



Case Report & Literature Review

Collision Tumors in Ovary: Case Series and Literature Review

Borges A^{1,2}, Loddo A³, Martins A^{1,4}, Peiretti M³, Fanni D⁵ and Djokovic D^{1,4*}

¹Department of Obstetrics & Gynecology, Hospital S. Francisco Xavier, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal

²Faculdade de Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal

³Division of Maternal-Fetal Medicine, Department of Surgical Sciences, University of Cagliari, Italy

⁴Department of Obstetrics & Gynecology, Nova Medical School - Faculdade de Ciências Médicas, Nova University of Lisbon, Lisbon, Portugal

⁵Division of Pathology, Department of Surgical Sciences, University of Cagliari, Italy

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ABSTRACT

Histologically distinct tumors that coexist in an organ without any histological admixture at their interface are denominated collision tumors. We report 3 cases of colliding mature cystic teratoma with mucinous cystadenoma and a case of mature cystic teratoma colliding with benign Brenner tumor in the ovary. We also provide a literature review based on 35 previously published ovarian collision cases. Ovarian tumors from all classes, benign, borderline and malignant lesions may collide. Both our case series and the literature review indicate that ovarian tumor collisions tend to be clinically and ultrasonographically/radiologically unrecognized. The awareness among surgeons, radiologists and pathologists of this rare phenomenon and histological recognition are crucial in order to offer adequate treatment to patients. There is a need to identify novel and more specific imaging clues pointing towards collision tumors in the ovary.

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Introduction

Collision tumors are histologically distinct neoplasms that coexist in the same organ without any histological intermixing [1]. Although very rare, they have been found to affect a range of organs, including skin, esophagus, stomach, colon, as well as the ovary [1-5]. We report and discuss the tumors colliding in the ovary that we witnessed in 4 patients and, also, provide a review based on 35 other cases identified by PubMed search for original articles electronically listed until October 2018 and by checking their respective references.

Presentation of the Cases

Case 1

A 37-year-old nulliparous woman, with regular menstrual cycles, no hormonal contraception use and medical history of psoriasis (medicated with methotrexate and glucocorticoids), presented with complaints of progressive abdominal-pelvic discomfort over six months, associated with the development of a low abdominal lump. She denied any other

symptoms. The patient was in a good general condition. Furthermore, on physical examination, the abdomen was soft while palpation revealed a mobile, elastic and tender mass in the right iliac fossa, approximately measuring 15 cm. With the exception of a vaginal discharge compatible with candidiasis, no other significant changes were noted. Namely, there were no signs of ascites or lymphadenopathies.

Abdominal and transvaginal ultrasonography revealed a cystic multilocular formation (2 locules), apparently originating from the right ovary and measuring 141 x 126 x 130 mm, with regular external and internal borders, "ground glass" content and Color Doppler score 1, *i.e.* no vascularization with Color Doppler (Figure 1A-C). The International Ovarian Tumor Analysis (IOTA) diagnostic prediction model ADNEX classified the lesion as a benign formation (Figure 1D). Tumor markers were negative (CEA = 1,80 ng/mL, CA19.9 = 12 U/mL and CA125 24,6 U/mL). Abdominal-pelvic magnetic resonance imaging (MRI) identified a cystic multiloculated tumor of the right ovary (170 x 113 x 137 mm), morphologically compatible with mucinous cystadenoma (Figure 1E and 1F). Signs of malignant disease were not observed. A laparotomic right

*Correspondence to: Dusan Djokovic, M.D. Ph.D, Department of Obstetrics & Gynecology, Hospital S. Francisco Xavier, CHLO, Estrada do Forte do Alto do Duque, 1449-005 Lisbon, Portugal; Tel: (+351) 91 6699603, E-mail: dusan.d.jokovic@gmail.com

salpingo-oophorectomy was performed. Histopathological examination established the diagnosis of colliding ovarian mature cystic teratoma and

mucinous cystadenoma. The patient had a favorable postoperative evolution, without complications.

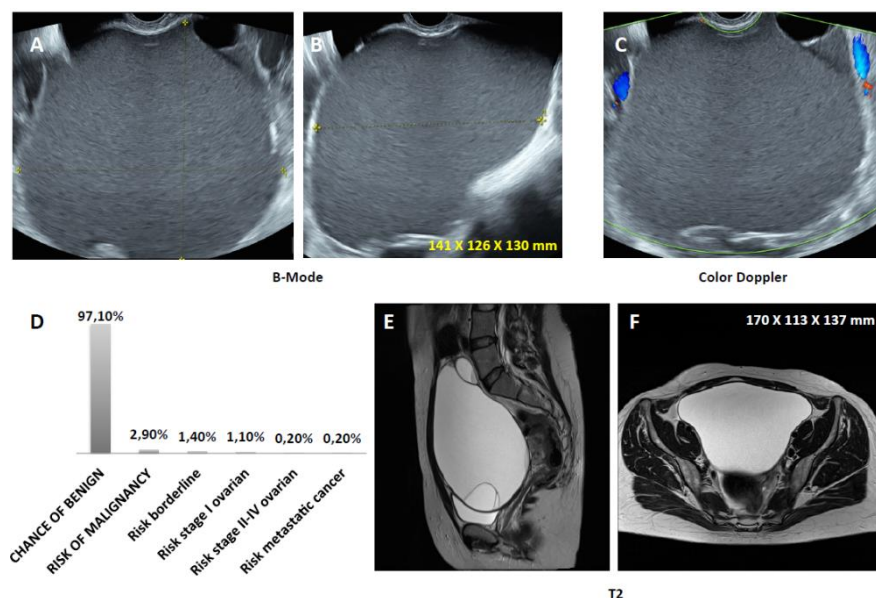


Figure 1: Collision of ovarian mature cystic teratoma and mucinous cystadenoma (case 1). **A-C:** Abdominal ultrasonography revealing a cystic multilocular formation (2 locules) with “ground glass” content and no vascularization with Color Doppler. **D:** Result of the preoperative formation assessment by the International Ovarian Tumor Analysis (IOTA) ADNEX prediction model. **E, F:** Abdominal-pelvic magnetic resonance imaging identifying a cystic multilocular tumor of the right ovary with morphology features compatible with mucinous cystadenoma.

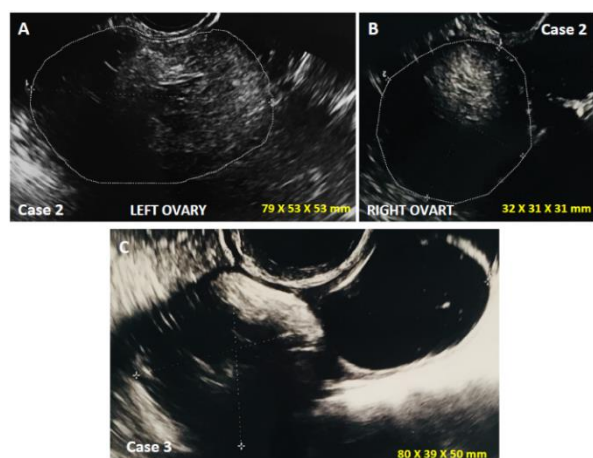


Figure 2: Collision of ovarian mature cystic teratoma and mucinous cystadenoma (cases 2 and 3). **A, B:** Case 2 transvaginal ultrasound detecting bilateral unilocular, mixed-content and non-vascularized formations (*i.e.* typical ultrasound morphology of mature cystic teratoma diagnosed in the left and right ovary); no findings suggesting a collision in the left ovary has been observed. **C:** Case 3 transvaginal ultrasound revealing a cystic bilocular formation, apparently originating from the left ovary, with mixed content in one of its locules and acoustic shadow.

Case 2

A 35-year-old nulliparous women, with regular menstrual cycles, no current hormonal contraceptive use, in good general condition and asymptomatic, underwent a routine gynecological check-up visit and transvaginal ultrasound which identified bilateral ovarian formations. A

level II transvaginal ultrasound subsequently detected unilocular, mixed-content and non-vascularized formation of 79 x 53 x 53 mm in the left ovary (Figure 2A and 2B). In parallel, another unilocular, mixed-content and non-vascularized formation of 32 x 31 x 31 mm was evidenced within the right ovary. There was no free fluid in pouch of Douglas. Tumor markers were negative (CEA = 3.90 ng/mL, CA19.9 = 32.5 U/mL and CA125 15.10 U/mL). The abdominal-pelvic MRI revealed an heterogenous nodular formation with a thin capsule, measuring 66 x 45 x 84 mm and containing a solid nodular component (45 x 36 x 51 mm) in the left ovary, and an heterogeneous nodular formation of 38 x 32 x 46 mm, with thin capsule and hypointense content in the right ovary, both lacking of enhancement. Morphologically these formations appeared compatible with bilateral teratomas. A laparoscopic bilateral salpingo-oophorectomy was performed. Histopathological examination established the diagnosis of colliding ovarian mature cystic teratoma and mucinous cystadenoma of the left ovary and ovarian mature cystic teratoma in the right ovary. The patient had a favorable postoperative evolution, without complications.

Case 3

A 44-year-old multiparous woman, with regular menstrual cycles under combined oral contraception, and with medical history of hypothyroidism and surgical history of benign ovarian cyst removal a decade ago, was referenced to our Unit due to persistence of a left ovarian formation, which was diagnosed by an abdominal ultrasound during her last pregnancy. Transvaginal ultrasonography revealed a cystic multilocular formation (2 locules), apparently originating from the left ovary and measuring 80 x 39 x 50 mm, with regular external and internal borders, acoustic shadow and a Color Doppler score 2 (Figure

2C). Tumor markers were negative (CEA = 1.50 ng / ml, CA19.9 = 8.4 U / ml, HE4 62.9 pm / l and CA125 19.25 U / ml). The IOTA diagnostic prediction model ADNEX classified the lesion as a benign formation. A laparoscopic removal of right ovary cyst was performed. Histopathological examination established the diagnosis of colliding ovarian mature cystic teratoma and mucinous cystadenoma. The patient presented an uneventful postoperative evolution.

Case 4

A 42-year-old nulliparous, on the course of her gynecological follow-up due to uterine fibromas, performed a transvaginal ultrasound, which identified a cystic multilocular formation (4 locules), apparently originating from the parenchyma of the right ovary and measuring 54 x 54 x 52 mm, with regular external and internal borders, mixed content and Color Doppler score 1 (Figure 3). The IOTA diagnostic prediction model ADNEX classified the lesion as a benign formation. Tumor marker CA125 was negative (25,2 U/ml).

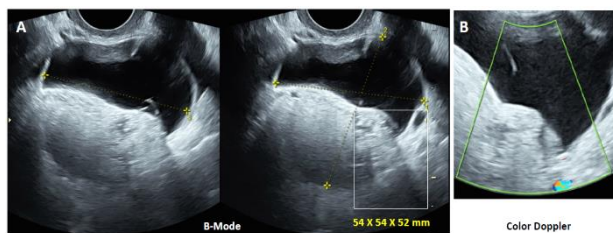


Figure 3: Collision of ovarian mature cystic teratoma and benign Brenner tumor (case 4). **A:** Transvaginal ultrasound (B-mode) identifying a cystic multilocular formation (4 locules), within the parenchyma of the right ovary, with regular external and internal borders and mixed content. **B:** Amplification of the area within the white rectangle from A, demonstrating no vascularization by the use of Color Doppler. No intra-cystic flux has been detected in whole lesion. Benign Brenner tumor, typically solid non-vascularized or minimally vascularized lesion, has not been preoperatively or intraoperatively recognized.

A laparotomic right salpingo-oophorectomy was performed. Histopathological examination established the diagnosis of colliding ovarian mature cystic teratoma (5 cm) and benign Brenner tumor (5 mm). This is the first reported case of a collision tumor of the ovary associated to a Brenner tumor, which was only postoperatively recognized. The patient had uneventful postoperative recovery.

Literature Review and Discussion

The concept of collision tumors implies the absence of histological admixture at the interface of two or more coexisting tumors in an organ [6]. As such, we witnessed 4 benign ovarian collisions and identified 35 previously published cases (Table 1), being both benign tumors in 19 patients (54.3%) and benign-malignant collisions in 16 cases (45.7%; including a patient with benign-borderline tumor collision). Mature teratoma appears in all our patients as well as the most frequently collision component in previous publications (21/35 cases, 60%), although the ovarian tumors from all classes, *i.e.* epithelial, germ cell and sex-cord/stromal neoplasms may collide. While others have reported that the combination teratoma-mucinous tumor is the most common, which

is indeed supported by our series, our literature review have found that mature teratoma-cystadenoma (serous in 5/21 and mucinous in 4/21 cases) and mature teratoma-carcinoma (serous in 6/21 and mucinous in 2/21 cases) predominate [7]. Thus, mature teratoma-serous epithelial lesion, whether benign or malignant, is actually the most frequent of all published combinations, including our cases. Furthermore, collision tumors tend to be a unilateral phenomenon (26/35 cases, 21 affecting right ovary). We identified in literature only one true bilateral case and 8 collisions accompanied by sole tumor in the contralateral ovary. Collision tumor pathogenesis is unknown, being the simplest theory the accidental development of two different tumors [6, 8]. Alternative hypotheses include:

1. common origin from pluripotent stem cell.
2. simultaneous proliferation of two different cell lines.
3. common carcinogenic agent interacting with different tissues and inducing different tumors, and
4. tumor growth promotion by microenvironmental changes induced by primary lesion such as oncogenic growth factor productions, neoangiogenesis and inflammation [6].

Collision tumors affect both pre- and postmenopausal women (median age: 50, range 18 to 83 years); however, the patients with benign lesions are younger (median age: 44, range 18 to 77 years) than patients bearing a malignant disease (median age 52, range 40 to 83 years). Their clinical manifestations include abdominal swelling (12/35 cases), palpable mass (12/35), abdominal pain (10/35), pelvic pain (7/35) and abnormal uterine bleeding (7/35) while less frequently they represent an accidental finding. The utility of tumor markers to predict benign vs. malignant lesion nature is limited as in single ovarian tumors. For instance, CA-125 levels have been found increased in 8/9 collisions including malignant lesion, but also in 2/8 benign collisions.

Generally, collision tumors are diagnosed postoperatively, by histopathological examination. Not expecting a collision, in our and most other cases, the imaging techniques usually to describe collision as a unique lesion. When mature cystic teratoma is present, classic ultrasound presentation, *i.e.* mixed content unilocular ovarian formation is commonly observed. However, it has been previously reported that the collisions with mature teratoma may have radiologic clues pointing towards the presence of two different tumors, such as the presence of non-fatty fluid in the cyst and a large solid component in the ovarian mass [6, 9].

Since most ovary collision tumors are not recognized by ultrasound or MRI, appropriate frozen section analysis and the surgeon and histopathologist awareness of the existence of collision tumors are fundamental to guide the type and extent of surgery. Importantly, collision tumors have to be histologically distinguished from mixed tumors, another type of composite ovarian tumor characterized by the intermingling of different components in one neoplastic mass (*e.g.* malignant mixed müllerian tumor) [6, 10]. In our 4 cases, benign tumors collided; thus, the curative treatment consisted on the excision of the affected ovary. In general, regarding both management strategy and prognosis establishment, the main factors to be considered are the types of colliding components, most aggressive component and the stage of malignant tumor.

Table 1: Collision tumor of the ovary (summary of previously published cases).

Case	Histology 1	Histology 2	Side	Counter-lateral	Age	Symptoms/Signs	Ultrasound	Other imaging	Tumor markers	Treatment	Survival	Ref.
1	Teratoma, mature cystic	Cystadenoma, serous	R		55	Pelvic pain, palpable mass, AUB	Unilateral adnexal formation	NA	NA	USO	Considered cured	[11]
2	Teratoma, mature cystic	Cystadenoma, serous	R	Teratoma, mature cystic	18	Pelvic pain, palpable mass	NA	CT: bilateral cystic-solid, septated lesion with fat components, calcified, (right 53 x 62 x 74 mm, left 84 x 112 x 134 mm)	NA	Bilateral tumorectomy	Considered cured	[12]
3	Teratoma, mature cystic	Cystadenoma, serous	R		42	Abdominal pain, AUB	Unilateral adnexal formation	NA	CA-125 ↑	USO	Considered cured	[6]
4	Teratoma, mature cystic	Cystadenoma, serous	L		60	Abdominal pain	Unilateral, cystic formation (200 x 160 x 60 mm)	NA	NA	UO	Considered cured	[13]
5	Teratoma, mature cystic	Cystadenoma, serous	R	Teratoma, mature solid	29	Pelvic pain, palpable mass, AUB	Unilateral, unilocular cystic formation (170 mm), regular margins, hypoechogenic content	NA	CA-125 N, CEA N	USO, contralateral tumorectomy	Considered cured	[14]
6	Teratoma, mature cystic	Cystadeno-fibroma, serous	L		69	Pelvic pain, palpable mass	Unilateral, cystic formation (64 x 44 x 32 mm)	NA	CA-125 N, CA 19.9 N	USO	Considered cured	[15]
7	Teratoma, mature cystic	Cystadenoma, mucinous	R		58	Abdominal swelling	Unilateral, unilocular cyst (150 mm), mixed content	NA	CA-125 N, CEA ↑, CA-19.9 ↑	AH, BSO, appendectomy, omentectomy	Considered cured	[16]
8	Teratoma, mature cystic	Cystadenoma, mucinous	R		35	Abdominal pain, palpable mass	Unilateral adnexal formation (100 x 90 x 60 mm)	NA	NA	USO	Considered cured	[6]

Table 1: Collision tumor of the ovary (summary of previously published cases), continuation

Case	Histology 1	Histology 2	Side	Counter-lateral	Age	Symptoms/Signs	Ultrasound	Other imaging	Tumor markers	Treatment	Survival	Ref.
9	Teratoma, mature cystic	Cystadenoma, mucinous	R		50	Palpable mass	Unilateral adnexal formation (80 x 70 x 25 mm)	NA	NA	USO	Considered cured	[6]
10	Teratoma, mature cystic	Cystadenoma, mucinous	R		27	Pelvic pain, abdominal swelling	Unilateral, "complex" cyst (80 x 40 x 40 mm)	NA	CA-125 N, CA 19.9 N	USO	Considered cured	[17]
11	Teratoma, mature cystic	Carcinoma, serous	R		45	Palpable mass	NA	NA	NA	AH, BSO, partial omentectomy	NA	[18]
12	Teratoma, mature cystic	Carcinoma, serous	L		45	Abdominal pain, abdominal swelling	Unilateral formation with "malignant features"	MRI: Unilateral formation with "malignant features"	CA-125 ↑	AH, BSO, PL, PAL, appendectomy, peritoneal metastasis resection + adjQT	Disease free 6 months	[1]
13	Teratoma, mature cystic	Carcinoma, serous	BL		50	Abdominal swelling	Bilateral cystic-solid formation, ascites	NA	CA-125 ↑	AH, BSO, omentectomy	NA	[19]
14	Teratoma, mature cystic	Carcinoma, serous	R	Teratoma, mature cystic	48	Abdominal pain, abdominal swelling	Bilateral cystic-solid formation, ascites	NA	CA-125 ↑	BSO, omentectomy, peritoneal biopsy	NA	[20]
15	Teratoma, mature cystic	Carcinoma, serous papillary	R	Carcinoma, serous papillary	40	Abdominal heaviness, AUB	Bilateral adnexal formation	NA	CA-125 ↑	BSO	NA	[6]
16	Teratoma, mature cystic	Carcinoma, serous papillary	R		83	Abdominal pain, AUB	Unilateral, cystic formation (67mm), calcified	NA	CA-125 ↑, CEA ↑	AH, BSO, omentectomy	NA	[21]
17	Teratoma, mature cystic	Carcinoma, mucinous	R	Carcinoma, mucinous	45	Pelvic pain, abdominal swelling	NA	NA	NA	AH, BSO, omentectomy	NA	[22]

Table 1: Collision tumor of the ovary (summary of previously published cases), continuation

Case	Histology 1	Histology 2	Side	Counter-lateral	Age	Symptoms/Signs	Ultrasound	Other imaging	Tumor markers	Treatment	Survival	Ref.
18	Teratoma, mature embryoid	Carcinoma, mucinous	L		36	Abdominal pain, palpable mass	Unilateral, multiloculated cyst f (120 × 120 × 90mm)	NA	NA	UO	NA	[23]
19	Teratoma, mature cystic	Adenomatoid tumor	R		44	Pelvic pain	Unilateral, unilocular cyst, mixed content, acoustic shadowing	NA	NA	USO	Considered cured	[24]
20	Teratoma, mature cystic	Fibrothecoma	R		77	Abdominal pain, palpable mass	NA	MRI: Unilateral, bilocular-solid formation (120 × 120 × 115 mm)	CA-125 N	AH, BSO	Considered cured	[25]
21	Teratoma, mature cystic	Granulosa cell tumor	R	Teratoma, mature cystic	40	Accidental finding	NA	NA	NA	BSO	Considered cured	[26]
22	Cystadenoma, serous	Fibrothecoma	L		63	Abdominal swelling, obstructive urinary symptoms	Unilateral, cystic formation	CT: Unilateral, cystic-solid formations (27 × 150 × 200 mm, solid component 90 × 50 mm), ascites	CA-125 N	AH, BSO	Considered cured	[27]
23	Cystadenoma, serous	Fibrothecoma	R		43	Abdominal pain, palpable mass	Unilateral cystic-solid formation (cystic component 57 x 50 x 76 mm, solid component 71 x 35 x 65 mm)	MRI: Unilateral, cystic-solid formation	CA-125 N, CEA N	UO	Considered cured	[28]
24	Cystadenoma, mucinous	Fibrosarcoma	R		61	Abdominal swelling	NA	NA	NA	AH, BSO, appendectomy + adjRT	†, 18 months	[29]

Table 1: Collision tumor of the ovary (summary of previously published cases), continuation

Case	Histology 1	Histology 2	Side	Counter-lateral	Age	Symptoms/Signs	Ultrasound	Other imaging	Tumor markers	Treatment	Survival	Ref.
25	Cystadenoma, mucinous	Granulosa cell tumor	R		49	AUB	NA	NA	NA	AH, BSO	Considered cured	[30]
26	BOT, mucinous	Neuroendocrine tumor	NA		55	Abdominal swelling	NA	CT: Unilateral solid formation with internal cysts (202 x 164 x 162 mm), ascites	CA-125 N, CEA ↑	USO	Considered cured	[31]
27	Carcinoma, serous	Steroid cell Tumor	L	Carcinoma, serous	68	Abdominal pain, virilization	NA	NA	CA-125 ↑	AH, BSO, PAL, peritoneal metastasis resection + adjRT	†, 12 months	[32]
28	Carcinoma, serous	Dysgerminoma	R		20	Abdominal swelling	NA	Unilateral solid tumor (130 x 90 mm)	NA	UO	Considered cured	[33]
29	Carcinoma, serous papillary	Granulosa cell tumor	L		75	Accidental finding	NA	NA	NA	USO	NA	[34]
30	Carcinoma, serous papillary	Granulosa cell tumor	L	Carcinoma, serous	50	Abdominal swelling	NA	CT: Unilateral, multilocular cystic formation (50 x 30 mm), ascites	CA-125 ↑	AH, BSO, omentectomy	NA	[35]
31	Carcinoma, mucinous	Sarcoma, undifferentiated	L		49	Abdominal swelling	NA	NA	NA	BSO, omentectomy, PAL	†, 1 week	[29]
32	Carcinoma, mucinous	Angiosarcoma	L		54	Accidental finding	Unilateral adnexal formation	MRI: Unilateral, multilocular-solid thick-walled formation (260 × 190 × 100 mm), vascularized multilocular	CA-125 ↑, CA-19.9 ↑	AH, BSO, peritoneal biopsy + adjQT	Recurrence (pleural metastases), 10 months	[36]
33	Carcinoma, endometrioid	Granulosa cell tumor	R		56	Palpable mass	NA	NA	NA	AH, BSO, PL, omentectomy, peritoneal biopsy	NA	[37]

Table 1: Collision tumor of the ovary (summary of previously published cases), continuation

Case	Histology 1	Histology 2	Side	Counter-lateral	Age	Symptoms/Signs	Ultrasound	Other imaging	Tumor markers	Treatment	Survival	Ref.
34	Carcinoma, hepatoid	Granulosa cell tumor	L		58	Palpable mass, AUB	Unilateral solid formation (large)	NA	NA	AH, BSO, appendectomy + adjQT	Disease free 18 months	[38]
35	Signet-ring stromal tumor	Steroid cell tumor	L		64	Accidental finding	NA	NA	NA	AH, BSO	Considered cured	[39]

Abbreviations: adjQT – adjuvant chemotherapy; adjRT – adjuvant radiotherapy; AH – abdominal hysterectomy; AUB – Abnormal uterine bleeding; BL – bilateral; BSO - bilateral salpingo-oophorectomy; L – left; NA – not available; PAL - para-aortic lymphadenectomy; PL – pelvic lymphadenectomy; R – right, UO – Unilateral oophorectomy; USO – unilateral salpingo-oophorectomy; † - death.

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Conclusion

As far as our knowledge goes, this is the most complete revision of collision tumor in the ovary, which aims to alert clinicians, radiologists and histopathologists about the phenomenon. Its rarity makes it difficult to plan the research in order to understand the etiopathogenesis of collisions. Since collision tumors tend to be clinically and ultrasonographically/radiologically indistinguishable from single lesions, histological recognition of such neoplasms is important, allowing appropriate treatment to be offered to patients according to the individual biological characteristic of each of the components. Careful revision of the images, whenever histology confirms the coexistence of ovarian tumors without intermixing, may contribute to the identification of novel and probably more specific imaging clues pointing toward the collision tumors.

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Conflicts of interest

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