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ORIGINAL ARTICLE – COLORECTAL CANCER

Indeterminate Pulmonary Nodules in Colorectal-Cancer: Do Radiologists Agree?

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ABSTRACT

Background. The clinical significance of indeterminate pulmonary nodules (IPN) at staging computed tomography (CT) for colorectal cancer (CRC), and the optimal diagnostic approach, are debated. This study aimed to analyse variability in radiologists' detection of IPN at staging CT for CRC.

Methods. All patients with CRC referred to our center between 2006 and 2011 were included. Primary staging CT scans were re-evaluated by an experienced thoracic radiologist whose findings were entered into a dedicated database and merged with data from the Danish Colorectal Cancer Group database, the National Patient Registry, the Danish Pathology Registry, and the primary CT evaluation. Inter-reader agreement was calculated by Kappa statistics, and associations between variables and malignancy of pulmonary nodules were analyzed with χ^2 and Mann–Whitney–Wilcoxon tests. Multivariable logistic regression analyses were used to adjust for potential confounding variables.

Results. In total, 841 patients were included. The primary CT assessment reported IPN in 9.8 % of patients and pulmonary metastases in 5.1 % of patients compared with 5.6 and 7.0 %, respectively, reported by the experienced thoracic radiologist. Kappa for agreement between the primary assessor and the thoracic radiologist on IPN was 0.31 and 0.65 for pulmonary metastases. Synchronous liver metastases were predictive of malignancy of IPN (adjusted odds ratio 20.1; 95 % confidence interval 2.64–437.66; $p = 0.012$), whereas no other investigated radiological characteristics or clinicopathological factors were significantly associated with malignancy of IPN.

Conclusion. The characterization of pulmonary findings on staging CT for CRC varied greatly between the radiologists, and double-reading of scans with IPN is recommended prior to further diagnostic work-up.

In international guidelines, a chest computed tomography (CT) scan is recommended for staging imaging in colorectal cancer (CRC) patients.[1–4] A staging chest CT is justified by the fact that the lungs are the most common extra-abdominal site for colorectal metastases and chest CT has a higher sensitivity than chest X-ray for pulmonary metastases.[5] Synchronous pulmonary colorectal cancer metastases (SPCM) are associated with a significantly impaired survival prognosis.[6] Early diagnosis of SPCM may increase the possibility of curative pulmonary resection.

CT staging may reveal indeterminate pulmonary nodules (IPN) in more than one-third of CRC patients, some of which prove to be metastatic disease.[7] However, the detection rate of IPN varies greatly between published studies. In settings other than CRC, the detection and characterization of IPN varies significantly depending on the evaluating radiologist.[8] As previous studies on this topic are very heterogeneous, and as most IPN ultimately prove to be benign, the clinical significance of IPN in the CRC setting is still unclear.[7]

This study analyzed the variability in the radiologists' detection and characterization of IPN at the primary pulmonary staging CT scan in newly diagnosed CRC patients. Furthermore, we investigated whether certain radiological characteristics, as assessed by an experienced thoracic

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radiologist, were associated with the malignant nature of IPN.

METHODS

Study Population and Data Collection

All patients with a first-time diagnosis of CRC referred to our center between 1 June 2006 and 31 May 2011 were assessed for inclusion because CT staging was fully integrated at the institution during this period. Data on all patients were extracted from the database of the Danish Colorectal Cancer Group (DCCG). Vital status, pulmonary imaging modalities applied during follow-up, data on invasive procedures, and histopathology of the primary tumor and synchronous metastases were extracted from the National Patient Registry (NPR) and the Danish Pathology Registry (DPR).

Inclusion in the study required histologically-verified CRC or evidence of a malignant colorectal tumor, as evaluated by a trained colorectal surgeon. Patients without a staging chest CT were excluded. Other reasons for exclusion were missing data on cancer stage and diagnosis of any other cancer (except skin cancers) ±5 years from the time of CRC diagnosis.

All available data from the DCCG database, the NPR, DPR, and multidisciplinary team conferences were scrutinized for diagnostic information on potential SPCM. The first author reviewed all records on thoracic radiological follow-up examinations of patients with IPN within 120 days from the primary diagnosis. Additionally, scan reports within the same timeframe for patients with a discrepancy between the radiological assessment and data on SPCM in the national registries were reviewed. All patients with IPN to a follow-up CT scan after 3 months. IPNs that had not increased in size and/or number were concluded to be non-malignant in the statistical analyses. A newly diagnosed SPCM on follow-up had to be located in the same location as an initially diagnosed IPN in order for it to be concluded that the SPCM originated from this IPN.

Image Acquisition CT scans were performed with a multidetector scanner (Brilliance 64; Philips Healthcare, Best, The Netherlands) using the following parameters: section thickness 3 mm; collimation 1–3 mm; pitch 1.0; reconstruction thickness 1–3 mm. A window width of 1,500 HU and a window level of −500 HU were used as the lung algorithm and, correspondingly, a width of 360 HU and level of 40 as the soft-tissue algorithm. If not contraindicated, 70–100 mL IV iohexol (Omnipaque-350; Daiichi Sankyo Co. Ltd, Tokyo, Japan) was administered, producing both arterial and venous phases.

Observers Seventy-one different radiologists with varying levels of specialization, ranging from residents to consultants, conducted the primary assessments of the staging chest CT scans. Their findings were evaluated against review by an experienced and dedicated thoracic radiologist with an interest in thoracic malignancies. This radiologist was aware of the diagnosis of CRC as the indication for the staging CT scan, but was blinded to the result of the primary CT assessment and which patients were proven to have pulmonary metastases at follow-up.

Diagnostic Criteria The diagnostic criteria for pulmonary nodules during the study period adhered to the recommendations of the Fleischner Society.[9] A pulmonary nodule was defined as a round opacity, moderately well-marginated, and no greater than 3 cm at maximum diameter at CT.[10] A 'normal' scan was defined as a scan with no radiological evidence of pulmonary nodules. A well-demarcated solid or ground-glass nodule ≤5 mm with complete calcifications was classified as benign, and lobular or spiculated nodules >5 mm (solid or ground-glass) were classified as SPCM. An IPN was defined as a nodule that could not be readily classified as either benign or malignant.

The study was reported to the Danish Data Protection Agency (ref. no. BBH-2012-03).

Studied Variables

The thoracic radiologist's review included a graduation of the chest CT scan into four categories: (1) normal scan; (2) benign pulmonary lesions; (3) IPN; and (4) SPCM. IPN and SPCM were assessed regarding size, number, laterality, intrapulmonary location, calcification, ground-glass opacity, and consistency. An independent research assistant manually searched the primary reports for the same information blinded to the thoracic radiologist's findings. Patients having both IPN and SPCM were classified as SPCM.

Data on potential confounders were extracted from the DCCG, DPR, and NPR, including age, sex, year of diagnosis, location of primary tumor, tumor stage, comorbidity, and extrapulmonary synchronous metastases. Comorbidity was assessed according to the Charlson index.[11]

Statistical Analyses

The level of agreement between the primary CT and the thoracic radiologist's assessments was calculated by Kappa statistics. Marginal homogeneity was calculated by the Bhapkhar test and McNemar's test. The performance of diagnosis was calculated as sensitivity and specificity. The

categories 'normal' and 'benign' were test negative results and 'SPCM' a test positive result.

The associations between the variables and malignant nature of IPN were analyzed using the χ^2 and Mann–Whitney–Wilcoxon tests for categorical and continuous variables, respectively. Variables with a p value <0.2 in the univariable analyses were entered into a multivariable logistic regression analysis.

For the subgroup of patients subjected to curative surgery for their index tumor, multiple linear regression was used to calculate the significance of IPN on the time to surgery.

A two-tailed p value of 0.05 was used as the level of significance. Statistical software used was R version 2.15.2[12] including the 'irr' package.[13]

RESULTS

A total of 1,287 patients were assessed for eligibility, of whom 841 (65.3 %) were included (Fig. 1). Of these, 73 (8.7 %) were classified as having SPCM. Median follow-up time was 1,181 days (interquartile range 766–1,640 days). The index tumor was colonic in 533 (63.4 %) patients, and rectal in the remaining 308 (36.6 %) patients (Table 1).

In total, 661 patients without definite pulmonary metastases at the primary CT assessment were subjected to curative surgery for their CRC. Median time to operation for patients with normal scan or benign nodules was 13 days compared with 20 days for patients with IPN. In multiple linear regression analysis, IPN was associated with an average surgical delay of 14 days (95 % CI 2–27 days; $p = 0.029$) compared with patients with normal/benign findings.

TABLE 1 Baseline patient characteristics ($n = 841$)

Sex	
Female	403
Male	438
Median age, years (IQR)	71 (63–78)
Charlson comorbidity index score	
<2	754
≥2	87
Year of diagnosis	
2006–2008	374
2009–2011	467
Index tumor location	
Right colon	166
Transverse colon	111
Left and sigmoid colon	256
Rectum	308
Smoking	
Never	267
Former	349
Current	170
Missing	55
Extrapulmonary synchronous metastases	
None	676
Liver	152
Other	9
Liver and other	4

IQR interquartile range

Inter-observer Variability Assessment

The overall rate of agreement between the primary and thoracic radiologist's CT assessments was 81.8 %

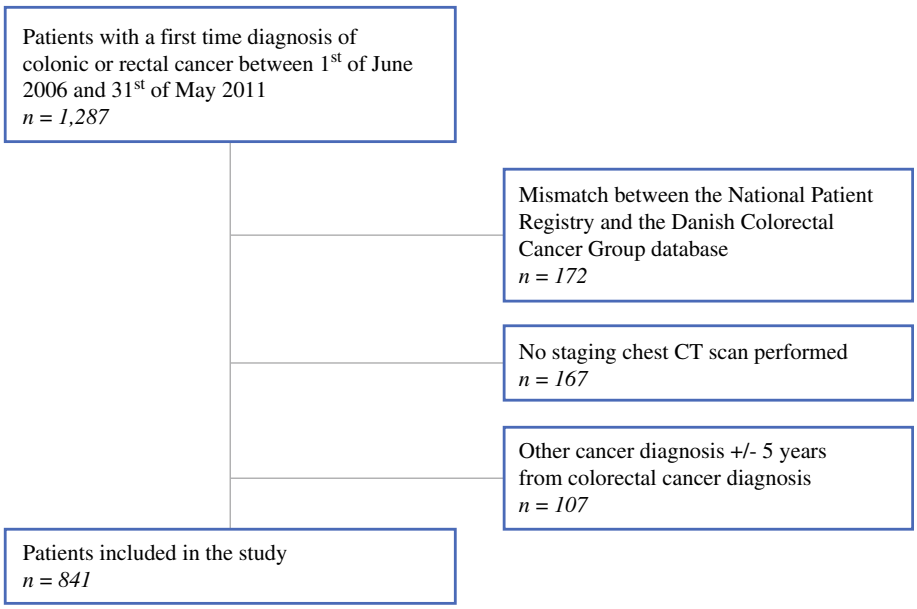

FIG. 1 Flowchart of inclusion criteria for patients in the study. *CT* computed tomography

(Table 2). Kappa was 0.49 (95 % CI 0.43–0.55), equivalent to moderate agreement.[14] The distribution of severity of the pulmonary findings from the primary assessment was significantly different from the thoracic radiologist's review ($p < 0.001$, Bhapkar test). More scans were classified as 'IPN' in the primary review compared with the thoracic radiologist's evaluation. Conversely, the thoracic radiologist was more inclined to use the category 'SPCM' than the primary assessors. Kappa for the category 'IPN' was 0.31 (95 % CI 0.24–0.37) ($p < 0.001$, McNemar's test) and 0.65 (95 % CI 0.58–0.71; $p < 0.001$) for the category 'SPCM', equivalent to fair and substantial agreement, respectively.[14] None of the primary evaluating radiologists were dedicated to thoracic radiology. A subgroup analysis was performed comparing the assessment of the two most experienced non-thoracic radiologists, who had long-lasting experience in staging of gastrointestinal malignancies, with the thoracic radiologist. These two radiologists had assessed 170 (20.2 %) of the scans and found IPN in 7.6 % of the cases compared with 5.3 % in the thoracic radiologist's review. Overall agreement was 82.9 % and overall kappa was 0.467 (95 % CI 0.36–0.60), equivalent to moderate agreement. Kappa for IPN was 0.32 (95 % CI 0.17–0.47; $p < 0.001$).

TABLE 2 Classification of CT findings

	Primary assessment				
	Normal	Benign lesion	IPN	SPCM	Total
Secondary assessment by thoracic radiologist					
Normal	609	35	32	3	679
Benign lesion	27	22	7	0	56
IPN	14	4	23	6	47
SPCM	5	0	20	34	59
Total	655	61	82	43	841

CT computed tomography; *IPN* indeterminate pulmonary nodule; *SPCM* synchronous pulmonary colorectal cancer metastases

Malignancy of Indeterminate Pulmonary Nodules

The results of the radiological assessments and development of SPCM at follow-up are shown in Fig. 2a and b. The diagnostic performance of the primary assessment yielded a sensitivity of 73.6 % (95 % CI 56.7–84.7) and specificity of 99.4 % (95 % CI 98.6–99.8). Sensitivity and specificity in the thoracic radiologist's review were 92.1 % (95 % CI 82.4–97.4) and 99.9 % (95 % CI 99.2–99.9), respectively. Of the 82 and 47 patients with IPN detected on the primary and thoracic radiologist's assessment, respectively, 73 (89.0 %) and 42 (89.4 %) were subjected to further radiological follow-up. The remaining patients died before further radiological intervention was performed.

In total, 20 of the 73 patients (27.4 %) with IPN at the primary assessment, and subjected to further follow-up, proved to have SPCM. All of these patients were registered, by the expert, as having IPN (3 of 20, 15.0 %) or SPCM (17 of 20, 85.0 %). Seven of the 20 patients (35.0 %) had their SPCM histologically confirmed. A positron emission tomography (PET)-CT was applied in 40 of the 73 patients (54.8 %), and was true positive in nine cases and true negative in 24 cases. Five patients had false positive findings and the PET-CT was false negative in two cases. Hence, the sensitivity and specificity of the PET-CT scan for this subset of patients were 81.8 % (95 % CI 48.2–97.2 %) and 82.7 % (95 % CI 64.2–94.1 %), respectively.

Data on radiological characteristics of IPN were sparsely and inconsistently reported in the primary assessment, and were therefore only available for analysis from the thoracic radiologist's review. In this review, none of the evaluated radiological characteristics proved to be statistically associated with malignancy of IPN. The presence of

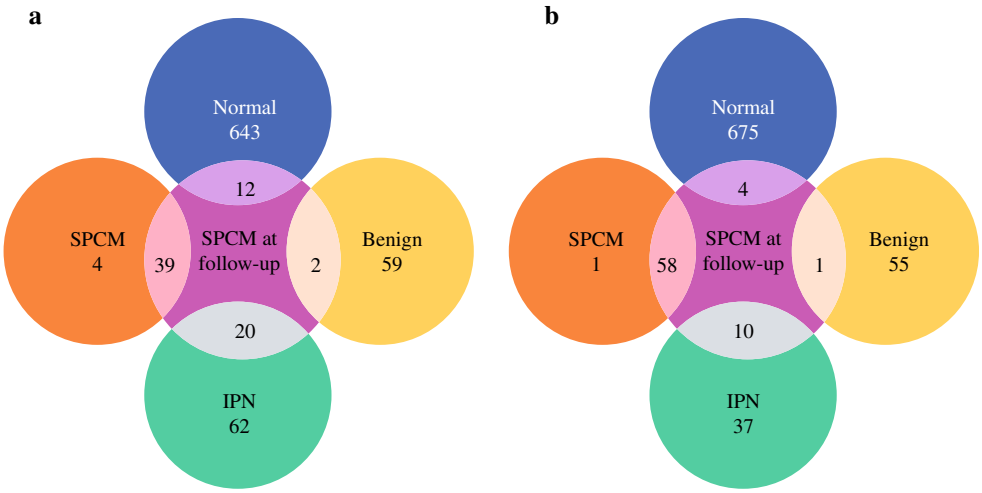

FIG. 2 Venn diagrams. **a** Primary CT assessment findings and synchronous pulmonary colorectal cancer metastases at follow-up. **b** Thoracic radiologist's CT assessment findings and synchronous pulmonary colorectal cancer metastases at follow-up. *CT* computed tomography, *SPCM* synchronous pulmonary colorectal cancer metastases, *IPN* indeterminate pulmonary nodules

TABLE 3 Predictive parameters for malignancy in IPNs at follow-up as assessed by a thoracic radiologist

$N = 42$	N	Univariable			Multivariable		
		OR	95 % CI	p value	OR	95 % CI	p value
Sex				0.592			
Female	20	1.00					
Male	22	0.67	0.14–2.96				
Age (per additional year)		0.95	0.86–1.03	0.230			
Index tumor				0.304			
Colonic	25	1.00					
Rectum	17	2.19	0.49–10.40				
Synchronous liver metastases				0.015			0.012
No	29	1.00			1.00		
Yes	13	7.43	1.57–43.10		20.1	2.64–437.66	
Comorbidity[a]				0.618			
<2	35	1.00					
≥2	7	0.56	0.03–4.02				
Number (per additional IPN)		0.34	0.02–1.25	0.249			
Size				0.088			0.061
< 5	12	1.00			1.00		
5–9.9	18	7.00	1.00–142.57		19.1	1.65–745.43	
≥10	12	0.50	0.04–5.91		1.00	0.03–31.79	
Laterality				0.861			
Right	29	1.00					
Left	10	1.26	0.06–13.93				
Bilateral	3	1.48	0.28–7.85				
Location				0.849			
Centrally	0	–	–				
Intermediary	4	1.00					
Peripherally	38	0.80	0.09–17.38				
Contour				0.777			
Smooth	27	1.00					
Lobular or spiculated	15	0.88	0.16–3.99				
Consistency				0.957			
Solid	23	1.00					
Non-solid	19	0.96	0.21–4.27				
Ground-glass				0.995			
Yes	7	1.00					
No	36	1.77	0.25–36.17				

OR odds ratio; *CI* confidence interval; *IPN* indeterminate pulmonary nodules

[a] Comorbidity according to Charlson Comorbidity Index score

synchronous metastatic spread to the liver was the only clinicopathological factor associated with malignancy at follow-up of the IPN (adjusted odds ratio 20.1; 95 % CI 2.64–437.66; $p = 0.012$).

DISCUSSION

This cohort study demonstrated a great variance among a high number of radiologists in the assessment of pulmonary findings on the staging CT scan in newly diagnosed CRC patients with respect to the classification of 'indeterminate' nodules. Synchronous liver metastases were associated with the malignant nature of IPN on follow-up. Time to surgery for the index tumor was prolonged in patients with IPN compared with patients with non-suspicious pulmonary CT findings, suggesting that additional diagnostic work-up for IPNs delays definitive treatment.

Overall 5-year survival is about 10 % in patients with metastatic CRC, compared with 65 % for patients without distant metastasis.[15] Median overall survival for patients with metastatic disease confined to the lungs is less than 400 days.[6] The importance of detecting potential curable pulmonary metastatic spread is therefore obvious. However, in the diagnostic work-up of indeterminate lesions detected at pulmonary staging CT, the personal psychological implications for patients should be kept in mind. This aspect has not yet been properly investigated in patients with CRC, but is known to cause significant psychological distress in other settings.[16,17] Furthermore, excess radiation, risk of surgical morbidity, and delay of treatment of the index cancer or preclusion for liver resection have been debated.[9, 18]

The inter-reader variability in the detection and characterization of pulmonary nodules on CT scans is substantial, even between expert radiologists.[8,19] A pulmonary nodule initially characterized as indeterminate may be reclassified as either benign or malignant on a second radiological review.[20,21] The thoracic radiologist was more inclined to use the category 'SPCM' than the primary assessors. On the other hand, more scans were classified as 'IPN' in the primary review.

A previous review reported that only one in 100 CT-staged CRC patients had an IPN that proved to be metastatic disease on follow-up. Therefore, no further preoperative diagnostic workup or follow-up besides routine regimens were recommended.[7] However, recommendations for the optimal diagnostic work-up of IPN in CRC patients range from no further follow-up to targeted surveillance, including PET-CT, depending on specific clinicopathological factors.,[9 22–29] The additional value of PET-CT is questionable as the resolution is only 5–6 mm. In small nodules, a PET-positive scan indicates malignancy, whereas the risk of a false test should be kept in mind in PET-negative results.,[9,20 30–32] The Fleischner Society recommends additional diagnostic modalities, including PET, for nodules larger than 8 mm.[9]

Our data suggest that 'IPNs', as concluded by a thoracic radiologist, are truly indeterminate without predictive characteristics. Nevertheless, 20 % of these lesions proved to be malignant, and herein lays the diagnostic problem. In a post hoc analysis (data not shown) it was found that a solid consistency and increasing size in addition to synchronous liver metastases were statistically associated with malignancy. The lack of consensus in the definition of IPN poses a great diagnostic challenge.[7] However, there seems to be consensus that calcification of pulmonary nodules implies a benign etiology,[9,29] whereas a positive nodal status and/or extrapulmonary synchronous metastatic disease warrant a higher risk of nodule malignancy, as found in the present study.[7,29] Preferably, further diagnostic work-up and treatment should be based on reproducible and objective patient and nodule characteristics, as proposed in a study on lung cancer screening detected pulmonary nodules.[33] A future predictive model in the assessment of IPN in CRC patients may benefit from the inclusion of biomarkers known to be associated with metastases, such as KRAS, and mismatch repair status of the index tumor.[34,35]

The inadequate accessibility of experienced thoracic radiologists for assessments of all staging scans is currently a limiting factor. To address this problem at our center, we have introduced a second review, by a group of experienced thoracic radiologists, of the scans with IPN. By using this approach, 10 % of the staging scans in the present study would have to be reviewed by a thoracic radiologist. If pulmonary nodules are still deemed 'indeterminate' at this second review, the patient is subjected to a PET-CT or a low-dose follow-up CT at 3-month intervals, depending on the size and presence of ground-glass morphology (Table 3).[9] A nodule that appears stable in size in similar projections in a follow-up CT scan is considered benign.[36] In the absence of growth or new nodules, we suggest allocation to the standard follow-up regimen of the index cancer. A tissue diagnosis by CT guided core biopsy may be particularly indicated for peripheral lesions, and has been associated with a moderate specificity and >95 % sensitivity.[37]

CONCLUSIONS

Only few of the pulmonary metastases were histologically confirmed, and patients were not subjected to a uniform follow-up regimen after the initial staging CT. Therefore, the given number of SPCM at follow-up may be flawed. The thoracic radiologist's review was obtained from a single radiologist rather than consensus from a group of experts. Finally, the number of expert-characterized IPN patients may be too small to detect associations between predictive parameters for a malignant nature of IPN. Nevertheless, the variability among radiologists in the detection of IPN in CRC should be kept in mind before comparing results from different studies. Implementation of a second review may potentially prevent numerous, costly, and time-consuming diagnostic work-ups and reduce the risk of over-diagnosis.

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CONFLICT OF INTEREST Andreas Nordholm-Carstensen, Lars N. Jorgensen, Peer A. Wille-Jørgensen, Hanne Hansen, and Henrik Harling have no conflicts of interest to declare.

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