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Reliability of Intraoperative Frozen Section for the Diagnosis of Renal Tumors Suspicious for Malignancy in Children and Adolescents

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Abstract

Background—The ability of Intraoperative Frozen Section (IFS) to reliably diagnose renal tumors in children and adolescents is largely unknown. The objective of our study is to evaluate the ability of IFS to establish a histologic diagnosis for renal tumors in this population.

Methods—We reviewed our experience with patients who underwent IFS at the time of surgery for a renal tumor suspicious for malignancy from 2005–15. The IFS was compared to the final pathology (FP). Data on concordance and reliability were analyzed.

Results—130 patients underwent surgical interventions for a renal tumor suspicious for malignancy, and 32 (25%) patients underwent IFS. Median turnaround time for IFS was 20 minutes (range 13 – 44). The histologic IFS diagnosis correlated with FP in 26 (81.2%) cases, was discrepant in 3 (9.4%) cases, and IFS was deferred to FP in 3 (9.4%) cases (kappa 0.71, 95% CI 0.52–0.899, $p<0.001$). The IFS correctly distinguished between Wilms tumor and non-Wilms tumor in 30 (94%) cases (kappa 0.874, 95% CI 0.705–1, $p<0.001$). A total of 17 of 19 (89.5%) Wilms tumors were correctly diagnosed by IFS, yielding a sensitivity of 0.89 (95% CI 0.67–0.99) and a specificity of 1 (95% CI 0.75–1).

Conclusion—IFS is a reliable tool to establish a histologic diagnosis, and to differentiate between Wilms and non-Wilms tumors in children and adolescents with renal tumors. The use of IFS should be encouraged in cases where obtaining a diagnosis will provide guidance for

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important “real-time” medical decision making, specifically additional adjunctive surgical procedures.

Keywords

Wilms; frozen section; pathology; renal tumor; children

Introduction

Renal tumors are the fourth most common tumor in children accounting for 5–7% of newly diagnosed childhood cancers[1,2]. Although Wilms tumor is the most common renal tumor in children, other tumors such as renal cell carcinoma (RCC), clear-cell sarcoma, mesoblastic nephroma, and rhabdoid tumors of the kidney can present in children and adolescents [3]. In addition, other benign or malignant processes can masquerade as renal tumors including neuroblastoma, xanthogranulomatous pyelonephritis, and lymphoma. While most renal tumors in children and adolescents require multimodal therapy including surgery, radiation, and/or chemotherapy, the treatment regimens vary. Selection of treatment modalities depends on a combination of clinical data including the patient age, tumor histology, tumor weight, disease stage, and protocol guidelines. Ideally, the surgical care of these patients would be consolidated such that all necessary invasive interventions (i.e., long-term central vascular access, bone marrow biopsy, etc.) are performed under one anesthetic when possible. However, this is not always possible as the diagnosis is often uncertain and ultimately relies on pathologic evaluation.

Intraoperative frozen section (IFS) is a diagnostic tool which has been extensively investigated in the adult literature with few reports in the pediatric literature. The use of IFS has the potential to guide the need for adjunctive surgical procedures and provide clinical information to the patient’s family in a timely manner. However, the true utility of IFS in the care of children and adolescents with suspicious renal tumors is largely unknown. The primary objective of our study is to evaluate the reliability of IFS for renal tumors in children and adolescents. We hypothesize that IFS is reliable to establish a histologic diagnosis in the management of children and adolescents with renal tumors.

Methods

Study Design

The electronic medical records of patients who underwent radical nephrectomy, partial nephrectomy, or incisional biopsy for a suspicious renal tumor at our tertiary referral center between January 2005 and December 2015 were reviewed. Pathology reports which included IFS and final pathology (FP) were independently reviewed by two reviewers, with discrepancies settled by a third reviewer. Diagnostic consistency was established for each case comparing the IFS and FP diagnosis according to histologic subtypes, benign/low malignant potential versus malignant pathology, and Wilms versus non-Wilms tumor classification. Benign/low malignant potential histology included cystic nephroma, congenital mesoblastic nephroma, angiomyolipoma, cystic metanephric adenoma, juxtaglomerular cell tumor, localized cystic disease, and pseudotumor. Malignant histology

included Wilms tumor, RCC, Clear cell sarcoma, Rhabdoid tumor of the kidney, and renal medullary carcinoma. For cases in which a formal histologic diagnosis was deferred at the time of IFS, the diagnosis was categorized as "other." Clinical management variations (e.g. placement or delay of central vascular access port) due to the influence of any discrepancy between IFS and FP diagnosis were also reviewed. Turnaround time for IFS was determined by review of the intraoperative event report or time recorded on the pathology report. Our hypotheses were that IFS is a reliable tool to establish a histologic diagnosis and to differentiate between Wilms and non-Wilms tumors in children and adolescents with renal tumors.

Study Criteria

Patients were excluded if they underwent nephrectomy, partial nephrectomy or biopsy for an indication other than a renal tumor suspicious for malignancy. Only IFS and FP from the primary tumor were evaluated. The IFS on lymph nodes, metastatic lesions, fine needle biopsy/aspiration, or surgical margins were excluded from this analysis.

Data Analysis

Cohen's kappa coefficient was utilized to assess the concordance rate between IFS and FP with regard to histologic subtypes, benign versus malignant pathology, and Wilms versus non-Wilms tumor classification. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) to differentiate malignant from benign tumors, and Wilms tumors from non-Wilms tumors were calculated with 95% confidence intervals (CI) for each parameter. The data analysis was generated using SAS software, Version 9.3 (Cary, NC).

Results

During the study period, 130 patients met study criteria and underwent surgical interventions for a renal tumor at a median age of 37 months (range 1 to 198). Of these, 12 (9.2%) patients had surgery for bilateral Wilms tumors. Radical nephrectomy, partial nephrectomy, or incisional biopsy was performed in 86 (66.2%) patients without the use of IFS. Final pathology (FP) for these cases were 69 (80%) Wilms tumor, 6 (7%) neuroblastoma, 3 (3.5%) cystic nephroma, 2 (2.3%) RCC, and 1 (1.2%) each for renal medullary carcinoma, clear-cell sarcoma, malignant rhabdoid tumor, adrenocortical carcinoma, undifferentiated sarcoma, and benign pseudotumor.

A total of 32 (25%) patients had intraoperative specimens submitted for IFS. Specimens submitted for IFS included nephrectomy (n=27, 84%), partial nephrectomy (n= 4, 12.5%), or incisional biopsy (n=1, 3%). Turnaround time was available for 29 patients. The median turnaround time was 20 minutes (range 13 to 44) with 52% of IFS results reported to the surgeon in less than 20 minutes. Table 1 outlines the concordant, discordant, and deferred rate for histologic diagnosis. Wilms tumor accounted for the majority of the cases (59%). The IFS correlated correctly with FP in 26 (81.2%) cases, incorrectly in 3 (9.4%) cases, and was deferred to FP in 3 (9.4%) cases.

The overall histologic agreement between IFS and FP was determine to be good (kappa 0.71, 95% CI 0.52–0.899, $p < 0.001$). When using IFS to determine if the specimen was

malignant or benign, 30 (94%) of the cases were correlated correctly with strength of agreement considered to be very good (kappa 0.834, 95% CI 0.615–1, p <0.001). The sensitivity and specificity of IFS for correct identification of histologic tumor type was of 0.92 (95% CI 0.74–0.99) and specificity of 1 (95% CI 0.59–1), respectively, with a negative predictive value of 0.78 (95% CI 0.4–0.97), and a positive predictive value of 1 (95% CI 0.6–0.91). Similarly, IFS was able to correctly distinguish between Wilms tumor and non-Wilms tumor in 30 (94%) cases, with strength of agreement considered to be very good (kappa 0.874, 95% CI 0.705–1, p <0.001). A total of 17 out of 19 (89.5%) Wilms tumors were correctly diagnosed with IFS. The use of IFS to diagnose Wilms tumor had a sensitivity of 0.89 (95% CI 0.67–0.99), a specificity of 1 (95% CI 0.75–1), a negative predictive value of 0.87 (95% CI 0.6–0.98), and a positive predictive value of 1 (95% CI 0.8–1).

Of the discordant cases, one was diagnosed as a cystic nephroma on IFS and then determined to be a cystic Wilms tumor on FP. Due to the age (less than 2 years old) of the patient and weight of the specimen (less than 550 grams), no additional invasive interventions were required as patient met the standards of a very low-risk Wilms tumor (VLRWT) as per the recent Wilms tumor protocols of the Children's Oncology Group (COG)[4,5]. This case was managed with surgery-only and no need for long-term central venous access for chemotherapy. The second discordant case was initially labeled xanthogranulomatous pyelonephritis on IFS, but was then determined to be a RCC on permanent pathology. No additional invasive intervention was required as surgical excision alone was appropriate therapy. The third case was initially labeled epithelial malignancy, not otherwise specified by the IFS at time of incisional biopsy, while permanent pathology determined it was a renal medullary carcinoma. This patient required placement of long-term central venous access under a second anesthetic. Of the cases for which diagnosis was deferred to permanent pathology, one was initially labeled a malignant blue cell tumor and ultimately classified as a Wilms tumor. This patient had central venous access placed at time of tumor resection. The other two deferred cases were called "blue cell proliferation" and "cellular neoplasm" on IFS, and both were determined to be congenital mesoblastic nephroma on FP. These two patients had unnecessary long-term central venous access placed which necessitated removal under a second anesthetic.

Discussion

Intraoperative frozen section was first brought into practice in 1905, and it now plays an important role in the management of many surgical patients[6–8]. In general, the use of IFS has a reported diagnostic accuracy between 78% and 98% in pediatric solid tumors[7,9–12]. However, this diagnostic tool is utilized in less than 8% of pediatric surgical specimens, with renal tumors accounting for less than 3% of these[7,10]. In our 10 year review of patients with renal tumors, IFS was utilized in 25% of the cases of unilateral nephrectomy, partial nephrectomy, and incisional biopsy. While clinical information such as age, radiographic findings, and intraoperative findings can point towards a likely diagnosis, it often remains unclear until FP. This uncertainty of diagnosis can predispose patients to undergo unnecessary, incomplete, or delayed procedures as part of their treatment.

Although the majority of renal tumors suspicious for malignancy in children are Wilms tumors, other pathologies both malignant and benign can be encountered. Some benign and malignant renal tumors, including very low-risk Wilms tumors (VLRWT), are managed with surgical resection alone[3,4,13], thus highlighting the importance of establishing a histologic diagnosis which can guide the need for adjunctive procedures at the time of tumor resection. In a patient who meets pre-operative criteria for VLRWT (tumor weight less than 550 grams, age less than 2 years, and no clinical evidence of metastatic disease)[4], obtaining IFS may not be beneficial for confirming VLRWT classification since FP of the entire specimen is needed to confirm favorable histology and no lymph node involvement. However, IFS may rule out other malignant tumor types which may require adjuvant chemotherapy (e.g. rhabdoid tumor and clear cell sarcoma of the kidney) and thus further supporting any decision for or against vascular access placement at the same operative setting. This can be similarly applied to older children and young adults who are more likely to have a non-Wilms tumor diagnosis such as RCC. While the role of a formal retroperitoneal lymphadenectomy in children and adolescents with RCC remains unclear[13,14], an intraoperative diagnosis of RCC may help direct the decision for a more aggressive lymph node dissection particularly in patients with bulky lymphadenopathy *in lieu* of just lymph node sampling. IFS can guide the need for additional adjunctive or more aggressive surgical procedures, but utilization of IFS would only be rational if it was highly accurate, as both false negatives and false positive results would lead to the same pitfalls of over- or under-treatment.

Dall'Igna et al. reported a diagnostic accuracy of 97% when evaluating IFS in 416 tumors involving multiple organs and tissue sites in pediatric patients. Their high accuracy rate was after adjusting for 8.6% deferred cases. In this report, there were 11 renal tumor specimens. The IFS accurately differentiated between Wilms (n=7) and non-Wilms (n=4) in 91% of cases, and correctly diagnosed Wilms tumors in 86% of cases. In our study, we found that IFS histology correlated correctly in 81% of cases (90% when adjusting for deferred cases). Similarly, IFS was able to correctly distinguish between Wilms tumor and non-Wilms in 94% of cases, and Wilms tumor was correctly diagnosed in 89.5% of cases. Thus, the use of IFS for diagnosis of Wilms tumor has a high sensitivity (89%) and specificity (100%). We observed a histologic discordant and deferred rate of 9.4% each. This is similar to the 7% to 9% discordant rate and 14% deferred rate previously observed in both adult and pediatric renal tumors [7,15]. These rates in renal tumors are within the 2% to 21% discordant and 2.5% to 25% deferred rates observed in all pediatric solid tumor specimens submitted for IFS[7,9–12]. In keeping with prior publications on this topic, we believe these rates to be acceptable[7,10,11].

Logistically, the addition of IFS should have little negative impact to the ongoing procedure. The median turnaround time for IFS in our study was only 20 minutes with 52% of IFS reported to the surgeon within the established 20 minute time frame set by the College of American Pathologists[16]. At our institution, we keep close communication with the pathology team by contacting them to notify them of potential need for IFS, and to discuss pertinent clinical factors which may aid in establishing a diagnosis in a timely manner. Pathologists are informed of start of surgery, during its progress, and made aware of any pertinent intraoperative findings. The duration of time needed for IFS should not discourage

surgeons from utilizing this diagnostic tool. The turnaround time can be effectively utilized for performance of a regional lymph node sampling or dissection, when clinically indicated or per protocol[17].

No prior study has specifically evaluated the performance of IFS to diagnose renal tumors in children and adolescents. However, it should be clearly stated, our study comes with several limitations. It is a retrospective review of a variety of rare renal tumors over a 10 year period at a high volume tertiary referral center. One major limitation to our study is that we were unable to determine what indication prompted the surgeon to obtain IFS. This was likely obtained at the discretion of the surgeon based on available clinical data and their suspicion for a certain diagnosis which would have impacted their intraoperative management. The use of IFS is a complex process and requires expertise from the surgical pathologist. Awareness of the limitations of IFS is important, and providers should work towards minimizing these limitations as much as possible to maximize the diagnostic yield. Limitations of IFS include sampling errors, technical problems, and interpretative errors[7]. At our institution, IFS is interpreted by fellowship-trained pediatric pathologists with experience with these rare tumors. As such, our results cannot be extrapolated to all centers. In addition, the IFS specimens were interpreted by more than two pathologists in 75% of cases, and FP was reviewed internally or externally in 91% of cases to confirm the diagnosis. To avoid sampling error, we only evaluated IFS performed on a segment from the whole specimen (97%) or incisional biopsy (3%), and we did not include needle biopsy specimens. It is important to note that IFS is typically performed in a small portion of the specimen, and therefore it is not a reliable way to detect anaplasia (unfavorable histology) an important pathologic factor in the management of Wilms tumor. Current protocols for the examination of specimens from patients with Wilms tumors or other pediatric renal tumors supports the use of IFS from a bi-valved nephrectomy specimen when the operative procedure will be altered by the results[18]. Thus, IFS should be used prudently in situations that will impact immediate intraoperative management, and indiscriminate usage, including performing IFS only for preliminary diagnostic information, should be avoided[7,10].

Conclusion

Based on our observations, IFS appears to offer a reliable and accurate tool to establish a histologic diagnosis, distinguish between malignant and benign tumors, and to differentiate Wilms from non-Wilms tumors in children and adolescents with renal tumors. Communication between the surgeon and pathologist is of utmost importance when dealing with these rare renal tumors to insure the proper and efficient use of IFS. Specifically, we advocate the use of IFS in cases where obtaining a histologic diagnosis will provide guidance for “real time” medical decision making and adjunctive surgical interventions.

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Abbreviations key

IFS	Intraoperative frozen section
FP	Final pathology
CI	Confidence interval
NPV	Negative predictive value
PPV	Positive predictive value
COG	Children's Oncology Group
RCC	Renal cell carcinoma
VLRWT	very low-risk Wilms tumors

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Table 1

Agreement of intraoperative frozen section according to histology

Final diagnosis	N	Concordant	Discordant	Deferred
Total	**32**	**26 (81.2%)**	**3 (9.4%)**	**3(9.4%)**
Wilms tumor	19 (59.4%)	17 (90%)	1 (5%)	1 (5%)
Renal cell carcinoma	3 (9.4%)	2 (67%)	1 (33%)	0 (0%)
Renal medullary carcinoma	1 (3.1%)	0 (0%)	1 (100%)	0 (0%)
Cystic nephroma	2 (6.3%)	2 (100%)	0 (0%)	0 (0%)
Congenital mesoblastic nephroma	2 (6.3%)	0 (0%)	0 (0%)	2 (100%)
Angiomyolipoma	1 (3.1%)	1 (100%)	0 (0%)	0 (0%)
Juxtaglomerular cell tumor	1 (3.1%)	1 (100%)	0 (0%)	0 (0%)
Cystic metanephric adenoma	1 (3.1%)	1 (100%)	0 (0%)	0 (0%)
Not otherwise specified benign renal tumor (localized cystic disease and pseudotumor)	2 (6.3%)	2 (100%)	0 (0%)	0 (0%)