Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

N. Reed1, D. Millan2, R. Verheijen3 & M. Castiglione
On behalf of the ESMO Guidelines Working Group*

1Beatson Oncology Centre, Glasgow; 2Department of Pathology, Glasgow Royal Infirmary, UK; 3Department of Gynecological Oncology, University Medical Center, Utrecht, The Netherlands; 4RGV, University of Geneva, Geneva, Switzerland

introductory remarks

These are all uncommon cancers and may generate difficulty in establishing a diagnosis. Nevertheless, careful review of tumour marker patterns [especially β-human chorionic gonadotrophin (β-hCG), α-fetoprotein (AFP) and lactate dehydrogenase (LDH)], clinical signs (such as so-called pregnancy signs, virilization and vaginal blood loss), and clinical findings (such as concomitant ovarian mass and endometrial thickening) may indicate at least germ cell or sex cord and stromal tumours. Often there is nothing to suggest an unusual diagnosis at presentation and only pathology and immunocytochemistry will make the diagnosis. The topic was clearly reviewed by Colombo et al. 2 years ago for the ESMO Clinical Recommendations. This article includes a stronger than usual emphasis on the role of the histopathologist in diagnosing these tumours but expert pathology review is essential. These tumours are best dealt with by specialist teams, and this may require referral to supra-regional centres for primary management but shared care protocols can be devised for follow-up. Management of these rare cancers requires specialist services. Registration of these tumours in a central or regional database is recommended and, wherever possible, clinical trials should be supported. Serum and tissue should also be archived for future research. Finally given their rarity, the literature is sparse with regard to clinical trials and guidelines but some general references and reviews have been added.

The following uncommon non-epithelial cancers are covered in this guideline. Much has been published on germ cell tumours so the emphasis is more on the less commonly seen tumours.

(i) Carcinosarcomas of the ovary
(ii) Sex cord and stromal tumours
(iii) Germ cell tumours
(iv) Small cell and NET tumours
(v) Squamous carcinoma arising within a dermoid
(vi) Struma ovarii malignum.

sarcomas (carcinosarcomas) of the ovary

incidence

These are rare cancers usually comprising <2%—4% of ovarian tumours. There is a general belief that, as with their uterine counterparts, the incidence of ovarian carcinosarcomas is increasing in recent years.

diagnosis

As with most of these tumours, pre-operatively the diagnosis will be that of a suspected malignant ovarian cancer and surgery should be planned accordingly. Tumour markers such as CA125 may be measured but are not diagnostic. Imaging with CT or MRI is carried out to assist in staging and planning surgery. Since the diagnosis is not usually suspected pre-operatively, most patients will be managed as per epithelial ovarian cancers (EOCs). The use of RMI scoring may help to determine when referral is made to a gynaecological oncology unit. It is also worth noting that in the pre-operative work-up of patients where there may be cytological analysis of ascitic fluid, that again the malignant epithelial component will be the dominant feature. It is very unusual to be able to make a diagnosis of a carcinosarcoma from pre-operative cytological preparations alone, as the malignant epithelial component will be the dominant feature.

surgery

The surgery should be planned as for any suspected ovarian cancer. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal washings are minimal requirements, and where appropriate lymphadenectomy and...
blind biopsies from diaphragmatic surface are included. The aim is to leave no residual disease.

**pathology**

The preferred term is carcinosarcoma replacing MMMT; surgeons and oncologists historically have been guilty of referring to carcinosarcomas as ‘sarcomas’. It is generally recognized that both uterine and ovarian carcinosarcomas should be regarded as a subgroup of malignant epithelial tumours. In recognition of this the term metaplastic carcinoma has been used by some groups. Histologically both show evidence of biphasic differentiation with malignant epithelial components and malignant sarcomatous components. The diagnosis is usually straightforward where there is an obvious malignant epithelial element and malignant heterologous stromal components such as malignant cartilage or bone. However, when there is little or no evidence of heterologous differentiation the diagnosis of a carcinosarcoma can be problematic. The greatest difficulty lies not with the identification of a malignant epithelial component but with the identification of a malignant stromal component. The diagnosis of a metastatic ovarian carcinosarcoma can also be problematic, as when carcinosarcomas metastasize they very often do so with a predominance of the malignant epithelial component and either a completely absent or only a very minor malignant sarcomatous component. Transperitoneal spread from a primary ovarian lesion often gives rise to metastatic deposits that are present as almost exclusively malignant epithelial tissues with only a very minor often difficult-to-find malignant stromal component. This lends further argument to the belief that ovarian carcinosarcomas are truly epithelial in nature with highly variable metaplastic sarcomatous tissues. Finally, the malignant counterpart of a fibroma, the fibrosarcoma, although less well defined histologically in previous studies has now got a more consistent robust set of criteria for its diagnosis but is notable by being a particularly rare entity.

**adjuvant therapies**

This is likely to be indicated in all cases of carcinosarcoma, as all are high grade even in stage 1. The dilemma is whether to treat as an epithelial cancer with carboplatin and paclitaxel, or whether to include an anthracycline or ifosfamide. There are several small series showing broadly similar response rates and survival with carboplatin and paclitaxel in optimally resected patients, a paper from Duska describes more recent experience. In poor performance status (PS) older patients, single-agent carboplatin may be offered. There have been no trials supporting use of anthracyclines but small series have shown activity with the TEC (paclitaxel, epirubicin and carboplatin) regimen. Ifosfamide has shown activity in relapsed disease and has been reported in first-line therapy in some older studies. To date there are no data beyond phase I or II trials on the molecular targeted agents but clearly they have potential use alone or in combination. A recent comprehensive review was published by Mano et al.

**prognosis**

Historically patients with these tumours have had a poor survival with few surviving beyond 1–2 years but the inclusion of more aggressive surgery and platinum-based regimens has shown equivalent outcome data to EOC stage for stage in the last decade. Follow-up will normally be as for EOCs.

**sex cord and stromal tumours of ovary**

**incidence**

These are uncommon and account for 5% of ovarian neoplasms and 7% of malignant ovarian tumours. Clinically they often present with no distinguishing features, but some are functional and may cause virilization or symptoms from excess estrogen secretion, such as endometrial hyperplasia and postmenopausal bleeding (PMB). The commonly seen tumours are listed below:

- granulosa cell tumours, adult and juvenile forms;
- fibromas, thecomas and fibrothecomas;
- Sertoli cell, Leydig cell and Sertoli–Leydig cell tumours;
- gynandroblastomas;
- sterol cell tumours;
- sex cord tumours with anular tubules;
- unclassifiable.

**diagnostic tests**

Unless functional, once again they are often not recognized until operated on. Granulosa cell tumours may bleed and cause pain, and in older women may be associated with PMB from endometrial hyperplasia, so a diagnostic hysteroscopy may be indicated. Rare androgen- or even cortisol-secreting tumours can present with virilization or Cushing’s syndrome. CA125 is non-diagnostic, and other tumour markers—such as oestradiol and inhibins (granulosa cell tumours), testosterone (Sertoli–Leydig cell tumours)—may be measured and be useful for serial measurement in follow-up. CT or MRI will be required for staging, haemorrhage in an ovarian cyst may suggest a granulosa cell carcinoma and the finding of endometrial hyperplasia should also arouse suspicion.

**pathology**

This group of tumours is derived from ovarian stromal structures and from the sex cords of the embryonic gonad which give rise to more specialized cells, such as Sertoli cells, Leydig cells, granulosa and thecal cells. The benign fibroma is the most common tumour within this group; however, the most common malignant tumour within this group is the granulosa cell tumour. Granulosa cell tumours occur in two main forms, namely adult and juvenile. In the adult form the tumour appears as a circumscribed, soft, focally haemorrhagic, distinctly yellow mass. Histologically they are highly cellular with typical small uniform cells with scanty cytoplasm, grooved nuclei and small eccentric nucleoli. Macrofollicular, microfollicular, solid, insular or trabecular patterns are well recognized and all form the characteristic Cal-Exner bodies to a variable degree. This reflects the difficulty of predicting the tumour’s behaviour from the histological features and tumour stage at the time of diagnosis remains the most important prognostic feature. Immunohistochemistry with positive staining with α-inhibin, calretinin, CD99 and melan A are very
useful confirmatory investigations for those more problematic or diagnostically difficult cases. The majority of tumours are unilateral and are confined to the ovary.

As their name suggests, the majority of juvenile granulosa cell tumours (80%) occur before the age of 20, often in prepubertal girls presenting with sexual precocity due to estrogen and, rarely, androgen secretion by the tumour. The tumours are usually unilateral and have a solid often predominantly cystic pattern in the more typical macrofollicular form of tumour. As with adult granulosa cell tumours juvenile granulosa cell tumours typically stain positive with inhibin and Calretinin.

Other rarer tumours within the subgroup include the often androgen-secreting tumours such as the Leydig cell tumour (hilus cell tumour) or the less specific diagnostic entity of steroid or lipoid cell tumour. These tumours together with the mixed tumour of Sertoli–Leydig cell tumour make up the bulk of the remaining entities within the sex cord stromal subgroup. The hilus cell tumour is invariably benign and is usually easily diagnosed with a typical presentation of virilization and distinctive biochemical profile which can identify a gonadal rather than an adrenal source of androgenic hormone. However, the Sertoli–Leydig cell tumour also typically occurs in younger patients and can be associated with hormonal production. Immunohistochemistry can be helpful with positive staining for α-inhibin and low-molecular-weight cytokeratin. Other stains, notably EMA, PLA, P&CEA, CA125 are usually negative. These negative findings are useful given that the differential diagnosis is often of either an endometrioid carcinoma or a carcinoid tumour although these are unusual diagnoses in a young patient population.

Other tumours within this group include the less specific diagnosis of steroid cell tumour and sex cord tumour with annular tubules (SCTAT). This latter entity is particularly rare but notable because of its association with Peutz–Jegher syndrome and a variety of other gastrointestinal anomalies. The term steroid cell tumour is usually resorted to where there is obvious evidence of hormone, usually androgenic, production often in young patients <40 years, and where there is less distinctive gross and histological patterns of differentiation they are more frequently reported as being malignant ranging from 25% to 43%, a feature that may simply reflect that they are more aggressive poorly differentiated tumours. It must also be recognized that it follows that sex cord stromal tumours may not be associated with hormone production and also lack any of the distinctive features of the recognized histological subtypes so that the final reluctant diagnosis of sex cord stromal tumour unclassified is a real entity.

surgery

In younger patients with apparently localized disease fertility-sparing surgery should be discussed, although recommended by some there is no indication that treatment or prognosis is affected by a full staging procedure. Sertoli–Leydig cell tumours are sometimes so small that it is hard to discern which ovary is affected. In these cases selective sampling by laparoscopy or Selinger technique of the left and right ovarian veins may indicate the tumour site. In the rare case of advanced disease the same standard approach as for EOC as described above is recommended. In selected cases second or subsequent surgery may be recommended to excise recurrent ‘isolated’ masses.

adjuvant therapy

Most cases are stage 1 and thus confined to the ovary; there is no firm evidence to support adjuvant therapies in this setting. Careful follow-up is recommended and long term as there is risk of relapse as late as 20 years. For higher risk cases of granulosa cell tumours, e.g. ruptured ovary or higher stage, adjuvant chemotherapy with EP or BEP (bleomycin, etoposide and cisplatin) is usually considered standard first line, but carboplatin and paclitaxel are under evaluation for second line and have shown activity. Hormonal therapies including tamoxifen, progestagens (including combined), LHRH analogues and aromatase inhibitors have all been investigated with varying levels of benefit reported. Some reports claim prolonged therapy is needed to see a response, sometimes in excess of 12 months. There is one recent case report of an HDAC inhibitor achieving a CR.

follow-up and prognosis

Many granulosa cell tumours are relatively indolent, slow-growing tumours but notoriously recur after many years, often up to 20 years after primary diagnosis. Long-term follow-up is therefore recommended. Serum tumour markers have a variable body of evidence for their use in follow-up, but estradiol, LH, FSH, inhibins (A, B and pro-AC) have all been used and are more useful in postmenopausal or castrated patients; whilst anti-Mullerian hormone (AMH) is an exciting potential new marker that may replace inhibin.

small cell and neuro-endocrine cancers

incidence

In addition to small cell cancers, this will briefly include carcinoid or neuro-endocrine cancers. They are rare and account for ~1% of ovarian cancers. Small cell cancers were only recognized as a separate entity in 1979. Three main variants of small cell carcinoma are seen: small cell carcinoma of hypercalcaemic type (SCCOHT), small cell carcinoma of pulmonary type (SCCOPT) and large cell variant of small cell carcinoma or non-small cell small cell carcinoma (NSCSCC). There are differences in age at presentation and clinical syndromes.

- Small cell carcinoma of ovary of pulmonary type (SCCOPT)
- Small cell carcinoma of ovary of hypercalcaemic type (SCCOHT)
- Non-small cell neuro-endocrine carcinoma (large cell variant) (NSCNEC)
- Classical primary carcinoid (well differentiated neuroendocrine cancer)
- Classical carcinoid metastatic from primary gastrointestinal site.

diagnosis

Rare as they may be, they are, except for carcinoids, often very aggressive with high mortality especially when diagnosed
Surgery
Standard surgical principles should apply with the aim of optimal debulking surgery leaving no residual disease. In younger women with an isolated ovarian lesion, conservative surgery may be offered and adjuvant treatment with chemotherapy followed on. Once again expert pathology opinion and review is essential.

Adjuvant treatments
There are no randomized trials but several small clinical reports and a series of 17 cases collected by the GCIG (Gynaecological Cancer InterGroup) and reported by Harrison and a review paper on all small cell cancers of the female genital tract by Crowder. Chemotherapy is usually similar to that for small cell lung cancer with platinum and etoposide as standard, carboplatin offers convenience of delivery. For relapsed disease ifosfamide-based regimes like VICE, or CAVE for poor PS patients may be considered. There are anecdotal reports of carboplatin and paclitaxel and the dose-dense weekly schedule offers potential promise in this highly aggressive cancer. The Harrison series paradoxically showed that pelvic radiation improved survival, and should be discussed.

Prognosis
There are few long-term survivors of small cell cancers and they are usually limited to stage I patients. Relapse is often seen early and carries a dismal prognosis but since they are often younger patients, second- or third-line therapies may be tried. Follow-up will be conventional with clinical and radiological examination.

Primary ovarian carcinoid or NETs are occasionally described, although more commonly seen are metastatic deposits. Primary ovarian carcinoids can have insular or trabecular pattern. Primary ovarian carcinoids are also interesting in that they can cause carcinoid syndrome without liver metastases. The ovarian vein drains directly into the vena cava and can lead to fibrosis of right heart valves leading to right heart failure and hepatomegaly. They are usually unexpected surgical findings and aggressive debulking surgery is advised, although tumours are often small and usually limited to the ovary. Standard work-up postoperatively for NETs is advised, this will include gut hormone analysis and radionuclide scintigraphy with Octreoscan.

germ cell tumours
incidence
These account for only ~5% of ovarian tumours but >75% of tumours in younger patients. Dermoid cysts (mature teratomas) are the commonest of ovarian tumours but are usually benign, dermoid cysts; they may account for ~20% of all ovarian tumours. They may have characteristic appearance on scanning with hair, teeth and cartilage. The management of these tumours is much more clearly refined and centres on fertility-preserving surgery and adjuvant chemotherapy. The following list shows a classification of germ cell tumours (GCTs):

- Dysgerminoma
- Endodermal sinus tumour
- Embryonal carcinoma
- Teratoma: immature
- Teratoma: mature
- Solid cystic: dermoid cyst (mature cystic teratoma) or dermoid cyst with malignant transformation
- Monodermal and highly specialized: struma ovarii carcinoind struma ovarii and carcinoid
- Mixed forms

diagnosis
They usually occur in younger women and present with symptoms of a pelvic mass; younger age should raise suspicions of a GCT. Tumour markers may not always be helpful but AFP, β-hCG and LDH should always be measured. Imaging is performed, especially MRI, when signs of fatty and calciferous content may be pathognomic for dermoid cysts. A solid mass on CT, MRI or ultrasound in a young patient should raise suspicion of dysgerminoma. Imaging otherwise is not specific, but it is essential for staging purposes. Genetic testing for Swire syndrome should be considered in younger women with dysgenetic gonads.

surgical management
Most are stage I and thus can be treated conservatively, fertility-sparing surgery is recommended. Radical surgery and also full staging should be avoided as it is usually unnecessary and inappropriate. The efficacy of salvage treatment is the main reason for abandoning full staging. In older postmenopausal women a standard approach is offered. Debunking surgery without compromising fertility is advised in more advanced cases as chemotherapy is effective in dealing with residual disease.

adjuvant therapies
About two-thirds of cases are stage I, so no adjuvant treatment is required for low-risk stage I cases but careful follow-up as per standard protocols. For more advanced cases, chemotherapy with BEP is advised. Most reviews recommend four cycles, although some recent data have suggested that a more conservative approach may be considered. Endodermal sinus
tumours have a more aggressive behaviour and adjuvant chemotherapy is normally recommended in all cases except stage IA where serial follow-up with AFP may be offered.

**follow-up**
Relapses most often occur within 12–18 months and most commonly in the peritoneal cavity or retroperitoneal lymph nodes. Tumour markers may give early warning of relapse, and imaging is useful in monitoring these patients. Hence in low-risk cases, this surveillance is likely to pick up the vast majority of cases that can be salvaged. Traditionally CT has been used but more recently with technological improvements, MR imaging has been used more often and avoids risks of excess radiation exposure in a usually young group of patients. Salvage chemotherapy is usually highly effective in chemonaive patients; however, unlike the situation in males, relapsed GCTs in pre-treated females are more difficult to treat and are usually incurable.

**struma ovari malignum**

**incidence and pathology**
Strumal carcinoids or malignant struma ovarii are of endodermal origin with evidence of thyroid or C-cell differentiation. They arise within teratomas and are very uncommon. Mature cystic teratomas are common accounting for up to 20% of ovarian tumours and ~15% may contain thyroid tissue. Struma ovarii is a variant that contains in excess of 50% thyroid tissue. They account for ~3% of ovarian teratomas. The incidence of malignant change is difficult to estimate and is certainly uncommon. It is said that the incidence of malignant change may be between 0.1% and 0.3%. Metastases are reported as being very rare, probably <0.1%. Rare metastatic cancers from the thyroid gland are also described and may cause diagnostic difficulties. Logani reported on a series of thyroid carcinomas with ovarian metastases so this must be excluded in all cases but is clearly a very rare clinical situation. A recent paper by Roth and Talerman has challenged some of the precepts and presents an alternative view of their behaviour. The incidence seems to peak postmenopaually with commonest ages of diagnosis being in the fifth and sixth decades of life. They are rarely diagnosed pre-operatively and are incidental findings usually. They are usually unilateral and more commonly arise in the left ovary.

**surgical management**
There is considerable debate in the literature not only about the primary surgical management but also about the need for any adjuvant investigations and treatment. Most series advise that if a strumal carcinoid is diagnosed unexpectedly in a postmenopausal woman or one who has completed her family, then a hysterectomy and bilateral salpingo-oophorectomy is advised. Conservative surgery may be considered in a younger woman with no extra-capsular spread and no associated mature cystic teratoma. However, some have advised that completion surgery should be carried out when the family is completed. In cases with obvious spread more aggressive surgery must be advised.

**postoperative management**
For malignant struma ovarii postoperative care should involve referral for discussion of total thyroidectomy and management as for differentiated thyroid carcinoma. Thyroidectomy is an essential pre-requisite to radio-iodine imaging and ablation otherwise any administered radio-iodine will be taken up preferentially by the thyroid and not any strumal tissue. This will involve whole body imaging with radio-iodine to search for any other functioning tissue and to destroy any residual thyroid tissue which in turn allows thyroglobulin to be used as a tumour marker. It is argued that this may be an excessive treatment but those series reporting this as a standard of care do report the best outcomes.

**follow-up and prognosis**
This is usually very good if treated optimally. Clinical examination and thyroid hormone replacement in doses that fully suppress the thyroid-stimulating hormone (TSH) is needed. Serial measurement of thyroglobulin (Tg) has replaced whole body radio-iodine scintigraphy. Thyroglobulin levels should be undetectable and any rising levels or the development of new thyroglobulin antibodies is a case for investigation of possible relapse. To date there is no reported value of PET/CT scanning. Follow-up is probably recommended as lifelong principally to monitor thyroid function and Tg.

**squamous cell carcinoma rising within dermoid cyst/teratoma**

**incidence**
Dermoid cysts are the commonest ovarian tumours but are nearly always benign. However, malignant transformation is rare and occurs in ~1%–2% of cases, typically in postmenopausal women. Squamous cell carcinoma (SCC) is the most common type of malignancy that arises and comprises >80% of cancers that are seen. They are often diagnosed late due to pressure symptoms or torsion, and usually occur in older women.

**surgery**
Standard surgical approaches are used to achieve pelvic clearance. Mean age of diagnosis is often nearly 20 years later than simple dermoids. Commonly the diagnosis is only made after adnexectomy or cystectomy for a presumed dermoid cyst. If the squamous cell carcinoma is confined to the ovary the prognosis is excellent, without needing more surgery than an adnexectomy. Conversely, if the tumour extends beyond the ovary and primary surgery has not eradicated the tumour even the short-term prognosis is dismal, and second surgery is therefore not advised. Individual discussions may indicate second surgery for highly selected cases.

**adjuvant therapies**
Given their rarity, there is no consensus on management. Chemotherapy and/or radiation have been advocated. In stage I patients without rupture, survival is excellent, not warranting adjuvant therapy. In more advanced cases, platinum-based
therapies are advised but are we treating the squamous component or the teratoma? For the former cisplatin and 5-fluorouracil-type regimes may be advocated, but alternatively BEP or even carboplatin and paclitaxel may be offered. Their rarity precludes a clinical trial but each centre should try and adopt a standard approach so some knowledge and experience may be gained. Through organizations such as the ESMO, ESGO and the GCIG, an international standard could be developed to allow greater understanding and sharing of knowledge. External beam pelvic radiotherapy is recommended in some units but again there is no proof of its benefit. It may be better reserved for isolated pelvic relapse.

**follow-up**

Once again standard patterns of follow-up are advocated, mainly relying on clinical and imaging examinations. Tumour markers are of little routine value. Follow-up to 5 years will be recommended.

**levels of evidence**

Given the rarity of most of these cancers, there are few randomized trials. Most of the supporting data comes from single centre series and small phase II studies. The authors have referred to guidelines where they are available.

**literature**