DOI: http://dx.doi.org/10.1590/0100-6991e-20181129

Pulmonary metastases in children: are we operating unnecessarily?

Metástases pulmonares em crianças: estamos operando desnecessariamente?

Andrey Kaliff Pontes[1]; Fabio Mendes Botelho Filho, AsCBC-MG[1]; Marcelo Eller Miranda[1]; Karla Emília de Sá Rodrigues[1]; Bernardo Almeida Campos[1]; Paulo Custódio Furtado Cruzeiro[1]; Clecio Picarro[1]; Edson Samesima Tatsuo[1]; Diogo Ramalho Tavares Marinho[1]; Thiago Luiz do Nascimento Lazaroni[1]; Renan Farias Rolim Viana[1]; Ricardo de Mattos Paixão[1]

A B S T R A C T

Objective: to determine, in pediatric patients with malignant neoplasms, the characteristics of pulmonary nodules identified on computed tomography, as well as the possibility of differentiating benign lesions from metastases. **Methods:** we conducted a retrospective study of patients submitted to pulmonary resections of nodules diagnosed as metastases in a period of seven years. We compared computed tomography and surgery findings, as well as results of anatomopathological examinations. **Results:** we studied nine patients submitted to 11 surgical interventions. Among the studied variables, only nodule size greater than 12.5mm proved to be statistically significant to predict malignancy. **Conclusion:** among the tomographic characteristics of pulmonary nodules in children with malignant neoplasms, only the size of the lesion was a predictor of malignancy.

Keywords: Lung Neoplasms. Neoplasm Metastasis/diagnostic imaging. Tomography, X-Ray Computed. Osteosarcoma. Thoracotomy. Child.

INTRODUCTION

The majority of lung tumors in children and adolescents correspond to metastases, especially from osteosarcomas. Today, for the detection of these metastases, the most commonly used exam is the computed tomography (CT), which, despite being a much better examination than conventional radiography, still has some limitations. Among them, the impossibility of differentiating between benign and malignant nodules, especially calcified and small lesions[1]. The medical literature is scarce on the subject, important doubts persisting. Although Brader *et al*.[2] have found a relationship between size, presence of calcification and pulmonary metastases of osteosarcomas in children and adolescents, many studies do not stratify the children from adults and group all tumors, regardless of the characteristics of each age group[3-5].

Works on this topic should be encouraged to assist the pediatric surgeon and the oncologist in the care of children with malignant tumors. The objective of this study is to determine the characteristics of pulmonary nodules identified in computed tomography in pediatric patients with malignant neoplasms, as well as the possibility of differentiating benign lesions from metastases.

METHODS

We carried out a retrospective study of pediatric patients undergoing exploratory thoracotomy to approach possible pulmonary metastases in a quaternary hospital over a seven-year period (April 2009 to April 2016). The preoperative image evaluation was performed with high resolution CT. We excluded patients with primary thoracic tumors from the study. We studied patients with extrathoracic primary tumor submitted to thoracotomy for evaluation of pulmonary metastases, assessing age, surgery performed, primary diagnosis, location, nodule size, presence of lymph node enlargement on CT scan, and anatomopathological examination with or without confirmation of malignity.

1 - Federal University of Minas Gerais, Pediatric Surgery, Belo Horizonte, MG, Brazil.

We approached the data through descriptive analysis, and calculated the central tendency (median) measures of the largest and smallest tumor diameters for the cases with and without metastasis. We constructed the Receiver Operator Characteristic (ROC) curve with the largest nodule diameters at CT that were subsequently diagnosed as metastasis, to find the best cutoff point for diagnosis. From that point, we calculated sensitivity, specificity, negative and positive predictive values. The programs used for analysis were R version 3.2.5, Stata version 14 and EpiInfo 7th edition.

The study was approved by the institution's Ethics in Research Committee, protocol numbering 1,425,036.

RESULTS

During the study period, 31 thoracic interventions were performed in 25 patients for resection and/or biopsy of lung lesions suspected of malignancy. Sixteen patients had primary tumor of intrathoracic location and were excluded from the study. Thus, we selected nine patients submitted to 11 interventions for this research.

The mean age of the operated patients was 8.6 years. One patient underwent bilateral thoracotomy at different times and another was reoperated for excision of new nodules from the same previously operated hemithorax. Six of the nine cases had osteosarcoma as primary diagnosis, and the others, nephroblastoma, hepatoblastoma and teratoid tumor.

In four interventions (out of 11), the number of nodules was greater than five, and they were bilateral in five. The size of the possible metastases ranged from 2mm to 75mm. Only one patient had lymph node enlargement at CT. This patient had previous diagnosis of hepatoblastoma and no sign of malignancy was found in the specimen sent to pathological anatomy (Table 1). In only five samples (out of 11), signs of malignancy were confirmed at the anatomopathological examination. In the others, no cellular atypia or mitotic activity was observed. The lesions were diagnosed as foci of hematopoiesis (one case), inconclusive (one case), reactional lymph node (one case), calcified nodules (two cases), and in one case, described as inflammatory nodule (Table 1).

Table 1. *Patients, their primary diagnosis, the anatomical-pathological result and the nodules' features at CT.*

				TC features			
	Year of surgery	Primary diagnosis	Anatomo-pathology	Number of nodules	Size of the nodules (mm)	Lymphadenomegaly	Age
1	2009	Teratoid Tumor	Inflammatory nodules	2-Bilateral	13-20	No	10
2	2010	Wilms Tumor	Metastasis	1-Unilateral	20-22	No	3
3	2011	Osteosarcoma	Metastasis	1-Unilateral	10-25	No	15
4	2014	Hepatoblastoma	Haematopoietic Tissue	>5-Bilateral	7-9	Yes	3
5	2015	Osteosarcoma	Metastasis	>5-Bilateral	3-75	No	9
	2015	Osteosarcoma	Metastasis	>5-Bilateral	4-26	No	9
6	2015	Osteosarcoma	Inconclusive	4-Bilateral	3-6	No	6
	2016	Osteosarcoma	Calcified Nodule	4-Unilateral	2.6-3.8	No	6
7	2015	Osteosarcoma	Metastasis	>5-Bilateral	6.5-12.5	No	11
8	2015	Osteosarcoma	Calcified Nodule	2-Unilateral	2-2.9	No	8
9	2016	Osteosarcoma	Lymph node	3-Unilateral	3-5	No	15

For the cases with metastases, the median of the nodules' smallest diameters identified on CT was 6.5mm, and the largest diameter, 25mm. For the cases without metastases, the medians were 3mm (smaller diameters) and 5.5mm (for the larger ones). In the present study, we identified a correlation between the largest nodule diameter found on CT and malignancy. For this, we constructed a table, ordering all the nodules by their largest diameter, and with each value we calculated sensitivity and specificity using this parameter as cutoff (Table 2). Thus, using the cutoff size of the smallest nodule of 2mm x 2.9mm, to say that the CT node is malignant, we would have a sensitivity of 100% (all malignant tumors would be found), but a specificity of 0 and accuracy of only 45.45%, that is, 45.45% of patients in this series would have the correct diagnosis at CT (Table 2). When we considered the cutoff point of 12.5mm (<12.5mm benign and ≥12.5mm malignant), we observed a sensitivity of 100%, with a specificity of 83.33% and an accuracy of 90.91%, these being the best values found (Table 2). Finally, was calculated the area under the ROC curve with the data obtained and the p-value of the equality test for statistical validation. We observed that the area under the ROC curve was 0.967, 95% confidence, interval 0.874-1.000, with a p-value of 0.011. Therefore, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) from the cut-off point of 12.5mm were 100%, 83.33%, 83.33%, and 100%, respectively.

Other features described as number of nodules, bilateral lesions or lymph node enlargement did not display statistical significance in differentiating patients with benign nodules from those with malignant ones, probably due to the small sample.

Table 2. *Cutoff values of the greater tumor diameter according to sensitivity, specificity and accuracy.*

Values	Sensitivity (%)	Specificity (%)	Accuracy (%)
=2.9	100.00	0.00	45.45
=3.8	100.00	16.67	54.55
=5	100.00	33.33	63.64
=6	100.00	50.00	72.73
=9	100.00	66.67	81.82
=12.5	100.00	83.33	90.91
=20	80.00	83.33	81.82
=22	80.00	100.00	90.91
=25	60.00	100.00	81.82
=26	40.00	100.00	72.73
=75	20.00	100.00	63.64
>75	0.00	100.00	54.55

DISCUSSION

Resection of secondary pulmonary nodules remains a part of the curative treatment for most pediatric oncological diseases[4-8]. Cliffton and Pool, in 1967, established the key points for the treatment of pulmonary metastatic disease in children, which are: 1) the number of metastases cannot be a contraindication to surgery; 2) the type of tumor must be respected; 3) staged resections are well tolerated; and 4) when in doubt, surgical excision is to be performed, to give the child a chance of healing[9].

Although chest CT has issues, such as failure to detect some metastatic nodules, difficulty in differentiating benign and malignant lesions, especially in calcified lesions, and radiation exposure, it is still the recommended examination for staging, with better accuracy for detection of lung nodules than chest X-ray[10]. Other tests, such as magnetic resonance imaging and positron emission tomography, are still in the improvement phase to detect these metastases and are not readily available technologies[11,12].

Once the pulmonary nodule has been diagnosed, in our Service, all children undergo surgical resection, regardless of nodules' size, in view of the lack of significant data in the literature to differentiate between benign and malignant nodules on chest CT. There is a preference for thoracotomy, due to the possibility of palpation of new lesions missed by the tomographic examination. In the presence of bilateral lesions we opt for a two-time treatment, with posterolateral thoracotomy in one hemithorax followed by thoracotomy in the other hemithorax about 15 days later. These conducts are accepted in the literature, although there is controversy as to the best access route (thoracotomy versus thoracoscopy). Another issue that exists in the preoperative period is the need to stage surgeries for bilateral lesions or to operate them in a single time[10,13-20].

Thoracoscopy is a promising access route, but it is better indicated in peripheral and small lesions[10,21]. Although there are studies that advocate its use, justified by the good correlation of tomography with intraoperative findings, it is known that CT accuracy is still insufficient[22,23]. The finding of lesions through palpation, not detected by CT, is frequent. We also ought to remember that intraparenchymal lesions offer greater technical difficulty for their excision through thoracoscopy. Thus, we chose to perform thoracotomy, staged when in the presence of bilateral lesions, given the greater pain tolerance of these patients with this type of conduct.

It is important to note that eight surgeries analyzed in this study were performed between 2014 and 2016, and it was this demand that led the authors to study in more depth the best surgical treatment tactic for these children and adolescents. Considering the diagnosis of millimetric CT lesions that could correspond to benign nonspecific alterations, we believe it is important to start looking for these predictive factors for malignant lesions to avoid unnecessary thoracotomy and pulmonary resections. From the initial case series, most children were submitted to surgeries for resection of lesions that were not malignant.

With the advance in imaging tests for tumor staging, as well as chemotherapy, the number of lung resections due to benign lesions is occurring more frequently. Despite the small number of cases, the results presented suggest that children with nodules greater than or equal to 12.5mm should be submitted to resection as early as possible, while in other cases a conservative approach could at first be accepted. Although some studies have been published with the same objective, there is still no consensus about the most reliable characteristics to predict malignancy. Further studies, preferably multicentric, are still needed to assess a greater number of patients and increase the reliability of the findings. In this way, we could elaborate protocols with robust evidence about the predictive factors of benignity or malignancy of the pulmonary nodules, with more precise criteria for the indication of exploratory thoracotomy or thoracoscopy.

R E S U M O

Objetivo: *determinar, em pacientes pediátricos portadores de neoplasias malignas, as características de nódulos pulmonares identificados à tomografia computadorizada, capazes de diferenciar nódulos benignos de metástases.* **Métodos:** *estudo retrospectivo de pacientes submetidos a ressecções pulmonares de nódulos diagnosticados como metástases em um período de sete anos. Achados de tomografia e da cirurgia, assim como resultados dos exames anatomopatológicos foram comparados.* **Resultados:** *nove pacientes, submetidos a 11 intervenções cirúrgicas, foram estudados. Entre as variáveis estudadas, apenas o tamanho do nódulo, maior do que 12,5mm provou ser estatisticamente significante para predizer malignidade.* **Conclusão:** *esse estudo sugere que, entre as características tomográficas de nódulos pulmonares de crianças portadoras de neoplasias malignas, apenas o tamanho da lesão foi preditor de malignidade.*

Descritores: *Neoplasias Pulmonares. Metástase Neoplásica/diagnóstico por imagem. Osteossarcoma. Tomografia Computadorizada por Raios X. Toracotomia. Criança.*

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Received in: 04/16/2018
Accepted for publication: 05/14/2018
Conflict of interest: none.
Source of funding: none.

Mailing address: Fabio Mendes Botelho Filho
E-mail: mendesbotelho@hotmail.com
fabiobotelhofilho@gmail.com