Review Article

Management of pulmonary nodules in women with pregnant intention: A review with perspective

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Abstract:

The process for the management of pulmonary nodules in women with pregnant intention remains a challenge. There was a certain proportion of targeted female patients with high-risk lung cancer, and anxiety for suspicious lung cancer in early stage also exists. A comprehensive review of hereditary of lung cancer, effects of sexual hormone on lung cancer, natural history of pulmonary nodules, and *computed tomography* imaging with radiation exposure based on PubMed search was completed. The heredity of lung cancer and effects of sexual hormone on lung cancer are not the decisive factors, and the natural history of pulmonary nodules and the radiation exposure of imaging should be the main concerns. The management of incidental pulmonary nodules in young women with pregnant intention is an intricate and indecisive problem we have to encounter. The balance between the natural history of pulmonary nodules and the radiation exposure of imaging should be weighed.

Keywords:

Female patient, pregnancy, pulmonary nodule, radiation exposure

High-volume screening trials, including National Lung Screening Trial,[1] NELSON,[2] and Lung cancer Screening Intervention (LUSI)[3] trials, have demonstrated that the reduced lung cancer mortality is associated with lung cancer screening. Nevertheless, another question arises about the increasing percentage of lung cancer in young and female patients.[4-6] The outcome of lung cancer in young patients remains a controversy,[5-7] and little is known about lung cancer in young women. The incidental pulmonary nodule in young female patients is a headache even as encountering a pregnant plan. Combined concerns about the uncertain outcome of the suspicious lung cancer and radiation exposure on fetus during surveillance make it hard to decide where to go. Under this circumstance, there may be anxiety from female patients and certain overtreatment.

Here, we reviewed the current evidences and proposed our clinical perspectives on the management of incidental pulmonary nodules in young women with pregnant intention.

Methods

We consecutively evaluated a series of female patients (no more than 40 years old) who underwent pulmonary surgery for nodules at our hospital between 2017 and 2020. Patients with pulmonary sequestration, bronchiectasis, or pneumothorax alone were excluded. The terms, including "female patient" or "women," "lung cancer," "pregnancy," "hereditary," "hormone," "natural history of pulmonary nodule," and "radiation exposure," were searched in PubMed in March 2022. Comprehensive reviews of hereditary of lung cancer, effects of sexual hormone on lung cancer, natural history of pulmonary nodules, and computed tomography (CT) imaging

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with radiation exposure were performed. Two authors screened the literature and cross-checked the review.

Results

Real-world outcome of female patients (40 years old) with pulmonary nodule surgery

A total of 394 female patients (40 years old) who underwent surgery for pulmonary nodules between 2017 and 2020 were included. The pathological diagnoses based on surgical tissues are listed in Table 1. One patient had both primary adenocarcinoma and metastatic choriocarcinoma.

According to the 8th edition Tumor-Nodule-Metastasis staging, 84% of cases confirmed as adenocarcinoma were classified as Stage IA and 15% of cases with adenocarcinoma were classified as Stage IB or higher stage. Forty-five of 125 (36%) patients with invasive adenocarcinoma had one or more risk factors for recurrence, including micropapillary or solid component, involvement of bronchus or pleura, pleural dissemination, lymphovascular invasion, spread through air space, and lymph node metastasis. Micropapillary component (22.4%), lymph node metastasis (18.4%), involvement of bronchus (16%) and visceral pleura (12%), and spread through air space (4%) were the top five risk factors.

No incidence of lung cancer in young women has ever been reported. In the real-world cohort, 66.50% of the targeted population with pulmonary nodule resection were diagnosed with primary non-small cell lung cancer (NSCLC) or precursor glandular lesions. Nearly 15% of cases with lung adenocarcinoma were classified as Stage it or more advanced stage. Nearly 36% of cases with invasive adenocarcinoma had one or more risk factors for recurrence. High-risk female population should be recognized and well managed.

Table 1: Pathological type of pulmonary nodules for female patients (≤40 years old)

Pathological diagnosis	*n* (%)
Primary lung cancer or precursor glandular lesion	262 (66.50)
Adenocarcinoma	202 (51.27)
Minimally invasive adenocarcinoma	77 (19.54)
Invasive adenocarcinoma	125 (31.73)
Adenocarcinoma in situ	35 (8.88)
Atypical adenomatous hyperplasia	9 (2.28)
Neuroendocrine neoplasms	8 (2.03)
Carcinosarcoma	2 (0.51)
Synovial sarcoma	2 (0.51)
Lymphoma	1 (0.25)
Leiomyosarcoma	1 (0.25)
Adenoid cystic carcinoma	1 (0.25)
Mucoepidermoid carcinoma	1 (0.25)
Pulmonary benign lesion	82 (20.81)
Infectious lesion	31 (7.87)
Pulmonary hamartoma	21 (5.33)
Not otherwise specified	17 (4.31)
Sclerosing pneumocytoma	9 (2.28)
Lymph node in the lung	1 (0.25)
Solitary fibroma	1 (0.25)
Capillary hemangioma	1 (0.25)
Congenital cystic adenomatoid malformation	1 (0.25)
Pulmonary metastatic tumor	51 (12.94)

Is lung cancer hereditary?

The history of lung cancer in a first-degree relative is generally a high risk for lung cancer. In 2012, an analysis from the International Lung Cancer Consortium revealed a 1.51-fold increase in the risk of lung cancer for a person with a first-degree lung cancer-affected relative after adjustment for smoking and other confounders.[8] Another study[9] in a twin cohort proved the heritability of lung cancer with 18% familiar risk, but lung cancer also had the highest shared environmental factors. Not only the history of lung cancer in a first-degree relative, but also the number of affected relatives including first-, second-, and third-degree relatives showed significant risk for lung cancer according to a complete family history study.[10] Nevertheless, a pooled meta-analysis[11] revealed that the familial risk of lung cancer was influenced by both genetic and nongenetic factors, including geographical regions, smoking status, sex, and age.

Theoretically, if pathogenic variants are present in the germline of an individual, their offspring can inherit the pathogenic mutations. However, little is known about definite pathogenic variants for lung cancer. Several rare germline variants with lung cancer-related genetic susceptibility include germline TP53 mutation (Li–Fraumeni syndrome)[12] and germline T790M variant.[13] Another study[14] of Chinese population indicated that pathogenic germline mutations fell most commonly in BRCA-2, followed by CHEK-2 and ATM; the TP53 and T790M did not show significant heritability, and the results also exhibited that the influence of germline mutations mimicked the effects of smoking and environmental factors, perhaps sharing the same pathway to DNA damage and repair. In 2016, a meta-analysis[15] illustrated that quitting smoking was highly beneficial to smokers for the decline of lung cancer risk regardless of their CHRNA-5 genetic status, which was associated with a high probability to develop lung cancer. What's more, Jiang *et al*.[16] performed a comprehensive analysis quantifying the heritability and genetic correlation of six cancers, and the results demonstrated that different solid tumors, including lung cancer, shared common germline genetic influences; another finding about the genetic correlation between cancers and noncancer traits such as smoking, psychiatric disorders, and metabolic factors was also reported. Recently, results from a

prospective cohort study[17] including 345,794 European ancestry participants revealed that both high genetic risk and smoking were independently associated with an increased risk of lung cancer; meanwhile, smoking cessation could provide protection against lung cancer regardless of genetic risk.

Vertical transmission of cancer cells to the placenta or the fetus has been reported in gestational lung cancer patients in advanced stage, with an incidence reaching 26%.[18] There is no report of this phenomena in early-stage lung cancer.

Taken together, unlike other genetic disorders (such as chromosomal disease and monogenic disease), the heritability of lung cancer for rare germline mutations was mixed with social and environmental factors, perhaps sharing the same mechanism with living habits to the development of lung cancer. Generally speaking, the probability of lung cancer passing from one generation to the next is extremely low, and changes in lifestyle and environment are potential to reduce some of the genetic predisposition.

Effects of hormone on lung cancer

The correlation between hormonal therapy and lung cancer has been reported by several studies, which indicated the certain effects of hormone on lung cancer, while the effects remained controversy. In 2006, Ganti *et al*.[19] conducted a retrospective review of women diagnosed with lung cancer at a community-based teaching hospital, demonstrating that overall survival was significantly higher in patients without hormone replacement therapy (HRT) compared with patients who received HRT, while the study also included small cell lung cancer and 36% of all cases had advanced-Stage (III B and IV) diseases. While another report from Katcoff *et al*.[20] according to Metropolitan Detroit Surveillance, Epidemiology, and End Results Registry suggested that HRT, especially estrogen plus progesterone, was associated with improved survival for NSCLC. Large-scale multicentric clinical trials, including Women's Health Initiative clinical trial[21-23] and Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial,[24,25] showed inconsistent results when compared with each other; even different conclusions were drawn per the same trial. Nevertheless, meta-analyses have revealed the protective roles of HRT in the incidence[26] and mortality[27] of lung cancer. Most participants in the HRT study were of postmenopausal.

Estrogen exerts biological effects by interacting with estrogen receptor (ER) α and β. The expression of ER α and ER β in lung cancer has been reported for a long time,[28,29] which also demonstrated a biological role through the signaling pathway. The expression of progesterone receptor (PR) has also been detected in lung cancer,[30-32] but no major differences were observed between men and women.[31]

Although many studies have demonstrated the presence of hormonal receptor expression in lung cancer, it remains unclear what the definite roles these biomarkers play in fact. In 2011, Sun *et al*.[32] reported that epidermal growth factor receptor (EGFR) mutation was independently associated with negative expression of PR. While a similar study[30] from M. D. Anderson Cancer Centre in 2019 found no correlation between PR expression and EGFR mutation status. No significant correlations between the expression of ER and PR were found, and the conclusion that PR expression had no prognostic value was also drawn by several other studies.[31,33]

The characteristic and prognostic value of ERs in NSCLC is inconsistent among different researches.[34] The study conducted by Raso *et al*.[30] revealed that cytoplasmic ER α expression was associated with worse recurrence-free survival for NSCLC, and ER α expression was correlated with EGFR mutation in adenocarcinoma. Rouquette *et al*.[31] thought that there was a positive link between ER and EGFR expression in lung cancer, but the expression of ER α was associated with improved disease-free survival. Not only ER α, but also ER β was found to be of important value in lung cancer. Wu *et al*.[35] declared for the first time the favorable prognostic factors of ER β in surgically resected Stage II and III NSCLC, while no ER α nuclear staining was detected. Toh *et al*.[33] showed that more EGFR mutations were seen in tumors with ER β positivity (60%) compared with those with negative expression (37.9%), and there was a tendency toward an inferior outcome for tumors with positive ER β expression.

In 2011, Nose *et al*.[36] elucidated the correlation between expression of ER β and the therapeutic effect of EGFR–tyrosine kinase inhibitors in lung adenocarcinoma, indicating that strong expression of ER β predicted a superior outcome for patients with lung adenocarcinoma after treatment with EGFR–tyrosine kinase inhibitors; it should be pointed out that the response rate amounted 22.7% in the weak expression group. Exception for cancer cells, ERs were also expressed on stromal and immune cells within the tumor microenvironment,[37] hinting at the potential role of ERs in the management of current cancer-related immunotherapy. In 2016, Hamilton *et al*.[38] used the ER antagonist fulvestrant to identify the capability of reducing mesenchymal features of human lung carcinoma cells, and finally indicated a potential role for estrogenic signaling in promoting tumor resistance to immune-mediated cytotoxicity in lung cancer; however, registered clinical trials of fulvestrant, including NCT00592007 and NCT00932152, have yielded no results.

Consequently, estrogen, progesterone, and their receptors perhaps have certain regular values during tumorigenesis; the rational use of the target may be able to neutralize some of the clinical side effects in selected patients. However, there is no significant decisive effect on the progression of lung cancer, even for the fluctuations of hormone levels during pregnancy. Recently, a retrospective study[39] demonstrated that pregnancy may have little influence on ground-glass opacities suspected for lung adenocarcinoma.

Natural history of pulmonary nodules

A pulmonary nodule appears as a rounded or irregular, well or poorly defined opacity, measuring up to 3 cm in diameter.[40] Considering the confusing and interchangeable use of the terms, the Fleischner Society recommended that "pure ground-glass nodule (GGN)" was preferred as more precise than "ground-glass opacity (GGO)," a combination of both ground-glass and solid components was referred to as "part-solid GGN," whereas the term "subsolid" nodules included both pure and part-solid GGNs.[41]

Studies have shown the association between radiological and pathological findings for pulmonary nodules.[42-44] As early as in 2003, Ohde *et al*.[45] conducted a retrospective investigation of high-resolution CT finding and pathological results, which classified the presence of lymph vascular invasion and lymph node metastasis into invasive disease, and proposed that the consolidation to the maximum tumor diameter (C/T) ratio of ≤0.5 was an effective predictor for noninvasive adenocarcinoma ≤3 cm. In 2011, a multicentric prospective study (JCOG 0201) illustrated that a pathologically noninvasive cancer could be predicted by a C/T ratio of ≤ 0.25 in tumors ≤2 cm with a specificity of 98.7%.[44]

Otherwise, the volume doubling time (VDT) was identified as an index of growth rate of primary lung carcinoma as early as in 1963 and varied in tumors with different pathological subtypes.[46] The relation between VDT and survival has also been documented by several studies.[47-49] The study conducted by Arai *et al*.[49] in 1994 included both NSCLC and small cell carcinoma and stratified the growing speed based on doubling times, in which a doubling time of more than 252.4 days was identified as "slow growing." The tumor sizes were measured according to chest X-ray in the researches above.

In 2000, Hasegawa *et al*.[50] reported the growth rates of 61 small lung cancers, and VDTs were calculated per CT images. The mean VDTs were 813, 457, and 149 days for GGOs, GGOs with a solid component, and solid nodules, respectively. In 2011, Oda *et al*.[51] illustrated that the mean VDTs for atypical adenomatous hyperplasia, bronchioloalveolar carcinoma, and adenocarcinoma were 859.2 ± 428.9, 421.2 ± 228.4, and 202.1 ± 84.3 days, respectively. Song *et al*.[52] conducted an evaluation of growth rates of subsolid nodules with the use of VDT and mass doubling time (MDT) and disclosed that the median MDT was 1556.1 days (range 642.5–3564.5 days) for pure GGNs, 1199.9 days (range 838.6–2578.7 days) for part-solid GGNs with solid components of ≤5 mm, and 627.7 days (range 340.0–921.2 days) for part-solid GGNs with solid components of >5 mm, and the VDTs showed the same tendency as MDTs. In 2020, Qi[53] investigated the nature of persistent pure GGNs with deep learning-assisted nodule segmentation, illustrating that the median VDT of 52 pure GGNs was 1448 days and the median MDT was 1332 days. The mean time to growth in volume was 854 ± 675 days. The various VDTs for different pulmonary nodules are listed in Table 2.

In 2016, Kakinuma *et al*.[55] reported the evolution of pulmonary subsolid nodules from a prospective multicentric study, in which pure GGNs and heterogeneous GGNs (solid component only in lung windows) did not exhibit the solid component growth of ≥2 mm during the first 2 years of follow-up, while part-solid nodules (solid component both in lung and mediastinal window) showed solid component growth of ≥2 mm at 6 months after the start of follow-up. The mean intervals of development into part-solid nodules for pure and heterogeneous GGNs were 3.8 ± 2.0 and 2.1 ± 2.3 years, respectively. In 2017, Sato *et al*.[56] investigated the natural course of multiple GGNs, of which 32% of the included patients experienced GGN progression at 36 months, thus suggesting that the optimal observation period for multiple GGNs was 36 months.

The typical CT images of GGNs with different GGO components during surveillance are shown in [Figure 1a-h]. All the GGNs exhibited were pathologically confirmed as invasive adenocarcinomas ultimately without lymph node metastasis, but the solid one [Figure 1g and h] had two risk factors for recurrence (solid component and spread through air space).

For a long time, National Comprehensive Cancer Network clinical practice guidelines in oncology[57] identified a doubling time of ≥400 days as one of the indications for sublobar resection of pulmonary nodules for their little invasiveness. In the NELSON trial,[2] pulmonary nodules with a volume >500 mm^3 or a VDT <400 days were identified as positive screening cases. The same VDT category was also applied in LUSI trial[3] for nodule stratification. Nevertheless, as reported by Song *et al*.,[52] Qi *et al*.,[58] and Kakinuma *et al*.,[55] the VDT did not show statistical difference among different

Table 2: Volume doubling time for different pulmonary nodules

Study	Pure GGN		Part-solid GGN		Solid nodule	
	n	VDT (days)	*n*	VDT (days)	*n*	VDT (days)
Qi *et al*., 2020[53]	52	1448 (range 339-8640)				
Song *et al*., 2014[52]	12	1832.2 (range 1230.7-4537.3)	9*	1228.5 (range 934.7-4617.7)		
			8†	759.0 (range 376.4-941.5)		
Chang *et al*., 2013[54]	12	769 (range 330-3031)				
Oda *et al*., 2011[51]	19	628.5±404.2	28	276.9±155.9		
Hasegawa *et al*., 2000[50]	19	813±375	19	457±260	23	149±125

*Referred to part-solid GGNs with solid components ≤5 mm, †Referred to part-solid GGNs with solid components >5 mm. GGN: Ground-glass nodule, VDT: Volume doubling time

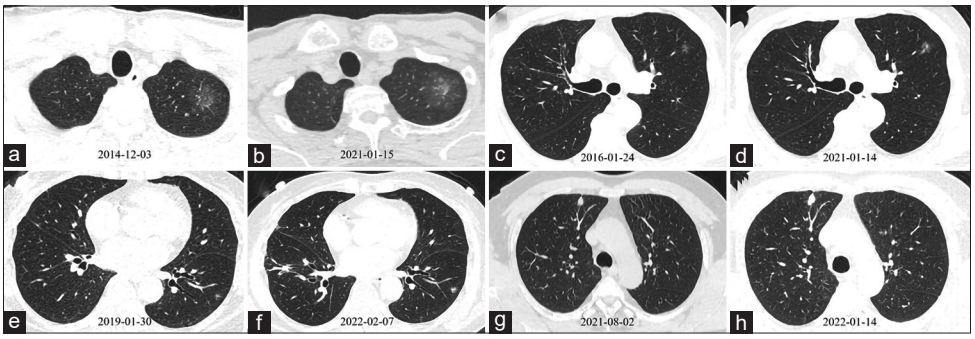

Figure 1: Typical CT images of different GGNs. (a and b) A pure GGN has been monitored annually for more than 7 years. (c and d) A part-solid GGN with GGO >50% has been under surveillance for 5 years. (e and f) A part-solid GGN with GGO of nearly 50% has been observed for 3 years. (g and h) A solid GGN (solid component could be detected in mediastinal window) showed obvious growth with 5 months. CT: Computed tomography, GGN: Ground glass nodule, GGO: Ground glass opacity

subtypes of adenocarcinomas. MDT may be more sensitive for the evaluation of growth rate of pulmonary nodules according to synthesized understanding from Song *et al*.[52] and Qi *et al*.,[58] which needs to be further confirmed.

Rational surveillance for conservative management of subsolid GGNs until signs of growth has proved the safety for patients.[56,59] The C/T ratio, VDT, MDT, or volume of nodules assesses the growth rates and risks of pulmonary nodules from different perspectives. How to detect the high-risk population with pulmonary nodules and avoid overtreatment using the current tools should be the key point.

Chest computed tomography with radiation exposure in pregnancy

How different imaging modalities contribute to fetal radiation dose and what the influences of different radiation doses on fetus might be the two primary questions, regarding imaging with radiation exposure in pregnancy.

It is difficult to measure the fetal dose in reality. The estimated fetal dose from a single chest CT acquisition is 0.01–0.66 mGy according to different reports.[60-62] In 2013, Osei and Darko[63] reported their results from a multinational study investigating the fetal doses after diagnostic radiology procedures with the use of FetDose software, (Grand River Regional Cancer Center, Kitchener, Ontario, Canada) in which three cases of chest CT examination showed fetal absorbed dose of 0.02 mGy/examination, and the risk of childhood cancer and risk of hereditary disease were 1 in 500,000 and 1 in 10,000,000, respectively, which were lower than the natural incidences. In 2021, Saeed[64] used the anatomical models to mimic pregnant patients receiving CT scan and then calculated the fetal doses with the aid of software; the calculated fetal doses for chest CT were 0.26–0.77 mGy. In fact, fetal dose should be estimated based on the actual technique parameters and the fetal condition.

Observational results[65-67] from nuclear accidents, animal studies, or radioactive therapy event revealed the consequences of radiation exposure to fetus, including pregnancy loss, congenital malformation, developmental retardation, and carcinogenesis. Exception for carcinogenesis as the stochastic effect, the other three phenomena are deterministic or threshold effects.[67] According to what Kumar and De Jesus summarized,[68] the radiational threshold of fetal malformation under 16 gestational week is about 100–200 mGy, the threshold is 500–700 mGy after 16th gestational week; a physical growth restriction is positively associated with increasing radiation dose, significantly above 1 Gy; the risk of mental retardation emerged as a linear function of dose exposed, with a threshold of 120 mGy at 8–15 week and 210 mGy at 16–25 week. Obviously, the gestational age and threshold of radiation

exposure are the decisive factors for the exposure-related consequences.

In 1952, Russell proposed that radiation exposure for medical purposes should be limited to 14 days preceding ovulation, which was changed to a 10-day option by the International Commission on Radiological Protection considering the variation of menstrual cycles.[69,70] In 2007, Patel *et al*.[71] summarized the radiation-induced effects in different gestational ages, which was endorsed by the American College of Radiology and American College of Obstetricians and Gynaecologists' Committee, thus guiding the diagnostic imaging during pregnancy and lactation.[62] Of particular concern, the estimated threshold dose before implantation (0–2 week after conception) is 50–100 mGy, while the effect is characterized by failure to implant or no significant effect (i.e. "all or none"); the gestational period of 8–15 week is of high risk because of the rapid neuronal development, and the corresponding threshold dose for severe mental retardation is 60–310 mGy.

The use of iodinated contrast media in pregnant or lactating women is another concern. Upon previous evidences on animals and human, the European Society of Urogenital Radiology declared that the iodinated contrast media may be given to pregnant women if the radiographic examination is essential in exceptional circumstances, but the thyroid function should be monitored in the neonate during the 1st week and there should be no interruption for breastfeeding during lactation; which was consistent with what was advocated by the American College of Obstetricians and Gynaecologists' Committee[62] and has been stayed unchanged in the latest version updated in 2019;[72] but for radioactive iodine, the committee banned the use of iodin 131 during pregnancy for the long half-life and the influence on fetal thyroid, and technetium 99 m was recommended as the alternative.

As suggested by several guidelines,[62,71] the estimated radiation exposure is low for chest CT when the fetus is outside the field of scan and if necessary, the examination should not be withheld from the pregnant woman; while the utilization of iodine 131 should be avoided. But in practice, how to weigh the absolute necessity for radiation exposure and avoid potential risk and stochastic the effect for fetus is the crucial problem.

Perspective

As with studies about the effects of radiological examinations on the fetus, we may not be able to conduct controlled trials to explore the outcomes of different interventions for young women with pulmonary nodules who have pregnant intention. Thus, we put forward this question in the hope of raising awareness on this topic and specifying the management of the targeted population in a more humanized and standard manner. Herein, we propose a preliminary, rough, and certain subjective management process based on the above reviews and the other guidelines [Figure 2]. In the process, we take into account the condition of complex gynecological diseases. For patients completing the pregnant plan first, a chest CT examination could be performed after the 15th week of gestation if necessary for high-risk GGNs or solid nodules especially when the interval after the last radiological surveillance exceeds 12 months. But the reality is more complicated, and we do not specifically discuss the significance of nodule size, the cumulative radiational exposure, and the influence of surgery with general anesthesia during the

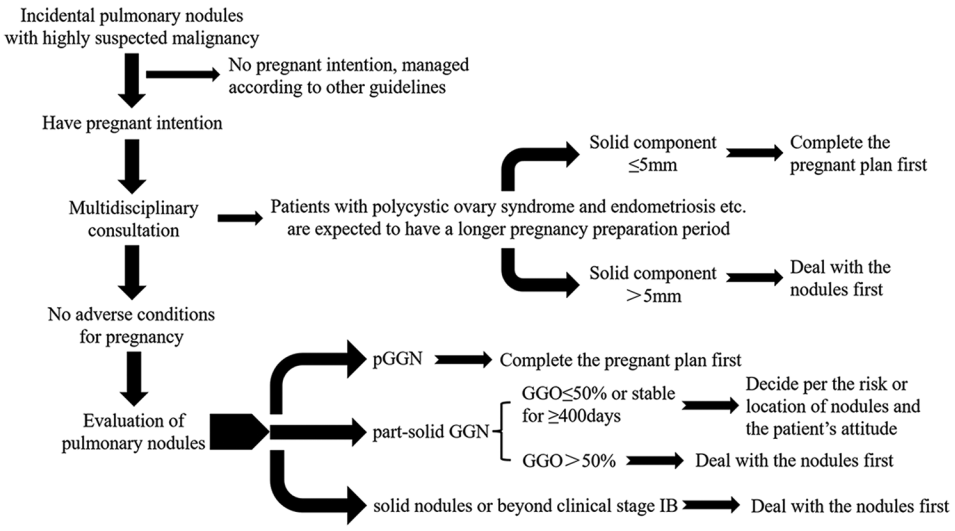

Figure 2: The preliminary management process for pulmonary nodules in young women with pregnant intention. GGN: Ground glass nodule, GGO: Ground glass opacity, pGGN: Pure GGN

whole pregnancy process in clinical decision-making. A multidisciplinary treatment model may benefit patient decision-making. Chest CT-based radiomics has potential for the recognition of radiological high-risk population. Like lung diagnostic assessment programs across Ontario, Canada,[73] our team wants to provide efficient and accessible diagnostic evaluation and treatment planning for suspected lung cancer in young female patients with pregnant intent. We will continue to improve this management process and seek out the beneficiary.

The management of incidental pulmonary nodules in young women with pregnant intention is an intricate and indecisive problem we have to encounter. The heredity of lung cancer and effects of sexual hormone on lung cancer are not the decisive factors, and the balance between the natural history of pulmonary nodules and the radiation exposure of imaging should be weighed.

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Conflicts of interest

There are no conflicts of interest.

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