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Original Research

Detection of lung carcinoma arising from ground glass opacities (GGO) after 5 years - A retrospective review

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ABSTRACT

Pure ground glass opacities (GGO) may indicate pre-invasive subtypes of lung carcinoma. These neoplasms typically demonstrate indolent patterns of growth; Fleischner Society guidelines recommend up to five years of serial imaging. Our aim was to determine the frequency of diagnosed carcinoma arising from GGO detected beyond 5 years of surveillance. We reviewed pathologic diagnoses of lung carcinoma (n = 442) between 2016 and 2018 of a tertiary academic hospital and National Cancer Institute-designated cancer center to identify all cancers that arose from ground glass opacities detected on CT scan. Of the 442 cases of lung carcinoma, 32 (7%) were found that arose from pure GGOs and were ultimately diagnosed as cancer. Among the subgroup of GGOs, 78% (n = 25) were diagnosed within five years of surveillance, but up to 22% (n = 7) required between five and twelve years of serial follow up prior to definitive diagnosis. In order to detect 95% of cancers, GGOs would need to be followed for 7.9–12.7 years based upon a Kaplan-Meier estimate (p = 0.05). No patients who had lung carcinoma arising from GGOs died (0/32) within a follow-up time of one to three years. These data suggest that a greater number of lung carcinomas would be detected upon routine follow up of GGOs that extended beyond the current recommendation of five years. The overall survival of the cohort was 100%, consistent with existing data that these cancers are indolent. It is unknown whether a higher detection rate from longer interval follow up would impact overall survival.

1. Introduction

Pure ground glass opacities (GGOs) are radiological findings on computed tomography (CT) of the chest that are described as hazy increased opacity of the lung with no solid, or entirely opaque components that obscure the underlying vessels ([1], Fig. 1). These may be a result of an inflammatory process but may also be a precursor of carcinoma of the lung [2,3]. It is commonly accepted that solid or subsolid nodules hold an increased risk of malignancy when compared with pure GGOs [4,5]. Current guidelines for the protocol of managing findings of GGOs on CT are based on the updated Fleischner Society 2017 guidelines [6]. Fleischner Guidelines are challenged by more recent research that suggest more extensive follow up may be required to identify potential cancers [7]. These more recent studies for suspicious lesions less than 6 mm, call for a single follow up within two to four years. For lesions 6–8 mm, follow up in six to twelve months was recommended with sequential follow up every two years [8–10]. These authors followed patients for 3.5 years, so their conclusions may be incomplete and require more extensive follow up because it has been demonstrated that a change in size of lung nodules may evade detection in lesions that are slow growing [11,12].

2. Materials and methods

Electronic medical records were reviewed from Thomas Jefferson University Hospital, a quaternary care center and teaching hospital for the Sidney Kimmel Cancer Center, a National Cancer Institute-designated cancer center. Cases of pathologically confirmed lung carcinoma between April 2016 and April 2018 (a two-year interval) were identified. The study was approved by the Institutional Review Board (IRB). A waiver of informed consent was requested and approved by the IRB.

Of the 442 carcinomas identified, we searched imaging reports to discern cancers that were initially identified as pure GGOs. The resulting 32 reports were manually examined to identify the time between initial GGO finding on CT and ultimate time to diagnosis of cancer. For all 32 patients we identified demographic data, reviewed imaging characteristics, noted intervention and recorded survival outcomes. Any previous

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Fig. 1. Original CT Image shows smoothly marginated lung nodule with visualization of the underlying vessels consistent with ground glass opacity.

CT scans were analyzed for subtle GGOs that may have been overlooked on initial read.

The CT results were evaluated for the initial size and characteristics of the lesions as well as those of the subsequent findings, in such cases where follow-up did occur. In some patients, the lesion changed over time and this was recorded. The clinical characteristics that were examined over time included size, location and attenuation (i.e. solid, subsolid or pure ground glass). Patient demographics were also noted including patient age, sex, race, ethnicity, comorbid conditions and smoking status.

We performed a retrospective cohort study Kaplan Meier analysis to describe the average time to diagnosis. Additionally, confidence intervals of the Kaplan Meier analysis were calculated to determine length of follow-up that would ensure identifying transformation to carcinomas in 95% of cases that begin as GGOs.

3. Results

Out of the 32 patients with carcinomas in the lung that began as an isolated GGO, 66% (n = 21) were females and 34% (n = 11) were males. The average age was 76 ± 9 years. Of the 32 participants 17% (n = 7) were active smokers, 59% (n = 19) were former smokers and 19% (n = 6) were never smokers at the time of diagnosis. 75% (n = 23) of patients with carcinoma qualified for lung cancer screening (LCS). None of the study participants died within a follow up of one to three years.

Among the subgroup of GGOs, 78% (n = 25) were diagnosed with lung carcinoma within the first five years of surveillance, but 22% (n = 7) required between five and twelve years of serial follow up prior to definitive diagnosis. (Figs. 2 and 3). While many patients were followed with repeat CT over time, the majority had minimal or no change. Of the group that was diagnosed after five years (n = 7), 29% (or 2 of these 7 patients) evolved from GGO to part-solid nodules between the first and last CT performed before carcinoma was detected and 5 remained ground glass for the entire period of observation. Forty three percent (3 of 7 patients) had a 2 mm or less change within 5 years. Of the remaining 4, one did not have a data point near the five-year mark. For subjects 5 and 6, change was not detected until 66 months (greater than 5 years). The nodules remained ground glass at the five-year mark. Data summarized in Table 1.

Of the caners that had minimal change, the reason for follow up CT varied from provider preference, another indication for chest imaging, and patient request. Of those 7 cancers, 4 qualified for LCS.

In order to detect 95% of cancers that are initially identified as GGOs, they would need to be followed for at least 7.9–12.7 years based upon a Kaplan-Meier estimate for time to diagnosis (p = 0.05).

4. Discussion

Current guidelines suggest follow-up on GGO found on CT incidentally or otherwise for at least five years [6]. In our cohort of patients 23% (7 of 32) were diagnosed with carcinoma and found to be initially detected as GGO.

In this series of patients with carcinoma arising as GGO, several were followed for extensive time frames yet none of the patients died during the period of radiographic follow up or one to three years of observation after definitive therapy. This suggests the possibility that these carcinomas are quite indolent may not require surgical intervention to assure favorable patient outcomes. Thus, a criticism of our work would be that outcome may not necessarily be improved from longer periods of observation. Nonetheless, the identification of indolent carcinomas well beyond five years is an important observation for investigators and public health professionals. Further prospective trials of expanded populations in multiple centers could help provide further guidance for these challenging management questions.

It is important to acknowledge that patients included in this study were not being managed under any particular protocol. Some were followed outside of this referral based urban academic center, others were managed by academic pulmonologists and academic thoracic surgeons outside of any clinical trial. Critics might conclude that lesions resected beyond 5 years and up to 12 years after detection should have been resected earlier. We believe, however, that outcomes of care by experienced clinicians working in the academic environment, represent a typical approach to patient management that may well reflect the experience across the country. Some of the reported cases were lost to

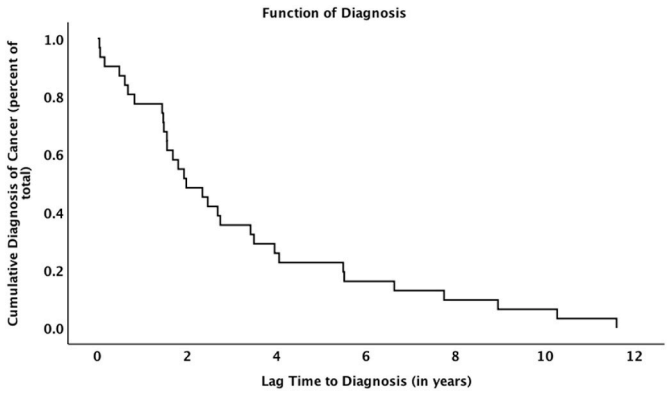

Fig. 2. Kaplan meier linear regression for time to diagnosis.

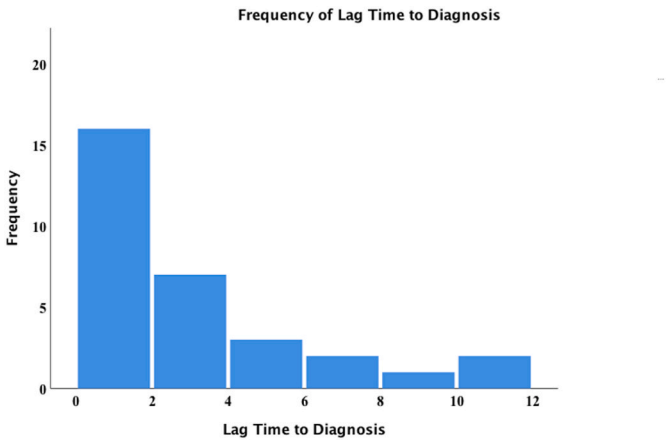

Fig. 3. Lag time to diagnosis bar chart.

Table 1
Summarization of records of patients in which diagnosis was greater than five years after initial diagnosis. Including subject number, date of diagnosis, and diagnostic modality.

Subject	Date of initial detection of ground glass opacity	Diameter at the time of diagnosis	Date of pathologic diagnosis	Diameter at the time of pathological diagnosis	Difference in time in months	Difference in largest diameter between initial diagnosis and pathological diagnosis	Difference in diameter between initial diagnosis and scan closest to, but after the 5-year mark.	Radiologic description of most recent CT report	Diagnostic modality	Detail of the pathology report	Cancer Stage
1	06–2010	13 mm	03–2018	20 mm	93 mo	7 mm	0 mm	Part solid	Surgical	Invasive adenocarcinoma, acinar predominant	IA3
2	06–2007	21 mm	09–2017	30 mm	123 mo	9 mm	1 mm	Part solid	Surgical	Invasive adenocarcinoma, acinar predominant	IA
3	11–2005	13 mm	06–2017	30 mm	139 mo	17 mm	2 mm[a]	Ground glass	Surgical	Bronchioalveolar adenocarcinoma	IA
4	08–2007	25 mm	07–2016	29 mm	107 mo	4 mm	N/A[b]	Ground glass	CT-guided biopsy	Adenocarcinoma	IV
5	03–2011	23 mm	09–2016	30 mm	66 mo	7 mm	3 mm	Ground glass	Surgery	Adenocarcinoma mixed subtype	IB
6	03–2010	10 mm	10–2016	15 mm	80 mo	5 mm	4 mm	Ground glass	Surgery	Multiple synchronous primary tumors: acinar adenocarcinoma, squamous cell carcinoma and broncho vascular carcinoma	IA
7	02–2011	10 mm	08–2016	15 mm	66 mo	5 mm	5 mm	Ground glass	Bronchoscopy	Adenocarcinoma	IA

[a] Patient lost to follow-up after five-year scan, but returned with nodule increase in length.
[b] No scan at 5-year mark, closest scan is at 3 years, with 1 mm change in diameter. The next scan is at 7 years with 3 mm change.

follow-up but returned with further imaging after several years. This too would be consistent with real-life scenarios among patients who might be lost to follow up [13]. The reality of follow-up even within formal lung cancer studies suggest that losing patients to follow up with low-risk lesions does occur.

The current guidelines indicate a change in lung nodule as 2 mm is considered within the margin of measurement error and significant to warrant action. Four of the 7 cancers did not meet or marginally met the required change of 2 mm at the 5-year mark that could be considered within a margin of error. Although we cannot prove that Subject 4 had a change of less than 2 mm, if data is interpolated the growth data, it would not meet the threshold within five years or it would have been another borderline case. In 2 of our cases, diagnosis was made at 5.5 years and radiographic evidence of change was present at or after the five-year mark. In one of the cases (Subject 7), while the cancer was not proven until 6.5 years, change was present at the 5-year mark. If one were to argue that these cancers were detected at 5 years, we still would have presented 4 patients (13%) who either lacked definitive change or were borderline at 5 years and were diagnosed between 93 and 129 months. While one may argue that only two cases represent case failure, it is important to recognize that the goal of guidelines should create a safe buffer to diagnose cancer. Therefore, there is reasonable concern that guidelines need to be extended beyond five years. The significance of our findings in a case series from routine practice (not part of a clinical trial) is that growth at 5 years was absent or so minimal in 13% of diagnosed cancers that it is difficult to determine without a continuing time horizon of greater than five years and anchoring to the index scan (the first detection of the GGO).

Additionally, the two cases that represent definitive failure of guidelines (subject 1 and 2) transformed from pure ground glass to part solid. This change in characterization which represents 6% of cancers in our study warrants further consideration as well.

These data suggest that a greater number of lung carcinomas would be detected upon routine follow-up of GGOs that extended beyond the current recommendations. Furthermore, the overall survival of the cohort was 100% (with one to three years of follow-up) consistent with existing data that these cancers are indolent. It is unknown whether a higher detection rate would impact overall survival. More extended observation time and a prospective approach are required for confirmation of our findings.

Of the 7 patients who had carcinoma detected between five and 12 years, several featured radiological reports had reported that the ground glass was stable when comparing to previous image. These reports did not comment on scans dating back to initial detection. This suggests that the standard for following nodules should routinely include comparison not only to the most prior image but to the index image when the lesion was initially identified [14]. As such a more definitive appraisal of nodule growth can be reported to the clinician.

While 5 of those 7 patients with cancer would have qualified for LCS if project retrospectively, the uptake nationally for LCS has been slow and the majority of the cancers were initially identified well before LCS was recommended [15].

This small case series from one urban academic center does not address several practical implications of extending the period of observation of GGOs. These practical considerations include the likelihood of increased numbers of patients who may be lost to follow-up during intervals of subsequent imaging that extend between two to five years. Furthermore, the cost benefit of extending observation for these common lesions has not been considered and should certainly be studied prior to any formal change in the current management guidelines. With no deaths in our cohort of 32 carcinomas which began as GGOs it would be impossible to calculate life years saved on the basis of screening and this should be considered prior to any formal change in the guidelines.

Perhaps like many patients with prostate cancer, patients might die with pulmonary carcinoma arising from GGOs rather than die from pulmonary carcinoma arising from GGOs. Thus, in patients whose survival is determined by other diagnoses or co-morbid conditions, continued follow up or intervention upon these lesions is probably not necessary. Still, in several patients with delayed diagnosis aggressive and invasive cancers were noted on the pathology report.

5. Conclusion

Based upon our case series, a greater number of lung carcinomas would be detected upon routine follow up of GGOs if follow up was extended beyond five years and up to twelve years. Because these cancers are indolent, it remains unknown whether a higher detection rate would impact overall survival. Additional long-term studies are warranted for greater clarity around this very important issue.

CRediT authorship contribution statement

Elissa Herskovitz: Conceptualization, Methodology, Software, Writing – original draft, Writing – review & editing, Visualization. **Charalamobos Solomides M.D:**, Data curation, Resources. **Julie Barta M.D.:** Methodology. **Nathaniel Evans III M.D.:** Resources. **Gregory Kane M.D.:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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