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# An algorithm for the pre-operative differentiation of benign ovarian tumours based on magnetic resonance imaging interpretation in a regional core hospital: A retrospective study

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ABSTRACT

*Objective:* For selecting minimally invasive surgery (i.e. laparoscopic ovarian cystectomy) for treating ovarian tumours (OTs) in premenopausal patients, the pre-operative differentiation of benign ovarian tumours (Be-OTs) based on magnetic resonance imaging (MRI) interpretation is important. This paper describes the authors' 8-year experience of approximately 1000 OT cases, and provides information about a diagnostic algorithm to help other hospitals.

*Study design:* The medical records of 901 patients aged $< 50$ years with OTs from 1 January 2015–31 March 31 2023 were reviewed. First, the accuracy of pre-operative differentiation between Be-OTs and borderline/malignant ovarian tumours (Bo/Ma-OTs) was compared in each type of OT. Second, to identify the factors influencing differentiation between Be-OTs and Bo/Ma-OTs in 164 serous/mucinous ovarian tumours (SM-OTs), a multi-variate logistic regression analysis was performed to assess the effect of 13 factors, including MRI findings, OT size and tumour markers.

*Results:* In the comparison of diagnostic accuracy of pre-operative MRI for each OT type, accuracy was found to be notably high for ovarian endometrial cyst (OEC) ($n = 409$), ovarian mature cystic teratoma (OMCT) ($n = 308$), ovarian endometrioid adenocarcinoma (OEA) ($n = 6$) and ovarian clear cell adenocarcinoma (OCCA) ($n = 14$). On the other hand, discrepancies between MRI and pathological findings often occurred in SM-OTs, including ovarian serous cystadenoma ($n = 86$), ovarian mucinous adenocarcinoma ($n = 61$), ovarian serous adenocarcinoma ($n = 12$) and ovarian mucinous adenocarcinoma ($n = 5$). In the multi-variate logistic regression analysis of the latter 164 patients, in addition to MRI findings, OT size and carbohydrate antigen 125 also had an effect to some extent. The combination of MRI interpretation and OT size may enhance differentiation of Be-OTs and Bo/Ma-OTs.

*Conclusions:* Among four types of OTs (OEC, OMCT, OEA and OCCA), MRI interpretation was able to differentiate between Be-OTs and Bo/Ma-OTs almost perfectly. Additionally, to mitigate the difficulty in differentiating SM-OTs, OT size may be useful in combination with MRI findings, although further accumulation and analysis of OT cases is needed.

## 1. Introduction

Since minimally invasive surgery has become increasingly important in the field of gynaecological surgery, laparoscopic ovarian cystectomy has been widely performed as an ovarian-sparing surgery for premenopausal patients with fertility preservation or hormonal support [1]. However, when detecting borderline/malignant ovarian tumours (Bo/Ma-OTs), total hysterectomy with bilateral salpingo-oophorectomy is the primary treatment approach [2,3]. Since recurrence and other risks seem to be related to FIGO stage, even when the final diagnosis is borderline ovarian tumour (Bo-OT) [4,5], which has the characteristics of benign ovarian tumour (Be-OT) and malignant ovarian tumour (Ma-OT), determination of the surgical type (i.e. salpingo-oophorectomy or ovarian cystectomy) may be important to prevent the spread of tumour cells, although Bo-OTs are usually diagnosed at early stages. Therefore, gynaecologists must perform a

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differential diagnosis between Bo/Ma-OTs and Be-OTs as accurately as possible before surgery. To ensure accurate classification of many types of ovarian tumours (OTs) at the same time, magnetic resonance imaging (MRI), considered one of the most reliable tools [6–9], is usually performed after the OT is detected by transvaginal ultrasound (TVUS) in an outpatient examination. At the study hospital, which is a moderate-scale regional institution, differential diagnosis is performed on the basis of MRI results. When the possibility of malignancy is excluded, ovarian cystectomy can be selected to preserve ovarian function. However, few studies have summarized the diagnosis of OTs comprehensively. Therefore, it is important to assess the feasibility of the pre-operative diagnostic algorithm through feedback of the outcomes of post-operative pathological findings, especially when targeting premenopausal patients. As these results may be helpful for other hospitals by providing information about the pre-operative diagnosis of OTs, this study sought to analyse the authors' 8-year experience of approximately 1000 OT cases.

## 2. Methods

### 2.1. Data collection

This study was reviewed and approved by the Human Ethical Committee of the University of Teikyo Hospital (Registration No. 20–054–3). From 1 June 2015–31 March 2023, 1228 female patients underwent surgery for OTs. Of these, 293 patients aged ≥ 50 years were excluded from this study as almost all of these women had selected salpingo-oophorectomy. This supported previous reports [4,10], probably because women at this age assumed menopause. Twelve of the remaining 935 cases were excluded because MRI was not performed in these cases. Although TVUS was performed for the first screening of OTs in all cases, TVUS findings were excluded from this analysis due to their inaccurate description of the characteristics of detected OTs. This situation likely occurred due to differences in screening by TVUS and the detailed examination by MRI. Among the remaining 923 cases, referring to the MRI interpretation, Be-OTs were classified as: ovarian endometrial cyst (OEC), ovarian mature cystic teratoma (OMCT), ovarian serous cystadenoma (OSC) or ovarian mucinous cystadenoma (OMC). Ma-OTs were classified as: ovarian serous adenocarcinoma (OSA), ovarian mucinous adenocarcinoma (OMA), ovarian endometrioid adenocarcinoma (OEA) or ovarian clear cell adenocarcinoma (OCCA). As Bo-OTs were only detected pre-operatively by MRI, it was not possible to include Bo-OTs as a separate category. Instead, Bo-OTs and Ma-OTs were addressed as a single category (i.e. Bo/Ma-OTs) in this study. When none of the above types applied, the OTs were classified as 'other type'. However, the 22 patients with 'other type' tumours were excluded from this study as this category included a great variety of types. Finally, the deidentified medical records of 901 patients were reviewed retrospectively (Table 1).

### 2.2. Classification of benign vs borderline/malignant ovarian tumours

In order to assess the accuracy of the MRI interpretation, data were collected from postoperative pathological examinations and pre-operative MRI findings. Both diagnoses were performed by experts in the fields of pathology and diagnostic radiology. Among the aforementioned eight types of OTs, each case was classified as a Be-OT or a Bo/Ma-OT based on both MRI and pathological findings. Next, to compare the diagnostic accuracy of pre-operative MRI interpretation for each type of OT, the following procedures were performed: (1) determination of the number of Be-OTs and Bo/Ma-OTs diagnosed by post-operative pathological examination; (2) determination of the number of Be-OTs and Bo/Ma-OTs diagnosed by pre-operative MRI interpretation; and (3) calculation of the accuracy of the pre-operative diagnosis of Be-OTs and Bo/Ma-OTs by comparing the pre-operative MRI interpretation with the postoperative pathological diagnosis.

**Table 1**
Ovarian tumour type and accuracy of pre-operative magnetic resonance imaging (MRI) diagnosis. (a) All ovarian tumours (OTs). (b) Serous/mucinous ovarian tumours.

| (a) Type | *n* | Be-OTs | Bo/Ma-OTs | Be-OT accuracy | Bo/Ma-OT accuracy |
|---|---|---|---|---|---|
| OEC | 409 | 99.5% (*n* = 407) | 0.5% (*n* = 2) | 100.0% (*n* = 402/402) | 28.6% (*n* = 2/7) |
| OMCT | 308 | 100.0% (*n* = 308) | 0.0% (*n* = 0) | 100.0% (*n* = 303/303) | 0.0% (*n* = 0/5) |
| OSC | 86 | 93.0% (*n* = 80) | 7.0% (*n* = 6) | 98.7% (*n* = 77/78) | 62.5% (*n* = 5/8) |
| OMC | 61 | 78.7% (*n* = 48) | 21.3% (*n* = 13) | 90.5% (*n* = 38/42) | 47.4% (*n* = 9/19) |
| OSA | 12 | 8.3% (*n* = 1) | 91.7% (*n* = 11) | 0.0% (*n* = 0/0) | 91.7% (*n* = 11/12) |
| OMA | 5 | 40.0% (*n* = 2) | 60.0% (*n* = 3) | 0.0% (*n* = 0/0) | 60.0% (*n* = 3/5) |
| OEA | 6 | 0.0% (*n* = 0) | 100.0% (*n* = 6) | 0.0% (*n* = 0/0) | 100.0% (*n* = 6/6) |
| OCCA | 14 | 0.0% (*n* = 0) | 100.0% (*n* = 14) | 0.0% (*n* = 0/0) | 100.0% (*n* = 14/14) |
| Total | 901 | 93.9% (*n* = 846) | 6.1% (*n* = 55) | 99.4% (*n* = 820/825) | 65.8% (*n* = 50/76) |

| (b) Type | *n* | Be-OTs | Bo/Ma-OTs | Be-OT correct | Bo/Ma-OT correct |
|---|---|---|---|---|---|
| OSC | 86 | 93.0% (*n* = 80) | 7.0% (*n* = 6) | 98.7% (*n* = 77/78) | 62.5% (*n* = 5/8) |
| OMC | 61 | 78.7% (*n* = 48) | 21.3% (*n* = 13) | 90.5% (*n* = 38/42) | 47.4% (*n* = 9/19) |
| OSA | 12 | 8.3% (*n* = 1) | 91.7% (*n* = 11) | 0.0% (*n* = 0/0) | 91.7% (*n* = 11/12) |
| OMA | 5 | 40.0% (*n* = 2) | 60.0% (*n* = 3) | 0.0% (*n* = 0/0) | 60.0% (*n* = 3/5) |
| SM-OT | 164 | 79.9% (*n* = 131) | 20.1% (*n* = 33) | 95.8% (*n* = 115/120) | 63.6% (*n* = 28/44) |

After dividing the 901 cases into eight OT types, differentiation was undertaken between benign ovarian tumours (BE-OTs) and borderline/malignant ovarian tumours (Bo/Ma-OTs). The accuracy of pre-operative MRI diagnosis was compared simultaneously for each OT type.
OCCA, ovarian clear cell adenocarcinoma; OEA, ovarian endometrioid adenocarcinoma; OEC, ovarian endometrial cyst; OMA, ovarian mucinous adenocarcinoma; OMC, ovarian mucinous cystadenoma; OMCT, ovarian mature cystic teratoma; OSA, ovarian serous adenocarcinoma; OSC, ovarian serous cystadenoma.

### 2.3. Main target of serous/mucinous ovarian tumours

As discrepancies between MRI and pathological findings were rare in the patients with OEC, OMCT, OEA and OCCA (Table 1), this study focused mainly on patients with OSC, OMC, OSA and OMA. Additionally, as a clear distinction between serous and mucinous cysts was not achieved pre-operatively in many cases, these four types were combined in a single category [i.e. serous/mucinous ovarian tumours (SM-OTs)] to assess the diagnostic algorithm based on MRI interpretation. As in principle, ovarian cystectomy could only be selected when a diagnosis of Be-OT, including OSC and OMC, was achieved, SM-OT cases were classified as Be-OT or Bo/Ma-OT by referring to pathological findings. In order to predict Be-OTs pre-operatively, various factors were evaluated retrospectively, including MRI interpretation and other OT characteristics.

### 2.4. Analysis methods

First, information was collected about both types of surgery and patient characteristics. The former was classified into the following categories: (1) bilateral salpingo-oophorectomy, bilateral ovarian cystectomy, unilateral salpingo-oophorectomy (USO), unilateral ovarian cystectomy (UOC), or USO with UOC; and (2) laparoscopic or abdominal surgery. The latter included the following indexes as well as MRI interpretation: (1) age; (2) body mass index (BMI); (3) parity; (4) serum tumour marker levels, including carbohydrate antigen 19–9 (CA19–9), carbohydrate antigen 125 (CA125) and carcinoembryonic antigen (CEA); (5) serum inflammation levels of white blood cells, C-reactive protein and lactate dehydrogenase (LDH); and (6) cyst characteristics, including size, serous or mucinous, unilocular or multi-locular, and unilateral or bilateral.

Second, the influence of the aforementioned patient characteristics on the prediction of Be-OTs was evaluated, particularly to identify influencing factors other than MRI interpretation. To control for confounding factors, the 164 patients were divided into two groups according to the presence or absence of the following factors, and multivariate logistic regression analysis was performed: (1) age > 40 years; (2) nulliparity; (3) high BMI, defined as BMI $\geq$ 25 kg/m$^2$ [11]; (4) positive CA19–9, defined as CA19–9 > 37 U/ml; (5) positive CA125, defined as CA125 > 35 U/ml; (6) positive CEA, defined as CEA > 5 ng/ml; (7) positive inflammation, defined as white blood cell count > 9000/mm and/or 0.3 mg/dl; (8) positive LDH, defined as LDH > 220 U/l; (9) bilateral cyst; (10) multi-locular cyst; (11) serous cyst; (12) standard size, defined as OT size from 5 to 15 cm; and (13) no malignancy, defined as cases that denied the possibility of malignancy. An OT size from 5 to 15 cm was considered as 'standard size' in this study based on the mean and standard deviation (SD) of OT size of all 164 patients.

Statistical analyses were performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and JMP Version 12 for Windows (SAS Institute, Inc., Tokyo, Japan) to determine correlations between the aforementioned 13 factors and Be-OTs diagnosed by postoperative pathological findings. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated to determine the strengths of the correlations. $p <$ 0.05 was considered to indicate significance.

## 3. Results

### 3.1. Patient characteristics in total and serous/mucinous ovarian tumour cases

Among the 901 cases, mean ( ± SD) age, BMI, parity and dominant OT size measured by MRI were 35.9 ± 8.1 (range 13–49) years, 22.0 ± 3.6 (range 15.1–45.1) kg/m$^2$, 0.5 ± 0.8 (range 0–4) and 7.4 ± 3.9 (range 1–32), respectively. Classification of the type of surgeryis described in Table 2. In approximately 90% of cases (789/901 cases), surgery was performed laparoscopically, and cystectomy was selected in > 70% of cases (661/901 cases). In comparison of the diagnostic accuracy of pre-operative MRI interpretation for each type of OT, the accuracy rates for OEC ($n$ = 409 cases), OMCT ($n$ = 308 cases), OEA ($n$ = 6 cases) and OCCA ($n$ = 14 cases) were notably high (Table 1). In particular, the pre-operative diagnosis rates of OEC and OMCT were similar to the diagnosis rate of Be-OTs, although there were a few cases in which it was difficult to achieve an accurate diagnosis of Bo/Ma-OTs by pre-operative MRI interpretation among the OEC ($n$ = 7) and OMCT ($n$ = 5) groups (Table 1a). On the other hand, diagnostic accuracy rates for OSC and OSA and, especially, OMC and OMA, were relatively poor (Table 1b). Additionally, in 86 of these 164 cases, a clear distinction between serous and mucinous cysts was not achieved pre-operatively. Therefore, the latter four types (Table 1) were combined into a single category, namely SM-OTs, and focused mainly on these 164 cases. The rates of laparoscopic surgery (112/164 cases) and cystectomy (96/164 cases) were relatively low (Table 2). Among 120 cases diagnosed with Be-OTs by MRI findings, Bo/Ma-OTs were detected in five cases by pathological examination, and among 44 cases diagnosed with Bo/Ma-OTs by MRI findings, 16 were diagnosed with Be-OTs. Among these 164 cases, mean ( ± SD) age, BMI, parity and dominant OT size measured by MRI were 36.7 ± 8.7 (range 15–49) years, 22.6 ± 4.0 (range 15.1–45.1) kg/m$^2$, 0.5 ± 0.8 (range 0–4) and 10.1 ± 6.0 (range 1–32), respectively. Additionally, to evaluate the relationship between the possibility of Be-OT and OT size, the 164 cases were classified as: < 4 cm, 5–9 cm, 10–14 cm, 15–19 cm or > 20 cm. In this classification, the relatively high possibility of Be-OT was indicated in the second and third categories, namely 5–9 cm (91.1%, 81/90 cases) and 10–14 cm (76.5%, 26/34 cases), whereas the rates were low in the other three categories (<4 cm, 60.0%, 6/10 cases; 15–19 cm, 60.0%, 9/15 cases; >20 cm, 53.3%, 8/15 cases). This result may correspond approximately with mean OT size among these 164 cases.

**Table 2**
Types of surgery.

| Type | Total | | SM-OTs | |
|---|---|---|---|---|
| | Laparoscopic surgery | Abdominal surgery | Laparoscopic surgery | Abdominal surgery |
| BSO | 5 | 38 (H: 35) | 0 | 16 (H: 16) |
| BOC | 144 (M: 9) | 4 (M: 4) | 4 | 0 |
| USO | 148 (M: 1, H: 14) | 49 (M: 1, H: 13) | 26 (H: 5) | 26 (H: 5) |
| UOC | 456 (M: 20, H: 10) | 11 (M: 2, H: 1) | 79 (M: 1) | 7 |
| USO with UOC | 36 (M: 1, H: 4) | 10 (M: 1, H: 3) | 3 | 3 |
| Total | 789 (M: 31, H: 28) | 112 (M: 8, H: 52) | 112 (H: 5, M: 1) | 52 (H: 21) |

BOC, bilateral ovarian cystectomy; BSO, bilateral salpingo-oophorectomy; SM-OTs, serous/mucinous ovarian tumours; UOC, unilateral ovarian cystectomy; USO, unilateral salpingo-oophorectomy.
In all 901 cases and in the 164 SM-OT cases, surgery was classified as: BSO, BOC, USO, UOS, and USO with UOC. Surgical types were also divided into laparoscopic or abdominal surgery. The cases with concomitant hysterectomy or myomectomy are indicated as 'H′ or 'M′, respectively, in brackets.

### 3.2. Factors influencing pre-operative diagnosis of benign ovarian tumours

To identify significant factors affecting the possibility of Be-OT which could be noted pre-operatively, multi-variate analysis of 13 representative factors was performed (Table 3). Apart from 'no malignancy' diagnosed pre-operatively by MRI, which was expected to have a strong influence (OR 40.3, $p < 0.001$), two factors indicated a significant influence, namely positive CA125 (OR 0.2, $p$ = 0.038) and standard size

**Table 3**
Factors influencing the pre-operative diagnosis of benign ovarian tumours (Be-OTs).

| Factor | OR (95% CI), $n$ | $p$-value |
|---|---|---|
| > 40 years old | 0.7 (0.3–1.5) $n$ = 51/67 | 0.97 |
| Nulliparity | 1.4 (0.6–3.1, $n$ = 86/105 | 0.37 |
| High BMI >22 kg/m$^2$ | 1.1 (0.5–2.4, $n$ = 59/73 | 0.14 |
| Positive CA19–9 | 0.5 (0.2–1.3, $n$ = 15/22 | 0.48 |
| Positive CA125 | 0.2 (0.1–0.5, $n$ = 24/41 | 0.038 |
| Positive CEA | 0.5 (0.0–5.6, $n$ = 2/3 | 0.8 |
| Positive inflammation | 0.7 (0.3–1.7, $n$ = 20/27 | 0.33 |
| Positive LDH | 1.0 (0.1–9.3, $n$ = 4/5 | 0.27 |
| Bilateral cyst | 0.6 (0.2–2.0, $n$ = 10/14 | 0.76 |
| Multi-locular cyst | 0.6 (0.3–1.2, $n$ = 42/57 | 0.46 |
| Serous cyst | 1.5 (0.7–3.3, $n$ = 81/98 | 0.33 |
| Standard size | 4.4 (1.9–10.0, $n$ = 110/128 | 0.022 |
| No malignancy | 40.3 (13.6–119.2, $n$ = 115/120 | <0.0001 |

BMI, body mass index; CA125, carbohydrate antigen 125; CA19-9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; CI, confidence interval; LDH, lactate dehydrogenase; OR, odds ratio; OT, ovarian tumour; SM-OT, serous/mucinous ovarian tumour.
Multi-variate analyses of the 164 SM-OT cases were performed to examine the influence of 13 factors, including magnetic resonance imaging findings (no malignancy), on the possibility of Be-OT. The number of patients with each factor, the ORs and 95% CIs for the occurrence of these indexes, and the $p$-values are shown in this table. Three indexes, including 'positive CA125′ and 'standard size', showed significant differences.

(OR 4.4, $p = 0.022$). Although the effects of these two factors were relatively small in the analysis of the diagnostic ability of MRI, these factors could have the potential to enhance accuracy when used in combination with MRI. To test this hypothesis, each OR and CI was calculated after creating the following groups by combining the aforementioned factors: (1) 97 cases with 'no malignancy' and 'positive CA125′ (OR 25.4, 95% CI 7.3–88.3); (2) 100 cases with 'no malignancy' and 'standard size' (OR 46.0, 95% CI 10.4–202.9); and (3) 85 cases with 'no malignancy', 'positive CA125′ and 'standard size' (OR 26.8, 95% CI 6.1–117.0). As a result, only one combination, namely 'no malignancy' and 'standard size', suggested better potential for accurate diagnosis when used in combination with MRI. However, the effect of OT size was limited when compared with the influence of MRI diagnosis.

## 4. Discussion

Consistent with the recent trend towards minimally invasive surgery [12], in the case of OT treatment for premenopausal patients, the judgement criterion of Be-OTs may become increasingly important for selecting laparoscopic ovarian cystectomy. When the possibility of a Bo/Ma-OT is detected, laparoscopic salpingo-oophorectomy may be selected to prevent the spread of tumour cells. Similar to previous studies [6–9], this differentiation between Be-OTs and Bo/Ma-OTs is performed based on MRI interpretation at the study hospital. Over 8 years, data from > 1000 OT cases were accumulated and analysed to evaluate the algorithm for selecting the type of surgery. As a result of this analysis, three important insights were obtained.

First, MRI interpretation was able to differentiate almost perfectly between Be-OTs and Bo/Ma-OTs, but not SM-OTs. The diagnosis of two common types of OT (OMCT and OEC) was sufficient from MRI interpretation. The difference in diagnostic accuracy between OEC, OMCT and SM-OTs may be derived from the relatively low possibility of malignant transformation of OEC and OMCT [13,14], and the relatively high frequency of serous Bo-OTs [15]. Moreover, in this study, OMCT and OEC accounted for approximately 80% of cases (Table 1). Since previous studies [16–18] have reported that common types of benign ovarian cysts include OEC, OMCT, OSC and OMC in young patients, the present results may indicate that approximately half of cases could be differentiated sufficiently by MRI.

Second, similar to previous reports [19,20], CA125 and OT size showed a significant impact in SM-OTs, although MRI interpretation had an overwhelmingly large influence on this differentiation. Regarding OT size, similar to past reports [19], the results of simple analysis could approximately show that OT size was negatively correlated with the possibility of Be-OT when considering cases with OT size > 5 cm. On the other hand, in cases with OT size < 4 cm, there was a relatively high possibility of Bo/Ma-OT, although the reason remained unclear because the sample size was small ($n = 10$). Together with the result of calculation of SM-OT size, the average-sized SM-OT had a relatively high possibility of being a Be-OT.

Finally, in SM-OT cases, as pre-operative differentiation between Be-OTs and Bo/Ma-OTs was difficult even with MRI interpretation, OT size may be helpful to some extent to decide whether to select salpingo-oophorectomy. However, the influence of OT size was relatively small, and, unfortunately, the influence of CA125 could not be shown. Conversely, this result may indicate the difficulty and limitation of pre-operative differentiation of SM-OTs. This information may help future diagnosis and treatment by providing an explanation for the pre-operative situation. Additionally, recent artificial intelligence with MRI images has been recognized as a reliable tool to assist the diagnosis of ovarian cancers and borderline tumours. Furthermore, some reports have shown accuracy of approximately 0.9. It may be necessary to use this technique in future [21,22].

This study had some limitations due to its retrospective nature. When comparing MRI and pathological findings, it was not possible to perform interventions other than referring to the reports submitted by each expert. Additionally, at the study hospital, there was some bias in the type of OT, and approximately 80% of OTs were OEC or OMCT. In this study, many types of OT were classified as 'other type' and excluded from the analysis. This category included ovarian fibroma ($n = 7$), struma ovarii ($n = 3$), adult granulosa cell tumour ($n = 2$), fibrothecoma ($n = 2$) and other types. Therefore, the utility value of these insights may also be limited.

## 5. Conclusions

Among OEC, OMCT, OEA and OCCA, MRI interpretation can differentiate Be-OTs from Bo/Ma-OTs almost perfectly. On the other hand, it is relatively difficult to perform this differentiation in SM-OTs. Additionally, OT size may be useful to enhance this process. After adding more cases with many types of OTs, further analyses should be performed to achieve general conclusions.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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*Conflict of interest*

None declared.

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