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RELIABILITY OF ULTRASOUND-GUIDED PERCUTANEOUS CORE NEEDLE BIOPSY IN DIAGNOSTICS OF PEDIATRIC SOLID TUMORS

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July 30, 2020

Abstract

Background: Ultrasound-guided percutaneous core needle biopsy (PCNB) has been used more and more frequently in diagnostics of pediatric solid tumors in our center. It is less invasive than an incisional biopsy. However, reports relating to its reliability in clinical practice are limited. Therefore, we aim to investigate the reliability of this technique in the pediatric population. Methods: A 7-year retrospective study including patients [?] 18 years who underwent ultrasound-guided PCNB in our center was conducted. Children who received PCNB and final surgical treatment were included. Their medical records were reviewed. Final surgical pathological diagnoses were used as the gold standard to assess the diagnostic efficiency of PCNB. Results: A total of 169 children were included in our analysis. 87.0% of patients underwent PCNB for abdominal and pelvic masses. 79.1% of biopsies were performed under local anesthesia. There were 141 malignancies and 28 benign lesions confirmed by surgery. The most common malignancy was neuroblastoma (73), and the most common benign condition was fibromatosis. The diagnostic yield was 94.1%. The success rate of PCNB in determining benign and malignant conditions was 94.3% (150/159). Consistency between PCNB and final diagnoses was found in 143 cases, giving a total accuracy of 89.9%. The accuracy for diagnosing malignancies was 96.8% (122/126), and for benign diseases 87.5% (21/24). The difference was not statistically significant (p=0.0818). Severe complications occurred in 6 patients (3.5%). No evidence of needle tract dissemination was found. Conclusions: Ultrasound-guided PCNB is safe and effective in diagnosing pediatric solid tumors, especially in malignancies.

Background:

Ultrasound-guided percutaneous core needle biopsy (PCNB) has been used more and more frequently in diagnostics of pediatric solid tumors in our center. It is less invasive than an incisional biopsy. However, reports relating to its reliability in clinical practice are limited. Therefore, we aim to investigate the reliability of this technique in the pediatric population.

Methods:

A 7-year retrospective study including patients [?] 18 years who underwent ultrasound-guided PCNB in our center was conducted. Children who received PCNB and final surgical treatment were included. Their medical records were reviewed. Final surgical pathological diagnoses were used as the gold standard to assess the diagnostic efficiency of PCNB.

Results:

A total of 169 children were included in our analysis. 87.0% of patients underwent PCNB for abdominal and pelvic masses. 79.1% of biopsies were performed under local anesthesia. There were 141 malignancies and 28 benign lesions confirmed by surgery. The most common malignancy was neuroblastoma (73), and the most

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common benign condition was fibromatosis. The diagnostic yield was 94.1%. The success rate of PCNB in determining benign and malignant conditions was 94.3% (150/159). Consistency between PCNB and final diagnoses was found in 143 cases, giving a total accuracy of 89.9%. The accuracy for diagnosing malignancies was 96.8% (122/126), and for benign diseases 87.5% (21/24). The difference was not statistically significant (p=0.0818). Severe complications occurred in 6 patients (3.5%). No evidence of needle tract dissemination was found.

Conclusions:

Ultrasound-guided PCNB is safe and effective in diagnosing pediatric solid tumors, especially in malignancies.

INTRODUCTION

Obtaining specimen before treatment for diagnosis is important for cancer treatment, especially for patients who might benefit from neoadjuvant chemotherapy. Core needle biopsy (CNB) as an accurate and less invasive method has been utilized widely in diagnosis of adult tumors such as breast cancer[1–3] and prostatic cancer[4,5]. The use of CNB is limited in diagnosis of pediatric solid tumors as people concern about the safety of the procedure itself and the sufficiency of specimen for accurate diagnosis, although previous studies suggest that CNB is both safe and effective[6–11]. In recent years ultrasound-guided percutaneous core needle biopsy (PCNB) has been used more and more frequently in diagnostics of pediatric solid tumors in our center as it is less invasive than an incisional biopsy and children are not exposed to radiation under ultrasound. However, reports relating to its reliability in clinical practice are limited. As pediatric solid tumors are rare, most studies are done in small groups. Besides few researchers used surgical pathology as the sole gold standard for success to assess the accuracy of PCNB. Most used excisional pathological diagnoses as well as follow-up outcomes to evaluate the success rate of CNB. In this study, a 7-year retrospective study of children undergoing PCNB for diagnosis of solid tumors at our center was conducted. Using surgical pathology as the gold standard, we aim to investigate the reliability of ultrasound guided PCNB in diagnosing pediatric solid tumors

METHODS

2.1 Patients

This was an institutional review board approved retrospective analysis of ultrasound guided PCNB performed in the Surgical Oncology Department at Beijing Children's Hospital from August 1st 2012 to January 31st 2019. Those whose PCNB pathology indicates non-surgical treatment such as inoperable malignant diseases (of which lymphoma comprised a large portion) and certain benign conditions were excluded. Those who chose to be treated elsewhere were also excluded as their final surgical pathologies were not traceable or obtained. Only patients whose PCNB reports indicating operations and received surgery in our department were included. Medical records were reviewed for patient demographics, the anatomical location of the tumor biopsy specimen, the method of tumor biopsy, pathology, and complications. Unfortunately, the number of cores taken for core needle biopsies and the gauge of needles were not always recorded. Therefore, we did not take the two variables into analysis in this study. Final surgical pathological diagnoses were used as the gold standard to assess the diagnostic efficiency of PCNB. The PCNB pathology and surgical pathology were analyzed for diagnostic test statistics. The flowchart of patient selection is shown in Fig. 1.

2.2 Methods of PCNB

2.2.1 Anesthesia requirements

PCNB were performed under general endotracheal anesthesia and local anesthesia. In older children and patients whose lesions were not easy to access, local anesthesia was preferred as it is less time consuming.

2.2.2 Techniques of PCNB

All biopsies were performed by pediatric surgical oncologists. Before PCNB, their cross-sectional imaging (CT/MRI) and ultrasonography were reviewed. Lesions were evaluated for adequacy of PCNB. If the tumor

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could be accessed directly under ultrasound without perceived high risks of injuries to adjacent important structures such as major vessels and bowels, then it would be considered appropriate for PCNB.

Informed consent for anesthesia (if general anesthesia would be applied) and biopsy was obtained from all the parents. Before biopsy, a full clotting screen and a routine blood test were mandatory as they are especially important in evaluating tumors suspicious of being related to angiogenesis. A large needle was chosen whenever it was deemed safe to obtain tissues, and the largest we applied was 14-gauge, although in recent 2 years we used 16-gauge needles.

All patients received CT or MRI scanning before biopsy to aid in evaluating the risk for biopsy and to preliminarily determine the possible entry. In our center, ultrasonography was the only imaging modality used in all biopsies. We do not perform CT-guided biopsies.

An experienced ultrasound radiologist scanned the tumor again and used Color Doppler to assess its blood supply and approximate major vessels. The radiologist then marked an ideal insertion site on the skin. With the aid of the transducer, a biopsy needle was guided into the tumor. Under real-time ultrasound monitoring, the needle was placed in and fired multiple times, taking pieces of tumor tissues. In our practice, 14G- (Precisa, tru-cut semiautomatic device for histological biopsy, H.S.Hospital Service S.p.A) ,16G- and18G-needles (BARD MAX-CORE Disposable Core Biopsy Instrument, Bard Biopsy) were used.

2.2.3 Specimen handling

Specimens were placed in formaldehyde and sent to the Department of Pathology of Beijing Children's Hospital within one hour after the procedure. There they were examined by two pathologists experienced in pediatric oncology pathology.

2.3 Statistical analysis

We used descriptive statistical analyses as appropriate. We summarized continuous data using means and standard deviations, and categorical data using counts and percentages. Diagnostic yield was defined as the proportion of PCNB specimens sufficient for pathologists to make confident diagnoses among all biopsies performed. The final diagnosis in all cases was defined as the results of histological examinations of excised specimens. Accuracy was calculated as the proportion of biopsies resulting accurate diagnoses among those being diagnostic. Comparisons between diagnostic accuracies in diagnosing benign and malignant lesions were assessed by Fisher's exact test. P value < 0.05 was considered statistically significant.

RESULTS

A total of 169 children aged 1 to 190 months (mean age$\pm$SD = 48.7 $\pm$ 40.9 months) who underwent both PCNB and surgery in our department from June 2009 to January 2019 were included in this study. All biopsies were performed under ultrasound guidance. Patients demographics is shown in table 1. Over half of all the patients underwent PCNB for abdominal and pelvic masses. And retroperitoneal and liver masses constituted a large portion. Local anesthesia was well tolerated in the majority.

Final surgical diagnoses are listed in table 2. Neuroblastoma is the most common malignancy, followed by nephroblastoma, rhabdomyosarcoma, hepatoblastoma and malignant germ cell tumor. There was more variety in the benign conditions confirmed by postoperative pathology. Fibromatosis and ganglioneuroma, mesenchymal hamartoma of the liver constituted nearly half of the benign cases.

In 5 cases the quality of PCNB specimens were too poor for pathologists and in another 5 cases the specimens were not sufficient for confident diagnoses. The diagnostic yield was 94.1%. In the remaining 159 cases, PCNB was successful in determining benign and malignant conditions in 150 cases, giving a successful rate of 94.3% (150/159). In 33 cases who were diagnosed of benign diseases by PCNB at first, only 24 were proven to have benign conditions by postoperative pathology. And in all 126 cases whose PCNB pathology indicated malignancies, surgical pathology confirmed malignant diagnoses. Consistency between PCNB and final diagnoses was found in 143 cases, resulting a total accuracy of 89.9%. In 3 benign cases, PCNB pathology was different from the final diagnoses, and the accuracy was 87.5% (21/24). Meanwhile, among the 126 malignant

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cases, difference in diagnoses was found in just 4 children. The accuracy for diagnosing malignancies was 96.8% (122/126). Fisher's exact test showed that the difference was not statistically significant (p=0.0818).

All the patients whose PCNB results were not consistent with surgical results were listed in table 3, including those with non-diagnostic PCNB samples. Neuroblastoma (6), immature teratomas (3), and tumors of angiogenesis (4) were more likely to be misdiagnosed. Necrosis was the main cause of failure to diagnose.

There were 6 complications in this 7-year study (3.5%). In general, the procedure was well tolerated by majority of patients and all patients were discharged within 24 hours. Only 6 severe complications occurred within 2 weeks after PCNB. Their information was listed in table 4. It should be noticed that patient 4 was also diagnosed of horseshoe kidney. Patient 5 experienced the tumor rupture during neoadjuvant chemotherapy shortly following the biopsy. And patient 6 accidentally fell to the ground before the rupture occurred. All recovered with conservative treatment including blood transfusion, sedation, close monitoring, and other supportive therapy.

During follow-ups, no evidence of needle tract dissemination was found.

DISCUSSION

Although there have been more options in the imaging mode for PCNB, such as CT (used more in bone lesions) and MRI, ultrasound is the dominant as it spares patients from additional radiation exposure. This is of more significance in pediatric populations than in adults. Besides, Michael Accord et al show that the addition of CT and 3D fluoroscopy in image guide does not increase the overall diagnostic yield[6].

Final diagnoses are crucial in evaluating the reliability of PCNB technique. We think the most accurate diagnoses are surgical pathology. In previous studies, it was impossible to obtain surgical pathology of every patient. Their final diagnoses were based on resection pathology, reaction to treatment, and follow-ups, which might be less reassuring. In our study we only enrolled patients with postoperative pathology to ensure the accuracy of the final diagnosis and the related statistics, adding more confidence and credibility to our results.

The choice of needles was controversial. In previous studies, some researchers found that needle sizes were unrelated to the accuracy[8,12,13] while some argued that larger needles were better as more samples were more likely to be of diagnostic value[14,15]. Unfortunately, the size of the needle used was not routinely recorded in every medical record in our center, so we could not analyze the relation between needle sizes and biopsy accuracy. In our cohort, larger needles were preferred whenever possible and safe. Before the year 2018 14G needles were the only option in our center. In recent 2 years we used 16G and 18G needles. We assumed that 18G needles might causing less damage so in obtaining pancreatic tumor tissues they are the only choices. In our study, no clinically significant pancreatic damage was found after biopsies. And for lesions close to intestines we also preferred the smaller needles. However, in one case the tumor was rich in calcification, and it was difficult to take out the 18G needle. When the needle was finally pulled out with more force than usual, it bent. Thus, we concluded that in tumors rich in calcification, larger needles such as 14G and 16G ones should be recommended if possible, to reduce the risk of fracture and difficulties to remove the instrument.

In previous studies, reported complications included pain, intra-abdominal infection, pneumothorax, hematuria, and hemorrhage[8,9,13,16–20]. Post-biopsy bleeding including intra-tumoral hematoma is the most common. However, the complication rate is generally low and nearly all were managed successfully with conservative therapy such as oral analgesics and blood transfusion. In our series, there were 6 major complications in our cohort. All were tumor ruptures within 2 weeks after biopsies. From table 4 no relation could be found between the tumor type and this serious complication except that these lesions were all located in the abdomen. It should be noted that one of the patients also had the congenital condition of horseshoe kidney which might increase the rupture risk. Another rupture occurred during neoadjuvant chemotherapy. Therefore, this incidence might be the result of biopsy and tumor lysis induced by chemotherapy combined. And the girl who received a biopsy in the pancreas fell onto the ground, which might partly explain the rupture. In our cohort we required all patients to be closely monitored for 4-6 hours before discharges. From our experience,

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although major complications are rare, we suggest more care should be directed onto patients with congenital defects and those receiving chemotherapy.

Another concern about PCNB is needle track seeding. In our cohort no tumor dissemination along the needle track is found. It is also quite rare in previous studies[9,13,19] and almost all the reports are related with nephroblastoma[18,21,22] and the prognosis is generally quite good after chemotherapy and excision. Another earlier research on biopsy of renal tumors suggest posterolateral entries to confine tumor soilage instead of peritoneal dissemination. We suggest marking the biopsy site on the skin during renal tumor biopsy and excising the needle track if possible.

In our study, the accuracy of PCNB in diagnosing malignant tumors is higher than that in benign tumors, although the difference was not significant (P=0.08, slightly over 0.05). This finding is consistent with previous researches [7–9,17,23]. It might be due to the high heterogeneity of pediatric solid tumors. Our studies also showed that for differentiating different teratomas PCNB was not reliable. Some researchers also reported higher diagnostic accuracy and/or diagnostic yield in homologous tumors[12,24,25]. Necrosis, missing tumor tissues, and crushed samples are common problems encountered in PCNB, and impact pathological diagnoses including genetic testing. Possible measures to improve PCNB reliability include standby sample assessment, more comprehensive imaging evaluation, and new diagnostic techniques. Standby sample assessment by onsite pathologists and cytologist could improve accuracy of PCNB in histology diagnoses and genetic examinations[26,27]. And new imaging modality for prebiopsy evaluation and/or guidance during biopsy may lead to more precise location of viable tissues, therefore improving diagnostic yield and accuracy. PET-CT[28,29], MRI[25,30]and contrast ultrasound[31] have shown promising utility. Moreover, augmented reality-assisted biopsy technique may facilitate more accurate passages towards targeted tissue[32]. Also, improvements in diagnostic techniques could improve reliability of PCNB[13,24]. Recently, liquid biopsy has been studied a lot as it may reflect the whole picture of the tumor. MYCN status is critical for staging neuroblastoma and guiding treatment[33]. Traditionally MYCN amplification (MNA) is measured by fluorescence in situ hybridization (FISH). As MNA is categorized into homologous and heterogeneous amplifications, theoretically PCNB may fail to obtain tissue with MNA in tumors with heterogeneous MNA which means MNA is unequally distributed in tumor cells and may not be present in certain clusters of cells. Droplet digital polymerase chain reaction (ddPCR) as a novel technique of liquid biopsy has been shown to replace FISH technique to overcome sampling insufficiency or inadequacy[34,35].

For diagnosing benign neoplasm PCNB is not as reliable as for malignancies, especially in tumors of angiogenesis, which is consistent with previous studies[7–9,12,17,23]. Some researchers suggest incisional biopsy on suspicion of benign tumors as a second core needle biopsy may not provide additional valuable information for diagnoses[17].

There are several limitations in our study.

First, our cohort is from a single academic third-tertiary children's hospital with an abundant ultrasound experience in pediatric populations. Ultrasound diagnoses are heavily dependent on personal experience. Our radiologists might be more experienced in evaluating the surrounding tissues and tumor compositions. Decisions of more appropriate and safe biopsy entry sites might be made more easily. Therefore, our results might not be replicated in other institutions.

Second, pediatric solid tumors are rare diseases[36–41]. Currently the diagnoses are mainly made based on pathology, morphology, immunohistology, and molecular biomarkers in some tumors[41]. The diagnoses are heavily dependent on pathologists' experience, and central pathology review may reduce mistakes. However up to now there has been no census on central pathology review for pediatric solid tumors in China. Although in some cases in our study the slides were reviewed by pathologists from other institutions, the accuracy of pathological diagnoses cannot be guaranteed.

Fourth, in our research few samples were stored for future research purposes. Although biological information has been more and more important in both diagnoses and guiding treatment of pediatric tumors[33], no fresh samples were reserved for genetic testing and other biological molecular assessment. Besides, currently there

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has been no central biobank for pediatric tumors and no standard for handling those biological samples. And clinical trials for pediatric solid tumors have just found their way into China. Collaboration between different hospitals is just taking the first step. We plan to store more samples for future research and look forwards to establishing a national central biobank for childhood solid tumors. More work will be done in the future.

In summary, ultrasound guided PCNB is generally safe and effective for diagnosing pediatric solid tumors, especially for malignancies. However, its reliability in diagnosing benign conditions is still in question. More comprehensive prebiopsy imaging evaluation, closer follow-ups, and new techniques might prevent misdiagnoses and/or failures to diagnose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ACKNOWLEDGEMENTS

We thank Dr. Wang Xiaoman and Dr. Lv Chuankai for their kind assistance with biopsies.

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LEGENDS

Figure 1 Flowchart of patient selection

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