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Malignant transformation arising from mature ovarian cystic teratoma

A case series

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Abstract

Malignant transformation arising in mature cystic teratoma (MT-MCT) is a rare neoplasm of the ovary. Herein, we aimed to evaluate the clinicopathological features and treatment outcome of the Han Chinese women with MT-MCT.

In this retrospective study, the clinical data of patients who had been surgically treated from January 2000 to November 2019 and in whom the diagnosis of MCT was confirmed based on the pathology were included. Fourteen patients with MT-MCT from a total of 569 cases (2.46% incidence) of MCT were reviewed.

The mean age of patients with MT-MCT was 51.3 (range, 31–71) years, while the mean age of patients with MCT was 45.3 (range, 17–62) years. Upon gross examination, the mean size of MT-MCT was 14.0 (range, 11–25) cm, whereas the mean size of MCT was 7.5 (range, 4–10) cm. Primary surgical staging was performed in all cases. Complete cytoreduction and suboptimal surgical resection were performed in 12 (85.7%) and 2 (14.3%) cases, respectively. Thirteen patients with malignant transformation of squamous cell carcinoma (SCC) whose Federation International of Gynecology and Obstetrics stage was >1 received chemotherapy, comprising carboplatin and paclitaxel. Response to the chemotherapy regimen was complete in 12 patients; 1/12 patients died within the median follow-up period of 16.5 months. The 5-year overall survival rate and disease-free survival rates were 31.2% and 31.6%, respectively.

From the data generated, we conclude that the rate of MT-MCT increases with age. The MT-MCT was much higher in women of postmenopausal age than in younger women. We described our experience of successfully treating patients with malignant transformation of SCC with primary surgical staging and adjuvant chemotherapy (cisplatin, paclitaxel, bleomycin, and etoposide) that might improve survival in patients with advanced-stage disease.

Abbreviations: ADC = adenocarcinoma, BEP = bleomycin, cisplatin, etoposide, BMI = body mass index, CI = confidence interval, DFS = disease-free survival, FIGO = Federation International of Gynecology and Obstetrics, HB = hysterectomy, bilateral adnexectomy, HBO = hysterectomy, bilateral adnexectomy, and omental excision, HBOA = hysterectomy, bilateral appendages, omentum, appendectomy, IC = intraperitoneal chemotherapy with carboplatin, IQR = interquartile range, MCT = mature cystic teratoma, MT-MCT = malignant transformation arising in mature cystic teratoma, OME = omentectomy, OS = overall survival, PAL = para-aortic lymphadenectomy, PLD = pelvic lymphadenectomy, SCC = squamous cell carcinoma, SOT = salpingo-oophorectomy, TAH = total abdominal hysterectomy, TP = cisplatin and paclitaxel.

Keywords: clinical features, malignant transformation, mature cystic teratoma, treatment outcome

1. Introduction

Mature cystic teratoma (MCT) or dermoid cyst is the most common benign germ cell tumors of the ovary. More than 80% of MCTs develop during the reproductive year.[1] However, malignant transformation of MCT (hereafter, MT-MCT) is one of the most serious complications of MCT. MT-MCT is exceedingly rare and occurs in only 1–3% of MCT cases.[2,3]

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The datasets generated during and/or analyzed during the current study are publicly available.

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Owing to its rarity and atypical symptoms, its diagnosis and treatment are challenging. Because MCT and MT-MCT have the same clinical features, most patients are asymptomatic or present atypical symptoms such as abdominal pain and distension.[4] Routine pelvic ultrasonography or computed tomography is widely used in outpatient follow-up visits, but the discrimination ability is limited; the preoperative diagnosis of MT-MCT is particularly difficult.[5,6]

Nowadays, MT-MCT is mainly diagnosed by postoperative pathological examination. Therefore, identifying patients with high risk for MT-MCT and performing preoperative intervention are both essential to gynecological oncologists. Owing to the rarity of MT-MCT, its treatment is also controversial. Currently, the standard treatment for MT-MCT is not well established, and there is no consensus regarding the optimal treatment protocol for this rare condition. Collectively, the clinicopathologic characteristics, treatment, and prognostic factors are not well understood. Thus, it is crucial to determine the clinical characteristics and treatment outcome.

This article describes the clinical features, treatment, and survival outcome of 14 patients with MT-MCT who had been surgically treated between January 2000 and November 2019. To the best of our knowledge, we present the largest case series study of Han Chinese women, and our findings further the understanding of this rare entity and hence will contribute to a better clinical understanding of MT-MCT.

2. Methods

2.1. Patient enrolment

The study included 14 patients with MT-MCT whose data were retrieved from the archives dating from January 2000 to November 2019 in the department of the Central Hospital of Enshi Autonomous Prefecture, Lichuan People's Hospital and Minda Hospital of Hubei Minzu University. The flowchart of patient enrollment is presented in Figure 1. All patients underwent surgical treatment and diagnosis results were based on histopathologic confirmation. The clinical presentation, treatment modality, and follow-up visit outcome of these 14 patients are presented in Table 1. Computed tomography (CT) imaging and measurement of serum tumor markers were carried out in all patients before surgery. Ethical approval was obtained from participating institutions through their respective institutional review boards or the chairperson of their ethics committee who waived the need for patient consent for this study when individual patient consents were not identified.

All patients' information was strictly confidential, and our study protocol was in accordance with the tenets of the Helsinki Declaration.

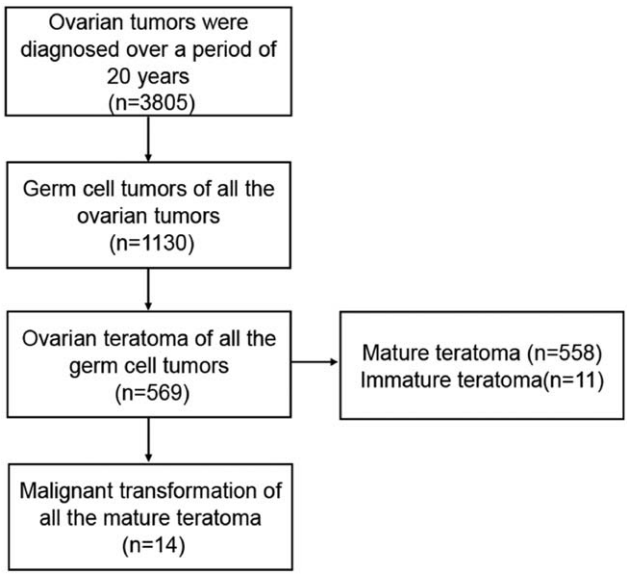

Figure 1. Flowchart of patient enrollment according to inclusion and exclusion criteria.

Table 1

Administration of chemotherapy regimens in the patients with MT-MCT.

Regimen	Case
Cisplatin, paclitaxel	2, 3, 5, 7–14
Bleomycin, etoposide, carboplatin	1, 4, 6
Intraperitoneal chemotherapy, carboplatin	10

Paclitaxel 175 mg/m^2, etoposide 120 mg/m^2, days 1–5, Interval: 3 weeks.
Cisplatin 20 mg/m^2, days 1–5, Interval: 3 weeks.
Bleomycin 30000 IU/d, days 1, 8, 15, 12 weeks.
Carboplatin 400 mg/m2, day 1.
MT-MCT = malignant transformation arising in mature cystic teratoma.

2.2. Surgical treatment

Under general anesthesia, all patients underwent complete reduction at the initial surgery including salpingo-oophorectomy (SOT), lymph node biopsy, and cytologic examination of ascites. Radical debulking surgery was recommended as much as possible; where possible, total abdominal hysterectomy, omentectomy, para-aortic lymphadenectomy , pelvic lymphadenectomy, colostomy, and proctatectomy were performed.

2.3. Adjuvant therapy

Chemotherapy and/or radiotherapy were performed based on the patient's postoperative performance status including age, Karnofsky performance status scores, and tolerance to treatment. Specific chemotherapy regimens and radiotherapy doses are presented in Table 1.

2.4. Follow-up

Clinical and follow-up data for all patients were mainly obtained from the outpatient medical records, supplemented by a telephone interview or online communication. The follow-up period ranged from 6 to 70 (mean follow-up period, 50) months. The final follow-up visit was recorded on July 31, 2020. The follow-up rate was 100%. The OS was defined as the time interval (in months) between the date of surgery and the date of death or censored. The DFS was defined as the time interval (in months) between the date of surgery and the date of recurrence or censored.

2.5. Statistical analysis

For descriptive analysis, continuous variables were presented as the mean with standard deviation or as median with interquartile range and compared using an unpaired, two-tailed *t*-test or

Table 2

Clinical characteristics of patients diagnosed with MCT, with and without malignant transformation.

Subject characteristics	MCT (N = 569)	MT-MCT (N = 14)	*t*	*P*-value
Age (yrs)	45.3 ± 12.7	51.3 ± 14.9	1.693	.092
BMI (kg/m^2)	23.7 ± 5.3	24.1 ± 5.5	1.579	.125
Tumor size (cm)	7.5 ± 2.4	14.0 ± 6.7	8.306	.000
SCC (ng/mL)	12.8 ± 3.9	15.1 ± 4.3	2.124	.035
CA125(U/mL)	35.9 ± 12.8	41.1 ± 10.2	1.488	.138
CA199 (U/mL)	387.5 ± 102.4	398.1 ± 115.7	0.372	.710

SCC, normal range <1.5 ng/mL, CA125, normal range <35 U/mL, CA199, normal range <35 U/mL.
BMI = body mass index, MT-MCT = malignant transformation arising in mature cystic teratoma, SCC = squamous cell carcinoma.

Mann–Whitney test. The Kaplan–Meier method was used for time-to-event data to estimate the median time and its corresponding 95% confidence interval (CI). All *P* values were two-tailed, and $P < .05$ was considered statistically significant. All statistical analyses were performed using the R programming language and environment (v.3.6.2; R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org).

3. Results

3.1. Clinical features

A total of 3805 ovarian tumors were confirmed over a period of almost 20 years. Among these, 1130 (29.7%) of all the ovarian tumors were germ cell tumors; 569 (50.4%) of these germ cell tumors were MCT, and MT-MCT was found in 14 (2.4%) of all the MCT cases. The mean age of patients with MT-MCT was 51.3 (range, 31–71) years, while the mean age of patients with MCT was 45.3 (range, 17–62) years. The main clinical symptoms included abdominal pain (8 [57.1%] cases), abdominal mass (3 [21.4%] cases), pelvic pain (2 [14.3%] cases), and micturition (3 [21.4%] cases). Considering that MCTs are not common in postmenopausal women, 21 (3.7%) postmenopausal patients of all the MCT cases were seen in this study, and 9 of these 21 cases were diagnosed with MT-MCT. With increasing age, the association between age and the chance of malignant transformation significantly increased ($P < .05$), which showed that older patients with MCT were more inclined to have malignant transformation. The disease duration ranged from 5 days to 6 months (mean, 50.2 days). The clinical features of patients are summarized in Tables 1 and 2.

3.2. Imaging findings

Considering that most patients with struma ovarii have clinical manifestations similar to those of MCT, while some patients with MCT may be asymptomatic. In this study, all patients underwent CT before surgery. Overall, 1 (7.1%), 7 (50.0%), and 6 (42.9%) cases were bilateral, left-sided, and right-sided, respectively. According to the imaging presentations (Fig. 2), the mean size of patients with MCT was 7.5 (range, 4–10) cm, whereas the mean size of patients with MT-MCT was 14.0 (range, 11–25) cm. Besides, these results suggested that the MCT was composed of multilocular cysts, fatty components, and a solid part.

3.3. Pathology findings

Gross examination showed that the cut surface of MT-MCT was predominantly filled with hair and fatty components, and a solid part (Fig. 3). Further, the mean size of MT-MCT was 13.5 (range, 12–26) cm, consistent with the results of CT. The association between tumor size and the chance of malignant transformation was significant ($P < .05$). Histological examination under light microscopy revealed that malignant transformation of SCC presented as a nest of malignant squamous cells infiltrating the stroma with keratinized pearls (Fig. 4A and B), whereas malignant transformation of adenocarcinoma (ADC) was identified as glands and numerous mitotic figures (Fig. 4C).

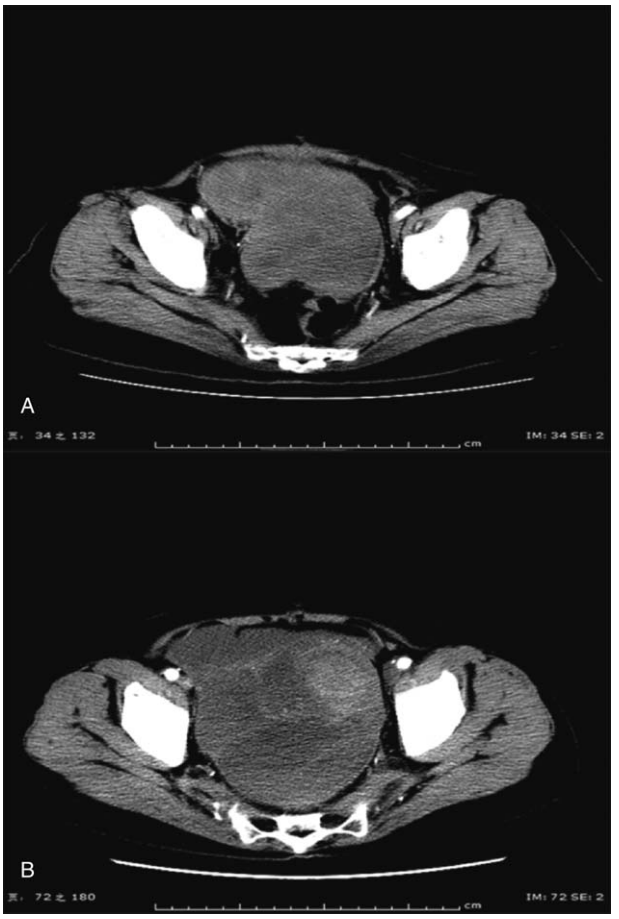

Figure 2. Computed tomography findings in patients with MT-MCT. (A) Pretreatment computed tomography of pelvis showed the irregularly shaped tumor of the left pelvis (Case 3). (B) Pretreatment computed tomography of pelvis showed the irregularly shaped tumor of the left pelvis and ascites in the pelvic cavity (Case 8). MT-MCT = malignant transformation arising in mature cystic teratoma.

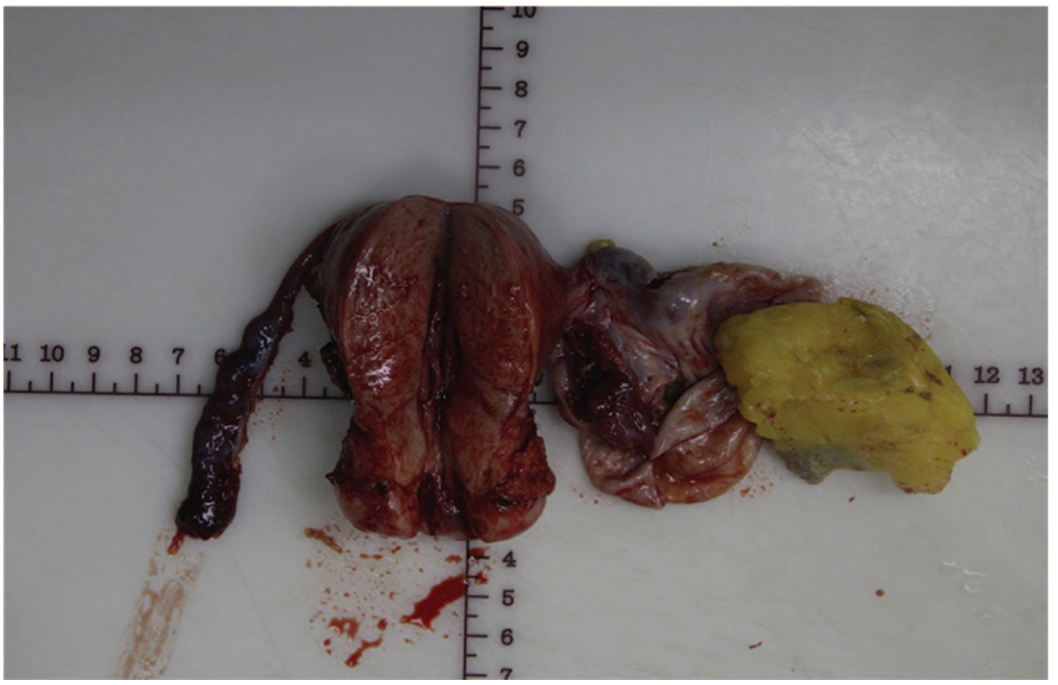

Figure 3. Gross examination of MT-MCT. MT-MCT = malignant transformation arising in mature cystic teratoma.

Immunohistochemical studies revealed that all patients were positive for P63 (Fig. 4D). Two patients (14.3%) were positive for EMA. The Ki-67 proliferation index ranged from 15% to 57%, and a moderate proliferation index was observed in most patients.

3.4. Treatment modalities and prognosis

As shown in Table 1, the surgical treatment modalities were hysterectomy, bilateral adnexectomy, and omental excision (n = 2 [14.3%]); hysterectomy and bilateral adnexectomy (n = 11 [78.6%]); and hysterectomy, bilateral appendages, omentum

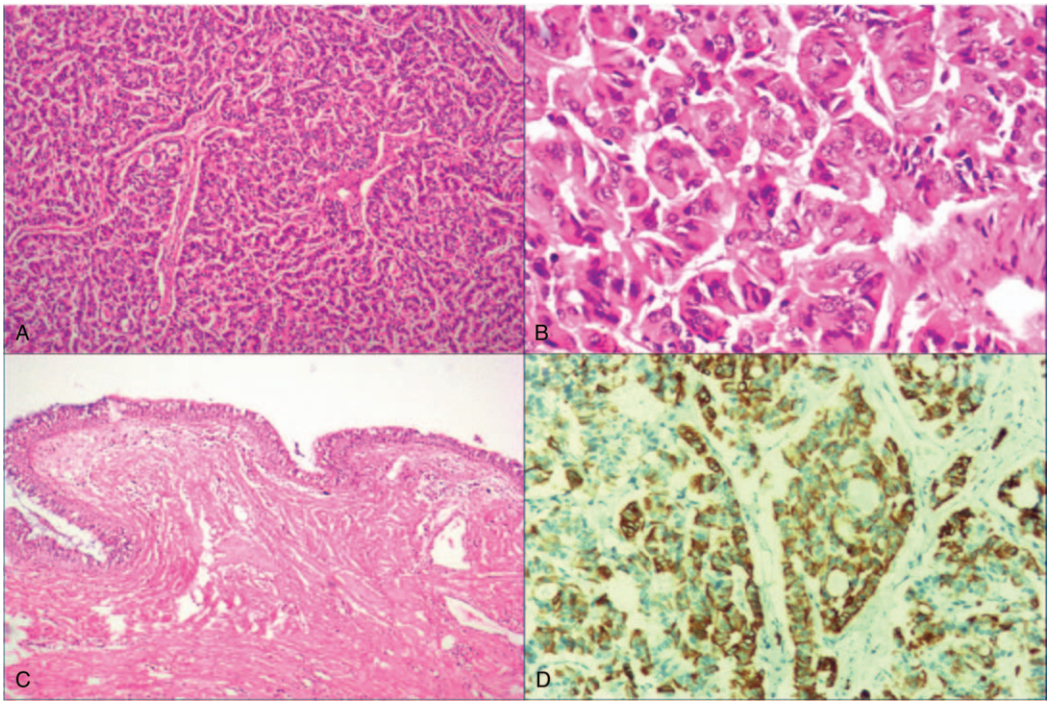

Figure 4. Pathological findings and immunohistochemical staining results. (A) Squamous cell carcinoma is shown within the MCT (H&E, 40×). (B) Nest of malignant squamous cells infiltrating the stroma with keratinized pearls (H&E, 200×). (C) Adenocarcinoma with glands and numerous mitotic figures (H&E, 200×). (D) Immunohistochemical staining showed positivity for P62 (IHC, 200×). MCT = mature cystic teratoma.

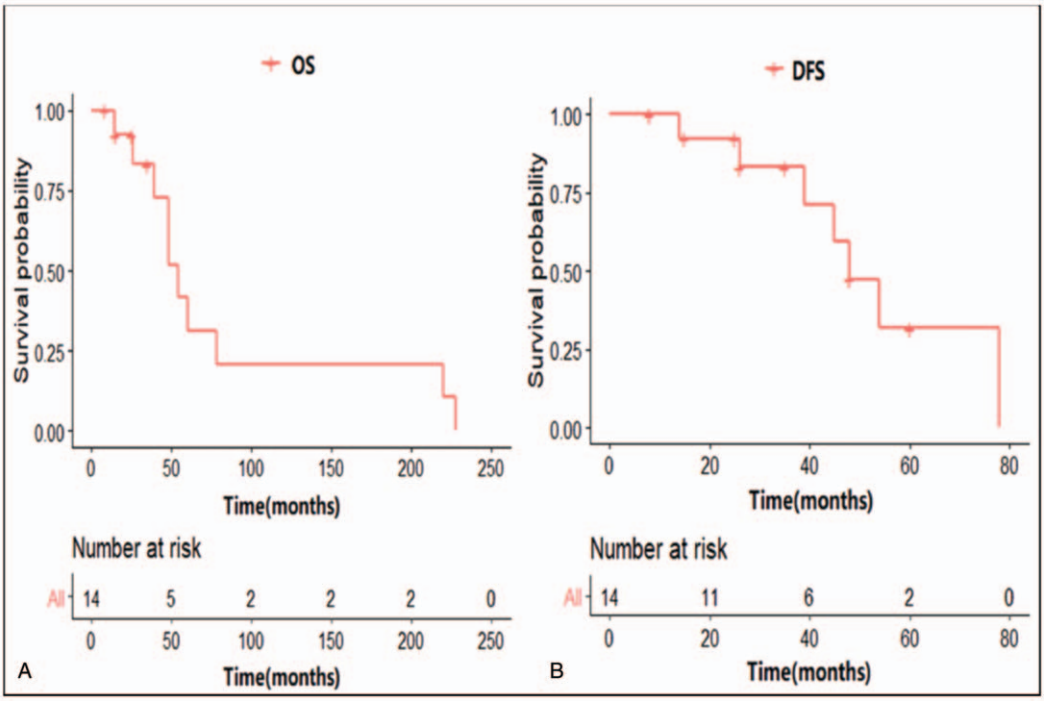

Figure 5. Kaplan–Meier analysis of (A) overall survival and (B) disease-free survival in patients with MT-MCT after treatment. MT-MCT = malignant transformation arising in mature cystic teratoma.

majus, and appendectomy (n = 1 [7.1%]). Tumor dissemination on the surface of the rectum and the peritoneum of the pelvic cavity was seen in two (14.3%) cases. The cytologic examination of ascites was negative in 11 (78.6%) cases and positive in 3 (21.4%). Complete cytoreductive surgery was performed in 12 (85.7%) patients, and suboptimal cytoreductive surgery was performed in 1 case with tumor dissemination on the surface of the rectum, but not in the upper abdomen. All patients received platinum-based chemotherapy. Bleomycin, cisplatin, etoposide was given to 3 (21.4%) patients; cisplatin, paclitaxel was given to 10 (71.4%) patients. Twelve patients underwent complete 6–8 cycles, and all these 12 patients attained complete remission. Therefore, the patients with MCT may respond well to chemotherapy; the remaining 2 patients with stage IIB underwent 2 cycles and discontinued later because of disease progression. Their median DFS time was 26.3 months, and they finally died because of advanced disease. The other 12 patients were alive at the time of the last follow-up. The estimated 5-year OS and DFS rates were 31.2% and 31.6%, respectively (Fig. 5).

4. Discussion

Mature cystic teratoma is a common ovarian germ cell tumor comprising 30–45% of all ovarian tumors, which occurs during reproductive age.[7] MT-MCT is one of the most serious complications of MCT. The incidence of malignant transformation varies from case report to case series, accounting for 1–3% of all the MCT cases.[3,8] Over a period of 40 years, only 2 case series have reported that the frequency of MT-MCT was as high as 6.67%[9] and 5%,[10] respectively. In our study, the incidence was 2.4%, which is consistent with the reported literature. To the best of our knowledge, this is the first retrospective study on Han Chinese women with MT-MCT, which partly provides a detailed comprehension of ethnic-related clinical features, treatment, and prognosis in patients with MT-MCT.

Because the presence of MT-MCT is usually similar to the presence of MCT, patients are usually asymptomatic or experience abdominal pain or pelvic solid mass.[11,12] In such cases, identifying patients with high-risk for MT-MCT is needed at the initial diagnosis. However, patients with MT-MCT do not present with definite symptoms or signs that distinguish them from MCT; hence, some cases are misdiagnosed preoperatively, which leads to suboptimal surgical resection and poor prognosis. Previous studies have demonstrated that MT-MCT typically occurs in postmenopausal women.[3,13,14] Kikkawa et al found that 37 cases with malignant transformation of SCC, the mean age of whom were older (55.2 years) than the mean age (37.5 years) of patients with MCT.[15] Wei et al found that 7.6% of patients with MCT had a malignant transformation, whereas the incidence of MT-MCT in the postmenopausal age group was 15%.[16] In our study, 9 out of 14 patients with MT-MCT were in postmenopausal state, which is consistent with previously published results.[15,16] Indeed, the chances of malignant transformation are higher in postmenopausal than in premenopausal women, which will prompt us to focus on the stratification of age-related risk factors in the future. For example, provided that a postmenopausal woman is diagnosed with MCT, we may need to be more vigilant about the possibility of malignant transformation.

Angiogenesis is a key process in cancer spread and metastasis.[17,18] Tumor size has been recognized as one of the biggest risk factors for ovarian tumors.[19] However, gross examination showed that the mean size of MCT and MT-MCT were >5 cm.[1,20,21] Kikkawa et al found that the mean size of MT-MCT was 15.2 cm and that of MCT was 8.8 cm.[15] In our study, the mean size of MT-MCT continued to increase by at least

11 cm, as compared to the mean size of MCT. Based on the rapidly enlarging tumors, although patients with MCT present with a painful abdominal or pelvic mass, the possibility of MT-MCT is still high. Owing to the lack of any distinguishable specific signs and symptoms, the preoperative findings may depend on the tumor size to some extent and might provide more practical and clinical information for clinicians.

Quite often, the usefulness of serum tumor markers in MT-MCT is not clearly understood.[19] Tseng et al reported that patients with malignant transformation of SCC had elevated SCC-Ag levels.[22] Mori et al found that patients (>40 years old) showed the high possibility of malignant transformation if the serum SCC-Ag exceeded 2.5 ng/mL.[23] In our study, 12/14 patients with MT-MCT showed elevated SCC-Ag levels, which was consistent with previous studies. Compared to the patients with MCT, the elevated SCC-Ag levels had a significant difference, especially for those patients with recurrent lesions, the SCC-Ag levels might act as serial SCC monitoring. Besides, the elevated serum tumor markers such as CA-125 and CA-199 were reported in patients with benign and malignant tumors. However, there was no obvious distinction between MT-MCT and MCT in our study, which is consistent with published results. It is therefore not surprising that MCT, such as epithelial tumors, cannot be definitely distinguished preoperatively.[24] Hence, more effort is required to develop novel biomarkers for early diagnosis, along with evaluation and monitoring of therapeutic treatments. In this study, immunohistochemical results showed that p62 was positive in all cases. Yan et al found that p62 and caspase 8 may become novel prognostic biomarkers for ovarian cancer treatment.[25] Previous findings have placed p62 at critical decision points that control cell death and survival.[26,27] Hence, we speculate that p62 may be a candidate molecular marker for diagnosis and prognosis in MT-MCT, but this needs to be further verified.

Surgery is the standard therapeutic option for MT-MCT. Previous studies showed that complete cytoreduction surgery can improve the prognosis for postmenopausal women.[22,28] Hackethal et al reported that complete cytoreduction surgery, including hysterectomy, bilateral SOT, and lymphadenectomy followed by adjuvant chemotherapy are associated with a better prognosis than postoperative radiotherapy in patients with MT-MCT and advanced-stage cancer.[4] Tseng et al demonstrated that unilateral oophorectomy is appropriate for patients with early stage disease.[22] Owing to the rarity of MT-MCT, there is a lack of evidence for an optimal treatment option. In our study, because patients were diagnosed with stage I and II cancers, we could perform optimal cytoreduction for most patients. At the same time, all the patients received platinum-based chemotherapy for adjuvant treatment. Sakuma et al reported that aggressive cytoreduction for advanced disease, followed by adjuvant therapy, might be related to a remarkable prognosis.[29] Indeed, considering that MT-MCT has a poor prognosis, the stage, cyst-wall invasion, rupture, and tumor type are prognostic factors; furthermore, early stage and optimal cytoreductive surgery might improve patients' survival. However, the optimal adjuvant therapy for this rare entity, especially for the advanced stage, has not been established. In previous studies, >80% malignant transformation were SCCs,[2] followed by ADCs,[30] neuroectodermal tumors,[31] sarcoma,[31] and malignant melanoma.[32] In our study, 6/14 patients with malignant transformation of SCC had higher than stage IA disease and received platinum-based chemotherapy, which showed an improvement in median survival. Cisplatin-based palliative chemotherapy is the only treatment option for epithelial ovarian cancer owing to its known activity.[33–35] However, 1 patient with malignant transformation of ADC received cisplatin-based palliative chemotherapy and appeared to have an unsatisfactory prognosis. It is not surprising that the poor prognosis of ADC might be related to its insensitivity to chemoradiation. Previous studies revealed that ADCs are less sensitive to radiation than squamous-cell carcinomas.[36,37] Fukase et al reported that patients with malignant transformation of SCC received surgery, followed by carboplatin, paclitaxel, and bevacizumab chemotherapy might improve prognosis in patients with advanced-stage disease.[38] According to previous report and our experience, we recommended platinum-based chemotherapy after optimal cytoreductive surgery for patients with malignant transformation of SCC and advanced-stage disease is useful.

5. Conclusion

Our study also has some limitations. First, the incidence of MT-MCT might be underestimated and hence, large cohort studies are needed in the future. Second, the retrospective nature of the study is inevitably associated with some inherent bias. Third, while we recommended that platinum-based chemotherapy might contribute to the prognosis of patients with malignant transformation of SCC, we acknowledge the inadequacy of these results owing to the limited sample size. Besides, the optimal treatment for other types of malignant transformation also needs further elucidation. However, according to the published report and our experience, we recommended that complete cytoreductive surgery, followed by platinum-based chemotherapy, might be helpful to prolong survival in patients with malignant transformation of SCC. To sum up, the metastatic transformation of mature cystic teratoma is a rare condition with a poor prognosis. Postmenopausal women, large tumor size (>10 cm), and suboptimal cytoreductive surgery are associated with an increased risk for developing malignant transformation. In the future, prospective cohort studies should be designed to address these limitations and validate our results.

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Visualization: Xin Gu.
Writing – original draft: Li Qin.
Writing – review & editing: Zaiping Wang, Du He.

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