JCS Journal of Chest Surgery
https://doi.org/10.5090/jcs.23.166
pISSN: 2765-1606 eISSN: 2765-1614
J Chest Surg. 2024;57(5):440-446

Clinical Research

Potential Survival Benefit of Upfront Surgery for Lung Tumors Unconfirmed but Highly Suspicious for Stage I Lung Cancer

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ARTICLE INFO
Received November 29, 2023
Revised February 16, 2024
Accepted February 26, 2024

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Background: Patients with early-stage lung tumors that are highly suspicious for malignancy typically undergo a preoperative diagnostic workup, primarily through bronchoscopy or transthoracic biopsy. Those without a preoperative diagnosis may alternatively be treated with upfront surgery, contingent upon the potential for intraoperative diagnosis. Previous studies have yielded conflicting results regarding the impact of upfront surgery on the survival of these patients. Our study aimed to elucidate the effect of upfront surgery on the survival outcomes of patients undergoing surgery for early-stage lung cancer without a preoperative diagnosis.
Methods: We analyzed the survival rate of 158 consecutive patients who underwent pulmonary resection for stage I lung cancer, either with or without a preoperative diagnosis.
Results: A total of 86 patients (54%) underwent upfront surgery. This approach positively impacted both disease-free survival (p=0.031) and overall survival (p=0.017). However, no significant differences were observed across subgroups based on sex, smoking status, forced expiratory volume in 1 second, histologic tumor size, or histologic subtype. Univariate analysis identified upfront surgery (p=0.020), age (p=0.002), maximum standardized uptake value (SUVmax) exceeding 7 (p=0.001), and histological tumor size greater than 20 mm (p=0.009) as independent predictors. However, multivariate analysis indicated that only SUVmax greater than 7 (p=0.011) was a significant predictor of unfavorable survival.
Conclusion: Upfront surgery does not appear to confer a survival advantage in patients with stage I lung cancer undergoing surgical intervention.

Keywords: Lung carcinoma, Diagnosis, Video-assisted thoracoscopic surgery, Surgery

Introduction

Upfront surgery, defined as surgery without any preoperative treatment or procedure, is recommended for patients with early-stage lung tumors and for those presenting with highly suspicious solitary pulmonary nodules, provided that an intraoperative diagnosis can be made [1]. This approach avoids the additional costs and delays associated with obtaining cytohistological results, as well as the interventional risks and potential complications of these procedures. Likewise, bronchoscopy may be performed during the same surgical session in such cases; this is because preoperative bronchoscopy offers no diagnostic or therapeutic benefit for lung cancer, particularly with peripheral tumors. Furthermore, the pathological results of transthoracic biopsy typically do not alter the decision to proceed with surgical intervention for such tumors. Notably, preoperative diagnostic interventions—including transbronchial biopsy, computed tomography (CT)-guided transthoracic fine-needle biopsy, or CT-guided Tru-Cut biopsy—carry a risk of disrupting the tumor and causing dissemination.

The literature contains conflicting reports on the effect of upfront surgery on recurrence-free and overall survival in patients with early-stage lung cancer [2-6]. To explore the potential impact of upfront surgery on survival, we performed a retrospective study of patients with stage I lung cancer. Our statistical analysis focused on the clinico-

pathological features and survival outcomes of patients with early stage I lung carcinoma, specifically in relation to upfront surgery.

Methods

Patient cohort

A total of 158 patients with stage I primary lung cancer underwent either open or video-assisted thoracoscopic pulmonary resection at our thoracic surgery department between June 2007 and November 2018 (Fig. 1). The preoperative workup included thoracic CT, positron emission tomography, and brain magnetic resonance imaging. Some patients also underwent preoperative fiberoptic bronchoscopy and/or transthoracic needle aspiration biopsy for diagnostic purposes. We matched these patients (that is, individuals with a preoperative diagnosis of lung cancer) with participants who underwent surgery without prior diagnostic procedures. We then analyzed survival outcomes between the 2 groups. While some individuals underwent mediastinoscopy, all patients received systematic lymph node dissection.

Statistical analysis

Upfront surgery, age, sex, smoking status (in pack-years), forced expiratory volume in 1 second (FEV1, measured during pulmonary function tests), maximum standardized uptake value (SUVmax), histological tumor size, and histologic subgroup were considered as potential predictors of survival. Age, smoking status, FEV1, SUVmax, and histological tumor size were categorized into high and low groups based on the median values. The Kolmogorov-Smirnov test was utilized to assess the distribution of continuous data. Categorical variables were examined using the chi-square and Fisher exact tests, as appropriate, in contingency tables. The Student t-test was employed for the comparison of continuous variables. Cumulative survival rates were computed using the Kaplan-Meier method, and differences were evaluated with the log-rank test. To clarify the influence of clinicopathological factors and preoperative diagnosis on survival, we applied a Cox proportional hazards model for both univariate and multivariate analyses. A stepwise backward elimination process was used to derive a final reduced model. This was accomplished by discarding variables that did not reach statistical significance, as evidenced by a p-value below 0.1. Data were presented as mean±standard deviation. Otherwise, a p-value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were conducted using IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA).

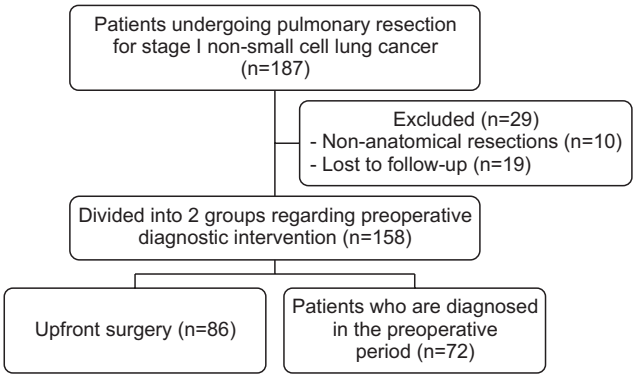

Fig. 1. Study cohort and exclusion criteria.

Ethical statements

This study was conducted in compliance with the ethical standards established by the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. This retrospective study received approval from the Ethics Committee of Istanbul University Medical Faculty, under the reference number 2021/2170. Written informed consent was obtained from all patients for their anonymized information to be stored in the hospital database and used for clinical research, as well as for its publication in this article.

Results

Clinicopathological features

The patient demographic consisted of 102 male (64.6%) and 56 female (35.4%) participants, with an average age of 59.7±10.4 years and a median age of 61 years (range, 15 to 82 years) (Table 1). Of these patients, 131 (82.9%) were smokers, with a mean smoking history of 40.2±23.2 pack-years and a median of 40 pack-years. Additionally, 25 patients (15%) had a history of cancer.

The mean radiological and histological tumor sizes at the greatest diameter were 20.5±6.3 mm and 21.3±7.6 mm, respectively. SUVmax data were available for 144 (91.1%) of the patients. The mean SUVmax as determined by fluorodeoxyglucose positron emission tomography-CT was 8.3±5.9, with a median of 7 (range, 0.6 to 46). The mean FEV1 across all patients was 2,437±664 mL, while the

https://doi.org/10.5090/jcs.23.166

Table 1. Comparison of disease-free and overall survival by clinicopathological features and the use of upfront surgery within variable subgroups

Variable	No.	No. of patients of upfront surgery (%)			Upfront surgery: 5-year DFS (%)			Upfront surgery: 5-year survival (%)		
		(+)	(-)	p-value	(+)	(-)	p-value	(+)	(-)	p-value
Total	158	86 (54)	72 (46)		85	68	**0.031**	87	77	**0.017**
Age (yr)										
≤61	83	50 (60)	33 (40)		87	69	0.083	91	82	0.285
>61	75	36 (48)	39 (52)	0.150	82	68	0.217	82	72	0.044
Sex										
Male	102	55 (54)	47 (46)		80	68	0.242	84	74	0.098
Female	56	31 (55)	25 (45)	0.869	93	69	**0.030**	93	82	0.090
Smoking status (pack-years)										
≤40	83	43 (52)	40 (48)	0.857	87	70	0.114	92	75	0.084
>40	48	26 (54)	22 (46)		83	66	0.238	83	78	0.066
FEV1 (mL)										
≤2,390	77	39 (51)	38 (49)		81	68	0.190	77	80	0.187
>2,390	78	44 (56)	34 (44)	0.628	90	69	0.103	95	73	0.111
SUVmax										
≤7	75	45 (63)	27 (37)		95	70	**0.022**	100	83	**0.018**
>7	73	29 (40)	43 (60)	**0.012**	66	68	0.793	67	74	0.952
Histological tumor size (mm)										
≤20	81	54 (67)	27 (33)		88	80	0.484	95	82	0.078
>20	80	32 (42)	45 (58)	**0.002**	80	61	0.154	74	74	0.430
Histological subtype										
Adenocarcinoma	96	56 (58)	40 (42)		83	65	0.114	88	75	0.070
Squamous cell carcinoma	44	17 (39)	27 (61)	**0.044**	81	70	0.744	75	81	0.971
Stage										
T1abcN0M0–stage 1A	130	73 (56)	57 (44)		83	63	**0.032**	88	74	**0.008**
T2aN0M0–stage 1B	28	13 (46)	15 (54)	0.349	87	93	0.769	84	86	0.984

Values are presented as number, number of patients (%), or % unless otherwise stated. Statistically significant results are marked in bold.
DFS, disease-free survival; FEV1, forced expiratory volume in 1 second; SUVmax, maximum standard uptake value.

mean FEV1 percentage of predicted values was 91.7%± 21.2%. The mean ratio of the diffusing capacity of the lung for carbon monoxide was 93.2%±24%, with data available for 122 (77.2%) of the patients.

Preoperative diagnostic procedures

Fiberoptic bronchoscopy was performed for 72 patients (45.5%), but it yielded a diagnosis in only 12 (16.6%) of these cases. In contrast, transthoracic needle aspiration biopsy was carried out among 70 patients (44.3%), with a definitive diagnosis obtained in 60 cases (85%). Ultimately, a preoperative diagnosis was established in 72 patients (45.6%). These patients were then matched with 86 individuals who underwent surgery without prior diagnosis. The average time from radiological detection to surgery was significantly shorter for the upfront surgery group, at 18.2±5.4 days, compared to 44.9±13.9 days for those with a preoperative diagnosis (p<0.0001).

Operative procedures

A total of 86 patients (54.4%) underwent upfront surgery without a preoperative diagnosis. Mediastinoscopy was performed in 34 patients (21.5%) during the same session, prior to resection. Video-assisted thoracoscopic surgery was the resection method for 124 patients (78.5%), while thoracotomy was performed in 34 patients (21.5%). The most common tumor location was the right upper lobe (affecting 53 patients [33.5%]), followed by the left upper lobe (40 patients [25.3%]). Intraoperative pathologic diagnosis was obtained for 50 patients (77.2%), whereas 36 patients (22.8%) underwent pulmonary resection without an intraoperative diagnosis. The most frequent procedure for intraoperative diagnosis was wedge resection (37 patients [23.4%]), followed by needle aspiration (10 patients [6.3%]) and segmentectomy with completion lobectomy (3 patients [1.9%]).

A total of 128 patients (81%) underwent lobectomy, while

segmentectomy, sleeve lobectomy, and bilobectomy were performed for pulmonary resection in 19 (12%), 6 (3.8%), and 5 (3.2%) patients, respectively. All patients underwent thorough mediastinal lymph node dissection for complete staging.

Postoperative outcomes, complications, and follow-up

The mean chest tube drainage time was 5.3±3.8 days for the upfront surgery group, compared to 5.8±4.2 days for the preoperative diagnosis group (p=0.483). The average length of hospital stay for the upfront surgery group was 7.1±4.7 days, while it was 7.4±5.4 days for the preoperative diagnostic group (p=0.694). Of the patients, 58 (36.7%) experienced postoperative complications, with postoperative air leak occurring in 26 (16.4%). Recurrence was observed in 41 patients (25.9%), with a median time to recurrence of 73 months. The median follow-up duration was 78 months (range, 3 to 171 months).

Histologic findings and staging

All patients were diagnosed with stage I and N0M0 disease. Histologically, the tumors were classified as T1a, T1b, T1c, and T2a in 10 (6.3%), 69 (43.7%), 51 (32.3%), and 28 (17.7%) patients, respectively. Adenocarcinoma was the predominant histologic subtype, found in 96 patients (60.8%), followed by squamous cell carcinoma (44 patients [27.8%]). Visceral pleural invasion was identified in 13 cases (8.2%). According to the revised eighth edition of the International Association for the Study of Lung Cancer staging system, the TNM (tumor, node, metastasis) stages were IA in 130 patients (82.3%) and IB in 28 patients (17.7%).

Survival analyses

The patient groups—that is, the participants who underwent upfront surgery and those with preoperative diagnoses—exhibited no statistically significant differences in clinicopathological features such as age (p=0.150), sex (p=0.869), smoking status (p=0.857), and FEV1 values (p=0.628), per contingency tables (Table 1). However, the mean age of the patients undergoing upfront surgery was significantly lower than that of the group with a preoperative diagnosis (p=0.013). Additionally, higher rates of preoperative diagnosis were observed among patients with SUVmax exceeding 7 (p=0.012), those with histological tumor size greater than 20 mm (p=0.002), and those with squamous cell carcinoma (p=0.044). Similarly, the mean SUVmax (p=0.009) and histological tumor size (p=0.010) were significantly higher for patients with a preoperative diagnosis. Patients with stage IA cancer displayed a higher rate of upfront surgery (56%) than those with a preoperative diagnosis (46%), although this difference was not statistically significant (p=0.349).

Relative to preoperative diagnosis, upfront surgery was associated with significantly better disease-free survival (p=0.031) (Fig. 2) and overall survival (p=0.017) (Table 1, Fig. 3). Among patients over 61 years old, those who underwent upfront surgery displayed a significant advantage in 5-year survival (p=0.044). Similarly, patients with a SUVmax of 7 or less who received upfront surgery experienced

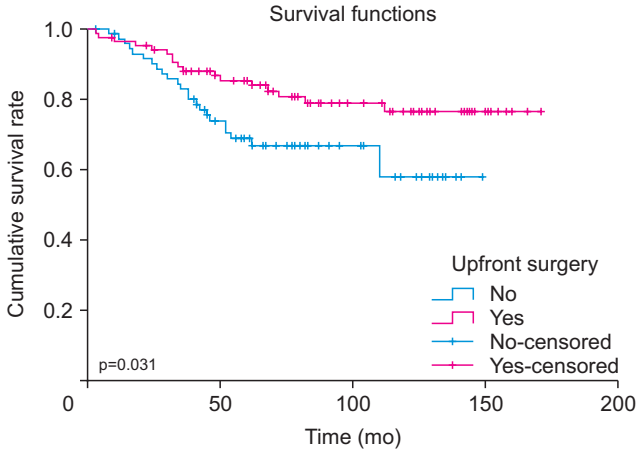

Fig. 2. Comparison of disease-free survival in patients undergoing upfront surgery.

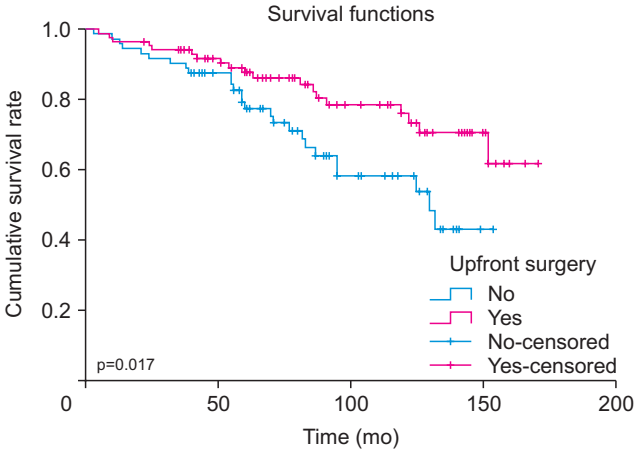

Fig. 3. Comparison of overall survival in patients undergoing upfront surgery.

https://doi.org/10.5090/jcs.23.166

Table 2. Prognostic predictors in univariate analysis using a Cox proportional hazards model

Variable	Hazard ratio (95% CI)	p-value
Upfront surgery (absent versus present)	2.036 (1.119–3.702)	**0.020**
Age (yr) (>61 vs. ≤61)	2.664 (1.414–5.020)	**0.002**
Sex (male vs. female)	1.949 (0.964–3.941)	**0.063**
Smoking status (pack-years) (>40 vs. ≤40)	1.626 (0.867–3.051)	0.130
FEV1 (mL) (≤2,390 vs. >2,390)	1.466 (0.812–2.645)	0.204
SUVmax (>7 vs. ≤7)	3.373 (1.688–6.741)	**0.001**
Histological tumor size (mm) (>20 vs. ≤20)	2.259 (1.225–4.168)	**0.009**
Histological subtype (SCC vs. adenocarcinoma)	1.440 (0.784–2.643)	0.239

Statistically significant results are marked in bold.
CI, confidence interval; FEV1, forced expiratory volume in 1 second; SUVmax, maximum standard uptake value; SCC, squamous cell carcinoma.

Table 3. Prognostic predictors in multivariate analysis using a Cox proportional hazards model

Variable	Hazard ratio (95% CI)	p-value
Upfront surgery (absent vs. present)	1.241 (0.643–2.393)	0.520
Age (yr) (>61 vs. ≤61)	1.991 (0.997–3.976)	0.051
Sex (male vs. female)	1.613 (0.712–3.656)	0.252
SUVmax (>7 vs. ≤7)	2.568 (1.245–5.295)	**0.011**
Histological tumor size (mm) (>20 vs. ≤20)	1.744 (0.889–3.420)	0.106

Statistically significant results are marked in bold.
CI, confidence interval; SUVmax, maximum standard uptake value.

relatively favorable 5-year survival outcomes (p=0.018). Female patients who underwent upfront surgery exhibited significantly greater 5-year disease-free survival than those with preoperative diagnosis (p=0.030). Additionally, patients with SUVmax values of 7 or less showed a favorable 5-year disease-free survival rate associated with upfront surgery (p=0.022). Patients with stage IA disease who underwent upfront surgery displayed significantly better disease-free (p=0.032) and overall survival (p=0.008) than those not treated with this intervention. However, these benefits were not significant among patients with stage IB disease, with p-values of 0.769 for disease-free survival and 0.984 for overall survival.

In the univariate analysis, independent predictors of survival included upfront surgery (p=0.020), age (p=0.002), SUVmax (p=0.001), and histological tumor size (p=0.009) (Table 2). However, in the multivariate analysis, upfront surgery did not retain significance as a predictor. Instead, an SUVmax greater than 7 (p=0.011) was the only significant predictor, associated with poor survival (Table 3).

Discussion

Our findings indicate that patients who underwent upfront surgery for stage I lung cancer experienced favorable disease-free and overall survival, as demonstrated with Kaplan-Meier analysis. This positive effect on survival was also observed in the univariate analysis conducted in this study; however, it was not evident in multivariate Cox proportional hazards analysis.

Under the National Comprehensive Cancer Network (NCCN) guidelines for non-small cell lung cancer, preoperative diagnostic intervention is not required in stage 1A. Preoperative diagnostic procedures can lead to delays in surgery, increased expenses, and additional risks, and they may not be necessary for determining the appropriate treatment options [1]. Furthermore, preoperative workup for the diagnosis of lung cancer with bronchoscopy and transthoracic fine needle biopsy is likely to disrupt bronchovascular structures and disseminate tumor cells [5]. Nakajima et al. [2] were the first to highlight the potential for diagnostic procedures to spread tumor cells and the associated likelihood of an unfavorable prognosis among patients with lung cancer who undergo transbronchial biopsy for preoperative diagnosis. They reported that upfront surgery and intraoperative diagnosis, followed by resection of non-small cell lung cancer, might improve surgical outcomes [2]. Similarly, transthoracic fine needle biopsy could result in implantation metastasis [7]; however, previous studies have indicated that transthoracic biopsy for lung cancer is a safe and feasible diagnostic procedure [8]. Nevertheless, some central pure ground-glass opacity lesions

that show progression on long-term follow-up, particularly those located adjacent to pulmonary vessels, may require upfront surgery without preoperative diagnosis.

Presumably, preoperative diagnostic workup to determine the nature of a primary tumor may extend the time to surgery in cases of early-stage operable lung cancer. This delay could be perceived as lost time for treatment. Sihoe et al. [6] reported that among select patients with lung tumors highly suspicious for malignancy, proceeding directly to surgery without a preoperative diagnosis was safe and reduced time to treatment. However, this abbreviated workup did not result in improved survival outcomes or lower recurrence rates in their patient series [6]. We similarly observed that performing upfront surgery significantly shortened the time to the operating room. However, our findings did not demonstrate a significant survival advantage for patients undergoing such surgery, aligning with the results of Sihoe et al. [6]. Separately, Mayne et al. [9] found no significant differences in survival rates between patients who underwent early versus delayed surgery for stage IA1 adenocarcinoma and IA1–IA3 squamous cell carcinoma, echoing our results. However, they did note that delayed surgery was associated with worse survival outcomes for patients with stage IA2–IB adenocarcinoma and IB squamous cell carcinoma. In a similar vein, a national study from the Netherlands revealed that the use of endobronchial ultrasound, endoscopic ultrasound, and transthoracic biopsy significantly postponed surgery. The authors of that study concluded that such delays were linked to poorer overall survival rates in stage II lung cancer. Nevertheless, they also reported that these delays did not significantly impact overall survival across all stages, including stage I, which is consistent with our findings [10]. Conversely, a national cohort study from Taiwan identified a strong correlation between the time to treatment and mortality in patients with non-small cell lung cancer, particularly in stages I and II. The researchers recommended minimizing the interval between tumor detection and surgery [11].

Thoracic surgeons have expressed concerns about the potential diagnosis of small cell lung cancer following upfront surgery. However, when mediastinal lymph node metastasis is not present, the NCCN guidelines recommend pulmonary resection, with lobectomy being the preferred approach for early-stage small cell lung cancer [1]. The treatment paradigm for early-stage small cell lung cancer has shifted in recent years, now favoring surgical intervention (specifically lobectomy) when feasible and in the absence of mediastinal lymph node involvement. A recent study demonstrated favorable surgical outcomes in a large cohort of patients with small cell lung cancer [12]. Additionally, Woo et al. [13] reported promising survival results following upfront surgery for patients with this form of cancer. Upfront surgery may offer benefits in the early stages of tumors with high mitotic activity, such as small cell lung cancer.

Taniguchi et al. [5] reported results that align closely with our findings. In our study, the mean histological diameter and SUVmax were significantly lower among patients who underwent upfront surgery. In their series, Taniguchi et al. [5] observed that solid tumor size and SUVmax were generally higher in patients who received preoperative biopsy. They also noted a potential negative impact of preoperative diagnosis on overall survival; however, this did not reach statistical significance in the multivariate analysis, mirroring our results. Consequently, those authors concluded that preoperative diagnosis did not significantly impact recurrence risk or prognosis. Similarly, Abe et al. [3] explored the potential detrimental effects of preoperative bronchoscopy on recurrence in stage IA non-small cell lung cancer. They found that patients who received a preoperative diagnostic workup presented with larger tumors, but preoperative bronchoscopy did not negatively influence recurrence rates [3]. In line with our findings, they did not identify tumor size as a predictor of recurrence. In our study, the only negative predictors for recurrence were female sex and SUVmax of 7 or lower. In contrast, Yasukawa et al. [4] have suggested foregoing preoperative pathological diagnostic procedures, such as transbronchial lung biopsy, and instead proceeding directly to surgery in patients with non-small cell lung cancer measuring less than 3 cm. They argue that upfront surgery could prevent delays in treatment and potentially lead to better outcomes for these patients [4].

Although preoperative workup for lung cancer may negatively impact recurrence and overall survival, suggesting that upfront surgery could be a beneficial intervention for early-stage I lung cancer, we conclude that upfront surgery does not exert a prognostic effect on overall survival in these patients.

The present single-center retrospective analysis included only cases of stage I, T1–T2aN0M0 patients, and T2N0M0 cancer, to exclude the adverse effects of lymph node involvement and metastasis on survival. This selection criterion limited the number of patients included in the study. However, the groups were well-matched, with no significant differences in clinicopathological features apart from SUVmax and histological tumor size. Nonetheless, further prospective randomized trials are warranted to further

clarify the impact of upfront surgery on patients with stage I lung cancer.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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