Risk of metastasis in non-calcified pulmonary nodules on initial staging CT in patients with primary extra pulmonary malignancy

Purpose: Detection of pulmonary nodules in patients with extra pulmonary malignancy is common. Consequently, differentiating malignant from benign lesions is important to determine adequate treatment protocol. This study aims first to detect pulmonary nodules at first staging CT for extra pulmonary malignancy; and second to evaluate the correlation between the morphological criteria of pulmonary nodules and the malignancy of nodules. By doing so, the study would be able to estimate the risk of metastasis in pulmonary nodules detected at first staging CT for extra pulmonary malignancy.

Methods: In this retrospective study, we included patients aged 18 years old and over that had a first staging CT between January 2010 and December 2012 for extra pulmonary malignancy and showed one or more pulmonary nodules, and that had been followed for more than 5 years. Each nodule detected was judged by a radiologist as suspicious or non-suspicious based on morphological characterization and confirmed on subsequent follow-up CT scans as metastatic or not metastatic.

Results: 108 patients were included with a male/female ratio of 1. The mean age at diagnosis was 58.56 years. In total, the study included 287 nodules measuring 4.54 mm ± 1.68 mm. The distance between each nodule and a pleural surface was in average 6.12 mm. 42.2% of nodules presented a septal tail, and 81.5% had regular margins. The round shape was the most frequent (35.9%). The concordance between the judgment of the nodules into suspicious and non-suspicious and their metastatic character was statistically proven (P<0.001).

The judgment showed a sensitivity of 80.2%, specificity of 68%, and positive predictive value of 67.7% and negative predictive value of 80.3%. The distance to a pleural surface of the non-suspicious nodules was significantly shorter than that of the suspicious nodules (P<0.001), the same for non-metastatic and metastatic nodules. The metastatic nodules were more common in patients with a larger number of nodules (P<0.001). The irregular margins were significantly correlated with the suspicious judgment of the nodules (P=0.001). 92.8% of oval nodules were non-suspicious whereas 74.7% were non-metastatic. 97.1% of round nodules were suspicious whereas 65% were metastatic.

Conclusion: The characterization of pulmonary nodules is essential in estimating the risk of metastasis. The nodule characteristics showed a higher capacity to exclude a metastasis than to confirm it.

KEYWORDS: Lung▪ Nodule▪ Metastasis▪ Characteristics▪ CT

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Introduction

The CT scan is the best technique for the diagnosis of pulmonary metastases which occur commonly [1]. The goal of the radiologic evaluation is to differentiate benign nodules from malignant ones. The risk of malignancy depends on many factors, such as the size, the shape, and the localization of the nodules [2]. Radiologists tend to predict that a nodule is a metastasis depending on the CT only, by evaluating their growth on the control CT scans. However, many characteristics help reduce the number of control CT scans, such as the wide implantation at a pleural base and the localization to a pleural surface [3,4]. Many studies have shown discordant results concerning the risk estimation of metastasis. Showed that 20% of nodules are metastatic, and 5% of nodules lesser than 10 mm and 9% of nodules existing at a distance less than 10 mm of a pleural surface are metastatic[5]. Caparica, et al. showed that 64% of nodules are metastatic, and that the presence of many nodules and the cavitation are the only variables associated to a high-risk metastasis [6]. The discordance depends on the populations included in the study and their characteristics. Thus, our retrospective study consists in analyzing the presence of non-calcified pulmonary nodules on the initial CT scan for extra-pulmonary malignancies. The non-calcified nodules detected were judged as suspicious or non-suspicious depending on specific criteria and were subsequently followed up by control CT scans to confirm or eliminate their metastatic origin.

Methods

▪ Study design

This retrospective study included patients aged 18 years old and over referred by oncologists

that had a first staging chest-abdomen-pelvis CT between January 1st, 2010 and December 31st, 2012 for extra pulmonary malignancy and showed one or more pulmonary nodules, and that had been followed for more than 5 years. This study was approved by the Institutional Board Review of the University Hospital.

▪ Data collection

Patients' first and follow-up CT scans were retrieved from the PACS (Picture Archiving Communication System) in the Medical Imaging Department at the University Hospital. All of the CT scans were done on GE « Light Speed » 64 channels. Patients with pulmonary tumors, hematologic malignancies, skin cancers other than melanoma, those who didn't have their first CT scan at our institution and those that had a follow-up for less than five years, were excluded. Subsequently, nodules with either a ground-glass appearance, fat containing, or calcified, were excluded.

Morphologic criteria collected for each nodule were localization, size, distance to a pleural surface, shape (round, oval, lentiform, triangular, lobulated), margins (well-defined, spiculated), and presence or absence of a septal tail. Upon the criteria cited above, each nodule was defined as suspicious (S+) or non-suspicious (S-) by a radiologist specialized in thoracic and oncologic imaging.

A nodule was considered non-metastatic and was defined as an M- if it showed no evolution. Hence, the date of the last CT scan showing stability was selected and the time of control was deducted. Its control was stopped at the last follow-up CT scan. A nodule was considered metastatic and was defined as an M+ if it showed any increase in size. Thus, the date of the first CT scan showing evolution was selected and the time of control was deducted. Its control was stopped at the first follow-up CT scan showing progression. If there were many nodules on the same CT scan, each nodule was treated separately.

▪ Statistical analysis

SPSS software version 23 was used for statistical analysis. Our clinical data was expressed in mean ± Standard Deviation (SD) or median for quantitative variables, and frequencies and percentages for qualitative variables. A two tailed P-value<0.05 indicated significance. The relationships between each of the variables were assessed by χ^2 and Fisher tests for qualitative variables, and by Student test for both qualitative and quantitative variables.

Results

▪ Sample characteristics

Overall, this study included 108 patients with multiples types of cancer. The male/female ratio was 1 and the mean age at the first CT scan was 58.56 ± 13.31 years (range 18–84 years). Primary tumor localization in order of frequency was as follows: Digestive tract, breast, pancreas, gynecologic, ENT, bladder, biliary tract, adrenal, sarcoma and melanoma.

▪ Patient based analysis

On initial imaging, 47.2% of patients had more than one extra pulmonary metastasis, 52.9% of which were in the liver, 43.1% in lymph nodes and 17.6% with peritoneal or pleural involvement. In average, patients had 2.66 ± 1.77 nodules (range 1–7 nodules). Among the 287 nodules that were detected, 35.9% were round, 28.9% were oval, 14.3% lentiform, 10.8% lobulated, 5.9% spiculated, 3.8% triangular and 0.3% convex unilaterally.

▪ Lesion based analysis

The concordance between judgment and the metastatic character of the nodules was statistically proven (P<0.001). Initial judgment of the nodules into suspicious and non-suspicious showedasensitivity (Se) of 80.2%, specificity (Sp) of 68%, Positive Predictive Value (PPV) of 67.7% and Negative Predictive Value (NPV) of 80.3% **(TABLE 1).**

On the one hand, size, distance to a pleural surface, shape, septal tail and the number of nodules per CT were all significantly correlated

Table 1. Correlation between nodular type S+1/S-2 and progression M-3/M+4.

			Nodular type		Total
			S+	S-	
Evolution	M+	N	105	26	131
		%	67.7	19.7	45.6
	M-	N	50	106	156
		%	32.3	80.3	54.4
Total		N	155	132	287
		%	54	46	100

with the suspicious and non-suspicious and the metastatic and non-metastatic judgment of a nodule **(TABLES 2-4).** On the other hand, nodular borders were significantly correlated with the judgment S+ and S- of nodules, but this correlation did not occur for the M+ M- judgment **(TABLE 5).** Presence of extra pulmonary metastasis on first imaging wasn't significantly correlated with the nodular judgment **(TABLE 6).**

Table 2. Correlation between nodular type and pleural distance, number and size.

	Nodules	N	Mean	SD	P
Distance to pleura	S-	132	2.8182	3.56364	<0.001
	S+	155	8.929	8.06074	
	M-	156	4.6474	5.28272	<0.001
	M+	131	7.8702	8.44293	
Number of nodules	S-	132	3.36	1.622	0.002
	S+	155	3.98	1.7	
	M-	156	3.26	1.63	<0.001
	M+	131	4.22	1.614	
Size	S-	132	4.1212	1.27231	<0.001
	S+	155	4.8903	1.89177	
	M-	156	4.0833	1.39565	<0.001
	M+	131	5.0763	1.82554	

Table 3. Correlation between nodular type and septal tail.

			Nodular type		Evolution		Total
			P<0.001		P=0.018		
			S-	S+	M-	M+	
Septal tail	Absent	N	49	117	81	85	166
		%	37.10%	75.50%	51.90%	64.90%	57.80%
	Present	N	83	38	75	46	121
		%	62.90%	24.50%	48.10%	35.10%	42.20%
Total		N	132	155	156	131	287

Table 4. Correlation between nodular type and shape.

		Nodular type				Evolution			
		S-		S+		M-		M+	
		N	%	N	%	N	%	N	%
Nodular shape	Oval	77	92.80%	6	7.20%	62	74.70%	21	25.30%
	Lentiform	41	100%	0	0%	36	87.80%	5	12.20%
	Triangular	11	100%	0	0%	10	90.90%	1	9.10%
	Convex	0	0%	1	100%	0	0%	1	100%
	Round	3	2.90%	100	97.10%	36	35%	67	65.00%
	Lobulated	0	0%	31	100%	9	29%	22	71%
	Spiculated	0	0%	17	100%	3	17.60%	14	82.40%

Table 5. Correlation between nodular type and nodular borders.

			Nodular type		Evolution		Total
			P=0.001		P=0.053		
			S-	S+	M-	M+	
Nodular borders	Regular	N	118	116	133	101	234
		%	89.40%	74.80%	85.30%	77.10%	81.50%
	Irregular	N	14	39	23	30	53
		%	10.60%	25.20%	14.70%	22.90%	18.50%

TABLE 6. Correlation between nodular type and the presence or absence of extra-pulmonary metastasis.

			Nodular type		Evolution		Total
			P=0.360		P=0.077		
			S-	S+	M-	M+	
Extra pulmonary	Absence	N	67	82	87	62	149
		%	50.80%	53.60%	56.50%	47.30%	52.30%
	Presence	N	65	71	67	69	136
		%	49.20%	46.40%	43.50%	52.70%	47.70%
Total		N	132	153	154	131	285

Discussion

With the improvement of image resolution on CT scanner, strategies nowadays tend to characterize a pulmonary nodule rather than just detect it [7]. The rate of metastatic pulmonary nodules varies among different studies and trials reflecting the variability within the studied populations. It is 13% for Chalmers and Best [8], 31% for [9], 42% for [10]. In our study, this rate was 45.6%, representing the risk that a nodule is metastatic.

In general, the smaller the nodule, the lesser the likelihood of its malignancy [11]. However, small size does not exclude the risk of malignancy because 15% of cancerous nodules measure less than 10 mm in diameter and approximately 42% are smaller than 20 mm [12,13]. Therefore, in a staging CT for primary extra pulmonary malignancy, any detected nodule should be considered as metastatic regardless of its size.

Intra parenchymal lymph nodes tend to be sub-pleural [14], their average distance to a pleural surface is 8 mm[15], they are detected in 60% of staging CT scans done for extra pulmonary neoplasms [16], and none has progressed into cancer. Our data showed a concordance with this characterization. Nonetheless, these characteristics are also found in metastases. Firstly, distance to a pleural surface was around 4.64 mm for non-metastatic nodules and 7.87 mm for metastasis, thus the value of 8 mm cannot be considered as a threshold for benignity. Secondarily, our study showed that 57.59% of sub-pleural nodules were lymph nodes, a rate close to that of literature data of 60%. Nonetheless, 83.2% of metastases were sub-pleural. This finding allows us to infer that even though the risk of metastasis in a sub-pleural nodule is low, secondary lesions are preferentially localized in a peripheral sub-pleural pattern which prompts us to have shorter interval follow up CT scans to avoid confusion.

Our study showed significantly higher rates of metastases in patients with a higher number of nodules per CT scan: A metastasis is present on a CT scan with 4 nodules (4.22 nodules) versus 3 nodules (3.26 nodules) per non-metastatic nodule. This is close to what we can find in worldwide data. In fact, 73% of nodules seen on a CT scanner showing multiple nodules are prone to be metastatic. Showed that the presence of multiple nodules greater than 5 mm is associated with a higher risk of metastasis.

Septal tail is a morphological criterion used with caution for it can be applied in one way but not the other. In our study, it is absent in the majority of the cases, however, it is seen in half of non-metastatic nodules. This implies that having a septal tail lowers the risk of metastasis, but if it is absent, the probability of having a non-metastatic nodule is substantial.

Our results showed that the nodular shape and borders are not significant features of metastatic potential. Although the round shape is typical of a metastasis [17], it has been frequently described in non-metastatic nodules. Whilst oval lesions were mostly found to be non-metastatic, they were also found in metastases. It is the same for borders, since metastatic and non-metastatic nodules are both most frequently seen with regular borders. Moreover, a metastasis may show signs of aggressiveness at an advanced stage, but its shape on a first staging CT scan differs from its evolutionary shape since it can take any form, such as round with regular borders. Thus, a pulmonary nodule detected on a first staging assessment is of greater risk of being a metastasis than an incidental nodule, and the management recommendations therefore cannot be applied [18]. The judgment in the study was based on well-defined characteristics that constitute a diagnostic tool with the ability to detect metastasis. Nodules were judged with a Se of 80.2%, Sp 68%, PPV 67.7% and NPV of 80.3%. This judgment has less false negatives than false positives, thus it consists in excluding a metastasis rather than confirming it.

The fact that our study has limitations is acknowledged: several patients were excluded because their first imaging was done in another hospital, others were lost to follow-up. Calcified nodules were excluded, however some malignancies such as sarcomas give calcified metastases. Only nodular lesions were included, although some metastases appear in cystic forms such as metastases of ovarian cancers. Finally, a prospective study with a larger sample size would be more powerful.

Conclusion

In conclusion, this retrospective study which consisted in detecting pulmonary nodules on a first staging CT scan in the context of an extra-pulmonary malignancy, allowed us to determine the risk of metastasis when facing a pulmonary lesion. Nowadays, it is rather a characterization of these nodules than a simple detection. Although a small sub-pleural nodule is most frequently non-metastatic, its discovery on a first staging assessment CT scan prompts a control CT scanner within a short time. Metastasis risk is higher if the number of lesions on the first staging CT is increased and if the lesions are round. Any progression must always be evocative of a malignant nodule. Judgment criteria have fewer false negatives than false positives. Therefore, they allow us rather to exclude a metastasis than to confirm it. Finally, it would be interesting to carry out a prospective study including a larger number of nodules, and to determine the influence of different therapeutic strategies and management on the evolutionary character and size of the nodules.

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