

A retrospective analysis of the pattern of care and survival in patients with malignant ovarian germ cell tumors

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Abstract

Objective: The objective of this study is to evaluate the pattern of care and survival outcome in patients with malignant ovarian germ cell tumors (MOGCTs). **Materials and Methods:** Between January 2004 and August 2017, 50 patients with MOGCT were identified at Amrita Institute of Medical Sciences and 48 included in analyses. Histologic subtypes were as follows: dysgerminoma 11; immature teratoma 16; yolk sac tumor 3; and mixed germ cell tumor 18. 31 (64.6% patients belonged to Stage I and 17 (35.4%) patients were advanced stage (Stage II-IV). **Results:** Median follow-up period was 34 months (range: 1–241 months). The 5- and 10-year disease-free survival (DFS) and overall survival (OS) for the entire cohort were 87.5% and 94.4%, respectively. DFS and OS of incomplete surgery Stage I patients 28.6% and 68.6%, respectively, were significantly lower than completely staged patients 100%. Out of 8 incomplete surgery patients, 5 recurred of which 2 died of disease within 4 and 9 months of recurrence. There was no survival difference with comprehensive surgical staging (CSS) and pediatric surgical staging (PSS) in Stage I MOGCT (DFS and OS 100%). Stage I dysgerminoma kept on active surveillance after PSS had equivalent survival of 100%. There was no survival difference in advanced stage MOGCT treated with primary debulking surgery and neoadjuvant chemotherapy (NAC) followed by fertility-sparing surgery (DFS and OS 100%). **Conclusion:** Incomplete surgery in Stage I MOGCT was associated with poor survival. There was no survival difference with CSS and PSS. NAC followed by surgery could be a reasonable option for patients of advanced stage MOGCT.

Key words: Active surveillance, comprehensive surgical staging, incomplete surgery, malignant ovarian germ cell tumor, neoadjuvant chemotherapy, pediatric surgical staging

Introduction

Malignant ovarian germ cell tumors (MOGCTs) exhibit one of the most extraordinary treatment and prognosis advancement history in the chronicles of gynecological cancers. Before the mid-1960s, virtually all young girls and women either died of disease or cured leaving them infertile with poor quality of life. During this era, treatment available included surgery alone or combined with adjuvant external radiation therapy, radioisotope therapies, or single alkylating agent.^[1-3] Over the subsequent five decades, tremendous evolution in surgical and chemotherapeutic approaches made this malignancy curable even with fertility preservation, with the reported 5-year survival rate of 100% for dysgerminomatous and 85% for nondysgerminomatous MOGCTs.^[4]

The current standard treatment regimen includes fertility-sparing surgery (FSS, preservation of the uterus and unaffected ovary) whenever appropriate along with a thorough staging procedure, followed by adjuvant combination chemotherapy with bleomycin, etoposide, and cisplatin (BEP, except for Stage IA pure dysgerminoma and Stage IA Grade 1 immature teratoma).^[5]

The issues which are still unresolved in the management of MOGCTs include the role of comprehensive surgical staging (CSS); worldwide, till date, there are number of variations in the practice of CSS;^[6] extent of completion staging surgery in cases of incompletely staged apparent early stage MOGCT; the role of secondary cytoreductive surgery in patients with recurrent or progressive MOGCTs;^[6] the role of surveillance in Stage IA MOGCTs;^[6] and the role of neoadjuvant chemotherapy (NAC) in the management of advanced stage MOGCTs.^[7,8]

The objective of our study was to evaluate the pattern of care and survival outcome in patients with MOGCTs treated at our institute.

Materials and Methods

This is a single-institution retrospective study conducted at Amrita Institute of Medical Sciences (AIMS), Kerala, India. The study was approved by the Institutional Ethical Committee. This included all women who were diagnosed with MOGCT from January 2004 to August 2017. Patients with monodermal teratoma and somatic-type tumors from dermoid cyst (mature cystic teratoma, struma ovarii benign/malignant, carcinoid, neuroectodermal-type tumor, sebaceous tumors, and carcinomas arising in mature cystic teratoma) and mixed germ cell-sex cord-stromal tumor and patients having ovarian cancer other than MOGCT were excluded from the study.

Demographic, clinical, surgicopathological characteristics, details of treatment, recurrence, and survival were collected from electronic medical records and hospital-based cancer registry. Staging in patients undergoing with NAC was based on clinical and radiological information. Histology followed the International Classification of Diseases for Oncology-3.

Patients were subdivided into cohorts based on the stage and treatment received [Figure 1]. Complete surgical staging group was dichotomized into CSS and pediatric surgical staging (PSS). CSS was defined as unilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies, washings, and bilateral pelvic and para-aortic lymphadenectomy.^[6] PSS was defined as the visual inspection surgical staging described by Billmire *et al.*, which includes complete resection of tumor-containing ovary with sparing of fallopian tube, inspection and palpation of contralateral ovary, omentum, peritoneal surfaces, and lymph nodes, and collection of peritoneal washings or ascites.^[9] Patients kept on

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active surveillance after surgery were evaluated with clinical examination and tumor markers and imaging was done when clinically indicated. Recurrence when suspected was confirmed by imaging.^[10]

Definition and statistical methods

Survival analysis was done using Kaplan–Meier method and compared using log-rank test. Disease-free survival (DFS) was defined as the time from diagnosis to date of recurrence, and overall survival (OS) was defined as the time from diagnosis to date of death or last follow-up. Survival after recurrence was defined as the time from relapse to date of death or last follow-up. Categorical variables were expressed as frequency and percentages. *P* > 0.05 was considered to be statistically significant. All analysis was performed using IBM SPSS v.20.0 (SPSS Inc, Chicago, USA).

Results

Patients’ characteristics

Of 874 ovarian malignancies during the study period, 50 (5.7%) patients had MOGCT of which 48 were included in the study (2 patients were excluded due to the lack of treatment details and follow-up).

Clinicopathological and treatment strategies are presented in Table 1. Median age at diagnosis was 20.5 years (range: 8–45 years). Most common presenting symptom was abdominal mass and pain in 85.4% patients. The most common histologic type was mixed germ cell tumor in 37.5% of patients. Nearly 64.6% patients were Stage I at the time of diagnosis.

Twenty-three (47.9%) patients received initial treatment elsewhere and were referred to AIMS for subsequent evaluation or for recurrence. Of 38 (79.2%) completely staged patients, 35/38 (72.9%) patients underwent FSS.

Pattern of care in Stage I malignant ovarian germ cell tumor

Of 31 Stage I MOGCT patients, 8 (25.8%) had dysgerminoma, 13 (41.9%) had immature teratoma (6 [46.2%] – Grade 1, 2 (15.4%) – Grade 2, and 5 (38.4%) – Grade 3), 9 (29%) had mixed germ cell tumor, and 1 (3.2%) had yolk sac tumor (YST). The Federation of Gynecology and Obstetrics (FIGO) stage was IA in 11 (35.5%) and IC in 13 (41.9%), whereas remaining 7 (22.6%) were apparently Stage IA at presentation but upstaged to IC due to intraoperative rupture of tumor and its piecemeal removal [Figure 2].

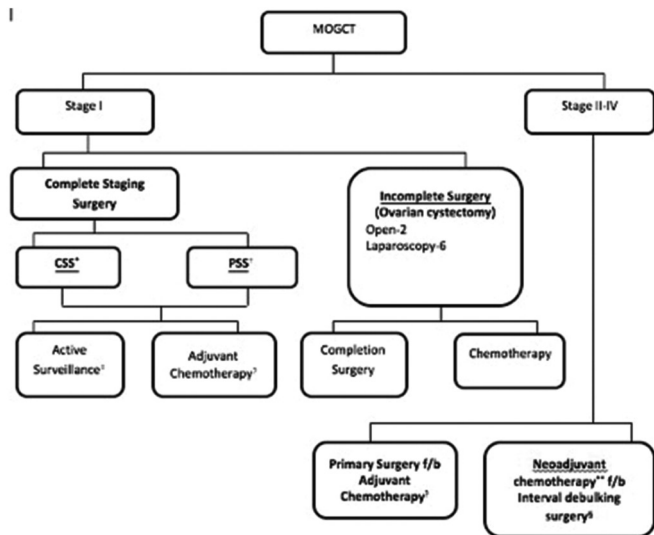
Surgery represented the first approach to the disease for all the Stage I MOGCT patients; 12 (38.7%) patients received surgical treatment in AIMS, whereas 19 (61.3%) were referred in the postoperative setting for subsequent evaluation and/or for recurrence.

Of 23 completely staged patients, 22/23 (95.7%) patients underwent FSS where all 8 incompletely staged patients underwent FSS in the form of ovarian cystectomy.

Out of 8 incompletely staged patients (all operated outside), only 1 (12.5%) patient received adjuvant chemotherapy, 5 patients presented with recurrence, and 2 patients referred to our center after diagnosis and were offered adjuvant chemotherapy but refused.

Pattern of care in Stage II–IV malignant ovarian germ cell tumor

Of 17 Stage II–IV MOGCT patients, 3 (17.6%) had dysgerminoma, 3 (17.6%) had immature teratoma (1 [33.3%] – Grade 1 and 2 [66.7%] – Grade 2), 9 (52.9%) had mixed germ cell tumor, and 2 (11.8%) had YST. The FIGO stage was II in 2 (11.8%), III in 12 (70.6%), and IV in 3 (17.6%) patients [Figure 3].



* CSS- Comprehensive Surgical Staging defined as unilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies, washings and bilateral pelvic and para-aortic lymphadenectomy
 † PSS- Pediatric Surgical Staging defined as the visual inspection surgical staging described by Billmire et al which includes: complete resection of tumor-containing ovary with sparing of fallopian tube, inspection and palpation of contralateral ovary, omentum, peritoneal surfaces and lymph nodes, and collection of peritoneal washings or ascites
 ‡ Active surveillance group (stage IA pure dysgerminoma, and stage IA grade 1 immature teratoma)
 § Adjuvant chemotherapy included the standard BEP (bleomycin, etoposide and cisplatin) usually administered for 4 cycles, in patients intolerant to bleomycin due to pulmonary issue, EP regimen was given
 ¶ Pathological diagnosis of MOGCT was made by biopsy before starting NAC
 **NAC regimen preferably used was the standard BEP regimen 3-4 cycles

Figure 1: Subdivision of malignant ovarian germ cell tumor patients based on stage and treatment received

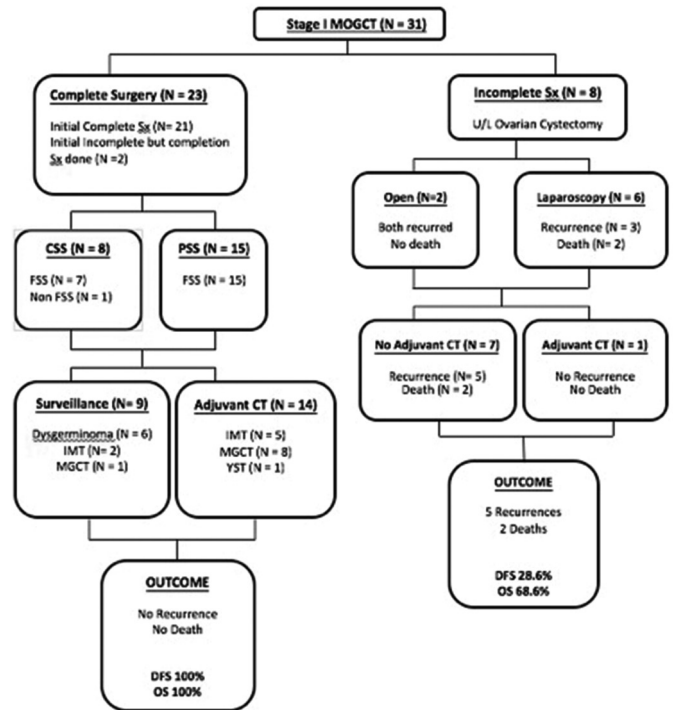


Figure 2: Pattern of care and outcome in Stage I malignant ovarian germ cell tumor

Six (35.3%) patients underwent primary debulking surgery (PDS) followed by adjuvant chemotherapy, whereas 11 (64.7%) patients received NAC followed by interval debulking surgery (IDS). Patients with poor performance status or not suitable for optimal cytoreduction were chosen for NAC. In NAC cohort, 8 (72.7%) achieved complete pathological response.

In PDS cohort, 4 (66.7%) patients underwent FSS, whereas in NAC cohort, all 11 (100%) patients underwent FSS.

Outcome

Median follow-up period was 34 months (range: 1–241 months). Total 5 of 8 (62.5%) incomplete surgery Stage I patients had disease recurrence, with a median time to recurrence of 6 months (range: 3–9 months) [Figures 2-4].

Clinical, treatment, and outcome profile of recurred patients is depicted in Table 2. There was piecemeal removal of cyst and intraoperative spillage of tumor in all. Three out of five patients were wrongly diagnosed as benign mature cystic teratoma initially and presented to our center only on recurrence. Original slides were reviewed and confirmed as immature teratoma. Of these, two died of disease within 4 and 9 months of recurrence.

Full cohort

DFS was 87.5% at 5 and 10 years; OS was 94.4% at 5 and 10 years [Figure 3a and b]. DFS (100% complete staging

vs. 73% incomplete surgery; log rank $P = 0.011$) and OS (100% complete staging vs. 87.8% incomplete surgery; log rank $P = 0.118$) of patients who received complete treatment at our

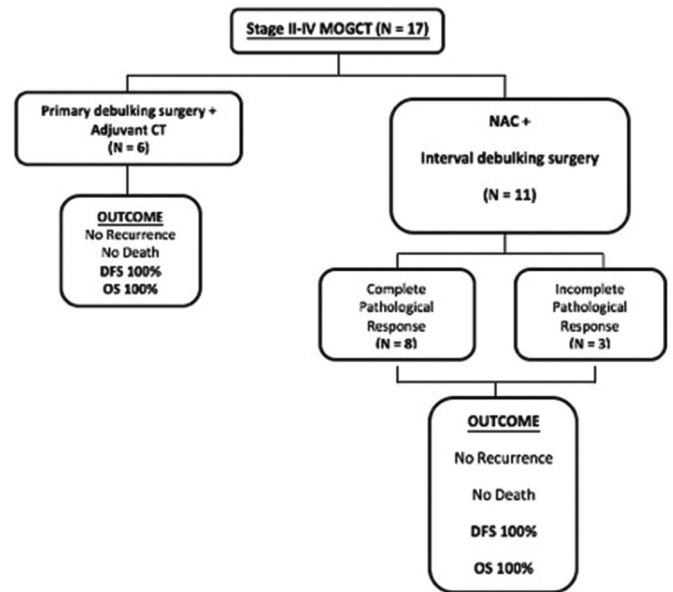


Figure 3: Pattern of care and outcome in advanced Stage (II–IV) malignant ovarian germ cell tumor

Table 1: Clinicopathological features (n=48)

Variable	n (%)
Age at diagnosis, median (range)	20.5 (9-45)
Follow-up period, median (range)	34 (1-241)
Marital status	
Unmarried	25 (52.1)
Married	23 (47.9)
Patients desirous of pregnancy (n=12)	
Achieved	10 (83.3)
Not achieved	2 (16.7)
Initial presenting symptoms	
Abdominal mass and pain	41 (85.4)
Acute abdominal pain	3 (6.3)
Incidentally diagnosed	4 (8.3)
Type of germ cell tumor	
Dysgerminoma (9060/3)	11 (22.9)
Immature teratoma (9080/3)	16 (33.3)
Yolk sac tumor (9071/3)	3 (6.3)
Mixed germ cell tumor (9085/3)	18 (37.5)
FIGO stage	
I	31 (64.6)
II	2 (4.2)
III	12 (25)
IV	3 (6.2)
Grade of immature teratoma (n=16)	
1	7 (43.8)
2	4 (25)
3	5 (31.2)
Place of first treatment	
Amrita	25 (52.1)
Outside	23 (47.9)
Type of first surgery	
Complete staging surgery	38 (79.2)
Fertility-sparing	35 (72.9)
Nonfertility sparing	3 (6.2)
Incomplete surgery	10 (20.8)

Table 2: Clinical, treatment, and outcome profile of malignant ovarian germ cell tumors patients with recurrence (n=5)

Variable	n (%)
Median age of recurred patients (range) in years	26 (15-33)
Median time of recurrence (range) in months	6 (3-9)
Stage	
I	5 (100)
II-IV	0
Histologic subtype	
Recurrent dysgerminoma	1 (20)
Recurrent immature teratoma	4 (80)
Grade 1	2/4
Grade 3	2/4
Place of first surgery	
Outside	5 (100)
Amrita	0
Type of first surgery	
Incomplete (ovarian cystectomy)	5 (100)
Complete staging surgery	0
Mode of first surgery	
Open	2 (40)
Laparoscopic	3 (60)
Adjuvant treatment after first surgery	
Yes	0
No	5 (100)
Site of recurrence	
Abdominal	5 (100)
Disseminated	2/5 (40)
Localized	3/5 (60)
Extra-abdominal	0
Treatment at recurrence	
Secondary cytoreductive surgery + chemotherapy	5 (100)
Outcome of recurred patients	
Alive no disease	3 (60)
Died of disease	2 (40)

FIGO=International Federation of Gynecology and Obstetrics

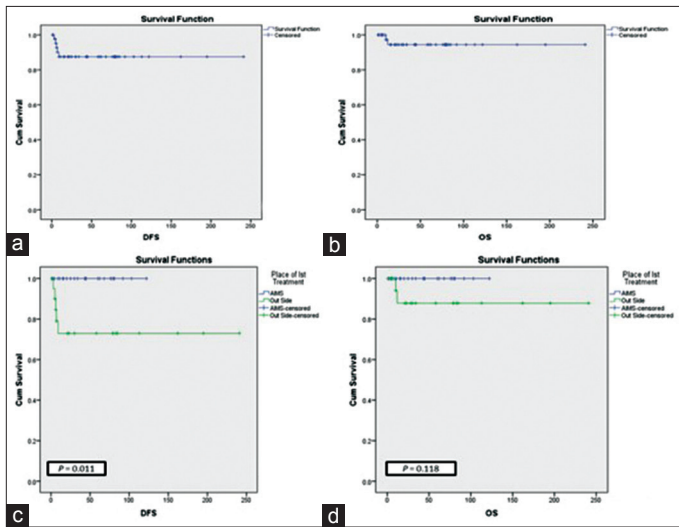


Figure 4: Survival analysis of full cohort (a) disease-free survival of full cohort, (b) overall survival of full cohort, (c) comparative analysis of disease-free survival according to place of treatment, (d) comparative analysis of overall survival according to the place of treatment

institute were significantly higher than patients treated outside and referred [Figure 4].

DFS and OS of Stage I MOGCT patients were 83% and 90%, respectively [Figure 4a and b]. DFS (100% complete surgery vs. 28.6% incomplete surgery; log rank $P < 0.001$) and OS (100% complete surgery vs. 68.6% incomplete surgery; log rank $P = 0.027$) of complete surgery (primary complete staging + primary incomplete surgery but complete staging surgery done) Stage I MOGCT patients were significantly higher than the incomplete surgery patients [Figure 4c and d]. CSS and PSS groups had equivalent survival (DFS and OS 100% in both).

DFS and OS of Stage II–IV MOGCT patients were 100%. There was no survival difference in the patients with NAC + IDS and PDS group (DFS and OS 100% in both).

Reproductive outcome

All 35 (72.9%) patients who underwent FSS resumed normal menstruation within 1 year of completing treatment. Of the 12 (25%) nulliparous patients desirous of pregnancy, 10/12 (83.3%) achieved pregnancy and delivered healthy full-term babies.

Discussion

Malignant ovarian germ cell tumors (MOGCTs) are rare but aggressive tumors, accounting for only 1%–2% of all ovarian malignancies in the Western world,^[11] but in Asian and black societies, they represent as much as 15%.^[12] At our institute, the rate of MOGCT was 5.7%.

MOGCTs principally occur during adolescence and early adulthood. In this study, the median age of diagnosis was 20.5 years which was similar to that (19 years) reported by Talukdar *et al.*^[7] Majority (64.6%) of patients presented in Stage I, as mentioned in literature.^[13]

Primary surgical management with FSS is the standard of care for patients with MOGCT (both early and advanced stage) desirous of fertility. The need for CSS in apparent Stage I MOGCT is still debatable.^[6] Billmire *et al.* and Liu *et al.* showed equivalent survival results in Stage I MOGCT with PSS.^[9,14] In this study, we found equivalent survival in the

8 patients who underwent CSS and 15 patients who underwent PSS with 100% DFS and OS at 5 and 10 years. However, in both these studies, all patients received adjuvant chemotherapy irrespective of their histological subtype. In other studies, authors emphasized the need for CSS to identify the occult metastatic (especially lymph node) disease if patients are to be kept on active surveillance.^[15–17] They concluded that CSS identified the subset of patients who would unequivocally benefit from adjuvant chemotherapy. Contrary to the evidence in literature, in this study, 33.3% (5/15) patients with Stage IA dysgerminoma with unilateral salpingo-oophorectomy were kept under surveillance and none of them recurred.

Evidence from large studies suggest that unilateral salpingo-oophorectomy of involved ovary is the standard of care and removal or biopsy of contralateral ovary is not associated with survival benefit.^[18–21] The issue of conservative surgery of involved ovary is still unanswered. In our study, 8 patients with Stage I MOGCT who underwent surgery with preservation of involved ovary (cystectomy alone) had significantly higher recurrence rate (5/8) and poor OS (2 deaths).

Active surveillance after CSS for Stage IA dysgerminoma and Stage IA Grade 1 immature teratoma is the treatment of choice.^[5] Patients with all other stages and histologic types receive adjuvant chemotherapy with standard BEP regimen. The results of pooled analysis of six studies (included 172 patients with Stage IA dysgerminoma, immature teratoma, YST, and mixed tumor) showed relapse rate of 16% after CSS on active surveillance with OS rate of 98%.^[22–28] Similarly, Billmire *et al.* showed the relapse rate of 48% in yolk sac and mixed tumor with 4-year survival rate of 96% in active surveillance group.^[29] These authors recommend active surveillance despite high relapse but good survival rate. On the contrary, Norris *et al.* reported the relapse rate of 70% in Grade 3 immature rate with active surveillance and hence strongly recommended adjuvant chemotherapy.^[30] Till date, there is no study which has compared the relapse rates and OS rates with CSS and PSS in patients undergoing active surveillance. In our study, 33.3% patients (5 of 15 patients with PSS) were kept under surveillance after PSS with no relapse rate and OS rate of 100% at 3 years.

Approximately 60% patients upstaged to Stage IC due to intraoperative tumor rupture in incomplete surgery cohort experienced disease recurrence. None of them had completion staging surgery and only one patient received adjuvant chemotherapy. One had recurrent dysgerminoma, while other four had recurrent immature teratoma (Grade 1–2 and Grade 3–2) within 3–9 months. They were treated with secondary cytoreductive surgery and chemotherapy. About 40% (2/5) had extensive disease at the time of recurrence and succumbed to death despite of secondary cytoreductive surgery and chemotherapy within 4 and 9 months of recurrence. Contrary to the relapse rate of 30%–40% in literature, the rate of relapse in this study was much higher. Contrary to the fact that YST is the most aggressive tumor with highest relapse, in this study, patients with dysgerminoma and immature teratoma have recurred. This may be attributed to the erroneous initial diagnosis of MOGCT as benign tumor and late detection of recurrences.

Retrospective reports suggest a possible role for secondary cytoreductive surgery in selected patients with recurrent MOGCT.^[31,32] Munkarah *et al.* reported improved survival only in immature teratoma with secondary surgery.^[32] Retrospective studies have proposed that ideal candidates for this surgery would be those with an isolated focus or limited foci of recurrence. Consistent this, we also found that secondary reductive surgery benefitted only patients with limited disease.

In advanced Stage (II–IV) MOGCT, we found equivalent survival with NAC followed by IDS and PDS followed by adjuvant chemotherapy. This study is in complete agreement with the study by Talukdar *et al.* who reported equivalent reproductive and survival outcome in advanced stage MOGCT in PDS and NAC followed by IDS group.^[7] Lu *et al.* showed better optimal cytoreduction rate, less perioperative morbidity, and similar DFS in patients with YST who were treated with NAC followed by IDS as compared to those who underwent PDS.^[8] Both the authors concluded that NAC could be a reasonable option for patients with advanced stage MOGCT, not suitable for optimal cytoreduction or with poor general condition.

MOGCT has excellent prognosis, with cure rates approaching 100% for those with early-stage disease and at least 75% for patients with advanced stage disease.^[33] In this study, we found overall DFS of 87.5% and OS of 94.4%. The cure rate of advanced stage MOGCT was 100%. The cure rate of Stage I MOGCT with complete surgery (CSS/PSS) followed by active surveillance or adjuvant chemotherapy was also 100%. However, DFS and OS of incompletely staged, Stage I MOGCT patients were significantly poor 28.6% and 68.6%, respectively.

Conclusions

Despite the limitation of being a small retrospective single institutional analysis, this study shows the importance of adequate preoperative workup of an ovarian mass in adolescent girls and young women with tumor markers and imaging, preventing spillage in case of minimally invasive surgery, correct pathological diagnosis, and timely referral to oncology unit.

This study also shows the equivalent survival in MOGCTs with CSS and PSS. Patients with Stage IA dysgerminoma may be considered for active surveillance after PSS. Secondary cytoreductive surgery may benefit patients with limited sites of recurrence. NAC may be an option in patients with advanced stage MOGCT with poor performance status and in whom optimal cytoreduction may not be possible.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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