



Should computed tomography and bronchoscopy be routine examinations for chronic cough?

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Abstract: Chronic cough is a common symptom of many diseases. Guidelines on cough from different countries recommend chest X-ray as the first-line examination. However, as compared to computerized tomography (CT), chest X-ray is insensitive in the diagnosis of many diseases. We speculate that CT is more helpful in excluding the causes of long-term cough, such as bronchial tumors and pulmonary interstitial diseases, which prevents patients from receiving unnecessary examinations and diagnostic treatments for chronic cough. In addition, a single chest CT is safe and affordable in some regions. Therefore, chest CT may be recommended as a first-line examination for patients with chronic cough. In addition, although bronchoscopy is employed as a further examination for chronic cough, it plays an important role in the diagnosis of chronic cough, especially in rare bronchial diseases such as amyloidosis and foreign body inhalation. Induced sputum cytology was not accepted as a necessary examination for chronic cough, but it becomes a first-line examination until physicians recognize that non-asthmatic eosinophilic bronchitis is a common cause of chronic cough. Therefore, we speculate that the roles of chest CT and bronchoscopy in the identification of causes of chronic cough are increasingly important; in some regions, or for patients suspicious for uncommon causes of chronic cough, CT and bronchoscopy are recommended as first-line examinations.

Keywords: Chronic cough; chest X-ray; computerized tomography (CT); bronchoscopy

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Introduction

Chronic cough is a common symptom of some diseases, and the accurate identification of the specific causes of chronic cough is crucial for the successful treatment. Current guidelines from different countries recommend chest X-ray (CXR) and lung function test as first-line examinations. However, whether chest computerized tomography (CT) and bronchoscopy may be employed as routine or preferred tests in the identification of causes of chronic cough is still poorly understood. We speculate that chest CT may be used as a routine examination, and bronchoscopy is also extremely

important in the diagnosis of causes of chronic cough.

Status of chest CT

In the guidelines of various countries, chronic cough patients refer to those with cough lasting no less than 8 weeks and normal CXR findings (1-4). The guideline of European Respiratory Society published in 2004 states that it is not cost-effective to include high-resolution chest CT in the baseline examinations of causes of chronic cough (5). Similarly, the guideline of American College of Chest Physicians recommends chest CT only when the

most common causes of chronic cough are excluded (6). However, the recent guideline of European Respiratory Society shows that the a very low evidence level of CT recommended as the preferred examination (4). Thus, whether chest CT should be employed as the preferred examination in the identification of causes of chronic cough is unclear. We discuss this issue as follows:

Advantages of chest CT

Diagnostic advantages for lung diseases

Undoubtedly, chest CT is more useful than CXR in diagnosing uncommon pulmonary conditions, such as mediastinal or hilar mass, lymphadenopathy, intraluminal lesions of the trachea and/or bronchia, early-stage interstitial lung disease, bronchiectasis, pericardial diseases and others.

Paioli *et al.* enrolled 215 patients aged over 40 years who had lung metastases alone as first pattern of recurrence after treatment for extremity osteosarcoma. The patients were followed up with CXR or chest CT for a median of 47 months (1–300 months). Their results showed the relapse-free interval was longer and the portion of patients with relapse-free interval <2 years was lower in the CXR group, which means that the disease condition in the CXR group was better than in the CT group. However, the second complete remission rate was lower in patients followed up by CXR (60%) than in those followed up by chest CT (88%). Five-year post relapse survival and overall survival were significantly lower in the CXR group than in the CT group. Finally, the investigators concluded that follow-up with chest CT led to a better prognosis (7).

Sometimes, CXR may make mistakes. Self *et al.* investigated 3,423 patients from 12 different emergency departments in the United States who received both CXR and chest CT. 73.1% of patients who had abnormal CXR findings had normal chest CT. 108 (3.5%) patients with normal CXR findings were found to have lung shadows on chest CT. For patients who have abnormal CXR findings, the majority of patients suffered twice radiations to confirm their normality, while the patients who have normal CXR findings have the risk of false negative, leading to the delayed treatment (8).

Since the chest CT has significant advantages over CXR, why do different guidelines recommend CXR as a routine examination of chronic cough instead of chest CT? In the cough guideline developed by the European Respiratory Society in 2020 (4), chest CT is not routinely recommended in patients with chronic cough who have normal findings

on CXR and physical examination, but the level of evidence on this recommendation is very low. Currently, clinical evidence is insufficient to confirm that CXR is enough to exclude pulmonary abnormalities. The common causes of chronic cough, such as cough variant asthma, upper airway cough syndrome, non-asthmatic eosinophilic bronchitis, and gastroesophageal reflux-induced chronic cough, are often confirmed on the basis of absence of lung abnormalities. Therefore, we speculate that chest CT may be employed as a routine examination for chronic cough patients, which is more conducive to exclude lung diseases, rather than chest CT performed after CXR.

In some cases of chronic cough, such as IgG4 related fibrosing mediastinitis, tracheobronchopathia osteochondroplastica, tracheobronchial amyloidosis, pulmonary lymphangitic carcinomatosis, and thoracic aortic aneurysm, the abnormalities can't be identified on CXR, and CT is often needed for the diagnosis (9-13). Of course, above causes account for a minority and do not represent the majority of cases.

In a study about the etiology of chronic cough, McGarvey *et al.* retrospectively reviewed 124 patients presenting with chronic cough. They found that CXR was helpful in establishing the cause of chronic cough in only 31% of cases, while chest CT identified pulmonary abnormalities in 59% of cases. Of note, the chest CT revealed pulmonary abnormalities in 28% of cases with normal CXR findings (14). Palombini *et al.* prospectively studied 78 non-smokers with cough who have normal CXR findings. Chest CT was performed in 64 patients and revealed the potential cause of chronic cough in 24% of cases. The positive predictive value of high-resolution chest CT was 83%, and negative predictive value 100%. Thus, we speculate that high-resolution chest CT is more cost-effective (15).

Similarly, Chang *et al.* investigated more than 300 children with chronic cough, and they found the negative predictive value of CXR in the diagnosis of specific cough was as low as 15% (16).

In a recent study, Truba *et al.* retrospectively analyzed 59 non-smokers with chronic cough, who received both CXR and chest CT. Results showed 95% of patients with normal CXR findings had abnormalities in the lung, mediastinum, or thorax on chest CT; these abnormalities in 36% of patients were confirmed to be associated with chronic cough, including bronchiectasis, mediastinal lymphadenopathy, and interstitial lung disease. Because some patients have no abnormalities on the CXR, examinations such as bronchial provocation test, sputum induction, and multichannel

Table 1 Cost between chest X-ray and CT in different cities of China

Location	Cost (¥)		Ratio of CT/chest radiography
	Chest radiography	CT	
Shanghai	70	170	2.4
Beijing	136	277	2.0
Hangzhou	107	243	2.3
Shenzhen	128	400	3.1
Shanxi	240	629	2.6
Taizhou, Zhejiang	54	222	4.1
Tongling, Anhui	151	241	1.6
Yinchuang	80	219	2.7
Heze, Shandong	117	220	1.9
Hefei	104	227	2.2
Qinhuangdao	160	308	1.9
Wenzhou	35	130	3.7
Taizhou	43	188	4.4
Zibo	120	300	2.5
Yixing	82	316	3.9
Suzhou	80	221	2.7
Lanzhou	80	495	6.2
Tianjin	135	560	4.1

esophageal impedance-pH monitoring are often performed. Even a series of empirical treatments, including the treatment for refractory cough (such as gabapentin) are employed, which may cause some adverse effects. Earlier resolution of chronic cough through early identification and early etiological treatment would reduce the economic burden associated with recurrent consultations (17).

According to above findings, chest CT is a more cost-effective examination in the diagnosis of causes of chronic cough.

Safety issues of chest CT

As we all know, the radiation dose of CT is significantly higher than that of CXR. The radiation dose is only 0.01–0.05 (mSV) for of CXR and 1.0–5.0 (mSV) for normal CT (18). Berrington de González *et al.* investigated the correlation between CT and projected cancer risk in the United States in 2007 (19). They found that 1/3 of projected cancers were ascribed to the CT performed at the age of 35–54 years

and 15% to the CT at the age of <18 years old; 66% of the projected cancers were found in females.

However, with the development of technology, technicians have worked on reducing radiation exposure to reduce the risk of tumors without compromising image quality and diagnostic accuracy (20,21). Hu-Wang *et al.* employed ultra-low-dose CT to follow up patients with lymphangioliomyomatosis in which the 6 mGy on normal CT was reduced to 0.3 mGy, which is almost equivalent to a CXR (22). According to the American Radiological Association, the yearly radiation exposure should be no more than 50 mSv, and the life-long radiation exposure should be no more than 10 mSv × age, and no more than 5 mSv (<10 screening is safe) for publics. The risk factor of CT is a cumulative dose of radiation, not a single dose. Therefore, as long as the routine CT is not repeatedly performed and low-dose CT is acceptable, the radiation dose is within the safe range and thus CT is suitable for patients with chronic cough.

In addition, the US guidelines for lung cancer recommend low-dose CT to screen lung cancer in high-risk populations, and the use of low-dose CT is also beneficial for the identification of coexisting conditions (23). The asymptomatic high-risk people are the candidates for screening with low-dose CT, and chest CT is also applicable in those who have cough for more than 8 weeks.

As mentioned above, when positive findings are found on CXR, chest CT scan may be performed to confirm the findings, which instead increases the radiation dose. Therefore, we recommend routine chest CT to exclude lung lesions.

Economic concern in some regions

In some regions, such as mainland China, the cost between CXR and chest CT is similar (*Table 1*), and thus economic concern may not be an obstacle to perform chest CT. However, the medical cost in the selection of CXR or CT should be taken into account in medicare system of western countries.

In summary, we speculate that CT, especially low-dose CT, should be the preferred examination for chronic cough patients due to its relatively high diagnostic efficiency and comparable safety of CT as compared to CXR.

Role of bronchoscopy in chronic cough

To date, bronchoscopy has not been recognized as a routine examination for chronic cough. In some cases, such as

tracheobronchopathia osteochondroplastica, bronchial tuberculosis, and tracheobronchial amyloidosis, which are not common causes of chronic cough, bronchoscopy is often employed to identify the cause of chronic cough (11,24). It seems that it should not be the first line examination for chronic cough.

As is known to all, non-asthmatic eosinophilic bronchitis is not regarded as one of the common causes of chronic cough at the early-stage of studies on chronic cough (25). Therefore, cytological examination after sputum induction is not necessary in the initial identification of causes of chronic cough. When non-asthmatic eosinophilic bronchitis is confirmed as an important and common cause of chronic cough, cytological examination after sputum induction becomes the first line examination for chronic cough patients. In clinical practice, chronic cough of unknown cause is not uncommon. It is estimated that chronic cough of unknown cause accounts for 5–10%, and even up to 46% in some studies. Thus, in patients with chronic cough of unknown cause, bronchoscopy may be performed (26).

In as early as 1980s, bronchoscopy was not employed in the diagnosis of chronic cough (27). By 2007, Decalmer *et al.* reported that bronchoscopy revealed abnormalities in 11% of patients with chronic cough of unknown cause (28). In 2019, Fracchia *et al.* investigated the role of endoscopy in the diagnosis of chronic cough in 243 children who underwent bronchoscopy, gastroscopy, and laryngoscope; their results showed 67.5% of children had abnormal bronchoscopic findings (29). These results indicate that increasing patients require bronchoscopy for the identification of cause of chronic cough, and bronchoscopy is likely to become a routine examination for chronic cough patients in the future. At present, more high-quality clinical studies are warranted to confirm the role of bronchoscopy in the diagnosis of chronic cough.

In summary, in order to rule out or confirm common or uncommon causes, reasonable, effective and safe examinations should be conducted as soon as possible. In a few developed areas, the examinations usually have a low cost, and can be easily and quickly performed in hospitals. We speculate that chest CT, especially low-dose CT, can be used as a routine examination for chronic cough patients, while repeated CT examinations are not recommended. For patients in whom the causes of chronic cough remain unclear after routine examinations and those who have no response to the treatment targeting common causes, bronchoscopy should be recommended as a first-line examination.

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