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Limited value of shape, margin and CT density in the discrimination between benign and malignant screen detected solid pulmonary nodules of the NELSON trial

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Abstract

Purpose: To evaluate prospectively the value of size, shape, margin and density in discriminating between benign and malignant CT screen detected solid non-calcified pulmonary nodules.

Material and methods: This study was institutional review board approved. For this study 405 participants of the NELSON lung cancer screening trial with 469 indeterminate or potentially malignant solid pulmonary nodules (>50 mm^3) were selected. The nodules were classified based on size, shape (round, polygonal, irregular) and margin (smooth, lobulated, spiculated). Mean nodule density and nodule volume were automatically generated by software. Analyses were performed by univariate and multivariate logistic regression. Results were presented as likelihood ratios (LR) with 95% confidence intervals (CI). Receiver operating characteristic analysis was performed for mean density as predictor for lung cancer.

Results: Of the 469 nodules, 387 (83%) were between 50 and 500 mm^3, 82 (17%) >500 mm^3, 59 (13%) malignant, 410 (87%) benign. The median size of the nodules was 103 mm^3 (range 50–5486 mm^3). In multivariate analysis lobulated nodules had LR of 11 compared to smooth; spiculated nodules a LR of 7 compared to smooth; irregular nodules a LR of 6 compared to round and polygonal; volume a LR of 3. The mean nodule CT density did not predict the presence of lung cancer (AUC 0.37, 95% CI 0.32–0.43).

Conclusion: In solid non-calcified nodules larger than 50 mm^3, size and to a lesser extent a lobulated or spiculated margin and irregular shape increased the likelihood that a nodule was malignant. Nodule density had no discriminative power.
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Keywords: Pulmonary nodules; Margin; Shape; Density; Multi-detector CT; Lung cancer; Screening

1. Introduction

Lung cancer is today the most frequent cause of cancer deaths in the world [1]. In the United States, it was estimated that

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171,600 people were diagnosed with this disease in 1999 (14.0% of the total number of cancer diagnosed), and about 158,900 people had died of this disease (28.2% of the total cancer death) [2]. More than two-thirds of these patients are diagnosed with locally advanced or metastatic disease, and their poor prognosis is due to late diagnosis and lack of effective treatment of metastatic disease. Less than 15% of the patients are surviving 5 years, and in several European countries the 5-year survival is far less [3]. Despite the optimal use of therapeutic resources, overall improvement in survival during the last decades has only

been modest and major reductions in lung cancer mortality can only come from primary prevention, early detection and truly innovative treatments.

Multi-detector low-dose spiral computer tomography (MDCT) is a relatively new technology that offers great potential as a screening tool because it is fast, potentially very accurate and relatively non-invasive. Therefore, the technology can be used for high throughput population screening purposes. Since the first publications of the use of the spiral CT in the early diagnosis of lung cancer, and especially the report from the Early Lung Cancer Action Program (ELCAP) in 1999 [4], the interest in lung cancer screening by low-dose spiral CT has increased tremendously. In several screening studies it has been demonstrated that 55–80% of lung cancers detected by spiral CT screening are at a very early stage [5–8].

With the increasing use of the MDCT technology for lung cancer screening and the use of thinner slices, the number of screen detected nodules has increased substantially, which poses clinicians often for diagnostic dilemmas. The Fleischner Society [9] has recently issued recommendations for periodic follow-up scanning for this type of nodules, depending on their initial size. According to this recommendation, a nodule is benign if no growth has been observed after 24 months. Once growth has been demonstrated the likelihood of malignancy increases, but also benign lesions may grow [10]. If it were possible to identify subgroups of small pulmonary nodules less likely to be malignant, the follow-up rate for this type of lesions could be reduced.

MDCT technology has not only led to an increased detection rate of pulmonary nodules, but at the same time improvements in spatial resolution and scanning time have given us the possibility to better analyse the internal and external characteristics of the nodules detected. Although many of these characteristics are already known for solitary pulmonary nodules (SPN) which are usually larger than 1 cm [11], their applicability in the discrimination between benign and malignant in sub-centimeter solid screen detected pulmonary nodules is yet unknown.

Purpose of this study is to evaluate prospectively the value of size, shape, margin and mean density in the discrimination between benign and malignant solid nodules detected at baseline screening of the Dutch-Belgian randomised lung cancer screening trial (NELSON).

2. Materials and methods

2.1. Participants

The participants of the NELSON study underwent baseline screening for lung cancer by low-dose multi-detector CT. They were between 50 and 75 years of age and were recruited via population registries through mail. They had to be current or former smokers with a smoking history of >15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years. Ineligible were those applicants who already underwent a pneumonectomy and those with a history of breast cancer, melanoma or hypernephroma. People with a history of other cancers were only eligible if curatively treated at least 5 years ago without

signs of recurrence at the time of inclusion. The NELSON study was approved by the Medical Ethical Committees of all institutions and all subjects provided written informed consent. From April 2004 until July 2006, 7310 participants underwent baseline screening. For this particular study a subgroup of 405 participants with 387 indeterminate solid pulmonary nodules between 50 and 500 mm^3 (≤0 mm in diameter) and 82 screen-positive solid pulmonary nodules with a volume >500 mm^3 (>10 mm in diameter) have been selected. The nodules had to be located purely intra-parenchymal without pleural-, fissure-attachment or juxtavascular location. For all these nodules either a 1-year follow-up or histological proof of benignancy or malignancy was available.

2.2. Data acquisition

At all four screening sites 16-detector MDCT scanners were used (Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, OH, USA, or Sensation-16, Siemens Medical Solutions, Forchheim, Germany). Scanning of the entire chest was performed in caudo-cranial direction. Scan data were obtained in spiral mode, with 16 mm × 0.75 mm collimation and pitch 1.5. No contrast was used. Low-dose settings were applied. Depending on the body weight (<50, 50–80 and >80 kg), the kVp settings were 80–90, 120 and 140 kVp, respectively, to achieve a Computed Tomography Dose Index Volume (CTDIvol) of approximately 0.8, 1.6 and 3.2 mGy, respectively. The mAs settings were adjusted accordingly dependent on the machine used. To minimize breathing artefacts, scans were performed at suspended maximal inspiration after appropriate instruction of the subjects. Data were reconstructed at 1.0 mm slice thickness, with 0.7 mm reconstruction increment.

2.3. Image analysis

All CT images were read twice independently. First readings were done by a radiologist with an experience in reading thoracic CT scans varying from 1 year to more than 20 years. Second readings were done by radiologists with 6 years of experience. In case of a discrepancy between the first and second reader, a third radiologist with more than 15 years of experience with lung CT made the final decision. The Syngo Lungcare$^©$ (Leonardo$^©$ workstation, Somaris/5 VB 10A Siemens Medical Solutions, Erlangen, Germany) software package designed to aid the radiologist in the diagnosis of pulmonary nodules was used in addition to visual readings. Baseline and follow-up images were reviewed and displayed simultaneously on one workstation. All images were interpreted both at lung window and mediastinal settings.

2.4. Nodule features

The non-calcified solid nodules detected at baseline screening were classified into four different categories based on size and benign characteristics as described earlier [12]. Indeterminate nodules (Category III) were defined as nodules with volumes between 50 and 500 mm^3, and screen-positive nod-

ules (Category IV) as nodules larger than 500 mm^3. In this study, all solid nodules were further classified based on shape (round/oval, polygonal or irregular) [13], margin (smooth, lobulated or spiculated/irregular) [14], and mean CT density in Hounsfield units (HU) ($\leq$0, 0–100 or >100 HU). A nodule was polygonal when the entire lesion surface was surrounded by concave margins only [15]. Spiculation was defined as the presence of thicker strands extending from the nodule margin into the lung parenchyma without reaching the pleural surface [16]. Lobulation was defined as an abrupt bulging of the lesion contour [17]. Mean CT density of the nodule was calculated automatically by the Lungcare$^©$ software instead of specifying a region of interest. Volumes were calculated by three-dimensional (3D) volumetric computer software (Lungcare$^©$ software). In case of inappropriate segmentation, the radiologist was able to enter manual measurements as well, which then overruled the automatically generated volume calculations as described earlier [12]. Because cancer risk was absent at 1 year of follow-up in indeterminate solid nodules attached to either a vessel, the pleura or a fissure [18], only purely intra-parenchymal indeterminate solid nodules and screen positive nodules have been included in this study. Nodules were classified as benign or malignant based on histological examinations of trans-thoracic needle biopsies or examination of surgical specimens. Nodules were also classified as benign if the volume doubling time (VDT) was >600 days or if the volume decreased at 1 year of follow-up.

2.5. Statistical analysis

The Chi-square test for independence was used for comparisons of the presence of lung cancer among nodules within different categories of size, shape, margin or density. Univariate and multivariate logistic regression analyses were used to investigate the effect of the different nodule characteristics on the presence of lung cancer. Results are presented as likelihood ratios (LR) with 95% confidence intervals. Because mean nodule density and size were not normally distributed, a logarithmic transformation was performed before statistical analysis. Correlation analysis between density and nodule volume for lung cancer positive and negative cases was performed by Pearson's test. Receiver operating characteristic (ROC) analysis was performed for density as a predictor for the presence of lung cancer. p values < 0.05 were considered statistically significant. All values are expressed as means $\pm$ standard deviation (S.D.) and all analyses have been performed in SPSS version 14.0.

3. Results

Between April 2004 and July 2006, in 405 participants 469 solid purely intra-parenchymal nodules of Category III and IV were detected which met the inclusion criteria. The mean age of the participants was 62 years ($\pm$5 years), 93% were males, 7% females.

Of these 469 nodules, 387 (82%) were Category III and 82 (18%) Category IV, 59 (13%) malignant and 410 (87%) benign. The median size of the nodules was 103 mm^3 (range

Table 1

Characteristics of the 469 indeterminate and screen positive pulmonary nodules detected at baseline screening of the NELSON trial

	N (%)	Lung cancer	
		No (%)	Yes (%)
Category			
III	387 (82)	371 (90)	16 (27)
IV	82 (18)	39 (10)	43 (73)*
Margin			
Smooth	262 (56)	261 (64)	1 (2)
Lobulated	106 (23)	93 (22)	13 (22)
Spiculated	101 (21)	56 (14)	45 (76)*
Shape			
Round	324 (69)	314 (77)	10 (17)
Polygonal	37 (8)	37 (9)	0 (0)
Irregular	108 (23)	59 (14)	49 (83)*
CT density (HU)			
<0	165 (35)	142 (35)	23 (39)
0–100	275 (59)	239 (58)	36 (61)
>100	29 (6)	29 (7)	0 (0)

HU, Hounsfield units.

* $p = 0.000$, chi-square test.

50–5486 mm^3; median diameter 4.7 mm). The median CT density for benign nodules was 39 HU (range, $-$195 to 192 HU), and 11 HU (range, $-$128 to 7 HU) for malignant nodules ($p = 0.002$). In Table 1 the distribution of the nodule characteristics is presented. For all variables except for nodule density, there was correlation with lung cancer ($p = 0.000$), which was confirmed in univariate analysis (Table 2). Lobulated, spiculated, irregular and Category IV nodules had an increased LR for lung cancer compared to smooth, round or polygonal and Category III nodules, respectively. The 95% CI intervals were very large, however, except for tumor volume. In multivariate analysis only tumor volume remained highly significant with a small 95% CI, while margin and shape just reached statistical significance, again with very wide 95% CI's (Table 3). The ROC curve (Fig. 1) illustrates that mean nodule CT density could not be used as a predictor for lung cancer (AUC 0.37, 95% CI 0.32–0.43). For lung cancer positive cases, the correlation coefficient between

Table 2

Likelihood of lung cancer for the different nodule characteristics by univariate analysis

Nodule characteristic	LR	95% CI	p-Value
Margin			
Lobulated vs. smooth	37	(5–283)	0.001
Spiculated vs. smooth	210	(28–1554)	0.000
Shape			
Irregular vs. round and polygonal	29	(14–61)	0.000
Category			
>500 mm^3 vs. 50–500 mm^3	26	(13–50)	0.000
Ln-volume	5	(3–6)	0.000
Ln-density	0.6	(0.3–1.1)	NS

Ln, natural logarithmic conversion; NS, non-significant; CI, confidence interval; LR, likelihood ratio.

Table 3
Likelihood of lung cancer for the different nodule characteristics by multivariate analysis

	LR	95% CI	p-Value
Margin			
Lobulated vs. smooth	11	(1–92)	0.03
Spiculated vs. smooth	7	(1–101)	NS
Shape			
Irregular vs. round and polygonal	6	(1–37)	0.04
Ln-volume	3	(2–4)	0.000

Ln, natural logarithmic conversion; NS, non-significant; CI, confidence interval; LR, likelihood ratio.
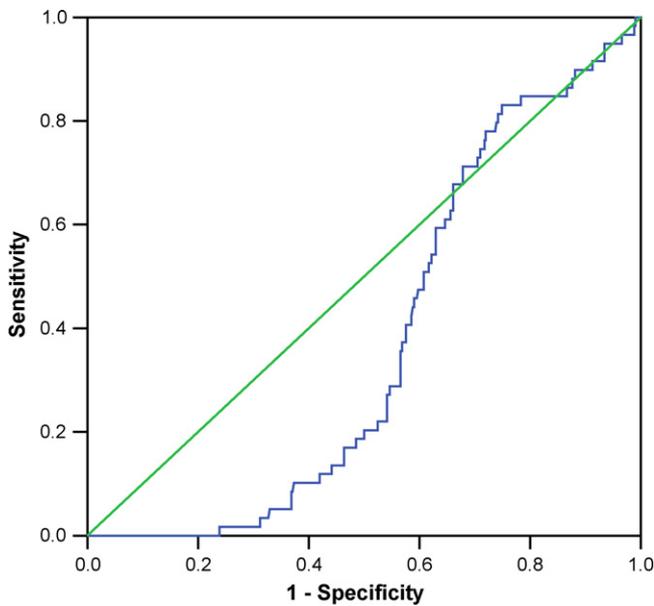

Fig. 1. The receiver operating curve (ROC) shows that nodule density is no predictor for lung cancer (AUC 0.37, 95% CI 0.32–0.43, $p = 0.03$).

tumor volume and mean density was -0.05 ($p = $ns), and for lung cancer negative cases 0.06 ($p = $ns) (Fig. 2A and B). Of the 469 solid nodules, 72 had a round contour, smooth margin and negative CT density (<0 HU). None of them became malignant at 1 year of follow-up.

4. Discussion

The differentiation of benign form malignant pulmonary nodules detected within the context of a lung cancer screening programme is of great importance in order to reduce costs, anxiety and unnecessary additional investigations. It is therefore a great challenge to the specialist because the nodule remains frequently indeterminate at the end of the diagnostic process and surgical resection is often needed before a definitive diagnosis can be made. In a previous study, Xu et al. have demonstrated that in solid indeterminate nodules between 50 and 500 mm^3 lung cancer risk is absent at 1 year of follow-up in nodules attached to either a vessel, the pleura or a fissure while all lung cancer cases originated from purely intra-parenchymal nodules without attachment to these structures [18]. In the current study we investigated prospectively whether size, margin, shape and CT density could help in the discrimination between benign and malignant nodules. Although univariate analysis showed that lobulated, spiculated, irregular and Category IV nodules had an increased likelihood for lung cancer compared to smooth, round or polygonal and Category III nodules, respectively, the 95% CI intervals were very large, except for tumor volume. In multivariate analysis only tumor volume (size) remained highly significantly associated with the presence of lung cancer with small 95% CI's, while margin and shape just reached statistical significance, again with wide 95% CI's. Furthermore, we demonstrated that nodule density could not be used as a predictor, neither for lung cancer negative nor for lung cancer positive cases, although the density of malig-
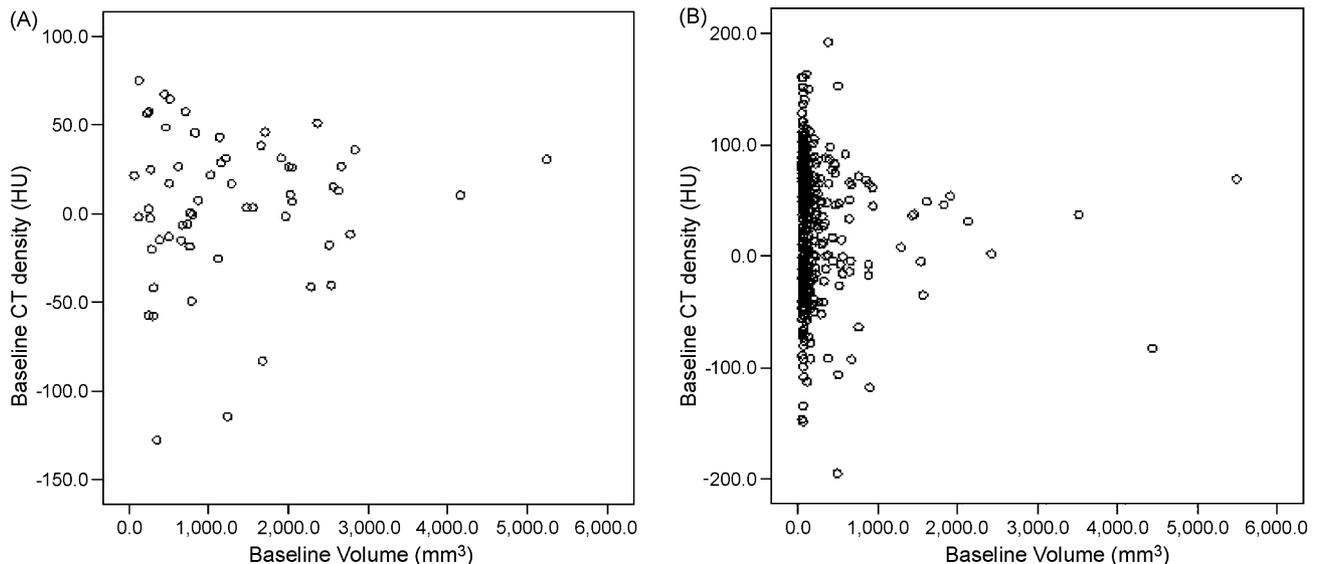

Fig. 2. (A and B) Scatter plots illustrating that there is no correlation between nodule volume and mean nodule density, neither in lung cancer positive (A) nor in lung cancer negative cases (B) (Pearson's correlation test, $r = -0.05$ and 0.06, respectively, $p = $ns).

nant nodules appeared to be significant lower than that of benign nodules.

The correlation between size and cancer risk found in our study has also been reported by other investigators [6,19–21]. The chance of being malignant is 0.9% for nodules between 4 and 7 mm, 18% for nodules 8–20 mm and 50% for those larger than 20 mm, while cancer risk is <0.2% for nodules less than 3 mm in diameter [9].

However, other features in addition to size can be helpful in the discrimination between benign and malignant pulmonary nodules [11,22]. The higher LR of cancer in nodules with a spiculated margin compared to round or polygonal nodules in our study is consistent with the results of previous studies in SPN's [22–24], in which a spiculated contour occurs significantly more often in malignant SPNs. However, 95% CI intervals were wide, also limiting its use for SPN's in clinical practice. In pathological studies a spiculated contour was found to be due to thickened interlobular septa, fibrosis caused by obstruction of pulmonary vessels or lymphatic channels filled with tumor cells or extension to the pleura with pleural infiltration [23,24]. Nevertheless, also in benign SPN such as in inflammatory pseudotumors or tuberculomas spiculated edges may be found due to a desmoplastic response.

With regard to the shape of benign and malignant SPN there is no agreement in the literature. Seemann reported that both benign and malignant SPN's could exhibit smooth edges [11,23], while others found round or polygonal margins more often in benign lesions [16,22,25]. The pathologic substrate for lobulation in malignant lesions is the presence of nodular excrescences of the tumor at its advancing edge or tumor growth in islands at the periphery of the nodule, indicating that the nodule has uneven growth rates [10,24].

In our study of solid non-calcified pulmonary nodules, we found that the cancer cases had a significant lower mean density compared to benign nodules ($p < 0.05$) most likely due to a lepidic growth pattern, the inclusion of air or an air bronchogram or regressive changes such as necrosis or hemorrhage within the tumor. This was consistent with the results of studies performed in usually larger SPN's [11,23,26,27]. Despite these findings, we do not recommend the use of nodule density in the differentiation between malignant and benign nodules because of the large overlap and the wide range of densities observed among the malignant nodules. In multivariate analysis nodule density was also not significant. Other investigators [11,23] also concluded that benign and malignant SNP's showed large variability in nodule density, particularly in the malignant group, with large overlap, and that size, shape and margin had only limited value in the identification of malignant from benign pulmonary nodules. Siegelman et al. suggested that a representative density value above 164 HU could be used to separate benign from malignant lesions, primarily because of diffuse calcifications in benign nodules [28]. However, this conclusion was not supported by the study by Seemann et al. [11], who demonstrated that both benign and malignant solitary pulmonary nodules showed large range in lesion densities, particularly in the malignant group, with large overlap. Our results in small screen detected nodules are more or less consistent with the conclusions for larger SPN's, showing that size, shape and margin had only limited value in the identification of malignant from benign pulmonary nodules [23–25].

In the literature, there are several nodule classifications in use based on the external and internal features of the nodules, such as ragged, densely spiculated, somewhat irregular with slight spiculation or irregular with spiculation, but so far no standard classification is being used. According to our experience, some of these classifications are too complex and subjective for research purposes. For example, it is difficult to differentiate ragged nodule from lobulated and the same holds true for slightly and densely spiculated or coarse spiculation. This was also concluded by Li et al. who found large variability in the classification of the CT features by three different radiologists, especially for the margins of the nodule [25]. In order to minimize the inter-observer variability, we used a more simplified nodule classification as described in the method section.

Future studies should focus on the further development of computer aided diagnosis (CAD) algorithms for small screen detected pulmonary nodules [29]. In our study, none of the round spherical nodules with a smooth margin and negative CT density became malignant at 1 year of follow-up, but the numbers are yet too small to draw final conclusions. Also changes in nodule shape and density over time might be associated with malignancy, and need further investigation.

In conclusion, in solid non-calcified nodules larger than 50 mm³, size and to a lesser extent lobulated or spiculated margin and irregular shape increased the likelihood that the nodule was malignant. Nodule density had no discriminative power.

Conflict of interest

Not reported.

Acknowledgements

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