Pregnancy May Have Little Influence on Ground-glass Opacities Suspected for Lung Adenocarcinoma

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Abstract

Purpose: Due to the popularity of low-dose computed tomography in lung cancer screening, young women spotted with ground-glass opacities (GGO) is a growing subgroup in clinical practice. We aim to investigate the influence of pregnancy on GGOs suspected for lung adenocarcinoma.

Methods: This retrospective study collected a series of female patients who were pregnant in follow-up of GGO lesions. The last CT images of GGO before pregnancy (CT1) and the first CT images after pregnancy (CT2) were reviewed to assess any radiologic change. Young female patients who were not pregnant in long-term (> 12 months) follow-up of GGO were enrolled as a comparison group. We also enrolled patients who gave birth within two years before surgical resection of GGOs.

Results: Four patients were enrolled according to the criteria. There was no significant change of the GGOs in all four patients with a median follow-up duration of 45.5 (range: 17-86) months. Two patients were diagnosed pathologically to be minimally invasive adenocarcinoma, one was invasive adenocarcinoma and one did not undergo surgery. Six patients were enrolled in the comparison group and no significant change was witnessed in all the nodules. In those patients who gave birth within two years before surgical resection of GGOs, we found that the majority present as pre-invasive lesions, and those with invasive adenocarcinomas were bigger in size and possess more solid component radiologically.

Conclusion: Pregnancy seems to have little impact on GGOs suspected for lung adenocarcinoma. Therefore, pregnancy might be safely planned during the follow-up of GGOs.

1. Introduction

Due to the increasing use of CT in lung cancer screening, an increasing number of GGO-featured adenocarcinomas are detected (Zhang, Fu, & Chen, 2020). Recent screening program based in both hospital and community using low-dose computed tomography (LDCT) detected lung cancer in a significant proportion of young female nonsmokers, and the majority of the nodules manifest as GGOs (Chong et al., 2005; Zhang, Jheon, et al., 2020). Young women spotted with GGOs suspected for adenocarcinoma is a growing subgroup in clinical practice and requires attention. For young women with childbearing plans, clinical management for incidental GGOs could be challenging, for no consensus has been achieved. GGO-featured lung adenocarcinoma is generally considered indolent and only requires long-term follow-up. However, hormone spikes, immunoediting during pregnancy and postpartum hormonal variations may interfere with the progression of the GGO, of which the possible impact is still unclear. Furthermore, mental pressure together with occupational stress may also lead the patients on to incorrect treatment decisions. To our knowledge, there has been few studies on this particular subgroup, mainly due to the scarcity of young female patients that underwent pregnancy during the follow-up of GGOs. Therefore, we reviewed the CT images of patients who went through pregnancy during the follow-up of GGOs to assess radiological change, investigated the clinicopathologic characteristics of female

patients that gave birth within two years before surgical resection of GGOs to speculate the possible influence that pregnancy may pose on GGOs, and provide evidence on the proper clinical management for this patient subgroup.

2. Materials And Methods

2.1 Patients

This study was approved by the institutional review board (Fudan University Shanghai Cancer Center IRB 2008223-9, date: 2020/07/14). We retrospectively reviewed the medical records and obstetrical history of patients with pulmonary GGOs who underwent surgical resection or paid a visit to outpatient at Fudan University Shanghai Cancer Center (FUSCC), Thoracic Department from April 2012 to June 2021.

Inclusion criteria was: (1) presence of persistent pulmonary GGO lesions; (2) pregnancy during the follow-up of GGOs (3) thin-section CT scans images before and after pregnancy; The last CT images of GGO before pregnancy (CT1) and the first CT images after pregnancy (CT2) were reviewed to assess any radiologic change. Young female patients (age:20-40) who were not pregnant in long-term follow-up (> 12 months) of GGO were enrolled as a comparison group. Patients who gave birth within two years before the surgery of GGOs were also enrolled. The following clinicopathologic variables were collected: age, smoking status, history of other malignancy, pathological subtype. This study was approved by the institutional review board of FUSCC. Informed consent was waived, because this was a retrospective study.

2.2 Radiologic and histologic evaluation

CT scans of the lung were performed with a helical technique using a 64 or 40 multi-detector scanner (Siemens Somatom Sensation, Berlin, Germany). We used the following scanning parameters: pitch, 1.2; section thickness and interval, 5.0 and 5.0 mm; reconstruction section width and interval, 1.0 and 1.0 mm; and FOV, 375 mm; 120 kV, 270 mAs. Two radiologists were responsible for the evaluation of nodule size, shape and density changes before and after pregnancy. Disagreements were resolved by a senior radiologist. The last computed tomography images before giving birth (CT1) and the first images after giving birth (CT2) were reviewed for each nodule. The size of the whole GGO lesion was defined as the maximum diameter on the axial plane measured on the lung window (window width: 1600 HU; window level: - 600 HU; width and interval, 1.0 and 1.0 mm, respectively). An increase of the whole GGO lesion size was defined as an increase of ≥ 2 mm from the size on CT1 to the size on CT2. This was based on a series of studies on the threshold to determine true nodule growth during follow-up(Kakinuma et al., 2012; Kim et al., 2016; Solomon et al., 2021). Changes in shape and density were determined by experienced radiologists. Postoperative pathologic diagnosis was made according to the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society/ European Respiratory Society classification as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma (IAD).

3. Result

3.1 Follow-up history and clinical characteristics of patients who went through pregnancy during the follow-up of GGOs

Four patients who went through pregnancy during the follow-up of GGOs were enrolled. Timeline and basic information were presented in Fig. 1 and the comparison of CT images were shown in Fig. 2. GGO was diagnosed incidentally in all four patients. They were all non-smokers, and had no specific co-morbidities. All six nodules show no significant change in size, shape or density. One of them display a subtle enlargement (patient D), from 6mm to 7mm, which did not meet our definition of enlargement, and the lesion was diagnosed pathologically to be minimal invasive adenocarcinoma. One patient did not underwent surgical resection (patient A). Only one of them had a pathological result of invasive adenocarcinoma (patient C), size of the nodule was 15mm, yet it has not changed in 86 months. She was not originally diagnosed in our hospital and did not seek medical advice during the follow-up. This same patient, however, had witnessed a new GGO appearing in the same lobe, with the size of 9mm. This new GGO pathologically turned out to be minimal invasive adenocarcinoma. Only one patient (D) had multiple nodules, with the size of 5mm, 5mm and 4mm.

Young female patients that was not pregnant in long-term (>12 months) follow-up of GGO was enrolled as a comparison group. Six patients with median follow-up length of sixteen months were investigated. Timeline, basic information, and the comparison of CT images were shown in Table 1 and Fig. 3. There was also no significant change in size, shape or density of the nodules. All six patients were surgically resected of their GGOs, the majority of the nodules were MIA.

Table 1
Clinicopathological characteristics of six female patients that was not pregnant in long-term (>12 months) follow-up of GGO

Patient	Follow-up length in months	Location	Size(mm)	Pathology	Age at surgery
E	13.4	RUL	8.5	MIA	30
F	16.6	LUL	6	MIA	29
G	19.6	LUL	6	MIA	25
H	51.1	LUL	7	AIS	23
I	13.4	RUL	6	MIA	27
J	11.8	RML	5	MIA	29
RUL: right upper lobe; LUL: left upper lobe; RUL: right upper lobe; RML: right middle lobe; AIS: adenocarcinoma in situ; MIA: minimally invasive adenocarcinoma;					

3.2 Clinicopathological characteristics of patients who gave birth within two years before surgery resection of GGOs

After delivery, women experience abrupt changes in the hormonal environment. To further investigate the influence of pregnancy and delivery on GGOs suspected for lung adenocarcinoma, we enrolled patients who gave birth within two years before surgery resection of GGOs. Clinicopathological factors of the forty patients enrolled were presented in Table 2. The majority of patients were under the age of thirty-five. Eleven of them went through surgical resection within one year after giving birth. None of them have a smoking history. Almost half of the patients deliver their children in the form of cesarean section. Interestingly, sixteen patients have a family history of malignancy, seven in first-degree relative and nine in second-degree relative. Radiologically, thirty-four patients present with pure GGO while six present with subsolid GGO. Those subsolid GGOs were also larger in size (Average size: 11.3mm vs 7.7mm). Two patients underwent lobectomy due to multiple lesions in the same lobe, while others underwent sublobar resection. Histologically, the majority of patients were AIS and MIA, three turned out to be invasive adenocarcinoma (Patient K, L, M). The three invasive adenocarcinoma all present with subsolid component and a bigger size (14, 17 and 15mm). CT images of the three invasive adenocarcinomas were presented in Fig. 4. No post-operative complication occurred in this cohort.

Table 2
Clinicopathological characteristics of forty female patients with GGOs who went through surgical resection

Patient profile	n=40
Age, years	
≤30	19(47.5%)
31-35	19(47.5%)
>35	2(5%)
Smoking history, n (%)	
Never	40(100%)
Ever	0(0%)
Birthgiving method, n (%)	
Natural labor	22(55%)
C-section	18(45%)
Years after pregnancy	
1	11(37.9%)
2	29(62.1%)
History of malignancy, n (%)	
Thyroid cancer	1(2.5%)
Family history, n (%)	
First-degree relative	7(17.5%)
Second-degree relative	9(22.5%)
CT manifestation, n (%)	
pure GGO	34(85%)
subsolid GGO	6(15%)
Nodule size, n (%)	
≥10mm	7(17.5%)
<10mm	33(82.5%)
Type of resection, n (%)	

GGO: ground-glass opacity; C-section: cesarean section; VATS: video-assisted thoracic surgery; AIS: adenocarcinoma in situ; MIA: minimally invasive adenocarcinoma; IAD: invasive adenocarcinoma;

Patient profile	n=40
Lobectomy or more	2(5%)
Sublobar resection	38(95%)
Surgical approach, n (%)	
VATS	37(92.5%)
Others	3(7.5%)
Histological type, n (%)	
MIA	31(77.5%)
AIS	5(12.5%)
IAD	3(7.5%)
Benign	1(2.5%)
GGO: ground-glass opacity; C-section: cesarean section; VATS: video-assisted thoracic surgery; AIS: adenocarcinoma in situ; MIA: minimally invasive adenocarcinoma; IAD: invasive adenocarcinoma;	

4. Discussion

In the recent decades, an increasing number of GGO lesions are detected, due to the popularity of LDCT as a lung cancer screening approach(Zhang, Jheon, et al., 2020). Histologically, GGO can be benign, pre-invasive or invasive adenocarcinoma(Zhang, Fu, et al., 2020). Lung adenocarcinoma manifesting as GGO is a special clinical subtype and is more prevalent in young female non-smokers who are not traditionally “high-risk” population. There is still no consensus on treatment or follow-up plans for young female patients with GGOs. Meanwhile, occupational pressure and potential childbearing plans make proper clinical management more challenging for clinicians. Therefore, we collected the follow-up CT images of four patients who went through pregnancy during the follow-up of GGOs. There was no significant change of the GGO in all four patients in a median follow-up duration of 45.5 (range: 17-86) months. In a comparison group of six patients, also no significant change was witnessed in all the nodules. We further analyzed a series of forty female patients who give birth within two years before surgical resection of GGOs to assess the possible impact of pregnancy and delivery. In this cohort, the majority of GGOs were pre-invasive lesions, and those with invasive adenocarcinomas were bigger in size and possess more solid component radiologically.

A major change induced by pregnancy is surging hormone levels. Estrogen has long been postulated as a contributor for lung cancer development and progression. Estrogen receptors (ER) are consistently found in lung cancer tissues and cell lines, especially adenocarcinoma, and mostly in the form of the ER β (Huang et al., 2019; Rodriguez-Lara, Hernandez-Martinez, & Arrieta, 2018). Estrogen promoted lung cancer cell migration via the ER β activation of the MEK/ERK signaling pathway. There are also evidences

showing that estrogen interacts with the EGFR signaling pathways, promoting lung cancer cell metastasis through epithelial mesenchymal transition(Zhao et al., 2015). Estrogen can also stimulate lung cancer cell proliferation, death resistance and angiogenesis(Rodriguez-Lara et al., 2018). However, there were controversies in the relationship between the hormone replacement therapy (HRT) and lung cancer. Although most studies reported estrogen or HRT adversely affected the prognosis of lung cancer patients, some reported HRT decreased the risk and favorably affected the prognosis(Ayeni & Robinson, 2009; Chen et al., 2007; Farquhar, Marjoribanks, Lethaby, Suckling, & Lamberts, 2009; Hsu, Chu, & Kao, 2017; Schabath, Wu, Vassilopoulou-Sellin, Vaporciyan, & Spitz, 2004; Schwartz et al., 2007). Discrepancy may be due to the different usage of HRT(Siegfried & Stabile, 2014). Another mechanism in pregnancy that might affect tumor progression is immunoediting. The immune escape mechanisms at the base of tumor progression resembles the immune tolerance mechanisms occurring at the maternal–fetal interface(Bruno et al., 2020). The part cancer and pregnancy share include inflammation, immune cell tolerance, and angiogenesis. There are case-reports of patients giving birth at advanced staged lung cancer, leading to complications(Mitrou, Petrakis, Fotopoulos, Zarkavelis, & Pavlidis, 2016), including one with acute respiratory failure(Watanabe et al., 2019), which might be related to the mechanisms above.

There are a few clinical or pre-clinical studies on the relationships between pregnancy characteristics and malignancies, yet most on them focus on breast, endometrial, and ovarian cancers due to more pronounced hormonal etiology and higher incidence. For non-hormone-related tumors, prolactin has been reported to promote pancreatic tumorigenesis in vivo(Tandon et al., 2019). Also, in an active surveillance program for patients with low-risk papillary thyroid microcarcinomas (PMC) in Japan, nine women who became pregnant during active surveillance were compared with 27 nonpregnant women matched by age(Shindo et al., 2014). It was noted that PMC enlarged significantly more in pregnant patients compared with controls. Another review of literature demonstrated a negative impact of pregnancy on glioma with exacerbation of neurological symptoms(Zwinkels, Dörr, Kloet, Taphoorn, & Vecht, 2013).

Little research has been made about impact of pregnancy on the progression of GGO-featured adenocarcinoma. Young female adults are confronted with career pressure and potential childbirth plan. Incidentally spotted GGOs present as a major barrier in life trajectories of young women. In a randomized lung cancer screening trial conducted in Europe, 63% of GGO nodules disappeared after a 3-month follow-up(Heidinger et al., 2017). Those nodules that showed regression during follow-up were considered as benign lesions pathologically. Due to the fact that the majority of patients who gave birth within two years before surgery resection of GGOs turned out to be pre-invasive adenocarcinomas, reasonable assumption could be made that those GGOs were present before pregnancy. In addition, our result with the four patients who went through pregnancy during their follow-up showed no significant change in their nodules. Collectively, it could be indicated that pregnancy has little influence on the progress of GGO-featured adenocarcinoma. Clinicians may pay less attention to potential childbearing plans and focus more on the essence of the nodule. Rather than anxious about GGO lesions, young females could plan their birth-giving safely in the follow-up of GGOs.

This study had several limitations. First, only four patients were included. This is probably due to the fact that young women tend to delay childbearing or resort to surgical resection after incidental discovery of GGOs. Second, we only evaluated radiological results and the size change may be difficult to be calculated accurately based on a two-dimensional size measurement. 3D volumetric display could not be applied because not all patients underwent CT in our hospital. Therefore, research with more patients and the introduction of 3D volumetric display may further our conclusion.

5. Conclusion

Pregnancy seems to have no impact on GGOs suspected for lung adenocarcinoma. Therefore, pregnancy might be safely planned during the follow-up of GGOs.

Declarations

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Conflicts of interest/Competing interest:

Not applicable

Availability of data and material:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability:

Not applicable

Ethics approval:

This study was approved by the institutional review board (Fudan University Shanghai Cancer Center IRB 2008223-9, date: 2020/07/14).

Consent to participate:

Informed consent was waived, because this was a retrospective study.

Consent for publication:

Informed consent was waived, because this was a retrospective study.

Disclosure:

Drs. Zhang and Chen contributed equally as co-senior and correspondence authors. The authors declare no potential conflicts of interest.

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Figures

Figure 1

Timeline and basic information of four patients who went through pregnancy during the follow-up of GGOs; GGO: ground-glass opacity; MIA: minimally invasive adenocarcinoma; IAD: invasive adenocarcinoma;

Figure 2

CT image comparison of four patients who went through pregnancy during the follow-up of GGOs, time point of CT examination was listed in the image. CT: Computed Tomography; GGO: ground-glass opacity;

Figure 3

CT images of patients who gave birth within two years before surgery resection of GGOs that were invasive adenocarcinoma. Patient L: CT size: 14mm; CTR: 35.30%; Pathological results: invasive adenocarcinoma (acinar: 40%, papillary: 30% lepidic: 30%); Patient M: CT size: 14mm; CTR: 61.54%; Pathological results: invasive adenocarcinoma (acinar: 80%, lepidic: 20%); Patient N: CT size: 17mm; CTR: 35.30%; Pathological results: invasive adenocarcinoma (lepidic: 65%, acinar: 20%, papillary: 15%)

Figure 4

CT image comparison of six patients that was not pregnant in long-term (>12 months) follow-up of GGO, time point of CT examination was listed in the image. CT: Computed Tomography; GGO: ground-glass opacity;