Radiology: Cardiothoracic Imaging

ORIGINAL RESEARCH

Clinical Outcomes of Ground-Glass Nodules Detected in a CT Lung Cancer Screening Program

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Author affiliation, funding, and conflicts of interest are listed at the end of this article.

Radiology: Cardiothoracic Imaging 2026; 8(1):e250293 • https://doi.org/10.1148/ryct.250293 • Content codes: CT CH

Purpose: To evaluate cancer outcomes, stage distribution, and mortality among patients with ground-glass nodules (GGNs) detected in a lung cancer screening program.

Materials and Methods: This retrospective study included patients in a CT lung cancer screening program (January 2015–July 2023) with a dominant GGN and a comparison group of patients with Lung Imaging Reporting and Data System (Lung-RADS) 1. All lung cancers in the GGN group were reviewed to determine whether they originated from the dominant nodule. Cancer stage and cause of death were obtained from medical records. Categorical variables were compared using the χ^2 test, and cancer development over time was compared using the log-rank test.

Results: Among 1724 patients (mean age, 65 years ± 6 [SD]; 917 female) in the screening program with a dominant GGN, 114 were diagnosed with lung cancer: 70 (61%) from the dominant GGN and 44 (39%) from another nodule. Stage 0 or I cancers were identified in 66 of 70 (94%) cancers arising from the dominant GGN versus 24 of 44 (55%) cancers from another nodule ($P < .001$). All 10 lung cancer–related deaths occurred from solid nodules unrelated to the GGNs. Patients with a dominant GGN were more likely than those with Lung-RADS 1 to develop cancers not related to the dominant nodule ($P = .007$).

Conclusion: Annual CT follow-up of patients with GGNs appears appropriate, as nearly all cancers were diagnosed at an early stage. However, these patients remain at risk for developing additional, separate lung cancers that may lead to mortality.

Ground-glass nodules (GGNs) are increasingly detected at CT, both incidentally and within lung cancer screening programs (1). Prior studies have estimated that approximately a quarter of these nodules represent a transient inflammatory process and will resolve (2,3). However, the majority of those that remain represent lesions along the adenocarcinoma spectrum—adenocarcinoma in situ, minimally invasive adenocarcinoma, or invasive adenocarcinoma. Cancers arising in subsolid nodules (ie, ground glass or part solid) are more indolent than those arising in solid nodules, with a lower risk of recurrence and better overall prognosis (4,5). The International Association for the Study of Lung Cancer clinical staging guidelines consider GGNs as clinical stage in situ, implying no invasive component (6), although multiple prior studies have shown that a substantial fraction (around 40%) do actually harbor invasive adenocarcinoma (7,8). Thus, the appropriate follow-up and treatment thresholds for GGNs remain controversial.

In the setting of lung cancer screening, the American College of Radiology developed the Lung Imaging Reporting and Data System (Lung-RADS) to standardize nodule reporting and management (9). The Lung-RADS (version 1.1 and later) designates category 2, recommending annual follow-up, for GGNs of less than 3 cm and for GGNs of 3 cm or more if stable or slowly growing; no treatment is recommended unless a GGN develops a solid component (ie, becomes part-solid nodule). Given the aforementioned rates of invasive adenocarcinoma within such lesions, it is unclear if these recommendations are appropriate. Some prior studies have evaluated the protocol of follow-up, rather than resection, of GGNs. Most notably, an Italian lung cancer screening study (the Plasma microRNA Profiling as First Line Screening Test for Lung Cancer Detection [BioMILD] study) followed such a protocol and reported that the majority of lung cancers arising from subsolid nodules were stage I and that no deaths from lung cancer related to subsolid nodules were observed (10). However, that study reported limited data on the specific characteristics of the nodules.

In this study, we aimed to perform a similar analysis in our lung cancer screening program and provide further insights into characteristics of nodules diagnosed as lung cancers arising from GGNs in a screening setting. Specifically, we aimed to evaluate the cancer outcomes, stage distribution, and lung cancer–specific mortality owing to cancers arising from GGNs.

Materials and Methods

Study Sample

This Health Insurance Portability and Accountability Act–compliant retrospective study was approved by the Mass General Brigham institutional review board (protocol no. 2021P001913) with a waiver of informed consent. No industry support was received for this study. We evaluated all lung cancer screening CT examinations performed between January 2015 and July 2023. Lung-RADS scores were extracted from the clinical CT reports.

The dominant nodule was determined from the clinical CT report. All screening CT scans were interpreted according to the current version of American College of Radiology Lung-RADS at the time of interpretation. Nodule characteristics were extracted from the CT report using regular expressions in a Perl script as follows: If nodule size was mentioned in the report impression, that nodule was considered the dominant lesion; otherwise, the largest nodule in the findings section was extracted.

Abbreviations

BioMILD = Plasma microRNA Profiling as First Line Screening Test for Lung Cancer Detection, GGN = ground-glass nodule, Lung-RADS = Lung Imaging Reporting and Data System

Summary

This study demonstrates that ground-glass nodules detected in a CT lung cancer screening program can be safely followed according to Lung Imaging Reporting and Data System guidelines, given their low risk of high-stage disease or death from those nodules, although affected patients remain at risk for other primary lung cancers.

Key Points

- Among 1724 patients in a CT lung cancer screening program with a dominant ground-glass nodule, 94% (66 of 70) of cancers arising from the dominant nodule were stage 0 or I.
- All 10 lung cancer–related deaths occurred from solid cancers unrelated to the ground-glass nodules.

Keywords

CT, Lung, Ground-Glass Nodules

Nodule attenuation was extracted from the same sentence in the report. Nodules described as "ground-glass" or "nonsolid" were included in the ground-glass group.

For the primary analysis, we identified scans with a GGN as the dominant finding and selected the first such scan for each patient. For the lung cancer risk analysis (described later), we also selected patients with Lung-RADS 1—that is, no nodules—as the comparison group. For that group, the index CT was defined as the first screening CT assigned Lung-RADS 1.

Lung cancer diagnoses and deaths were reviewed at a cutoff date of September 2024. Lung cancer diagnoses were identified by searching for diagnosis codes of lung cancer. Pathology reports and/or patient charts were then reviewed manually by either an attending radiologist (M.M.H., with 8 years of posttraining experience) or radiology resident (K.A.S., with 1 year of experience) to confirm a true diagnosis of lung cancer. Cancer stage was extracted from pathology reports and/or clinical notes.

Deaths in patients with lung cancer diagnoses were reviewed by an attending thoracic radiologist (M.M.H.) to determine whether the death was attributable to the lung cancer versus another cause (eg, cardiac).

Nodule Review

Patients with a dominant nodule identified as a GGN were selected from the total screening population. The first CT showing a GGN for each patient was defined as the index CT.

All lung cancer diagnoses were reviewed by an attending radiologist (M.M.H.) to determine whether the lung cancer arose from the dominant GGN on the index CT. If the index CT report described a dominant finding that was not a nodule (eg, consolidation or lymphadenopathy), that CT was excluded.

The nodule size and attenuation on the last CT before treatment were manually extracted from the CT reports and classified as GGN, part-solid nodule, or solid. If a report was ambiguous—generally regarding the size of the solid component—the nodule was manually measured on 1-mm-thick lung windows by an attending thoracic radiologist (M.M.H.).

Statistical Analysis

Data were analyzed in R (version 4.4.3; R Foundation) (11) using the packages tidyverse (12), gtsummary (13), and survival (14). Differences in categorical variables were analyzed with the χ^2 test. Differences in continuous variables were analyzed with the Wilcoxon rank sum test.

The risk of lung cancer development over time was analyzed using a Fine-Gray competing risk model. For the analysis evaluating whether a GGN confers increased risk of lung cancer not related to the dominant nodule, lung cancers not arising from the dominant nodule were treated as events, while death or diagnosis of cancer arising from the dominant GGN were considered competing events. The comparison group comprised patients with a Lung-RADS 1 CT (first such CT per patient), with any diagnosis of lung cancer considered an event. The initial comparison was performed using the log-rank test, followed by a Fine-Gray proportional hazards analysis including patient age, sex, and smoking status. A *P* value less than .05 was considered statistically significant.

Results

Patient and Nodule Characteristics

A total of 37 111 lung cancer screening CT examinations were performed in 15 762 patients. Of these, 1724 patients (mean age, 65 years ± 6 [SD]; 917 [53%] female, 807 [47%] male) had a dominant GGN on at least one CT scan; a patient flow diagram is shown in Figure 1. The median nodule size on the index CT was 6 mm (IQR, 4–9 mm; total range, 1–38 mm). The median follow-up time for patients without a lung cancer diagnosis was 3.75 years (IQR, 2.10–6.16 years).

Cancer Diagnoses and Stage Distribution

A total of 114 patients with a dominant GGN were diagnosed with lung cancer: 70 (61%) arising from the dominant GGN and 44 (39%) from another nodule. Diagnoses of lung cancer related to the dominant GGN by GGN size are shown in Table 1. Nodule attenuation and cancer stage are presented in Table 2. Among cancers arising from another nodule (n = 44), 35 (80%) were solid and 16 (36%) were visible, at least in retrospect, on the index CT scan (eight of nine subsolid and eight of 35 solid cancers), although some were small.

Of cancers arising from the dominant GGN (n = 70), 63 (90%) were resected, and seven (10%) were treated with empirical radiation therapy. The rate of stage 0 or I cancers was 66 of 70 (94%) for those arising from the dominant GGN and 24 of 44 (55%) for those arising from a different nodule (P < .001). Ten deaths occurred from lung cancer in this cohort—all from solid nodules, with none arising from the dominant GGN. Notably, one patient was initially diagnosed with a cancer arising from the dominant GGN but later developed a second cancer from a solid nodule that caused death.

Cancers Associated with GGN

At the time of treatment, 26 of 70 (37%) cancers arising from the dominant GGN remained pure GGN, 39 of 70 (56%) were part-solid nodules, and five of 70 (7%) had become fully solid. The median nodule size at cancer diagnosis was 13 mm (IQR,

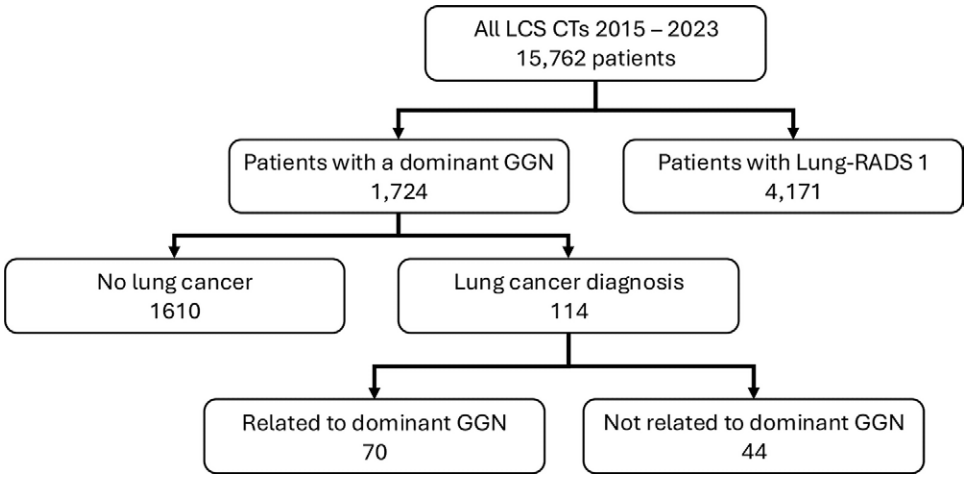

Figure 1: Patient flow diagram. GGN = ground-glass nodule, LCS = lung cancer screening, Lung-RADS = Lung Imaging Reporting and Data System.

Table 1: Diagnoses of Lung Cancer Arising from the Dominant GGN by Initial GGN Size

Variable	<6 mm (*n* = 737)	6–10 mm (*n* = 655)	11–19 mm (*n* = 261)	≥20 mm (*n* = 71)
Lung cancer arising from dominant GGN	12 (1.6)	28 (4.3)	25 (9.6)	5 (7.0)

Note.—Values are expressed as numbers with percentages in parentheses. GGN = ground-glass nodule.

Table 2: Nodule Attenuation and Cancer Stage for Cancers Diagnosed in the GGN Group

Characteristic	Cancer from Dominant GGN (*n* = 70)	Cancer from Other Nodule (*n* = 44)	*P* Value*
Nodule attenuation			<.001
Solid	0	35 (80)	
Subsolid (GGN or PSN)	70 (100)	9 (20)	
Stage			<.001
Stage 0	5 (7.1)	0	
Stage I	61 (87)	24 (55)	
Stage II	2 (2.9)	5 (11)	
Stage III	2 (2.9)	11 (25)	
Stage IV	0	4 (9.1)	

Note.—Values are expressed as numbers with percentages in parentheses. GGN = ground-glass nodule, PSN = part-solid nodule.
* *P* values were analyzed with the χ^2 test.

10–19 mm). Cancer stage by nodule attenuation and size at treatment is shown in Table 3. Nearly all cancers were diagnosed at stage 0 or I. Of the GGNs of less than 20 mm with available pathology (*n* = 20), one (5%) was adenocarcinoma in situ, 10 (50%) were minimally invasive adenocarcinoma, and nine (45%) were invasive adenocarcinoma (T1a and T1b). Pathologic data for staging purposes were not available for two of 22 (9%) GGNs of less than 20 mm, and for GGNs of 20 mm or more (*n* = 4), one (25%) was T1a, one (25%) was T1b, and two (50%) were T2a, all adenocarcinomas.

Two cancers were stage II, each with positive N1 lymph nodes (Fig 2). Two additional cancers were classified as clinical stage III. One patient had two isolated GGNs in different lobes of the same lung that were treated with radiation therapy; clinical notes indicated stage III (T4), although these lesions were likely separate primary tumors (no pathologic confirmation). The other patient had a mixed ground-glass and cystic nodule that became fully solid and developed metastatic disease in the right mediastinal and hilar lymph nodes (Fig 3).

Outcomes of Large (≥2 cm) GGNs

After the initial version of Lung-RADS, the American College of Radiology committee increased the upper size limit for category 2 GGNs from 2 to 3 cm such that all GGNs of less than 3 cm receive annual surveillance. Therefore, we examined the outcomes of GGNs of 2 cm or more in our population. A total of 71 GGNs met this criterion. During follow-up, 33 (46%) resolved, five (7%) were interpreted as interstitial lung disease or scarring, three (4%) were resected with benign pathology, and five (7%) were diagnosed as lung cancer (three remained

Table 3: Cancer Stage by Nodule Characteristics at the Time of Treatment of Cancers Arising from the Dominant GGN

Variable	GGN <20 mm (*n* = 22)	GGN ≥20 mm (*n* = 4)	PSN, Solid <6 mm (*n* = 24)	PSN, Solid ≥6 mm (*n* = 15)	Solid (*n* = 5)
T stage					
Tis	1 (5.0)	0	3 (15)	0	0
T1mi	10 (50)	0	5 (25)	3 (23)	1 (20)
T1a	7 (35)	1 (25)	11 (55)	5 (38)	2 (40)
T1b	2 (10)	1 (25)	1 (5.0)	5 (38)	0
T2a	0	2 (50)	0	0	1 (20)
T2b	0	0	0	0	0
T3	0	0	0	0	1 (20)
No pathology*	2	0	4	2	0
Total stage					
Stage 0	2 (9.1)	0	3 (13)	0	0
Stage I	20 (91)	3 (75)	19 (79)	15 (100)	4 (80)
Stage II	0	1 (25)	1 (4.2)	0	0
Stage III	0	0	1 (4.2)	0	1 (20)
Stage IV	0	0	0	0	0

Note.—Values are expressed as numbers with percentages in parentheses. GGN = ground-glass nodule, PSN = part-solid nodule.
* "No pathology" refers to patients treated empirically with radiation or ablation without resection for pathologic T staging. Percentages in the T stage section were calculated without the no pathology instances.

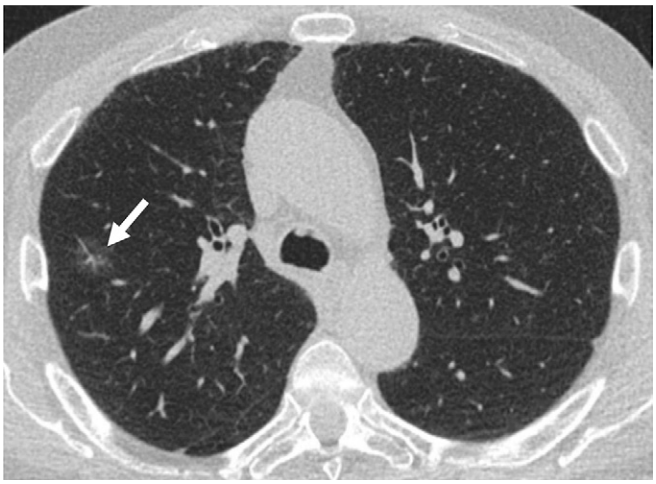

Figure 2: Example of a stage II lung cancer arising from a ground-glass nodule (GGN). Axial lung cancer screening CT image shows a GGN in the right upper lobe (arrow) with internal heterogeneity but no defined solid component. At resection, pathology demonstrated invasive adenocarcinoma measuring 1.9 cm with a 1.2-cm invasive component and level 11 lymph node positive (pT1bN1, stage II).

GGNs and two became part-solid nodules). Additionally, two patients developed cancers from other nodules while the dominant GGN remained stable. The remaining nodules were stable in 11 (15%) cases for less than 5 years and in six (8.5%) cases for 5 years or more, and six (8%) were lost to follow-up. Of the five cancers, four (80%) were stage I and one (20%) was stage II (a 4.1-cm pure GGN diagnosed as pT1aN1).

Risk of Cancer Diagnosis over Time

The median interval from index CT to cancer diagnosis was 3.17 years (IQR, 1.92–5.45 years). The estimated 5-year risks of cancer diagnosis are shown in Table 4.

We also evaluated whether the presence of a GGN was associated with increased risk of developing cancer unrelated to the dominant GGN, to determine whether the presence of a GGN represents a separate risk factor for lung cancer elsewhere in the lungs. Patients with a dominant GGN (*n* = 1724) were compared with 4171 patients with Lung-RADS 1 (no nodules). Cumulative incidence curves are shown in Figure 4.

Patients with a dominant GGN were more likely to develop cancers not arising from the dominant GGN than those with no initial nodule (*P* = .007). In multivariable regression, including age, sex, and smoking status, this difference was not statistically significant (hazard ratio, 1.41; 95% CI: 0.95, 2.09; *P* = .09).

Discussion

In this study, we evaluated a large number of patients with GGNs detected during lung cancer screening. We found that 94% of cancers arising from the dominant GGN were stage 0 or I; however, these patients remained at risk for developing lung cancer from other nodules, of which only 55% were stage 0 or I. All lung cancer–related deaths were caused by cancers arising from other solid nodules. Additionally, the presence of a GGN appeared to confer an increased risk of lung cancer developing elsewhere in the lungs.

Our results that demonstrate the favorable outcomes of lung cancers arising from a GGN in screening support the conservative Lung-RADS recommendation for annual surveillance of such nodules. The findings are consistent with those of the BioMILD screening trial (10). Notably, in our study—as in the BioMILD trial—some GGNs underwent resection despite Lung-RADS guidance to defer intervention until a solid component develops; 37% of the nodules were still pure GGNs at the time of cancer diagnosis. Only one of these was stage II, a 4.1-cm GGN. Thus, our findings reinforce that adenocarcinomas arising from a GGN typically have an indolent course, slow growth, and low metastatic potential. Within this context, continued surveillance until a solid component develops appears appropriate, given the low likelihood of progression to a higher stage and the correspondingly low morbidity associated with such lesions.

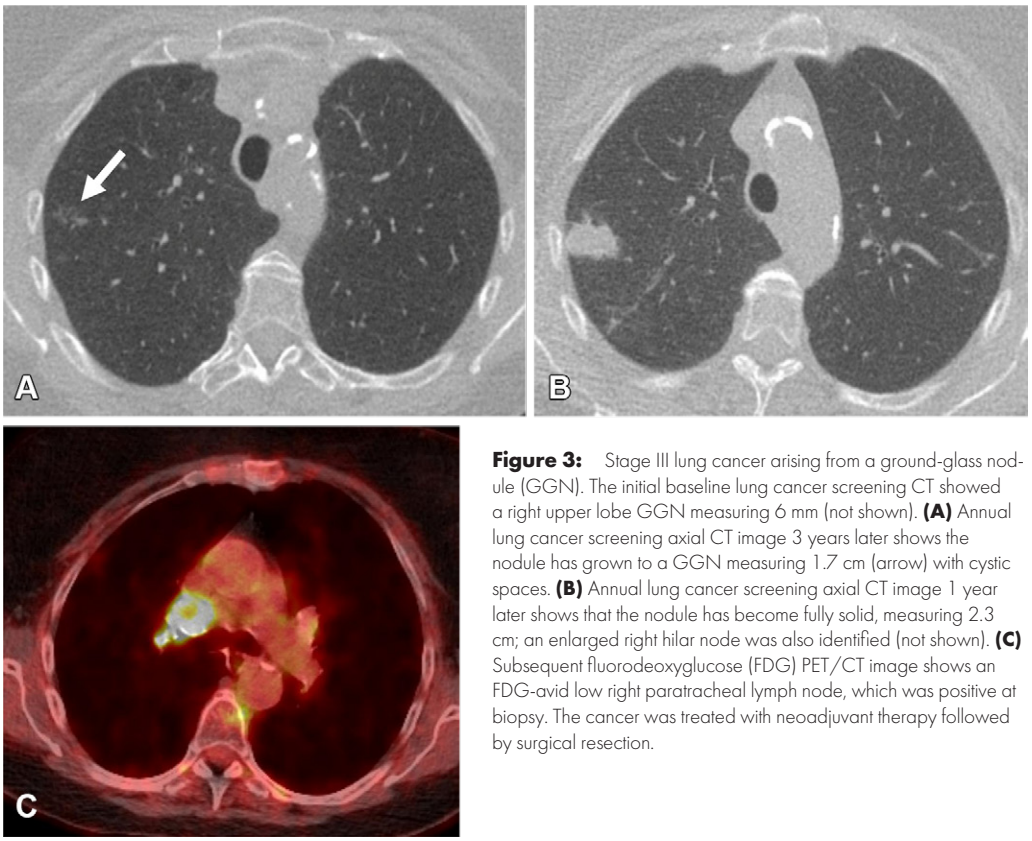

Figure 3: Stage III lung cancer arising from a ground-glass nodule (GGN). The initial baseline lung cancer screening CT showed a right upper lobe GGN measuring 6 mm (not shown). **(A)** Annual lung cancer screening axial CT image 3 years later shows the nodule has grown to a GGN measuring 1.7 cm (arrow) with cystic spaces. **(B)** Annual lung cancer screening axial CT image 1 year later shows that the nodule has become fully solid, measuring 2.3 cm; an enlarged right hilar node was also identified (not shown). **(C)** Subsequent fluorodeoxyglucose (FDG) PET/CT image shows an FDG-avid low right paratracheal lymph node, which was positive at biopsy. The cancer was treated with neoadjuvant therapy followed by surgical resection.

Table 4: Estimated Risk of Lung Cancer Diagnosis from the Dominant Ground-Glass Nodule at 5 Years

Dominant GGN Initial Size	Estimated Cancer Risk at 5 Years
<6 mm	2.7 (1.1, 4.4)
6–10 mm	5.8 (3.4, 8.2)
11–19 mm	12 (7.1, 17)
≥20 mm	6.3 (<0.1, 12)

Note.—Values are expressed as estimated risk with 95% CIs in parentheses and are presented as percentages. GGN = ground-glass nodule.

However, our findings also suggest that resection may be reasonable for GGNs exceeding a certain size threshold. In our cohort, two of four pure GGNs of 2 cm or more were T2a tumors, in addition to the stage II cancer. The optimal size cutoff prompting surgical consideration remains controversial. Indeed, the original version of Lung-RADS used 2 cm as the upper limit for category 2, which was later increased to 3 cm in version 1.1. Our data suggest that for pure GGNs of 2 cm or more, resection should be considered, given the observed risk of higher-stage disease in this size range.

Our results also corroborate those of previous reports showing imperfect concordance between CT attenuation and histopathologic invasiveness, in contrast to the clinical staging guidelines of the International Association for the Study of Lung Cancer. We found that 45% of GGNs of less than 2 cm were invasive adenocarcinoma, consistent with earlier studies and a systematic review (7,8). Moreover, 13% of part-solid nodules were stage 0, indicating that CT can sometimes overestimate the extent of invasion.

Finally, we observed that the presence of a GGN was associated with a higher risk of developing lung cancer elsewhere in the lungs compared with screening patients without nodules. Although this association was not statistically significant in multivariable analysis, the lack of significance may reflect limited sample size. The BioMILD trial reported a similar finding (15). In our study, all lung cancer–related deaths were due to solid-nodule cancers arising elsewhere in the lungs, again parallelling the BioMILD trial (10). These results emphasize the importance of strict adherence to annual screening, particularly for patients with GGNs, to facilitate detection of some secondary cancers and potentially prevent deaths.

This study had limitations. First, nodule characteristics were extracted from radiology reports using an automated algorithm, which may introduce errors. Second, as a retrospective analysis, there was no standardized treatment protocol, although radiologists interpreted studies according to Lung-RADS guidelines. Third, follow-up duration varied because patients were included from a range of screening dates, and some were lost to follow-up. Fourth, nodules were not independently remeasured; instead, reported size and attenuation values were used. However, most examinations were interpreted by thoracic subspecialty radiologists, supporting data reliability.

In conclusion, annual CT surveillance for GGNs detected during lung cancer screening appears appropriate. Nearly all

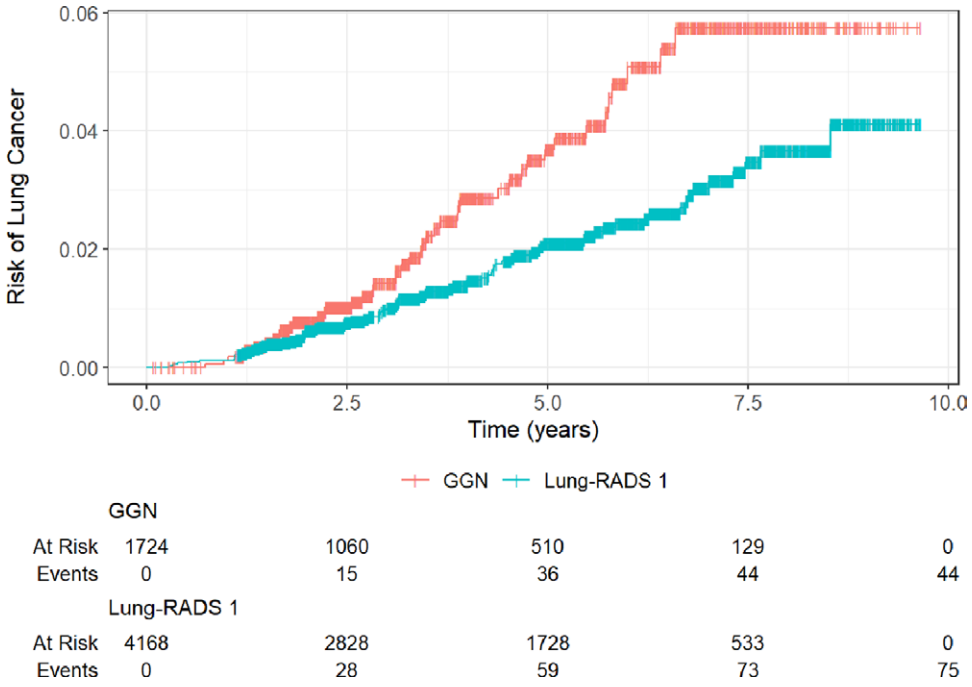

Figure 4: Risk of lung cancer not arising from the dominant ground-glass nodule (GGN) versus lung cancer risk in patients without nodules. Lung-RADS = Lung Imaging Reporting and Data System.

cancers diagnosed during surveillance were early stage, and no deaths occurred from GGNs themselves. However, GGNs of 2 cm or more demonstrated an increased risk of higher stage disease, suggesting that resection could be considered for this subgroup. Larger multicenter studies are needed to confirm this potential benefit. Separately, patients with GGNs appear to be at increased risk of developing additional independent lung cancers arising elsewhere in the lungs. These findings underscore the importance of maintaining adherence to annual screening protocols to enable early detection of both progressive and new lesions.

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Received May 13, 2025; revision requested June 19; revision received November 3; accepted November 19.

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Supplemental material: Supplemental material is available at *Radiology: Cardiothoracic Imaging* online.

Funding: M.M.H. is supported by the National Cancer Institute (5R01CA260889).

Author contributions: Mark M. Hammer: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing; and Kathryn A Schulz: Data curation, Investigation; Suzanne C. Byrne: Conceptualization, Investigation, Methodology, Writing - review & editing.

Disclosures of conflicts of interest: M.M.H. is a member of the *Radiology: Cardiothoracic Imaging* editorial board. Please see ICMJE form(s) for author conflicts of interest. These have been provided as supplemental materials.

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