Clinical Features and Survival Outcome of Patients with Malignant Transformation Arising in Mature Cystic Teratoma: A 20-Year Experience at Multicenter Institution and Literature Review on 342 Cases

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Research article

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Background: To analyze the clinicopathologic characteristics and prognosis in malignant transformation of mature cystic teratoma (MT-MCT).

Methods: We retrospectively reviewed 23 patients (cohort 3) diagnosed with MT-MCT from the medical center (Tongji Hospital and Hubei cancer hospital), between January 1990 to June 2020. Cohort 2 was obtained from the PubMed, CNKI, Web of Science, and MEDLINE database, between January 1990 to June 2020. Cohort 3 was based on the surveillance, epidemiology, and results registry (SEER) database, between January 1975 and December 2016.

Results: Among 3865 cases diagnosed with mature cystic teratoma, the incidence of MT-MCT is 23 (0.59%). The mean age of 23 patients was 50.6 years (median 49.0, range 24 to 71 years). Patients mainly had abdominal pain (21.7%) or complained about an abdominal mass (30.4%). The mean tumor size was 11.6 cm (median 11.9, range 5.2 to 14.8 cm). According to the FIGO stage, eight patients were in stage I (34.8%), two cases were in stage II (8.6%), III (47.8%), and IV (8.7%), respectively. Most patients were diagnosed with squamous cell carcinoma (91.3%). Most patients received total hysterectomy, salpingo-oophorectomy, and omentectomy. Five patients (21.7%) received lymphadenectomy. Platinum-based chemotherapy and radiotherapy were selectively used for patients after surgical resection. The mean of disease-free survival was 27.3 months (median 22.0, range 3.0 to 67.0 months). According to the published data analysis of 342 cases, the 1-, 3-, and 5-year overall survival rates were 53.2%, 33.1%, and 23.2%, respectively. The young patients (≤55 years) showed better prognosis.

Conclusion: MT-MCT has an aggressive clinical course, with poor long-term prognosis. The high incidence in postmenopausal women should not be ignored. The effectiveness of adjuvant chemotherapy or radiotherapy after surgery is needed to elucidate in the future.

Abstract

Background

Mature cystic teratoma (MCT), as one of the common ovarian benign germ cell-derived tumors in women of childbearing age, the appearance of the tumor is cystic, the histology is typically characterized by mature multiple germ layer tissue components[1]. Even for mature teratoma, a few cases will eventually undergo malignant transformation. Previous studies have shown that the probability of malignant transformation of mature cystic teratoma (MT-MCT) ranges from 0.5–4.0%[2, 3]. Besides, patients with mature teratoma arising from malignant transformation are easily underestimated and misdiagnosed with MCT. Therefore, strengthening the understanding of MT-MCT will help clinical diagnosis and treatment, as well as improve the prognosis of patients more optimally.

Methods

Study design

The ovarian mature teratoma malignant cases collected in this study were divided into three parts. The 264 cases (cohort 1) was from the published case report study, the following medical subject headings or specific terms were used as follows: “Mature teratoma”, “Mature teratoma with the malignant transformation”, “Mature cystic teratoma”, “Case report”, “Prognosis”. The second part included a multi-center of 23 cases (cohort 2) was from three medical centers. 78 patients(cohort 3) were identified using the Surveillance, Epidemiology, and End Results (SEER) database[7]. This was a retrospective collaborative multicenter observational cohort study because the study was done with anonymized patient records, so patient consent to review their records was not required by the institutional review board. All patients’ information was carried out according to the Declaration of Helsinki. The retrospective chart review of the 23 patients cohort was approved by the institutional research ethics committee of Tongji Hospital and Hubei Cancer Hospital.

Case collection

The inclusion criteria of the case report were as follows: (i) the patient’s clinical data and follow-up outcome information were recorded completely. (ii) all patients had an accurate pathological diagnosis, tumor stage, and location within the ovary. (iii) all patients had a detailed treatment plan and efficacy evaluation. The case inclusion criteria of the multicenter retrospective study were consistent with the above criteria.

Follow-up

According to published literature and multi-center retrospective cases, this study mainly conducted follow-up analysis on the prognosis of patients, including overall survival (OS) and disease-free survival (DFS). The OS is defined as the time from receiving treatment to death due to any cause. DFS is contained the period from the date of resection to the date of first recurrence or last follow-up.

Statistical analysis

The survival outcome of patients with reported follow-up was estimated by the method of Kaplan-Meier, stratified survival analysis by variables such as age, tumor stage, treatment. Survival outcome differences were assessed with the Log-rank test. Mann-Whitney U-test was used to estimate significant differences in quantitative parameters. The two-tailed t-test was used for categorical and numerical variables, respectively. A P value of less than 0.05 was significant.

Results
Clinical Features and Treatment

The demographic features of 23 patients enrolled in this study were shown in Table 1. During 30 years period (1 January 1990 to 30 June 2020), a total of 3865 cases diagnosed with MCT were reviewed and 23 cases of MT-MCT were identified from multicenter institutions. In this study, the incidence of MT-MCT was 0.59%. The mean age of patients at the diagnosis time was 50.6 years (median 49.0, range 24 to 71 years). Patients mainly had abdominal pain (21.7%) or complained about an abdominal mass (30.4%). The other presenting symptoms were pelvic pain (4.3%) or urinary frequency (4.3%). The mean tumor size was 11.6 cm (median 11.9, range 5.2 to 14.8 cm). Most patients with a larger tumor size of more than 10 cm. Twenty-two patients had unilateral tumors of the ovary. Only one patient had a bilateral tumor. According to the FIGO stage, eight patients were in stage I (34.8%), two cases were in stage II (8.6%), III (47.8%), and IV (8.7%), respectively. Most patients were diagnosed with squamous cell carcinoma (91.3%), only two patients were diagnosed with endometrioid adenocarcinoma (4.3%) and adenocarcinoma (4.3%), respectively. Most patients received total hysterectomy, salpingo-ophorectomy, and omentectomy. Five patients (21.7%) received lymphadenectomy. Most of them received complete six cycles of platinum-based chemotherapy. Four patients (17.4%) were received two to seven cycles bleomycin, cisplatin, etoposide (BEP) chemotherapy. Intraperitoneal chemotherapy with carboplatin (IC) was given to 2 cases (8.7%). Radiotherapy was given to 1 case who received six cycles of complete nedaplatin and paclitaxel (TP) chemotherapy.

Pathology Findings

Grossly, the mean size of MT-MCT was 12.0 cm (median 10.2, range 4.7-16.9 cm). The tumor showed keratinized stratified squamous epithelium, sebaceous glands, skeletal muscle, and adipocytes. Squamous cell carcinoma was the most frequent MT-MCT (Figure3A), followed by adenocarcinoma (Figure3B). Areas with malignant transformation into squamous cell carcinoma, the nests of malignant squamous cells infiltrating the stroma with entrapped hair follicles. One case diagnosed presented with ascites had adenocarcinoma in the peritoneum. In four patients where the suspicion of metastasis was taken along with the removal of the tumor and peritoneal biopsy. In two cases accompanied by torsion of the MCT, the tumor size more than 10 cm presented with partial necrosis and hemorrhage. Immunostaining was performed in eight cases, the results were expressed as “positive/total numbers”, among these biomarkers, P16(0/7), CK7(2/4), CD56(6/11), EMA (4/9), S-100(3/16), ER (3/3) and PR (1/10).

Imaging Findings

The computed tomographic (CT) findings of nine cases were evaluated with the presence or absence of nodular formation, border, size, and transmural growth as well as metastasis (lymphadenopathy or disseminated disease). On CT imaging, the size of the tumor ranged from 10.0 to 20.0 cm. Among these patients, soft tissue components were observed in six cases (66.7%) of nine tumors (Figure3C and D), six (18.2%) cases had nodular formation, two cases (22.2%) showed transmural growth, and the soft tissue components invaded the adjacent structures. Two cases (22.2%) showed disseminated disease. One case (11.1%) showed bone, lung, and liver metastases.

Survival outcome and Prognosis analysis

As of June 30, 2020, eight patients (34.8%) were alive. Two patients (8.7%) had distant metastasis at diagnosis, after received surgery, following platinum-based chemotherapy. Finally, both died during the follow-up time, while the rest of the twenty-one patients received surgery and adjuvant therapy without recurrence. The mean of disease-free survival was 27.3 months (median 22.0, range 3.0 to 67.0 months). Based on a large population cohort, a total of 342 patients with MT-MCT were enrolled from the SEER database and published case reports. Patient characteristics were summarized in Table 2. The 1-, 3-, and 5-year overall survival rates were 53.2%, 33.1%, and 23.2%, respectively. There was no statistical difference in overall survival between pathological type, tumor size, age, and FIGO stage. For patients with early-stage had a significant prognostic outcome compared with advanced stage (P<0.0001, Figure1A). For young patients (<55 years) compared to older age (≥55 years), the young patients showed better prognosis (P<0.01, Figure1B). However, the differences in survival between squamous cell carcinoma and adenocarcinoma, also endometrioid adenocarcinoma, had no significance (P=0.63, Figure2).

Discussion

MT-MCT is rare and occurs in approximately one percent of all cases[8, 9]. Because of the rarity of this disease, there are no established criteria of diagnosis before surgery for carcinoma arising from MCT[1]. Most of the previous studies detailed the clinicopathological features, the prognosis was not analyzed due to the limited samples. In the past 40 years, adenocarcinoma, sarcoma (2%), melanoma, basal cell carcinoma, and carcinoid were reported. Consistent with previous studies, ranking according to pathological type incidence rate, the most common histology arising in mature cystic teratoma is squamous cell carcinoma, followed by adenocarcinoma[1, 6, 10]. For several case reports, the age of patients with MT-MCT at diagnosis tended to be older than patients diagnosed with MCT. Based on the large population cohort, we concluded that the mean age of patients was 55.0 years old, which demonstrated that most of the patients were in a postmenopausal state, and the concentration of high risk in postmenopausal women should not be ignored. According to the imaging examination results, the tumor size seemed to be positively correlated with adverse prognosis, which was highly consistent with the survival outcome related to tumor stage[11]. In our study, the median size of the tumor was 11.6 centimeters, tumor size more than 10 centimeters seemed to indicate a worse prognosis. Collectively, more attention should be paid to the joint analysis of the clinical characteristics, auxiliary examinations, and treatment outcomes in patients with MT-MCT.

Besides, this study also relied on a large population cohort for survival stratification analysis. Studies to date indicate that drugs should be considered for chemotherapy regimens, especially alkylating drugs were associated with increased survival in advanced tumor stage, however, postoperative radiotherapy did not show dominated benefit and might adversely affect survival outcome[2, 3, 12]. Collectively, the optimal adjuvant therapy for this rare tumor has not been established. In this study, most of the patients mainly received platinum-based chemotherapy, due to its known effect against epithelial ovarian cancer. From the literature review, the adjuvant treatment effect was consistent with this study. Herein, it is necessary to conduct clinical trials to elucidate the appropriate treatment options for patients with MT-MCT.
Our study has some limitations. First, because of the rarity of this disease, data on characteristics, treatment, and prognosis were available for 342 patients, however, detailed data collection on published cases and databases was difficult, prognostic factors for MT-MCT were not acquired. Second, from 1 January 1980 to 30 June 2020, the FIGO stage and treatment strategy had been revised and developed, biases in survival analysis were inevitably existed, especially adjuvant therapy including chemotherapy or radiotherapy, which might conduct heterogeneity. Third, this was a retrospective study, concerning confound variables or potential key factors that might be the consequence of the prognosis, however, prospective studies are needed to elucidate in the future. Collectively, we have limited cases for analyzing and finding definite conclusions as to optimal adjuvant therapy.

**Conclusion**

MT-MCT is rare, but the long-term prognosis is poor. A multimodality aggressive approach including adjuvant chemotherapy or radiotherapy after surgical resection is needed to elucidate depending on prospective clinical trial and follow-up. The high incidence in postmenopausal women should not be ignored and preventive monitoring and clinic screening are necessary. As more experience is gathered with this rare entity, more specific guidelines can become available in the future.

**Abbreviations**

MT-MCT: malignant transformation of mature cystic teratoma  
MCT: mature cystic teratoma  
FIGO: International Federation of Gynecology and Obstetrics  
SEER: Surveillance, Epidemiology, and End Results database  
OS: overall survival  
DFS: disease-free survival  
HBOL. hysterectomy, bilateral salpingo-oophorectomy, omenterectomy, lymphadenectomy.  
HU. Hysterectomy, unilateral salpingo-oopherectomy, excision of tumor.  
HBO. Hysterectomy, bilateral salpingo-oopherectomy, omenterectomy.  
HB. Hysterectomy, bilateral salpingo-oopherectomy, excision of tumor.  
HUOL. Hysterectomy, unilateral salpingo-oopherectomy, omenterectomy, lymphadenectomy.  
BEP. bleomycin, cisplatin, etoposide.  
TP. nedaplatin and paclitaxel.  
IC. intraperitoneal chemotherapy with carboplatin.  
DC. docetaxel and carboplatin.  
NA. unknown.

**Declarations**

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Not applicable

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**Availability of data and materials**

The datasets used and or/ analysed during the current study are available from the published report and database on reasonable request.

**Authors' contributions**

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

**Ethics approval and consent to participate**
This was a retrospective collaborative multicenter observational cohort study because the study was done with anonymized patient records, so patient consent to review their records was not required by the institutional review board. All patients' information was carried out according to the Declaration of Helsinki. The retrospective chart review of the 23 patients cohort was approved by the institutional research ethics committee of Tongji Hospital and Hubei Cancer Hospital.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables
| ID  | Age (year) | BMI | Symptom                          | Site | Size(cm) | Stage* | Differentiation | pathological | Surgery | Chemotherapy | Radiotherapy |
|-----|------------|-----|----------------------------------|------|----------|--------|----------------|-------------|---------|--------------|-------------|
| case1 | 47         | 22.2 | Abdominal swelling               | L    | 11       | IC     | NA             | SCC         | HBOL    | BEP          | No          |
| case2 | 54         | 18.8 | Mass, weight loss                | L    | 16.9     | IIIC   | well-moderately | SCC         | HBOL    | DP           | No          |
| case3 | 46         | 30.8 | Abdominal swelling               | L    | 13       | IIIC   | well           | SCC         | HBOL    | TP           | No          |
| case4 | 52         | 27   | Abdominal swelling & fever       | R    | 14.5     | IIIC   | moderately     | SCC         | HU      | NA           | No          |
| case5 | 44         | 17.2 | Abdominal swelling               | R    | 11.6     | IIIB   | moderately     | SCC         | HBOL    | TP           | No          |
| case6 | 59         | 23.8 | Abdominal swelling               | R    | 4.9      | IIIC   | poorly         | ADC         | HBOL    | TP           | No          |
| case7 | 51         | 21.2 | Abdominal pain                   | L    | 14.9     | IC     | NA             | SCC         | HBOL    | TP           | No          |
| case8 | 47         | 24.3 | Abdominal pain                   | R    | 16.5     | IC     | moderately     | SCC         | HBOL    | TP           | No          |
| case9 | 41         | 21.6 | Abdominal pain                   | L    | 9.5      | IIIA   | well           | SCC         | HBOL    | TP           | No          |
| case10 | 64        | 22.5 | Abdominal pain                   | L    | NA       | IIIA   | NA             | SCC         | HBOL    | TP           | No          |
| case11 | 49        | 32.8 | Mass                             | L    | 12.1     | I      | NA             | SCC         | HBO     | IC           | No          |
| case12 | 49        | 25.3 | Mass                             | R    | NA       | IC     | moderately     | SCC         | HBOL    | TP           | No          |
| case13 | 24        | 18.4 | Abdominal pain                   | R    | 14.2     | IIC    | well-moderately | SCC         | HBOL    | TP           | No          |
| case14 | 53        | 18.6 | Abdominal pain                   | R    | NA       | II    | poorly         | SCC         | HBOL    | TP           | No          |
| case15 | 39        | 15.4 | Abdominal pain & abdominal swelling | L  | NA       | IV     | moderately     | SCC         | HBOL    | TP           | No          |
| case16 | 48        | 18.8 | Mass                             | R    | NA       | IV     | moderately-poorly | SCC         | HBOL    | DP           | No          |
| case17 | 65        | 21.9 | Mass, abdominal pain             | R    | 4.7      | IIIC   | well-moderately | SCC         | HBO     | TP           | No          |
| case18 | 49        | 21.5 | Abdominal swelling & urinary frequency | R  | NA       | IC     | NA             | SCC         | HBOL    | BEP          | No          |
| case19 | 65        | 17.8 | Mass                             | L&R | NA       | IIIC   | NA             | SCC         | HBOL    | IC           | No          |
| case20 | 44        |       | Abdominal pain                   | R    | NA       | IIIC   | poorly         | EC          | HBOL    | BEP          | No          |

Notes: 23 patients were from the Tongji hospital and Hubei Cancer hospital.

*. According to the International Federation of Gynecology and Obstetrics staging manual.

Abbreviations: L. left; R. right. ADC. adenocarcinoma; EC. endometrioid adenocarcinoma. SCC. squamous cell carcinoma. BMI. body mass index.

HBOL. hysterectomy, bilateral salpingo-oophorectomy, omentectomy, lymphadenectomy.

HU. Hysterectomy, unilateral salpingo-oophorectomy.

HB. Hysterectomy, bilateral salpingo-oophorectomy.

HUOL. Hysterectomy, unilateral salpingo-oophorectomy, omentectomy, lymphadenectomy.

BEP. bleomycin, cisplatin, etoposide.

TP. nedaplatin and paclitaxel.

IC. intraperitoneal chemotherapy with carboplatin.

DC. docetaxel and carboplatin.

NA. unknown.
| ID    | Age (year) | BMI | Symptom | Site | Size(cm) | Stage* | Differentiation       | pathological | Surgery | Chemotherapy | Radiotherapy | Notes                                                                 |
|-------|------------|-----|---------|------|----------|--------|-----------------------|--------------|---------|---------------|--------------|------------------------------------------------------------------------|
| case21| 59         | 20  | Mass    | L    | 8.6      | IA     | NA                    | SCC          | HB      | BEP           | No           | 23 patients were from the Tongji hospital and Hubei Cancer hospital.  |
| case22| 43         | 9.6 | Mass    | R    | 9.6      | IIIC   | moderately-poorly     | SCC          | HBOL    | BEP           | No           | * According to the International Federation of Gynecology and Obstetrics staging manual. |
| case23| 71         | NA  | Mass    | L    | NA       | IC     | moderately-poorly     | SCC          | HUOL    | TP            | Yes          | Abbreviations: L. left; R. right. ADC. adenocarcinoma; EC. endometrioid adenocarcinoma. SCC. squamous cell carcinoma. BMI. body mass index. |

HBOL. hysterectomy, bilateral salpingo-oophorectomy, omenterectomy, lymphadenectomy.
HU. Hysterectomy, unilateral salpingo-oopherectomy, excision of tumor.
HB. Hysterectomy, bilateral salpingo-oopherectomy, excision of tumor.
HUOL. Hysterectomy, unilateral salpingo-oopherecotomy, omenterectomy, lymphadenectomy.
BEP. bleomycin, cisplatin, etoposide.
TP. nedaplatin and paclitaxel.
IC. intraperitoneal chemotherapy with carboplatin.
DC. docetaxel and carboplatin.
NA. unknown.
Table 2
Characteristics of 342 patients diagnosed with MT-MCT according to the published data.

| Findings                      |         |         |         |
|-------------------------------|---------|---------|---------|
| **Age, year (n = 342)**       | Mean (± SD, Min, Max) | 54.2(14.6, 12.0–90.0) |         |
|                               | Median (Q1, Q3) | 55.0(43.0, 65.8) |         |
| **SCCA, ng/ml (n = 14)**      | Mean (± SD, Min, Max) | 20.0(21.4,0.6–61.0) |         |
|                               | Median (Q1, Q3) | 14.0(3.13, 24.2) |         |
| **CA125, U/ml, (n = 20)**     | Mean (± SD, Min, Max) | 156(122, 15.6–480) |         |
|                               | Median (Q1, Q3) | 135(57.3, 232) |         |
| **Size, cm (n = 156)**        | Mean (± SD, Min, Max) | 14.6(6.84,0.13-40.0) |         |
|                               | Median (Q1, Q3) | 13.0(10.0, 18.0) |         |
| **Site (n = 130)**            |         |         |         |
| Left                          | 60 (46.2%) |         |         |
| Right                         | 70 (53.8%) |         |         |
| **Grade (n = 287)**           |         |         |         |
| I                             | 117 (40.8%) |         |         |
| II                            | 52 (18.1%) |         |         |
| III                           | 70 (24.4%) |         |         |
| IV                            | 11 (3.8%) |         |         |
| Unknown                       | 37 (12.9%) |         |         |
| **Type (n = 247)**            |         |         |         |
| Thyroid carcinoma             | 3 (1.2%) |         |         |
| Anaplastic carcinoma          | 1 (0.4%) |         |         |
| Borderline malignancy         | 1 (0.4%) |         |         |
| Carcinoid                     | 3 (1.2%) |         |         |
| Squamous cell carcinoma       | 177 (71.7%) |         |         |
| Squamous cell carcinoma with sarcoma | 2 (0.8%) |         |         |
| Sebaceous adenocarcinoma      | 1 (0.4%) |         |         |
| Sarcoma                       | 1 (0.4%) |         |         |
| Papillary carcinoma           | 1 (0.4%) |         |         |
| Clear cell carcinoma          | 1 (0.4%) |         |         |
| Undifferentiated carcinoma    | 1 (0.4%) |         |         |
| Fibrosarcoma                  | 1 (0.4%) |         |         |
| Adenocarcinoma                | 14 (5.7%) |         |         |
| Primitive neuroectodermal tumor | 1 (0.4%) |         |         |
| Mucoepidermoid carcinoma      | 1 (0.4%) |         |         |
| Missing                       | 38 (15.4%) |         |         |
| **Treatment (n = 169)**       |         |         |         |
| Surgery                       | 84 (49.7%) |         |         |

Notes. 342 patients were from the SEER database and published case reports.
| Findings                       | Count | Percentage |
|-------------------------------|-------|------------|
| Surgery + radiotherapy        | 13    | 7.7%       |
| Surgery + chemoradiotherapy   | 18    | 10.7%      |
| Surgery + chemotherapy        | 53    | 31.4%      |
| Radiotherapy + chemotherapy   | 1     | 0.6%       |

Notes. 342 patients were from the SEER database and published case reports.