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· Original Article ·

Which surgery for ground glass opacity lung nodules?

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Abstract **Objective:** Pulmonary ground glass opacity (GGO) nodules represent a significant dilemma in oncology since its diagnosis in clinical practice has increased because of growing application of low dose computed tomography and screening program. The aim of this study is to analyze the clinical and pathological features, the overall survival (OS) and disease-free interval (DFI) in surgically resected solitary ground glass nodules in order to assess the surgical treatment of choice. **Methods:** We retrospectively analyzed 49 patients (M/F=25/24) with a mean age of 67.7 (range, 40–81) years who underwent lung resection for solitary GGO nodules among 570 reviewed CT of patients who were treated for lung neoplasms between 2010 and 2016. The cohort included 22 pure GGO nodules and 27 part solid GGOs (also called mixed GGOs). **Results:** Median maximum diameter of GGOs, defined as the largest axial diameter of the lesion on the lung-window setting, was 17 (range, 5–30) mm. GGO nodules were removed by wedge resection, segmentectomy, or lobectomy in 17 (35%), 9 (18%), and 23 (47%) cases, respectively. Pathologic diagnosis was atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), invasive adenocarcinoma (IA) or multifocal adenocarcinoma (MAC) in 4 (8.2%), 9 (18.4%), 11 (22.4%), 22 (44.9%) and 3 (6.1%) cases, respectively. With a median follow up of 47 months the OS and DFI of the entire cohort was 46.3 and 43 months, respectively. The histotype (P=0.008), the dimension of GGO (P=0.014) and the PET-SUV max (P=0.001) were independent prognostic factors of worse survival. Sex, age, previous lung surgery, type of surgical resection and the mediastinal lymph-node evaluation did not impact on OS and DFI. Analyzing the 22 pure GGO nodules, we found a 3-year OS and DFI of 98% and 100% respectively, significantly different from 80% and 75% respectively of part-solid GGOs (log-rank P=0.043 and P=0.011). **Conclusion:** Our data suggest an indolent behaviour of tumour presenting as solitary GGO nodules, especially in case of pure GGOs. In our series wedge resections guarantee the same results in terms of OS and DFI when compared to

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lobectomies. Sublobar resections without mediastinal lymph-nodes evaluation represent the treatment of choice for pure-GGO. More studies are needed to assess its role for part-solid GGO nodules.

Keywords ground glass opacity; GGN; non-small cell lung cancer; surgery

The increasingly use of low-dose CT and high-resolution computed tomography (HRCT) for both cancer surveillance and screening program, had significantly augmented the detection of solitary pulmonary nodules and ground-glass opacities (GGOs). GGOs that have been defined as focal area of hazy increased attenuation on CT through preservation of bronchial and vascular structures, are radiologically distinguished into 2 types: pure GGOs which do not present a solid component and part-solid o mixed GGOs that have both a pure GGO area and a consolidated part[1].

A recent paper, published by Van Haren *et al.*, has revealed that age (older *vs.* younger), sex (male *vs.* female), non-smokers and race (non-white *vs.* white) are significant independent predictors of identifying GGOs in CT scan[2].

In the last years several guidelines have been drawn up in order to establish which is the best management of GGOs. Follow-up plays a central role in clinical assessment and management of GGOs since ground glass opacities can be both benign lesions and tumours. Although most GGOs are transient (disappearance rate of 38% in pure GGO and 49% in part solid GGO)[3], persistent subsolid nodules, especially part-solid, have a high probability of malignancy[4].

Even though subsolid nodules are more likely to be malignant when compared to solid nodules incidentally detected, semisolid lesions have a better prognosis because they may correspond to preinvasive and invasive lesions with a slow progression. Pure GGOs (especially those <5 mm) are generally non-invasive lesions (AAH or AIS), part solid GGOs are minimally invasive lesions (MIA) or invasive lesions[5-6].

For this reason, lung cancer presenting as GGOs has been reported with an excellent long-term survival: 5-year overall survival, 97% versus 84% of patients having a solid nodule without GGO component[7]. Moreover, analysing only pure GGO group, the 5-year OS and DFS rates are 100% and 99.1%, respectively[8].

The role of surgery in the management of persistent GGOs is poorly defined. According to several studies the role of non-surgical biopsy is limited: considering the high rate of false negative results, the use of fine needle biopsy (FNAB) for GGO lesion should be considered for part solid GGOs with diameter >1 cm[4,9].

For this reason, surgery seems to offer better diagnostic accuracy and, given the advantages of minimally invasive technique, guarantees low morbidity and mortality[10-12].

Although lobar resection is still considered the optimal treatment for early-stage non-small cell lung cancer (NSCLC), sub-lobar resections (anatomical segmentectomy or wide wedge resection) are gaining increasing consents for small, non-invasive, or minimally invasive lesions, especially those with GGO characteristics[13].

The aim of our study is to evaluate the clinical and pathological features, the OS and DFI in surgically resected solitary ground glass nodules in order to assess the surgical treatment of choice.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.3978/j.issn.2095-6959.2021.07.002).

1 Materials and Methods

1.1 Materials

Among 570 reviewed CT scan of patients treated for lung tumours between 2010 and 2016, we have retrospectively analysed data of all solitary GGOs (pure or part solid) that underwent lung resection.

1.2 Methods

The specimens were reviewed by two pathologists, the preoperative CT-scans of patients were reviewed by one radiologist and two thoracic surgery residents. Median maximum diameter of GGOs was defined as the largest axial diameter of the lesion on the lung-window setting.

Indications for surgery were debated in all patients during the weekly multidisciplinary team meeting (MDT). Preoperative assessment included clinical examination, blood exams, thoracic and abdomen computed tomography scan, cardiological assessment and respiratory function tests. In 28/49 (57%) cases, a positron emission tomography (PET-CT scan) was executed.

Sex, age, previous malignancies, type of lung surgery (wedge resection, segmentectomy, lobectomy) and approach (VATS, ROBOT, or thoracotomy), lymph-nodal status, relapse, length of hospital stay and OS of patients were analysed. R0 resection (negative surgical margins) was established by the pathologists as the macro and microscopically absence of tumour cells on resection

margins.

Postoperative mortality and morbidity were defined within 30, 60 and 90 days from surgery. The Clavien-Dindo classification was used to stage the post-operative complications. The VIII edition of TNM was used to restage all specimens.

This retrospective research was carried out according to principles outlined in the Helsinki declaration (as revised in 2013) and in agreement with Italian laws on biomedical research and institutional guidelines. Approval by the institution ethics committee was not required as dictated by local laws. All patients presented full consent about data collection and its use in the current study

1.3 Statistical analysis

Descriptive statistics were expressed as mean and standard deviation for quantitative variables and as frequencies (percentages) for categorical ones.

The OS was considered from the time of surgery until decease or the day of the last follow-up. DFI was considered from the time of surgery to the first relapse.

The Kaplan-Meier method was utilised to estimate the cumulative survival. We considered values of $P<0.05$ as statistically significant. The COX proportional hazard regression was utilised to univariate analyses.

Statistical analysis was performed using SPSS statistic software (IBM SPSS statistics20 IBM Corporation, Chicago, IL).

2 Results

The data of 49 patients with solitary pulmonary GGOs who underwent surgical resection between 2010 and 2016 were analysed. Data on population were described in Table 1.

Median maximum diameter of GGOs was 17 (range, 5–30) mm. The open approach was used in 32 cases (65.3%). GGO nodules were resected by wedge resection, segmentectomy, or lobectomy in 17 (35%), 9 (18%), and 23 (47%) cases, respectively (Table 1).

Pathologic diagnosis was atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), invasive adenocarcinoma (IA) or multifocal adenocarcinoma (MAC) in 4 (8.2%), 9 (18.4%), 11 (22.4%), 22 (44.9%) and 3 (6.1%) cases, respectively (Table 2).

The TNM of all lesions, according to the VIII edition, was reported in Table 3.

No post-operative mortality was reported. Eleven patients (22.4%) had post-operative complications: 7 prolonged air leaks (3 grade I, 3 grade II, 1 grade IIIb), 2 atrial fibrillation (grade II) and 1 anaemia (grade II).

With a median follow up of 47 months the OS and DFI of the whole cohort was 46,3 and 43 months respectively. Six patients experimented recurrences (2 distant and 4 local) (Figure 1).

Table 1 Patients characteristics and surgical results

Number of patients	Values (total *n*=49)
Male/female, n	25/24
Mean age in years, mean (range)	67.7 (40 to 81)
Smoker, n	
Active	11
Former	26
Never	12
Previous malignancies (%)	15 (30.6)
Size of nodule (mm), mean (range)	17 (5 to 30)
Pure GGOs, n (%)	22 (44.9)
Pet positivity, n	
Positive	19
Negative	9
Not done	21
Surgical approach, n (%)	
Thoracotomy	32 (65.3)
VATS	9 (18.4)
Robot	8 (16.3)
Type of surgery, n (%)	
Wedge resection	17 (35.0)
Segmentectomy	9 (18.0)
Lobectomy	23 (47.0)
Lymph node dissection, n (%)	
Yes	38 (77.6)
Not done	11 (22.4)
Surgical complications, n (%)	11 (22.4)
Grade I	3
Grade II	7
Grade III	1
Grade IV–V	0
Post-operative stay (days), mean (range)	7 (3 to 32)
Post-operative chest tube (days), mean (range)	3 (1 to 30)

Table 2 Pathological results

Histology	Number of cases	3-year survival, %
Pure GGOs		
AAH	4	100
AIS	9	99
MIA	7	100
IA	1	95
MAC	1	—
Mixed GGOs		
MIA	4	90
IA	21	78
MAC	2	50

Table 3 TNM staging (VIII edition)

TNM	Number of cases
Pre-invasive lesions (AAH)	4
T	
Tis	9
1 (mi)	11
1a	8
1b	7
1c	2
2	5
2b	1
3	2
4	0
N	
X	11
0	35
1	2
2	1
3	0
M	
1 (1a-1b)	0
2	0

The histological type (*P*=0.008), the dimension of GGO (*P*=0.014) and the maximum standard uptake value (SUV max) of PET-CT (*P*=0.001) were independent prognostic factors of poor survival. Age, sex, previous pulmonary resections, type of surgery and the mediastinal lymph-node evaluation did not impact on OS and DFI (Table 4).

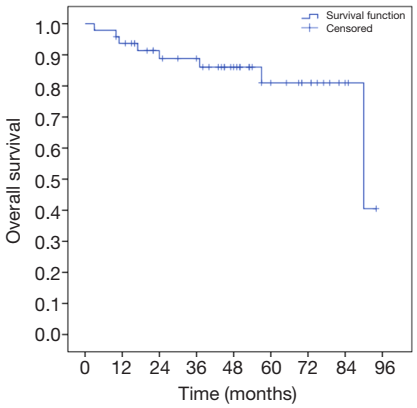

Figure 1 Overall survival of the entire cohort.

Table 4 Univariate analysis for Overall Survival

Variable	Univariate analysis	HR (95% CI)
Age	n.s.	—
Sex	n.s.	—
PET positivity	*P*=0.001	1.82 (1.28–2.01)
GGO dimension	*P*=0.014	1.19 (1.03–1.37)
Type of resection (wedge *vs.* segmentectomy *vs.* lobectomy)	n.s.	—
Previous lung surgery	n.s.	—
Histology (AAH + AIS *vs.* MIA *vs.* IA *vs.* MAC)	*P*=0.008	10.1 (1.84–55.8)
Mediastinal lymph node evaluation	n.s.	—

n.s., no statistical significance.

Examining the 22 pure GGOs, we observed a 3-year OS and DFI of 98% and 100% respectively, significantly better than 80% and 75% respectively of part-solid GGOs (log-rank *P*=0.043 and *P*=0.011) (Figures 2,3).

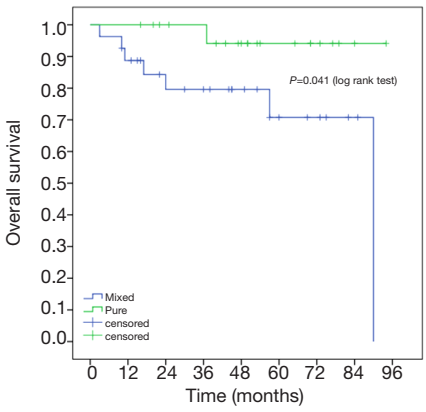

Figure 2 Overall survival according to GGO type (pure versus mixed).

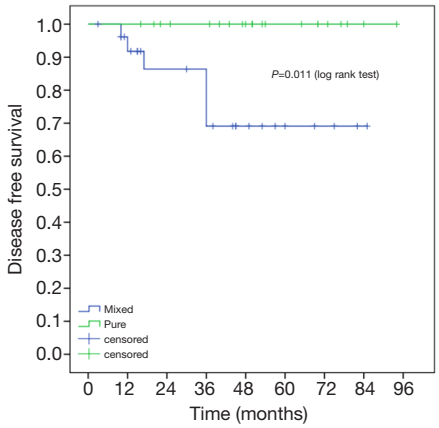

Figure 3 Disease free survival according to GGO type (pure versus mixed).

3 Discussion

The best surgical approach for early-stage NSCLC is still debating. Even though lobectomy is still considered the gold standard, sub-lobar resections seem to offer promising results for small, non-invasive, or minimally invasive lesions, particularly those with GGO characteristics[13].

Recently, two reviews and one meta-analysis state that sub-lobar resection for pure adenocarcinoma *in situ* ≤2 cm, produce comparable long-term outcomes as lobar resection[14-16].

A recent systematic review and metanalysis conducted by Ijsseldijk *et al.* analyses oncological outcomes of patients who underwent lobar or sub-lobar resections showing for pT1a NSCLC no difference in 5-year OS between lobectomy and parenchymal sparing resection[17].

However, conclusive recommendations will only be obtained when the results of large randomised trials are available. The on-going JCOG0802/WJOG4607L, JCOG0804/WJOG4507L and JCOG1211 trials have been originated to confirm the equivalence of sub-lobar resection for stage I NSCLC patients stratified according to preoperative thin-slice CT findings[18-19].

The JCOG0804/WJOG4507L trial, analysing the impact on long term survival of wide wedge resection in peripheral lung cancer presenting as predominantly GGO (with maximum tumour diameter ≤2.0 cm and with consolidation tumour ratio ≤0.25), has shown a 5-year relapse-free survival (RFS) of 99.7%, with no local relapses. This study has revealed that sub-lobar resection (primarily wedge resection) offers adequate local control and RFS for peripheral lung cancer presenting as predominantly GGO[20].

More data on the comparison between lobectomy versus sub-lobar (segmentectomy or wedge) resection in NSCLC ≤2 cm will be available after the completion of the ongoing randomized clinical trial (RCT) CALGB/ALLIANCE 140503, a phase III RCT of lobectomy versus sub-lobar resection for small (≤2 cm) peripheral T1aN0 NSCLC. Primary data on perioperative outcomes (morbidity and mortality) has shown comparable results between lobectomy and sub-lobar resections[21].

According to the mentioned studies, we have reported in our analysis and excellent OS and DFS. Moreover, while the histological type (P=0.008), the dimension of GGO (P=0.014) and the SUV max at PET-CT (P=0.001) are independent prognostic factors of worse survival, the type of surgical resection and the mediastinal lymph-node evaluation did not impact on OS and DFI. Several studies have shown that pure GGOs have a low risk of lymph node spread[22-23]. In a recent review which analyses 6,137 patients, in sub-population of 821 AIS/MIA cases, only one patient had N1 lymph node metastasis and no one showed N2 positive nodes; the disease-free survival ranged from 93% to 100%[24].

The main limitations of our study are the number of enrolled patients and the retrospective nature of the analysis. However, we believe that the obtained results, in line with the existent literature, can give a further evidence on the role of surgery in lung cancer presenting as sub-solid lesions.

Our data, confirmed by large literature studies, advocate an indolent behavior of tumor presenting as solitary GGO nodules, particularly for pure GGOs. In our series wedge resections produce the same results in terms of OS and DFI comparing with lobectomy. Sub-lobar resections without mediastinal lymph-nodes assessment represent the treatment of choice for pure-GGO. Additional studies are required to evaluate its role for part solid GGO nodules.

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