Simplified Method of Dynamic Contrast-Enhanced Computed Tomography in the Evaluation of Indeterminate Pulmonary Nodules

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Key Words

Contrast-enhanced computed tomography • Pulmonary nodule • Lung cancer

Abstract

Background: Dynamic contrast-enhanced computed tomography (CECT) is one of the methods used in the evaluation of lung nodules. **Objectives:** The aim of the study was to evaluate the accuracy of the simplified method (based on only 2 postcontrast measurements) of dynamic CECT in determining the nature of pulmonary nodules. **Methods:** Forty nodules (solid, 10–40 mm in diameter, spherical, with no visible calcification or fatty tissue) in 40 patients were analyzed. In 30 patients, the nature of the nodule was confirmed by pathological examination. In 10 cases, the nodules were assumed to be benign, as no growth within 2 years was radiologically documented. All patients underwent CECT according to a simplified protocol (based on pre-enhancement and 2 postcontrast measurements at 30 s and 4 min after contrast injection). **Results:** Twenty-three (57.5%) nodules were proved to be malignant and 17 (42.5%) benign. The 7 benign and none of the malignant nodules showed an enhancement value of ≤ 15 Hounsfield units. Thus, the sensitivity, specificity, positive and negative predictive value and diagnostic accuracy of shortened dynamic CECT were 100, 41, 70,

100 and 75%, respectively. **Conclusions:** In CECT, contrast enhancement of a pulmonary nodule ≤ 15 Hounsfield units is a reliable predictor of its benignity. Reduction in the number of postcontrast measurements in the simplified method of dynamic CECT does not influence its sensitivity.

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Introduction

Pulmonary nodules are increasingly found during routine radiological examinations or during lung cancer screening programs with low-dose computed tomography (CT) scanning [1, 2]. Noninvasive methods of discrimination between malignant and benign pulmonary nodules need to be validated. This is essential in the early selection of patients with malignant nodules eligible for surgery and helps to avoid unnecessary thoracotomies in patients with benign lesions. Among diagnostic procedures there are nuclear medicine methods such as positron emission tomography with ¹⁸F-fluorodeoxyglucose, depreotide single-photon emission CT and dynamic contrast-enhanced CT (CECT) [3–5]. The accuracy of these methods in diagnosing solitary pulmonary nodules seems comparable [6]. Despite its high sensitivity and high specificity, positron emission tomography with ¹⁸F-

Table 1. Characteristics of the patients

	Benign (n = 17)	Malignant (n = 23)
Age, years	60 (21–76)	62 (24–82)
Gender, male/female	10/7	17/6
Smoking history		
Smokers	6	12
Exsmokers	2	8
Nonsmokers	9	3
Pack years ¹	15 (0–42)	30 (0–80)

Values are presented as the median, with ranges in parentheses.

¹ One pack year = 20 cigarettes/day/year.

fluorodeoxyglucose still remains a costly examination and the access to this technique is still limited in some countries. In the recent guidelines of the American College of Chest Physicians, dynamic CECT is recommended as one of the methods used in the evaluation of indeterminate solitary pulmonary nodules [3].

Swensen et al. [7] described the CECT protocol based on 4 measurements of enhancement at 1, 2, 3 and 4 min after the onset of contrast injection. It has been suggested that 4 measurements might improve the sensitivity of the test. The absence of significant lung nodule enhancement (≤ 15 Hounsfield units, HU) after intravenous contrast injection has been suggested to be strongly predictive of its benignity [8]. Due to its high sensitivity and negative predictive value, widespread availability and relatively low costs, this method may be helpful in estimating the likelihood of benignity of indeterminate pulmonary nodules [1, 3, 7, 8].

We proposed a simplified method of dynamic CECT to simplify the protocol and to reduce the radiation dose of the method. The aim of our study was to evaluate the accuracy of the simplified (based on only 2 postcontrast measurements of enhancement) method of dynamic CECT in determining the nature of pulmonary nodules.

Materials and Methods

The study was approved by the institutional review board. It was a retrospective analysis of all patients with indeterminate pulmonary nodules, hospitalized in our institution between 2002 and 2006, in whom dynamic CECT was performed.

Forty patients with solitary solid pulmonary nodules were enrolled into the study. They were selected from a group of 70 pa-

tients with indeterminate pulmonary nodules consecutively evaluated in our institution between 2002 and 2006, in whom CECT had been performed. Thirty patients were excluded due to the lack of follow-up (n = 18) or the lack of definitive diagnosis (n = 12). The most frequent reason of loss of follow-up was lack of consent for additional radiological examination (n = 8) or not attending the scheduled control visit (n = 10). In 12 patients, the definite diagnosis was not established because of previous death (n = 3) or lack of consent for invasive procedures, if the dimension of the nodule increased (n = 9).

In 40 patients, dynamic CECT was performed, and subsequently, the definitive diagnosis was established based on either pathological examination or radiological criteria of the benignity of the nodule. The latter was defined as lack of growth for at least 2 years or partial or total resolution of the nodule [9].

Solid nodules, round or spherical in shape, of a diameter ranging between 10 and 40 mm (mean 22 mm, 95% CI 19.3–24.7), containing no calcifications and no fatty tissue in the CT scan, were submitted for further analysis. Demographic data of the study group are shown in table 1.

All 40 patients underwent a CT scan of the thorax and upper abdomen after contrast injection. CT scans of the nodule were obtained 3 times: before contrast, 30 s and 4 min after onset of intravenous contrast injection (Iomeron, Bracco; 2 ml/s, 300 mg of iodine/ml, 420 mg iodine/kg body weight). In 28 cases, CECT was performed with a single-slice CT scanner (PQ 2000; Marconi Medical Systems, Cleveland, Ohio, USA) and in 12 cases with a 16-slice sCT (Light Speed 16; General Electric Medical Systems, Milwaukee, Wisc., USA). On PQ 2000, all nodules were analyzed with 3-mm collimation spiral scans, pitch 1:1, 130 kVp, 100 mA, 1 s scanning time. On Light Speed 16, the nodules were examined with 1.25-mm slice collimation, pitch 1.375, 120–140 kVp, 100–250 mA, 0.5 s scanning time.

The nodules were homogenous at the mediastinal window settings on pre-enhancement scans. The mean diameter of each nodule was calculated as the mean of the short and long axis diameter at lung window settings. The enhancement was measured in the region of interest (ROI) which was manually drawn at the mediastinal window image. In most cases, the mean diameter of the ROI was approximately 70% of the mean diameter of the nodule. In 10 patients in whom postcontrast CT scans revealed significant heterogeneity of the nodule, the ROI was reduced to the region of the highest and relatively homogenous enhancement. The nodule enhancement value (in HU) was defined as the difference between the maximal enhancement after contrast administration and the precontrast attenuation value. The measurements were performed by a chest radiologist with 15 years of experience, who was unaware of the final diagnosis of the nodule.

In all 40 patients, subsequent evaluation enabled the definite discrimination between malignant and benign nodules. In 30 patients, invasive diagnostic procedures (transbronchial or trans-thoracic needle aspiration, video-assisted thoracic surgery, thoracotomy) were applied to establish the definitive diagnosis. In 10 patients, the diagnosis was based on radiological criteria of benignity.

The sensitivity, specificity, positive and negative predictive value and diagnostic accuracy of CECT (at various cutoff levels: 10, 15, 20 and 30 HU) in relation to the character of the nodule (benign or malignant) were analyzed. Sensitivity was defined as the proportion of patients with a malignant nodule who showed

contrast enhancement greater than the suggested threshold. Specificity was defined as the proportion of patients with a benign nodule who showed enhancement below an assumed cutoff level. Statistical analysis of the results was performed with the nonparametric Mann-Whitney U test, with $p < 0.05$ being regarded as significant. The 95% confidence intervals were calculated using the adjusted Wald method.

Results

We examined 40 pulmonary nodules in 40 patients: 23 (57.5%) nodules were proved to be malignant and 17 (42.5%) benign. The malignant tumors were pathologically classified as follows: non-small cell lung cancer ($n = 10$), squamous cell carcinoma ($n = 5$), adenocarcinoma ($n = 4$), large cell carcinoma ($n = 1$), typical carcinoid ($n = 1$), small cell lung cancer ($n = 1$) and metastasis of thyroid carcinoma ($n = 1$). The benign character of the remaining nodules was either confirmed by pathological investigation ($n = 7$, i.e. 4 hamartoma, 2 tuberculoma and 1 intrapulmonary lymph nodule) or assumed by radiological follow-up ($n = 10$).

Comparison of the mean diameter of the nodules in baseline CT scans showed a significant difference between malignant and benign nodules; the malignant nodules were larger (25 vs. 14 mm; $p = 0.007$). No other differences in baseline CT were found between these groups. The comparison of CT features in both groups is presented in table 2.

All but 1 nodule showed a maximal enhancement at 4 min after contrast administration. The exception was a malignant nodule (typical carcinoid).

Based on the results of Swensen et al. [7], we used an enhancement value ≤ 15 HU as cutoff level for the benignity of the nodule. Seven of 17 benign nodules (41%, 2 tuberculomas and 5 benign nodules without pathological verification) and none of the malignant nodules had an enhancement value of ≤ 15 HU. All malignant (23/23, 100%) and 10 (59%) benign nodules showed an enhancement value of >15 HU (fig. 1). The latter included: hamartoma ($n = 4$), intrapulmonary lymph nodule ($n = 1$) and 5 nodules without pathological diagnosis. In 2 of these 5 cases, the patients were disqualified from thoracic surgery because of general contraindications (severe cardiac failure and advanced Parkinson’s disease), and 2 years of radiological follow-up revealed no growth of the nodule. In the remaining 3 cases, surgical treatment was abandoned as preoperative chest X-ray showed a decrease in the size of the nodule.

Fig. 1. Distribution of the enhancement value in all nodules.

Table 2. Characteristics of the nodules

	Benign (n = 17)	Malignant (n = 23)
Size, mm	14 (10–33)*	25 (12–40)*
Location**		
Right/left	9/8	12/11
Upper/middle/lower lobe	7/4/6	13/3/6
Preenhancement attenuation, HU	14 (–26 to 79)	17 (–32 to 50)
Postcontrast attenuation at 30 s, HU	34 (–26 to 77)	38 (–8 to 80)
Postcontrast attenuation at 4 min, HU	57 (–20 to 99)	54 (23–90)
Maximal enhancement, HU	22 (0–103)	33 (21–65)

Values are presented as median, with ranges in parentheses.
* $p < 0.05$, statistically significant; ** number of patients are shown; lingula was classified as substitute of the middle lobe.

No other radiological features differed between benign nodules which enhanced ≤ 15 HU and those which enhanced >15 HU.

Applying 15 HU as the cutoff level, the sensitivity, specificity and diagnostic accuracy of CECT in diagnosing malignant nodules were 100% (95% CI 0.83–1.00), 41% (95% CI 0.21–0.64) and 75% (95% CI 0.60–0.88), respectively. In table 3, we present the features of CECT at different cutoff levels. At a cutoff of 10, 15 and 20 HU, the

Table 3. Characteristics of the simplified dynamic method of CECT in the evaluation of pulmonary nodules

Cutoff value	10 HU	15 HU	20 HU	30 HU
Sensitivity, %	100 (0.83–1.00)	100 (0.83–1.00)	100 (0.83–1.00)	70 (0.49–0.85)
Specificity, %	35 (0.17–0.59)	41 (0.21–0.64)	47 (0.26–0.69)	59 (0.36–0.78)
Diagnostic accuracy, %	72 (0.57–0.85)	75 (0.60–0.88)	77 (0.62–0.90)	65 (0.50–0.80)
Positive predictive value, %	68 (0.51–0.81)	70 (0.52–0.83)	72 (0.55–0.85)	70 (0.49–0.85)
Negative predictive value, %	100 (0.56–1.00)	100 (0.59–1.00)	100 (0.63–1.00)	59 (0.36–0.78)

95% confidence intervals are given in parentheses.

sensitivity and negative predictive value were the same and equal to 100%. However, the highest specificity and diagnostic accuracy in our study was found at the value of 20 HU.

Discussion

The results of our study showed that an enhancement of 15 HU or less is strongly predictive of the benignity of a pulmonary nodule. This is consistent with the results of the multicenter study by Swensen et al. [7]. Due to the high sensitivity and negative predictive value, dynamic CECT of the pulmonary nodule may be applied to confirm its benign character. However, only 41% of all benign nodules enhanced ≤ 15 HU, which is less than in the study by Swensen et al. [7], but more than in the study by Christensen et al. [8].

Wide availability of CT equipment, the opportunity to avoid invasive diagnostic procedures and the relatively low cost-effectiveness ratio are important values of CECT [7, 8, 10]. However, the sensitivity, specificity and diagnostic accuracy of CECT in determining solitary pulmonary nodules are not higher than those of standard CT [6, 11]. Besides, CECT also has its limitations, such as measurement inaccuracy, which may result from errors of enhancement measurements, heterogeneity of nodule enhancement, measuring pre- and postenhanced attenuation in different scans due to different locations of the nodule during breath-holds, or manual drawing of the ROI [12].

In most of the studies, the ROI was drawn manually and differed from 60–70 to almost 100% of diameters of the nodule [7, 8, 13–16]. Subjective choice of the ROI may lead to false-negative results when intratumoral necrosis is present [13, 15]. In a recent study by Mori et al. [17], a 3D tumor reconstruction was applied to extract the whole nodule as the ROI.

The important difference between our study and the study of Swensen et al. [7] was the reduction in the number of measurements of postcontrast enhancement values. Swensen et al. [7] used 4 measurements at 1, 2, 3 and 4 min after contrast injection. The first measurement allows to control the correct influx of contrast. We concentrated on measurements at 30 s for the evaluation of the number of tumor vessels and at 4 min for the evaluation of contrast flow to papillary vessels and the interstitial tissue of the nodule [17]. According to Yi et al. [18], the peak nodular enhancement during CECT occurs 30–180 s after intravenous contrast injection. Therefore, it seems that the measurement of postcontrast enhancement only once after 60 or 90 s might be equally sensitive, but a further trial in which all patients would undergo measurements of enhancement at all time points is required to answer this question.

The suggested numbers of postcontrast measurements differed in previous studies. Yamashita et al. [13] measured attenuation 2 and 5 min after the onset of contrast injection, Tateishi et al. [16] at 35 s and 2 min, and Kim et al. [14] used 5 enhancement values after 1, 2, 3, 4 and 5 min. Swensen et al. [7] used 4 measurements to improve the sensitivity of the test. It may be noteworthy that the limitation of measurements after contrast injection in our study did not decrease the sensitivity of CECT described by Swensen et al. [7]. However, it resulted in the decrease in its specificity in comparison with dynamic CT described by Swensen et al. [7] (58% versus 41% in our study). On the other hand, in the study by Christensen et al. [8], the specificity was lower (29%) than in our study, although 4 postcontrast measurements were performed.

One of the advantages of the measurement number reduction is a decrease in the radiation dose which linearly grows when CT scans are repeated on the same region [19]. Using the Monte Carlo computer technique [20], we estimated that on PQ 2000, the reduction in ra-

diation dose expressed as dose length product (DLP) in the simplified method is approximately 96 mGy·cm as compared with the method based on 4 postcontrast measurements (the DLP in the whole CECT was approximately 382 mGy·cm). Similarly, the radiation dose on Light Speed 16 in a simplified method of CECT amounted to about 260–300 mGy·cm compared with 400–500 mGy·cm if CECT had been performed with 4 postcontrast measurements (a reduction of 140–200 mGy·cm per 1 CECT). It is noteworthy that the reduction in the estimated radiation in the simplified method of CECT (measured as DLP) amounted to about one fourth of the radiation dose during the whole standard method of CECT and to about one fourth of the conventional (but not low-dose) spiral CT of the chest.

We believe that the high sensitivity and negative predictive value of simplified CECT in our study resulted from careful analysis of the nodule structure after contrast injection. In the cases where the nodules were evidently heterogeneous after contrast injection, we reduced the area of the ROI to that with the highest homogenous enhancement (the ROI diameter was about 40% of the diameter of the nodule). Another factor that may have influenced our results is relying on the measurement at 4 min after contrast injection which is believed to represent contrast flow to papillary vessels and interstitial tissue of the nodule [17].

The diagnostic utility of CECT in discriminating benign and malignant pulmonary nodules has been widely studied, but the optimal borderline enhancement value suggestive of the malignant character of the nodule is still discussed. Swensen et al. [7] proposed a value >15 HU suggestive of the malignant nature of the nodule. Initially, in our study, we analyzed the cutoff level of 15 HU as suggested by Swensen et al. [7] and we achieved a 100% sensitivity, 41% specificity and 75% diagnostic accuracy. Further analysis of our results revealed that the best diagnostic accuracy (77%) in diagnosing malignant nodules was reached at a cutoff of 20 HU. Similar diagnostic accuracy was achieved by other authors, who also applied 20 HU as the cutoff level [14]. Yi et al. [18] found the highest diagnostic accuracy (78%) of CECT in differentiating malignant and benign nodules at 30 HU. Higher cutoff values are found when multislice CT is applied [21].

There are some limitations of our study. First of all, it was performed retrospectively and included a relatively small number of patients. The main obstacle in the patients' enrollment was lack of pathological diagnosis or documented radiological follow-up for at least 2 years. Secondly, the radiological criteria of benignity are widely

used, but remain controversial [9]. Special caution is recommended in the analysis of radiological stability of small nodules (<10 mm) where a subtle change of size may be overlooked [4, 22]. Another limitation is the manual drawing of the ROI which has already been discussed. A new method of extracting whole nodules by reconstruction of 3D images and computer-aided diagnosing systems have been proposed. Estimation of nodule growth and discriminating benign and malignant nodules with the help of these methods gave promising results [17]. It seems that replacing manual procedures by more objective means of nodule estimation should be considered, as it may significantly increase the diagnostic yield of CECT. Comparative studies of these methods are required.

It is important to realize that the study design has not addressed the question whether the simplified protocol is as accurate as the 4-measurement protocol used by Swensen et al. [7] in a multicenter study. A prospective, appropriately powered equivalence trial in which all patients would undergo measurements of enhancement at all time points is required to answer this question.

Finally, the studied group may not be representative of the whole population with pulmonary nodules (selection bias). First of all, we did not enroll patients who did not have verification of the histological diagnosis or radiological follow-up for at least 2 years. Secondly, we focused on indeterminate pulmonary nodules and we did not investigate nodules with an evidently low or high probability of malignancy.

In spite of its limitations, CECT seems to be a useful method in the diagnosis of indeterminate pulmonary nodules [1, 3, 4, 7, 8]. The accurate diagnosis of any pulmonary nodule is crucial not only for early detection of malignancy, but also to avoid unnecessary thoracotomies for benign lesions.

Conclusions

The study confirmed that in CECT, contrast enhancement of a pulmonary nodule ≤ 15 HU is a reliable predictor of its benignity. Reduction in the number of measurements after contrast injection in CECT of pulmonary nodules does not influence its sensitivity.

References

- Swensen SJ, Jett JR, Sloan JA, Midthun DE, Hartman TE, Sykes AM, Aughenbaugh GL, Zink FE, Hillman SL, Noetzel GR, Marks RS, Clayton AC, Pairorero PC: Screening for lung cancer with low-dose spiral computed tomography. *Am J Respir Crit Care Med* 2002;165:508–513.
- Diedrich S, Thomas M, Heindel W: Lung cancer screening with low-dose CT. *Eur J Radiol* 2003;45:2–7.
- Gould MK, Fletcher J, Iannettoni MD, Lynch WR, Midthun DE, Naidich DP, Ost DE: Management of patients with pulmonary nodules. When is it lung cancer? *Chest* 2007;132(suppl 3):108S–130S.
- Winer-Muram HT: The solitary pulmonary nodule. *Radiology* 2006;239:34–49.
- Naalsund A, Maublant J; on behalf of the European NeoSpect Trial Group: The solitary pulmonary nodule – is it malignant or benign? Diagnostic performance of the ^{99m}Tc-depreotide SPECT. *Respiration* 2006;73:634–641.
- Cronin P, Dwamena BA, Kelly AM, Carlos RC: Solitary pulmonary nodules: meta-analytic comparison of cross-sectional imaging modalities for diagnosis of malignancy. *Radiology* 2008;246:772–782.
- Swensen SJ, Viggiano RW, Midthun DE, Muller NL, Sherrick A, Yamashita K, Naidich DP, Patz EF, Hartman TE, Muhm JR, Weaver AL: Lung nodule enhancement at CT: multicenter study. *Radiology* 2000;214:73–80.
- Christensen JA, Nathan MA, Mullan BP, Hartman TE, Swensen SJ, Lowe VJ: Characterization of the solitary pulmonary nodule: ¹⁸F-FDG PET versus nodule-enhancement CT. *AJR Am J Roentgenol* 2006;187:1361–1367.
- Yankelevitz DF, Henschke CI: Does 2-year stability imply that pulmonary nodules are benign? *AJR Am J Roentgenol* 1997;168:325–328.
- Comber LA, Keith CJ, Griffiths M, Miles KA: Solitary pulmonary nodules: impact of quantitative contrast-enhanced CT on the cost-effectiveness of FDG-PET. *Clin Radiol* 2003;58:706–711.
- Gould MK, Sanders GD, Barnett PG, Rydzak CE, Maclean CC, McClellan MB, Owens DK: Cost-effectiveness of alternative management strategies for patients with solitary pulmonary nodules. *Ann Intern Med* 2003;138:724–735.
- Wormanns D, Diedrich S: Characterization of small pulmonary nodules by CT. *Eur Radiol* 2004;14:1380–1391.
- Yamashita K, Matsunobe S, Tsuda T, Okuda K, Matsumoto K, Oyanagi H, Konishi J: Intratumoral necrosis of lung carcinoma: a potential diagnostic pitfall in incremental dynamic computed tomography analysis of solitary pulmonary nodules. *J Thorac Imag* 1997;12:181–187.
- Kim JH, Kim HJ, Lee KH, Kim KH, Lee HL: Solitary pulmonary nodules. A comparative study evaluated with contrast-enhanced dynamic MR imaging and CT. *J Comp Assist Tomogr* 2004;28:766–775.
- Zhang M, Kono M: Solitary pulmonary nodules: evaluation of blood flow patterns with dynamic CT. *Radiology* 1997;205:471–478.
- Tateishi U, Kusumoto M, Nishihara H, Nagashima K, Morikawa T, Moriyama N: Contrast-enhanced dynamic computed tomography for the evaluation of tumor angiogenesis in patients with lung carcinoma. *Cancer* 2002;95:835–842.
- Mori K, Niki N, Kondo T, Kamiyama Y, Kodama T, Kawada Y, Moriyama N: Development of a novel computer-aided diagnosis system for automatic discrimination of malignant from benign solitary pulmonary nodules on thin section dynamic computed tomography. *J Comput Assist Tomogr* 2005;29:215–222.
- Yi CA, Lee KS, Kim EA, Kamiyama Y, Kodama T, Kawada Y, Moriyama N: Solitary pulmonary nodules: dynamic enhanced multi-detector row CT study and comparison with vascular endothelial growth factor and microvessel density. *Radiology* 2004;233:191–199.
- Tack D, Gevenois PA: Radiation in computed tomography of the chest; in Bankier A, Gevenois PA (eds): *Imaging, European Respiratory Monograph 30*. The Charlesworth Group, Wakefield, 2004, pp 39–50.
- Jarry G, DeMarco JJ, Beifuss U, Cagnon CH, McNitt-Gray MF: A Monte Carlo-based method to estimate radiation dose from spiral CT: from phantom testing to patient-specific models. *Phys Med Biol* 2003;48:2645–2663.
- Jeong YJ, Yi CA, Lee KS: Solitary pulmonary nodules: detection, characterization and guidance for further diagnostic workup and treatment. *AJR Am J Roentgenol* 2007;188:57–68.
- Kostis WJ, Reeves AP, Yankelevitz DF, Henschke CI: Three-dimensional segmentation and growth-rate estimation of small pulmonary nodules in helical CT images. *IEEE Tran Med Imaging* 2003;22:1259–1274.