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Ovarian metastases of pancreatic adenocarcinoma: clinical presentation, role of surgery, and potential value of the mutational profile for the differential diagnosis with primary mucinous ovarian carcinoma

Alice de Malet^{ID}, Magali Svrcek, Anne Kerbaol, Nathalie Theou-Anton, Sandra Granier, Safi Dokmak, François Paye, Thierry André, Louis de Mestier, Jérôme Cros and Pascal Hammel

Abstract

Background: Ovarian metastases (OM) of pancreatic adenocarcinoma (PA) (OM-PA) can mimic primary ovarian mucinous carcinoma (POMC) on imaging and histology. These metastases are often symptomatic and not highly chemosensitive, so that oophorectomy may be considered.

Aims: The aims of this study were to compare the characteristics of OM-PA and POMC, and discuss the role of surgery.

Patients and Methods: Clinical, imaging, and histological data of patients with OM-PA and POMC (2000–2017) in three tertiary centers were reviewed. Twenty-six genes were analyzed by next generation sequencing (NGS) on both primary PA and OM-PA.

Results: Twenty-two women with OM-PA ($n=13$, 11 with surgical resection) or POMC ($n=9$) were selected. OM-PA were smaller than POMC ($p=0.02$); imaging, histological, and immunohistochemistry data did not clearly differentiate OM-PA from POMC in 12 of 22 cases (54%). Seven PA/OM-PA pairs were analyzed, and a concordant KRAS mutation was identified in all cases. In four OM-PA, concordant mutations were also found in TP53 ($n=3$), SMAD4 ($n=1$), MET ($n=1$), and PDGFRA ($n=1$) genes. The aim of oophorectomy in 11 OM-PA was for antalgic ($n=6$) or curative ($n=5$) intent. Pain improved in 4/6 of the former patients, but 2/6 had significant morbidity, and 2/6 died of rapid tumor progression. After oophorectomy, median progression-free and overall survivals were 6 (0–11) and 8 months (1–131), respectively.

Conclusion: Analysis of mutation profiles in both primary PA and ovarian tumors, especially KRAS, can help to determine the pancreatic origin of OM-PA. Surgical resection of OM-AP in highly selected patients may improve pelvic symptoms but may also cause significant morbidity. The benefit to survival requires further studies.

Keywords: KRAS mutation, molecular testing, ovarian metastases, ovarian mucinous carcinoma, pancreas adenocarcinoma

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Introduction

Five to 22 percent of ovarian tumors are metastases (OM) from nongynecological cancers, mainly

of the digestive tract (80%).¹ The main primary sites of OM are gastric (7–30%), colorectal (6–32%), appendix (20%), breast (8–22%),

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Correspondence to:

Pascal Hammel
Digestive and Medical
Oncology, Paul Brousse
Hospital, Assistance
Publique – Hôpitaux de
Paris (AP-HP), Université
de Paris Saclay, 12 avenue
Paul Vaillant-Couturier,
94800 Villejuif, France
pascal.hammel@aphp.fr

Alice de Malet
Digestive and Medical
Oncology, Paul Brousse
Hospital, Assistance
Publique – Hôpitaux de
Paris (AP-HP), Université
de Paris Saclay, Villejuif,
France

Magali Svrcek
Department of Pathology,
Saint-Antoine Hospital,
Assistance Publique –
Hôpitaux de Paris (AP-HP),
Université Paris-Sorbonne,
Paris, France

Anne Kerbaol
Radiology, Beaujon
Hospital, Assistance
Publique – Hôpitaux de
Paris (AP-HP), Université
de Paris, Clichy, France

Nathalie Theou-Anton
Biochemistry and
Genetics, Bichat Hospital,
Assistance Publique –
Hôpitaux de Paris (AP-HP),
Université de Paris, Paris,
France

Sandra Granier
Digestive and Medical
Oncology, Paul Brousse
Hospital, Assistance
Publique – Hôpitaux de
Paris (AP-HP), Université
de Paris Saclay, Villejuif,
France

Safi Dokmak
Digestive Surgery, Hôpital
Beaujon, Assistance
Publique – Hôpitaux de
Paris (AP-HP), Université
de Paris, Clichy, France

François Paye
Digestive Surgery,
Saint-Antoine Hospital,
Assistance Publique –
Hôpitaux de Paris (AP-HP),
Université Paris-Sorbonne,
Paris, France

Thierry André
Digestive Oncology,
Saint-Antoine Hospital,
Assistance Publique –
Hôpitaux de Paris (AP-HP),
Université Paris-Sorbonne,
Paris, France

Louis de Mestier
Gastroenterology-
Pancreatology, Beaujon
Hospital, Assistance
Publique – Hôpitaux de
Paris (AP-HP), Université
de Paris, Clichy, France

Jérôme Cros
Pathology, Beaujon
Hospital, Assistance
Publique – Hôpitaux de
Paris (AP-HP), Université
de Paris, Clichy, France

pancreas (5–12%), biliary tract (12%), small intestine (7%), kidney (5%), hepatocellular carcinoma (3%), and gallbladder (2%).^{2–6} Krukenberg's criteria^{7,8} (i.e. ovarian carcinoma containing signet-ring cells, mucine filled, with an important sarcomatoid proliferation of the ovarian stroma) are often applied to all OM, without consideration of their histological features. The prevalence of OM is probably underestimated. The rate in an autopsy series of patients who died of PA was 4–19%.^{3,6,9} Several genetic syndromes predispose patients to both ovarian and pancreatic tumors (e.g. *BRCA1* or *BRCA2* germline mutations), complicating the assessment of the origin of ovarian masses in the context.

Data in the literature on ovarian metastases from PA (OM-PA) are limited.^{1,2,3,6,9–16} Distinguishing these metastases from primary ovarian mucinous tumors (POMC) can be difficult on imaging and even on pathology examination, although the clinical context of diagnosis is often different. It is important to differentiate these tumors because this affects their prognosis and management. The genetic alteration profiles of OM-PA and POMC also differ: *KRAS*, *TP53*, *SMAD4*, and *CDKN2A* mutations are more prominent in PA, while *KRAS* and *TP53* (27%) but also *CDKN2A*, *BRAF*, and *RNF43* are predominant in POMC with no *SMAD4* mutations.^{2,9,13–17}

While PA and OM-PA are often diagnosed simultaneously, OM may dominate the initial presentation. They are often bulky and symptomatic, resulting in pelvic pain and/or heaviness.⁶ Because of the poor prognosis of metastatic PA, there is very little indication for surgery in these cases. However, an oophorectomy may occasionally be considered when OM-PA are the single or main extra-pancreatic tumor location, especially in patients with longer-term disease control following pancreatectomy or effective systemic chemotherapy. The role of surgery in relieving pelvic symptoms or even increasing survival has not been clearly defined.^{1,9,18}

The aims of this study were (1) to describe the clinical, radiological, and histological characteristics of OM-PA, and the indications for and limitations of surgical resection, and (2) to improve the understanding of the histology and mutational profile of these metastases, as well as to identify features for the differential diagnosis with POMC.

Patients and methods

Patients

All consecutive patients treated for PA with ovarian metastases in Beaujon, Bichat and Saint-Antoine hospitals (AP-HP, Clichy and Paris, France) between 2000 and 2017 were included in this retrospective study after a clinical and pathological review. PA were histologically proven, and ovarian lesions were defined by CT scan (ovarian tumors, unique or multiple, solid and/or cystic) and, whenever possible, histological analysis of oophorectomy specimens.

The control group included patients with POMC based on the same criteria. OM secondary to other primary cancers, and primary serous ovarian tumors, were not included, because the histopathological features of the latter are clearly different from those of OM-PA, making them relatively easy to identify. In case of diffuse peritoneal carcinomatosis, ovarian tumors with isolated superficial involvement (“contact” carcinomatosis rather than hematogenous disseminated OM) were also excluded.

Data collection

The following data were collected:

- Clinical and biological presentation at oophorectomy: synchronous or metachronous OM, delay between the diagnosis of PA and OM, pancreatic tumor location (head, body, tail), unilateral or bilateral ovarian involvement, the presence of other metastases at the diagnosis of OM including peritoneal carcinosis and ascites, assay of tumor markers (CEA, CA 19.9, CA 125) at the time of OM diagnosis.
- Imaging features: the last CT scans performed before oophorectomy were reviewed by a radiologist with more than 10 years' experience in imaging of the digestive tract (AK). Collected data included the size of the ovarian tumor, the presence of a cystic (uni- or multilocular) portion, intra-cystic bulkheads, tissue buds, calcifications, thickened walls, ascites, peritoneal carcinomatosis nodules, and/or tumor enhancement after contrast administration.
- Histological presentation: cystic and mucinous nature, invasion of the ovarian stroma, micro-tumoral deposits on the surface,

Table 1. Genes analyzed using NGS in the patients with ovarian metastases.

<i>EGFR</i> (exon 12/18/19/20/21), NM_005228.3	<i>MET</i> (exon 2/14/15/16/17/18/19), NM_001127500.1
<i>KRAS</i> (exon 2/3/4), NM_033360.3	<i>FBXW7</i> (exon 5/8/9/10/11), NM_012179.3
<i>BRAF</i> (exon 11/15), NM_004333.4	<i>ERBB4</i> (exon 3/4/6/7/9/15/23), NM_005235.2
<i>MAP2 K1</i> (exon 2), NM_002755.3	<i>KIT</i> (exon 8/9/11/13/14/17/18), NM_000222.2
<i>CTNNB1</i> (exon 3), NM_001098209.1	<i>MET</i> (intron 13/14), NM_001127500.1
<i>SMAD4</i> (exon 4/6/7/9/10/11/12/13), NM_005359.3	<i>PTEN</i> (exon 1/3/6/7/8), NM_000314
<i>NOTCH1</i> (exon 26/27), NM_017617.3	<i>NRAS</i> (exon 2/3/4), NM_002524.4
<i>FGFR2</i> (exon 7/9 / 12.14), NM_022970.3	<i>STK11</i> (exon 1/4/5/6/8), NM_000455
<i>HRAS</i> (exon 2/3/4), NM_NM_001130442.1	<i>DDR2</i> (exon 6/9/13/14/15/16/18), NM_006182
<i>PIK3CA</i> (exon 10/21), NM_006218.2	<i>TP53</i> (exon 2a / 5b / 6/7/8/11), NM_000545
<i>AKT1</i> (exon 3), NM_001014432.1	<i>FGFR3</i> (exon 14/16/18), NM_000142.4
<i>ERBB2</i> (exon 19/20), NM_004448.3	<i>FGFR1</i> (exon 7a / 11), NM_023110
<i>ALK</i> (ex. 22/23/24/25), NM_004304.4	<i>PDGFRA</i> (exon 12/14/18), NM_006206

immunohistochemical analyses. Ovarian and pancreatic histological specimens were reviewed by two experts in pancreatic pathology (MS and JC).

- Analysis of treatment before and after oophorectomy, reasons for oophorectomy when performed (symptomatic or cytoreductive intent), and efficacy on symptoms, as well as potential influence on survival.

Molecular analyses

Paired pancreatic and ovarian histological specimens were analyzed whenever possible using Next Generation Sequencing (NGS) to determine whether the mutational profile could help differentiate OM-PA from POMC.

Technique: Extraction of the DNA on Maxwell automate (Promega, Madison, Wisconsin, USA) with the FFPE Plus LEV DNA kit, then search for genetic variations by NGS (PGM – Life Technologies, Carlsbad, California, USA) following PCR ampliseq. The 26 genes analyzed with the NGS panel (CEIVD targeted kit Oncomine tumor solid DNA and complementary panel – Life Technologies) are described in Table 1.

Data analysis was carried out with Torrent Suite Software (Life Technologies) with alignment to

the hg19 human reference genome. Variant Caller and annotation was carried out with the Ion Reporter suite Software (Life Technologies). All detected variants were manually reviewed with the Integrative Genomics Viewer (IGV, Broad Institute, Cambridge, Massachusetts, USA). Sensitivity and accuracy for detecting variants at an AF > 3% was 100% for commercial reference standards.

Statistical analyses

Quantitative variables were presented as medians and standard deviations, due to the foreseeable small number of patients included. Qualitative variables were presented as frequencies and percentages. The clinical, histological, imaging, and genetic features of patients with OM-PA were compared with those with POMC, to search for discriminant factors.

Overall survival was defined as the time between the initial diagnosis and date of death, whatever the cause, or the last news from the patient. Progression-free survival was defined as the time between oophorectomy and tumoral progression (whatever the site) or death. Median survivals were calculated using the Kaplan-Meier method.

Ethics approval and consent to participate

This retrospective observational study meets the ethical criteria with regard to our committee for the protection of individuals for medical research in our hospital group, and follows international and national regulations in accordance with the Declaration of Helsinki.

Patient consent for publication

We declare that the patients or, failing this, one of their parents or relatives, have given their informed written consent according to a systematic policy for the publication of any associated data and accompanying images.

Results

Description of OM-PA, and comparison with POMC

Clinical characteristics of OM-PA. Thirteen patients with OM-PA and 9 patients with POMC were selected for the study, including 11/13 and 9/9 patients who underwent surgical resection of ovarian tumors, respectively.

The median age at diagnosis of OM was 56 years old (38–81) in the OM-PA group, and 61 years old (34–85) in the POMC group. OM were metachronous in all patients but one. The only patient with synchronous metastases underwent concomitant surgical resection of both OM-PA and primary PA.

Primary pancreatic tumors were located in the pancreatic head ($n=4$), body ($n=5$), or tail ($n=4$). One patient had a cystadenocarcinoma of the tail. Another patient had a germline mutation in the *BRCA1* gene.

Six of thirteen patients (46%) had undergone surgical resection of primary PA. All patients but one underwent systemic chemotherapy with the following regimens: gemcitabine ($n=4$), gemcitabine plus oxaliplatin (GEMOX) ($n=3$), 5-fluorouracil (5-FU) plus irinotecan and oxaliplatin (FOLFIRINOX) ($n=2$) or gemcitabine plus nab-paclitaxel ($n=2$). One patient received a duodenal stent to treat symptomatic duodenal stenosis, and another a biliary stent for obstructive jaundice.

Biological characteristics of OM-PA. The median serum CA125, CA19.9 and CEA measurements

at the diagnosis of OM-PA, available in respectively 5, 12, and 8 patients with OM-PA were 58 IU/L (7–3426), 266 IU/mL (2–19,000), and 16 ng/mL (0.8–398).

Imaging characteristics of OM-PA and POMC. At diagnosis the median size of the largest tumor in each patient was smaller in OM-PA [120 mm (46–220)] than in POMC [165 mm (100–290)] (Table 2). In OM-PA patients, ovarian tumors were bilateral in 8/13 patients (62%) and unilateral in 5/13 (38%) (right ovary: $n=3$, left ovary: $n=2$), while POMC were mainly unilateral (7/9, 78%).

CT scan images were available for review in 8/13 patients with OM-PA, and 4/9 with patients with POMC. All tumors were cystic. Contrast enhancement occurred in 12/13 OM-PA (92%), and in 1/4 POMC (25%). Thickened walls were found in 3/8 OM-PA (38%), and in none of the POMC. Tissue buds were found in 6/8 OM-PA (75%) and in 1/4 POMC (25%), while 3/8 OM-PA (38%) were accompanied by ascites compared with none of the POMC. There was no difference in other characteristics (cystic portion, intra-cystic walls, calcifications, tissue nodules). Figure 1(a) and (b) shows CT scans of typical lesions.

Histological features of OM-PA and POMC. All OM-PA and POMC specimens had a mucinous and cystic appearance, and ovarian stromal invasion (Table 2). Four of the 11 patients with OM-PA (36%) had only ovarian surface implants, versus 2/9 patients with POMC (22%).

Histology could not determine whether the ovarian lesion was primary or metastatic in 7/11 patients with OM-PA (64%), and 5/9 patients with POMC (56%). Either the histological appearance of the locations of the pancreatic and ovarian tumors in OM-PA patients was different, or the tissue samples from endoscopic ultrasound (EUS) fine-needle aspiration of the primary pancreatic lesion did not provide enough information for histological comparison (PA samples were obtained by surgical resection in 6 patients (46%), and by EUS-needle biopsy in 7 patients (54%)). Examples are shown in Figure 2(a) and (b).

Immunohistochemical study. Immunohistochemical markers could be tested in 9/11 OM-PA and 6/9 POMC. Cytokeratin 7 and 20 and CDX2 were overexpressed in all tested tumors in both

Table 2. Comparison of imaging and histological features of eight ovarian metastases of pancreatic adenocarcinoma (OM-PA) and four primary ovarian mucinous carcinoma (POMC).

Characteristics	OM-PA	POMC	p value
Imaging			
Bilateral ovarian tumors	8/13 (62%)	2/9 (22%)	0.099
Cystic portion	3/8 unilocular (38%), 5/8 multilocular (63%)	2/4 unilocular (50%), 2/4 multilocular (50%)	
Walls	5/8 (63%)	2/4 (50%)	
Thickened walls	3/8 (38%)	0/4 (0%)	0.491
Tissular buds	6/8 (75%)	1/4 (25%)	0.222
Calcifications	1/8 (13%)	2/4 (50%)	
Ascites	3/8 (38%)	0/4 (0%)	0.491
Nodules of peritoneal carcinomatosis	3/8 (38%)	2/4 (50%)	
CT enhancement after injection	7/8 (88%)	1/4 (25%)	0.032
Pathology			
Pancreatic primitive location	4/11 head (36%), 4/11 body (36%), 3/11 tail (27%)		
Maximal ovarian tumoral size (mm)	120 (46–220)	165 (100–290)	0.024
Cystic aspect	11/11 (100%)	10/10 (100%)	
Mucinous aspect	11/11 (100%)	10/10 (100%)	
Invasion of surface	3/11 (27%)	1/10 (10%)	0.603
Stromal invasion	11/11 (100%)	10/10 (100%)	
Necrosis	4/11 (36%)	6/10 (60%)	0.39
Peritoneal carcinomatosis at the time of oophorectomy	7/11 (64%)	3/10 (30%)	
Difficulties in differential diagnosis between ovarian metastasis or ovarian primary	7/11 (64%)	5/10 (50%)	
Immunohistochemistry			
Cytokeratin 7 overexpression	5/5 (100%)	4/4 (100%)	
Cytokeratin 20 overexpression	4/5 (80%)	4/4 (100%)	
CDX2 overexpression	4/4 (100%)	2/2 (100%)	
CT, computed tomography; OM-PA, pancreatic adenocarcinoma; POMC, primary ovarian mucinous carcinoma.			

groups (except one OM-PA with cytokeratin 7 overexpressed but no overexpression of cytokeratin 20, and no test performed for CDX2). On the other hand, there was no expression of estrogen or progesterone receptors. Other markers

(cERBB2, CD19, MUC1, MUC2, MUC5CA, TP53, hENT1, BRAF, NRAS, EGFR, PAX8, P16, MMR, PI3KCA, HBME1, CA125) were studied in small groups of patients, and no significant difference was observed.

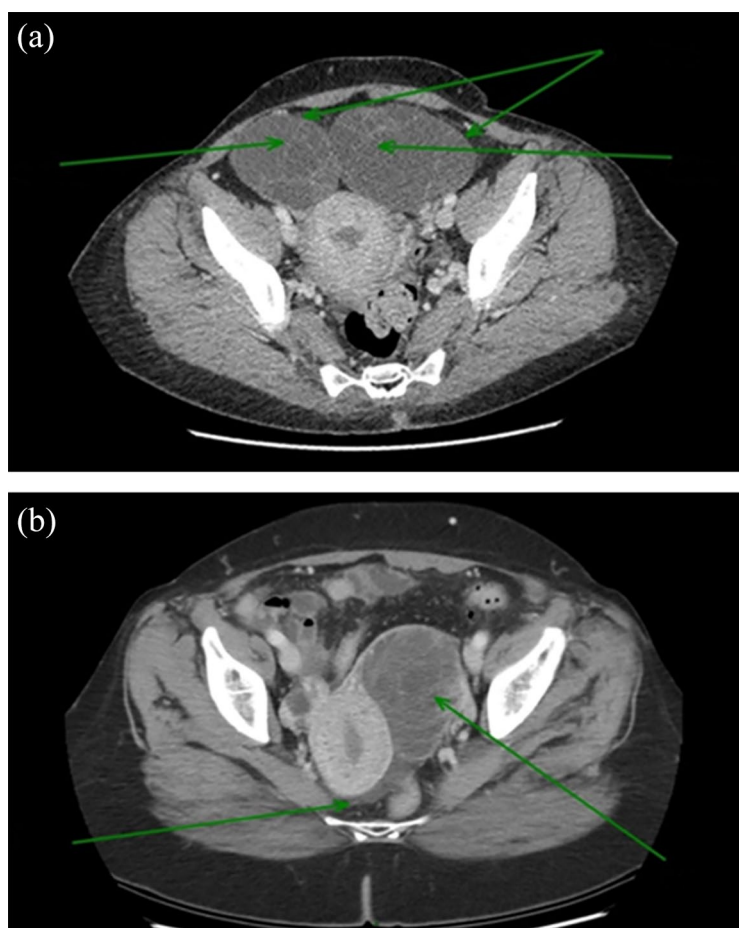


Figure 1. CT scan – examples of ovarian metastases of pancreatic adenocarcinoma (OM-PA) and primary ovarian mucinous carcinoma (POMC). (a) Patient P2 (OM-PA): Multiple thin septa (left arrow), cystic walls (right arrow), reaching the two appendages. (b) Patient O1 (POMC): Ascites blade (left arrow), multiple thin septa (right arrow).

Somatic genetic analysis – search for KRAS mutation. In 5/11 patients with OM-PA, only *KRAS* gene mutations were searched for on pairs of ovarian and pancreatic samples at diagnosis (Table 3). In 4 of the 6/11 remaining patients, another genetic analysis was performed on each pair of samples at the time of the study, using Next Generation Sequencing (NGS) to test a panel of 26 genes that are often mutated in PA.

The search for somatic mutations of the *KRAS* gene at diagnosis in the 5/11 former patients with OM-PA identified an identical mutation in three of them in both OM-PA and PA samples (G12 V, G12A, and G12D, respectively). The fourth patient had a G12 V *KRAS* mutation in the OM-PA but the pancreatic tumor could not be assessed due to the insufficient sample (<5% of

tumor cells). The fifth patient had a G12R *KRAS* mutation in the OM-PA (G12R), and a mutation in the *TP53* gene (K132Q), but assessment was not possible in pancreatic tumor due to the poor quality of the pancreatic tumor DNA.

The additional genetic analysis using NGS performed on each pair of samples in the 4/11 later patients with OM-PA identified identical *KRAS* mutations in the ovarian and pancreatic samples of all four available pairs (G12D: $n=2$ and G12 V: $n=2$). Moreover, identical *TP53* gene mutations were found in 3/4 pairs (R248 W, N131Del, and G199E, respectively). An identical mutation in the *PDGFRA* gene (I565 V) was present in one pair, and two identical *SMAD4* and *MET* mutations in another pair (E337 K and N375 S, respectively), with similar numbers of detected copies.

Pancreatic tissue was not available for analysis in the remaining 2/11 patients, and the comparison could not be performed.

In summary, identical *KRAS* mutations were present in all seven patients (100%) whose ovarian/pancreas paired samples could be analyzed.

It should also be noted that one of the two patients with no available pancreatic tissue (P9) had a germline *BRCA1* mutation (c68_69del, p.Glu23Valfs*17). The diagnosis of PA was revealed by a peritoneal carcinomatosis, and she started FOLFIRINOX administration. Four months later, contrasting with an objective response with FOLFIRINOX, she developed bilateral ovarian tumors. Both the OM and PA remained stable after 8 months of a second-line treatment with gemcitabine and nab-paclitaxel. The ovarian tumors were resected 12 months after they developed: the histological appearance suggested metastases of a pancreatic tumor, and the molecular analysis identified a rare *KRAS* mutation on exon 3 (Q61 H) and a *TP53* mutation (E339fs deletion). Nineteen months later (3 years after the initial PA diagnosis), the patient developed a single brain metastasis, treated by neurosurgical resection and adjuvant radiation therapy on the surgical bed. She remained asymptomatic with no cerebral relapse 7 months after this treatment. The histological analysis of the resected cerebral metastases revealed a papillary adenocarcinoma whose phenotype was compatible with a pancreatic origin, and the molecular analysis revealed the same *KRAS* (Q61 H) and *TP53* (E339) mutations as the ovarian tumors.

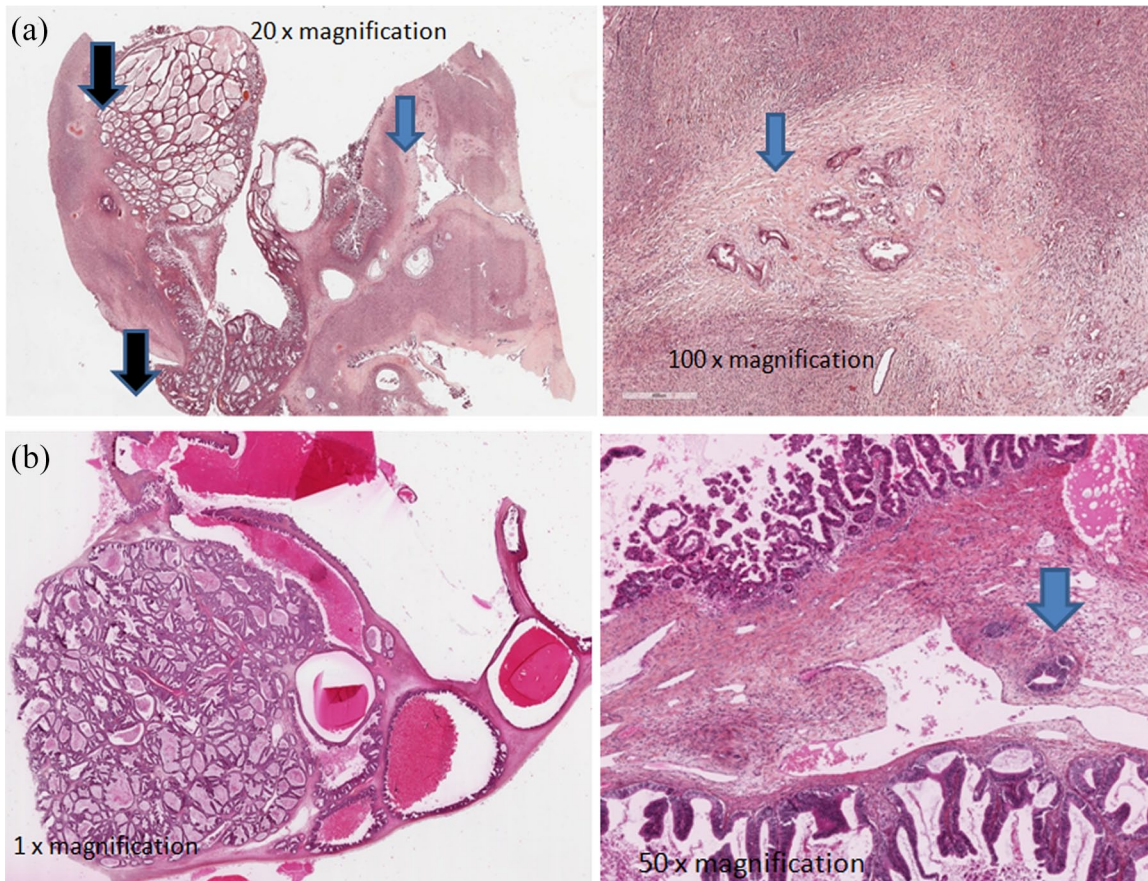


Figure 2. Histological examples of ovarian metastases of pancreatic adenocarcinoma (OM-PA) and primary ovarian mucinous carcinoma (POMC). (a) Patient P3 (MO-AP): Resected specimen of ovarian metastasis from pancreatic adenocarcinoma: polymorphic ovarian lesion with (i) multicystic areas that are morphologically very similar to primary ovarian lesions (black arrows). It is also difficult to confirm the invasive nature of the lesion in these areas (few atypical cells) with little stroma; (ii) more areas resembling a pancreatic adenocarcinoma (blue arrow) with tumor atypical glands, less differentiated and dispersed in fibrous stroma. (b) Patient O5 (POMC): Ovarian primary mucinous carcinoma sample – Presence of areas of extensive fibrosis with glands with tumoral appearance, resembling pancreatic adenocarcinoma (arrows).

Therapeutic management of OM-PA: oophorectomy

Eleven of the 13 patients with OM-PA underwent surgical resection of OM. The median time between the diagnosis of PA and ovarian surgery was 20 months (0–44). Seven of the eight patients with bilateral metastases underwent resection of both ovaries during the same procedure. In the remaining patient, the second ovary was resected after 25 months.

In the 11 operated patients, the goal of surgery was to reduce the tumor burden in 5 patients (45%) and to treat disabling pelvic symptoms in 6 patients (55%). Eight of these patients (73%) underwent postoperative systemic chemotherapy. Rapid deterioration of the general status

prevented the administration of a systemic chemotherapy in the 3 remaining patients (27%). Tumor relapse occurred in 8 of the 11 operated patients (73%) as follows: diffuse peritoneal carcinomatosis: $n=4$ (50%) (after 1, 2, 8, and 12 months), liver metastases: $n=2$ (25%) (after 7 and 9 months), and involvement of the contralateral ovary: $n=1$ (13%) (after 6 months). Finally, the primary pancreatic tumor progressed in 1 patient 1 month after oophorectomy.

Six patients underwent surgery for pelvic symptoms, including abdominal and pelvic pain ($n=5$, 84%), pelvic heaviness ($n=1$, 17%), post-urinary and post-exoneration discomfort ($n=1$, 17%), severe constipation ($n=1$, 17%), or an increase in abdominal volume ($n=1$, 17%). Symptoms

Table 3. Analysis of somatic mutations (*KRAS* and other, using next generation sequencing: NGS) in both pancreatic and ovarian samples of 11 patients with ovarian metastases from pancreatic adenocarcinoma.

Patient code	<i>KRAS</i> mutation in pancreatic primitive	<i>KRAS</i> mutation in ovarian metastases	NGS analysis: Common mutations
P1	c.35G > T; p. Gly12Val (G12V)	c.35G > T; p. Gly12Val (G12V)	No NGS performed
P2	No mutation found but poor and contaminated sample (tumor cells < 5%)	c.35G > T; p. Gly12Val (G12V)	No NGS performed
P3	c.35G > C; p. Gly12Ala (G12A)	c.35G > C; p. Gly12Ala (G12A)	No NGS performed
P4	c.35G > A; p. Gly12Asp (G12D)	c.35G > A; p. Gly12Asp (G12D)	No NGS performed
P5	c.35G > A; p. Gly12Asp (G12D)	c.35G > A; p. Gly12Asp (G12D)	- <i>KRAS</i> (c.35G > A; p. Gly12Asp (G12D)) - <i>TP53</i> (c.596G > A; p. Gly199Glu (G199E)) - <i>SMAD4</i> (c.1009G > A; p. Glu337Lys (E337K)) - <i>MET</i> (c.1124A > G; p. Asn375Ser (N375S))
P8	c.35G > A; p. Gly12Asp (G12D)	c.35G > A; p. Gly12Asp (G12D)	- <i>KRAS</i> (c.35G > A; p. Gly12Asp (G12D)) - <i>TP53</i> (c.742 C > T; p. Arg248Trp (R248W))
P9	No available pancreatic tumoral sample for molecular analysis. In the ovarian tumors: <i>KRAS</i> (exon 3 Q61 H) and <i>TP53</i> (E339fs deletion) somatic mutations In the brain metastasis: histological features compatible with a pancreatic origin, and identical <i>KRAS</i> (exon 3 Q61 H) and <i>TP53</i> (E339fs deletion) somatic mutations		
P10	No available pancreatic tumoral sample		
P11	c.35G > T; p. Gly12Val (G12V)	c.35G > T; p. Gly12Val (G12V)	<i>KRAS</i> (c.35G > T; p. Gly12Val (G12V)) <i>TP53</i> (c.393_395delCAA; p. Asn131del (N131Del))
P12	c.35G > T; p. Gly12Val (G12V)	c.35G > T; p. Gly12Val (G12V)	<i>KRAS</i> (c.35G > T; p. Gly12Val (G12V)) <i>PDGFRA</i> (c.1693A > G; p. Ile565Val (I565V))
P13	Unamplifiable DNA (2 attempts)	c.34G > C; p. Gly 12Arg (p.G12R) (+ Mutation of <i>TP53</i> c.394A p.Lys132Gln (K132Q))	No NGS performed

markedly improved in two patients following surgery (33%), with no significant procedural complications. In two other patients (33%), pollakiuria with urinary incontinence occurred in one, and severe diarrhea with up to 10 stools per day occurred in the other, despite pain improvement. The two remaining patients (33%) had rapid post-surgical tumoral progression (they died 2 and 5 months after surgery, respectively) with no significant improvement in pelvic symptoms.

Survival data of OM-PA

The median delay between the diagnosis of PA and OM was 16.2 months (0–43) (Figure 3). Median overall survival and progression-free

survival after OM-PA surgery in the 11 patients who underwent oophorectomy was 8 months (1–132) and 5 months (0–12), respectively. Median overall survival from the time of diagnosis of primary PA to death or the last contact with the patient (including the two non-ovariectomized patients) was 26 months (6–176). Median overall survival after the diagnosis of OM was 7 months (1–134). At the point date, 6/13 patients were still alive and receiving antitumoral treatment.

Discussion

Our study describes a population of 13 patients with OM-PA, which is a large series for this rare disease. However, this pattern of metastases may

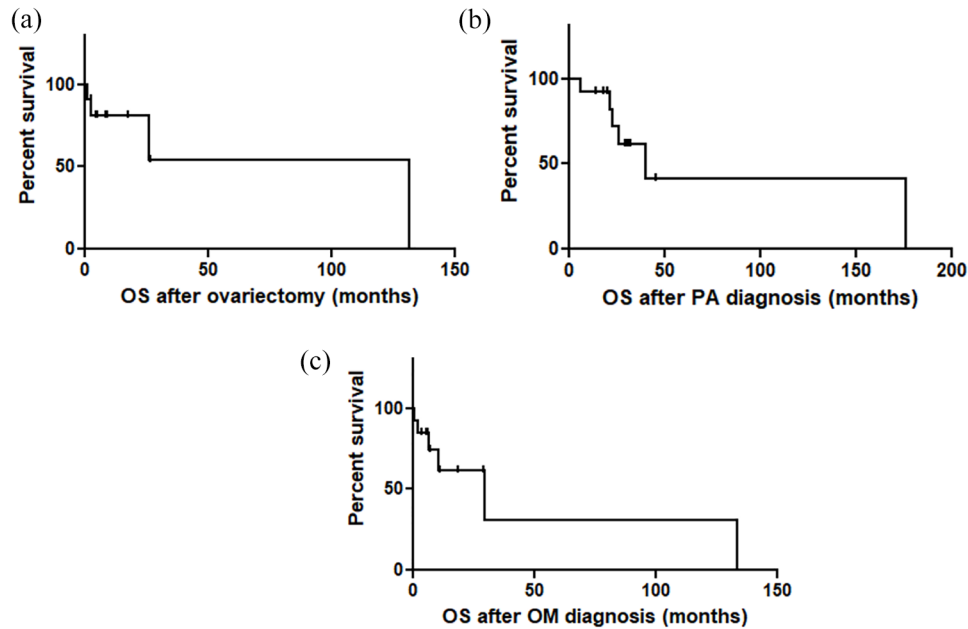


Figure 3. Kaplan-Meier survival curves: (a) Overall survival after oophorectomy in 11 patients with ovarian metastases of pancreatic adenocarcinoma. (b) Overall survival after pancreatic adenocarcinoma diagnosis in 13 patients with pancreatic adenocarcinoma. (c) Overall survival after diagnosis of ovarian metastases in 13 patients with pancreatic adenocarcinoma.

be diagnosed frequently in the future because of improved imaging procedures and survival in PA patients with more effective treatments, such as FOLFIRINOX and gemcitabine-nab-paclitaxel combinations. The close similarity of the imaging/histological features of OM-PA and primary ovarian cancer can make diagnosis and therapeutic decisions difficult. There are three practical possibilities in these cases: First, a resectable PA and an independent ovarian cystic tumor may be diagnosed simultaneously. In that case, the ovarian tumor should be resected for pathological analysis before deciding on pancreatic resection (in case of an incidental and localized ovarian tumor, such as POMC) or not (when synchronous OM-PA is found alone or with concomitant peritoneal carcinomatosis). Second, when an ovarian cystic tumor is discovered in a patient treated for advanced PA, this suggests an OM-PA. Also, the development of both a PA and an ovarian tumor, in particular a serous cystadenocarcinoma in the same patient, strongly suggests a genetic predisposition. Finally, ovarian tumor(s) may be discovered as a new site of metastatic and progressive PA. In these latter cases, the major goal is to achieve optimal tumor control with systemic chemotherapies, and surgical debulking should be limited to patients with intractable pelvic symptoms clearly due to OM-PA (Figure 4).

One patient in our series had a germinal *BRCA1* mutation and primary PA with synchronous peritoneal carcinomatosis and metachronous bilateral ovarian tumors. It is unlikely that the ovarian tumors were another independent primary cancer caused by the patient's genetic disease, because of their rapid and bilateral development, the morphological features suggesting a pancreatic origin and the presence of *KRAS* and *TP53* genes mutations, which are not specific but often encountered in PA. Thirty-one months later, the patient developed a single cerebral metastase with the same *KRAS* and *TP53* mutations. The ovarian and cerebral tumors most probably had the same primary tumor, although it was not possible to prove the link to primary PA, because there was no pancreatic tissue for comparison. In the POLO assay, the *BRCA1* mutation was not rare in patients with PA: *BRCA1* and *BRCA2* mutations were present in 32% and 67% of patients, respectively.¹⁹ It is important to note that, in the patient in our series with *BRCA1* mutation, both OM and primary PA remained stable after 8 months of a second-line treatment by gemcitabine and nab-paclitaxel. The efficacy of the gemcitabine and nab-paclitaxel combination has also been recently suggested in patients with PA and deficient homologous recombination ATM repair gene.²⁰

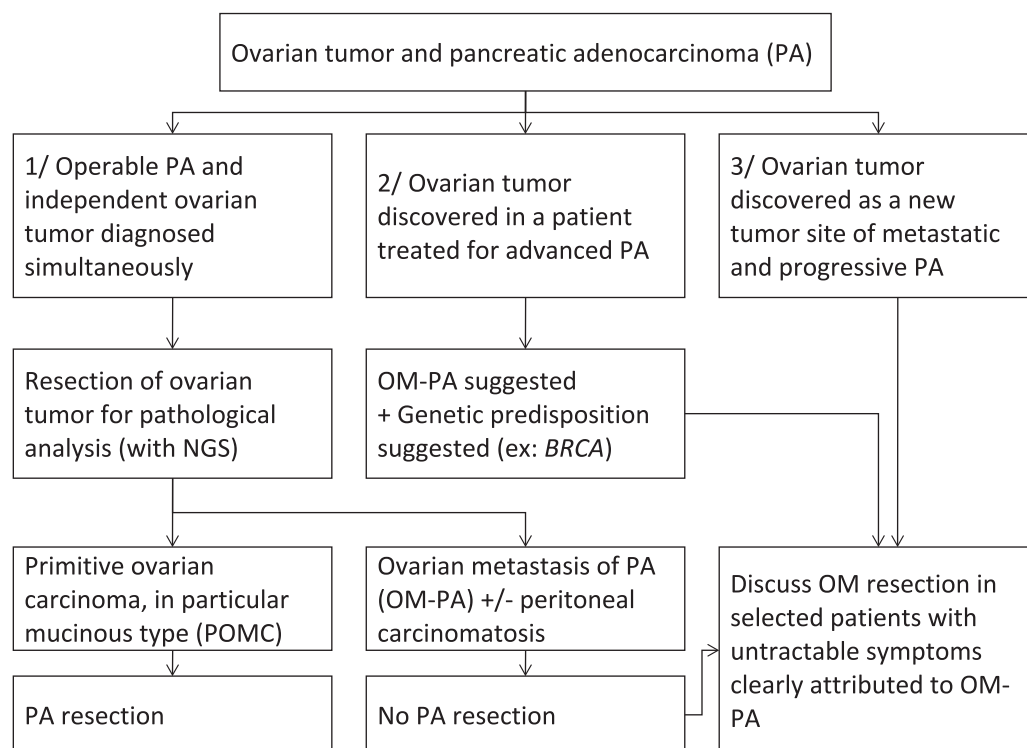


Figure 4. Decisional tree in the presence of an ovarian tumor and pancreatic adenocarcinoma.

Interestingly, most of the OM-PA in our study (9/13) were diagnosed when the tumoral disease was controlled in other sites. In the specific hormonal microenvironment of the ovary, metastases appear more likely to become cystic and mucinous, with limited diffusion of cytotoxins (“ovarian sanctuary”). This has been suggested for OM from colorectal adenocarcinoma,^{1,21} but not from gastric adenocarcinoma.²²

OM-PA and POMC may occur in different clinical contexts with close imaging features and histological similarities, and the difficulty of distinguishing these entities pre- or even perioperatively has been reported by several authors.^{1,13,16,17,19–21} It has even been suggested that the rate of POMC may be overestimated because of these similarities.¹ On the other hand, rare pancreatic metastases of serous papillary ovarian cancer can mimic a primary pancreatic tumor.²³

An overlap in the immunohistochemical expression of current markers (i.e. CK7, CK20, CDX2, DPC4, CK17, CEA, WT1, and CA 125), and estrogen and progesterone receptors in both POMC and MO has been reported.^{14,24–28} CK7–/CK20+ and MUC1–/MUC2+ phenotypes suggest a digestive origin, in particular when they are

combined with positive CDX2. On the other hand, CK7+/CK20– and MUC1+/MUC2– phenotypes suggest an excreto-biliary-pancreatic origin while positive detection of estrogen and progesterone receptors indicates a gynecological origin.

As reported in other studies, the OM-PA in our study were smaller (120 *versus* 160 mm, $p=0.02$) and more often bilateral than POMC, with frequent stromal invasion.^{1,14,16,29} It is often difficult or impossible to compare pancreatic and ovarian biopsies because of the small amount of pancreatic tissue obtained by fine-needle aspiration. Thus, we evaluated the potential role of a molecular study.

The *KRAS* pro-oncogene is often mutated in both PA and POMC (Supplementary Tables 1a and 1b). In primary ovarian tumors, the rate of mutations is higher in mucinous (50–60%) than serous tumors (35% in borderline tumors, and only 9% in invasive serous carcinoma).³⁰ In the COSMIC database reporting 130 cases of primary mucinous ovarian tumors, *KRAS* was mutated in 44% of cases, and the two most frequent mutations were G12D (41.5%) and G12V (37.7%).^{17,30} *KRAS* gene alterations, mainly

located at codons 12 or 13, are present in up to 85% of PA.^{17,31–33} They include G12D (49%), G12 V (31%), and G12R (13%) mutations.¹⁷ Because of the very low intra-tumoral heterogeneity for *KRAS* gene status, the mutations should be similar in both primary and metastatic sites.³¹ It also does not vary with tumoral stage, unlike *DPC4* and *TP53* gene alterations which usually occur in late stages of disease. The most common *KRAS* mutation is G12D in both PA and primary ovarian tumors. Because of the narrow spectrum of *KRAS* mutations, it is impossible to exclude that both of these tumors harbor the same mutation by chance. Our analysis of seven available pancreas/ovary pairs revealed the same somatic *KRAS* mutation in both sites in all cases, which supports that there is a relationship between them. Moreover, the same *TP53*, *SMAD4*, *MET*, and *PDGFRA* gene mutations in both sites in some patients further confirm this hypothesis. In contrast, a diagnosis of a primary ovarian tumor could have been made if the mutational profile had been different. Although NGS analysis was not performed in the POMC samples in our study, the mutational profiles of OM-PA and POMC reported in the literature were similar to ours; however, the prevalence of *KRAS* mutations was higher in PA (56% to 95%) than in POMC (44%).^{17,30,32,33}

The resection of PA metastases is currently not recommended because of the poor disease prognosis. However, oophorectomy may occasionally be considered in the presence of invalidating pelvic symptoms clearly due to OM, or when PA relapse/progression limited to the ovaries occurs.¹ Although this study and others suggest that oophorectomy may improve these symptoms, the results should be interpreted with caution because of the retrospective design of the study, and of the lack of standardized measurement of pain, specific symptoms or quality of life. In addition, digestive or urological morbidities as well as rapid progression of metastatic PA disease may occur after oophorectomy. This should be discussed with patients before surgery.

In our study, the progression-free survival time after oophorectomy (4.6 months), and the overall survival after oophorectomy (8.4 months), as well as the overall survival after the initial diagnosis of primary PA (26 months), shows that patients had unusual “favorable” slow-growing and/or well-controlled metastatic PA. Falchook *et al.*¹ also estimated that longer survival after OM resection

versus chemotherapy alone (16.5 months *versus* 8.5 months, respectively; $p=0.28$) could reflect a bias due to selection of patients with a more favorable course of PA, such as that reported in OM from gastric adenocarcinoma.²²

In conclusion, the differentiation of OM-PA from primary ovarian tumors such as POMC is difficult, but could be facilitated by comparison of tumor mutational profiles. Although resection of symptomatic OM-PA can be considered on a case-by-case basis in PA patients with slow disease progression, the morbidity of surgery should be kept in mind.

Author contributions

Conceptualization: AdM, PH, JC, and MS; methodology: PH and LdM; software: AdM; validation: PH and JC; formal analysis: LdM; investigation: AdM, MS, AK, NTH, SG, and JC; resources: PH, SD, FP, TA, MS, and JC; data curation: AdM and LdM; writing-original draft preparation: AdM; writing-review and editing: PH and JC; supervision: PH and JC; project administration: PH.

Conflict of interest statement

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ORCID iD

Alice de Malet  <https://orcid.org/0000-0001-7940-2560>

Supplemental material

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