

DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF FOCAL GROUND-GLASS OPACITIES

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ABSTRACT

Focal pulmonary Ground-Glass Opacities (GGOs) can be associated with bronchioloalveolar carcinoma. This retrospective study aims at testing the validity of a multistep approach to discriminate malignant from benign localized (focal) GGOs, identifying useful diagnostic features on CT, and suggests appropriate management guidelines. A stepwise approach including oral antibiotics, follow-up High-Resolution CT 40-60 days later, and CT-guided core biopsy was used. All cases with localized GGOs detected since 2001 were reviewed, CT features were described according to a structured scheme.

40 patients were evaluated. Eleven patients were diagnosed with benign GGOs, 19 patients had lung cancer, and 10 are still undetermined.

Non-polygonal shape ($p=0.006$), apparent radial growth ($p=0.010$), and clear-cut margins ($p=0.003$) were associated with a malignant histology. The specificity of CT findings was low.

Diagnostic accuracy increased after oral antibiotics, follow-up High-Resolution CT, and percutaneous core biopsy. 18 patients underwent surgery for lung cancer.

In conclusion, malignant GGOs have a fairly typical appearance, but some benign lesions closely mimic their malignant counterparts. The stepwise approach we adopted increases the diagnostic specificity and reduces time to definitive diagnosis. Segmentectomy might be the ideal resection volume for such tumours.

INTRODUCTION

Ground-Glass Opacity (GGO) is a radiological term indicating an area of hazy increased lung opacity through which vessels and bronchial structures may still be seen. It is less opaque than consolidation, in which such structures are obscured [1]. Most commonly, diffuse GGOs are associated with widespread inflammatory or infiltrative lung disorders [2].

Focal GGOs, also called non-solid or part-solid nodules [3], are circumscribed areas of hazy lung opacity. Their association with early-stage bronchioloalveolar carcinoma (BAC) was first reported in the nineties by Japanese and Korean Authors [4-5], shortly after the advent of low-dose spiral CT (LDCT) for lung cancer screening.

Since then, a number of publications have addressed the clinical significance of focal GGOs and their relationship with atypical adenomatous hyperplasia (AAH), BAC and invasive adenocarcinoma [6-10].

A number of such cases have come to our attention since 2001 due to our ongoing lung cancer screening trial [11], and we were thus confronted with several issues: how to distinguish benign, non-evolving GGOs from those associated with BAC or adenocarcinoma; how to reach a definitive diagnosis in a reasonably short time; how to manage poor- risk surgical patients, whom and how to treat.

We have retrospectively analysed our series of patients with localized GGOs, and our findings are herewith discussed in an attempt to establish practical guidelines in the management of these patients.

PATIENTS AND METHODS

Study design

All cases with localized GGOs, either screening-detected or incidentally found from June 2001 to November 2007 at the Istituto Clinico Humanitas Hospital, Milan, Italy were retrospectively reviewed.

A stepwise management scheme has been used with pulmonary localised GGOs of undetermined origin on a regular basis as per our screening trial management guidelines [11]. It consists of:

1. oral antibiotics (levofloxacin 500 mg daily for 8 days)
2. repeat high-resolution CT of the lesion (HRCT) with contiguous 1 mm slice thickness reconstructions 40 to 60 days later
3. a tissue diagnosis is sought if no regression has occurred.

The GGOs were described by two radiologists (R.F.L. and S.I.) blinded to the final pathological or clinical diagnosis according to a structured scheme derived from the work of Li and coll. [12]. Pathology and surgical reports, follow-up data and outcomes were also reviewed.

Incidentally found GGOs were included if there was no known history of respiratory infection, chest

trauma, pulmonary or systemic disease which could explain their presence.

Diffuse GGOs, mild heterogeneity of lung parenchyma, GGOs associated with massive consolidation, or centrilobular GGOs associated with bronchiolitis were excluded.

Methods

The shape of a GGO was classified as rounded, oval, lobulated (when gross indentations were visible along its borders), or polygonal (when all margins were roughly linear). Its surface could be defined as smooth or non-smooth (finely or grossly irregular), while the margins were defined as smooth or irregular, and clear-cut or ill-defined in comparison with the surrounding normal lung parenchyma. A lesion was defined a pure GGO when no solid component was visible, or a mixed GGO when a minimal (<25% of the GGO area) or major (>25% of GGO area) solid density was visible.

If the lesion spread along the pulmonary lobular or segmental structures, a lobular/segmental distribution pattern was indicated, while if the GGO apparently extended through adjacent lobules in a centrifugal fashion, a radial growth pattern was indicated.

Multislice CT scanners and workstations have been used for the evaluation of GGOs. Determinations of each CT feature were established by consensus readings.

Based on the first spiral CT findings, the lesions were initially categorized as possibly benign, undetermined or possibly neoplastic. After reviewing the cases, the radiologists formulated a tentative consensus diagnosis (inflammatory GGO, undetermined or lung cancer) according to the results of antibiotic trial and short-term follow-up high-resolution CT. Radiological-pathological correlations were made afterwards.

Pathological diagnoses were based on the WHO 2004 criteria [13]. In the absence of a biopsy, GGOs were classified as benign if they had remained stable for at least three years.

Statistical Analysis

Continuous data are presented as median and range whereas categorical data are presented as numbers and percentages. Relationships between each single radiological or clinical feature and the final diagnosis were analysed using the t-test or the Fisher's exact test. A significance level of 5% was adopted. Atypical adenomatous hyperplasia (AAH) was grouped together with benign lesions.

RESULTS

This series comprises 40 patients, 35 males and 5 females. In 29 patients, the GGOs were screening-detected while in 11 cases they were found incidentally during investigation for an unrelated medical condition.

The mean age of the whole group was 67±6 years, and 39 (97%) were current (N=17) or former (N=22) smokers.

Four patients had an associated synchronous solid lung cancer which was resected in three. One patient had had a stage I lung cancer resected several years earlier.

Respiratory function tests were available for 21 patients; they were normal in 8, and abnormal in 13. Twelve out of 19 patients with lung cancer (65%) had documented chronic obstructive and/or restrictive pulmonary disease on spirometry testing. Patient workup, diagnostic procedures and final diagnoses have been outlined in Figure 1

The number of lesions was 1 in 30 patients (75%), while in 10 cases the lesions were two or more, either ipsilateral (2 cases) or bilateral. The mean age of patients with lung cancer was 68.9 ± 7 , while in those with benign lesions it was 65.4 ± 7 . The difference was not significant ($p=0.15$).

The shape of malignant GGOs tended to be rounded, oval or grossly lobulated, e.g. non-polygonal ($p=0.006$). Apparent radial growth was associated with neoplastic GGOs ($p=0.010$), however in 7/26 cases (27%) it was observed in a benign lesion. A central or eccentric solid density (mixed GGO) was associated with malignancy in 75% of the cases, but overall the association between a solid component and lung cancer was not significant ($p=0.27$). Clear-cut margins, best appreciable on HRCT scans, were instead significantly associated with a malignant histology ($p=0.003$), although they were also observed in benign GGOs (Figure 2). There was no demonstrable association with lung cancer risk for the number of lesions ($p=0.42$), lesion diameter ($p=0.14$), or surface characteristics ($p=0.26$) in this series.

The diagnosis based on the initial spiral CT only was undetermined in 55% of the cases. A course of oral antibiotics ruled out 5 cases (12.5%) with inflammatory lesions by observing partial or complete regression at repeat CT-scan after 2 months. It is worth mentioning that six patients were evaluated on the basis of follow-up only (i.e. no antibiotics were given) as the lesion was retrospectively visible in earlier CT scans.

The sensitivity, specificity, accuracy, positive and negative predictive values of the tentative diagnosis after antibiotics and/or follow-up HRCT were 1.00, 0.55, 0.86, 0.82, and 1.00 respectively, and the diagnosis remained undetermined in 12% of the cases only.

Percutaneous CT-guided core biopsy was carried out in 19 patients.

It was indicative of a BAC or a mixed-type adenocarcinoma (i.e. adenocarcinoma with bronchioloalveolar features) in 12 patients, of an AAH in two (confirmed by resection in one and followed in the second one), of an inflammatory lesion in two more, and it was non-diagnostic in three cases (17%). Two of these underwent surgical resection based on clinical suspicion and were demonstrated to have multifocal BAC in one case and mixed-type adenocarcinoma in the other one. The third one declined further evaluation and has been followed without signs of progression for 21 months so far. Complications were limited to mild pneumothorax in 4 patients (one only was drained) and mild haemoptysis in one.

Three patients refused percutaneous biopsy and further evaluation. One of them had a 20-mm

mixed GGO in the left upper lobe at the time of detection by screening CT. He was admitted to the emergency department four years later in severe distress, with massive left lung atelectasis, and died shortly afterwards. A firm diagnosis could not be established. The second patient died of disseminated cancer of unknown origin 24 months later, and the third one, who had a 9 mm pure rounded GGO in the right upper lobe is still alive and well after 30 months.

The lesions of ten patients overall are still undetermined either because the follow-up is less than three years, or core biopsy was refused, or (in two cases) withheld due to significant comorbidities.

A PET scan had been obtained in 12 cases with histologically proven neoplastic GGOs prior to resection and it was positive in 3 (25%).

Surgery and outcomes

Overall, 18 (45%) patients underwent surgical resection for neoplastic GGOs. The mean time from initial detection to resection was 4.7 ± 3.4 months. One patient was operated on twice, one year apart, for two synchronous lesions (case No. 34). One patient underwent a middle lobectomy for a solid adenocarcinoma together with bilateral wedge resections through a median sternotomy for multifocal mixed GGOs (mixed-type adenocarcinoma on histology).

No patient in this series had a thoracotomy for an inflammatory lesion. However, one patient with a small mixed GGO in the left upper lobe underwent segmentectomy after a core biopsy had correctly diagnosed AAH preoperatively. The management procedures in our series are summarised in table 3.

Two patients developed recurrent lung cancer in the ipsilateral lung:

the first one did so after 6 months following right lower lobectomy for stage I BAC; she eventually underwent re-resection (right upper lobe segmentectomy) which demonstrated stage IIA mixed-type adenocarcinoma with one metastatic hilar lymph node, and she is currently alive and well.

The second recurrence was detected 30 months after left upper lobectomy for stage I mixed-type adenocarcinoma. Completion pneumonectomy was carried out and multifocal mixed-type adenocarcinoma was demonstrated in the resected specimen.

A third patient died with bone metastasis 10 months following right upper lobectomy for Stage I mixed-type adenocarcinoma. Two years earlier he had undergone a left lower lobectomy for a stage I solid adenocarcinoma.

DISCUSSION

A previously unknown radiological-pathological entity, localized bronchioloalveolar carcinoma associated with focal ground-glass opacity, is now encountered with relative frequency due to the widespread use of spiral CT for lung cancer screening and for routine pulmonary imaging studies. In this retrospective work we analysed a series of 40 cases with localized GGOs potentially

associated with lung cancer in the search for practical guidelines, which could help reduce time to final diagnosis and treatment of lung cancer, and at the same time avoid unnecessary anxiety in patients with benign GGOs. We also tried to address some of the relevant management problems that may descend from finding such lesions, in particular regarding the indications and timing of surgery, and the appropriate volume of surgical resection.

To summarise our findings, the absence of a solid component, a polygonal shape and ill-defined margins were associated with benign, non-evolving GGOs (Figure 3), while apparent radial growth, a non-polygonal shape and clear-cut margins were associated with BAC or invasive adenocarcinoma.

Malignancy was more likely with a mixed GGO pattern (positive predictive value=0.76), although the correlation did not reach statistical significance. The diameter of the lesions was however not associated with malignancy in this series, possibly because some larger GGOs were inflammatory. We found the margins of the lesion to be especially important, and they should always be assessed in detail by HRCT.

Our findings are consistent with the observations of Li and coll. [12], who reported that a rounded shape was more likely in malignant than in benign GGOs, and that a mixed GGO pattern was associated with malignancy in 85% of the cases. Nambu and coll. [14] similarly reported that 90% of malignant GGOs in their series had well-defined margins, but this feature was present in 50% of benign GGOs as well.

These findings indicate that with growing experience it may become relatively easy to identify suspicious lesions based on the recognition of certain patterns, but it is not possible to reliably discriminate malignant from benign GGOs based on CT findings alone, as some benign lesions closely resemble their malignant counterparts (Figure 2).

Response to antibiotic trial is a simple criterion to rapidly exclude patients from further workup, and we therefore recommend it as the first management step.

In GGOs persisting beyond 2 months after antibiotics, core biopsy under CT guidance yielded a meaningful tissue fragment and helped to select patients for resection or follow-up in over 80% of the cases in our series, and it is now commonly employed in the evaluation of such lesions. Core biopsy for GGOs has been reported to have a low complication rate, a positive predictive value of 97% and a negative predictive value of 75% [15].

Oral antibiotics, repeat High- resolution CT and percutaneous core biopsy when indicated will delay appropriate surgery by about three months only.

In our experience the sensitivity of PET was low, 25% overall, and similarly poor results have been reported by several other authors [6, 10]. Therefore the routine use of PET in the evaluation of suspicious GGOs is not recommended.

Among our patients, 65% of focal GGOs for which a definitive diagnosis was made turned out to be

associated with BAC or mixed-type adenocarcinoma after careful workup, a finding consistent with Henschke's series in the USA [3], in which the malignancy rate was 18% for non-solid nodules (i.e. pure GGOs) and 63% for part-solid nodules. (i.e. mixed GGOs). HY Kim and coll. [10] found the malignancy rate for persistent GGOs to be 75%, whereas other Japanese or Korean groups observed malignancy rates in the range of 19% to 38%, perhaps due to different study populations [14,16,17].

Knowing that a relevant proportion of focal GGOs are associated with BAC or invasive adenocarcinoma, it would be logical to routinely proceed to biopsy and/or resection when one is encountered. However, at present it is impossible to tell which persistent GGOs will progress to aggressive disease with certainty, and how long it would take for them to do so.

According to Takashima's report [9], about 25% of the lesions remain radiologically stable for several-hundred days, even in the case of histologically proven BAC or adenocarcinoma. In another report by Kodama and coll. on 19 patients with pure GGOs, forty-two percent of the lesions were radiologically unchanged after 26-48 months [18].

Lesions progressing so slowly may remain clinically silent for the whole life of the patient, representing possible examples of overdiagnosis. As to atypical adenomatous hyperplasia, which normally presents as a pure GGO of limited size, no data are available about the actual risk and timing of progression to more aggressive forms if left untreated.

Therefore, especially with poor-risk surgical candidates, and with small pure GGOs, some lesions might be carefully followed after thorough discussion with the patient until signs of progression become evident.

When resection is chosen, treatment planning should take into account that a good correlation has been established between high-resolution CT findings and invasiveness in malignant GGOs. BAC without stromal invasion predominates in pure GGOs, while invasive adenocarcinoma becomes more frequent in mixed GGOs as the solid component increases [9].

Nakata and coll. [19] observed that 87% of GGOs with no or a minimal solid component represented pure BAC, whereas 56% to 91% of GGOs with a more abundant solid component represented invasive adenocarcinoma.

Similarly, in a number of reports by Japanese authors, the likelihood of nodal metastasis was nil for tumours with no or minimal solid component on high-resolution CT, and increased to 27-31% for those with a more evident solid component. [19-24].

Larger GGOs with a solid component are more likely to be PET-positive, and a high standardised uptake value has been reported to correlate with stromal invasion and lymphatic spread [25].

A visible solid component in the preoperative HRCT scan should thus warrant a more extensive resection, whereas a pure GGO could be approached more conservatively.

Treatment planning should also take into account that multifocality is a relatively common occurrence, with up to 25% of the patients harbouring multiple GGOs [9, 14].

In our series, six out of 19 patients with pathologically proven malignant GGOs had two or more lesions at the time of detection, and two more patients with a single GGO developed recurrent foci of carcinoma in the ipsilateral lung and we operated on again.

Multiple resections may therefore be required immediately or over several years' time, thus calling for lung-sparing procedures.

In fact, the prognosis after surgical resection for BAC associated with pure focal GGOs is excellent even after simple VATS wedge resection, which would be inadequate for solid lung carcinomas [26-29]. The reason may be that pure bronchioloalveolar carcinomas are true early lesions [13].

In a recent study, the cure rate of small early-stage tumours with anatomic segmentectomy was shown to be equivalent to that obtained with standard lobectomy, but with significantly less impact on postoperative respiratory function. Although the study was not randomized, it reported on over 500 patients in a controlled fashion [30].

Segmentectomy could thus be an oncologically acceptable operation for small early-stage lung cancer, allowing for adequate resection margins, removal of the local lymphatics, and preservation of functional lung tissue at the same time.

We therefore advocate it for GGOs, especially for those showing a minor solid component. If segmentectomy is difficult to perform with adequate margins, or if the solid component is greater than 50%, a standard lobectomy would be the preferred treatment. Simultaneous wedge resections are acceptable for multiple synchronous GGOs.

Preoperative percutaneous hook-wire marking is always carried out in our centre when a limited resection is planned, as focal GGOs may not be palpable at all [16].

This is a retrospective, single institution study on a relatively small series of patients. Despite these limitations, this study reproduces the findings reported by other groups, and supports a simple multistep approach to these patients, which can be applied regardless of personal experience with this entity.

In conclusion, while GGOs with selected features should be considered clearly suspicious, no single radiological trait is 100% accurate and predictive, and some benign lesions closely mimic their malignant counterparts. A stepwise management protocol based on oral antibiotics, short-term follow-up with high-resolution CT, and percutaneous core-biopsy increases the diagnostic accuracy over low-dose CT alone, and reduces time to definitive diagnosis without delaying appropriate treatment significantly. Segmentectomy might be the ideal resection volume for such tumours when feasible. The management of individual patients should be personalised.

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References

1. Hansell DM, Bankier AA, Mc Mahon H, Mc Loud TC, Müller NL, Remy J. Fleischner Society: Glossary of terms for thoracic imaging. *Radiology* 2008; 246: 697-722
2. Collis J, Stern EJ. Ground-Glass Opacity at CT: the ABC. *AJR Am J Roentgenol* 1997;169:355-367
3. Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley D, Miettinen OS; ELCAP Group. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. *AJR Am J Roentgenol* 2002;178(5):1053-7
4. Kushihashi T, Munechika H, Ri K, Kubota H, Ukisu R, Satoh S, Motoya H, Kurashita Y, Soejima K, Kadokura M, et al. Bronchioloalveolar adenoma of the lung: CT-pathologic correlation. *Radiology* 1994;193(3):789-93
5. Jang HJ, Lee KS, Kwon OJ, Rhee CH, Shim YM, Han J. Bronchioloalveolar carcinoma: focal area of ground-glass attenuation at thin-section CT as an early sign. *Radiology*. 1996;199(2):485-8
6. Gandara DR, Aberle D, Lau D, Jett J, Akhurst T, Heelan R, Mulshine J, Berg C, Patz EF Jr. Radiographic imaging of bronchioloalveolar carcinoma: screening, patterns of presentation and response assessment. *J Thorac Oncol* 2006;1:S20-S26
7. Nakata M, Saeki H, Takata I, Segawa Y, Mogami H, Mandai K, Eguchi K. Focal ground-glass opacity detected by low-dose helical CT. *Chest* 2002;121(5):1464-7
8. Kakinuma R, Ohmatsu H, Kaneko M, Kusumoto M, Yoshida J, Nagai K, Nishiwaki Y, Kobayashi T, Tsuchiya R, Nishiyama H, Matsui E, Eguchi K, Moriyama N. Progression of focal pure ground-glass opacity detected by low-dose helical computed tomography screening for lung cancer. *J Comput Assist Tomogr* 2004;28(1):17-23
9. Takashima S, Maruyama Y, Hasegawa M, Yamanda T, Honda T, Kadoya M, Sone S. CT findings and progression of small peripheral lung neoplasms having a replacement growth pattern. *AJR Am J Roentgenol* 2003;180(3):817-26
10. Kim HY, Shim YM, Lee KS, Han J, Yi CA, Kim YK. Persistent pulmonary nodular ground-glass opacity at thin-section CT: histopathologic comparisons. *Radiology* 2007;245(1):267-75
11. Infante M, Lutman FR, Cavuto S, Brambilla G, Chiesa G, Passera E, Angeli E, Chiarenza M, Aranzulla G, Cariboni U, Alloisio M, Incarbone M, Testori A, Destro A, Cappuzzo F, Roncalli M, Santoro A, Ravasi G; for the DANTE Study Group. Lung cancer screening with spiral CT Baseline results of the randomized DANTE trial. *Lung Cancer* 2008;59:355-363
12. Li F, Sone S, Abe H, Macmahon H, Doi K. Malignant versus benign nodules at CT screening for lung cancer: comparison of thin-section CT findings. *Radiology* 2004;233(3):793-8
13. Travis WD, Garg K, Franklin WA, Wistuba II, Sabloff B, Noguchi M, Kakinuma R, Zakowski M, Ginsberg M, Padera R, Jacobson F, Johnson BE, Hirsch F, Brambilla E, Flieder DB, Geisinger KR, Thunnissen F, Kerr K, Yankelevitz D, Franks TJ, Galvin JR, Henderson DW, Nicholson AG, Hasleton PS, Roggli V, Tsao MS, Cappuzzo F, Vazquez M. Evolving concepts in the pathology and computed tomography imaging of lung adenocarcinoma and bronchioloalveolar carcinoma. *J Clin Oncol* 2005;23(14):3279-87
14. Nambu A, Araki T, Taguchi Y, Ozawa K, Miyata K, Miyazawa M, Hiejima Y, Saito A. Focal area of ground-glass opacity and ground-glass opacity predominance on thin-section CT: discrimination between neoplastic and non-neoplastic lesions. *Clin Radiol* 2005;60(9):1006-17
15. Kim TJ, Lee JH, Lee CT, Jheon SH, Sung SW, Chung JH, Lee KW. Diagnostic accuracy of CT-guided core biopsy of ground-glass opacity pulmonary lesions. *AJR Am J Roentgenol* 2008;190(1):234-9
16. Oh JY, Kwon SY, Yoon HI, Lee SM, Yim JJ, Lee JH, Yoo CG, Kim YW, Han SK, Shim YS, Kim TJ, Lee KW, Chung JH, Jheon SH, Sung SW, Lee CT. Clinical significance of a solitary ground-glass opacity (GGO) lesion of the lung detected by chest CT. *Lung Cancer* 2007;55(1):67-73
17. Ohtsuka T, Watanabe K, Kaji M, Naruke T, Suemasu K. A clinicopathological study of resected pulmonary nodules with focal pure ground-glass opacity. *Eur J Cardiothorac Surg* 2006;30(1):160-3
18. Kodama K, Higashiyama M, Yokouchi H, Takami K, Kuriyama K, Kusunoki Y, Nakayama T, Imamura F. Natural history of pure ground-glass opacity after long-term follow-up of more than 2 years. *Ann Thorac Surg* 2002;73(2):386-92
19. Nakata M, Sawada S, Yamashita M, Saeki H, Kurita A, Takashima S, Tanemoto K. Objective radiologic analysis of ground-glass opacity aimed at curative limited resection for small peripheral non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2005;129(6):1226-31.
20. Asamura H, Suzuki K, Watanabe S, Matsuno Y, Maeshima A, Tsuchiya R. A clinicopathological study of resected subcentimeter lung cancers: a favorable prognosis for ground glass opacity lesions. *Ann Thorac Surg* 2003;76(4):1016-22
21. Matsuguma M, Yokoi K, Anraku M, Kondo T, Kamiyama Y, Mori K, Tominaga K, Tsuura Y, Honjo S. Proportion of ground-glass opacity on high-resolution computed tomography in clinical T1 N0 M0 adenocarcinoma of the lung: A predictor of lymph node metastasis. *J Thorac Cardiovasc Surg* 2002;124:278-284
22. Suzuki K, Kusumoto M, Watanabe S, Tsuchiya R, Asamura H. Radiologic classification of small adenocarcinoma of the lung: radiologic-pathologic correlation and its prognostic impact. *Ann Thorac Surg* 2006;81:413-20
23. Okada M, Nishio W, Sakamoto T, Uchino K, Hanioka K, Ohbayashi C, Tsubota N. Correlation between computed tomographic findings, bronchioloalveolar carcinoma component, and biologic behavior of small-sized lung adenocarcinomas. *J Thorac Cardiovasc Surg* 2004;127(3):857-61
24. Ohde Y, Nagai K, Yoshida J, Nishimura M, Takahashi K, Suzuki K, Takamochi K, Yokose T, Nishiwaki Y. The proportion of consolidation to ground-glass opacity on high resolution CT is a good predictor for distinguishing the population of non-invasive peripheral adenocarcinoma. *Lung Cancer* 2003;42(3):303-10
25. Okada MD, Tauchi S, Iwanaga K, Mimura T, Kitamura Y, Watanabe H, Adachi S, Sakuma T, Ohbayashi C. Associations among bronchioloalveolar carcinoma components, positron emission tomographic and computed tomographic findings, and malignant

behavior in small lung adenocarcinomas. *J Thorac Cardiovasc Surg* 2007;133:1448-54

26. Watanabe S, Watanabe T, Arai K, Kasai T, Haratake J, Urayama H. Results of wedge resection for focal bronchioloalveolar carcinoma showing pure ground-glass attenuation on computed tomography. *Ann Thorac Surg* 2002;73(4):1071-5
27. Nakamura H, Saji H, Ogata A, Saijo T, Okada S, Kato H. Lung cancer patients showing pure ground-glass opacity on computed tomography are good candidates for wedge resection. *Lung Cancer* 2004;44(1):61-8
28. Yamada S, Kohno T. Video-assisted thoracic surgery for pure ground-glass opacities 2 cm or less in diameter. *Ann Thorac Surg* 2004;77(6):1911-5
29. Mun M, Kohno T. Efficacy of thoracoscopic resection for multifocal bronchioloalveolar carcinoma showing pure ground-glass opacities of 20 mm or less in diameter. *J Thorac Cardiovasc Surg* 2007;134(4):877-82
30. Okada M, Koike T, Higashiyama M, Yamato Y, Kodama K, Tsubota N. Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study. *J Thorac Cardiovasc Surg* 2006;132(4):769-75

TABLE 1 - Sensitivity, specificity, accuracy and predictive values of selected CT features

FEATURE	TP	FP	TN	FN	Sensitivity (95% C.I.)	Specificity (95% C.I.)	Accuracy (95% C.I.)	PPV (95% C.I.)	NPV (95% C.I.)
Multiple	6	2	9	13	0.32 (0.13-0.57)	0.82 (0.48-0.98)	0.50 (0.31-0.69)	0.75 (0.35-0.97)	0.41 (0.21-0.64)
Non-polygonal	19	6	5	0	1.00 (0.83-1.00)	0.45 (0.16-0.76)	0.80 (0.61-0.92)	0.76 (0.55-0.91)	1.00 (0.48-1.00)
Mixed GGO	13	4	7	6	0.68 (0.43-0.87)	0.64 (0.31-0.89)	0.67 (0.47-0.83)	0.76 (0.50-0.93)	0.54 (0.25-0.81)
Non-smooth	17	6	5	2	0.89 (0.67-0.99)	0.45 (0.17-0.77)	0.73 (0.54-0.88)	0.74 (0.52-0.90)	0.71 (0.29-0.96)
Radial growth	19	7	4	0	1.00 (0.82-1.00)	0.36 (0.11-0.69)	0.77 (0.58-0.90)	0.73 (0.52-0.88)	1.00 (0.40-1.00)
Clear-cut margin	19	6	5	0	1.00 (0.83-1.00)	0.45 (0.16-0.76)	0.81 (0.62-0.92)	0.76 (0.55-0.91)	1.00 (0.48-1.00)
Clear cut + radial	19	4	7	0	1.00 (0.82-1.00)	0.64 (0.31-0.89)	0.87 (0.69-0.96)	0.83 (0.61-0.95)	1.00 (0.59-1.00)

TP=True Positives; FP=False Positives; TN=True Negatives; FN= False Negatives; PPV=Positive predictive value; NPV=Negative predictive value

TABLE 2- Patients' management and pathological findings

	MANAGEMENT					
	Lobectomy	Segmentectomy	Lob+We	Chemo/RT	FU	Total Pts.
PATHOLOGY				0	0	
Adeno/BAC	6	3	2	1	0	12
BAC	6	0	0	1	0	7
AAH	0	1	0	0	1	2
Benign	0	0	0	0	9	9
Undetermined	0	0	0	0	10	10
Total Procedures	12	4	2	2	20	40

One patient had two synchronous GGOs and was operated on twice

LEGENDS - Adeno/BAC= mixed-type adenocarcinoma , BAC= bronchioloalveolar carcinoma, AAH= Atypical adenomatous hyperplasia, Lob+We=Lobectomy + wedge resections, RT=radiotherapy, FU= follow-up

FIGURE LEGENDS

Figure 1 – Diagram of patients’ management procedures

In six patients, the lesion was retrospectively visible in an earlier CT scan, and antibiotics were not administered.

AAH= Atypical adenomatous hyperplasia.

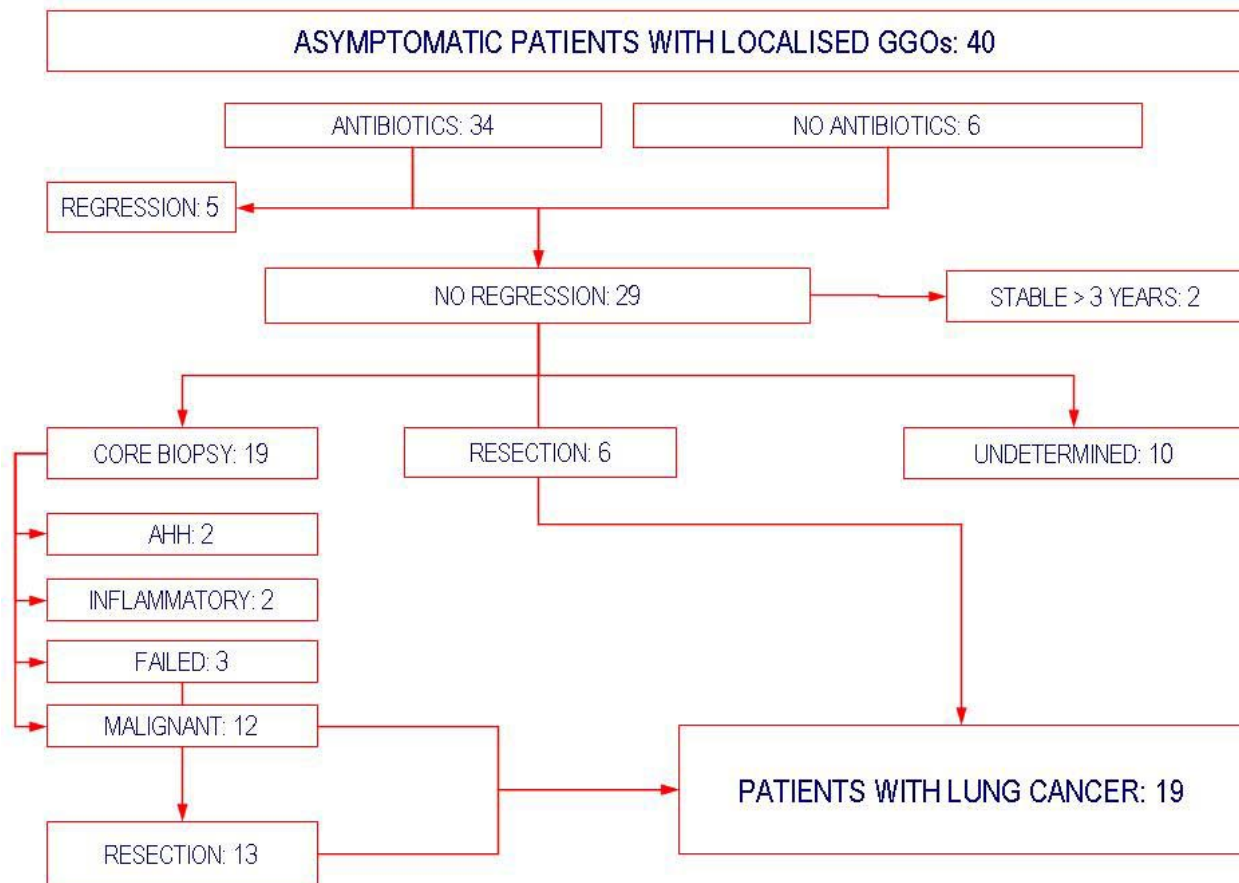


Figure 2 - Benign and malignant GGOs with close resemblance

A: Persistent ground-glass opacity in the left upper lobe with irregular contour, clear-cut margins, a minimal solid component and tiny air spaces. Mixed-type adenocarcinoma.

B: Similar aspect in this lesion which persisted for over 3 months after antibiotics. Core biopsy yielded inflammatory tissue. The lesion eventually regressed over several months’ time.

C: Persistent ground-glass opacity in the right lower lobe with irregular shape and minimal solid component. Core biopsy was suggestive for bronchioloalveolar carcinoma, confirmed by resection.

D: Similar aspect in this lesion in the left lower lobe. Core biopsy yielded inflammatory tissue and fibrosis.

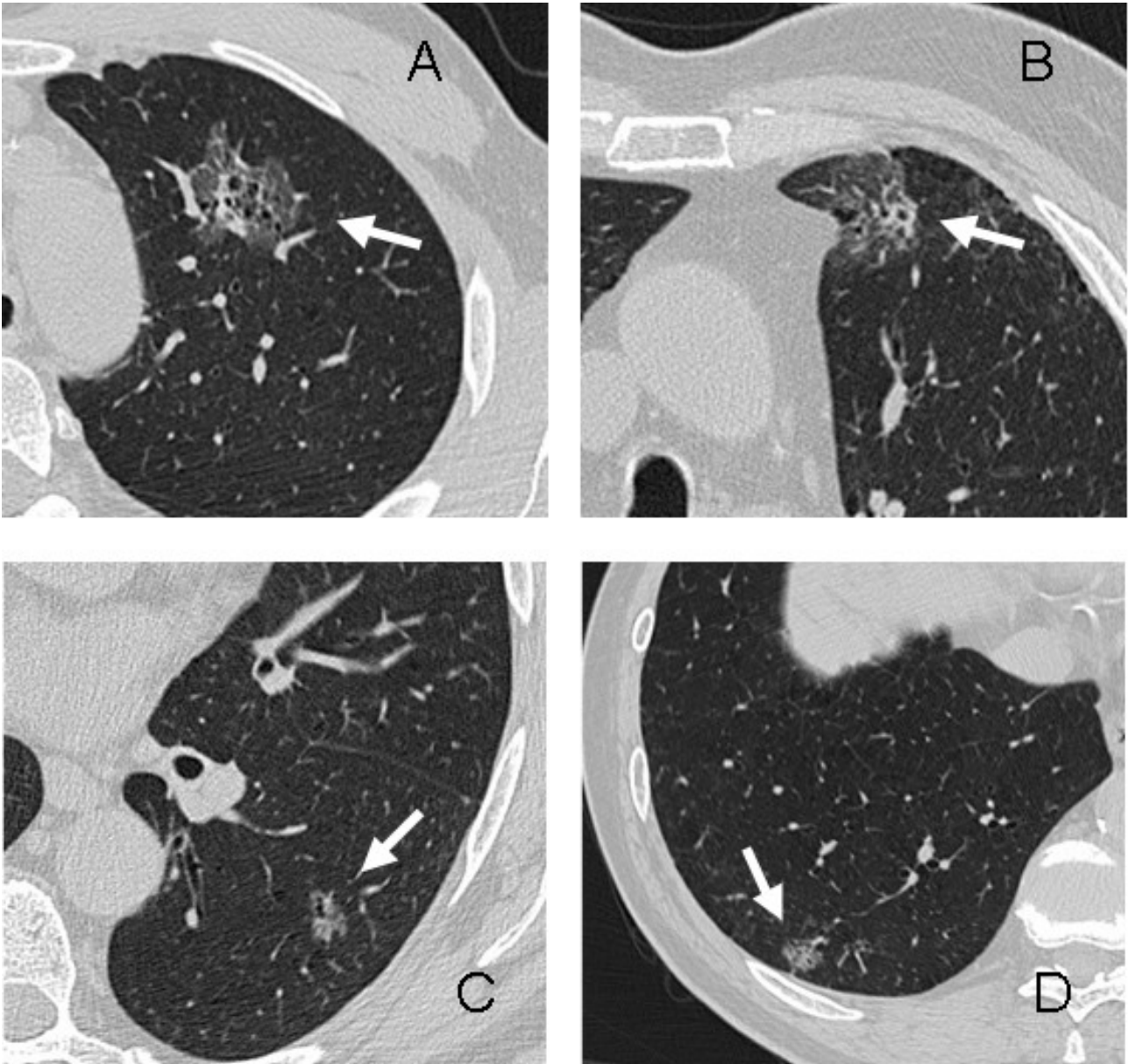


Figure 3 - Benign GGOs

A: large ground-glass opacity in the right lower lobe with irregular contour and subsegmental distribution. Following antibiotic treatment, the lesion regressed in three months.

B: persistent pure ground-glass opacity in the left upper lobe with polygonal shape. This patient had a synchronous contralateral stage I solid adenocarcinoma, which was resected. The lesion has remained stable for 46 months.

