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The influence of age and other prognostic factors associated with survival of ovarian immature teratoma — A study of 1307 patients

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HIGHLIGHTS

- The survival of patients with stage I disease was 99.7%.
- Children and adults had corresponding survivals of 100% and 99.6% in stage I disease.
- The proportion of Asian patients with immature teratomas is disproportionately high.

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ABSTRACT

Objective. To determine impact of age and other prognostic factors on the survival of ovarian immature teratoma (IT) patients.

Methods. Data obtained from the SEER database between 1973 and 2012. Kaplan-Meier methods and multivariate Cox regression models were used for statistical analyses.

Results. Of 1307 patients (median: 24 years; range: 0–93), 78%, 5%, 13%, 4% were stages I, II, III and IV, respectively. 25%, 35%, and 40% had grades 1, 2, and 3. Whites were less likely to be diagnosed, and Asians had a nearly 3-fold higher proportion of IT compared to the proportion of Asians in the U.S. census. The 5-year disease-specific survival (DSS) was 91.2%. Those with stages I, II, III and IV disease had survivals of 99.7%, 95%, 81%, and 71.8% ($p < 0.001$) and grades 1, 2, and 3 had DSS of 98.7%, 95.8%, and 91% ($p < 0.001$), respectively. Of those who underwent fertility-preserving surgery, the DSS was 98.8%. Over time from 1973 to 1986, to 1987–1999, to 2000–2012, the survivals were 76.4%, 92.8%, and 94.7% ($p < 0.001$). Of stage I patients, no patient <18 years ($n = 214$, used as adult cutoff) and 2 of 283 patients >18 years died of cancer, with corresponding 5 years DSS of 100% vs. 99.6% ($p > 0.05$). Older age (by year, HR: 1.05; 95% CI: 1.04–1.06; $p < 0.0001$) and higher stage (HR: 11.52; 95% CI: 4.08–32.48; $p < 0.0001$) were independent factors indicating poorer survival.

Conclusion. The outcome of patients with stage I disease was excellent at 99.7%, with children and adults having corresponding survivals of 100% and 99.6%.

1. Introduction

Immature teratomas (IT) of the ovary are a type of germ cell cancer that accounts for <1–3% of malignant ovarian cancers [1–3]. These tumors are usually diagnosed in children and young women ranging from 10 to 30 years and have a good prognosis [1–3]. Age, race, and stage of disease are important predictors for survival. In a previous report on 417 IT patients, Chan and colleagues showed that younger patients have a better prognosis compared to older patients (age < 30: 97.7%, age 31–40: 93%, age > 40 70.1%) [2]. Asians also had a better survival compared to Whites and Blacks (98.7% vs. 94.9% and 89.6%). The majority (78.2%) presented with stages I–II disease with a survival of 97.1%. However, those with advanced stage disease had a lower survival rate of 84.3%.

Currently, there is a difference in the standard treatment of IT in children and adults. The role of surveillance has been advocated for stage I IT in pediatric patients [4–6]. In contrast, adjuvant chemotherapy is recommended by NCCN for all adults except those with stage I, grade 1 tumors [7]. Combination chemotherapy with bleomycin, etoposide, and cisplatin may result in serious, life-threatening and permanent disabilities including: secondary malignancies, cardiovascular disease, renal

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nephrotoxicity, and hearing impairment [8]. Prior studies have shown that the role of adjuvant chemotherapy in adults needs to be re-evaluated [3,9] Most of the studies on this issue were limited by the small number of patient with various types of germ cell cancers enrolled in a clinical trial. Given these shortcomings, we proposed to study the impact of age and other prognostic factors in the survival of IT patients reported in the SEER database.

2. Materials and methods

The Surveillance, Epidemiology, and End Results (SEER) database from years 1973–2012 was used for this study. Patient pretreatment data including year of diagnosis, patient age at diagnosis, race, tumor stage, grade, and surgery were abstracted. We used ICD-0-3 codes 9080–9084 to select patients with IT (excluded mixed germ cell tumors). We defined a uterine-preserving procedure as fertility-sparing surgery as previously reported [2]. We grouped patient pretreatment factors by race (Non-Hispanic Whites, Blacks, Hispanics, Asians, others), age, FIGO stage, grade (1, 2, 3), and surgery type. Chi-squared tests were used to determine differences in the pretreatment parameters with respect to outcomes. These tests were also employed to identify differences based on demographic, clinico-pathologic, and survival changes over time. Disease-specific survival was defined as death from IT of the ovary and taken from time of diagnosis to death or to the date last seen (whichever occurred first). Survival curves for different groups of patients were determined using Kaplan-Meier methods.

For multivariate analysis, we employed Cox proportional hazard models, adjusted for patient and clinical information (age and year of diagnosis, race, stage and grade of disease, surgery type). To include patients who were missing covariate data for these patient-level characteristics in multivariate analysis, we implemented multiple imputation by chained equations (MICE) [10]. Multiple imputation is a common procedure that maintains the variability of the data while reducing the bias inherent to missing data [11–13]. All statistical analyses were performed in R (Version 3.1.0, Vienna, Austria) and SAS (Version 9.3, Cary, NC). Because this study involved a national, de-identified database it was exempt from IRB approval.

3. Results

3.1. Demographics and surgical data

Of 1307 women (median: 24 years; range: <1–93 years) with ovarian IT, 47.3% were White, 22% Hispanic, 15.3% Black, 13.5% Asian, and 0.6% other races (1.3% missing) (Table 1). Whites are less likely to be diagnosed with IT, and Asians have a nearly 3-fold higher proportion of IT compared to the proportion of Asians in the U.S. census. Of women with detailed surgical information, 74.8% of patients underwent fertility-sparing surgeries (defined as unilateral oophorectomy without hysterectomy). Only 15.1% of patients underwent hysterectomies. Of patients with known stages of disease, 78%, 5%, 13%, 4% were stages I, II, III and IV disease. Of patients with known grade, 25%, 35%, and 40% were grades 1, 2, and 3, respectively.

3.2. Survival of population

The 5-year disease-specific survival (DSS) of the overall group was 91.2%. Table 2 summarizes the 5-year DSS by pretreatment patient characteristics and type of surgery. The association of race, age, stage, and grade on DSS is shown in Fig. 1. The DSS of Hispanics and Asians were higher at 94.7% and 94.5% compared to 89.3% and 90% in the Whites and Blacks respectively ($p < 0.01$). Those with stages I, II, III and IV disease had survivals of 99.7%, 95%, 81%, and 71.8% ($p < 0.001$) and grades 1, 2, and 3 had DSS of 98.7%, 95.8%, and 91% ($p < 0.001$), respectively. 404 patients underwent fertility-preserving surgery with a DSS of 98.9%. Of the 418 stage I patients, only 2 (0.5%) died of disease, and 1 was 22 years old while the other was 52. Since the standard adjuvant treatment of high-risk stage I disease differs between children (<18 years) and adults (≥18), we evaluated the 5-year DSS of these groups. The younger patients had a better survival rate compared to that of adult patients (96.7% vs. 88.7%, $p < 0.001$). Of stage I patients, no children ($n = 134$) and 2 of 284 adults died from cancer, with corresponding 5-year DSS of 100% vs. 99.6% ($p = 0.35$).

Of 111 patients who died of disease, 19 had known factors including year of diagnosis, age, race, and stage and are summarized in Table 3. Among this group, no patients had grade 1 tumors. Of the 3 deaths in patients with grade 2 tumors, one had stage 3 and two had stage IV cancers. Eight patients with grade 3 tumors died of disease, including 2 with stage I disease and 6 with stage 3 disease.

3.3. Trends in presentation and survival

We divided the study group into 3 time periods from 1973 to 1986, 1987–1999, and 2000–2012. Across the three time intervals, the median age at diagnosis was 26, 22, and 24, respectively ($p < 0.001$). There was

Table 1
Patient demographics and treatment ($N = 1307$).

Factor	Number of patients (%)
Age (years)	
Median (range)	24 (0–93)
Race	
White	618 (47.3)
Black	200 (15.3)
Hispanic	288 (22.0)
Asian	176 (13.5)
Other	8 (0.6)
Unknown or missing	17 (1.3)
Stage	
I	418 (32.0)
II	24 (1.8)
III	71 (5.4)
IV	21 (1.6)
Unknown or missing	773 (59.1)
Grade	
I	245 (18.7)
II	338 (25.9)
III	384 (29.4)
Unknown or missing	340 (26.0)
Surgical procedures[a]	
Oophorectomy	643/657 (97.9)
Hysterectomy	103/681 (15.1)
Fertility-sparing surgery	404/557 (72.5)
Stage	
I	
Grade I	103 (24.6)
Grade II	114 (27.3)
Grade III	118 (28.2)
Missing	83 (19.9)
II	
Grade I	0 (0)
Grade II	7 (29.2)
Grade III	13 (54.2)
Missing	4 (16.7)
III	
Grade I	7 (9.9)
Grade II	11 (15.5)
Grade III	40 (56.3)
Missing	13 (18.3)
IV	
Grade I	1 (4.8)
Grade II	4 (19.0)
Grade III	5 (23.8)
Missing	11 (53.4)

[a] Fertility-sparing surgery includes unilateral oophorectomy without hysterectomy. Some women were coded by SEER as having "either a unilateral or bilateral oophorectomy" or an oophorectomy for which it was unknown if a hysterectomy was also performed. These women were considered missing in the fertility-sparing surgery group due to the uncertainty about their hysterectomy status, and this accounts for the differing denominators.