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ONCOLOGY: RESEARCH ARTICLE

Diagnostic accuracy of image-guided core needle biopsy of non-central nervous system tumors in children

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Abstract

Background and aims: Core needle biopsies (CNB) are less invasive, cause less morbidity, and have lower costs than open biopsies (OB). However, the number of studies reporting CNB accuracy in pediatric tumors is limited and series are small. The aim of this study is to investigate if CNB diagnosis is concordant with the final diagnosis in pediatric solid non-central nervous system (CNS) tumors.

Methods: Data from all patients treated in a single center between November 2014 and December 2019 were collected from the national pathology database and from local medical records. Data collection included age, sex, CNB diagnosis, final diagnosis, number of cores obtained, number of cores used for histology, cumulative core length, greatest dimension of the lesion, lesion volume, and complications.

Results: Out of 361 CNB, 95.6% (345/361) provided a diagnosis. A resection or follow-up biopsy was performed in 201 cases. The final diagnosis was concordant with the CNB in 100% (201/201) of cases. The age, number of cores used for histology, and the greatest dimension of the lesion did not significantly differ between diagnostic and nondiagnostic CNB. The cumulative core length of diagnostic CNB was significantly higher than in the nondiagnostic group (24.72 mm vs. 13.37 mm, *p*-value .022). Complications occurred in 2.1% (7/337) of CNB procedures. Molecular analysis was successful in 228/233 (98%) of cases in which it was performed.

Conclusions: CNB diagnosis is highly concordant with the final diagnosis and the diagnostic rate is high. The complication rate in CNB is low.

KEYWORDS
core needle biopsy, histology, pediatric cancer, radiology

1 | INTRODUCTION

Every year about 600 children in the Netherlands are diagnosed with cancer.[1] Survival rates are improving every year, but still 25% of the children succumb to the disease, which makes cancer the leading cause in disease-related deaths among children.[1,2] Many tumors are large and may be fast-growing at presentation, thus a prompt and accurate diagnosis is of great importance. Tissue biopsy plays a crucial role in the diagnosis of cancer and in determining further treatment.

Abbreviations: CNB, core needle biopsies; CNS, central nervous system; OB, open biopsies.

Open biopsy (OB) used to be the "gold standard" for diagnosing cancer. This technique is accurate, but since it requires surgery, it also poses a higher risk of bleeding or infection, possible tumor spill, and upstaging of the tumor. Furthermore, it is invasive, time consuming, and uses hospital resources. Core needle biopsy (CNB) is performed under image guidance and does not require surgery. CNB therefore offers substantial advantages compared to OB regarding invasiveness, complications, and costs.[3–5] However, diagnostic yield should not be compromised by the smaller amount of tissue taken.

CNB in the adult population has proven to be a safe and accurate method of diagnosing cancer.[5–10] However, there is a difference in occurrence and distribution of tumor types between adults and pediatric patients. In adults the most commonly diagnosed cancers originate from the breast, prostate, lung, and colon.[11] In children lymphomas, neuroblastomas, osteosarcomas, and soft tissue tumors are the most common solid tumors.[12] The number of studies that focus on the use of CNB in pediatric patients is limited. Several studies have been conducted in pediatric centers, but the majority consists of studies with a limited number of CNB or a focus on only one specific tumor type.[4,13–22] The aim of this study is to establish the diagnostic accuracy of CNB in children by comparing the CNB diagnosis to the final diagnosis after resection. We collected clinical, pathological, and radiological data that could affect the diagnostic accuracy. In addition, we examined complications as a secondary outcome of this study.

2 | METHODS

Data from all patients in the Princess Máxima Center for Pediatric Oncology in the Netherlands (adherence area 17 million people) that underwent CNB or that were referred after CNB elsewhere between November 2014 and December 2019 were retrospectively collected. Data collection and analysis were approved by the Medical Ethical Committee, who waived the requirement to obtain informed consent. All CNB examined in this timeframe were included in the study and primary surgical, incisional, and excisional biopsies were excluded. This yielded a total of 361 CNB; 320 CNB from patients who underwent CNB and were treated in the Princess Máxima Center and 41 CNB that were done elsewhere and that were reviewed in the context of further patient treatment in the Princess Máxima Center.

The primary aim of this study was the diagnostic accuracy of CNB of solid non-central nervous system (CNS) tumors in children. Therefore, the CNB diagnosis and final diagnosis were obtained from the Dutch national pathology database (PALGA). This final diagnosis was made on the basis of a resection specimen, or a follow-up biopsy performed after the initial CNB. If identical, the CNB diagnosis was considered concordant.

Data collection included age, sex, number of cores obtained, number of cores used for histology, cumulative length of the cores, greatest dimension of the lesion, and the volume of the lesion. These data were acquired from the national pathology database or obtained from electronic medical records. The cumulative length of the cores was measured using the local Picture Archiving and Communication System (PACS – Sectra AB, Linköping, Sweden).

The secondary aim of this study was the occurrence of biopsy-related complications. Information about potential complications was obtained from electronic medical records. The complications were graded based on their morbidity using the Clavien–Dindo classification.[23]

Statistical analysis was done with the Student's *t*-test for independent samples using SPSS 25.0.0.2. A *p*-value lower than .05 was considered statistically significant.

2.1 | Core needle biopsy procedure

In our center, CNB represents the preferred biopsy modality for pathology-based diagnosis. This is generally done when the tumor can be reached safely, is not closely related to great vessels, and the differential diagnosis does not require analysis of tumor architecture, such as an entire lymph node.

All biopsies were performed by a radiologist except for the bone tumors, when an orthopedic surgeon did the biopsy. In all cases, a pediatric surgeon was present. The vast majority of CNB were taken under ultrasound guidance. CT-guided biopsies were performed in a minority, and only in case of lesions that were deemed upfront to be difficult to access, or in lesions that were not visible using the ultrasound. The standard needle size for bone tumors was 11 gauge and for all other tumors 16 gauge. In rare instances, 14 gauge was used for bone tumors and 18 gauge was used for other tumors. However, due to the rarity of biopsies with alternative needle sizes, this parameter was not included in the correlation analyses. This was also the case for image guidance modality, which in most cases consisted of ultrasound.

All CNB were taken through a guiding needle. When bleeding occurred during the procedure or bleeding might occur in relation to tumor vascularization, a compressed gelfoam plug (Hunter Biopsy Sealing Device; Vascular Solutions, Minneapolis, MN) was inserted in the needle track.

Routinely up to five CNB were taken, ideally with a length of 20 mm, which is the maximum length of the biopsy needles used. When biopsies were shorter or fragmented, more biopsies were taken, and in case of bleeding or other problems less biopsies may have been taken. These biopsies are sent to the pathology laboratory for visual inspection of tissue quality by a pathologist or pathology assistant. Usually two of five biopsies are used for tissue-based diagnosis, while the remaining biopsies are used for molecular analysis and research. Frozen sections are prepared from the cores for molecular analysis upon arrival in the pathology lab. However, in the rare cases no conclusion could be reached based on these two cores, the remaining frozen cores were processed for formalin-fixed paraffin-embedded slides and additionally used for diagnostic purposes. The cores that were used for diagnostic purposes were included when measuring the cumulative length of cores. The cores that remained frozen and were solely used for molecular analysis and research were not included.

TABLE 1 Diagnosis core needle biopsy (CNB) and final diagnosis

Tumor type	Only diagnosed with CNB ($n = 142$)	CNB and final diagnosis ($n = 201$)	Total ($n = 361$)	Percentage
Malignant	107	180	287	79.5
Neuroblastoma	15	77	92	25.5
Soft tissue 30	40	70	19.4	
Hematological	37	9	46	12.7
Osteosarcoma	11	16	27	7.5
Liver	6	16	22	6.1
Kidney	2	10	12	3.3
Other	6	12	18	5.0
Benign	35	21	58	16.1
Nondiagnostic			16	4.4

3 | RESULTS

A total of 361 CNB were included, of which 208 were performed on male patients (57.6%) and 153 on female patients (42.4%). The mean age of the patients was 7.6 years, ranging from 0 to 18 years. CNB were diagnostic in 95.6% of the cases (345/361). In 79.5% (287/361) of cases the tumor was malignant, in 16.1% (56/361) the tumor was benign, and in 4.4% (16/361) the CNB was nondiagnostic. In six cases, the amount of tissue was sufficient but no unequivocal pathological diagnosis could be made, four CNB were fully necrotic, four cases did not contain a sufficient amount of tissue for accurate diagnosis, and two CNB were not representative for the lesion.

The most frequently diagnosed tumor was neuroblastoma ($n = 92$, 25.5%), followed by soft tissue tumors ($n = 70$, 19.4%), including rhabdomyosarcoma ($n = 36$) and Ewing sarcoma ($n = 22$), benign tumors ($n = 57$, 15.5%), and hematological malignancies ($n = 46$, 12.7%). There were only few renal tumor biopsies in our series, as these are not routinely biopsied, according to the International Society for Pediatric Oncology (SIOP) 2001 and UMBRELLA 2016 protocols.[24,25] Table 1 shows the frequencies of all diagnosed tumors. A resection or follow-up biopsy was performed in 201 cases: 171 resections and 30 follow-up biopsies. Most of these follow-up biopsies ($n = 28/30$) were taken because of tumor progression and the remaining two biopsies because of an earlier nondiagnostic biopsy. The CNB diagnosis was concordant with the final diagnosis in 100% of cases (201/201). There was no change in risk group between initial biopsy and resection or follow-up biopsy for those tumors for which this applied, such as neuroblastic tumors.

There was no significant difference in age, number of cores used for histology, and greatest dimension of the lesion between the diagnostic and nondiagnostic CNB. However, there was a significant difference in the cumulative core length of the cores between the diagnostic group and the nondiagnostic group (24.72 mm vs. 13.37 mm: $p = .022$). Table 2 shows all factors that were analyzed when comparing diagnostic and nondiagnostic CNB.

Complications are listed in Table 3. Complications occurred in 2.1% (7/337) of the cases. In 24 cases, information about potential complications was not available, as CNB was performed at a referring hospital. Decrease of hemoglobin (Hb) concentration was the only complication that was registered more than once, occurring in 0.9% (3/337) of the cases. In two cases, the decrease of Hb concentration was severe (one patient had a decrease from 7.3 to 4.7 mmol/L over the course of 2 days; another patient had a decrease from 4.6 to 3.2 mmol/L), with both patients requiring blood transfusion and the first patient being readmitted to the hospital. Other complications seen were hypoglycemia, fluid accumulation in the upper and lower extremities and face, pancreatitis, and pneumothorax (all $n = 1$), the pain resulting from pancreatitis was treated with morphine and the pneumothorax required a drain. All other complications were classified in category 1 using the Clavien–Dindo classification.[23]

Molecular analysis was performed in 223/361 (62%) cases, 218/223 (98%) yielding an interpretable result, including all neuroblastoma cases. Reasons for not performing molecular analysis included benign entities or entities for which molecular analysis did not play a role in diagnostic decision-making.

4 | DISCUSSION

In this study, we show that the diagnostic rate of CNB in children is high (95.6%) and the concordance with the final diagnosis is eminent (100%). In similar studies, diagnostic rates differ between 71% and 96% in both children and adults and concordance varies between 80% and 97%.[3–9,10,13,15–21] Both are on average lower than the results found in this study. A potential explanation for our superior results could be the high number of patients in one dedicated oncology center, which might result in better diagnostic and concordance rates. The diagnostic rates for OB differ between 96% and 100%, which is slightly higher than the diagnostic accuracy of CNB according to the present study.[26,27]

The only factor that proved to correlate with the accuracy of CNB is the cumulative core length. Only one other study investigated this parameter by comparing diagnostic and nondiagnostic CNB in children and showed a higher cumulative length in the diagnostic group, although this was not statistically significant. This might be

TABLE 2 Comparison of factors associated with diagnostic and nondiagnostic core needle biopsy (CNB)

	Diagnostic ($n = 345$)				Nondiagnostic ($n = 16$)				*p*-Value
	Number	Median	Lower quartile	Upper quartile	Number	Median	Lower quartile	Upper quartile	
Age	345	7.00	2.00	13.00	16	10.00	4.00	12.00	.325
Number of cores used for histology	311	3.00	2.00	4.00	15	2.50	2.00	3.5(	.083
Cumulative length of cores in mm	309	24.72	17.23	33.08	16	13.37	9.08	19.22	.022
Greatest dimension of lesion in cm	333	8.80	5.20	11.90	14	3.90	2.00	11.7(	.419

explained by the lower number of CNB included in that study (134 vs. 361).[13]

Furthermore, complications occurred in 2.1% of the cases, mainly bleeding after biopsy. This is similar to the results found in other studies.[7,9,15–21,28] The frequency is certainly lower than the complication rate of OB, which may be up to 48%, though most larger studies report a complication rate below 17%.[3,9,17,18,21] The low complication rate of CNB compared to OB implicates that CNB is a safe intervention. In previous reports complications most frequently related to CNB were minor complications such as local bleeding, minor pneumothorax, post-biopsy pain, and wound infection.[15,16,20,21,28] Only a few major complications were reported, all related to major bleeds or infection.[15,16] With respect to the type of complications, our findings are in accordance with the literature results, including decrease of Hb concentration, hypoglycemia, fluid accumulation, pancreatitis, and pneumothorax. In the present study, both hypoglycemia and fluid accumulation were related to anesthesia and were not directly attributed to the CNB.

The nondiagnostic CNB group could be separated in a group where the biopsied tissue was not adequate and a group where a diagnosis could not be reached. The former group included cases with complete necrosis, nonrepresentative tissue, or too little tissue to base a diagnosis on. The latter group consisted of rare and complex hematological disorders, where the discrimination between malignancy and reactive or infectious etiology frequently requires a substantial amount of tissue, such as an entire lymph node, or more specific clinical information and follow up. It is tempting to speculate whether a higher cumulative core length of CNB might diminish the number of nondiagnostic CNB. However, it should be noted that there were only a few nondiagnostic cases based on too little tissue in the present study, which makes it impossible to draw firm conclusions on this issue. However, sufficient biopsy numbers and length without compromising patient safety should always be the goal during this diagnostic procedure.

The most important strength of this study is the high number of CNB included in a single-center study that were obtained with a uniform CNB procedure. A limitation of this study is the fact that we could only show a statistically significant difference between the cumulative biopsy length and diagnostic accuracy. This could be due to the low number of nondiagnostic CNB, which impeded significance for other variables, such as the number of cores used for histology. Another potential weakness is the fact that several CNB were fragmented and this may have resulted in incorrect measurement of the cumulative length due to lack of correct orientation of all fragments. Figure 1 provides an example of a fragmented core and how it was measured. It is not to be expected that this altered the outcome of this study, as fragmentation occurred in both the diagnostic and nondiagnostic group.

In our center, CNB represents the preferred biopsy modality for pathology-based diagnosis, unless clinical and/or imaging characteristics have already established a diagnosis with sufficient certainty to allow upfront resection or excisional biopsy. The above findings show that CNB are diagnostic in the vast majority of cases and support the routine use of CNB in pediatric oncology practice. We therefore recommend CNB as the standard procedure when diagnosing pediatric non-CNS tumors.

TABLE 3 Complications of core needle biopsy (CNB)

	Number ($n = 337$)	Percentage	Clavien–Dindo classification
No complications registered	330	97.9	
Complications	7	2.1	
Decrease of hemoglobin concentration (Hb)	3	0.9	1 ($n = 1$)
			2 ($n = 2$)
Hypoglycemia	1	0.3	1
Fluid accumulation	1	0.3	1
Pancreatitis	1	0.3	2
Pneumothorax	1	0.3	3

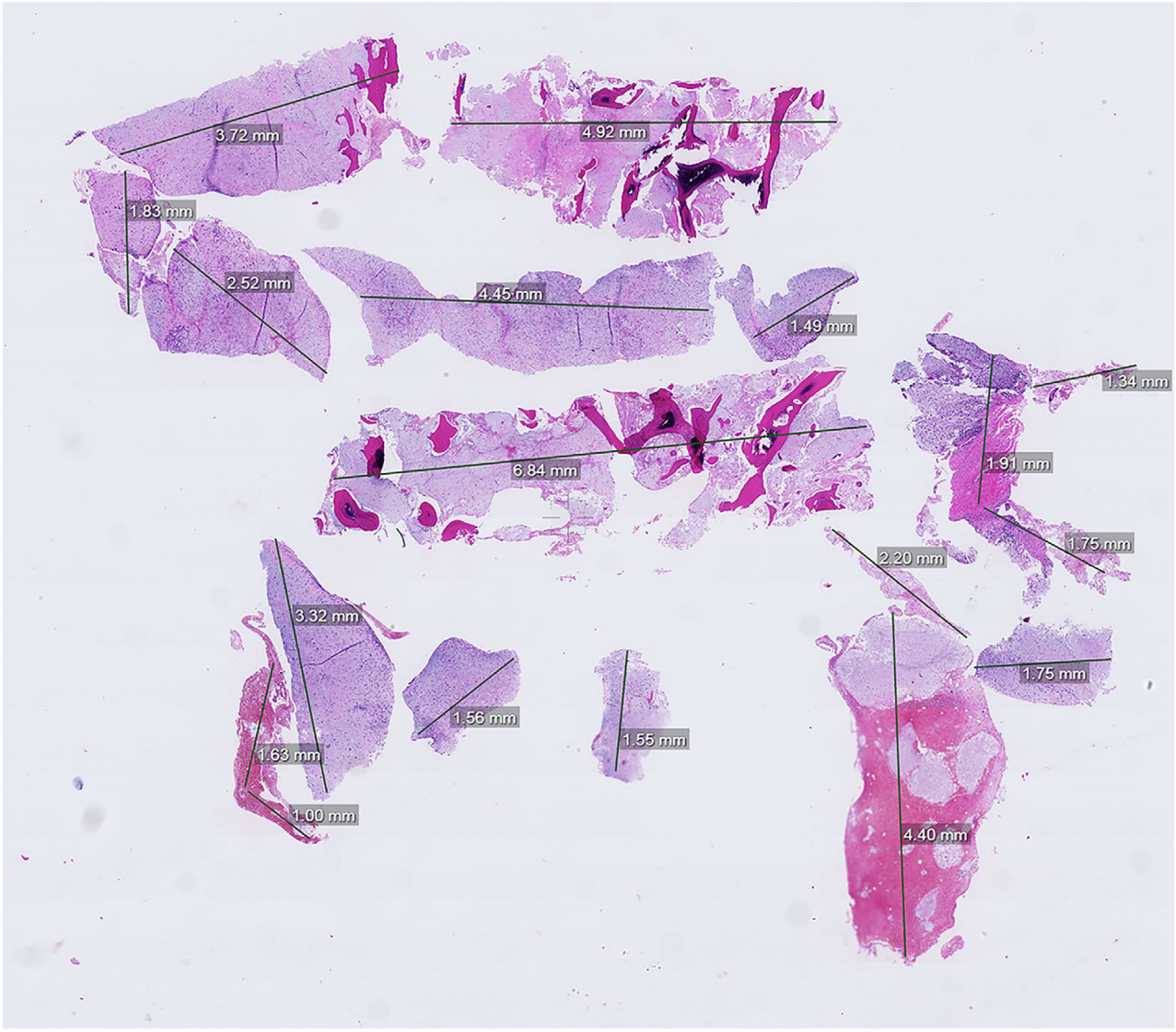

FIGURE 1 Measurement of fragmented core colored with hematoxylin and eosin stain, using the local picture archiving and communication system (PACS)

5 | CONCLUSION

This study shows that CNB is an accurate and safe technique to obtain tissue samples and diagnose solid non-CNS tumors in children. These results are in concordance with the results of other studies. The large majority of CNB resulted in a classifying diagnosis. Only a small proportion of CNB were nondiagnostic, which was due to an equivocal differential diagnosis, complete necrosis, insufficient tissue, or nonrepresentative CNB. We recommend CNB as state of the art in diagnostic tissue sampling in pediatric non-CNS tumors. One should be aware of the need for a sufficient cumulative biopsy length in order to ensure enough tissue for adequate diagnostic and secondary purposes.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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