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Diagnostic utility of core needle biopsy versus open wedge biopsy for pediatric intraabdominal solid tumors: Results of a prospective clinical study

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ABSTRACT

Purpose: The best method for diagnosing pediatric nonnephroblastoma solid intraabdominal tumors is unknown. We hypothesized that core needle biopsy (CNB) is noninferior to open wedge biopsy (OWB) for pathologic diagnosis.
Methods: We prospectively enrolled children aged 1 day to 17 years with radiographic evidence of nonnephroblastoma solid intraabdominal tumors scheduled for OWB from 5/2013 to 12/2015 at a single institution. Four 16-gauge CNBs were obtained, followed by OWB. Two pathologists independently reviewed all specimens to determine adequacy for diagnosis.
Results: Fourteen patients enrolled, 57% male, with an average age of 4 years (range 7 days to 16 years). Both pathologists agreed OWB was completely sufficient for diagnosis in 13 patients (93%), compared to 4 patients for CNB (29%: Burkitt lymphoma, adrenocortical tumor, inflammatory myofibroblastic tumor, $p = 0.001$, $\delta = -0.64 \pm 0.27$, 95% CI). In 6 patients (43%), CNB was incompletely diagnostic according to at least one pathologist (neuroblastoma, hepatoblastoma). In 4 patients (29%), both pathologists determined that CNB was nondiagnostic (ganglioneuroblastoma, teratoma, hepatoblastoma, and recurrent neuroblastoma).
Conclusions: In a prospective clinical study, CNB is inferior to OWB for the pathologic diagnosis of pediatric nonnephroblastoma solid intraabdominal tumors. These data suggest that OWB should generally be performed in these patients.
Level of evidence: Study of Diagnostic Test, Level I.

The optimal method of obtaining a tissue diagnosis for many pediatric solid intraabdominal tumors, including hepatoblastoma, rhabdomyosarcoma, nonrhabdomyosarcoma soft tissue sarcomas and neuroblastoma, is unknown. The method of biopsy is left to the discretion of the treating physician. Commonly practiced methods include open wedge biopsy (OWB) and core needle biopsy (CNB). While CNBs are less invasive than OWBs, there may be concern that they will not provide sufficient tissue for diagnosis, and thus require further procedures, delaying diagnosis and treatment [1].

In adults, radiologically guided CNBs are generally adequate for making the diagnosis in many kinds of intraabdominal tumors [2–4]. Few studies have investigated the use of CNB in children, and while encouraging, all are retrospective in nature [5–8]. For instance, Garrett et al. determined that CNBs were able to identify a malignancy with 93% accuracy on retrospective analysis [6]. Unfortunately, no prospective clinical studies have been performed to confirm these positive results.

At our institution, some of our pediatric surgeons routinely obtained CNB at the time of OWB for pediatric intraabdominal tumors. We saw this as an excellent opportunity to prospectively compare the diagnostic utility of each method on the same tumors, while minimizing added patient risk. Therefore, this practice was formalized into a prospective research protocol in which we asked if CNBs are noninferior to OWBs in diagnosing pediatric nonnephroblastoma intraabdominal solid tumors.

Abbreviations: CNB, Core needle biopsy; MKI, Mitosis–karyorrhexis index; OWB, Open wedge biopsy.

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1. Materials and methods

1.1. Enrollment

Data were collected in a prospective fashion. Patients aged 1 day through 17 years with radiographic evidence of a solid intraabdominal tumor suspected to be hepatoblastoma, rhabdomyosarcoma, nonrhabdomyosarcoma soft tissue sarcoma, or neuroblastoma scheduled for OWB at Children's Hospital Colorado from 5/1/2013 through 12/31/2015 were approached for enrollment. Exclusion criteria included suspected nephroblastoma since biopsy and tumor capsule disruption result in upstaging of these tumors [9]. Informed consent was obtained from the patient's parents, and assent was also obtained from children aged 7 through 17 years, when able. Internal review board approval (Colorado multiple institutional review board protocol #12-1300) was obtained for this study.

1.2. Tissue collection

Once enrolled, patients were taken to the operating room for an OWB and CNB performed under direct visualization of the tumor. The surgeon began the operation for an OWB in standard fashion under general anesthesia. Once the tumor was visualized, the surgeon obtained four 16-gauge CNBs using a Bard Monopty disposable core biopsy instrument (Bard Biopsy Systems, Tempe, AZ). This was followed by OWB in the same location as the CNB. The wedge biopsies were at least 1 cm^3 in size, dissected sharply. Hemostasis was obtained, the incision closed, and the patient was extubated and recovered in the postanesthesia care unit, followed by monitoring on the ward. All tissue samples were sent fresh to pathology for analysis. Indicated staining and analyses were performed on the tissue using all tissue samples to make the diagnosis. For the purpose of the study, the tissue samples were then labeled with CNB and OWB paired in a deidentified fashion for future blinded pathologic comparison.

1.3. Tissue analysis

Two pathologists blinded to initial pathologic reads reviewed deidentified slides of OWB and CNB from enrolled patients. The pathologists first reviewed the CNB only and determined if a complete diagnosis was possible. The pathologists then reviewed the OWB and determined if a complete diagnosis was possible. The diagnostic accuracy of the specimens was then compared to the gold standard of final pathology on the excisional tumor specimen (when available) or clinical outcome including expected response to chemotherapy when not resected.

A biopsy specimen was considered diagnostic if it was sufficient to reach the final diagnosis and if there was sufficient material for additional studies needed to confirm the diagnosis when needed. A biopsy was considered nondiagnostic if it contained no or minimal tumor or lacked a pathologic component necessary for diagnosis. A biopsy was considered incomplete if it was sufficient for diagnosis, but not sufficient for determining tumor subtype or other important prognostic features.

1.4. Theory/calculation

Prior to enrollment of patients, a power analysis was performed, which determined that 117 patients would be required to conclude noninferiority of CNB compared to OWB, with a type 1 error risk of 5%, a type 2 error risk of 20%, a pretest assumption of 95% accuracy of OWB, and a least relevant difference of 10%. Initially, a ten-year enrollment period was estimated to be required. Interim analysis was planned once 10–20 specimens were obtained to detect emerging trends. Owing to the higher than expected difference between OWB and CNB identified on interim analysis, further enrollment was not required. Descriptive data are presented as the mean ± standard deviation. Additional statistical analysis including Fisher's Exact test ($p < 0.05$), and noninferiority testing ($\delta > -0.1$) [10] were used where appropriate and were performed with Graphpad Prism software (Graphpad Software, Inc., La Jolla, CA).

2. Results

2.1. Patient characteristics

Fourteen patients were enrolled during the study period. Patient demographics included 8 males (57%), with an average age of 4 ± 4 years (range 7 days to 16 years). None of the patients carried a diagnosis of a known syndrome prior to biopsy. Two patients (patients #13 and 14) were born prematurely. Only one patient (patient #4) received any treatment prior to biopsy; this patient had undergone 4 cycles of cyclophosphamide, vincristine, and doxorubicin for a previous diagnosis of stage III neuroblastoma (Table 1). Two patients developed postoperative complications (14%); patient #14 had postoperative bleeding requiring a blood transfusion, and patient #12 developed a wound dehiscence. Twelve patients underwent later resection of the tumor, while one patient (patient #12) had a separate excisional biopsy of a nearby metastasis at the time of the CNB and OWB. One patient (patient #8) did not have an excisional biopsy specimen, but the clinical treatment response supported the diagnosis.

2.2. Characteristics and comparison of tumor biopsies

The tissue samples from CNB and OWB were compared, with results for each tumor displayed in Table 2. CNB differed from OWB in its ability to accurately provide a complete pathologic diagnosis ($p = 0.001$ for pathologist #1 and $p = 0.03$ for pathologist #2) (Fig. 1). By noninferiority testing, CNB

Table 1
Patient characteristics.

Patient Number	Sex	Age (years)	Preoperative Comorbidities	Tumor
1	F	3	None	8 cm periappendiceal mass
2	M	0.9	Asthma	5 cm left paraspinal mass
3	F	1.8	None	6 cm right paraspinal mass
4	F	1.8	Previous stage III neuroblastoma diagnosis	7 cm left lower abdominal mass
5	M	0.02	Large for gestational age	7 cm right upper abdominal mass
6	M	3	None	11 cm liver mass
7	M	16	Asthma, Wolf–Parkinson–White	17 cm left suprarenal mass
8	M	6	None	10 cm pelvic mass
9	F	0.08	None	11 cm left retroperitoneal mass
10	F	8	Asthma	16 cm right retroperitoneal mass
11	M	4	Speech delay	15 cm retroperitoneal mass
12	M	7	Speech delay	16 cm right lower abdominal mass
13	M	2	Prematurity (25 weeks), bronchopulmonary dysplasia	9 cm liver mass
14	F	1.9	Prematurity (32 weeks)	15 cm liver mass