Published in final edited form as:

J Surg Res. 2018 April ; 224: 38–43. doi:10.1016/j.jss.2017.11.046.

Disparities in fertility-sparing surgery in adolescent/young women with Stage I ovarian dysgerminoma

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Abstract

Background—In many cancers, racial and socioeconomic disparities exist regarding the extent of surgery. For ovarian dysgerminoma, fertility-sparing (FS) surgery is recommended whenever possible. The aim of this study was to investigate rates of FS versus non-fertility sparing (NFS) procedures for Stage I ovarian dysgerminoma in adolescents and young adults (AYAs) by ethnicity/race and socioeconomic status.

Materials and Methods—The National Cancer Data Base was queried for patients with ovarian dysgerminoma from 1998-2012. After selecting patients aged 15-39 years with Stage I disease, a

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Author Contributions:

Drs. Gow, Goldin, Goldfarb, Langer, Raval, Doski, Nuchtern, Vasudevan, and Beierle are members of the CCDR, a collaborative group investigating the pediatric data available in the National Cancer Data Base. All authors reviewed and participated in the revision of the manuscript. Drs. Stafman and Maizlin participated in project conception, data evaluation, and writing of the manuscript. Dr. Maizlin and Dr. Dellinger performed statistical evaluation. Dr. Beierle assisted in project conception, manuscript writing, and editing.

Author Disclosure Statement:

None of the authors have any financial or personal relationships to disclose.

multivariate regression analysis was performed and rates of FS and NFS procedures were compared, first according to ethnicity/race, and then by socioeconomic surrogate variables.

Results—Amongst the 687 AYAs with Stage I ovarian dysgerminoma, there was no significant difference in rates of FS and NFS procedures based on ethnicity/race alone ($p=0.17$), but there was a significant difference in procedure type for all three socioeconomic surrogates. The uninsured had higher NFS rates (30%) than those with government (21%) or private (19%) insurance ($p=0.036$). Those in the poorest ZIP codes had almost twice the rate of NFS procedures (31%) compared with the most affluent ZIP codes (17%). For those in the least educated regions, 24% underwent NFS procedures compared to 14% in the most educated areas ($p=0.027$).

Conclusions—AYAs with Stage I ovarian dysgerminoma in lower socioeconomic groups were more likely to undergo NFS procedures than those in higher socioeconomic groups, but there was no difference in rates of FS vs. NFS procedures by ethnicity/race. Approaches aimed at reducing socioeconomic disparities require further examination.

Keywords

Dysgerminoma; race; socioeconomic; disparity; surgery; fertility

Introduction

Malignant ovarian germ cell tumors (MOGCTs) are a rare form of gonadal malignancy that occur across all age groups, but are most prevalent in adolescents and young adults (AYAs). The most common subset of MOGCTs is dysgerminoma, accounting for about 35% of MOGCTs and 3-5% of all primary ovarian malignancies across all age groups.¹⁻³ Ovarian dysgerminomas tend to present at an early stage, with approximately 50-80% of patients presenting with Stage I disease.^{2, 4-7}

In the past, it was believed that there was a high prevalence of bilateral disease and thereby a high risk of recurrence in the contralateral ovary, even with low stage ovarian dysgerminoma.⁸ In the 1950s, Pedowitz *et al.* found that even amongst patients believed to have unilateral involvement, 36.2% had involvement of the other ovary shortly after unilateral salpingo-oophorectomy. These findings led to the recommendation for extensive surgery in the form of bilateral salpingo-oophorectomy and hysterectomy for ovarian dysgerminoma.⁹ In the 1960s, surgeons started to question this aggressive approach and discuss the possibility of performing more conservative procedures coupled with other treatment modalities.⁸ Most studies within the past 35 years have found that less than 15% of ovarian dysgerminomas were bilateral at presentation, 10-14 leading to a change in the overall surgical approach, with increased emphasis on fertility sparing (FS) procedures.^{12, 15} Vicus *et al.* reported a case in 2010 in which a patient had bilateral ovarian dysgerminoma, underwent a FS procedure and chemotherapy, and was disease-free at 5 years.⁶ Retaining childbearing potential is important in women with these tumors, as they most commonly present during or prior to their childbearing years. As such, the guidelines of the National Comprehensive Cancer Network of the United States now recommend FS surgery whenever possible for patients desiring to maintain fertility, even for those with advanced disease.¹⁶

Multiple studies in the adult literature have demonstrated that racial and socioeconomic disparities exist in the surgical treatment of other types of ovarian cancer and in access to FS procedures.^{17–19} Reports addressing these disparities in ovarian dysgerminomas do not exist in the current literature. The purpose of this study was to assess rates of FS versus non-fertility sparing (NFS) procedures for Stage I ovarian dysgerminoma in the AYA population in the United States according to ethnicity/race and socioeconomic status. We focused on the AYA age group, given that these women are those whose childbearing potential is most relevant. Additionally, Stage I ovarian dysgerminoma is the most commonly encountered stage for this tumor and the stage for which FS procedures are most frequently possible.

Methods

Data source

The National Cancer Data Base (NCDB) is jointly maintained by the American Cancer Society and the American College of Surgeons Commission on Cancer. Database records are created by over 1500 accredited centers nationwide, using highly standardized methods and definitions, consistent with specifications by the North American Association of Central Cancer Registries. Records include patient characteristics, cancer properties, treatment modality specifics, and basic outcome information. Data definitions are readily available online (<https://www.facs.org/quality-programs/cancer/ncdb/puf>). Approximately 70% of all cancer cases in the United States are captured in the database, 20, 21 with at least 71% of cases under 19 years of age being captured.²² Since its inception, data from the NCDB have been consistently verified for validity and have been used in over 350 articles over the last 25 years.²³

Study cohort

Institutional review board exemption was obtained from the University of Alabama, Birmingham IRB. The AYA age group as defined from 15-39 years old was derived from the Children's Oncology Group guidelines.²⁴ All AYA women with primary diagnosis of dysgerminoma were examined from the NCDB from 1998 to 2012. Dysgerminoma diagnosis was determined based on the histological (ICD-O3) code designation of 9060. Further stratification by stage at diagnosis was performed, with a special focus on those patients at Stage 1. Tumor stage was determined by the NCDB analytic stage, which uses pathologic staging when known, otherwise clinical staging is used for the NCDB analytic stage. Multiple characteristic variables were examined, including ethnicity/race and socioeconomic status. Three socioeconomic surrogate variables were identified – insurance type, income, and education level. The median income and percent of people with no high school degree by ZIP code were classified into quartiles using US Census data from 2012. The outcomes of interest were rates of FS and NFS procedures. NFS procedures were defined as any procedures including bilateral oophorectomy and/or hysterectomy. FS procedures were defined as unilateral or partial oophorectomy.

Statistical analysis

Statistical analysis utilized SAS software, version 9.4 (Cary, North Carolina). Variable distributions were presented using standard descriptive statistics. Amongst AYA females

with Stage I disease, a multivariate regression analysis was performed to determine the degree to which variables contributed to the outcome of interest (NFS procedure). Hazard ratios were calculated using the regression equation. χ^2 tests were used to compare rates of FS and NFS procedures for each variable, controlling for age and ethnicity/race. Due to missing data, not all patients could be utilized for every variable. Missing data points were deemed to meet all assumptions of missing at random (MAR).²⁵ As such, pairwise deletion at variable level was performed, resulting in available case analysis. Entries lacking survival data were excluded in a list-wise deletion. For comparison of medians, the groups were assessed for independence of observations and similarity of distribution, which then allowed for a Mann-Whitney U-test to be performed. Statistical analysis was completed with SAS software, version 9.4 (Cary, North Carolina), and significance determined at $p = 0.05$.

Results

Descriptive analysis of patients with ovarian dysgerminoma

Of the total 1407 women with ovarian dysgerminoma the NCDB captured during the 14-year time period, 1360 cases contained survival data. Of those, 1200 (88.2%) women were aged 15-39 and thus defined as AYA. 697 AYA subjects had Stage I disease at diagnosis, of which 678 (97.3%) had survival data available and comprised the study population (Figure 1). The median age of the study cohort was 24 years (Interquartile Range [IQR] 19-30 years). The age of those undergoing FS versus NFS procedures was compared. For NFS procedures, the median age was 23 years (IQR 17-26) and for FS procedures, the median age was 25 years (IQR 18-29), with no statistically significant difference in median age between the two groups ($p=0.199$). Overall, for AYA subjects with Stage I dysgerminoma, FS was the most common surgical procedure type (Table 1).

Rates of FS and NFS surgery were unchanged based on ethnicity/race

Amongst subjects with Stage I ovarian dysgerminoma, the majority were identified as Non-Hispanic White (Table 1). Amongst Non-Hispanic White subjects, 69% underwent FS procedures compared to 31% who underwent NFS procedures. Hispanic White, Black and Asian subjects also underwent FS procedures more commonly than NFS procedures (Table 1). A multivariate regression analysis revealed no significant difference in rates NFS procedures based on ethnicity/race ($p=0.520$, Table 2).

Rates of FS and NFS varied based on socioeconomic surrogate variables

Controlling for ethnicity/race and age, subjects with Stage I ovarian dysgerminoma who were uninsured had higher rates of NFS procedures (35%) compared to those with government (29%) or private (27%) insurance ($p=0.036$, Tables 2 and 3). Those living in ZIP codes in the lowest median income quartile had a significantly higher rate of NFS procedures (36%) compared with those in the highest median income quartile (23%) ($p=0.003$, Tables 2 and 3). For those subjects living in ZIP codes with the highest quartile for percent of people without a high school degree, 24% underwent NFS procedures whereas only 14% underwent NFS procedures in ZIP codes with the lowest quartile for percent of people without a high school degree ($p=0.027$, Tables 2 and 3). There was no correlation

between ethnicity/race and insurance status ($p=0.240$), education quartile ($p=0.090$) or income quartile ($p=0.115$).

Discussion

We found that AYA women of a lower socioeconomic status (defined by insurance type, income, and education level) were more likely to undergo NFS procedures for Stage I ovarian dysgerminoma than those of a higher socioeconomic status when controlling for ethnicity/race and age. This study is the first to demonstrate socioeconomic disparities in the management of ovarian dysgerminoma, and specifically in type of surgical procedure.

While each surgical operation is approached with the goal of the best oncologic treatment, one must similarly take into account the impact on the patient's quality of life. Studies have shown that for many women, infertility negatively impacts quality of life and adds psychological distress.^{26, 27} The guidelines of the National Comprehensive Cancer Network of the United States now recommend FS procedures whenever possible for ovarian dysgerminoma.¹⁶ The current study revealed that these guidelines are potentially followed less rigorously for patients of a lower socioeconomic status.

The socioeconomic surrogate variables examined have also been utilized and determined to be accurate markers of socioeconomic status by other researchers.²⁸ Although this is the first report on socioeconomic disparities in surgical procedure type for dysgerminoma, there have been studies examining socioeconomic disparities in outcomes for dysgerminoma. Solheim *et al.* found that there was no difference in cause specific mortality in dysgerminoma by education level.²⁹ However, all ages and stages of dysgerminoma were included in their analysis, unlike our study. Additionally, other researchers have found that women with epithelial ovarian cancer who lived in poorer neighborhoods were less likely to receive chemotherapy.³⁰

There was no difference in rates of NFS versus FS procedures by ethnicity/race. While no prior studies have examined this particular variable, there have been studies examining racial disparities in treatment and survival in ovarian germ cell tumors. Bryant and colleagues found that race was not an independent predictor of survival³¹ and Merrill showed no difference in fertility-conservative management based on race³² for ovarian germ cell tumors. Conversely, Hinchcliff *et al.* found that African Americans had significantly worse 5-year survival but received similar treatments for MOGCTs.^{31, 33} Racial disparities have been examined in epithelial ovarian cancer as well, but these data are also unclear. Some studies demonstrated that African Americans were less likely to receive standard or aggressive treatment and others demonstrated no difference in adherence to guidelines for treatment based on race.^{34, 35} With regards to fertility-conservative management, there is a paucity of data for ovarian germ cell tumors. However, consistent with our findings, a study examining all types of ovarian cancer demonstrated no difference in fertility-conservative management based on race.³²

In this study, AYA patients with ovarian dysgerminoma most frequently presented with Stage I disease. This frequency is similar to what has been found previously, conferring

external validation to the dataset, although there has been a wide range of results published. Most references state that approximately 50-80% of patients with ovarian dysgerminoma present with Stage I disease.^{2, 4-7}

Motivations underlying the difference in utilization of NFS or FS procedures by socioeconomic status are unclear. Potentially, those in lower socioeconomic groups may seek care in resource-poor or low-volume facilities in which the surgeons performing the procedures may be unfamiliar with current guidelines. This difference in type of facility in which patients from different socioeconomic groups undergo treatment has been observed in ovarian cancer previously.^{36, 37} Another conceivable reason for the difference in procedure type may be variability in the surgeon-patient relationship based on socioeconomic status – either due to surgeons’ attitudes toward patients or patients’ attitudes toward surgeons. The dynamics of this relationship vary significantly and may hinder effective communication, which impacts decision-making and trust from both sides.

The fear of potential recurrence or presence of microscopic disease in the contralateral ovary may be driving some surgeons to choose a NFS procedure. For dysgerminoma, Husaini *et al.* demonstrated no difference in survival between those undergoing FS versus NFS procedures.⁷ Additionally, for all MOGCTs, the extent of resection (FS versus NFS) has not been shown to be a predictor of recurrence or death, and conservative surgery even in advanced stages has not been associated with relapse or poor prognosis.³⁸ Even when recurrences do happen, dysgerminoma is a highly chemosensitive tumor and most patients may be salvaged with cisplatin-based chemotherapeutic regimens.⁶ Additionally, with the improvement in surveillance imaging techniques, recurrences may be detected even earlier, allowing for rapid initiation of treatment. Taking this information into account, both the National Comprehensive Cancer Network of the United States and the European Society of Medical Oncologists have concluded the FS procedures are safe in dysgerminoma and should be performed whenever possible.^{16, 39}

A potential weakness of this study was the inability to determine whether there was a baseline difference in bilaterality of the Stage I ovarian dysgerminomas based upon ethnicity/race or socioeconomic surrogate variables. Stage I ovarian dysgerminoma includes T1a, T1b, and T1c tumors with N0 nodes and M0 metastases. T1a tumors are unilateral, T1b tumors are bilateral, but T1c tumors, which involve capsular rupture, tumor on the ovary surface, or malignant cells in the peritoneal fluid, may be unilateral or bilateral.⁴⁰ As such, although the NCDB does include T, N, and M status, the information regarding bilaterality cannot be determined. However, we would not expect a difference in frequency of bilaterality by ethnicity/race or socioeconomic status, and even in bilateral cancers, a FS procedure may be possible.

It is also unclear in the database whether patients are being offered different procedures based on socioeconomic status or whether patients from different socioeconomic backgrounds are choosing different procedures after the options are presented and discussed. Further investigation into the surgeon-patient relationship and patients’ social and behavioral motivators to undergo a particular type of procedure may provide more clarity regarding the

underlying reason for the socioeconomic disparity in receipt of FS procedures for Stage I ovarian dysgerminoma in AYA women.

Conclusions

AYA women with Stage I ovarian dysgerminoma from a lower socioeconomic background are more likely to undergo NFS surgical procedures for Stage I ovarian dysgerminomas than those in higher socioeconomic groups. Given the impact these findings may have on patients, efforts should be focused to eliminate this disparity. An examination of care providers' attitudes and patients' social and behavioral components that factor into this decision may provide insight into the etiology of this disparity.

Acknowledgments

This work funded in part by the National Institutes of Health (Grant number T32CA091078 to LLS).

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Figure 1. 1200 AYA with the diagnosis of ovarian dysgerminoma were identified in the NCDB over a 14-year period. The majority of subjects had Stage I disease at diagnosis.

Table 1

Type of surgery (none, FS, or NFS) for Stage I ovarian dysgerminoma in AYAs by ethnicity/race.

	Surgery Type (%)			Total (N)	Hazard Ratio of NFS (95% CI)
	None	FS	NFS		
Non-Hispanic White	0.0%	69.3%	30.7%	446	Ref
Hispanic White	0.8%	69.9%	29.3%	133	0.946 (0.818–1.092)
Black	2.5%	62.5%	35.0%	40	1.316 (0.907–1.788)
Asian	0.0%	74.5%	25.5%	55	0.752 (0.700–1.233)
Other	0.0%	75.0%	25.0%	4	0.730 (0.616–1.139)
Total	0.3%	69.5%	30.2%	678	

Table 2

Stepwise Cox multivariate regression model examining effect of age, ethnicity/race, and socioeconomic surrogates on rate of NFS procedures for Stage I ovarian dysgerminoma in AYAs.

Covariate	Parameter Estimate	Standard Error	p-value
Intercept	1.722	0.087	<0.001
Age	0.001	0.015	0.177
Ethnicity/Race	0.042	0.020	0.520
Insurance Type	−0.270	0.031	0.036 *
Median Income Quartile	−0.390	0.021	0.003 *
Percent without High School Degree	−0.280	0.037	0.027 *

* indicates statistically significant difference

Table 3

Type of surgery (none, FS, or NFS) for Stage I ovarian dysgerminoma in AYAs by socioeconomic surrogate variables.

Insurance Type	Surgery Type (%)			Hazard Ratio of NFS (95% CI)
	None	FS	NFS	
None	0%	65.0%	35.0%	1.774 (1.539–1.804)
Government	0.2%	70.4%	29.4%	1.634 (1.523–1.689)
Private	0%	73.1%	26.9%	Ref
Median Income Quartile				
<\$38,000	1.4%	62.3%	36.2%	1.516 (1.321–1.562)
\$38,000–\$47,999	0%	66.7%	33.3%	1.412 (1.330–1.513)
\$48,000–\$62,999	0%	74.0%	26.0%	1.304 (1.149–1.328)
\$63,000+	0%	77.2%	22.8%	Ref
Percent without High School Degree				
21%	1.2%	75.2%	23.6%	1.661 (1.507–1.697)
13.0–20.9%	0%	73.7%	26.3%	1.558 (1.383–1.572)
7.0–12.9%	0%	75.4%	24.6%	1.429 (1.259–1.445)
<7.0%	0%	85.5%	14.5%	Ref