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Is Adjuvant Chemotherapy indicated in Ovarian Immature Teratoma? A Combined Data Analysis from The Malignant Germ Cell Tumor International Collaborative (MaGIC)

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Condensed Abstract: Grade is the most important risk factor for relapse in ovarian immature teratoma, and there were no relapses in patients with Grade 1 tumors, irrespective of stage, or age. Postoperative adjuvant chemotherapy did not decrease the risk of relapse in the pediatric patients, but its role in adults remains unclear.

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Abstract

Background: There is debate regarding management of ovarian immature teratomas (IT). In adult women, postoperative chemotherapy is standard, except for Stage I, grade 1 disease, whereas surgery alone is standard in pediatric patients. To determine the role of chemotherapy, we conducted a pooled analysis of pediatric and adult clinical trials.

Methods: Data from seven pediatric and two adult trials were merged in the MaGIC dataset. Four trials included patients with newly diagnosed pure ovarian IT and were selected (INT 0106, GC2, GOG 0078 and 0090). Adult and pediatric trials were analyzed separately. Primary outcome measures were event-free (EFS) and overall survival (OS).

Results: One hundred and seventy-nine patients were included (98 pediatric; 81 adult). Ninety pediatric patients were treated with surgery alone whereas all adult patients received chemotherapy. The 5 year EFS and OS were 91% and 99% in pediatric cohort compared with 87% and 93% in adults. There were no relapses in grade 1 patients, irrespective of stage or age. Only one adult patient with grade 2 IT relapsed. Among grade 3 patients, the 5 year EFS for Stage I/II was 0.92 (0.72-0.98) compared to 0.52(0.22-0.75) (p=0.005) for Stage III in pediatric cohort and 0.91(0.69-0.98) compared to 0.65(0.39-0.83) (p=0.01) in adult cohort. Postoperative chemotherapy did not decrease relapse in pediatric cohort.

Conclusion: Grade is the most important risk factor for relapse in ovarian IT. Among grade 3 patients, stage was significantly associated with relapse. Adjuvant chemotherapy did not decrease relapse in pediatric cohort, its role in adults remains unresolved.

Introduction

Immature teratomas (IT) of the ovary represent about 1% of ovarian tumors. IT are a specific histological subtype of germ cell tumor (GCT) and are composed of tissues derived from all three embryonic layers, namely mesoderm, endoderm and ectoderm. They are graded based on the proportion of tissue containing immature neural elements. The grade and stage of these tumors have been shown to be of prognostic significance and are therefore used to make therapeutic decisions.[1, 2]

There is no consensus on the management of patients with ovarian IT. Significant differences exist between pediatric and adult groups about the necessity and utility of chemotherapy for patients with higher grade and stage disease. Therapeutic recommendations in adult women are based on two seminal studies. In 1976, Norris et al performed a retrospective analysis of 58 patients, and observed an 18% recurrence rate in grade 2 tumors and 70% recurrence in grade 3 tumors, resulting in the recommendation to use chemotherapy for grade 2 and 3 tumors[3]. Gershenson et al reported outcomes of 41 patients with Stage I-IV ovarian IT and observed recurrences in 94% of patients treated with surgery alone compared with 14% in patients treated with surgery and chemotherapy[4]. Henceforth, the standard of care for adult women with ovarian IT has been postoperative chemotherapy for all patients except Stage I, grade 1 tumors.

Clinical practice in children has been led by evidence provided by a pediatric intergroup trial INT 0106 conducted in the US. Patients with completely resected ovarian IT were observed closely without postoperative chemotherapy[5, 6]. Forty-four patients with completely resected ovarian IT were enrolled; 31 patients had pure IT with tumor grade 1 (n=17), 2 (n=12) or 3

(n=2). Thirteen patients had microscopic foci of yolk sac tumor (YST). Gliomatosis peritonei (GP) was present in 27% of patients and three of the sixteen patients with lymph node sampling had nodal gliomatosis. At four years, the event-free survival (EFS) was 97.7% with an overall survival (OS) of 100%. This study concluded that surgery alone is curative for children with completely resected ovarian IT, regardless of grade or presence of microscopic foci of YST[5]. A similar study conducted in the United Kingdom followed 124 patients with IT (54 ovarian) after surgical resection. Eleven patients had GP and six patients had nodal gliomatosis. The EFS and OS was 85.9% and 95.1%, respectively and the authors concluded that treatment of ovarian IT is primarily surgical[7].

To highlight these differences and gain clarity on the role of postoperative chemotherapy in the management of pure IT of the ovary, we conducted a pooled analysis. The Children's Oncology Group (COG) and the Children's Cancer and Leukemia Group (CCLG) agreed to merge 25 years of clinical trial data on pediatric GCT to form the Malignant Germ Cell International Collaborative (MaGIC). Subsequently data from the Gynecologic Oncology Group (GOG) GCT clinical trials were added. This report presents our analysis of pediatric and adult patients with ovarian IT. We compare these two groups and identify similarities and differences, with the goal of establishing a uniform treatment approach across all age groups. Data from some of these trials have been previously published as separate reports[5, 7, 8].

Methods

After signing a memorandum of understanding, which specified the variables to be included and how data were to be de-identified, patient data from seven GCT clinical trials conducted by COG or CCLG between 1983 and 2009 were included in the MaGIC dataset. Data from two GOG clinical trials were added subsequently. Four of the nine trials included patients with IT. These were INT 0106 (COG), GC 2 (CCLG), GOG 0078 and GOG 0090. Each study had different eligibility criteria for inclusion of IT patients. The INT 0106 study included patients up to 21 years of age with biopsy proven IT, Stages I and II, grades 1-3. Presence of GP within the abdomen or pelvis did not result in upstaging in this study. The GC2 study included patients younger than 16 years with biopsy proven IT, all stages and grades. The pediatric studies included IT at all sites in both genders. The GOG 0078 study included patients with IT, Stage I, grades 2 and 3, completely resected Stage II and III, all grades. The GOG 0090 protocol included patients with incompletely resected Stage II, III and IV, grades 1-3. Each trial had received research ethics board approval from the relevant agencies. This project was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board.

From the larger dataset, we selected only females with newly diagnosed, pure IT of the ovary. Patients with mixed malignant GCT of the ovary and patients with extragonadal IT were excluded. Patient characteristics that were included in the dataset were age at diagnosis, histology, tumor markers, stage, grade, whether adjuvant chemotherapy was administered, and clinical outcome.

Staging

Patients treated on GOG protocols were staged using the FIGO staging[9], whereas pediatric patients were staged using the COG or CCLG staging systems[5, 7]. There are several differences

between the COG/ CCLG staging system and the FIGO staging system. For instance positive peritoneal washings is Stage III in COG staging, but can be Stage Ic or IIc in FIGO. Similarly positive lymph nodes are Stage III in FIGO, but are Stage II in COG if less than 2 cms and Stage III if greater than 2 cms. Extension to pelvis is Stage IIb in FIGO and Stage III in COG. Due to irreconcilable differences in staging between these systems, adult and pediatric patients were analyzed separately. A few adolescents were treated on GOG protocols. They were analyzed with the adult cohort as they were staged and managed following the adult treatment algorithm. Within the pediatric staging systems, a major difference between the COG and the CCLG systems was that the presence of GP in the COG system did not result in upstaging of Stage I patients, whereas in the CCLG system, patients with GP were classified as Stage III. To resolve this discrepancy, we retrospectively applied the CCLG staging to COG patients, so that all patients with GP were defined as Stage III disease.

Grading

All tumors required central pathology review at the time of enrollment by the respective cooperative group pathologist to confirm histology and were graded according to the criteria by Norris et al.[3] and Robboy and Scully[10]. Grade 1 was defined as immature tissue present in <1 low power field (LPF) (x 4) /slide, grade 2 as immature tissue 1-3 LPF/slide and grade 3 as >3 LPF/slide.

Tumor markers

Serum alpha-fetoprotein (AFP) levels were available for most patients, and they were classified as being normal if <10 ng/ml, and elevated if ≥10 ng/ml. Patients with AFP >1000 ng/ml were

excluded, as this level of AFP elevation was considered more likely to indicate malignant GCT elements, warranting more aggressive treatment[11].

Treatment

Complete surgical excision at diagnosis was undertaken when feasible. In the pediatric trials (INT 0106 and GC2), chemotherapy was not recommended after surgery. However, some patients did receive chemotherapy immediately after surgery at the discretion of the treating physician. In the GOG trials (GOG 0078 and GOG 0090), chemotherapy was administered postoperatively for all patients.

Statistical analysis

The primary outcomes were EFS and OS. EFS was defined as the time interval from date of diagnosis to relapse or progression, second malignancy, death, or date last seen (whichever occurred first). Patients who experienced a relapse, progression or second malignancy were considered to have experienced an event; otherwise the patient was censored at last contact. OS was defined as the time interval from date of diagnosis to death or date last seen (whichever occurred first). Patients who died, regardless of cause were considered to have experienced an event; otherwise the patient was censored at last contact.

The effects of various factors including age at diagnosis, stage, grade, tumor marker levels, and treatment received on risk for EFS-event or death were estimated using relative risk regression[13]. We constructed survival curves using the Kaplan-Meier method [12]. Ninety-five percent confidence intervals for the Kaplan-Meier estimates at specified time points were calculated by using the complementary log-log transformation.[13] The two-sided log-rank test to compare EFS

across groups defined by the risk factors[13] was used to assess the prognostic significance of the characteristics with P-values <0.05 considered significant.

For adult patients, a backwards stepwise procedure was used to identify factors that were significantly associated with risk for an EFS-event. A selection probability of 0.05 was used to retain factors in the model. Because of issues with colinearity of predictor variables, only stage and grade could be entered into the starting model for the selection process. All analyses were conducted using Stata version 13.1 (College Station, TX).

Results

A total of 193 patients with pure ovarian IT were identified from the four clinical trials. Six pediatric patients were excluded as they had mixed malignant GCT on central review. Eight adult patients were excluded; seven patients had recurrent IT at time of enrollment and one patient had mixed malignant histology on central review. One hundred and seventy-nine patients with pure IT were included in the final analysis; 98 patients were treated on the pediatric trials and 81 patients treated on adult GOG trials.

Characteristics, Treatment and Outcome of Pediatric Patients

Characteristics of the pediatric patients are presented in Table 1. The mean age at presentation was 10 years (range 0-17 years). Sixty percent of patients had Stage I disease. The mean serum AFP was 83 ± 182.7 ng/ml. Ninety of the 98 patients were treated with surgery alone and eight patients received postoperative chemotherapy. Median follow up was 6.8 years (range 1.7-14 years)

Nine of the 98 patients relapsed, with a 5-year EFS and OS of 0.91 (0.84-0.95) and 0.99 (0.93-1.00), respectively. As shown in Table 2, there were no relapses in patients with grade 1 or

grade 2 tumors, irrespective of stage. Among patients with grade 3 tumors, 8/38 patients (21%) relapsed. Stratifying grade 3 tumors by stage (Fig 1), the estimated 5-year EFS for patients with grade 3, Stage I and II disease was 0.92 (0.72-0.98), compared with 0.52 (0.22-0.75) for grade 3, Stage III patients (p=0.005). The OS for all grade 3 patients, irrespective of stage was 100 percent. Neither age at diagnosis nor AFP level was related significantly to the risk of relapse. Administration of postoperative chemotherapy did not decrease the risk of relapse in the pediatric cohort.

Table 3 outlines the clinical characteristics of the nine pediatric patients who relapsed. All but one of the nine patients were salvaged, three with surgery alone.

Characteristics, Treatment and Outcome of Adult Patients

Characteristics of the 81 adult patients are outlined in Table 4. Fifty-six percent of patients had grade 3 disease, compared with 39% in the pediatric cohort. Additionally, 7% of adult patients, but no pediatric patients, had Stage IV disease. The mean AFP was 63.17 ± 155.18 ng/ml. All patients, regardless of stage, were treated with chemotherapy after surgery. Median follow up was 12 years (range 0.3-21.9 years)

Eleven of the 81 patients relapsed, with an estimated 5-year EFS and OS of 0.87 (0.77-0.93). and 0.93 (0.85-0.97) respectively. There were no relapses in patients with grade 1 tumors, irrespective of tumor stage. Among patients with grade 2 tumors, only 1 of 27 patients (3.7%) relapsed; this patient had Stage IIIc disease. Among patients with grade 3 tumors, 9 of 45 patients (20%) experienced a relapse. Stratifying grade 3 disease by stage, the estimated 5-year EFS for patients with grade 3, Stage I and II disease was 0.91 (0.69-0.98) compared with 0.65 (0.39-0.83) for grade 3, Stage III and IV disease (p = 0.01). The estimated 5-year OS for grade 3,

Stage I and II disease was 0.91 (0.68-0.98) compared with 0.88 (0.61-0.97) for grade 3, Stage III and IV disease (p = 0.41) (Fig 2).

Extent of resection was not available in the database, however the eligibility criteria for the adult sudies (GOG0078 and GOG0090) were based on stage and extent of resection. Patients with Stage III disease were enrolled on GOG0078 if they had complete resection and GOG0090 if they had incomplete resection. Stage IV patients were enrolled only on GOG0090. Stratifying grade 3, Stage III patients by protocol, the observed 5-year EFS was 0.75 (0.13-0.96) for GOG0078 and 0.67 (0.28-0.88) for GOG0090. As the numbers were so small (9 patients on GOG 0090 and 4 patients on GOG 0078), log rank test for this comparison was not performed.

Stepwise selection identified grade and stage as significantly associated with risk of relapse (Table 5). Age at diagnosis and AFP level were not significant risk factors for relapse. As all the adult patients received postoperative chemotherapy, the effect of surgery versus chemotherapy could not be assessed. Table 6 shows the clinical characteristics of the patients who relapsed. Six of the eleven patients died.

Discussion

This combined analysis was performed in an attempt to simultaneously compare pediatric and adult patients with ovarian IT, to identify common risk factors and compare outcomes in two cohorts with different treatment strategies. Our analysis shows several striking similarities in the two groups, both in risk factors and in overall outcomes, despite differences in treatment. Risk factor analysis shows that for ovarian IT, grade is the most important risk factor for relapse across all age groups. In patients with grade 1 tumors there were no relapses, irrespective of stage. Among the 47 pediatric and adult patients with grade 2 tumors there was only a single

relapse. This was an adult patient with Stage IIIc disease. The majority of relapses occurred in patients with grade 3 tumors. Twenty percent of patients (17/83) with grade 3 tumors relapsed, 21% in the pediatric cohort compared with 20% in the adult cohort. For patients with grade 3 tumors the risk of relapse significantly differed by stage at presentation. Grade 3 patients with Stage I and II disease had an excellent EFS compared to Stage III and IV patients, in both the pediatric and adult cohorts. In addition to stage, completeness of resection influenced EFS. Adult patients were enrolled on two protocols, with eligibility based on stage and extent of resection. In grade 3, Stage III patients, the EFS was improved in patients with complete resection compared to those with incomplete resection.

There were important differences in the treatment approach between the pediatric and adult cohorts in our study. Only eight of the 98 pediatric patients received chemotherapy, whereas all 81 adult patients received postoperative chemotherapy. Despite this, the 5-year EFS and OS were higher in the pediatric cohort compared with the adult cohort. This difference in outcome is likely to be a reflection of tumor grade, rather than treatment. Tumor grading varied by age, and grade 1 tumors were more frequent in the pediatric cohort compared with adults (31% vs. 9%), whereas grade 3 tumors were more common in the adult cohort (56% vs. 39%). It is important to note that Stage I, grade 1 tumors were not enrolled in the adult GOG studies.

Other smaller studies have corroborated our results. Grade, stage and completeness of resection have been shown to be important risk factors for relapse[1,3,14]. In the study by Norris et al, the recurrence rate was 70% in patients with grade 3 tumors and 18% in patients with grade 2 tumors[3]. In a study by Gobel et al, including 116 patients with extracranial IT, 38 patients had incomplete resection. They found that immaturity in incompletely resected teratomas was a risk factor for relapse; there were no relapses in patients with completely resected IT, even amongst

grade 3 tumors[14]. It therefore appears that in patients with grade 3 tumors, stage and lack of complete resection are associated with increased risk of relapse.

Similar to our study, other pediatric studies have shown no benefit of adjuvant chemotherapy postoperatively in the management of ovarian IT. In a non-randomized study by Gobel et al, 76 patients were treated by surgery alone and 40 patients received adjuvant chemotherapy. There was no reduction in the number of subsequent relapses in the IT group receiving chemotherapy. However, risk factors were not balanced between the two treatment groups in this study[14].

In contrast to the pediatric data, chemotherapy has been used for all adult patients with pure ovarian IT except those with Stage I, grade 1 tumors [3, 4]. Vicus et al, reported on 34 women with ovarian IT, 32 of whom were Stage I, one was Stage IIB, and one was Stage IIIA. Three out of 32 patients with Stage I disease recurred, all of whom had grade 2 or 3 disease. Consequently they recommended surveillance only for Stage I, grade I tumors and chemotherapy for Stage I, grade 2 or 3 tumors[15]. Recently, several studies in adults have questioned the role of chemotherapy for IT. A multicenter Italian trial (MITO-9) reported on 28 patients with Stage I disease. Nineteen patients were treated with surgery alone, and nine patients received adjuvant postoperative chemotherapy. Four out of nineteen patients treated with surgery alone and 2/19 patients treated with adjuvant chemotherapy recurred. At recurrence, all patients were salvaged. The authors concluded that all patients with Stage I ovarian IT, regardless of grade, may be treated with surgery alone, with chemotherapy reserved for recurrence[16]. A UK study by Patterson et al adopted a close surveillance program post surgery for all Stage IA ovarian GCT. Four of fifteen patients relapsed, and only one of these patients could not be salvaged. They recommended surveillance for all Stage IA IT, regardless of grade[17]. Bonazzi et al undertook a

prospective trial of patients with pure ovarian IT. Surgery alone was recommended for patients with Stage I or II and grade 1 or 2 tumors. Twenty two patients were followed after surgery alone. Two patients relapsed after surgery alone, and were salvaged, leading to the conclusion that such patients may be treated with surgery alone[18]. In our adult cohort all patients received adjuvant chemotherapy and therefore we are unable to comment on its efficacy. However, the risk of relapse in the grade 3 patients was not different between the adult and pediatric cohorts (20% vs. 21%, respectively), despite major differences in management.

Our study has several limitations. It was a combined database analysis of patients treated on multiple studies; hence, there were missing data and different staging systems were used. Although a small number of pediatric patients and most adults were treated with chemotherapy, there was no explicit documentation of objective response to chemotherapy. In addition clinical details at relapse were missing for adult patients, including pathologic information and treatment at relapse. Despite these limitations, several important clinical messages may be drawn from our data.

In conclusion, our study shows that for all patients with ovarian IT, grade is the most important risk factor for relapse. In patients with grade 1 tumors, no patients relapsed in the pediatric or adult population.. We would thus advocate that for grade 1 tumors, surgery alone should be recommended for all stages across all age groups. In patients with higher grade tumors, the risk of relapse differed by stage, and patients with Stage I and II tumors had excellent EFS compared to Stage III and IV tumors. We currently have joint COG-NRG clinical trial under review that proposes observation for all Stage I tumors regardless of grade. The results of this analyses further justify this approach. With regards to the approach for grade 2 and 3 tumors with higher stages, in our analyses we observed only a two percent failure rate in grade 2 tumors.

The only group in which the failure rate was of concern was in the grade 3 tumors, stage III-IV. Adjuvant chemotherapy did not decrease the relapse risk in the pediatric cohort. Given our doubts that this subtype of GCT is chemosensitive, even in this higher stage and grade group, we would be in favor of a prospective trial of observation after surgery for patients with grade 2 or 3 tumors, Stages II-IV, with consideration of second surgery as the first line of treatment in the setting of relapse.

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Conflicts of Interest:

The authors do not have any conflicts of interest

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Figure 1. Event Free Survival for Pediatric Patients with Ovarian Grade 3 Immature Teratoma, by Stage

The figure shows pediatric patients with grade 3, stage I and II ovarian immature teratoma had significantly reduced risk for EFS event when compared with patients with grade 3, stage III disease

Figure 2. Event Free and Overall Survival for Adult Patients with Ovarian Grade 3 Immature Teratoma, by Stage

The figures shows adult patients with grade 3, stage I and II ovarian immature teratoma had significantly reduced risk for EFS event when compared with patients with grade 3, stage III and IV disease. The overall survival was not significantly different between the two groups.