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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. Central surgical review was undertaken during a study of malignant pediatric germ cell tumors.
Methods: Children's Oncology Group study AGCT0132 included central surgical review during the study. Completeness of submitted data and confirmation of assigned stage were assessed. Review responses were: assigned status confirmed, assignment withheld pending review of additional information requested, or institutional assignment of stage disputed with explanation given. Changes in stage assignment were at the discretion of the enrolling institution.
Results: A total of 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% with 17/21 discordant patients reassigned to stage recommended by central review. Four ovarian tumor patients not meeting review criteria for Stage I remained in that stratum by institutional decision. Two-year event free survival in Stage I ovarian patients was 25% for discordant patients compared to 57% for those meeting Stage I criteria by central review.
Conclusions: Central review of stage assignment improved complete data collection 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.

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. This is a descriptive study of a completed protocol for malignant germ cell tumors in children that employed rapid review for a subset of the enrolled patients.

1. 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

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(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–III 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 caused by 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 (pediatric oncologist) and action on the evaluation was at the discretion of the enrolling institution. There was no required involvement of the designated COG surgeon at each institution to review the surgical data form.

A retrospective analysis of those patients undergoing central surgical review was done. The number of patients in whom additional data were 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 consider 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 [10]. 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.

2. 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. Only Stage I gonadal tumors were reviewed in rapid fashion and provided an opportunity to reassign stage prior to planned therapy. Review of the Stage II and III patients usually occurred after chemotherapy was completed and stage was not reassigned at that time.

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 because of 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. Reasons for stage discrepancy in the four discordant patients included evidence of tumor rupture documented in the operative note and or pathology report in three cases and failure to collect peritoneal cytology in one. Relapse events in less than 4 months were seen in the patient with no peritoneal cytology collected and in two of those with rupture. 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 (Fig. 1).

All other stage I 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 request for clarification was noted in 40% of patients overall with a range of 17%–52% by stage. The information requests included the 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 is not a required data point but 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).

3. 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 stage 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 [9], 3% in a study of ovarian germ cell tumors [5], 69% in testicular germ cell tumors [4], and 57% in paratesticular rhabdomyosarcoma [8]. This is particularly relevant when intensity of