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Management and prognosis of ovarian yolk sac tumors; an analysis of the National Cancer Data Base

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HIGHLIGHTS

- Administration of adjuvant chemotherapy results is better survival for OYSTs.
- Age and disease stage are independently associated with mortality.
- Lymphadenectomy and omentectomy may be omitted when staging OYSTs.

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ABSTRACT

Objective. To evaluate the clinico-pathological characteristics, management and prognosis of women diagnosed with ovarian yolk sac tumors (OYSTs).

Methods. The U.S National Cancer Data Base was queried for women diagnosed with OYST between 2004 and 2014. Overall survival (OS) was calculated following generation of Kaplan-Meir curves. Univariate analysis was performed with the log-rank test. A Cox model was constructed to determine independent predictors of mortality.

Results. A total of 561 women were identified with a median age of 23 years. The majority (58.5%) had early stage (I–II), while 29.6% and 11.9% had stage III and IV disease respectively. Five-year OS for women with stage I, II, III and IV disease were 94.8%, 97.1%, 70.9% and 51.6% respectively, $p < 0.001$. Better 5-yr OS was observed for adolescents (94.4%) and young adults (89.3%) compared to older premenopausal (67.6%) and postmenopausal women (30.6%), $p < 0.001$. Omentectomy, hysterectomy and lymph node sampling/dissection (LND) were not associated with better OS. Women who received adjuvant chemotherapy had superior OS compared to those who did not, $p = 0.016$. Early disease stage, younger age and receipt of adjuvant chemotherapy, but not LND were independently associated with better mortality.

Conclusions. Women with OYST commonly present with early stage disease. Administration of adjuvant chemotherapy, early stage and younger age are associated with superior outcomes.

1. Introduction

Malignant ovarian germ cell tumors (MOGCTs) represent approximately 2–3% of all ovarian tumors and most commonly arise in young premenopausal women [1,2]. Yolk sac tumor (YST), also known as endodermal sinus tumor, is the second most prevalent MOGCT histologic subtype following ovarian dysgerminoma [3]. Microscopically YST resembles to the extraembryonal yolk sac and vittelline stalk and is diffusely positively for alpha feto-protein (AFP) [4]. Serum AFP is a useful marker, not only for diagnosing YST, but also for monitoring response to chemotherapy and tumor recurrence, as well [5,6]. Optimal management includes surgery (most commonly unilateral salpingo-oophorectomy) followed by the administration of a platinum-based multi-agent chemotherapy regimen [5,6]. However, prognosis is relative unfavorable compared to the other germ-cell histologic subtypes. Currently, the majority of evidence on the management and outcomes of ovarian yolk-sac tumors derives from small, single-institutional retrospective studies with limited statistical power. Many of them also focus on adolescents and young adults or group pure yolk-sac tumors with mixed germ-cell tumors and span decades before the establishment of the current chemotherapeutic regimen (bleomycin, etoposide, cisplatin, BEP) [3–5,7–16]. The aim of the present retrospective study was to examine the clinico-pathological characteristics and treatment

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modalities employed in the management of women with ovarian YSTs using a multi-institutional hospital-based database.

2. Materials and methods

A cohort of women diagnosed between 2004 and 2014 with OYST, (ICD-O-3 histology code, 9071/3) was drawn from the National Cancer Data Base (NCDB) [17]. The NCDB, was established jointly by the American Cancer Society and Commission on Cancer of the American College of Surgeons [18]. It is a nationwide oncology outcomes database, currently capturing approximately 70% of all malignancies diagnosed in the United States. Detailed patient data are prospectively collected from the 1500 participating commission-accredited cancer programs and are frequently audited to ensure their high-quality [18]. All data are de-identified and available for research purposes. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytical or statistical methodology employed, or the conclusions drawn from these data.

Clinico-pathological, treatment and demographic variables were extracted from the de-identified NCDB dataset. Cases without microscopic confirmation were excluded from the present study. Patient race was recoded into White, Black, Asian/Native American/Pacific Islander and Other/Unknown while age was grouped as premenarchal/adolescent (≤19 yrs), young adults (20–35 yrs), premenopausal (36–50 yrs) and postmenopausal (>50 yrs). Staging information was based on the pathological stage but if unknown the clinical stage was used. If both values were not available, stage was recoded as unknown. Information available at the collaborative staging fields, was employed to identify women with apparent early-stage disease (T1,2/NX/M0). Site-specific surgery codes were used to determine the performance of hysterectomy and/or omentectomy and the nature of the surgical procedure performed. Extent of lymph node sampling/dissection (LND) and the status of resected lymph nodes (LNs) were determined based on information from the pathology report. For comparison purposes, fertility-sparing surgery (FSS) was defined as unilateral salpingo-ophorectomy without hysterectomy while definite surgery as hysterectomy with bilateral salpingo-oophorectomy. Surgical approach was categorized into minimally invasive (robotic, laparoscopic) and open; however was only available only for cases diagnosed in 2010–2014.

Observed survival (OS) was defined as the duration from tumor diagnosis to the date of death or last-follow up. Kaplan-Meier curves were generated to determine median and 5-year survival rates and univariate analysis between different groups was made using the log-rank test. Patients who were alive at the last follow-up were censored. In addition, a Cox hazard regression analysis was performed to identify factors independently associated with overall mortality. Variables statistically significantly associated with OS by univariate analysis were entered in the multivariate model. Vital status and number of months from tumor diagnosis to the date of last contact or death are suppressed for cases diagnosed in 2014, as such survival analyses were restricted to cases diagnosed in 2013 and earlier. Frequency of distribution of categorical variables was compared with the chi-square test or Fisher's exact test and continuous variables with Mann-Whitney *U* test. All statistical analysis was performed with the SPSS v.24 statistical package (IBM Corp. Armonk, NY) and the alpha level of statistical significance was set at 0.05.

3. Results

A total of 561 patients diagnosed with OYST were identified. Median age was 23 years (range: <1–86 yrs); 35.1% and 46% were ≤19 yrs and 20–35 yrs old, while 11.4% and 7.5% were 36–50 and >50 yrs old. The majority of patients were White (61.9%), followed by Black (26.4%) and Asian/Native American (8%). Table 1 summarizes demographic characteristics of the study patient cohort.

Table 1
Demographic characteristics of women with ovarian yolk-sac tumor.

Variable	N (%)
Age	
≤19	197 (35.1%)
20–35	258 (46%)
36–50	64 (11.4%)
>50	42 (7.5%)
Race	
White	347 (61.9%)
Black	148 (26.4%)
Asian/Native American	45 (8%)
Other/unknown	21 (3.7%)
Year of diagnosis	
2004–2007	174 (31%)
2008–2011	212 (37.8%)
2012–2014	175 (31.2%)
Insurance status[a]	
Uninsured	57 (10.3%)
Private	340 (61.4%)
Medicaid/medicare/government	157 (28.3%)
Income[a,b] (in U.S $)	
<38,000	121 (21.6%)
38,000–47,999	112 (20%)
48,000–62,999	141 (25.1%)
≥63,000	181 (32.2%)
Education[a,c]	
≥21%	117 (21.1%)
13–20.9%	156 (28.1%)
7–12.9%	169 (30.5%)
<7%	113 (20.4%)
Comorbidity (Charlson/Deyo)	
0	525 (93.6%)
≥1	36 (6.4%)
Location[a]	
Large metropolitan (>1 million population)	329 (60.6%)
Other	214 (39.4%)
Facility type[a]	
Academic/research	38 (47.5%)
Other	42 (52.5%)

[a] Based on available information.
[b] Median household income in patient's zip code.
[c] Percent of adult residents in patient's zip code with no high school degree.

Based on available information, median tumor size was 15.4 cm (n = 468, range 0.4–40 cm). The majority were unilateral (93.9%), and 54.2% were arising from the right ovary.

Based on site specific surgery codes, all but 13 patients underwent cancer-directed surgery (CDS) while 55.3% also had lymph node sampling/dissection (LND). The extent of LND could be assessed for 272 patients; 55.5% had <10 LNs removed while 24.6% and 19.9% had 10–19 and ≥20 LNs removed respectively. Overall according to pathology report, rate of LN metastasis was 14%. Premenarchal girls and adolescents (age < = 19 yrs) were less likely to receive LND (48.1%) compared to young adults (age 20–35 yrs, 63.9%) and older women (age > 35, 69.6%), p = 0.007. Among patients with apparent early-stage disease (T1,2/Nx/M0), 58.4% had LND with a documented rate of LN metastasis of 7.3%. Rate of LN metastasis did not differ based on the extent of LND (p = 0.47) or tumor spread (T1 vs T2, p = 0.42). According to information provided by the NCDB, most women had early stage disease (I–II) (58.5%) while 29.6% and 11.9% had stage III and IV disease respectively. Among those with early stage disease, 36.9% had IA, 39% IB-IC, 10.5% INOS and 13.6% stage II disease, respectively. Adolescents and young adults were less likely to present with advanced stage (III–IV) disease (34.3% and 38.2%, respectively) compared to older premenopausal (59.6%) and postmenopausal women (65%), p < 0.001.

Information on the surgical approach selected was available for 222 cases; 83.8% had open surgery (including laparoscopic cases converted to open), while 16.2% had a minimally invasive approach (robotic or laparoscopic). No difference was found between the two groups in regards to tumor size and presence of gross residual disease. However, median hospital stay was slightly shorter (3 vs 4 days) in the minimally

invasive group (p = 0.025). Overall, a total of 210 women had unilateral salpingo-oophorectomy or tumor excision (USO), 43 had bilateral salpingo-oophorectomy (BSO) while 172 had USO or BSO combined with omentectomy and 110 underwent an extended surgical procedure (debulking). Based on available information rate of uterine preservation was 61.8%. However, when examining women without metastatic disease (stage I–III), aged ≤ 35 yrs, rate of uterine preservation was 75.2% (84% for pediatric/adolescent patients and 68.7% for young adults, p = 0.001). Absence of residual gross residual disease following surgery was documented for 85% (147/173) of cases.

Adjuvant chemotherapy was administered to a total of 461 patients (86.8%) at a median of 27 days following tumor diagnosis. Use of adjuvant chemotherapy was higher among patients diagnosed between 2012 and 2014 (91.4%) compared to those diagnosed between 2008 and 2011 (83.1%) and 2004–2007 (86.8%), p = 0.065. No differences in the use of adjuvant chemotherapy were noted based on disease stage (p = 0.35), performance of LND (p = 0.95) or hysterectomy (p = 0.12), patient race (p = 0.53) or age (p = 0.62) and insurance status (p = 0.37). Table 2 summarizes clinico-pathological and treatment characteristics of women with OYST.

According to the reverse Kaplan-Meier method, median follow-up of the cohort was 60.32 months while five year OS was 83.1%. For women who did not undergo CDS, median OS was 4.2 months. For women who had CDS, 5-yr survival rates for those with stage I, II, III and IV disease were 94.8%, 97.1%, 70.9% and 51.6% respectively, p < 0.001 (Fig. 1). No difference in OS was noted between substage IA and IB/IC, p = 0.84 (5-yr OS: 96.6% vs 93.7%). Moreover, no statistically significant difference in OS was observed based on patient race (p = 0.79), type of surgical approach (p = 0.81), presence of residual disease (p = 0.41) or tumor grade (p = 0.29). Presence of residual disease was not associated with OS even when examining patients with stage II–IV disease (p = 0.64), separately (19/60 had gross residual disease). However, higher 5-yr OS rates were observed among pediatric/adolescents (≤19 yrs, 94.4%) and young adults (age ≤ 35 yrs, 89.3%) compared to older premenopausal (age 36–50 yrs, 67.6%) and postmenopausal women (age > 50 yrs, 30.6%), p < 0.001 (Fig. 2). No difference in OS was observed between premenarchal girls (age < 12 yrs, n = 35) and adolescents (n = 151, age 13–19 yrs), p = 0.12; 5-yr OS: 100% vs 93.1% respectively. For patients with non-metastatic disease, aged ≤ 35 yrs, FSS (n = 138) was not associated with worse OS compared to a small group (n < 10) of patients who had definite surgery, p = 0.67. Overall, women aged ≤ 35 yrs with non-metastatic disease, who did not undergo hysterectomy (n = 227) had better OS compared to those who did (n = 72); however following stratification by disease stage, only women with stage III who did not undergo hysterectomy (n = 46) had better OS (5-yr rate 96.4%) compared to those who did (n = 45, 5-yr OS: 76.1%), p = 0.005. Rates of adjuvant chemotherapy between the two groups were similar (90.2% vs 89.8%, p = 0.95) but women who had hysterectomy were older (median age 24 vs 18 yrs, p < 0.001). Regardless of disease stage, performance of LND was not associated with superior OS (p = 0.29). Even for patients with apparent early-stage disease, LND did not confer a survival benefit (p = 0.43). Moreover, for patients with early-stage disease (I–II), omentectomy did not confer a survival benefit (p = 0.79), even after controlling for the receipt of chemotherapy (HR: 1.4, 95% CI: 0.43, 4.6). Administration of adjuvant chemotherapy was associated with better OS, p = 0.016 (5-yr OS: 85.5% vs 77.1%) (Fig.3), even when examining stage I patients (p = 0.062). By Cox multivariate analysis, for women who underwent CDS, disease stage, age and receipt of adjuvant chemotherapy but not LND were associated with overall mortality (Table 3).

Table 2
Clinico-pathological characteristics and treatment of patients with ovarian yolk sac tumors.

Variable	
Laterality	
Unilateral	511 (93.9%)
Bilateral	33 (6.1%)
Stage[a]	
Stage I	255 (50.6%)
Stage II	40 (7.9%)
Stage III	149 (29.6%)
Stage IV	60 (11.9%)
Cancer directed surgery	
No surgery	13 (2.3%)
USO	210 (37.4%)
BSO	43 (7.7%)
USO/BSO with omentectomy	172 (30.7%)
Debulking	110 (19.6%)
Other	13 (2.3%)
Route[a]	
Open	186 (83.8%)
Robotic/laparoscopic	36 (16.2%)
Hysterectomy[a,b]	
No	312 (61.8%)
Yes	193 (38.2%)
LND[a,b]	
No	240 (44.7%)
Yes	297 (55.3%)
Residual disease[a,b]	
No	147 (85%)
Yes	26 (15%)
Chemotherapy[a,b]	
No	70 (13.2%)
Yes	461 (86.8%)

[a] Based on available information.
[b] If cancer-directed surgery was performed, LND: lymph node sampling/dissection.

4. Discussion

To our knowledge this is the largest cohort of women diagnosed with OYST presented in literature. Our study, supports the safety of fertility-sparing surgery for these patients while underlines the necessity of adjuvant chemotherapy. Age and disease stage were also identified as an independent predictors of mortality.

In our cohort, the vast majority of OYSTs were unilateral and were most prevalent in young adults; median patient age in our study was 23 yrs. Age was a strong predictor of mortality, with older (36–50 yrs) premenopausal and postmenopausal (>50 yrs) women exhibiting lower overall survival rates, even after controlling for disease stage and the receipt of chemotherapy. Previous studies on OYSTs have failed to identify any difference in OS between age groups, possibly due to small sample size and the extremely low incidence of MOGCTs among older women [7,9,10,12]. There are only 20 cases of OYSTs arising in postmenopausal women reported in the literature, with poor outcomes [14,19]. In the present study, older women (>35 yrs) were more likely to present with advanced stage disease. In accordance to our findings, an analysis of 2541 patients with MOGCTs drawn from the Surveillance, Epidemiology, and End Results database revealed that age > 40 yrs at diagnosis was significantly associated with cancer-specific mortality [20]. Biological behavior of OYSTs in these age groups may differ and future studies should elucidate the molecular characteristics of these tumors. Interestingly, as noted in our study, reported outcomes of MOGCTs in pediatric and adolescent patients are excellent, regardless of disease stage [21,22]. On the other hand, disease stage was also identified as an independent predictor of mortality. Patients with stage III and IV disease had worse OS than those with early stage disease (I-II) similar to previous studies [3,5,8–12,13,15]. Other prognostic factors reported in literature include tumor diameter [11], presence [3] and quantity [8,9,12] of ascites at tumor diagnosis, papillary or intestinal histologic pattern [12], rate of AFP decline [5,13], and time to AFP normalization [3,5].

Based on evidence extrapolated from the management of epithelial ovarian tumors, FIGO and the NCCN guidelines recommend a complete staging procedure for MOGCTs that includes lymphadenectomy, omentectomy, peritoneal washings, and biopsies [23,24]. However,

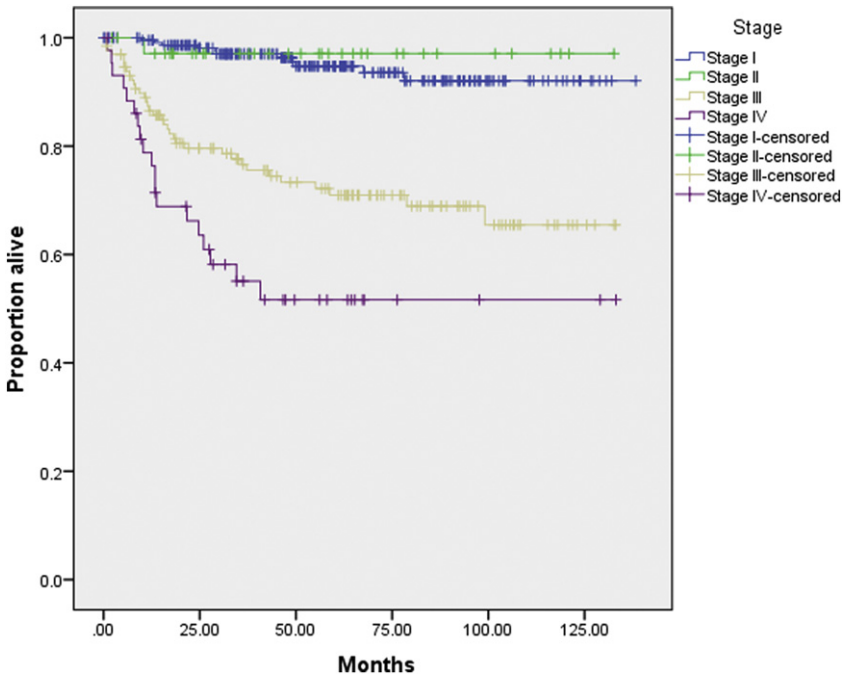

Fig. 1. Overall survival of surgically managed patients with ovarian yolk-sac tumor stratified by disease stage (n = 229 for stage I, n = 36 for stage II, n = 131 for stage III and n = 44 for stage IV, p < 0.001 from log-rank test).

the necessity of a complete staging procedure for MOGCTs has been recently questioned [24–26]. More specifically, the value of systematic lymphadenectomy in the management of MOGCTs is controversial [2,24]. In our cohort, more than half women underwent LN sampling/dissection; among them 44.5% had at least 10 LNs removed. Regional LN involvement was frequent (14.2%) even for women with apparent early-stage disease (7.3%). However, LND was not associated with a better mortality even for patients with apparent early-stage disease supporting evidence deriving from smaller studies [3,5,8,10,13]. A large population-based study also failed to demonstrate a survival benefit for women with MOGCTs who had LND [27]. Women with other histologic subtypes of MOGCTs and stage I disease, can be safely spared of adjuvant chemotherapy only following comprehensive staging that includes LND [24,28]. However, this approach is not applicable to OYST given that adjuvant chemotherapy is routinely administered regardless of disease stage and the presence or absence of LN metastases [2,23,29]. Moreover, in our study patients with early-stage disease (I-II) who had omentectomy did not have a better OS compared to those who did not. Similar to our results, Liu et al., failed to detect a survival benefit when comparing the OS of women with stage I–II disease, who

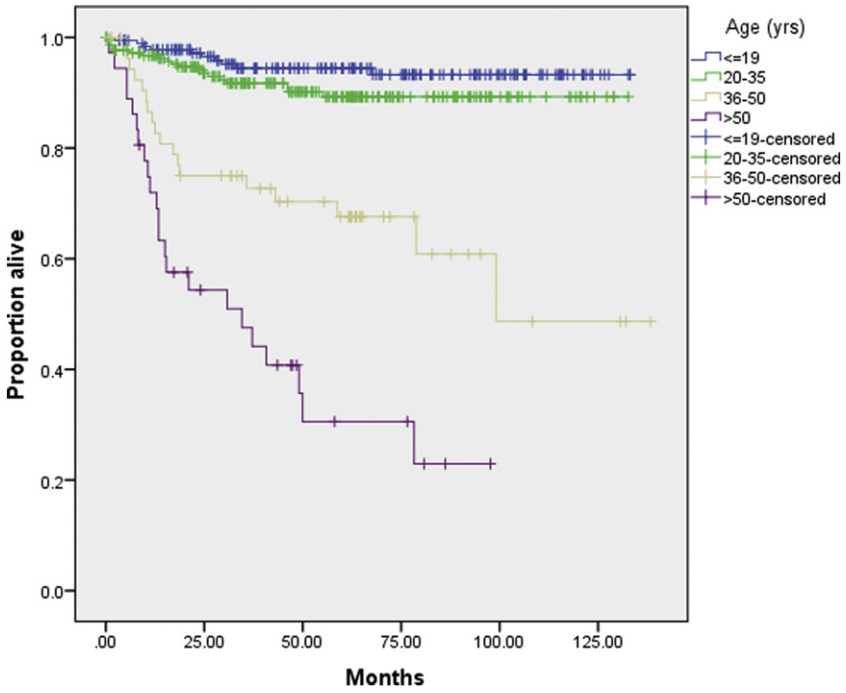

Fig. 2. Overall survival of surgically managed patients with ovarian yolk-sac tumor stratified by age (n = 186 for ≤19 yrs, n = 218 for 20–35 yrs, n = 55 for 36–50 yrs and n = 36 for >50 yrs, p < 0.001 from log-rank test).

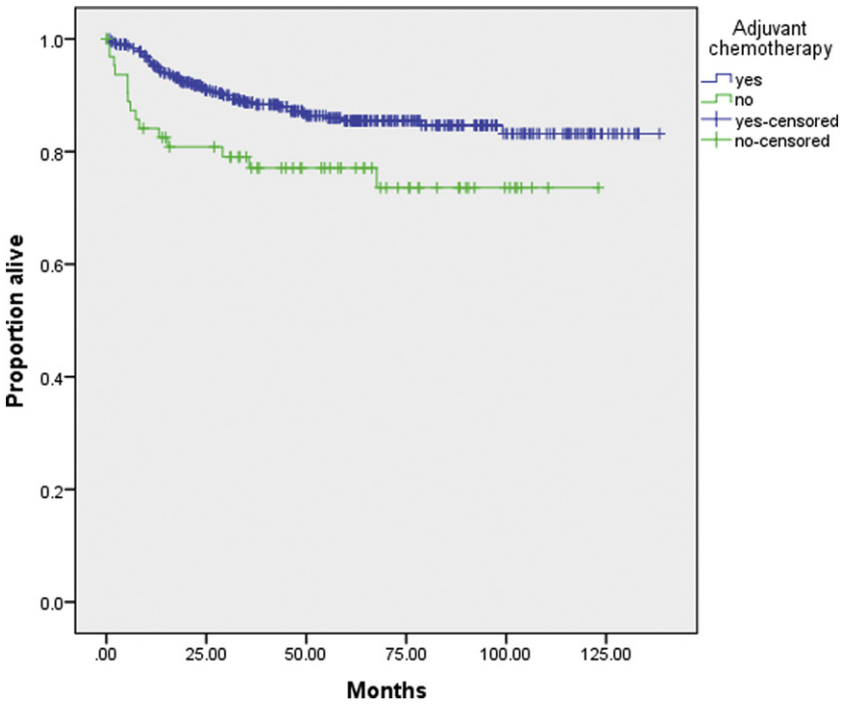

Fig. 3. Overall survival of surgically managed patients with ovarian yolk-sac tumor stratified by receipt of adjuvant chemotherapy (n = 414 for those who did and n = 65 for those who did not receive, p = 0.016 from log-rank test).

did (n = 36) and did not (n = 9) undergo omentectomy; only one patient had microscopic omental metastases [13]. Given the excellent chemosensitivity of OYSTs, a thorough inspection of the abdominal cavity, collection of peritoneal washings, excision of grossly abnormal LNs and any omental lesions is a reasonable approach when staging these tumors [26]. Interestingly, contrary to previous reports, presence of gross residual disease was not associated with worse OS for patients with stage II-III disease, possibly due to the efficacy of the current adjuvant chemotherapy [8,11–13]. Studies identifying residual disease as a prognostic factor are heterogeneous and include patients managed before the introduction of the modern BEP chemotherapy regimen.

A total of 36 patients underwent a minimally invasive (laparoscopic or robotic) staging procedure that was associated with a slightly shorter hospital stay without a detrimental effect on their survival. Currently, laparoscopic staging of early-stage ovarian cancer, including MOGCTs, while feasible remains controversial due to the lack of high-quality data [30,31]. However, since as discussed above, a complete staging procedure may not be required for patients with OYST, a minimally invasive approach in the hands of an experienced surgeon could be an attractive option.

Table 3
Multivariate analysis for predictors of overall mortality in surgically treated patients with ovarian yolk-sac tumors.

	Hazard ratio	95% confidence intervals	
Age (yrs)			p < 0.001
≤19	Referent		
20–35	1.59	0.71, 3.57	
36–50	5.63	2.51, 12.63	
>50	13.37	5.9, 30.28	
Stage			p < 0.001
Stage I	Referent		
Stage II	0.85	0.11, 6.65	
Stage III	6.38	3.11, 13.1	
Stage IV	9.34	4.14, 21.04	
Chemotherapy			p < 0.001
Yes	Referent		
No	3.42	1.8, 6.5	
LND			p = 0.12
No	Referent		
Yes	0.66	0.4, 1.12	

LND, lymph node sampling/dissection.

Given that the majority of women with OYST may have not completed their reproductive potential, fertility-sparing surgery should be pursued. In accordance, to previous reports most patients underwent USO only and rate of uterine preservation for women aged ≤ 35 yrs and early stage disease was 75.2%. Uterine preservation was not associated with worse OS. Similarly, women who had FSS (USO) did not have a worse OS compared to those who had definite surgery (BSO and hysterectomy). It should be noted that for patients wishing to retain their reproductive potential, FSS is recommended even in the case of disseminated disease, [2]. Reported fecundity rates following treatment for OYSTs are encouraging [3,4,10,13].

Both the National Cancer Network and European Society of Medical Oncology (ESMO) clinical guidelines recommend the administration of multi-agent adjuvant chemotherapy for any stage OYST [24,29]. Currently, the bleomycin, etoposide and cisplatin (BEP) regimen has become standard of care for all MOGCTs including OYSTs. Its efficacy for OYSTs was evaluated in a retrospective study examining 52 patients; 5-yr OS rate was excellent (94%), while 97% resumed menstruation and fecundity rate was 75% among women attempting conception [4]. In our cohort the majority of patients (86.8%) received adjuvant chemotherapy and had a better survival even after controlling for disease stage and patient age. Due to their rarity, centralized care of MOGCTs can be advocated. An analysis of 123 MOGCTs from the Multicentre Italian Trials in Ovarian Cancer (MITO) identified treatment outside a referral center as an independent predictor of recurrence [32]. Also, data from the Norwegian cancer registry support the management of patients with metastatic MOGCTs at large cancer centers [33]. In our study, women with stage IV disease had inferior outcomes compared to those with non-metastatic disease, regardless of the administration of chemotherapy or patient age, underlying the need for novel therapeutic options for the management of metastatic MOGCTs.

A major strength of the present study is the large number of patients included, deriving from a multi-institutional database. Moreover, all women were diagnosed between 2004 and 2014, a period during

which the BEP chemotherapy regimen had been established in the management of MOGCTs. However several limitations should be noted. Firstly due to the lack of central pathology report, possible tumor misclassifications cannot be excluded. In addition, detailed information on the staging procedure performed was not available and due to the lack of data on tumor recurrence we were not able to investigate progression free survival. Lastly, presenting symptoms, pre/post-operative serum AFP values, and number of chemotherapy cycles administered are not captured in the NCDB.

OYSTs are typically large unilateral tumors commonly arising in young adults. Fertility-sparing surgery can be safely pursued, while omentectomy and LND could be potentially omitted when staging these tumors. However, adjuvant chemotherapy with BEP should be administered given the observed survival benefit. Future research should focus on the clinical behavior and treatment of OYSTs arising in older women.

Conflicts of interest

Nothing to declare.

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