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Review

A 15-year comprehensive literature review of 99 primary ovarian carcinoid tumors

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Abstract

Objective: Primary ovarian carcinoids are neuroendocrine tumors, representing up to 1% of all ovarian tumors. In this paper, the authors aimed at analyzing the clinical and pathological aspects of all recently published ovarian carcinoid, providing new correlations regarding them. **Mechanism**: The authors have reviewed all cases of primary ovarian carcinoid reported in international journals since 2005 to date. A total of 99 cases published in 68 articles have been found and analyzed. **Findings in brief**: Our results up to 29.31% of patients presented with carcinoid heart disease, and 17.24% had an abdominal mass, which caused them to present to the physician. Patients presenting with metastases had more frequently the insular subtype (33.33%) and had similar median age as those without metastases. A teratoma component was noticed in 58.9% of cases and was also associated with the insular pattern of carcinoid. To our best knowledge, this paper includes the largest review of primary ovarian carcinoid to date. **Conclusions**: The incidence of carcinoid heart disease might have been underestimated up to this moment, thus, requiring further imagistic investigations of patients presenting with these symptoms. Additionally, the insular variant was most frequently associated with the presence of both teratoma (52.94%) and metastases (33.33%), although previous reports have noticed a higher incidence of teratoma in the mucinous variant. In our opinion, these apparently divergent results warrant further studies of this rare subtype of ovarian tumor.

Keywords: Primary ovarian carcinoid; Carcinoid heart disease; Metastatic ovarian carcinoid

1. Introduction

Ovarian cancer occupies fifth place in the woman cancer death hierarchy, accounting for more deaths than any other cancer of the female reproductive system and sharing similar genetic pathways with breast cancer [1]. Ovarian carcinoid is a well-differentiated neuroendocrine tumor of germ cell origin, resembling those arising within the gastrointestinal and pulmonary tracts. Primary ovarian carcinoid represents 0.3%–1% of all carcinoid tumors and less than 1% of all ovarian neoplasms [2]. These tumors are considered monodermal teratomas, arising from neoplastic transformation of neuroendocrine cells intermixed with mucinous intestinal-type epithelium present in mature cystic teratoma or other neoplasms. They can be either pure or associated with other teratomatous elements. Based on their histopathological pattern, primary ovarian carcinoids can be classified into insular, stromal, trabecular and mucinous. Niu *et al.* [3] have analyzed the histogenesis of this tumor and have concluded that the insular and mucinous subtypes are of midgut derivation, while trabecular and strumal subtypes are of foregut or hindgut derivation. Ovarian teratoma affects a wide age range, from reproductive to postmenopausal women, with a mean age of 53 years. Patients are asymptomatic or present with abdominal swelling, pain, and ascites. Carcinoid syndrome secondary to serotonin production is rare in contrast to metastatic carcinoid and affects one third of patients with insular carcinoid. It is associated with elevated 5-hydroxyindole acetic acid levels in urine and disappears after resection. Trabecular carcinoids may rarely be associated with Cushing syndrome and chronic constipation due to peptide YY production. In this paper, we aim to provide an up-to-date and comprehensive review of literature, including all ovarian carcinoids that have been reported in the scientific literature during the past 15 years.

2. Materials and methods

We have performed a literature search on the following MESH (medical subject headings) terms: "carcinoid tumor", "neuroendocrine tumors", "ovary" going back 15 years. In the present paper, we focused the search with filters: case report (CR) and clinical case series (CCS). The last updated search was done on 10/08/2021. The review protocol assumed a search on PubMed®/MEDLINE and Google Scholar.

The study included all scientific papers reporting unilateral or bilateral ovarian carcinoid tumors, with or without an associated teratoma, including those studies which summarized neuroendocrine tumors of the gynecologic tract.

Exclusion criteria were the following: suspicion of secondary carcinoid or metastatic disease to the ovary warranted exclusion from the database.

To carry out the study, data were extracted and analyzed regarding the year of publication, the language in which the study was written, the relevance, the accuracy of the information. We analyzed the data following the study objectives. The statistical analysis was completed using Microsoft Excel® 2013 (Microsoft® Corporation, Redmond, WA, USA).

PubMed®/MEDLINE data search for CR/CCS during the last 15 years using the selected keywords revealed a total of 68 published papers.

3. Results

Table 1 (Ref. [4–71]) summarizes the main characteristics of all the 99 patients with primary ovarian carcinoid reported in the scientific literature during the last 15 years.

Clinically, the patients age ranged from 18 to 80 years, with an average age of 53.13 years old. One patient was diagnosed while pregnant [32], adding ovarian carcinoid to the list of malignant tumors described during pregnancy [72]. Symptoms were present only in 69.88% cases. Among these, 29.31% presented with carcinoid heart disease (CHD), 12.06% with constipation, 17.24% had an abdominal mass or distension, 6.8% suffered from abnormal uterine bleeding and 3.44% had endocrine manifestations. Other authors have seen an association between the presence of carcinoid heart disease and a poor outcome of the disease [55]. Additionally, case reports are stating a persistence of the cardiac manifestations, despite total removal of the ovarian carcinoid [25,55]. Unfortunately, the ultrasound aspect of malignant tumors of the ovary are not characteristic and can provide little information regarding the subtype of the tumor. However, in late stages one can find infiltrates in the surrounding tissues or, in rare instances, even metastases [73].

Regarding the histopathological subtype, after exclusion of those cases in which the subtype was not specified, the most frequently encountered patterns were: insular (43.48%), trabecular (20.29%), and stromal (17.39%). Only a minority of cases featured a mixed (8.7%) or mucinous (7.25%) histopathological pattern. A teratoma component has been reported in 58.9% of a total of 47 cases, where this feature was specified.

The size of the tumor ranged from 10 mm to 200 mm, with an average size of 78.51 mm. However, these sizes usually reflected the size of the whole cyst, not specifically of the carcinoid component which usually was present in small foci [35]. Nasioudis *et al*. [74] has reported a worse prognosis in those tumors with a size larger than 4 cm.

Out of the 40 cases where the presence or absence of metastases was specified, 27.5% of cases had metastases. The metastases stemmed mostly from an insular variant of carcinoid (33.33%), but strumal (26.67%) and atypical (26.67%) subtypes have also led to secondary dissemination of the tumor. Age of patients that have developed metastases varied from 30 to 74, with an average age of 50.63 years. A teratoma component has been reported in 58.9% of a total of 47 cases, where this feature was specified. Teratoma was encountered in 52.94% of the insular variant of carcinoid, closely followed by the strumal (29.41%) and mucinous (11.76%) subtypes.

4. Discussion

4.1 Imaging features

Although there are many imaging methods available that can identify and describe the characteristics of ovarian carcinoids, the most commonly encountered scenario is that of a patient undergoing a transvaginal ultrasound examination, subsequently followed by a CT. Some papers report a particular ultrasound aspect, that of a cystic vascular mass [52]. A PET-CT scan can show moderate or intense uptake of gallium octreotate, an aspect suggestive for this diagnosis [37,62]. A cystic or multicystic component can be readily identifiable through the mentioned techniques and can give an accurate assessment of the tumor dimensions [60]. Additionally, the presence of ascites can also be noted through a CT scan. Nonetheless, although the imaging techniques provide vital information regarding the dimensions of the tumor as well as the presence of solid and/or cystic components, they are not specific nor diagnostic for a primary ovarian carcinoid. In fact, in some of the reported cases, the CT aspects, were actually in favor of a teratoma and did not explain the prominent carcinoid symptoms of the patient [65]. Nonetheless, given the rarity of primary ovarian carcinoids, it is recommended to further investigate the patient imagistically with magnetic resonance imaging (MRI) or indium-111-pentetreotide scan, to avoid missing another probably primary site [74].

4.2 Gross features

Primary ovarian carcinoid is almost invariably unilateral and presents either as a small nodule or thickening in a mature cystic teratoma wall or as a solid mass with variably firm, tan to the yellow cut surface. In mucinous variants, the mucoid or gelatinous cut surface may be noted. Coffey

Table 1. Case reports and series of primary ovarian carcinoid reported between 2005 and 2020.

Author (s)	Cases	Age	Type	Symptoms	Metastases	Treatment	Survival
Kopf *et al.* (2005) [4]	1	79	Insular	No	No	BSO	DFS >10 yr
Diaz-Montes *et al.* (2006) [5]	1	80	Insular	Yes	No	TAH, BSO	DFS >6 wk
Chatzipantelis *et al.* (2006) [6]	1	57	Insular	No	No	N/A	N/A
Morken *et al.* (2007) [7]	1	N/A	N/A	Insulin secreting	No	TAH, BSO, O	DFS >1 yr
Kawano *et al.* (2007) [8]	1	N/A	Strumal	Constipation	No	TAH, BSO, LND, O	DFS >18 mo
Nyktari *et al.* (2007) [9]	1	66	N/A	CHD	No	TAH, BSO	DFS >6 mo
Bonaros *et al.* (2007) [10]	1	N/A	N/A	CHD	No	LSO	DFS >10 mo
Djordjevic *et al.* (2007) [11]	1	N/A	Trabecular	No	Yes, lymph node, liver, pelvis	RSO, tumor debulking, CT	OS >18 yr + recurrences and mets
Chargui *et al.* (2007) [12]	3	23–50 (33, 67)	N/A	No	N/A	TAH, BSO	N/A
Somak *et al.* (2008) [13]	1	55	Mixed	No	No	TAH, BSO	N/A
Dotto *et al.* (2008) [14]	1	50	Insular	No	No	TAH, BSO, LND, O, tumor debulking	N/A
Pelosi *et al.* (2008) [15]	1	69	Strumal	No	No	LSO	DFS >1 yr
Lagoudianakis *et al.* (2008) [16]	1	44	Insular	No	No	LSO	DFS >3 yr
Engohan-Aloghe *et al.* (2009) [17]	1	75	Insular	No	No	TAH, BSO, LND, O, PB	DFS >4 mo
Takahashi *et al.* (2009) [18]	1	52	N/A	CHD	No	TAH, BSO	N/A
Gungor *et al.* (2009) [19]	1	47	N/A	No	No	TAH, BSO, LND, O, AP	N/A
Chen *et al.* (2010) [20]	1	N/A	Strumal	Constipation	No	RSO, tumor excision	N/A
Buis *et al.* (2010) [21]	1	39	Mucinous	WL, AD/P	Yes, right ovary	LSO	OS >15 yr with meta after 10 yr
Bai *et al.* (2010) [22]	1	55	Trabecular	No	No	TAH, BSO	N/A
Aggeli *et al.* (2010) [23]	1	60	N/A	CHD	No	N/A	N/A
Alexander *et al.* (2011) [24]	1	59	N/A	No	Yes, sigmoid mesentery	RO followed by TAH, BSO, CT	N/A
Mordi *et al* (2011) [25]	1	50	N/A	CHD	No	TAH, BSO	DFS >4 yr
Roberts *et al.* (2011) [26]	1	53	N/A	CHD	Yes, liver	None (autopsy)	DOD 1 yr
Djurovic *et al.* (2011) [27]	1	49	N/A	Yes	No	TAH, BSO	DFS >6 mo
Huang *et al.* (2012) [28]	1	41	Mucinous	AD/P, fatigue	No	TAH, LSO, LND, O	DFS >2 yr
Hinshaw *et al.* (2012) [29]	1	74	Strumal	No	No	TAH, BSO, LND, O, PB	DFS >6 mo
Buda *et al.* (2012) [30]	1	78	Insular	CHD	No	TAH, BSO	DOD 1 mo
Takatori *et al.* (2012) [31]	1	48	Strumal	Constipation	No	RSO	DFS >18 mo
Yamaguchi *et al.* (2012) [32]	1	24	Strumal	Constipation	No	RSO	DFS >11 mo
Amano *et al.* (2013) [33]	1	67	N/A	CHD	Yes, paraaortic lymph nodes	TAH, BSO, CT	OS >13 yr with LN metastases
Bassi *et al.* (2013) [34]	1	45	N/A	No	No, synchronous gall bladder carcinoid	TAH, BSO, O, hepatic resetion, cholecystectomy, CT	N/A
Petousis *et al.* (2013) [35]	1	28	Trabecular	No	No	Tumorectomy	DFS >9 mo
Ting *et al.* (2014) [36]	1	N/A	Insular	No	No	BSO	DFS >1 yr

Table 1. Continued.

Author (s)	Cases	Age	Type	Symptoms	Metastases	Treatment	Survival
Damen (2014) [37]	1	69	N/A	CHD	No	BSO, O, bowel & rectal biospies, AP	N/A
Horikawa *et al.* (2014) [38]	1	57	Trabecular		No	TAH, BSO	N/A
Goldman *et al.* (2014) [39]	1	61	Insular	CHD	No	BSO, O	DFS >1 yr
Huang *et al.* (2014) [40]	1	46	N/A	Cushing	No	TAH, BSO, LND, O, CT	DFS >5 yr
Spaulding *et al.* (2014) [41]	1	51	Trabecular	No	No	TAH, BSO	DFS >1 yr
Sharma *et al.* (2014) [42]	1	50	Trabecular	No	No	TAH, BSO	DFS >3 mo
Muller *et al.* (2015) [43]	1	34	Trabecular	Constipation	No	RSO, LND, O	DFS >1.5 mo
Dessauvagie *et al.* (2015) [44]	1	69	N/A	CHD	No	BSO	N/A
Quinonez *et al.* (2015) [45]	1	N/A	Mixed	No	No	TAH, BSO, O, AP	DFS >5 mo
Agarwal *et al.* (2015) [46]	1	75	N/A	CHD, right-sided heart failure	No	LSO	N/A
Tarcoveanu *et al.* (2015) [47]	1	55	Trabecular	No	No	LSO	DFS >1 yr
Mcgrath *et al.* (2016) [48]	18	18–77 (46, 78)	Insular (8), strumal (2), trabecular (1), N/A (7)	AD/P (9), CHD (1), menorrhagia (2), oligomenorrhea (1), constipation (1), endometrial carcinoma (1), limb edema (1), none (2)	N/A	Stage 1: cystectomy (1), TAH & BSO (5), USO (5), TAH & USO (2), N/A (1); Stage 3 & 4: TAH & BSO (2), N/A (2); Stage 4: O, small bowel resection, liver resection, CT	Stage 1: DFS 37–103 mo; Stage 3: DOD 10–22 mo; Stage 4: DOD 18–66 mo
Metwally *et al.* (2016) [49]	2	48–59 (53, 5)	(I) Insular (II) Trabecular	AD/P	No	TAH, BSO, LND, O, PB, AP	(I) DFS >2 yr, (II) >1.5 yr
Kolouch *et al.* (2016) [50]	1	77	Insular	CHD	Yes, paravertebral	TAH, BSO	DFS >1 yr
Kim *et al.* (2016) [51]	1	39	Mixed	No	No	RSO	N/A
Orsi *et al.* (2016) [52]	1	65	Insular	CHD, diarrhea	No	TAH, BSO, LND, O	N/A
Doraiswami *et al.* (2017) [53]	1	54	Mucinous		No	BSO	DFS >6 mo
Tadokoro *et al.* (2017) [54]	1	73	N/A	CHD, diarrhea	No	TAH, USO, incomplete tumor excision	OS >7 yr
Saraf *et al.* (2017) [55]	1	75	Insular	CHD	No	TAH, BSO, O	DFS >2 mo
Salhi *et al.* (2017) [56]	4	28–75 (50)	Mucinous (1), trabecular (1), insular (2)	AD/P, dysuria, peritonitis	Yes, lymph node (1)	TAH (3), BSO (3), LND (3), CT (1)	>23 mo DF (3), Bone metastasis after 14 mo, DOD after 4 mo (1)
Van Rompuy *et al.* (2018) [57]	1	55	Mucinous	WL, AD/P, fatigue, backache	Yes, from ADK arising in mucinous carcinoid	TAH, BSO	N/A
Antovska *et al.* (2018) [58]	1	59	Strumal	Perimenopausal uterine bleeding	No	TAH, BSO, O, PB	N/A
Ishida *et al.* (2019) [59]	2	46–52 (49)	Strumal (2)	Enlarged ovaries (2)	No	BSO	DFS >4 mo
Hsu *et al.* (2019) [60]	1	33	Atypical	Recurrence, hydronephrosis, dead	No	LSO, LND, AP	Recurrence after 5 yr, DOD after 86 mo
Chai *et al.* (2019) [61]	1	63	Strumal	WL, AD/P	No	TAH, BSO	N/A
Shah *et al.* (2019) [62]	1	55	Trabecular		No	TAH, BSO	DFS >1 yr

Table 1. Continued.

Author (s)	Cases	Age	Type	Symptoms	Metastases	Treatment	Survival
Lou *et al*. (2019) [63]	1	30	Atypical	MEN1 syndrome	Yes, rib and contralateral ovary	USO, CT	OS >2 yr
Borghese *et al*. (2019) [64]	1	61	Strumal	No	Yes, lymph nodes	RO, LND	N/A
Malla *et al*. (2019) [65]	1	54	Insular	Carcinoid syndrome, AD/P	No	TAH, BSO, O	N/A
Tsikouras *et al*. (2019) [66]	7	37–71 (56, 86)	Trabecular (2), insular (2), mixed (3)	N/A	No	TAH, BSO, LND, O	DFS >20 yr
Zhai *et al*. (2020) [67]	2	49–61 (55)	Insular (2)	AD/P, diarrhea, constipation	(I) No; (II) Yes, liver spleen, appendix	(I) TAH, BSO, LND, O, AP; (II) RSO, cervical resection, AP, CT	(I) DFS >18 mo; (II) OS >17 mo
Cortes *et al*. (2020) [68]	1	53	N/A	Diarrhea	No	BSO	N/A
Cagino *et al*. (2020) [69]	1	48	Insular	AD/P, abnormal uterine bleeding	No	LSO, RS, followed by TAH, RO	DFS >6 mo
Halvorson *et al*. (2020) [70,71]	1	NA	Insular	AD/P	Yes, paraaortic lymph nodes	TAH, BSO	N/A
Tewari *et al*. (2020) [71]	1	60		Postmenopausal bleeding	No	RSO	N/A

Abbreviations: N/A, not available; CHD, carcinoid heart disease; WL, weight loss; AD/P, abdominal distension and/or pain; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; USO, unilateral salpingo-oophorectomy; LSO, left salpingo-oophorectomy; RSO, right salpingo-oophorectomy; LND, lymph node dissection; O, omentectomy; RS, right salpingectomy; RO, right oophorectomy; PB, peritoneal biopsies; AP, appendectomy; CT, chemotherapy; DFS, disease free survival; DOD, died of disease; yr, year; mo, months; wk, weeks.

DM *et al*. [76] affirm that the mucinous variant is more often associated with teratoma than other subtypes of carcinoid, which are often solid brown tumors. However, our literature review did not support this hypothesis, which identified more insular subtype cases associated with a teratoma. Nonetheless, these results might be a consequence of the higher incidence of this subtype, and further studies focused especially on the presence of teratomatous elements in ovarian carcinoid should be conducted. Cystic degeneration may occur, and other tumoral components such as mature teratoma, mucinous cystadenoma or Brenner tumor may be present. Authors have reported different mean sizes of the ovarian neuroendocrine tumor, ranging from 48 mm to 97 mm [56,77], mainly depending on the number of cases incorporated in the study. Soga *et al*. [78] has reported larger sizes and higher rates of overall metastases in cases of pure ovarian carcinoid, compared to those associated with teratoma. On the other hand, the mean size of malignant ovarian carcinoids has been reported to be 38 mm [74].

4.3 Histopathology

Four subtypes of ovarian carcinoid are recognized in the Classification of the World Health Organization (WHO), namely: insular, stromal, trabecular, and mucinous [79–81]. The most frequent subtypes are insular and trabecular, which are composed of tumoral nests with a pseudocribriform aspect in the periphery, respectively parallel trabeculae and ribbons.

The mucinous variant is made out of glands lined by goblet cells, floating inside mucin pools [79]. This subtype is usually pure, only rarely associating a strumal component, and is regarded as a more aggressive subtype [58].

The strumal variant imposes the differential diagnosis with struma ovarii, due to the presence of thyroid follicles in both entities. Nonetheless, in the strumal carcinoid, islands of insular of trabecular carcinoid can also be identified. Additionally, strumal carcinoid can clinically manifest as hyperthyroidism or as carcinoid syndrome [76]. Noteworthy is the fact that many scientific papers report a higher incidence of this variant in patients of Asian origin. The incidence of the strumal variant in this cohort has been reported to be up to 51.9%, while the insular variant represented only a minority (5.7%) [82].

Atypical carcinoid is characterized by the presence of confluent growth, cribriform areas, and a crowded architectural disposition of glands [79].

Contemporary scientific literature provides similar results to those encountered in our study. For example, the association of a teratomatous component was reported in up to 69% of cases [77], compared to 58.9% revealed by our study. On the other hand, among patients who exhibited symptoms, our review identified 29.31% cases of CHD, while the literature reports these symptoms in only 2% to 10% of cases [25,77]. Other sources mention that between 11% and 60% of carcinoid tumors manifesting with carcinoid syndrome will also develop carcinoid heart disease [83].

The metastatic potential of ovarian carcinoids carries a significant interest in the clinical management of those patients. Nasioudis *et al*. [74] have reported a rate of lymph node metastasis of up to 8.4% in malignant ovarian carcinoids. Nonetheless, the 5-year overall survival rates in those with advanced stages of the disease have been reported as being up to 50.9%. In comparison, stage I malignant ovarian carcinoid cases have a survival rate of 95.1% after 5 years [74]. Other studies have concluded that nearly all patients presenting with metastasis will develop recurrences in the following 7 years [55,84]. A worse prognosis has been reported in cases of mucinous or undifferentiated variants of primary ovarian carcinoid, compared to insular, trabecular, and stromal subtypes [85,86].

4.4 Differential diagnosis

The main challenge for the pathologist in diagnosing primary ovarian carcinoid is represented by the intraoperative examination. Due to the polymorphic aspect of the tumor, frozen section examination is highly dependent on the regions submitted upon gross examination. Therefore, confusion may occur when the sample contains only teratomatous components, and the carcinoid area is being omitted. Fortunately, with thorough sampling, all the tumor components will become apparent upon hematoxylin and eosin examination of paraffin embedded specimens. The presence of salt and pepper chromatin and cytoplasmic argentaffin granules can help differentiate an ovarian carcinoid from endometrioid adenocarcinoma [76].

Another challenge for the pathologist in diagnosing primary ovarian carcinoid is represented by actually confirming that the tumor is primary to the ovary and not a metastasis. In some cases, this task is utterly impossible, even with the use of ancillary testing. The microscopic appearance of primary and metastatic carcinoids shows striking overlap. Studies have reported that most carcinoids that have metastasized to the ovary are of intestinal origin (81.5%), while metastases from the pancreas (14.8%) and from the posterior thorax (3.7%) represented only a minority of cases [87]. Prior history of gastrointestinal carcinoid tumor is obviously the most helpful clue. From a histopathological standpoint, multinodular growth, bilateral involvement, peritoneal deposits, lymphovascular invasion and absence of teratomatous elements are signs of metastatic carcinoid [10]. A large systematic review reports that approximately half of all cases of ovarian carcinoid associate a teratomatous component [78]. Prominent fibromatous background as well as cystic change are more subtle histopathological aspects favoring metastatic insular or trabecular carcinoid. The persistence of carcinoid syndrome after resection of the ovarian tumor (due to tumor deposits outside the ovary) is another helpful clue in differentiating between primary and metastatic ovarian carcinoid.

Probably the most helpful clues in differentiating between primary and metastatic ovarian carcinoid are provided by imaging and clinical data, namely the unilaterality or bilaterality of the lesion. While primary ovarian carcinoids are invariably unilateral, metastatic carcinoids have bilateral involvement in 66.7% of cases [88]. Zhang *et al*. [88] have analyzed the expression of Ki67 proliferation index in both primary and metastatic ovarian carcinoids and noticed a significant difference between the two values. Primary ovarian carcinoids had a median Ki67 of 2.3%, while metastatic carcinoids had a median of 9.7% [88]. Desouki *et al*. [87] have studied the utility o CDX2 in differentiating carcinoid metastases from the gastrointestinal tract from primary ovarian carcinoids. Diffuse or focal expression was noted in 90% of ovarian carcinoid metastases, while only 18.8% of primary ovarian carcinoids showed weak positivity [87].

Finally, the least difficult challenge for the pathologist in diagnosing primary ovarian carcinoid is represented by differentiating it from other histopathological mimickers. Unlike trabecular carcinoid, the gross aspect of strumal carcinoid is that of a beefy, brown tissue, similar to normal thyroid or goiter. Patients usually have symptoms related to thyroid activity and histopathological examination reveals a component of thyroid tissue and thyroglobulin and PAX-8 positivity in strumal areas.

Granulosa cell tumors usually present with hormonal manifestations [89]. Histopathologically, these tumors feature typical architectural patterns besides microfollicular, cells which have pale chromatin with nuclear grooves and are positive for Inhibin, SF1, FOXL2 and negative for Chromogranin [90].

Finding of prominent stromal luteinization in ovarian carcinoid should not be misinterpreted as Leydig cells in Sertoli-Leydig cell tumor. These neoplasms frequently present with hormonal manifestations, which are positive for Inhibin and negative for Chromogranin. If cords are present, these are typically shorter and within the edematous stroma. Moreover, cell nuclei within cords are not oriented perpendicular to the main axis of the cords.

Low-grade endometrioid carcinoma can be confused with insular carcinoid, but the former usually appears in endometriois or adenofibromatous background and is composed of tall cells with luminal mucin or squamous differentiation. Such an example has been recently reported by Tewari *et al*. [71], where an ovarian carcinoid has been initially misdiagnosed as an endometrioid carcinoma arising in a mature teratoma. However, the ancillary studies aided in this differential, namely the neuroendocrine markers (chromogranin and synaptophysin) were diffusely positive, while Estrogen receptor and Inhibin were negative [71].

Differential diagnosis should also take into consideration serous borderline tumor, Brenner tumor and androblastoma.

Regarding the therapeutic option in relation to the stage of the disease, the available data from the scientific literature are variable, considering the rarity of this entity. However, Nasioudis *et al*. [74] has reported that 55.2% of all patients with stage I malignant ovarian carcinoid underwent hysterectomy with bilateral salpingoophorectomy, while lymph node dissection was performed in only 19.1% of cases. The latter did not have any impact on the overall survival of the patients with stage I disease [74]. Nonetheless, Zhai *et al*. [67] advises towards considering lymph node dissection in patients with mucinous ovarian carcinoids. For these patients, who did not have an advanced stage of disease, chemotherapy was administered in only 1.1% of patients. In comparison, both lymph node dissection and chemotherapy were employed in up to 23.8% of all patients with advanced disease [74]. Zhai *et al*. [67] has also emphasized that in the development of the therapeutic plan, fertility desire should also be considered and, consequently, fertility sparing therapy should be implemented in young patients.

The fact that most patients are diagnosed in early stages of the disease (88%) can be reflected in better 5 years overall survival rate, which reached up to 95.1%, contrasting with the low survival in patients with advanced stage (50.9%). According to Nasioudis *et al*. [74], a size of the tumor larger than 4 cm is also correlated with a worse prognosis. This observation has also been supported by Kanayama *et al*. [91], who reported a case of a 17 cm stage I ovarian carcinoid which developed metastases soon after. Patients with advanced stage disease can benefit from therapy with lanreotide and octreotide, aiming to control the symptoms [77,83]. Additionally, everolimus has also been proposed as a therapeutic option for these patients [92]. Chemotheraputic agents (alkylating, anthracyclines and antime-tabolites) represent a controversial point of view among specialists. Neither Nasioudis *et al*. [74], nor Davis *et al*. [75] have managed to prove a benefic impact of chemotherapy in the series of cases that they have reported concerning patients with advanced ovarian carcinoid.

5. Conclusions

In this paper we present the largest literature review to date regarding primary ovarian carcinoid, with emphasis on the relationship between the histologic subtypes and clinical symptoms, occurrence of metastases and presence or absence of teratomatous elements.

Based on our findings, the actual incidence of carcinoid heart disease appears to be significantly higher (29.31%) than that commonly reported by other studies, while the mean size of the tumor (78.51 mm) was consistent with that reported in previous studies. The insular variant was the most frequently encountered subtype and the most prone variant associated with metastases and teratoma. Since the specialty literature does not fully support

these results, further studies should be conducted in order to confirm the results. The differences between our results the ones previously reported are most likely due to the large cohort of patients included in our study and due to the large, representative variety of subtypes that included.

Author contributions

TAG, REB, ACL and CG performed the literature research. TAG and ACL wrote the manuscript. VV, OM and FF made the final revision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final draft.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

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