# Malignant Transformation in a Mature Cystic Teratoma of the Ovary: A 5-year Descriptive Study

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## ABSTRACT

**Background and Objective.** Malignant transformation (MT) in mature cystic teratoma of the ovary (MCTO) is rare. This descriptive study primarily aims to determine the prevalence rate of MT in MCTO and describe clinicopathologic features, management, and prognosis of patients who developed this rare type of tumor and likewise deliver a review in the light of recent literature.

**Methods.** This is a descriptive observational study of 22 patients with MT in MCTO at a Level 3 Tertiary Public Hospital in Baguio City, Philippines. The clinical and pathological records of each patient were reviewed. Descriptive statistics were used.

**Results.** Between January 2016 to December 2020, of the 369 cases of mature cystic teratoma, 22 cases with malignant transformation were reported with an incidence of 6%. The mean age of diagnosis was 52 years, of which 70% are aged 50 years old and above. Fifty-nine percent (13/22) and 32% (7/22) of the cases were squamous cell carcinoma and mucinous adenocarcinoma, respectively. Very rarely, malignant transformations were carcinoid tumors (1) and follicular carcinoma (1). The most common reason for consult among patients is a palpable abdominal/pelvic mass (45.5%). Around 60% percent of cases have an elevated CA-125 value with a mean level of 180 U/ml. Seventy-two percent of cases with malignant transformation measured 10 cm or more with the largest mean diameter of 13 cm. Five patients underwent fertility-sparing surgery. Fourteen had staging procedures. Twelve patients were at Stage I. Three were at Stage II. Four and three patients were at Stage III and IV, respectively. Ten patients received adjuvant platinum-based chemotherapy and nine patients warrant no treatment after surgery. The median survival time is 14 months.

**Conclusion.** Although not common, malignant transformation in MCT should be considered in older patients with large tumor sizes and elevated CA-125 assessed as MCT in preoperative and intraoperative assessment. This ovarian malignancy suggests an aggressive behavior but complete resection with systematic staging and indicated adjuvant platinum-based chemotherapy may improve survival.

*Keywords: malignant transformation of teratomas, mature cystic teratoma, ovarian cancer, squamous cell carcinoma of the ovary*



*Oral Presentation - 27th Asia Oceana Federation of Obstetrics and Gynecology Hybrid Congress, May 23-26, 2022, Bali, Indonesia.*

eISSN 2094-9278 (Online)
Published: August 30, 2024
https://doi.org/10.47895/amp.vi0.8023

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## INTRODUCTION

In the Philippines, ovarian cancer is the tenth most common malignancy with the fifth highest mortality rate. The 5-year prevalence of 25.05 per 100,000 (Globocan 2020) suggests ovarian cancer is a remarkable health burden in the country.[1] Between 2018 and 2019, ovarian cancer remained top 6 of the causes of gynecologic admission in Baguio General Hospital and Medical Center and was the leading cause of death among gynecologic malignancies. Furthermore, ovarian cancer is the 6th most common malignancy managed in our Cancer Center for the year 2022. Over 80% of ovarian cancers are epithelial in origin,

while the remaining percentage include germ cell tumors, sex cord-stromal tumors, and metastatic tumors.[2]

The most common germ cell tumor of the ovary is a benign mature cystic teratoma (MCT), comprising 10–25% of all ovarian neoplasms and malignant transformation, which is reported as a rare phenomenon that occurs in 1–3% of all mature cystic teratoma.[3] Squamous cell carcinoma (SCCA) is MCT's most common malignant tumor (MT-MCT). Between 2013 and 2015, our clinical pathology unit recorded four cases of MT-MCT among 169 MCT cases (2.4%). Two cases of mucinous adenocarcinoma, one SCCA, and one papillary thyroid carcinoma. Last 2020, we reported on extremely rare MT-MCTs, carcinoid tumors, and papillary thyroid carcinoma.[4]

Since there are no specific clinical signs and symptoms, or radiological and laboratory markers specific to the MT-MCT, it is important to realize that malignant transformation is rarely diagnosed preoperatively and is mostly diagnosed through postoperative pathological examination.[5] Thus, patients with this rare complication may not receive the optimal surgery and staging procedure for ovarian cancer. Due to its rarity, the comprehensive surgical staging of malignant ovarian germ cell tumors was derived from the epithelial ovarian carcinoma treatment guidelines, and omission of such was associated with an increased risk of disease recurrence.[6] Moreover, a systematic review and meta-analysis regarding the attributable value of comprehensive surgical staging in epithelial ovarian carcinoma learned that 23% of clinically FIGO Stage I patients were upstaged after comprehensive surgical staging.[7] At present, definite evidence is controversial over the procedures in MT-MCT.

It has been an observation that MT-MCT is becoming more common in our institution as we do our Surgico-pathologic and Multidisciplinary Audits, hence this study. This descriptive study primarily aims to determine the prevalence rate of malignant transformations in a mature cystic teratoma of the ovary and describe clinicopathologic features, management, and prognosis of patients who developed this rare type of tumor and likewise deliver a review in the light of recent literature. In the Philippines, most articles presented were individual case reports of malignant transformations from ovarian mature cystic teratoma. The result of this study will provide a first-hand summary of our experience in managing accumulated cases and might be included in the evidence to come up with a standard protocol for managing these rare gynecologic tumors.

## OBJECTIVES

### General Objective

To determine the prevalence rate of malignant transformation in a mature cystic teratoma of the ovary encountered at a tertiary training institution in a span of five years from January 2016 to December 2020.

### Specific Objectives

To describe the clinicopathologic characteristics of patients with malignant transformations arising from mature cystic teratoma, in terms of the following:

1. Mean age
2. Major signs and symptoms
3. Level of preoperative CA-125
4. Procedure done
5. The mean size of the ovarian mass
6. Final stage post-surgery
7. Adjuvant treatment after surgery
8. Survival of patients

## METHODS

This descriptive study reviewed clinical records of patients with MT in MCTO from January 2016 to December 2020 in a Tertiary Level Public Hospital. The study population included subjects diagnosed with malignancy from ovarian mature cystic teratoma of all ages operated on for new ovarian growth in this institution. Total population sampling was used. The total number of charts and/or electronic medical records reviewed was the total number of cases with a malignant transformation from MCTO.

This review was completed primarily by the investigators in coordination with the Health Information Management Office and the Department of Anatomic Pathology. Convenience sampling was used where the available data were utilized. A list of patients with the histopathologic report of mature cystic teratoma was retrieved from the Section of Anatomic Pathology. Subsequently, patients with a diagnosis of malignant transformation arising from Mature cystic teratoma were included in this study. Data on demographics, presenting symptoms, preoperative CA125, surgical management, pathological findings, adjuvant therapy, follow-up, and treatment outcomes were obtained from the medical records (charts or Electronic Medical Records). Data needed for the study were recorded in the Data Extraction Form. Immature teratoma cases were excluded.

Data was encoded and analyzed using Microsoft Excel 16.27 (2019). Data were analyzed using descriptive statistics. Categorical variables were presented as frequency and percentages while continuous variables were presented as mean and median values. Prevalence was computed using frequency and percentage. Age, levels of CA125, and size of ovarian mass were presented as mean values. Presenting symptoms, the procedure, the final stage, and adjuvant therapy were presented in percentages. Status during follow-up was described as the median value in months.

### Ethical Considerations

The study was approved by the Research Ethics Committee. There were no conceivable risks from the study that would affect patients. Confidentiality of gathered data

was observed. Data collection and publication upheld the rules of the Data Privacy Act 2012.

## RESULTS

Between January 2016 to December 2020**,** the Department of Pathology received 1,025 specimens for ovarian pathology of which 75% were benign diagnoses. Of the 369 cases of mature cystic teratoma, 22 cases with malignant transformation were reported with an incidence of 6%. Table 1 summarizes the characteristics of these 22 patients. The mean age of diagnosis was 52 years old (range 33-70 years old), of which 70 % are aged 50 years old and above. Mean Gravidity and Parity were 3. Fifty-nine percent (13/22) and 32% (7/22) of the cases with malignant transformation were squamous cell carcinoma and mucinous adenocarcinoma, respectively. A very rare malignant transformation reported was carcinoid tumor (1) and follicular carcinoma (1). The most common reason for consult among patients is a palpable abdominal/pelvic mass (45.5%). Around 60% percent of cases have an elevated CA-125 value with a mean level of 180 U/ml. Seventy-two percent of cases with malignant transformation measured 10 cm or more with a largest mean diameter of 13 cm. Ninety-five percent were unilateral. Three cases were associated with a contralateral mature cystic teratoma.

Twenty-two percent of patients underwent fertility-sparing surgery. Sixty-four percent had staging procedures. Twelve patients were at Stage I. Three were at Stage II. Four and three patients were at Stage III and IV, respectively. Ten patients received adjuvant platinum-based chemotherapy and nine patients warrant no treatment after surgery. Ten out of the 22 patients are deceased with a median survival time of 14 months.

**Table 1.** Clinicopathologic Features of Patients with Malignant Transformation

| Variables | N = 22 (%) |
|---|---|
| ***Age (years)*** | |
| 30-39 | 3 (13.6) |
| 40-49 | 4 (18.2) |
| 50-59 | 12 (54.6) |
| 60 and above | 3 (13.6) |
| ***CA 125*** | |
| Normal (<35 mIU/ml) | 6 (27.3) |
| Low normal (>35 to <100 mIU/ml) | 4 (18.2) |
| High normal (>100 mIU/ml) | 9 (40.9) |
| No record | 3 (13.6) |
| ***Reason for consult*** | |
| Abdominal enlargement | 5 (22.7) |
| Abdominal/Pelvic pain | 4 (18.2) |
| Palpable mass | 10 (45.5) |
| Others (incidental findings, vaginal bleeding, body weakness) | 3 (13.6) |
| ***Size of ovarian mass*** | |
| <10 cm | 6 (27.3) |
| 10-15 cm | 9 (40.9) |
| 16-20 cm | 6 (27.3) |
| >20 cm | 1 (4.5) |
| ***Procedure done*** | |
| Salpingo-oophorectomy | 5 (22.7) |
| THBSO | 17 (77.3) |
| With staging | 14 (63.6) |
| Without staging | 8 (36.4) |
| ***Final stage*** | |
| IA | 8 (36.4) |
| IB | 1 (4.5) |
| IC | 3 (13.6) |
| II | 3 (13.6) |
| III | 4 (18.2) |
| IV | 3 (13.6) |
| ***Adjuvant treatment given*** | |
| Observation | 9 (40.9) |
| Chemotherapy | 10 (45.5) |
| None (no consent/did not follow up) | 3 (13.6) |
| ***Alive status since diagnosis*** | |
| <6 months | 4 (18.2) |
| 6-12 months | 6 (27.3) |
| >12-24 months | 4 (18.2) |
| >24 months | 8 (36.3) |

## DISCUSSION

Mature cystic teratoma, the most frequent germ cell tumor is benign in its pure composition, however, malignant transformation has been reported in less than 3% of cases.[5,8] The most common malignant transformation is SCCA followed by adenocarcinoma as shown in the result of this study. As previously reported, carcinoid tumor, sarcoma, and papillary carcinoma are extremely rare with an estimate of 0.1 to 0.3%.[4,9]

The major challenge concerning these malignant transformations is that there are no specific symptoms; imaging and biochemical features to make preoperative diagnosis, hence difficult to establish definitive surgical procedures.[10] Therefore, several risk factors are suggested to suspect malignant transformation. Our study showed that malignant transformation is more common in women above 50 years old, with elevated CA 125, and those with an ovarian tumor of more than 10 cm. Park et al.[10] reported that risk factors for malignant transformation include elevated CA-125 levels, age over 40 years old, postmenopausal status, and large tumor size. A tumor size of ≥10 cm should be highly suspected for MT.[2,11-13] A tumor size of ≥15.0 cm appeared to be associated with more aggressive disease.[2] A long-standing existence of MCT without tumor removal is implied to be associated with malignant transformation. In a systematic review by Li et al.[11] involving 435 cases, the mean age of diagnosis was 53.5 (range 19–87) years old, while in the report of Chiang et al.[2] (TGOG Study), the median age at diagnosis was 52 years which is similar to this study. A more recent case series of 14 patients with MT-MCT from a total of 569 cases revealed that the mean age was 51.3.[12] Similar to common histology of ovarian cancer, patients with MT-MCT generally present with palpable abdominal mass, abdominal distension, and abdominal pain.[2,11,12]

As previously published, some reported that SCC transformation in MCTO may be associated with high-risk human papillomavirus (HPV) infection, and alterations in the tumor proteins, p53, and p16 may be involved in the process of malignant transformation.[2,14] Conversely, the recent next-generation sequencing analysis reported that no SCC was positive for HPV. The most frequently altered genes in SCC were TP53 in 80% of cases, while PIK3CA and CDKN2A in 52% and 44% of cases, respectively. In addition, a mutation in TP53 was associated with improved overall survival.[15,16] KRAS proto-oncogene mutation is implicated in mucinous adenocarcinoma transformations.[17] Inherited multiple endocrine neoplasia type 1 (MEN-1) and p53 are rarely reported in carcinoid tumors.[18] No molecular markers have been reported for thyroid carcinomas arising within MCT without struma ovarii.[19] This potential molecular abnormality was not conducted among the patients in the study.

The gross pathologic appearance of benign ovarian teratoma is characteristic. However, for a concealed malignancy, the following features are suggested to consider: nodularity, papillary or solid growths, adhesions to the pelvic wall and peritoneum, presence of ascites, areas of necrosis, and hemorrhages, together with the presence of risk factors would aid the physician to suspect malignancy.[10] It is important to do a meticulous gross examination intraoperatively. A rush frozen section (RFS) may be indicated in some instances, especially in patients who wish to retain fertility to provide a provisional intraoperative pathologic diagnosis to guide extent of surgery. The sensitivity, specificity, and overall accuracy of RFS on malignant ovarian masses are 86%, 100%, and 97%, respectively. However, it must be emphasized that RFS on germ cell tumors has a 13% discordant rate.[20]

Definitive diagnosis of MT-MCT is primarily based on histopathologic studies. Immunohistochemical biomarkers may play an active or complementary role in the accurate classification. Reports presented that SCCA in MCTO was positive staining for pancytokeratin, p63, and Ki67, and alteration in p53.[21,22] For extremely rare cases such as carcinoid tumors and papillary thyroid transformations, neuroendocrine markers (chromogranin, synaptophysin, and CD56) and thyroid biomarkers (HBME-1, galectin-3, thyroglobulin, and Thyroid Peroxidase) are excellent immunohistochemistry stains, respectively. [9,23-25]

The optimal management of these malignant transformations is uncertain because of their rarity, and there is no gold standard and direct comparisons between treatment approaches. The rarity suggests a low likelihood of future prospective studies to determine the best treatment options.[5] Due to mostly low tumoral behavior, complete resection is the main mode of treatment. All of our patients underwent complete resection of the ovarian mass by salpingo-oophorectomy with or without hysterectomy. Furthermore, the treatment modalities for malignancy in mature ovarian teratoma depend on the stage of the disease and fertility desire. Conservative treatment is often offered to younger patients who wish to retain their fertility and it consists of unilateral salpingo-oophorectomy or cystectomy without adjuvant therapy. Conservation of ovarian tissue on the affected side is acceptable.[5,26] For perimenopausal and postmenopausal women, bilateral salpingo-oophorectomy and hysterectomy should be performed. Complete cytoreduction surgery and lymphadenectomy improve the treatment outcome.[10,11]

The advantages of adjuvant radiotherapy or chemotherapy stated in the retrospective study of Gainford et al.[27] have never been prospectively reviewed. For Stage 1 tumors, additional therapy is debatable for they have a fairly good prognosis. Likewise, no universally accepted regimens or dosages for more advanced diseases exist. However, cisplatin-based chemotherapy for patients with more advanced cancer provided improved survival. Other authors suggest that chemotherapy with alkylating agents is related to better prognosis in patients with SCC transformation in MCTO.[28] A systematic review endorses individualized and integrated treatment based on platinum-based chemotherapy.[2] In our institution, a carboplatin-paclitaxel chemotherapy regimen was mostly utilized, similar to the accounts of the previous reports.[8,12,29] A 30-year-old woman reported attaining remission for 45 months after radical cytoreduction with combination chemotherapy, consisting of carboplatin, paclitaxel, and bevacizumab, followed by maintenance therapy with bevacizumab.[30]

Prognosis is primarily dependent on the stage of the disease, with stage I patients having a relatively good prognosis, but the outcome is very poor when the disease has spread beyond the ovary.[2] Malignant tumors evolving from ovarian teratomas sometimes present with locally invasive disease or with distant metastases.[5] The prevalent sites of metastasis are contiguous pelvic structures, including the contralateral ovary and hematologic dissemination may occur in the lungs, bone, liver, and brain, however, metastasis is rare. Other important predictors of prognosis include tumor grade, vascular involvement, cyst wall invasion, tumor infiltration, capsular rupture, and adhesions.[12,31] There is no standardized approach to post-treatment surveillance, however, routine physical examination and radiographic imaging are warranted.

## CONCLUSION

MT-MCTO is rare and a challenging complication. The preoperative diagnosis of this transformation is difficult, and the definitive diagnosis would be achieved post-operatively as there are no specific symptoms; imaging and biochemical features to make suspicion, hence difficult to establish definitive surgical procedures. The following risk factors would indicate malignant transformation developing from MCTO: advanced age, elevated CA-125 value, and large tumor size. Histopathologic examination of multiple tissue sections and immunohistochemical staining aid in definitive diagnosis.

This study illustrates the aggressive behavior of this ovarian malignancy and the optimal treatment strategy remains the main challenge, but optimal removal of the tumor and complete surgical staging with indicated adjuvant chemotherapy may render improvement of prognosis. Thus, patients with these characteristics need to be referred to a higher center that can provide appropriate diagnosis and management, which includes complete resection with surgical staging and adjuvant treatment.

Despite the limitation of being a small sample size retrospective single institutional study, this report shows the importance of adequate preoperative workup of an ovarian mass, correct surgical and pathological diagnosis, and judicious referral to the oncology center. Prospective and multicenter collaborative studies are needed to provide satisfactory evidence to establish consensus management, and to strengthen and validate the recommendations provided by various guidelines.

### Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

### Author Disclosure

Both authors declared no conflicts of interest.

### Funding Source

None.

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