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Review

Non-epithelial Ovarian Cancer: Elucidating Uncommon Gynaecological Malignancies

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Abstract. *Non-epithelial ovarian cancers (NEOC) are a group of fascinating but uncommon malignancies which can be extremely challenging to treat. Collectively, these tumours only represent 10-15% of all ovarian cancers and occur in all age groups from childhood to old age. This broad term includes diverse tumours of germ cell origin, sex cord-stromal cell origin, as well as extremely rare types of ovarian cancer, such as small-cell carcinomas and sarcomas, each of which require specialist management. It is imperative that these rare tumours are managed with accurate diagnosis, staging and treatment in order to optimize patient outcomes. The aetiology and molecular origins of each sub-group of NEOC remain poorly understood and international cooperation to facilitate high quality translational research is needed. This review summarizes the published literature on the incidence, clinical presentation, pathology, therapeutic interventions, survival and prognostic factors of each sub-type of NEOC.*

Non-epithelial ovarian cancer (NEOC) are a group of uncommon, histologically and clinically distinct tumours. The two most frequently diagnosed NEOC are germ cell tumours (GCTs) and sex cord-stromal cell tumours (SCSTs), each of which have several histological sub-types (Table I) (1). Ovarian small cell cancers (hypercalcaemic and non-hypercalcaemic types) and sarcomas are extremely rare and aggressive cancers, with an aggressive clinical course and a generally dismal prognosis.

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GCTs are diagnosed principally in the first three decades of life (2). In contrast, SCSTs occur in women of all ages but increase in frequency during the fourth and fifth decades of age and patients have a median age at diagnosis of 52 years (3, 4). The incidence rates of these two most common subtypes of NEOC also differ by race. GCTs of are more frequent in Asian and African women (5), whereas SCSTs occur more commonly in women of Caucasian background (3). The yearly adjusted incidence rate is approximately 4 per 1,000,000 and 2 per 1,000,000 women for GCTs and SCSTs, respectively (6). The aetiology of these tumours remains largely unresolved. Ovarian small cell cancers of hypercalcaemic type affect young women, with a median age of diagnosis of 24 years (7). Small cell ovarian carcinomas of pulmonary type affects older women (median age 59 years) (8); with a clinical course and prognosis most similar to that of small cell lung cancer. Sarcomas of the ovary are extremely rare and heterogenous tumours including primary ovarian fibrosarcoma, angiosarcoma and rhabdomyo-sarcoma. The International Federation of Gynecology and Obstetrics (FIGO) staging system for epithelial ovarian cancer is also adopted for NEOC, however, due to high chemotherapy sensitivity and good prognosis of GCTs, the recommended surgical staging is much less aggressive.

Treatment of NEOC, as a group, should be on the basis of sound oncological principles. Due to the rarity of NEOC, randomised trials for assessing the relative benefits of different treatment modalities are extremely challenging. Cooperation is also required to further our knowledge of the molecular events which lead to NEOC and aid identification of novel drug targets.

The main purpose of this review was to show how an interdisciplinary model of case management, involving representatives from pathology, radiation, medical and gynecology–oncology can be invaluable in optimizing patient outcomes.

GCTs

These tumours occur principally in children and young women aged 10-30 years, with a mean age in the teenage years. GCTs are the most common ovarian neoplasm in women aged <30 years (9).

Clinical presentation. Presenting signs and symptoms can include abdominal pain with a palpable pelvic-abdominal mass in the majority of patients (85%), abdominal distension (35%), fever (10%), and vaginal bleeding (10%). A small proportion of patients exhibit symptoms of pregnancy or precocious puberty, related to β-human chorionic gonadotropin (β-hCG) production by the tumour (10). The disease is unilateral in most patients with early disease and the presence of bilateral ovarian involvement suggests dysgerminoma or mixed histology with a predominant dysgerminoma element, of which 10-15% will involve both ovaries at presentation (11).

Due to the age of patients affected by ovarian GCT, this disease can manifest during pregnancy. The results of a recent study indicated that advanced-stage GCT-complicated pregnancies were an independent prognosticator of decreased maternal survival (12). The timing of oncological intervention and delivery both significantly impacted on the outcomes both of foetal and maternal survival.

Diagnosis. Diagnosis can usually be made on morphological features, and immunohistochemical markers and chromosome 12p fluorescence *in situ* hybridisation can be used to confirm the diagnosis in difficult cases. Sal-like protein 4 (SALL4) is a sensitive and specific marker for GCT and is positive in dysgerminomas, yolk sac tumours (YSTs), the germ cell component of gonadoblastoma, embryonal carcinoma, some immature teratomas (13), however, it is also positive in rare alpha-fetal protein (AFP)-producing fetal-type gastric carcinomas (14). OCT3/4, a nuclear transcription factor, also known as POU5F1, is also widely used. In addition, expression of sex determining region Y-box 2 (SOX2) in embryonal carcinoma and primitive neuroectoderm of teratoma has been recently recognised (4).

Many, but not all, GCTs produce serum tumor markers that can aid in the establishment of diagnosis, monitoring during therapy, and have a useful role in post-treatment surveillance. YSTs and choriocarcinoma are characterized by production of AFP and β-hCG, respectively. Around one-third of immature teratomas will produce AFP, and raised lactate dehydrogenase can be a useful marker in dysgerminomas. Correspondingly, mixed GCT may produce either AFP, β-hCG, both, or no markers, depending on their composition.

Classification. According to the 2003 WHO classification system, GCT are divided into three categories: primitive GCT, biphasic or triphasic teratoma, and monodermal teratoma and somatic-type tumours associated with dermoid cysts (Table I) (1). This latter group will follow the clinical course of the somatic-type tumour, therefore their treatment should be tailored to the somatic-tumour type rather than the benign germ-cell element.

Table I. *Classification of non-epithelial ovarian cancer (modified from the World Health Organization Histological Classification of Tumours of the Ovary) (1).*

Primitive GCT
1. Dysgerminoma
2. YST
3. Embryonal carcinoma
4. Polyembryoma
5. Choriocarcinoma
Biphasic or triphasic teratoma
1. Immature teratoma
2. Mature teratoma
Mixed type (two or more of the above types)
SCST
1. GrCT
a. Adult-type GrCT
b. Juvenile-type GrCT
2. Theca-fibroma group
a. Thecoma
b. Fibroma
c. Fibrosarcoma
d. Sclerosing stromal tumor
e. Signet-ring stromal tumor
3. Sertoli-stromal cell tumor
a. Well-differentiated
b. Of intermediate differentiation, variant with heterologous elements
c. Poorly differentiated (sarcomatatoid), variant with heterologous elements
d. Retiform, variant with heterologous elements
4. SCST of mixed or unclassified cell type
a. Gynandroblastoma (specify components)
b. SCST, unclassified
Metastatic tumours, *e.g.* Krukenberg

GCT: Germ cell tumours, YST: endodermal sinus tumours, SCST: sex-cord stromal tumours, GrCT: granulosa cell tumours.

Like GCT in males, in clinical practice, ovarian GCTs are commonly divided into dysgerminomas (analogously to male seminomas) and non-dysgerminomatous tumours. The latter include the more common YSTs and immature teratomas, as well as the rarer embryonal carcinoma, non-gestational choriocarcinoma, and polyembryoma sub-types. Current approaches to the treatment are summarised in Table II.

Dysgerminomas

Dysgerminomas account for 30-40% of ovarian GCT cases, and 20-30% of ovarian malignancies associated with pregnancy (15). These tumours uncommonly secrete low levels of β-hCG (from multinucleated syncytiotrophoblastic giant cells), but AFP secretion is not expected with pure dysgerminomas.

Table II. *Management options for of germ cell tumours (GCT).*

	GCT		
	Dysgerminomas	Immature teratomas	Other GCT
Stage I	USO with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH-BSO is acceptable.		
Stage IA	Observation without adjuvant treatment.	G1: Observation without adjuvant treatment G2: Adjuvant treatment may be considered G3: Adjuvant chemotherapy	Adjuvant chemotherapy
Stage IB/C	Adjuvant chemotherapy	Adjuvant chemotherapy	Adjuvant chemotherapy
Stage II	USO with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH-BSO is acceptable. Adjuvant chemotherapy		
Stage III and IV	USO with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH-BSO is acceptable. Following maximal surgical debulking, adjuvant chemotherapy is indicated. Neoadjuvant chemotherapy can be considered for patients with extensive intra-abdominal disease, when initial debulking surgery is not an option.		
Recurrent tumours	Chemotherapy Radiation therapy in selected circumstances	Chemotherapy	Chemotherapy

USO: Unilateral salpingo-oophorectomy, TAH-BSO: total abdominal hysterectomy and bilateral salpingo-oophorectomy, G: grade.

About 75% of dysgerminomas are stage I at diagnosis, and bilateral disease is reported in 10-15% of patients; inevitably leading to surgical challenges to maintain fertility. For patients who present with more advanced disease, spread is most commonly *via* the lymphatics (15), however, direct extension through the capsule of the ovary and haematogenous spread may also occur.

Approximately 5% of dysgerminomas are discovered in phenotypic females with abnormal gonads (15). Therefore, pre-menarchal patients with a pelvic mass should have their karyotype determined.

The treatment of patients with dysgerminoma is primarily surgical, including the resection of the primary lesion and surgical staging. To preserve fertility, the contralateral ovary, fallopian tube, and uterus should usually be conserved, even in the presence of metastatic disease because of the exquisite chemotherapy sensitivity of this sub-type. Stage IA pure dysgerminoma can safely be treated with surgery and surveillance alone as the recurrence rate is low (15-25%) and patients can be successfully salvaged with combination chemotherapy at relapse, thereby avoiding chemotherapy for the majority of women. The role of adjuvant chemotherapy for stage 1b-1c disease remains controversial (16), although data supporting surveillance alone in paediatric patients are encouraging (17).

Immature teratomas

Pure immature teratomas are the second most common sub-type, and may also be mixed with other sub-types. Immature teratomas are highly chemotherapy-sensitive and contralateral involvement is rare (11), permitting fertility-sparing surgery, with or without adjuvant chemotherapy for most patients. The requirement for chemotherapy depends upon tumour stage and grade: Patients with stage 1A grade 1 immature teratomas can be safely spared chemotherapy. In contrast, chemotherapy is recommended for patients grade 2 or 3 tumours of any stage and stage ≥1a tumours irrespective of tumour grade (16).

YST

YSTs, formerly known as endodermal sinus tumours, are the third most common malignant ovarian GCTs (18). Five patterns of YST have been described, comprising microcystic, endodermal sinus, solid, alveolar–glandular, and polyvesicular vitelline sub-types. Mixed histological patterns have been described but co-existence with an epithelial malignant component is rare and may actually represent adenocarcinomas with aberrant YST differentiation. This is supported by their occurrence in older patients, an aggressive

clinical course and poor prognosis. For rare patients with mixed epithelial/YST, adjuvant platinum-based chemotherapy, such as carboplatin and paclitaxel, which has activity against both components (19).

YSTs typically secrete AFP and positive staining for AFP is present in >75%. Other immunohistochemical markers that are typically positive in YST include SALL4 (13) which is useful in distinguishing YST from ovarian clear cell adenocarcinoma, and glypican-3, which is more sensitive than AFP for YST, but less specific (20).

YSTs are confined to one ovary in about half of patients and bilateral ovarian involvement is rare. Prior to introduction of combination chemotherapy, the prognosis was poor even for patients with stage I disease. Surveillance with AFP monitoring and regular imaging has been investigated as a strategy to avoid adjuvant chemotherapy in paediatric patients, but over half of all patients experienced relapse. The majority were salvaged with chemotherapy (17) but the applicability of this strategy to adult patients has not yet been determined.

Surgical approaches

I. Primary surgery. a. Non-fertility-sparing surgery: In all postmenopausal women and pre-menopausal patients with bilateral ovarian involvement, abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) with careful surgical staging is usually recommended. Fertility-sparing surgery may be feasible in pre-menopausal patients with bilateral disease, if followed by adjuvant chemotherapy.

b. Fertility-sparing surgery: Unilateral salpingo-oophorectomy (USO) with preservation of the contralateral ovary and the uterus is now considered to be adequate surgical treatment for the majority of pre-menopausal patients with GCT. In children and adolescents, an Intergroup study reported excellent survival for all stages despite limiting surgical treatment to USO in the majority of cases. Support for such an approach in adults arises from experiential evidence: There was no detrimental effect on prognosis in a study of 182 patients who underwent fertility-sparing surgery for radiologically stage I tumours (21). For some patients, even cystectomy of the involved ovary may be adequate surgical treatment, but there are currently insufficient data to support this approach routinely. If proven to be safe, this could be especially valuable for pre-menopausal patients with bilateral disease in whom fertility preservation is desired.

c. Comprehensive surgical staging: Comprehensive surgical staging (comprising of full inspection and biopsies of the peritoneal surfaces, inspection of para-aortic and pelvic lymph nodes and infracolic omentectomy in addition to either USO or TAH/BSO) remains the gold standard (22). Biopsy of a macroscopically normal contralateral ovary is not required for fertility-sparing procedures, but endometrial biopsy is commonly performed if TAH is not planned. A commonly encountered clinical dilemma is whether surgical restaging after emergency USO is necessary. Postoperative computed tomography (CT) imaging followed by adjuvant chemotherapy for patients with normal scans and tumour markers is a pragmatic approach for patients with high of risk tumours. For unstaged tumours with good prognosis (dysgerminoma or grade 1 immature teratoma), surveillance alone is an option for those with normal tumour markers and postoperative imaging. However, patients with persistent disease on CT or raised tumour markers should ideally have staging surgery, as they could avoid adjuvant chemotherapy if stage 1A disease is confirmed (23). Avoidance of further surgery but proceeding with adjuvant chemotherapy with careful tumour marker monitoring is an alternative.

d. Cytoreductive surgery: In advanced disease, radical cytoreductive surgery should not include non-gynaecological organ resection, as adjuvant chemotherapy obviates the need for such morbid surgery for the majority of patients.

II. Secondary surgery. a. Salvage surgery: Second-look surgery should be considered for patients with incompletely resected tumour that contains teratoma elements (24). In practice, a second resection is generally limited to patients with residual immature teratoma following adjuvant chemotherapy, or growing teratoma syndrome (25).

Adjuvant treatment. Prior to the advent of combination chemotherapy, the prognosis for patients with GCT was bleak. Platinum-based regimens have been the gold standard treatment for more than a decade and the bleomycin, etoposide, and cisplatin (BEP) regimen is most widely used. The optimal number of cycles of BEP remains unresolved, but 3 cycles will prevent recurrence in the majority of patients with completely resected disease. Four to five cycles (omitting to bleomycin after cycle 3 to minimise lung toxicity) are recommended for patients with macroscopic residual disease (16), although arguably this should be continued for up to six cycles in patients with evidence of ongoing radiological or biochemical response.

The standard BEP regimen is a 5-day course of daily cisplatin and etoposide with additional weekly bleomycin doses on days 1, 8 and 15. An alternative more convenient 3-day regimen has been investigated in randomised studies in male GCT and in non-randomised trials in ovarian GCT and appears to be both safe and effective, with a 96% 5-year disease-free survival reported (26).

Recurrent disease. Most recurrences occur within 24 months of initial GCT diagnosis and the most common sites of relapse are the peritoneal cavity and retroperitoneal lymph nodes (15). There is no internationally accepted standard treatment for relapse of ovarian GCT and the approach is largely based on data in male GCT. The most commonly employed salvage

regimens therefore include vinblastine, ifosfamide, and cisplatin; etoposide, ifosfamide, and cisplatin; and paclitaxel, ifosfamide, and cisplatin (27). The salvage rate for chemotherapy in patients with ovarian GCT is approximately 50% (11). Depending upon the site and distribution of relapse, radiotherapy may be an effective alternative, but this must be balanced against the morbidity including loss of fertility if abdomino-pelvic radiation is required. Retrospective reports suggest a possible role for secondary cytoreductive surgery in selected patients with recurrent GCT. Ideal candidates for such consideration would be those with limited sites of recurrent tumour. In particular, patients with relapsed dysgerminoma that was incompletely staged at diagnosis may be cured by this approach (28).

Prognosis. Despite the rapid rate of growth associated with malignant GCT, the majority (60-70%) are diagnosed at an early stage, with cure rates now approaching 100%. Even in advanced-stage (III-IV) disease, at least 75% of patients will be cured. In addition to advanced FIGO stage, poor prognostic factors may include residual tumour after salvage surgery, raised tumour markers at diagnosis, non-dysgerminoma histology and age >40 years at diagnosis (29).

Late effects of therapy of GCT. With such an excellent prognosis, especially for women with early-stage disease, de-intensification of treatment and avoidance of late effects is an important area of research.

The majority of young women who are treated with fertility-sparing surgery and combination chemotherapy for ovarian GCT may expect recovery of ovarian function, usually within a few months after treatment. Fertility seems to be only marginally affected by treatment, with many reports of successful pregnancies (30). The rate of miscarriages is within the expected range for the general population, however, the congenital malformation rate in offspring of previous GCT patients is slightly higher than in the general population (31). Premature menopause is more common following chemotherapy (32), therefore these patients must be advised to avoid significant delay starting a family, if possible. Extrapolating data from breast cancer trials and prescribing gonadotropin-releasing hormone analogues with chemotherapy is a reasonable approach to reducing the rate of premature menopause and protecting fertility (33).

The risk of a second primary cancer is a significant concern following curative treatment for ovarian GCT. The risk of malignancy appears to correlate with the cumulative dose of etoposide, a factor which must be taken into consideration when determining the number of cycles of BEP/etoposide and cisplatin chemotherapy to deliver (34). Research into de-intensification of chemotherapy for high-risk patients and avoidance of adjuvant chemotherapy altogether for patients with early good prognosis disease remain the most important strategies to minimise the risk of second malignancy.

SCSTs

SCSTs account for 5-8% of ovarian malignancies (15). They arise from the sex cords and ovarian stroma and represent a heterogeneous group of neoplasms with variable biological behaviour, clinical presentation and prognosis: Whilst these are generally indolent, slow growing tumours, more aggressive behaviour can be exhibited. Granulosa cell tumours (GrCTs) are the most common sub-type; Sertoli-Leydig cell tumours (SLCT) and theca cell tumours are rare.

SCSTs can occur over a wide age range, but most commonly present in the 5th and 6th decade of life. Younger age, early-stage and low tumour grade are the most important predictors for improved disease-specific survival for SCST (35).

GrCTs

Ovarian GrCTs have an incidence of approximately one case per 200,000 women per year (36), representing 2-5% of all ovarian cancer (4). For the majority of patients presenting with stage I disease, the short-and medium-term prognosis is excellent. However, even early-stage disease frequently recurs but due to the relatively indolent nature of this disease, such recurrences often occur years after the initial treatment, with a resultant 20-year survival rate of 67% (4).

GrCTs are divided into juvenile and adult types based on clinical presentation and histologic characteristics: The juvenile type accounts for only about 5% of GrCT and has a distinctive histological appearance. Histologically, their architecture is often lobulated, Call-Exner bodies are rare, and signs of luteinisation are common (37). Characteristically juvenile GrCT occur in children and young adults, comprising 85% of GrCT observed before puberty. Immunocytochemically, juvenile GrCT are similar to adult types except around 50% are positive for expression of epithelial membrane antigen (EMA) (38).

Adult GrCT typically presents during the perimenopausal or early postmenopausal period and occurs only rarely in children and young women (39). Histological features include monomorphic proliferation of uniform cells containing vesicular nuclei and high nuclear to cytoplasmic ratios, with low mitotic rates. A prominent longitudinal nuclear groove is helpful in confirming the diagnosis. There are five subtypes, of which microfollicullar is the most common (40). Forkhead box L2 (FOXL2) mutations are usually present in adult GrCT and rare in juvenile GrCT, aiding diagnosis, especially where the patient's age is outside the usual range (41).

Table III. *Summary of chemotherapy regimens for granulosa cell tumours (GrCT).*

Author	Year of publication	Regimen	Response	Overall RR (%)
Gershenson *et al*. (71)	1987	CAP	3/8 CR	63
Pecorelli *et al*. (72)	1988	PVB	12/38 CR	
			11/38 PR	60
Zambetti *et al*. (49)	1990	PVB	3/7 CR	66
			1/7 PR	
Pectasides *et al*. (73)	1992	CAP	5/10 CR	60
			1/10 PR	
Gershenson *et al*. (74)	1996	BEP	2/6 CR	83
			3/6 PR	
Savage *et al*. (46)	1998	PVB	1/5 CR	80
			3/5 PR	
		BEP	1/3 PR	33
Homesley *et al*. (75)	1999	BEP	6/38 CR	26
			4/38 PR	
Al-Badawi *et al*. (76)	2002	CDDP/ADR/CTX/MTX	1/1 CR	100
		CDDP/ADR/BLEO/V	1/4 PR	25
Uygun *et al*. (77)	2003	CTX/ADR/CDDP	5/14 CR	
			5/14 PR	
			4/14 SD	100
Brown *et al*. (50)	2005	BEP	6/8 CR	75
		CDDP/PaC	2/2 PR	100
		Ca/PaC	6/13 SD	46
Pectasides *et al*. (78)	2008	CTX/ADR/CDDP or CDDP/Ep/CTX	6/13 CR	54
		BEP	1/1 PR	100
Pautier *et al*. (79)	2008	BEP	9/20 CR	
			9/20 PR	
			1/20 SD	95
van Muers *et al*. (80)	2014	BEP	1/9 CR	
			1/9 PR	
			7/9 SD	100

CAP: Cyclophosphamide, doxorubicin, cisplatin, PVB: cisplatin, vinblastine, bleomycin, BEP: bleomycin, etoposide, cisplatin, CDDP: cisplatin, ADR: doxorubicin, CTX: cyclophosphamide, MTX: methotrexate, BLEO: bleomycin, V: vinblastine, PaC: paclitaxel, Ca: carboplatin, Ep: epirubicin, CR: complete response, PR: partial response, SD: stable disease.

Clinical presentation. The most common presenting symptoms are abnormal uterine bleeding and abdomino-pelvic pain. Haematoperitoneum may occur uncommonly due to tumour rupture. Pre-menopausal patients may have menstrual irregularities, menorrhagia, intermenstrual bleeding or amenorrhea. The majority of GrCTs produce oestradiol, therefore in juvenile GrCT, 80-90% of patients under 8 years of age display signs of precocious puberty. Jjuvenile GrCT may also rarely cause virilisation in older patients. In older patients, the symptoms may mimic those of common epithelial ovarian cancer with bloating and altered bowel habit.

Tumor markers. *Oestradiol:* Although oestradiol is commonly secreted by GrCT, oestradiol levels are not a reliable marker of disease activity (42). Oestradiol is not produced at all in around 30% of cases due to the lack of theca cells in the tumour stroma.

Inhibin: Inhibin is a dimeric, ovarian glycoprotein hormone consisting of α- and two β-subunits which give rise to measurable inhibin-A and inhibin-B in the serum, respectively. Inhibin suppresses the synthesis and secretion of pituitary follicle-stimulating hormone. Either or both inhibins, may be secreted by GrCT, although inhibin B is more frequently elevated (43). Inhibin levels typically rise 11 months before radiological progression is evident (3).

Treatment. *Surgery:* GrCTs are bilateral in only 3% of patients, therefore fertility-sparing surgery with USO is feasible for stage IA tumours in pre-menopausal patients wishing to retain their fertility. If hysterectomy is not planned then endometrial biopsy is recommended, as a synchronous endometrial cancer is present in about 5% of cases; and endometrial hyperplasia secondary to excess oestrogen is present in a further 25% (15). Endometrial carcinomas related to GrCT are usually well-differentiated,

Table IV. *Summary of reported hormonal regimens for granulosa cell tumours.*

Author	Year of publication	Regimen (no. of patients)	Response
Malik *et al*. (81)	1991	MPA (n=2)	2 PR
Isaacs *et al*. (82)	1992	MPA (n=1)	1 CR
		Tamoxifen (n=1*)	1 PD
		Megestrol acetate (n=1*)	1 PR
Kauppila *et al*. (83)	1992	Goserelin(n=4)	2 PR
			2 PD
		Goserelin + tamoxifen (n=1)	1 PD
Maxwell *et al*. (84)	1994	Leuprolide (n=2)	2 PD
Fishman *et al*. (85)	1996	7.5 mg Leuprolide acetate (n=5)	2 PR
			3 SD
		Tamoxifen (n=1)	1 SD
Briasoulis *et al*. (86)	1997	160 mg Megestrol acetate (n=1)	1 PR
Crew *et al*. (87)	2005	Leuprolide (n=1)	1 SD
Ameryckx *et al*. (88)	2005	Ganirelix(n=1)	1 PD
Hardy *et al*. (89)	2005	Alternating biweekly cycles of megestrol and tamoxifen (n=1)	1 CR
Freeman *et al*. (90)	2006	Anastrozole(n=2)	2 CR
		Leuprolide (n=2)	1 SD
			1 PD
Korach *et al*. (91)	2009	Anastrozole(n=2)	1 CR
			1 PR
		Letrozole(n=2)	2 CR
Kim *et al*. (92)	2009	3.75 mg Leuprorelin (n=1)	1 PR
Teoh *et al*. (93)	2010	22.5 mg Leuprolide acetate every three months and 20 mg tamoxifen twice daily (n=1)	1 PD
		40 mg Megestrol acetate orally four times daily for 3 months (n=1)	1 PD
Abdul Munem *et al*. (94)	2012	Anastrozole(n=1)	1 PR
Alhilli *et al*. (95)	2012	Letrozole(n=1)	1 PR
Keskin *et al*. (96)	2012	11.25 mg Leuprolide every 3 months and 20 mg tamoxifen twice daily (n=1)	1 CR
Kourie *et al*. (97)	2013	Letrozole (n=1)	1 CR

MPA: Medroxyprogesterone acetate, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease. *This patient received two lines of hormonal treatment.

early-stage and associated with a good prognosis. In peri- and postmenopausal women, TAH, BSO and full staging surgery should be performed. In contrast to GCT, GrCTs are not highly chemotherapy sensitive, so complete debulking surgery is key to improving survival (44). Spread of GrCT is usually local, by direct extension and peritoneal seeding, but may also spread haematogenously to the lungs, liver, and even brain. Metastatic disease at presentation is rare and more commonly develops years after initial treatment.

Radiotherapy: Adjuvant radiotherapy and targeted radiotherapy for oligometastatic but inoperable recurrent disease has been investigated (45, 46). A retrospective study of 103 patients of whom 31 received adjuvant radiotherapy, suggested a survival advantage from this treatment (47). However, efficacy has not been consistently reported (48).

Chemotherapy: There are no randomised trials to guide clinical practice. The majority of patients with stage I disease have an excellent prognosis and will not require adjuvant treatment following surgical resection (46). However, for patients with poor prognosis factors such as large tumour size, high mitotic activity-index or ruptured tumours, adjuvant chemotherapy is commonly considered. BEP is the most accepted regimen in this setting (16), as well as for recurrent disease that is refractory to hormone therapy (46, 49). The potential activity of taxanes has been studied in this disease (50) and the combination of carboplatin and paclitaxel, is not unreasonable. Reported response rates to chemotherapeutic regimens are summarized in Table III.

Hormonal therapy: Hormone treatment is a logical treatment for advanced GrCT, given their frequent oestrogen dependence and usually indolent course (51). Bone density monitoring is indicated for patients receiving aromatase inhibitors, as is the standard of care in breast cancer treatment. A recent systematic review of hormonal therapy for GrCT reported a pooled response rate of 71% and aromatase inhibitors appear to be the most effective agents, with no reported responses to tamoxifen (52). The role of anastrozole in GrCTs is being assessed in the international multicenter phase II PARAGON trial (ANZGOG 0903), run by the Australia New Zealand Gynaecological Oncology Group. At present, there are no data to support the use of hormone therapy in the adjuvant setting. Available data for hormonal therapy are summarized in Table IV.

Prognosis: The prognosis for patients with JGrCT is more favourable than for the adult-type, and recurrences are observed almost exclusively within 3 years of operation (53).

The stage at diagnosis is the most important determinant of prognosis for GrCT. The 5-year survival rate for patients with stage I is in excess of 90% (35). Tumour size has been reported to be prognostic but this has not been consistently reported (44). Unsurprisingly, poorly differentiated diffuse or sarcomatoid type GrCT is associated with poorer outcome. Nuclear atypia and increased mitoses have also been suggested as predictors of recurrence (44). Conflicting results have been reported regarding the prognostic impact of p53 overexpression and Ki-67, where some investigators have reported these as adverse prognostic factors (54), while others reported no association with outcome (55).

SLCTs

Common to other NEOC, SLCTs are also usually confined to one ovary. They occur most frequently in the third and fourth decades, with 75% of cases occurring in women aged less than 40 years. SLCTs are characterised by the presence of testicular structures that produce androgens, therefore virilisation is present in 70-85% of patients (56).

Pathology. These are most commonly well- or moderately differentiated tumours, comprising uncontrolled proliferation of tubules lined by Sertoli cells with intervening nests of Leydig cells (57). Leydig cells are typically found in clusters in interstitial stroma as polygonal cells with well-defined margins, centric nuclei, prominent nucleoli, and eosinophilic cytoplasm. Mesenchymal heterologous elements are present in 22% of SLCTs and, rarely, these can mimic aggressive tumours such as rhabdomyosarcomas (58). Usually, SLCTs stain positively for inhibin, calretinin, Wilm's tumour 1 and CD56 (59), and negatively for EMA (60).

Treatment. Surgery is key to both the diagnosis and treatment of SLCT. Usually, fertility-sparing surgery with USO is sufficient, but in postmenopausal patients, or those with more radiologically advanced disease, cytoreductive surgery with TAH/BSO is appropriate. Lymph node metastases are rare; therefore lymphadenectomy may be safely omitted during staging surgery (61).

There is no standard adjuvant therapy for SLCTs, and adjuvant chemotherapy is not usually recommended for stage IA-1B disease due to the excellent prognosis with surgery alone (62). For patients with grade 2-3 disease, advanced stage or heterologous elements, adjuvant BEP chemotherapy may be considered. The BEP regimen is active in recurrent or incompletely resected SLCT, but does not offer durable remissions (63). Taxanes may be an effective alternative, with less toxicity compared to BEP in a retrospective study (50).

Prognosis. Tumour stage and grade are the most consistently reported prognostic factors for SLCT. Interestingly, differentiation correlates with age, where poorly differentiated tumours occur at a lower median age than well-differentiated tumours. Relapse in SLCT is usually early; two-thirds of relapses occur within 1 year of diagnosis and only 7% of relapses occur after 5 years. The abdominal cavity and retroperitoneal nodes are the most common sites of recurrent disease (64).

Very Rare Ovarian Tumours

There are several rare malignant ovarian tumours that together comprise ~0.1% of ovarian malignancies (15). These include small cell carcinomas (hypercalcaemic and non-hypercalcaemic types), and ovarian sarcomas.

Small-cell carcinomas

Small-cell carcinoma of the ovary (SCCO), hypercalcaemic type, occurs at a median age of 24 years, and is usually (but not always) accompanied by hypercalcaemia at diagnosis (7). These tumours rapidly enlarge with local pressure symptoms at presentation and are typically unilateral, therefore the main differential diagnosis is GCT. Despite unilateral ovarian disease, these are commonly advanced (stage 3) at diagnosis (65).

The non-hypercalcaemic type of SCCO are analogous to neuroendocrine, pulmonary-type small cell tumours. These typically occur in older, postmenopausal patients and follow a similar clinical course to small-cell lung cancer.

Pathology. Hypercalcaemic-type SCCO has been recently sequenced and confirmed to be a malignant rhabdoid tumour by virtue of consistent deleterious mutations in SMARCA4 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4), a chromatin-remodelling gene (66). Although these tumours resemble neuroendocrine small-cell tumours morphologically, these are now recognized to be a distinct clinical and pathological entity.

Like small-cell lung cancer, pulmonary-type SCCO is characterised histologically by the presence of small round (or spindle-shaped) cells, with sparse cytoplasm and hyperchromatic nuclei. Pulmonary-type SCCO may grow in pre-existing malignant or benign ovarian tumours, such as endometrioid carcinoma and Brenner tumour (8).

Treatment. For hypercalcaemic-type SCCO tumours, no prospective studies have been performed and treatment decisions are therefore based on case series. A multi-modality treatment approach is recommended including debulking surgery to relieve symptoms and assess the extent of disease followed by chemotherapy and possibly

radiotherapy. As the disease is unilateral in 99% of cases, fertility-sparing surgery with unilateral oophorectomy and debulking of visible disease is reasonable. In the largest case series, reported by Harrison et al. (67), all patients received adjuvant platinum-based chemotherapy, irrespective of stage. Common regimens include BEP, carboplatin and paclitaxel, and carboplatin plus etoposide. Of interest, most of the long-term survivors also received adjuvant radiotherapy either following or concurrently with chemotherapy: Five out of seven patients with stage 1 disease who received radiotherapy were alive beyond 50 months. In addition to the primary treatment of the disease, control of hypercalcemia may require aggressive hydration and intravenous bisphosphonates. Hypercalcaemia typically resolves after removal of the primary tumour.

For pulmonary-type SCCO, primary surgery was recommended for operable disease in a recent consensus statement, followed by adjuvant carboplatin and etoposide (68). Arguably, the treatment of these aggressive cancer s should be extrapolated from the more common small-cell lung cancers, with primary chemotherapy with carboplatin and etoposide, and responses consolidated with chemoradiation if the disease is loco-regional. However, there is no evidence base for the optimal treatment of these rare cancers, which are associated with a very poor prognosis.

Prognosis. These are aggressive malignancies with a dismal prognosis. For hypercalcaemic-type SCCO, the majority of patients relapse despite the multi-modality treatment and the 5-year overall survival rate for all stages is approximately 10% (65). For patients with stage III disease, the median survival is just 6 months (67). Age over 30 years, normal preoperative calcium at presentation, tumour size less than 10 cm, and histological absence of large cells appear to be favourable prognostic features in stage 1A disease (69).

Sarcomas

Primary ovarian/fallopian tube sarcomas are rare, and treated according to their histological sub-type, which may include angiosarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma and osteosarcoma. These tumours should be managed by specialist sarcoma units according to their sub-type, rather than their ovarian site of origin. This will normally comprise aggressive surgery for localised cancers and palliative chemotherapy for metastatic disease.

Malignant mixed mesodermal tumours (MMMTs, previously known as carcinosarcomas) of the ovary are rare, aggressive cancers, occurring most commonly in postmenopausal women. Their presentation is similar to that of epithelial ovarian cancer, although few patients present with disease confined to the ovary and many will have visceral metastases at presentation. The epithelial component may be endometrioid, serous, clear cell, or solid (transitional) types. The concomitant sarcomatous components are either of homologous type, usually high-grade sarcomas, leiomyosarcoma, or endometrial stromal sarcoma. However, heterologous types such as rhabdomyosarcomas, chondrosarcoma and, less commonly, liposarcoma may also be present. Any of these patterns may overgrow and obliterate other components. These tumours are treated in the same way as high-risk epithelial ovarian cancer but their prognosis is usually poor (70).

Conclusions and Future Directions

NEOC are a heterogenous group of rare tumours that affect mainly young patients. Whilst patients with GCT have an excellent prognosis, with cure rates approaching 100% for those with early-stage disease, the 1-year survival for those with SCCO is just 50%. SCSTs are generally more indolent with an excellent short-term prognosis, but carry a significant risk of late relapse.

There is a genuine need for more pre-clinical work on these rare diseases to allow investigation of novel drug targets which could lead to clinical trials. Due to the rarity of NEOC, randomised trials for assessing the relative benefits of different treatment modalities are extremely challenging, but could be achieved with international cooperation.

Conflicts of Interest

The Authors declare no conflict of interest.

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