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UTILITY OF FROZEN SECTION IN PEDIATRIC AND ADOLESCENT MALIGNANT OVARIAN NONSEMINOMATOUS GERM CELL TUMORS: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

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Abstract

PURPOSE: In adult women, most malignant ovarian tumors are epithelial in origin. The use of intra-operative frozen section to distinguish between benign and malignant histology is reliable in guiding operative decision-making to determine the extent of surgical staging required. Pediatric and adolescent patients with ovarian masses have a much different spectrum of pathology with most tumors arising from germ cell precursors. This review was undertaken to assess the concordance between the intra-operative frozen section and the final diagnosis as an aid to guide

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extent of surgical staging in a group of pediatric and adolescent patients with malignant ovarian germ cell tumors.

METHODS: Records of patients aged 0 to 20 years with malignant ovarian germ cell tumors enrolled on Children's Oncology Group study AGCT0132 were reviewed. Pathology reports from patients who had both intra-operative frozen section diagnosis and final paraffin section diagnosis were compared using descriptive statistics. By inclusion criteria for the study, all patients had a final diagnosis of malignancy with required yolk sac tumor, choriocarcinoma or embryonal carcinoma histology. Available central review of pathology final paraffin section slides were compared with final institution pathology reports.

RESULTS: Of 131 eligible patients with ovarian germ cell tumors, 60 (45.8%) had both intra-operative frozen section and final paraffin section diagnoses available. Intra-operative frozen section diagnoses were classified as: incorrect diagnosis of benign tumor (13.3%), confirmation of malignancy (61.7%), immature teratoma (16.7%), germ cell tumor not otherwise specified (5%) and no diagnosis provided (3.3%). Intra-operative frozen section was incorrect in 23 of 60 (38.3%) patients evaluated. Central pathology review was concordant with the final institution pathology diagnosis in 76.3% of patients. Central pathology review identified additional germ cell tumor components in 23.7% of patients.

CONCLUSIONS: In pediatric and adolescent patients with a confirmed final diagnosis of ovarian germ cell malignancy, intra-operative frozen section diagnosis is not reliable to inform the extent of surgical staging required. Central review by an expert germ cell tumor pathologist provides important additional information to guide therapy.

Keywords

Malignant; Germ Cell Tumor; Ovary; Frozen Section

Introduction

The use of intra-operative frozen section diagnosis for adult women with ovarian tumors is widely accepted as a valuable tool in guiding the extent of surgical staging procedures for malignant epithelial tumors.[1–7] Intact removal of the tumor with immediate transport of the mass to pathology for frozen section is used to determine whether a full staging operation that includes peritoneal washings, peritoneal biopsies, infracolic omentectomy and lymph node dissection is needed. This is important to avoid under-staging and the potential for increased morbidity with more extensive procedures if they are not needed. Multiple studies have shown high accuracy for identification of malignant and benign surface epithelial neoplasms (SENs) by frozen section in adult ovarian tumors but some difficulty in interpretation of borderline/low malignant potential (LMP) epithelial tumors.[3, 4, 8] To the best of our knowledge, no studies have evaluated frozen section in the management of pediatric malignant germ cell tumors. The spectrum of histology in children and adolescents with ovarian tumors is markedly different from that of adults with a higher percentage of germ cell tumors overall, and a higher rate of malignancy in the germ cell group. SENs among pediatric ovarian tumors are rare.[9] This study was undertaken to assess the value of frozen section analysis as an aid for intra-operative decision making in a group of pediatric

and adolescent malignant germ cell tumors. In addition to comparison of frozen section with final histology diagnosis from the primary institution, an additional comparison was done to compare institutional results with a central pathology review performed by a Pediatric Pathologist with specific expertise in germ cell tumor histology.

Materials and Methods

Data used for this manuscript are from the Children's Oncology Group (COG) study AGCT0132, a phase III clinical trial conducted from November 2003 to July 2011 and are current as of December 31, 2020. To be eligible for the study, patients must have had an extracranial malignant germ cell tumor containing yolk sac tumor, embryonal carcinoma, choriocarcinoma, or a mixture of these histologies with or without a component of teratoma. Pure dysgerminoma and immature teratoma patients were excluded. This review includes only patients with a primary ovarian tumor. The details of AGCT 0132 have previously been published and provide the stratification and management of this cohort of patients.[10] Using the Children's Oncology Group (COG) staging criteria, Stage 1 tumors are considered low risk, and stages 2 and 3 are considered intermediate risk (Table 1). Low risk patients were treated with observation after surgery and intermediate risk patients received platinum-based chemotherapy after surgery.[11] Institutional pathology reports and, when available, frozen section results were submitted after the relevant surgery. Pathology reports from the primary institution were submitted for all patients. Intra-operative frozen section was not required by protocol but was frequently performed; those with available pathology reports for review were included. In this study, we compare the frozen section diagnosis to the final diagnosis based on institutional pathology reports, which identified malignant germ cell tumor histology for all patients. Frozen section diagnoses were reviewed and classified by two authors (BD and DB) into five categories: malignant, benign, immature teratoma, germ cell tumor not otherwise specified, and no diagnosis provided. This definition was agreed upon by the current COG central pathologist (FKH). At the time of the AGCT 0132 study, synoptic reports for frozen section were not required by study protocol. This contributed significantly to the observed missing data. However, when we reviewed those patients with and without frozen section, they were similar in all patient characteristics. Frozen section diagnoses were deemed to be in agreement with the institutional pathology reports if the intra-operative diagnosis was any combination of the following: malignant germ cell tumor, malignant neoplasm, yolk sac tumor, dysgerminoma, or choriocarcinoma. A diagnosis was considered incorrect if no malignant component was identified by frozen section. If immature teratoma was identified but no malignant component (yolk sac tumor, embryonal carcinoma, dysgerminoma/germinoma or choriocarcinoma) was identified by frozen section, the patient was classified as "immature teratoma only." As immature teratoma is managed differently by pediatric and adult providers, this category was analyzed as a separate group. For some patients, the frozen section identified a germ cell tumor, but no additional information was provided. These were classified as "germ cell tumor not otherwise specified." To compare frozen section diagnoses with institutional final diagnoses, we present the number and percent of patients in each of the five categories specified above.

We also compare the results of the institutional pathology reports with those of central pathology review. Central pathology is a COG pathologist with expertise in the pathological

evaluation of malignant germ cell tumors. For this trial central pathology review was recommended within 72 hours of enrollment for Stage I patients. Stage II and III patients were not required by protocol to have central review. We considered whether additional malignant histologies or teratoma were identified by central review but not by the institution, and whether central review did not identify histologies identified by the institution. Similarly, to compare the diagnoses based on institutional reports to that of central review, we present the percentage of patients that fall into each of the specified categories, defined by level of agreement.

Results

Demographics

A total of 131 eligible ovarian germ cell tumor patients from 84 sites were enrolled in AGCT0132. Of the 84 sites, 52 institutions enrolled 1 patient each, 22 sites enrolled 2 patients, 5 sites enrolled 3 patients, and 5 sites enrolled 4 patients each. Among the 131 ovarian germ cell tumor patients, 118 (90%) had both an institutional and central pathology review. Sixty (45.8%) patients had both an intra-operative frozen section performed and an available pathology report. Table 2 presents the baseline characteristics of patients in the low and intermediate risk strata. Because we had a low percentage of patients with intra-operative frozen section, we present the baseline characteristics for patients who either did not have frozen section or institutional reports available (71 patients) and those with both reports available (65 patients). Overall, the median levels of alpha-fetoprotein (AFP) were lower in patients with both frozen section and institutional reports. Similarly, the median β-human chorionic gonadotropin (β -HCG) was lower for patients with frozen section in the low-risk group. As a cohort, AFP and B-HCG were collected preoperatively in 44% – 73% and in 55% – 73% of patients respectively. It should be noted that sites were asked to measure tumor markers pre-operatively (preferred) or as soon as possible after surgery.

Frozen Section Comparison

Sixty patients with ovarian germ cell tumors enrolled in AGCT0132 had both an intra-operative frozen section performed and an available pathology report. Table 3 compares the diagnosis from the intra-operative frozen section to the final diagnosis provided in the institutional pathology reports. When we compared the results of frozen section report with final diagnosis report for low-risk (stage I) and intermediate-risk (stage II or III) patients, we found a similar distribution of classification in both groups. In 37 (61.7%) patients the frozen section report of a malignant tumor agreed with the institutional final pathology report. A diagnosis of immature teratoma alone was reported in 10 (16.7%) patients on frozen section. Currently there are treatment discrepancies between pediatric and adult oncologist with respect to immature teratoma, however, if immature teratoma is considered a malignant tumor, as reported in adult oncology, the concordance of frozen section to final pathology results improved to 78.4%. Germ cell tumor not otherwise specified (NOS) was identified in 3 (5.0%) of patients. In only 2 (3.3%) patients, the frozen section failed to give any diagnosis. Eight (13.3%) patients had an intra-operative frozen section diagnosis of benign disease. Overall, intra-operative frozen section analysis led to an incorrect diagnosis in 23 of 60 (38.3%) patients.

Central Review

Central pathology review reports were available for 118 (90%) patients. The institutional pathology report was congruent with the central pathology report in 76.3% of cases overall. There was no difference in the correct identification of malignancy between the low and intermediate risk groups (Table 4). Central review identified additional malignant histology not seen by the primary institution in 12 (10.2%) cases. Conversely, the institutional pathologist identified 4 (3.4%) cases of additional malignant elements that were not recognized by central pathology review. Finally, central pathology review identified additional findings of teratoma (9.3%) and a discrepancy in the grading of immature teratoma (0.8%) that was not seen by institutional pathology review. These cases highlight the complexity of these tumors and the importance of central review and expertise in pathology in correctly characterizing these rare tumors.

Discussion

There are multiple reports regarding the accuracy and utility of frozen section guidance in the management of adult ovarian epithelial tumors.[1–8] In this report agreement between frozen section and institutional reports was well below that seen in the adult literature. There are several reasons for this. Ovarian tumors in adults are mainly epithelial in origin accounting for 95% of patients in a general series.[12] In general, malignant SENs arise from a single cell type with a characteristic architectural proliferative pattern that can be recognized by frozen section. There is, however, significant challenge in distinguishing between borderline tumors/LMP tumors and carcinoma. Pediatric and adolescent neoplasms, on the other hand, are predominantly of germ cell origin. The prevalence of ovarian germ cell neoplasms range from 60–80% in most pediatric series.[13] This report includes only malignant germ cell tumors in patients aged 11 months to 20 years of age. The pre-operative diagnosis of malignant germ cell tumors by imaging alone can be challenging as reported by Billmire et al. [14] In that report, the authors reviewed imaging characteristics of a series of malignant ovarian germ cell tumors and showed that 83.5% of those pediatric ovarian germ cell malignant tumors had a solid and cystic appearance considered characteristic of benign teratoma. These tumors were of mixed histology that included both mature and immature teratoma in 54% of cases, in addition to malignant histology. Those tumors had a similar distribution of imaging appearance to those seen in a series of combined malignant and benign ovarian neoplasms from individual institutions.[13] The mixed nature of ovarian germ cell tumors, often with more than one malignant histology (yolk sac, dysgerminoma, embryonal carcinoma, choriocarcinoma), may lead to sampling error on frozen section. In addition, the histologic patterns for the malignant components are not as characteristic on frozen section analysis. The heterogeneity of this rare tumor may lead to discordant findings between the intra-operative frozen section and the final permanent pathology report. For surgeons accustomed to using frozen section to help guide operative staging, this may pose a problem that may lead to inadequate staging. Failure to do compete staging leads to inability to confirm stage I and will eliminate the opportunity to manage the patient with surgery and observation only. Stage II and III patients receive Cisplatin-based chemotherapy regimen. These differences magnify the importance of both complete staging and pathologic identification.

In this report, we retrospectively reviewed all eligible patients from the COG AGCT0132 study presenting with malignant ovarian germ cell tumors that had an intra-operative frozen section evaluation, as well as those followed by both institutional and central pathological review. For this study, misclassification referred to a diagnosis of benign. This occurred in 8 (13.3%) patients evaluated. Immature teratoma only was identified in 10 (16.7%), germ cell tumor not otherwise specified in 3 (5%), or no diagnosis provided on frozen section occurred in 2 (3.3%) patients. Overall, the frozen section diagnosis was incorrect in 38.3% of cases. This is in stark contrast to the frozen section accuracy reported in adult studies in which 80.7 – 99% correctly identify ovarian malignant surface epithelial neoplasms.[1–8] Furthermore, no opinion was reached in these studies on frozen section in 2.4% of cases.[1]

Frozen section has poor accuracy for confirming malignancy in pediatric ovarian germ cell tumors. By definition, malignant germ cell tumors are heterogeneous proliferations with a wide variety of histologic features and architectural growth patterns. These characteristics coupled with their protein expression profiles, as determined by immunohistochemistry, aid pathologists in establishing the diagnosis. It can be challenging to make the diagnosis at the time of frozen section. This process is inherently fraught with pitfalls that include, but are not limited to, frozen section artifacts (tissue chaffing, cell swelling/shrinkage, etc.), the inability to consistently appreciate important distinguishing nuclear characteristics in frozen cells and the lack of access to immunohistochemistry to distinguish between some malignant components. Additionally, ovarian germ cell tumors tend to be large and thorough sampling standards are to examine one section of tumor (approximately the size of a postage stamp) per one cm of tumor tissue. While the tumors are often completely sectioned when received from the operating room for frozen section analysis, intraoperative time constraints preclude extensive histologic evaluation. Due to these time constraints, only limited tumor sampling for frozen section analysis can be practically performed. This incomplete tumor sampling may lead to a lack of representation of all malignant components.

The presence of immature teratoma alone identified by frozen section occurred in 10 (16.7%) cases adds to the difficulty in classification and to the surgical management. This arises due to the philosophical differences in management of immature teratoma between adult and pediatric oncology physicians. Immature teratoma of the ovary represents approximately 1% of tumors. Although it is recognized that immature teratoma may spread to lymph nodes, peritoneal surfaces and distant sites, the need and efficacy for platinum-based chemotherapy remain controversial. These tumors are graded using either a 3-tiered or 2-tiered system based upon the proportion of tissue containing immature neural elements.[15] The grade and clinical stage are considered to have prognostic value and are used to direct chemotherapeutic decisions. In the adult population, the standard of care is to administer chemotherapy to all patients except those with Stage 1, grade 1 immature teratoma.[16] In contrast, for pediatric patients with immature teratoma, surgery alone was curative for completely resectable disease, regardless of grade or the presence of microscopic foci of yolk sac tumor.[17] Given the differences in approach to this issue, a frozen section diagnosis of immature teratoma in the hands of an adult surgeon very likely will lead to a different intra-operative plan than the same diagnosis with a pediatric surgeon. In adult centers, the patient would undergo a complete staging laparotomy that includes, among additional steps, systematic lymphadenectomy, with demonstratable

surgery-related morbidity, and may be considered over-treatment in more than 80% of cases.[18] The LION trial[19] reported no improved outcomes and higher complication and mortality rates associates with lymphadenectomy, with longer operative times, blood loss, transfusion requirements, and intensive care stays. In contrast, a frozen section diagnosis of immature teratoma in the hands of a pediatric surgeon, with appropriate COG-based staging is associated with much less morbidity, as it is driven by lymph node biopsy of abnormal clinical findings only. These surgical differences highlight the potential value that an intra-operative test might provide both in directing appropriate staging maneuvers and thereby avoiding unnecessary procedures. In our study, the frozen section was unable to provide definitive direction. In an ongoing COG trial AGCT1531, all patients with Stage 1 immature teratoma, regardless of grade, will be observed after initial surgery. At present, we are without a sensitive intra-operative test that will direct appropriate staging procedures, while preventing over-staging and the attendant difficulties with these surgeries.

The limitations of this study relate primarily to the small sample size and missing data. This is due in part to the relatively rare nature of pediatric malignant ovarian gem cell tumors with recruitment of only 131 tumors over the nearly 8- year period of the study. As frozen section was not required by protocol and is not standard practice for pediatric ovarian tumors, the proportion of patients who had frozen section done was also limited. We feel this sample, however, is representative of clinical practice. Eighty-four participating institutions enrolled between one and five ovarian germ cell tumor patients each. This suggests that the experience of institution pathologists may be limited and may have contributed to the observed findings. Only malignant tumors were included in this study; however, the intent of this study was to evaluate the accuracy of frozen section to guide extent of surgical staging for malignant ovarian germ cell tumors in the pediatric and adolescent population.

In the pediatric population compliance with surgical staging ranges from 24–27%. If frozen section was a reliable aid in identifying malignant elements, it would potentially improve adherence with COG staging recommendations.[20, 21] Table 5 presents how frozen section might impact intra-operative decision making regarding extent of staging in the pediatric population with malignant germ cell tumor of the ovary. However, with 38.3% of cases having an incorrect diagnosis, we cannot recommend frozen section analysis as a reliable means of identifying malignant components in this population of patients. Rather, we strongly advocate for complete surgical staging as recommended by the Children’s Oncology Group Germ Cell Tumor Committee. Imaging alone as a guide to directing surgical planning and staging, is not sufficiently sensitive nor specific as shown by Billmire et al. where 54% of ovarian tumors that would be presumed to be benign on pre-operative imaging contained malignant elements in addition to teratoma.[14] Complete staging should occur in any pediatric and adolescent patient presenting with an ovarian tumor and must include sampling of peritoneal fluid for cytology, complete evaluation of the peritoneal surfaces with biopsy of suspicious nodules, evaluation of the omentum and resection where abnormal, evaluation of the retroperitoneal lymph nodes and biopsy of abnormal nodes with intact removal of the ovarian tumor whenever possible. Complete staging can be completed with no added morbidity and substantially impacts the care plan.

Finally, as this protocol involved only malignant nongerminomatous ovarian germ cell tumors, we have no data regarding the accuracy of frozen section for confirming benign disease. For malignant histology, an accurate confirmation in 61.7% of patients is not sufficient for proper intra-operative decision-making regarding extent of surgical procedure. Reliable confirmation of benign histology would also be important however, as an erroneous frozen section diagnosis of malignancy could lead to over-staging and the possibility of unnecessary morbidity. Our data indicate that frozen section alone should not be used by surgeons in the management of ovarian germ cell tumors.

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Highlights

- Most malignant ovarian tumors in the pediatric and adolescent population are Germ Cell tumors
- Intra-operative frozen-section widely used in adult population of epithelial-based ovarian tumors.
- Compliance with surgical staging for malignant germ cell tumors of the ovary is lower than desired.
- Frozen section is not reliable to inform the extent of surgical staging required for MGCT

Table 1:

Children's Oncology Group Staging Criteria for Malignant Ovarian Germ Cell Tumors.[11]

Stage	Ovary
I	Limited to ovary, no clinical, histological, or radiological evidence of disease outside of ovary
II	Microscopic residual, peritoneal evaluation negative, failure of tumor markers to normalize
III	Lymph node involvement, metastatic nodule, gross residual disease or biopsy only, contiguous visceral involvement (omentum, intestine, bladder), peritoneal evaluation positive for malignant disease.
IV	Distant metastatic disease, including liver.

Table 2:

Baseline characteristics of eligible ovarian germ cell tumor patients from AGCT0132.

Patient Characteristic	Low Risk		Intermediate Risk	
	N (%) or Median (Range)		N (%) or Median (Range)	
	FS & Institutional Reports Available	FS or Institutional Reports Not Available	FS & Institutional Reports Available	FS or Institutional Reports Not Available
N	9	15	51	56
Age (yrs)	13 (9 – 16)	12 (0.9 – 16)	12 (0.9 – 20)	12 (5– 18)
Stage				
I	9 (100%)	15 (100.0%)	-	-
II	-	-	26 (51.0%)	20 (35.7%)
III	-	-	25 (49.0%)	36 (64.3%)
AFP (ng/mL)	925 (19 – 344830)	3199 (3 – 56221)	3220 (2 – 280003)	3610 (2 – 4233000)
BHCG (mIU/mL)	0 (0, 4)	2 (0.60, 21000)	2 (0, 926870)	2 (0, 999140)
Central Review	9 (100%)	15 (100.0%)	44 (86.3%)	50 (89.3%)
Frozen Section (FS)	9 (100%)	0 (0%)	51 (100%)	4 (7.1%)

Table 3:

Frozen section diagnosis for low- and intermediate-risk patients. It should be noted that all were diagnosed as malignant based on institutional reports.

Frozen Section Classification	Low Risk N (%)	Intermediate Risk N (%)	Total N (%)
N =	9	51	60
Malignant	6 (66.7%)	31 (60.8%)	37 (61.7%)
Benign	1 (11.1%)	7 (13.7%)	8 (13.3%)
Immature teratoma only	1 (11.1%)	9 (17.6%)	10 (16.7%)
Germ cell NOS *	1 (11.1%)	2 (3.9%)	3 (5.0%)
No diagnosis	0 (0.0%)	2 (3.9%)	2 (3.3%)

* NOS: Not Otherwise Specified

Table 4:

Central review findings compared to institutional reports.

Central Review	Low Risk	Intermediate Risk	Total Patients
N	24	94	118
Findings Agree with Institutional Report	18 (75%)	72 (76.6%)	90 (76.3%)
Additional Malignant Histology	3 (12.5%)	9 (9.5%)	12 (10.2%)
Additional Findings of Teratoma	1 (4.2%)	8 (8.5%)	11 (9.3%)
Missed Malignant Elements	0 (0%)	4 (4.2%)	4 (3.4%)
Discrepancy in Grading IT	0 (0%)	1 (1.1%)	1 (0.8%)

Table 5:

Impact of intra-operative frozen section results on operative decision-making.

Frozen Section Report	Leads to PROPER staging	Leads to UNDER staging	NOT helpful in staging
Yolk sac, embryonal, choriocarcinoma, malignant germ cell tumor	**x**		
Benign teratoma		**x**	
Immature teratoma[#]	**X**	**x**	**x**
No guiding decision on frozen section, defer to permanent section, Germ cell tumor NOS[*]			**x**

[*] NOS – not otherwise specified

[#] Management of immature teratoma differs between adult and pediatric oncologist.