PRIMARY OVARIAN CARCINOID: EXTENSIVE CLINICAL EXPERIENCE WITH AN UNDER-RECOGNISED UNCOMMON ENTITY

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ABSTRACT

PURPOSE:

Primary ovarian neuroendocrine tumours (NETs) develop in pure form or in association with other tumours, mainly teratomas. The available data regarding this rare condition are limited. Much of the literature focuses on single case reports, previously dismissed as a totally benign disorder, and thus long-term considerations and evidenced-based management guidelines are lacking. The objective of the current study was to describe the clinical and pathologic characteristics and the effect of various therapeutic modalities on patient morbidity and mortality from two major centres. A secondary objective was to highlight that carcinoid syndrome may manifest in the absence of metastatic disease.

METHODS:

The authors retrospectively studied a cohort of 34 consecutive patients with primary ovarian NETs who attended either the Oxford University Hospitals or Beatson Oncology Centre, Glasgow, between 1984 -2014, and had their ovarian carcinoid data (e.g. tumour growth, chemotherapy regime) and mortality outcomes assessed.

RESULTS:

All patients were women, average age was 53, range 23-87 years at diagnosis. Of the 34 patients, 8 patients (23.5%) presented with the carcinoid symptoms. Carcinoid heart disease was evident in 2 of the 34 patients (6%). All patients had a primary ovarian carcinoid tumour on histopathology and two

patients had bilateral ovarian carcinoid. Teratoma associations could be assessed in 29 tumours, with 20/29 (69%) showing a pathological association. The mean tumour size was 48mm (range 4-120mm, SD 40mm). The mean follow up was 4.5 years, with up to 17 years.

The disease has been quiescent with no evidence of relapse in 22 of 34 patients; in 12 of 34 patients it was metastatic. There were 5 patients who received treatment with somatostatin analogues or chemotherapy. 8 patients died of disease (23.5%). Metastatic disease was found up to 11 years from initial diagnosis.

CONCLUSIONS:

Primary ovarian NET is rare and likely under-represented in the literature. It can no longer be simply dismissed as a generally benign entity. It requires careful evaluation and review.

INTRODUCTION

The majority of neuroendocrine tumours (NETs) arise in the gastro-intestinal tract or lung, but a small minority will arise in other locations (1). Whilst gastrointestinal NETs have become a well recognised entity and thus more readily amenable to identification, similar lesions arising from other sites such as the female reproductive organs, are often not considered and may be overlooked or subject to a considerable delay in diagnosis: primary ovarian NETs are one such example. Familiarity with such unusual sites of origin facilitates appropriate recognition and characterisation of such tumours, allowing for timely intervention and appropriate management. Specifically, early identification of an ovarian NET would also allow clinicians the ability to identify the best options for diagnosis and treatment. As these are rare tumours, large randomised trial data are not available, and currently consensus statements guide our management (2).

Ovarian NETs may be primary or metastatic. Primary ovarian NETs are rare and include small cell carcinomas, large cell variants and well-differentiated NETs, classically referred to as ‘carcinoids’. They were first described by Stewart *et al* in 1939 (3). Primary ovarian NETs develop in either pure form or in association with teratomas, and originate from endocrine cells, either ovarian or teratomatous in origin. They are categorised in groups based on the pattern of their histopathology: insular, trabecular, mucinous (goblet) and stromal, but are often mixed, containing two or more types (4, 5). Due to the fact that they often contain teratoid components, primary ovarian NETs have

been considered as “specialised teratomas” (4). However, while the histopathological reporting of primary ovarian NETs is not as yet standardised, the subtype may be of importance for prognostic purposes. In addition, the Ki-67 index of proliferation, used in other NETs, historically was often not reported, although it is now recognised to be of significant clinical importance (6). As ovarian carcinoids drain directly into the systemic venous circulation, they may present with a carcinoid syndrome independent of the presence of liver metastases, and thus may present relatively early; indeed, it has been suggested that there is a correlation between the size of the tumour and the presence of a clinically detectable carcinoid syndrome, with the critical cut-off being 10cm (7).

The diagnosis of a primary ovarian NET needs to be considered whenever a unilateral ovarian tumour is found: careful examination and evaluation of the intestinal tract as well as the contralateral ovary is indicated with an experienced histopathologist before the definitive diagnosis is made. Bilateral ovarian involvement is possible, albeit rarely. However, all patients with suspected primary ovarian carcinoids need to be evaluated for a possible NET metastatic to the ovary, most likely from a gastrointestinal origin (8-10). With the benefit of new imaging modalities, pre-operative work up with ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) can be combined with functional imaging with ^{111}In-octreotide and more recently ^{68}Ga-octreotate PET scanning. The presence of teratoid elements generally confirms that an ovarian NET is of primary ovarian origin (4).

As we represent two large tertiary centres for NETs, we considered it would be of value to present our experience retrospectively with these rare tumours, especially in terms of their presentation, diagnosis, therapy and outcomes.

METHODS

All patients were identified from clinical lists and databases held within the two centres, the Beatson Oncology centre in Glasgow, a major cancer referral centre in Scotland, and the ENETS Centre of Excellence for NETs at the Churchill Hospital, Oxford, UK. Patient files were reviewed and, where possible, clinical review was sought to detail the type of surgery and any evidence of recurrence. Imaging findings and comparison studies were reviewed to document the rate of change of any tumour and recurrence. Of patients undergoing surgery, the histopathology was uniformly reviewed by one subspecialised histopathologist at each centre. For survival analysis the first presentation was considered as time zero, and patients were followed until death or last contact. Surviving patients continue to attend for regular follow-up in the specialist centres. The study was registered as an Audit Project in both centres.

RESULTS

We identified 34 female patients with a diagnosis of primary ovarian carcinoid at the two centres. Their mean age was 53 years (range 23-87 years) at diagnosis. Of the 34 patients, 8 patients (23.5%) presented with symptoms of the carcinoid syndrome, i.e. flushing, diarrhoea and/or wheeze. The remaining cohort presented with a variety of symptoms ranging from abdominal bloating

to post-menopausal bleeding or incidentally-discovered ovarian pathology on imaging. Of the patients presenting with the carcinoid syndrome, a third had metastatic disease at presentation. Overall, clinical evidence of carcinoid heart disease was present in 2 of the 34 patients (6%), but this was absent on clinical grounds in all other patients. Six of the 34 patients were hypertensive. Cardiac assessment beyond physical examination was not routinely performed pre-operatively across the cohort.

All patients had a primary ovarian carcinoid tumour on histopathology: two patients had bilateral primary ovarian carcinoids, in one in association with bilateral teratomas. Of the cohort, 29 tumour cases were able to be assessed for the presence of a teratoma, which was identified in 20/29 cases (69%). The mean size of the NET was 48mm (range 4-120mm, standard deviation [SD] 40mm). Unfortunately, Ki-67 immunostaining, or assessment of chromogranin A and urinary 5-HIAA, were not routinely available across the series, dating back to 1984.

Of the 34 patients, 28 patients underwent oophorectomy, either unilateral (9) or bilateral, with some undergoing simultaneous subtotal or total abdominal hysterectomy. Three patients had simple cystectomy/cyst-oophorectomy.

At follow-up, there was no evidence of disease recurrence at a mean of 4.5 years in 22/34 (65%) patients. The disease has been in remission in 22 of 34 patients; however, in 12 of 34 patients it was metastatic at a mean follow-up

of 4.5 years. Five patients received treatment with somatostatin analogues or chemotherapy (varying protocols including doxorubicin or capecitabine or capecitabine, etoposide, platinum and temozolomide or cisplatin, 5-fluorouracil and streptozocin, which reflects the changes in practice over the time period)). Eight patients of the 34 died of disease (23.5%), including patients with a late presentation dying within 6 weeks of diagnosis. All deaths were in late presenters who had metastases at diagnosis (Table 1). There were 24 patients (70.5%) who were alive at the end of follow-up, with 2 patients dying of other causes. The average follow up was 4.5 years, with up to 17 years of follow-up. Metastatic disease was found up to 11 years from initial diagnosis at surgery. One patient went on to have a successful pregnancy.

Table 1 – Patient characteristics who died of ovarian carcinoid.

Patient	Initial Staging	Time to recurrence	Diagnosis clinical or radiological
1	FIGO 1V	metastatic at presentation, DOD 6/12	clinical widespread peritoneal nodules at diagnosis
2	FIGO IV	metastatic at presentation, DOD 6/52	Clinical
4	FIGO 1	2years	clinical, rising 5HIAA and radiological peritoneal & bony mets
5	FIGO 1C	6 years	rising 5HIAA, radiological
6	FIGO 3C	2years	radiological omental & liver mets
7	FIGO 1V	metastatic at presentation	clinical with radiological mets to small bowel
8	FIGO 1V	metastatic to sigmoid colon & pelvic region at presentation	clinical & radiological

DISCUSSION

Primary ovarian NETs are very rare, and most series in the literature are anecdotal or comprise only a small series. They account for less than 5% of all carcinoid tumours and less than 0.1% of all ovarian neoplasms (7) (11). Most NETs of the ovary are metastatic, usually arising from the gastrointestinal tract, tend to be bilateral, and are associated with diffuse intra-abdominal disease arising from a gastrointestinal source. For right-sided tumours, the proximity to the appendix should always raise the suspicion of a primary appendiceal tumour. Newer imaging techniques, particularly functional imaging, may now allow a diagnosis to be made preoperatively if there is a suspicion of a neuroendocrine origin and also may provide staging information. However, for most of these tumours there is rarely a suspicion that these may be primary ovarian NETs, and they are assumed to be primary ovarian malignancies which need to be managed in a very different manner.

Given their rarity, there are no specific trials for these tumours and at present no functional registry to collect cases. Our clinical cohort is to our knowledge the largest to be followed to date, utilising data across two tertiary referral centres in the UK: their care has involved clinicians in a number of specialties, including gynaecologists, oncologists and endocrinologists. There has been one large series published in 2000, from the Niigata Registry, where world-wide information on gut-pancreatic endocrinomas has been analysed providing information comparing ovarian cystic teratoma/dermoid groups

versus no teratoma/dermoid derivative, rather than the providing information on the clinical trajectory of individual patients (12).

In general, NETs may present due to local effects of the tumour, symptoms due to tumour-induced fibrosis, or symptoms and signs resulting from the secreted products of the tumour or its metastases. When symptomatic, carcinoid tumours can mimic a variety of common conditions, and can go undiagnosed for many years, with the average delay between symptom onset to diagnosis being approximately 10 years (13). Similarly, primary ovarian carcinoids may be discovered incidentally whilst undergoing radiological investigation for other reasons. From a histopathology perspective, accurate diagnosis and classification depends on experience with other NETs. There is to date no consensus for formal staging, rather adopting the FIGO ovarian cancer staging (2, 14). According to the SEER data-base, the diagnosis of all types of NETs has increased dramatically in recent years, at least in part due to better pathological clarification. In addition for ovarian carcinoids as well as many tumours labelled as sex cord /stromal tumours or small cell carcinomas of the ovary, these may have been more accurately diagnosed in recent times as ovarian carcinoids. Although not routinely reported in this cohort reflecting the changing practice over 30 years, the Ki-67 labelling index is now routinely used in other more common NET grading systems and is widely accepted as a marker of aggressiveness for prognostic behaviour of tumour biology, based on the tumour cell proliferative rate (15). In keeping with other NETs, we would likewise recommend routinely grading the tumour based on Ki-67 labelling.

In our cohort almost a quarter of patients presented with the carcinoid syndrome (24%). The clinical presentation for primary ovarian NET may be similar in history and examination to other NETs, with symptoms of carcinoid syndrome (facial flushing, telangiectasia, pellagra, secretory diarrhoea, wheezing and right-sided cardiac disease) (16). Careful clinical examination and investigation, including biochemistry with plasma chromogranin A and urinary 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin, are necessary, although these were not routinely performed in all our patients. In the future we would recommend their measurement and on-going evaluation for recurrence of functionality.

In our cohort, 6% of the total and 25% of those with carcinoid symptoms had cardiac involvement. However, this was in the main clinically assessed: brain natriuretic peptide (NT-pro-BNP) and transthoracic echocardiography (TTE) was not uniformly performed, although ideally it would now be part of the routine clinical evaluation of such patients. One of our recent patients presented in florid right-sided heart failure with resolution after resection of her primary ovarian carcinoid (17). In the literature there are numerous case reports and anecdotal references to isolated right-heart failure, in the absence of pulmonary hypertension, which should prompt the clinician to consider the possibility of carcinoid heart disease (18) (19). In view of the high proportion of patients with ovarian carcinoids with a carcinoid syndrome, we would suggest that, as for other types of NET with a high preponderance of a carcinoid syndrome, patients should be screened with measurement of NT-

proBNP and where necessary TTE (20, 21). Referral to a specialist cardiac centre with an interest in carcinoid heart disease should be considered where there is doubt.

In the setting of florid right heart failure requiring valvular replacement, medical management with octreotide to control the vasoactive mediating factors certainly plays an important role in preoperative management to prevent a carcinoid crisis i.e. the sudden and dramatic release of excess mediatory substances causing shock and circulatory collapse (6). Patient care should be in a specialist cardiothoracic unit experienced in managing patients with carcinoid heart disease. Newer more minimally-invasive techniques may allow safe, aortic and pulmonary valvular replacement (and patient foramen ovale (PFO) closure) in patients, but valvular surgical interventions will depend on the patient factors and disease status. Surgical timing is also a balance between the extent of disease and surgical risk (19).

Of note, the drainage of the ovaries is such that there may be carcinoid syndrome *without* hepatic metastases by virtue of direct access to the inferior vena cava (right ovary) or renal vein (left ovary) and bypass of the hepatic-portal circulation, thereby avoiding hepatic degradation of vasoactive metabolites (7), (22). This differs from mid-gut NETs which degrade vasoactive metabolites, generally presenting only with the carcinoid syndrome when hepatic metastases are present, or rarely if there is widespread peritoneal disease. In our patients with a carcinoid syndrome, while the published literature had suggested that a critical tumour size of 100mm

(10cm) exists for clinical functionality and thus presentation with carcinoid symptoms, we had 3 patients within our cohort having insular or mixed carcinoids, as small as 25mm with carcinoid symptoms, even smaller than a case report of a functional tumour of 60mm (4, 7). Thus, any primary ovarian carcinoid needs to be assessed clinically and biochemically for the presence of the carcinoid syndrome.

Primary ovarian carcinoids more frequently occur in peri-menopausal women and our data bear this out, with a mean age of presentation of 53 years. However, the range was large and the disease was seen in as young as 23 years of age, with the oldest aged 87 years. For the younger age-group, management will clearly have to take into account the possibility of future fertility.

The management of these tumours is extrapolated from that for the more common gastrointestinal or pulmonary NETs. Experience with adjuvant therapy is limited, due to the rarity of the reported primary ovarian NETs. The options for adjuvant treatments would include somatostatin analogues such as octreotide and lanreotide, or chemotherapy. There is no indication for any adjuvant treatment in well-differentiated tumours completely excised. Extrapolating from the PROMID and CLARINET trials, one could speculate that for residual tumours that are asymptomatic, intervention with a somatostatin analogue might delay tumour progression (23, 24). Davis *et al* demonstrated that postoperative adjuvant therapy showed limited success in 20% of cases (25). Adjuvant therapy was used with success in 5 patients of

our cohort. Two patients declined any chemotherapy, despite metastatic disease. There appears to be varying lengths of survival between 2-6 years for stage IV disease, with liver and bony metastases, using varying protocols including doxorubicin or capecitabine or capecitabine, etoposide, platinum and temozolomide or cisplatin, 5-fluorouracil and streptozocin. There is no evidence for the preference for any of these agents over any other.

For symptomatic metastatic disease, particularly when the patient is somatostatin-receptor positive, the use of somatostatin analogues should be used to control symptoms, and it may be expected that there would be some anti-proliferative effect. For larger disease burden or more progressive tumours, treatment with peptide radioreceptor therapy would be an appropriate therapy to be considered in view of its efficacy in other receptor-positive NETs (26).

For patients with receptor-negative tumours or those that have progressed on somatostatin analogues, other treatments need to be considered. If the disease is liver dominant then ablative treatments including surgical resection, radiofrequency ablation and hepatic artery embolisation with or without chemotherapy will be recommended. Where there is more diffuse extensive disease, as noted above, chemotherapy has only a limited effect but around 20-30% of patients may benefit from chemotherapy using one of the regimens listed above. Everolimus is now approved for gastrointestinal, pulmonary and pancreatic NETs resistant or recurrent after other treatments, and it is

reasonable to consider that this drug would be active in metastatic ovarian carcinoids, but currently experience is limited.

The high-grade tumours such as small cell carcinomas or large-cell variants of small cell carcinoma need aggressive multidisciplinary management with surgery chemotherapy and radiotherapy, and if beyond stage II long-term survival and cure are unfortunately exceedingly rare.

Analysis of our cohort has demonstrated that recurrence can indeed occur years after the original diagnosis, up to 11 years. This is in keeping with the literature, which includes recurrence at 8-13 years post- primary surgical intervention and diagnosis (8, 27). This therefore reinforces the importance of warranting long-term patient follow-up. Although level 1 evidence is difficult to present in such a rare entity, from our cohort we propose follow as per table 2.

Table 2; Table of our current staging protocol

Routine investigation time	Clinical evaluation	Biochemistry	Radiology
at diagnosis	Clinical examination of wheeze, right sided heart failure, abdominal mass, flushing….	24 hour urinar 5-HIAA, chromogranin A, BNP	Ultrasound of the pelvis
6/12 follow up			CT Pelvis +/- MRI Pelvis + Octreotide scan +/- cardiac echo if BNP elevated
12 monthly followup			CT Pelvis +/- MRI Pelvis + Octreotide

			scan +/- cardiac echo if BNP elevated

LIMITATIONS

This was a retrospective analysis and suffers from the limitations of such an assessment. Many patients were seen before the current protocols, pathological and radiological interventions recommended by the European Neuroendocrine Tumour Society (ENETS), and thus suffer from such deficiencies. However, there are few data on a like number of patients, and thus we believe all such information should be used to guide future assessments and treatments. Most importantly, we have been able to identify key features of such tumours and their diagnosis and prognosis to aid in future management.

CONCLUSIONS

The clinician should be alert to the possibility of primary ovarian NET. Much of the literature focuses on single case reports of this unusual tumour, previously dismissed as a benign disorder and thus long-term considerations and management have not been emphasised. We performed a retrospective case series study of primary ovarian NETs, based on histopathology, and are concerned that they may be under-represented in the current literature; they are seen across all age groups, may present late with metastatic disease with a significant delay in diagnosis, and in a small yet significant number of patients, be fatal. Many may present with a carcinoid syndrome even in the

absence of metastases. Long-term follow up of patients is therefore essential, particularly for those patients 'incidentally' diagnosed with ovarian carcinoid confined to the ovary, and who have not linked in with a NET multidisciplinary service. We would like to propose that long-term post-surgical review with active clinical surveillance is necessary. Where feasible this should be at a NET centre, for identification of recurrence or progression. In addition, regular cardiac assessment is warranted. This is based on our series in which, although many patients have had disease which was apparently cured by surgery, a significant percentage demonstrated significant morbidity and mortality, with metastases appearing years from the originally diagnosed primary ovarian carcinoid. The diminution of the likelihood of inadvertently neglecting these often benign, indolent neoplasms that are well known to metastasise if unaddressed would represent an important advance.

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