	70 (13.5)	

Data are presented as mean ± SD or n (%). LF, low frequency; HF, high frequency; BMI, body mass index; FEV1, forced expiratory volume in one second; DLCO, carbon monoxide diffusion capacity; ASA, American Society of Anesthesiologists; ADC, adenocarcinoma; SCC, squamous-cell carcinoma; TC, typical carcinoid; AC, atypical carcinoid; LCNEC, large cell neuroendocrine lung carcinoma; SCLC, small cell lung cancer; SD, standard deviation.

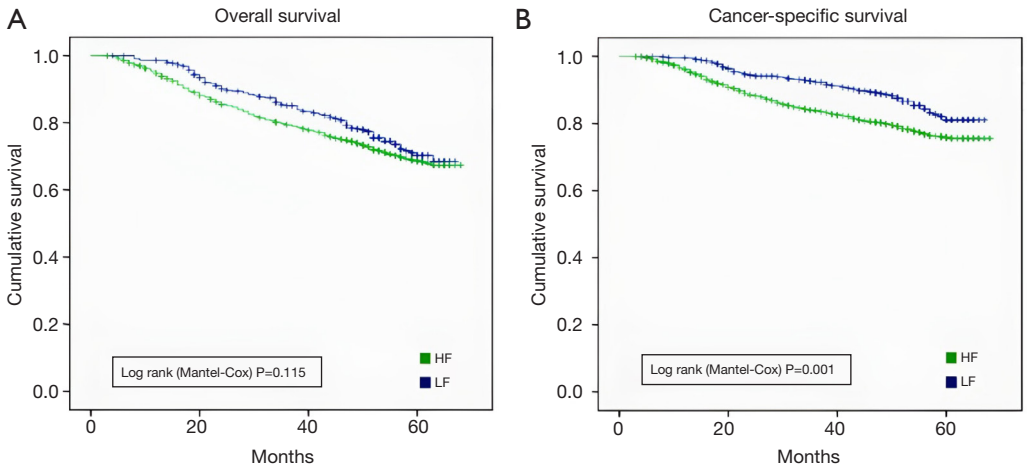

Figure 2 Overall survival (A) and cancer-specific survival (B) by the Kaplan-Meier method, log-rank test, and Cox regression method of HF and LF groups. HF, high frequency; LF, low frequency.

P=0.25}. In survival analysis, no significant differences were found concerning overall survival [LF 57.753 months (95% CI: 56.178–59.329) *vs.* HF 55.791 months (95% CI: 54.751–56.832); HR 1.18, 95% CI: 0.960–1.452; P=0.12]; whereas statistically significant differences were demonstrated between both groups in relation to cancer-specific survival [LF 61.762 months (95% CI: 60.492–63.033) *vs.* HF 58.523 months (95% CI: 57.555–59.491); HR 1.590, 95% CI: 1.210–2.096; P=0.001] (*Figure 2*).

Subanalysis was performed, and no significant differences were found in disease-free interval, cancer-specific survival, and overall survival between both follow-up groups regarding different tumor stages, histological types, or the presence of adjuvant treatment.

A propensity score matching was performed by pairing for the variables tumor stage, histology, lymphadenectomy, and adjuvant therapy, resulting in a final sample of 852 matched patients. After the analysis of the balanced groups, statistically significant differences were observed between the LF and HF groups in the subanalysis of cancer-specific survival only in those patients who received adjuvant therapy [LF 53.021 months (95% CI: 48.622–57.421) *vs.* HF 58.836 months (95% CI: 55.343–62.330); HR 0.453, 95% CI: 0.242–0.849; P=0.01] and in the analysis of overall survival only for those patients with squamous cell carcinoma [LF 54.394 months (95% CI: 51.424–57.364) *vs.* HF 61.578 months (95% CI: 59.091–64.065); HR 0.491, 95% CI: 0.299–0.806; P=0.01] or those who had received adjuvant treatment [LF 50.176 months (95% CI: 45.609–54.742) *vs.* HF 57.189 months (95% CI: 53.599–60.778); HR 0.503, 95% CI: 0.293–0.865; P=0.01] (*Figure 3*).

Discussion

As inferred from the results of our study, no statistically significant differences were found between HF and LF radiological follow-up groups in terms of overall survival and disease-free interval in patients with surgically treated lung cancer. However, significant differences were found concerning cancer-specific survival, with the LF follow-up group exhibiting greater survival. Initially, it was noted that this LF group significantly comprised patients in earlier stages.

Subgroup analysis could suggest that patients who underwent lung cancer surgery with factors associated with worse oncological outcomes, such as insufficient surgical sampling of lymph nodes (25,26) or the presence of advanced tumor stage, might benefit from a more intensive surveillance strategy. Nevertheless, in our study, we did not find any statistically significant differences in various subgroup analyses, including the tumor stage or the presence of adequate systematic lymphadenectomy, concerning the impact of a close radiological follow-up frequency on the improvement of oncological outcomes.

These results suggest that close radiological follow-up may not be necessary for the overall population of patients with resected lung cancer and are consistent with recent studies demonstrating that there is no survival benefit with an increase in the frequency of radiological follow-up in early stages (19,20) or when is conducted on a widespread

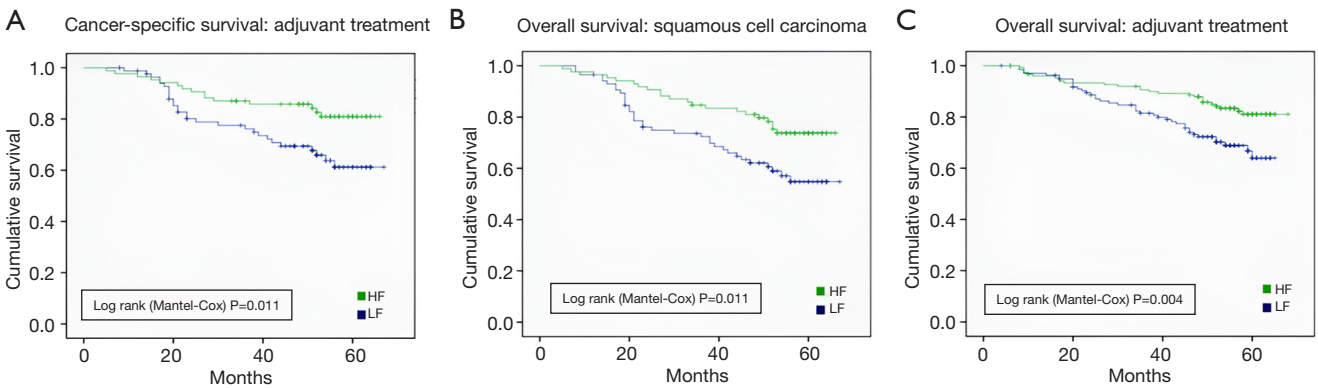

Figure 3 Subanalysis of cancer-specific survival (A) in adjuvant treatment and overall survival in squamous cell carcinoma (B) and adjuvant treatment (C) using the Kaplan-Meier method, log-rank test, and Cox regression method for the HF and LF groups after propensity score matching. HF, high frequency; LF, low frequency.

basis (21). There is no solid evidence at the current time to justify that intensive follow-up improves the survival of patients with lung cancer, as the studies analyzed present a complex heterogeneity of patients and frequencies of radiological follow-up (27). Studies on follow-up might lack the sensitivity required to detect that an early radiological diagnosis of recurrent and/or metastatic disease has an impact on survival, likely due to universally poor outcomes among patients with tumor relapse (18,28).

The improvement of lung cancer treatments and their consequent enhancement of oncological outcomes (29) could lead to a more detailed analysis of the impact of follow-up frequency on the survival of resected lung cancer patients in the future.

Nevertheless, our study should be considered a starting point for the need to individualize radiological follow-up frequency among patients with surgically treated lung cancer, as HF surveillance didn't seem beneficial for the average patient, but our study reports that this HF follow-up did indeed improve survival outcomes in those patients who had received adjuvant treatment or had a squamous cell carcinoma. Other groups following this direction have highlighted the need to define new evidence-based surveillance strategies to enhance diagnostic yield, such as implementing a HF radiological follow-up in patients in stages IIIA or including unscheduled follow-up visits for symptomatic patients in oncological follow-up protocols (30).

Determining the optimal individual frequency of radiological surveillance during the survival period following cancer is a significant challenge, but we believe it is necessary to redesign patient-centered surveillance regimens that optimize the benefits of such intervention and weigh the secondary risks and economic costs of such medical care (31).

It is essential to emphasize that our findings should not be interpreted as a recommendation to weaken oncological follow-up in most patients with surgically treated lung cancer, but rather as a recommendation for the need to individually evaluate the radiological follow-up frequency depending on each patient's risk profile. Additional studies are needed to confirm these findings, as this study presents several limitations that should be considered when interpreting its results.

In the course of this discussion, it is critical to acknowledge that our study was conducted within Spain's public health system, where the individual economic status of the patient does not play as limiting a role as it might in other countries, due to universal healthcare coverage. Such conditions may render the applicability and interpretation of our findings in environments where healthcare access is significantly affected by individual economic capabilities.

As an observational study, causal relationships between surveillance frequency and oncological outcomes cannot be established, and despite using propensity score analysis to adjust baseline differences between both groups, uncollected confounding factors may exist. Furthermore, in our study, patients lost to follow-up were excluded, which could introduce selection bias. These limitations do not invalidate the study's findings but should be considered when applying its results in clinical practice. Despite the aforementioned limitations, the implementation of a relatively short recruitment period 15 months helps mitigate the impact of confounding factors and effect modifiers that may arise over extended periods.

Conclusions

In summary, our findings indicate that only a selected minority of patients with surgically treated lung cancer benefit from more frequent radiological follow-up, suggesting that decreasing the recommended follow-up frequency could be a viable option for most of these patients. Designing individualized surveillance regimens based on each patient's risk/benefit profile should be a priority research objective for healthcare professionals involved in lung cancer follow-up.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1973/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1973/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1973/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Clinical Research Ethics Committee of University Clinical Hospital of Valladolid (No. CASVE-PS-16-273). All participating hospitals/institutions were informed and agreed the study. Informed consent was obtained from the recruited patients to use their clinical data for scientific purposes.

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