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IMPACT OF CENTRAL SURGICAL REVIEW IN A STUDY OF MALIGNANT GERM CELL TUMORS

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Abstract

BACKGROUND—Verification of surgical staging has received little attention in clinical oncology trials for both children and adults. Central surgical review in a study of malignant pediatric germ cell tumors provided an opportunity to assess the impact of this process.

METHODS—Children’s Oncology Group study AGCT0132 data submission at study entry required operative note, surgical checklist, pathology and imaging reports. Central surgical review during the study included assessment for completeness of submitted data and confirmation of assigned stage. Review resulted in one of three conclusions: assigned status confirmed, assignment withheld pending review of additional information requested, or institutional assignment of stage disputed with reasons for recommended stage assignment explained. Changes in stage assignment based on central surgical review were left at the discretion of the enrolling institution.

RESULTS—206 patients underwent central review. Failure to submit required data elements or need for clarification was noted in 40%. Disagreement with stage assignment occurred in 10%; the highest rate of discordance was in ovarian tumors submitted as stage I (34%). 17 of 21 discordant

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patients were reassigned to the stage recommended by central review. 4 patients with ovarian tumors not meeting central review criteria for Stage I remained in that stratum by institutional decision. Two-year event free survival (EFS) in Stage I ovarian tumor patients was 25% (1/4) for discordant patients compared to 57% (9/21) in patients who met Stage I criteria by central review.

CONCLUSIONS—Central review of stage assignment by a dedicated study surgeon improved collection of complete data and assignment of correct tumor stage at study entry, and allowed for prompt initiation of chemotherapy in patients determined not to have Stage I disease.

Keywords
surgical quality; malignant germ cell tumors; surgical clinical trials

Introduction
Oncology clinical trials require careful and accurate data collection for reliable interpretation. Although the details for administration and monitoring of chemotherapy and radiation are specifically defined and recorded, the surgical aspects of cancer treatment have been less rigorously evaluated. The concept of quality assessment in surgical oncology has had limited attention. In most studies, surgical data have been assumed to be consistent or reviewed only in retrospect. It is difficult to define and monitor the technical details that may be important for a given procedure. This has the most impact when adjuvant therapy is stage dependent for a planned protocol, and surgical details relevant to stage assignment are not scrutinized. 1, 2

Most studies of pediatric cancer require multi-institutional trials carried out over several years and are particularly challenging. Available studies of surgical factors in pediatric solid tumors have revealed frequent lack of compliance with existing guidelines which may have an impact on stage assignment and outcome. 3–8 In some studies, retrospective analysis of the required elements of the surgical staging procedure has permitted evidence based modification for the surgical approach to the tumor. 5, 9 The goal of accurate and appropriate surgical staging may be accomplished by the timely confirmation and review of complete data collection. Real time review of operative information while a study is ongoing can provide an opportunity for dialogue with the individual centers to clarify details in the operative notes, capture missing data, confirm appropriate staging assignment, and allow quality assessment and education.

METHODS
The Children’s Oncology Group (COG) protocol AGCT 0132 was designed to investigate a surveillance strategy after complete tumor excision for low risk gonadal tumors, and reduced chemotherapy for intermediate risk pediatric extra cranial malignant germ cell tumors (MGCT). The low risk (LR) stratum included Stage I tumors of the testis and ovary. Low risk tumors were treated with surgical resection and surveillance only, and compressed platinum based chemotherapy (PEB) was reserved for patients with persistently elevated markers or evidence of relapse. The intermediate risk (IR) stratum included Stage I-II extragonadal tumors, Stage II-IV testicular tumors, and Stage II-III ovarian tumors.
Intermediate risk tumors were treated with resection and compressed platinum based therapy at diagnosis. IRB approval was obtained at all participating centers. Required malignant histology included at least one of the following: yolk sac, choriocarcinoma, or embryonal carcinoma. Patients with pure germinoma, pure immature teratoma and those with additional somatic malignancies were excluded.

Required data at enrollment included submission of “on study” form, operative note, surgical checklist, institutional pathology report, and reports of imaging studies for evaluation of metastasis at diagnosis. Central review of pathology was also done. Assignment to the surveillance strategy for Stage I testis and ovary patients required strict adherence to COG surgical guidelines to ensure accurate assessment.

Data monitoring during the study revealed a higher than expected event rate in the low risk stratum and enrollment was temporarily suspended. This was due to a miscalculation in the failure model that predicted a uniform rate of relapse events over the first three years, when most relapses occurred within one year. The low risk arm was reopened with increased monitoring to include rapid central surgical review of the data by a COG study surgeon within 72 hours of enrollment. Those patients submitted for enrollment as intermediate risk (Stage I extragonadal, Stage II and III gonadal and extragonadal tumors, Stage IV testicular tumors) also underwent central surgical review while the study remained open, but without the 72 hour deadline (real time review). Data were submitted and catalogued through the electronic remote data entry system (eRDS) and study surgeons were sent electronic notification that data were available for review. Review of the operative note, pathology report, surgical checklist and imaging findings was undertaken to confirm stage status for all patients. Any missing data forms or discrepancies in submitted data generated a request by the study surgeon to the enrolling institution for additional information and/or clarification. Central stage assignment was completed after requested information was submitted or clarified by the enrolling institution. If the study surgeon concluded that the patient should have a different stage assignment, this was communicated to the institutional investigator and action on the evaluation was at the discretion of the enrolling institution.

A retrospective analysis of those patients undergoing central surgical review was done. The number of patients in whom additional data was requested to assess status was determined. The number and final stage assignment for those patients who did not meet central review criteria for their enrolled stage was also determined.

Event free survival (EFS) was defined as the time from enrollment to disease progression, death from any cause, diagnosis of a second malignant neoplasm, or last follow-up whichever occurred first. Patients who did not experience disease progression, death or second malignancy were considered event-free at last contact; all other patients were considered to have experienced an event. EFS as a function of time since enrollment was estimated by the method of Kaplan and Meier. Event free survival was examined for those who were concordant and discordant with central review. Because a small number of patients was considered discordant, the calculation of meaningful statistical tests was prevented.
RESULTS

Of the 286 patients on the protocol, 206 were enrolled after central review was instituted. The number of patients in whom there was discordance between institutional stage assignment and central review of stage is shown in Table 1. Central review of the assigned stage was confirmed in 90% of patients overall ranging from 66% in Stage I ovarian tumors to 97% in Stage I testicular tumors. Disagreement in stage assignment was noted in all categories. The highest rate of discordance was in stage I ovarian tumors. Seven of 21 (34%) eligible patients with Stage I ovarian tumors were under-staged due to incomplete staging or failure to meet stage definition. Although 3 of 7 had their stage at enrollment changed to a higher stage as recommended by central review, 4 remained in the low risk stratum at the discretion of the enrolling institution. Event free survival for the patients with Stage I ovarian tumors was 57% (12/21) in those who were concordant by central review and 25% (1/4) in those who did not meet criteria for Stage I by central review. All other patients in whom there was discordance of stage assignment after central review were changed to the recommended stage and received protocol chemotherapy as appropriate for the revised stage. Additional information or requests for clarification were noted in 40% of patients overall with a range of 17–52% by stage. The information requests included need for submission of one of the required forms and/or clarification of inconsistencies regarding interpretation of findings in the operative, pathology or imaging reports. Missing data for ovarian tumors were most often the reports of peritoneal cytology or imaging findings. Missing data for testis and extragonadal tumors were most often imaging results.

Specialty of operating surgeon was examined for ovarian primary tumors and confirmed the variety of surgical providers for this patient population. For the 99 patients in which specialty of the operating surgeon could be determined, 71 were pediatric surgeons, 14 were gynecologic oncologists, 9 were gynecologists and 3 cases were done by 2 specialists (pediatric surgeon/gynecologic oncologist, general surgeon/gynecologic oncologist, general surgeon/gynecologist).

Discussion

Anatomical staging is the traditional basis for treatment and prediction of prognosis for all solid tumors. Although anatomic constraints during an individual operation preclude a fixed surgical approach to every patient, there are many components of a staging procedure that may be objectively categorized. Increasing knowledge based on patient characteristics and tumor biology has led to modified and more complex risk-adapted strategies. Although details for chemotherapy and radiation therapy are quite specific and carefully monitored in most protocols, compliance with guidelines for surgery has received limited attention. Anatomic and procedural factors that impact risk assignment are understudied. This is particularly problematic in pediatric tumors since the incidence is quite low and each institution will contribute only a small number of patients to each protocol. In addition, the child may be operated on by surgical specialists with training in a variety of pediatric and adult disciplines, and there is no shared mechanism for education regarding staging procedures across these specialties. Retrospective review of compliance with surgical guidelines in several pediatric solid tumor studies revealed compliance of 84% in a study of
neuroblastoma,\textsuperscript{9} 3\% in a study of ovarian germ cell tumors,\textsuperscript{5} 69\% in testicular germ cell tumors,\textsuperscript{4} and 57\% in paratesticular rhabdomyosarcoma.\textsuperscript{8} This is particularly relevant when intensity of treatment depends on stage assignment. In a study of patients enrolled on the National Wilms Tumor Study 4, Shamberger et al\textsuperscript{3} demonstrated a 6-fold increase in relative risk for relapse in stage I patients in whom lymph nodes were not biopsied as expected for stage assignment. This discrepancy in risk was not seen in the higher stage patients who received more intensive chemotherapy. An interesting finding was also seen in a study of neuroblastoma.\textsuperscript{9} In this review of patients with localized neuroblastoma, patients without lymph node biopsy were separated into two categories: those in whom lymph nodes had been sought but none were found (22.8\%) and those in whom lymph nodes were present but the surgeon chose not to biopsy. Survival was superior in those who had lymph nodes sought but not found, compared to those assumed to have normal nodes that were not biopsied. This finding also emphasizes the importance of documentation rather than assumption in stage assignment. For those children with Stages B/C tumors one year of age and older: 5-year survival was 69\% in those who had lymph nodes sought and 40\% in those who did not. This study also reviewed the location and yield of lymph node biopsies to provide an objective recommendation for subsequent surgical guidelines. For each anatomic area of primary tumor, documentation of search for lymph nodes in specific locations, with biopsy of any nodes found, was required.

A review of surgical compliance in pediatric malignant ovarian germ cell tumors also demonstrated excellent outcome despite failure to follow traditional staging guidelines that were based on adult epithelial cancers. Based on the yield of each component of the staging procedure that was performed, new guidelines were proposed for malignant pediatric ovarian germ cell tumors.\textsuperscript{5} The observation that random biopsies of normal tissues for pediatric malignant ovarian germ cell staging has negligible yield has been further confirmed in a subsequent study of malignant pediatric ovarian tumors of varied histology.\textsuperscript{11} Both of these studies demonstrate the value of careful review of data in evaluating extensive guidelines based on tradition. The guidelines may be modified based on objective data to minimize surgical morbidity, while retaining those components of the surgical procedure that contribute useful staging information.

Germ cell tumors are rare and complex malignancies with multiple anatomic primary sites and histologies. Advances in chemotherapy have allowed successful treatment for the majority of these patients, but with significant toxicities and long-term effects. Surgical therapy also carries inherent risks and complications. In the previous pediatric intergroup study for malignant germ cell tumors, scrotal violation in testicular tumors was associated with a significant decrease in event-free survival.\textsuperscript{4} In the ovarian tumors, peritoneal cytology was recognized to be an important component of the staging procedure. Sixteen of 58 (28\%) of specimens obtained in stage III ovarian patients revealed malignant cells. Five of 58 girls were recognized to be stage III by the peritoneal cytology findings alone and would otherwise have been mistakenly assigned to stage I.\textsuperscript{5} Surgical overtreatment and morbidity was seen in six girls who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy that was not recommended by protocol and one had iliac artery injury from lymph node dissection.\textsuperscript{5} A retrospective study of post surgical surveillance for ovarian germ cell tumors from France noted an increase in tumor events in those patients who had
incomplete staging. In the current study, tumor events were also seen more frequently in those who did not meet central review criteria for Stage I surveillance.

An additional benefit of real time review was the opportunity for interaction with the enrolling institutions. Clarification of uncertainties and discrepancies in operative, imaging and pathologic data improved accuracy. Feedback on discordance with stage assignment provided an educational opportunity for the enrolling institutions. Lack of clarity in the description of details in staging information in the protocol was exposed and provided an opportunity to improve descriptions and definitions for future protocols. The ability to communicate electronically in a secure fashion demonstrated the feasibility of successful confirmation of complete data submission and review within a 72 hour time frame when needed.

As risk groups are defined that allow a reduction in chemotherapy for solid tumors based on surgical stage, it is imperative that the details of the anatomic information be assessed for accuracy, completeness and relevance. Acknowledgment that the surgical procedure has an impact on outcome is important in advancing the care of these patients. Many components of surgical staging procedures are based on tradition rather than evidence based. Analysis of surgical procedures requires complete data collection to allow critical appraisal of the relevant operative details. Incomplete information should not be assumed to be negative as seen with the findings from peritoneal cytology sampling in malignant ovarian germ cell tumors, and in the lymph node studies in Wilms tumor and neuroblastoma. The application of a real time review of the data submission at entry by a dedicated study surgeon in this study revealed questions or incomplete data submission in 41% of patients, and a discrepancy between institution and study surgeon stage assignment in 3–34% of patients. Data requests by the study surgeons allowed retrieval of complete information, and provided an opportunity to undertake a detailed analysis of the potential risk factors for relapse events related to the anatomic findings. Improved assignment of stage at study entry allowed timely chemotherapy for those patients recognized to be greater than stage I and allowed event rates to be more accurately calculated. The inclusion of real time surgical review of data in solid tumor protocols at all ages and in all tumor types should be encouraged to assist in achieving complete anatomic and staging information that is consistent and reliable. Proper assignment of tumor stage will lead to more accurate interpretation of treatment protocols and improved design of future trials.

References


Table 1
Summary of real time review findings by stage with impact on stage assignment.

<table>
<thead>
<tr>
<th>SITE (total # eligible submitted as listed stage with review)</th>
<th>ADDITIONAL INFORMATION REQUESTED TOTAL (%)</th>
<th>REVIEW CONFIRMED STAGE TOTAL (%)</th>
<th>REVIEW SHOWED HIGHER STAGE AND STRATUM ASSIGNED CHANGED TOTAL (% eligible)</th>
<th>REVIEW SHOWED HIGHER STAGE BUT STRATUM ASSIGNMENT NOT CHANGED TOTAL (% eligible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW RISK</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAGE I OVARY (21)</td>
<td>6/21 (29%)</td>
<td>14/21 (66%)</td>
<td>3/21 (14%)</td>
<td>4/21 (19%)</td>
</tr>
<tr>
<td>STAGE I TESTIS (60)</td>
<td>26/60 (43%)</td>
<td>58/60 (97%)</td>
<td>2/60 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>INT RISK</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAGE II/III OVARY (77)</td>
<td>40/77 (52%)</td>
<td>71/77 (92%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>STAGE II–IV TESTIS (18)</td>
<td>5/18 (28%)</td>
<td>15/18 (83%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>STAGE I–II EXTRAGONADAL (30)</td>
<td>5/30 (17%)</td>
<td>27/30 (90%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>