GUIDE

Gynaecological Oncology Network

Gynaecological cancer: A guide to clinical practice in NSW

NSW GOVERNMENT

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Working with Aboriginal people

The ACI is committed to improving the health of all patients across NSW, particularly those who have significantly higher rates of health problems and less access to appropriate health services. Data suggests there is increasing prevalence of overall deaths related from Cancers within the NSW Aboriginal Community including those suffering from gynaecological cancers.

Indigenous Australians diagnosed with cervical and uterine cancers had a lower chance of survival compared with their Non-Indigenous counterparts. However, there may be cultural sensitivities that make conversations around prevention and treatment of gynaecological cancers less likely to be recognised and discussed openly. This results in lower chance of cervical screening which is likely to have flow-on effects on cancer incidence and mortality in Indigenous women.

An Aboriginal Health Impact Statement was undertaken prior to commencement of this project and consultation has occurred with senior Aboriginal health workers, focus groups and representative organisations. We would like to thank the key stakeholders whose contributions have informed the recommendations arising from this project. These stakeholders, including those who work closely with Aboriginal people, will continue to be involved in the implementation of the recommendations.

It is important that the appropriate steps are taken to ensure that services are delivered in culturally safe and competent ways across the project lifespan. To achieve optimal health outcomes for Aboriginal women with gynaecological cancers, we will need to undertake a cultural audit to identify and address the barriers to access to care and ongoing management. The audit, along with the development of culturally competent and safe services, is described in detail in the *Chronic Care for Aboriginal People Model of Care*.

Glossary

AIS	Adenocarcinoma in situ
ANZGOG	Australia New Zealand Gynaecological Oncology Group
AUC	Area under the curve
BRCA mutation	A mutation in either of the BRCA1 and BRCA2 genes, which are tumour suppressor genes
CARA	Cancer Research in Australia
CIN	Cervical intraepithelial neoplasia
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTV	Clinical target volume
CXR	Chest x-ray
CR	Complete response
D&C	Dilatation and curettage
EMA-CO	Chemotherapy regimen of etoposide, methotrexate, actinomycin-D, vincristine and cyclophosphamide
EMA-EP	Chemotherapy regimen of etoposide and cisplatin with etoposide, methotrexate and dactinomycin
EMA-PE	Chemotherapy regimen of etoposide and cisplatin with etoposide, methotrexate, and dactinomycin
EUA	Examination under anesthesia
EUC	A blood test measuring electrolytes, urea and creatinine
FBC	Full blood count
FDG-PET	Fluorodeoxyglucose PET scan
FIGO	International Federation of Gynecology and Obstetrics
FNA	Fine needle aspiration
g-CSF	Granulocyte-colony stimulating factor
GOG	The Gynecological Oncology Group Foundation, Inc
GTN	Gestational trophoblastic neoplasia
GTV	Gross tumour volume
HDRB	High dose-rate brachytherapy
HPV	Human papillomavirus
HRD	Homologous recombination DNA repair deficiency
HSIL	High-grade squamous intraepithelial lesion
IHC	Immunohistochemistry
IMRT	Intensity modulated radiotherapy
IUCD	Intrauterine contraceptive device
IVP	Intravenous pyelogram
LDH	Lactate dehydrogenase
LFT	Liver function test
LLL	Lower leg lymphoedema
LMT	Low malignant potential
LSIL	Low-grade squamous intraepithelial lesion
LVSI	Lymphovascular space invasion
MDT	Multidisciplinary team
MLH1	A gene that provides instructions for making protein
MMMT	Malignant mixed Müllerian tumour
MMR	Mismatch repair gene
MRI	Magnetic resonance imaging
NACT	Neo-adjuvant chemotherapy
NHMRC	National Health and Medical Research Council
NOS	Undifferentiated sarcoma
OCP	Oral contraceptive pill
OS	Overall survival
PALND	Para-aortic lymph node dissection
PARP	Poly ADP ribose polymerase enzyme
PD	Progressive disease
PET	Positron emission tomography
PLD	Pegylated liposomal doxorubicin
PMS2	A gene that encodes for DNA repair proteins involved in mismatch repair
PR	Partial response
PLND	Pelvic lymph node dissection
RCPA	The Royal College of Pathologists of Australasia
RT	Radiation therapy or radiotherapy
SCC	Squamous cell carcinoma
SD	Stable disease
STIC	Serous tubal intraepithelial carcinoma
VIN	Vulvar intraepithelial neoplasia
VMAT	Volumetric modulated arc therapy
WART	Whole abdominal radiotherapy
WHO	World Health Organization

Contents

Introduction

This document is an update of the *Gynaecological Oncology Clinical Practice Guidelines*, which were originally published in 2004. These consensus-based guidelines were developed by a working group involving gynaecological oncologists, radiation oncologists, medical oncologists, gynaecological pathologists, palliative medicine consultants, and nurse oncologists from New South Wales, Queensland, Tasmania and New Zealand, led by Professor Neville Hacker at the Royal Hospital for Women.

The guidelines were widely used as a resource in the initial planning for management of women gynaecological cancer, with treatment decisions reviewed by the Gynaecologic Cancer Multidisciplinary Team. This document is intended as a guide for clinicians to use prior to referral for multidisciplinary management. It is intended that the document be updated when major changes in management occur.

Cervical cancer

Cervical cancer is almost always caused by high risk human papillomavirus (HPV). Vaccination and HPV-based cervical screening programs are likely to greatly reduce its incidence.

Staging of cervical cancer

As most cases occur in the developing world, the staging system has historically been based on clinical examination and biopsy (FIGO Staging). The staging system has recently been updated to include imaging and pathological findings where these are available.(1)

The key histological features are:

- histological cell type
- tumour dimension (microscopic and macroscopic)
- depth of invasion
- lymphovascular space invasion
- lymph node metastases where surgically staged.

Further information

For information about cervical cancer anatomical pathology reporting, histologic type and grading, see Gynaecological pathology.

Table 1. Carcinoma of the cervix uteri

Stage	Description	
Stage I	**The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded).**	
	Stage IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5mm[a]
	Stage IA1	Measured stromal invasion of <3.0mm in depth
	Stage IA2	Measured stromal invasion of >3.0mm and <5.0mm in depth
	Stage IB	Invasive carcinoma with measured deepest invasion >5mm (greater than Stage IA), lesion limited to the cervix uteri[b].
	Stage IB1	Invasive carcinoma >5mm depth of stromal invasion, and <2cm in greatest dimension.
	Stage IB2	Invasive carcinoma >2cm and <4cm in greatest dimension.
	Stage IB3	Invasive carcinoma >4cm in gretest dimension
Stage II	**The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall.**	
	Stage IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement.
	Stage IIA1	Invasive carcinoma <4.0cm in greatest dimension.
	Stage IIA2	Invasive carcinoma >4cm in greatest dimension.
	Stage IIB	With parametrial involvement but not up to the pelvic wall.

Stage	Description	
Stage III	**The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes[c]**	
	Stage IIIA	The carcinoma involves lower third of the vagina, with no extension to the pelvic wall.
	Stage IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause).
	Stage IIIC	Involvement of pelvic and/or para-aortic nodes, irrespective of tumour size and extent (with r and p notations)[c]
	Stage IIIC1	Pelvic lymph node metastasis only
	Stage IIIC2	Para-aortic lymph node metastasis
Stage IV	**The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum.** (A bullous oedema, as such, does not permit a case to be allotted to Stage IV).	
	Stage IVA	Spread to adjacent organs.
	Stage IVB	Spread to distant organs.

Source: (1)

Note: When in doubt, the lower staging should be assigned.

a – Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumor size and extent, in all stages.

b – The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.

c – Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. Example: If imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r, and if confirmed by pathologic findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented.

The following examinations are permitted for staging work-up:

- rectal/pelvic examination – the size of the cervix is best determined by rectal exam and is also necessary to determine parametrial extension
- colposcopy
- cystoscopy, proctoscopy/sigmoidoscopy, intravenous pyelogram (IVP) (optional for ≥ Stage IB2 lesions) – bladder and/or rectal involvement should be confirmed histologically
- x-ray examination of lungs (and skeleton if symptomatic)
- cervical biopsy (or diagnostic cone biopsy if definitive diagnosis cannot be made on cervical biopsy).

Imaging modalities such as CT, MRI or PET scans are commonly utilised and are of value for planning treatment. They may also be useful in identifying macroscopic or microscopic nodal disease that is more extensive than anticipated clinically. MRI provides the best imaging of the primary tumour and extent of soft tissue disease, while PET/CT is recommended for assessment of nodal involvement and distant metastases.(2)

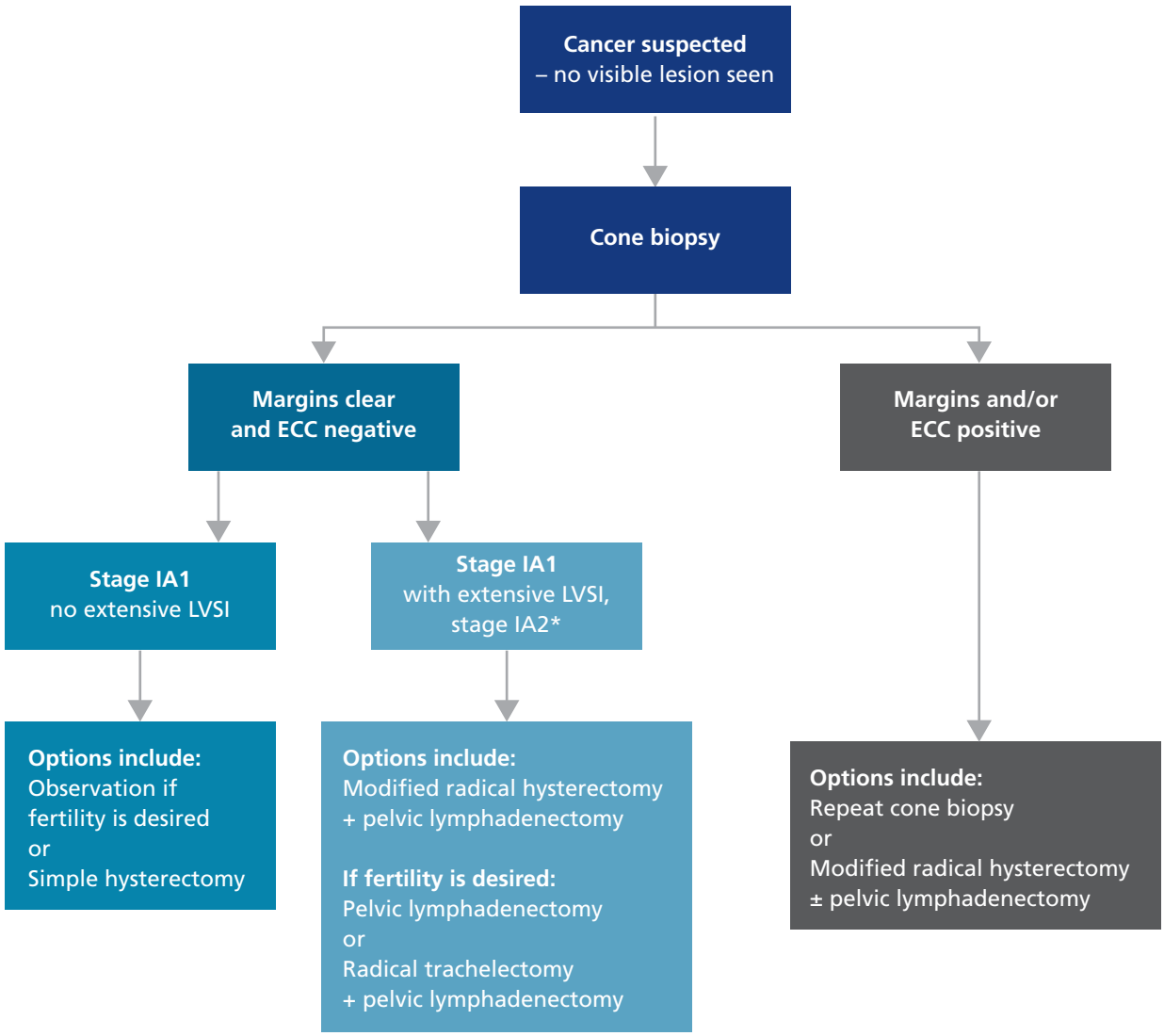
Non-randomised studies of surgical staging have failed to demonstrate a survival benefit over clinical staging. Patients are likely to experience increased morbidity and mortality, particularly with trans-peritoneal dissection of the para-aortic lymph nodes. Some series have suggested a benefit from laparoscopic surgical staging for patients with stage IB2 – stage III disease, but PET scanning is the preferred approach.(3–5)

Stage IA – Microscopically identified disease

The following treatment recommendations (Figure 1) apply to squamous cell carcinoma, adenocarcinoma and adenosquamous lesions. Other histologic types require individualised treatment.

Radical vaginal trachelectomy and laparoscopic pelvic lymphadenectomy may be an option for squamous cell cancers of <2cm diameter where preservation of fertility is desired. Several series have reported recurrence rates comparable to radical hysterectomy, and encouraging live-born pregnancy rates.(6–9) Radical abdominal trachelectomy with pelvic lymphadenectomy may also be an option. Appropriate cases should be referred to centres where sufficient experience and volume exists.

Figure 1. Management of early invasive cervical cancer



*Note: Radical trachelectomy with pelvic lymphadenectomy is an option for stage 1B1 tumours (<2cm)

Stage IB and selected Stage IIA disease

The following treatment recommendations (Figure 2) apply to squamous cell carcinoma, adenocarcinoma and adenosquamous lesions. Small cell or neuroendocrine tumours, melanomas and adenoid cystic tumours represent distinct histologic categories requiring individualised treatment.

Surgery and radiotherapy have similar efficacy in early stage cervical tumours(10) but with different side-effect profiles.(11)

The use of PET scan/MRI to determine parametrial and/or nodal involvement pre-operatively can be used to avoid treatment with both radical surgery and radical radiotherapy.

Results from five randomised phase III trials(12) have shown an overall survival advantage with the addition of cisplatin-based chemotherapy concurrently with radiotherapy, demonstrating a reduction in the risk of death of 30–50%.(12) Concurrent cisplatin-based chemotherapy should therefore be incorporated with planned radiotherapy.

High-risk node-negative disease

Approximately 15% of patients with negative nodes will develop recurrent disease, with approximately 75% of these recurrences occurring in the pelvis.(13) The Gynecologic Oncology Group (GOG) scoring system (Table 2) is an attempt to quantify the clinico-pathologic risk of recurrence following radical hysterectomy.

Risk factors for disease recurrence include:

- outer-third stromal invasion
- capillary lymphatic space invasion
- large clinical tumour diameter.

Adjuvant whole pelvic radiotherapy following radical surgery has been shown to reduce the number of recurrences at the cost of 7% grade 3–4 toxicity versus 2.2% in the untreated group.(12)

Small field pelvic radiotherapy has been used to improve survival with reduced morbidity in node negative patients in two small studies.(14) Whilst used in some centres, others continue to use whole pelvic radiotherapy.

Extra-uterine disease (positive nodes, parametria or surgical margins)

Combined adjuvant chemotherapy and pelvic radiotherapy following primary surgery for extra-uterine disease improves both relapse-free and overall survival compared to radiation alone.(12)

The role of extended-field (para-aortic) radiotherapy is controversial. The RTOG (reference) study showed a survival advantage with pelvic radiotherapy and concurrent cisplatin compared to extended-field radiotherapy alone.(15) Extended-field radiation with concurrent cisplatin-based chemotherapy may require dose-reduction of chemotherapy to allow completion of treatment.

Table 2. Relative-risk of recurrence after radical hysterectomy for stage I cervical cancer

	Variable	Relative-risk
Depth of tumour penetration (mm)	**3***	**1.0**
Superficial	4	3.0
	5	7.2
	6	14
	7	21
	8	26
	10	31
Middle	5	20
	6	22
	7	23
	8	25
	10	28
	12	32
	14	36
Deep	7	28
	8	30
	10	34
	12	37
	14	41
	16	45
	18	49
	20	54
Clinical tumour size (cm)	**Occult**	**1.0**
	1	1.6
	2	1.9
	3	2.4
	4	2.9
	6	4.4
	8	6.6
Capillary /lymphatic space invasion	**No**	**1.0**
	Yes	1.7

Source: Delgado 1990 (16)

GOG score calculation

The GOG score is calculated by multiplying
the relative-risk for depth x tumour size x capillary/lymphatic space involvement.

For example, a 7mm superficial tumour, measuring 2cm, with lymphovascular space invasion (LVSI) would be 68.

21 x 1.9 x 1.7 = 67.8

Stage IB2 disease

Bulky stage IB tumours (>4 cm) can be treated with:

- primary chemoradiotherapy
- primary surgery as for stage IB1
- neo-adjuvant chemoradiotherapy followed by hysterectomy.

The primary treatment modality of Stage IB2 disease should determined based on patient factors and treatment morbidity profiles. Primary chemoradiation is the most common therapy.

Primary surgery for stage IB2 is associated with an increased risk of requiring adjuvant radiotherapy.(15)

Neo-adjuvant chemotherapy followed by radical surgery (hysterectomy) is used in rare circumstances. It is a possible alternative to conventional chemoradiotherapy for locally advanced disease.(17–19) There is a paucity of data comparing neoadjuvant chemotherapy followed by radical surgery with chemoradiotherapy alone.

Stage II – Stage IVA

Treatment will depend on whether patients have locally advanced disease or bulky nodes on pre-operative CT scan (Figure 2).

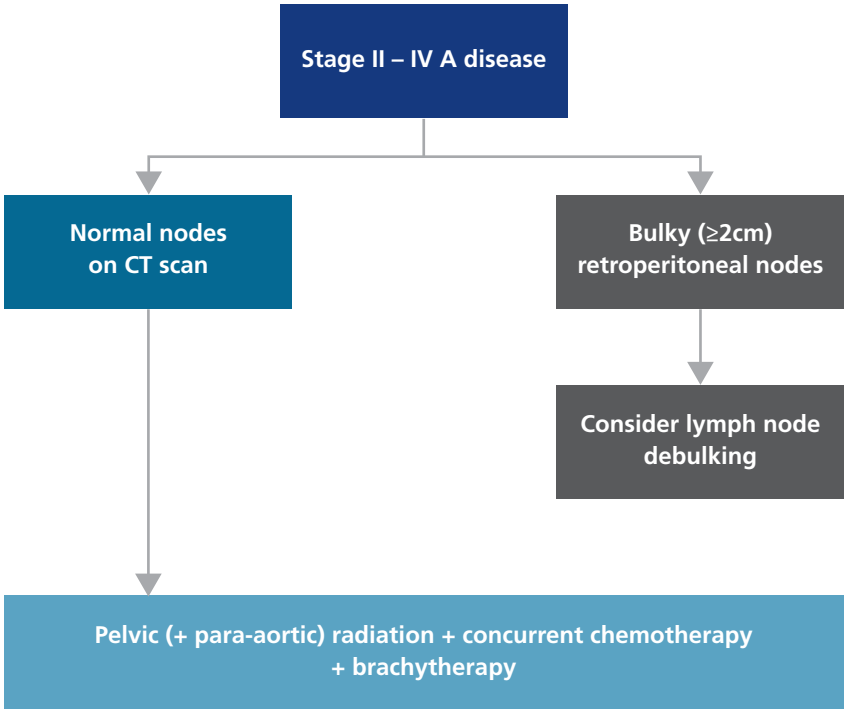
Locally advanced disease

Cisplatin-based chemotherapy given concurrently with radiotherapy increases overall survival.(20)

Metastatic disease

For patients with metastatic disease present on pre-treatment imaging, an investigational approach is to perform a pre-radiotherapy extraperitoneal surgical debulking of all macroscopic lymph nodes followed by extended-field radiotherapy and brachytherapy.

Figure 2. Management of advanced stage cervical cancer



Source: International Federation of Gynecology and Obstetrics(21)

Advanced or recurrent disease

Treatment of advanced or recurrent disease depends on:

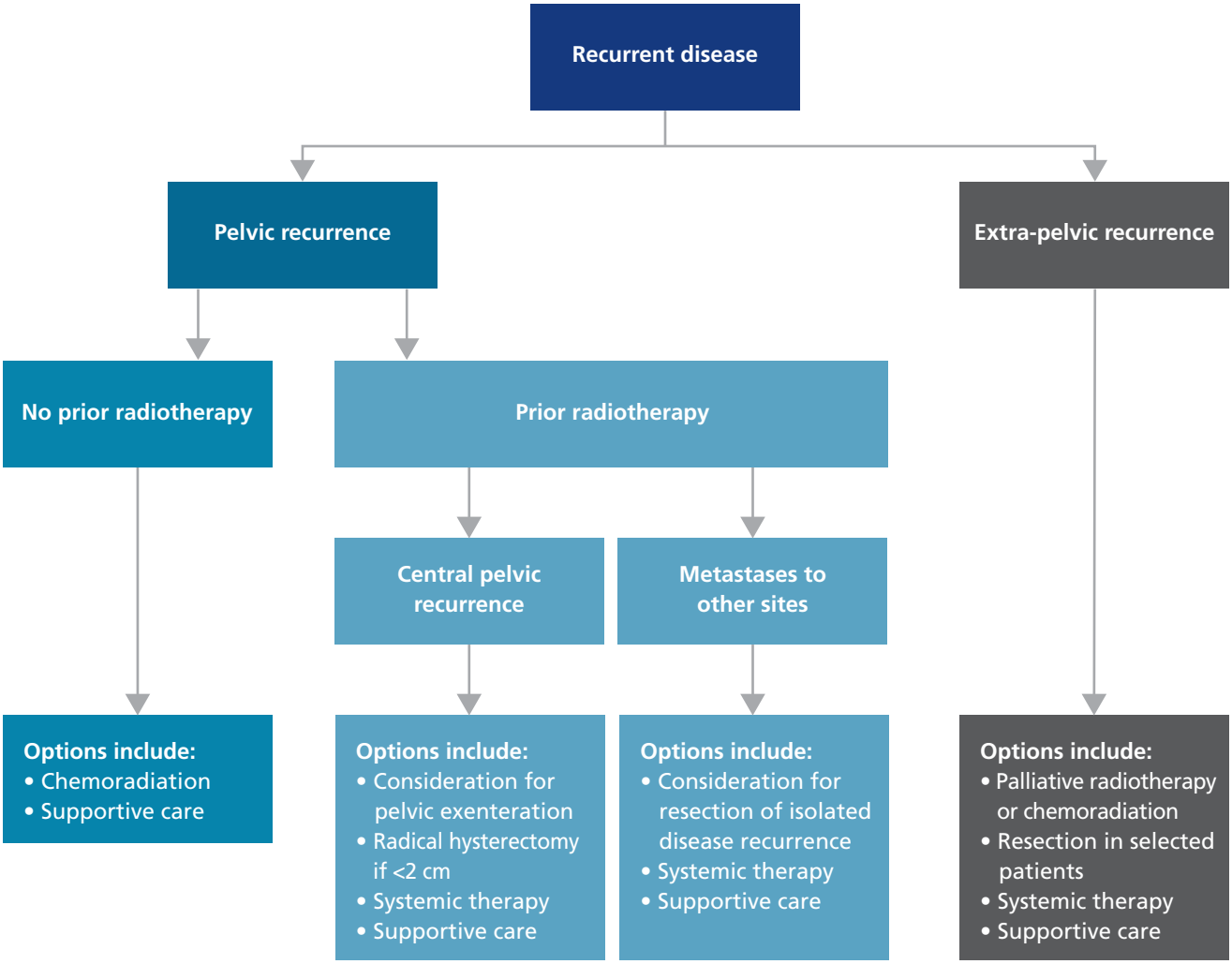
- previous treatment given
- the site or extent of recurrence
- the disease-free interval
- patient performance status at presentation.

Treatment should be individualised with optimised psychological and symptomatic care. Multidisciplinary team (MDT) review is recommended in planning treatment with curative or palliative intent. Participation in clinical trials should be an option.

Radiotherapy in combination with chemotherapy may cure 40-50% of patients with recurrence in the pelvis following radical surgery.(22)

Platinum-based combination chemotherapy is associated with higher response rates and longer progression-free survival than single-agent cisplatin therapy, but with no difference in overall survival (OS).(22) Bevacizumab results in improved OS (median 17 months vs. 13.3 months) and improved response rate (48% vs. 32%) at the cost of extra toxicity.(22)

Figure 3. Management of recurrent cervical cancer



Small cell carcinoma (neuroendocrine)

The literature suggests that the poor survival and outcome for women with small cell carcinoma of the cervix is consistent with the biology of small cell carcinomas arising in other sites.(23)

Patients should have:

- histologic diagnosis of small cell carcinoma of the cervix; or
- a mixed carcinoma (e.g. small cell carcinoma in addition to squamous cell carcinoma or adenocarcinoma elements) providing the small cell elements comprise a significant proportion of the tumour; and
- adequate haematological, liver and renal function and performance status <2.

Prior to treatment, the following investigations should be performed:

- FBC, EUC, LFTs, and LDH
- CT scan of chest, abdomen and pelvis, and brain.

In the absence of randomised prospective trials or established guidelines, the following treatment protocols are suggested (Tables 3 and 4).

Table 3. Treatment schema for patients with small cell cervical cancer

Stage of disease	Treatment schema
Early stage disease (stage IB or stage IIA)	1. surgical resection (e.g. radical hysterectomy and pelvic lymphadenectomy 2. three cycles chemotherapy 3. pelvic radiotherapy 4. further three cycles chemotherapy
Locally advanced disease	1. three cycles chemotherapy 2. pelvic radiotherapy + brachytherapy 3. further three cycles chemotherapy
Metastatic/recurrent disease	1. two cycles chemotherapy, then assess response 2. responders continue to maximum of six cycles

Table 4. Chemotherapy regime for patients with small cell carcinoma of the cervix

Day of cycle	Drug	Dose and route	Cycle frequency
1	Carboplatin	AUC 5	q3weekly
	+	+	
1–3	Etoposide	100 mg/m2	

Special circumstances

Inadvertent hysterectomy

Treatment options for patients discovered to have squamous cell carcinoma after simple hysterectomy include:(24)

- full pelvic radiotherapy
- radical surgery consisting of parametrectomy, upper vaginectomy and pelvic lymphadenectomy.

If there is gross lymphadenopathy (≥2 cm) demonstrated on radiological examination, an extraperitoneal lymphadenectomy should be performed followed by radiotherapy.

Re-operation should not be performed if there is evidence of metastatic disease, or an indication for post-operative radiotherapy on the basis of the hysterectomy specimen.

Cancer arising in the cervical stump

Radiotherapy for patients with cancer of the cervical stump is effective, yielding results comparable to those seen in patients with an intact uterus at the cost of higher complication rates than for patients with an intact uterus.

Radical trachelectomy and pelvic lymphadenectomy may be an alternative treatment option for stage IB tumours.

Cervical cancer in pregnancy

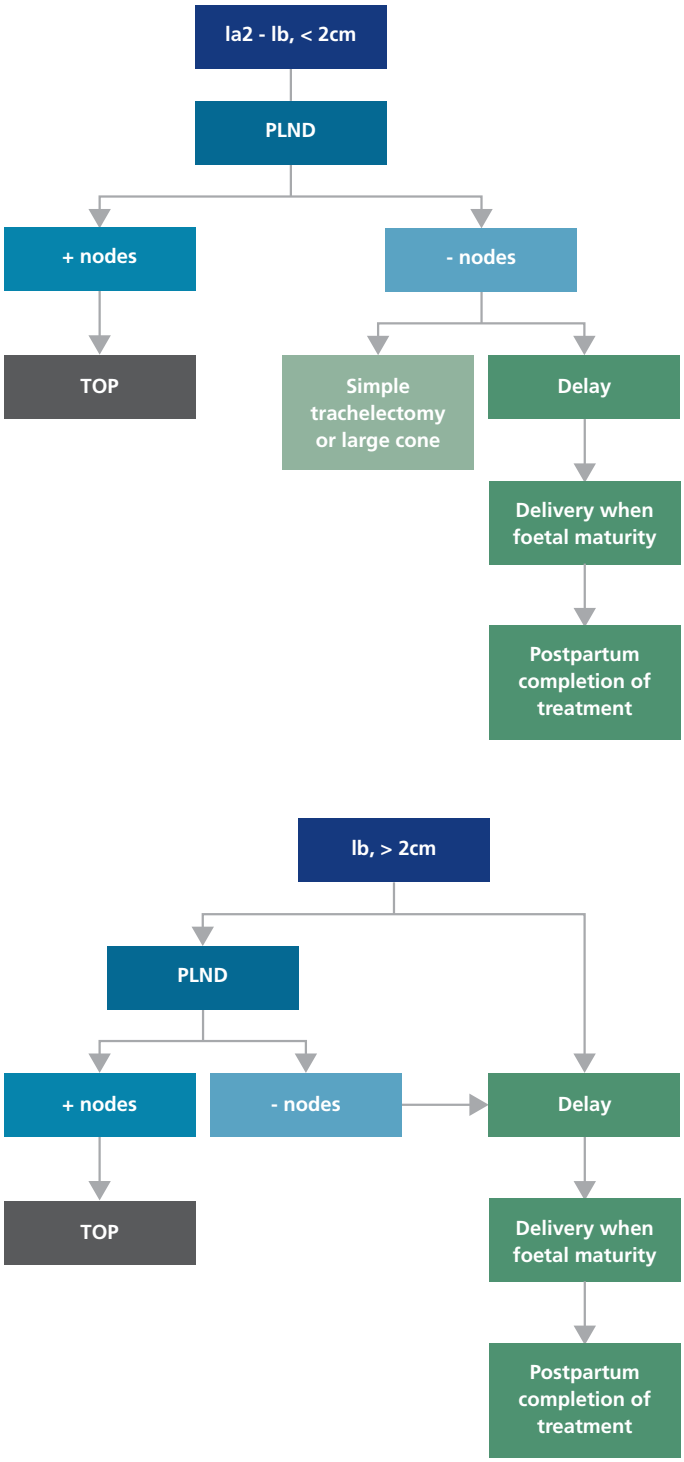
Cervical cancer in pregnancy requires attention to the health of both the woman and the foetus. There must be consideration for ethical concerns, cultural and religious issues, and the patient's desire whether or not to continue with the pregnancy (after informed consent). Counselling requires an interdisciplinary approach.(25)

During pregnancy, no therapy is warranted for pre-invasive lesions. However, expert colposcopy is recommended to exclude invasive cancer.

Treatment of invasive cancer during pregnancy depends on the stage of disease and gestational age at diagnosis:

- When cervical cancer is diagnosed before 22–25 weeks, offer immediate treatment appropriate to the stage of disease (see Figure 4). Delay treatment only if the cancer is detected in the third trimester.
- For patients with stage IA and early stage IB disease, deliberate delay may be a reasonable option to allow improved foetal outcome.
- Neoadjuvant chemotherapy may be considered to allow further development of the foetus prior to surgery.(26)
- Para-aortic lymph node dissection (PALND) is only recommended for tumours measuring 4cm and above. Pelvic lymph node dissection (PLND); PALND, para-aortic lymph node dissection; neoadjuvant chemotherapy (NACT) or termination of pregnancy (TOP) are options for these women.(26)

Figure 4. Treatment strategy for cervical cancer diagnosed before 22–25 weeks of pregnancy



Radiotherapy

Radiotherapy maybe delivered as adjvant treatment after surgery or as primary treatment. The treatment protocol is based on the clinical, surgical, pathological and imaging findings.

Standard-field (whole pelvis) external beam radiotherapy

45 Gy – 54 Gy in 1.8 Gy – 2.0 Gy fractions, delivered by four-field technique.

Extended-field (para-aortic) external beam radiotherapy

45 Gy in 1.6 Gy – 1.8 Gy fractions, delivered by four-field technique, with extension to L1 at a minimum.

Brachytherapy

Brachytherapy should be given within two weeks of external beam radiotherapy. Fraction sizes greater than 7.5Gy should be avoided.

If brachytherapy is not feasible, further 10Gy of external beam radiotherapy maybe given with reduced fields.

Uterine cancer

Uterine cancer is the most common gynaecological malignancy in the developed world. It may present with abnormal vaginal bleeding or less commonly, with symptoms caused by uterine enlargement.(27)

Histological assessment of endometrial curettings or biopsy prior to definitive surgery is mandatory.

The key histological features are:

- histological cell type
- depth of invasion (expressed as mm invasion/mm myometrial thickness)
- cervical stromal involvement
- lymphovascular space invasion
- lymph node metastases where surgically staged.

All cases of proven or suspected malignancy should be referred to a gynaecological oncologist prior to surgery. A summary of the optimal care pathway for endometrial cancer is available at http://www.cancer.org.au/ocp.

Further information

For information about uterine cancer anatomical pathology reporting, histologic type and grading, see *Gynaecological pathology*.

Histological types of uterine cancer

Endometrioid carcinoma

This accounts for 80% of cases of uterine cancer.(28) The risk factors are related to excessive unopposed oestrogen due to:

- obesity (often with diabetes and hypertension)
- hormone replacement therapy
- anovulatory menstrual cycles
- polycystic ovary syndrome
- oestrogen secreting tumours
- tamoxifen usage of >1–2 years.(29)

Premalignant conditions may present with abnormal vaginal bleeding. Endometrial hyperplasia, an overgrowth of the endometrium, is a result of oestrogen stimulation. Simple or complex hyperplasia without atypia can be treated with progesterone therapy. Complex atypical hyperplasia may contain areas of occult endometrial carcinoma and should be treated by hysterectomy in most cases.

In women with prolonged symptoms and complex endometrial hyperplasia on histology, occult carcinoma should be suspected and referral to a gynaecological oncologist considered.

Endometrial intraepithelial neoplasia is a clonal aberration in endometrial glandular epithelial growth and has a high positive predictive value for the development of endometrial carcinoma. Confirmed cases should be treated by hysterectomy.(30, 31)

Endometrioid carcinoma contains glandular elements that resemble those of non-neoplastic endometrium. It may demonstrate benign focal or morular squamous differentiation (up to 30%) and is occasionally accompanied by a malignant squamous cell component. It may display focal mucinous differentiation (about 30%), may be predominantly or exclusively mucinous (10%) and uncommonly may arise within endometriosis, i.e. outside the uterus.(30)

Serous and clear cell carcinoma

Serous cancers differ from endometrioid carcinomas in that they:

- resemble serous ovarian tumours histologically
- are almost always of high grade
- are not associated with endometrial hyperplasia or hyperoestrogenism
- commonly exhibit lymphovascular space invasion (LVSI) and distant metastatic spread in apparent early stage disease.(32)

Clear cell carcinomas may metastasise distantly, even in early stage disease or arise within endometriosis.

Carcinosarcoma

Previously called malignant mixed Müllerian tumour (MMMT), carcinosarcomas are thought to:

- be a form of metaplastic carcinoma, rather than a mixture of sarcoma and carcinoma
- share epidemiological risk factors with endometrioid adenocarcinomas (obesity, hyperoestrogenism)
- exhibit patterns of spread similar to those of carcinomas rather than those of pure sarcomas.(33)

Leiomyosarcoma

These cancers are derived from the smooth muscle of the myometrium or cervical stroma. Malignant tumours generally exhibit at least two of following histological features:

- mitotic count of >10/10 high power fields
- coagulative tissue necrosis
- at least moderate and diffuse nuclear atypia.

Tumours with features intermediate between benign leiomyomas (fibroids) and unequivocal leiomyosarcomas have an uncertain but generally favourable clinical course.(34)

Endometrial stromal sarcoma

These resemble the stroma of the endometrium and:

- may exhibit a propensity to produce tongues of tumour spreading within lymphatic vessels
- are divided into low-grade endometrial stromal sarcomas or high grade endometrial stromal sarcomas
- typically have strong staining with the CD10 immunohistochemistry marker.

High grade endometrial stromal sarcomas are a small subset of mesenchymal tumours harbouring a distinctive YWHAE-FAM22 genetic fusion.

Anaplastic lesions are designated as 'undifferentiated uterine sarcoma' as they are not recognisable as having endometrial stromal differentiation.(35)

Familial uterine cancer

All patients should have a comprehensive family history recorded in order to identify families with a genetic predisposition to cancer.

Lynch syndrome (previously known as hereditary non-polyposis colon cancer or HNPCC) is an autosomal dominant inherited cancer susceptibility syndrome characterised by a family history of bowel cancer and other cancers, including cancer of the uterus.(36) Lynch syndrome is due to an inherited defect in the mismatch repair (MMR) genes and the tumours have loss of the relevant MMR protein(s) when stained using immunohistochemistry (IHC).

Women who have Lynch syndrome have 24–34% lifetime risk of uterine cancer and up to a 15% lifetime risk of ovarian cancer. Individuals with Lynch syndrome have a 10–46% risk of colon cancer (the risk varies according to the gene involved). They also have an increased risk of pancreatic, upper gastrointestinal and renal pelvis/ureter cancers. (37) Features such as a family history of bowel/uterine cancer, early onset (<50 years old) of cancer, or thin women with uterine cancer should arouse suspicion of Lynch syndrome.

The tumours from all women <60 with invasive endometrial cancer should undergo mismatch repair protein IHC regardless of their family history.(38)

Loss of MLH1/PMS2 is common (up to 30% of cancers) and may be due to somatic mutation rather than germline MMR mutation (Lynch syndrome).(39) Where Lynch syndrome is suspected in tumours with loss of MLH1/PMS2, methylation studies of the tumour can identify cancers due to somatic mutation as methylation is absent in Lynch related tumours.

Referral to a family cancer clinic is recommended in most cases where there is loss of mismatch repair protein staining on IHC (particularly loss of both MSH2/MSH6, MSH6 alone or PMS2 alone) or where there is suspicion of Lynch syndrome. Genetic counselling and genetic testing may be appropriate. Since loss of MLH1/PMS2 is common (up to 30% of cancers), if the patient is over 50 and has no relevant family history, referral may not be needed. In younger women or those with a family history, methylation studies may be necessary to identify those few women with likely Lynch syndrome.(40) (See also *Familial Aspects of Gynaecological Cancers*).

Principles of management

If malignancy is proven or suspected (e.g. longstanding vaginal bleeding and complex atypical endometrial hyperplasia on curettings), consult a gynaecological oncologist.

Uterine cancer is treated primarily with surgery. Treatment should be based on:

- endometrial sampling (office endometrial biopsy or curettage)
- preoperative imaging, including a chest xray and CT scan of the abdomen and pelvis
- histological confirmation by an expert gynaecological pathologist with review by a multidisciplinary team (MDT)
- the risk of vaginal vault, pelvic, para-aortic or distant relapse.

Initial treatment

Primary surgery

Primary surgery for uterine cancer is tailored to the histology, distribution of disease and patient characteristics. It should include a collection of peritoneal washings, frozen section of enlarged pelvic or para-aortic nodes and hysterectomy (with bilateral salpingo-oophorectomy unless premenopausal with leiomyosarcoma or endometrial stromal sarcoma).

Pelvic +/– para-aortic lymphadenectomy are indicated, where feasible, in women with moderate or high risk disease.

Laparoscopic hysterectomy, bilateral salpingo-oophorectomy and lymphadenectomy were shown to be equivalent in oncologic safety (with reduced risk of short-term adverse effects) compared with open surgery in two randomised controlled trials.(41–43)

An alternative to complete lymphadenectomy is sentinel node biopsy using intracervical indocyanine green dye combined with near-infrared laparoscopy. This is an emerging technique which may reduce the morbidity of lymph node dissection whilst retaining the prognostic information gained with complete lymphadenectomy.(44, 45)

Primary radiotherapy

Primary radiotherapy is reserved for:

- women who are unfit for surgery due to medical comorbidities
- women with locally advanced disease who are not suitable for primary surgery.

Radiotherapy usually involves both external beam radiation and vaginal brachytherapy, delivered as fractionated treatment.(46)

Endocrine therapy

Uterine conserving management with high dose progesterone (oral and/or progesterone releasing IUD) may be offered to carefully selected patients with:

- a desire to retain fertility
- grade 1 endometrioid carcinoma with positive PR receptor expression on immunohistochemistry of curettings
- only superficial myometrial invasion on MRI imaging.

These patients require close surveillance with six-monthly curettage and replacement of the progesterone releasing IUD. Approximately 60-70% will revert to normal endometrium in 6-12 months.(190) Assisted reproduction techniques should be employed when the endometrium has normalised.

Uterine cancers are surgically staged according to International Federation of Gynecology and Obstetrics (FIGO).

Table 3. Uterine cancer stage and survival rate

Stage	Extent of disease	Five-year survivial by stage
Stage I		
	IA – no or invasion to less than half of the myometrium	88%
	IB – invasion to greater than half the myometrium	75%
Stage II		
	II – cervical stromal invasion	69%
Stage III		
	IIIA – tumour invades surface of uterus and/or ovaries, and/or positive peritoneal washings	58%
	IIIB – vaginal and/or parametrial involvement	50%
	IIIC – metastases to pelvic and/or para-aortic lymph nodes	47%
	IIIC1 – pelvic lymph node involvement	47%
	IIIC2 – paraaortic lymph node involvement	47%
Stage IV		
	IVA – tumour invades bladder and/or bowel mucosa	17%
	IVB – distant metastases including intra-abdominal and/or inguinal lymph nodes	17%

Source: American Cancer Society(47)

Adjuvant treatment

Adjuvant treatment is recommended on the basis of the estimated risk of recurrence.

Endometrioid carcinoma

Adjuvant radiotherapy

Adjuvant radiotherapy is offered according to the pathology of the tumour and the extent of surgical staging performed.

Stage I

The risk factors for recurrence are:

- grade 3 tumours
- outer half myometrial invasion (Stage IB)
- LVSI
- age >60 years.

Adjuvant pelvic radiotherapy has traditionally been considered for women with ≥2 risk factors.(48) A meta-analysis of five trials showed that adjuvant external beam radiotherapy should not be used in low or intermediate risk cancer but was associated with a small survival advantage for patients with stage IB grade 3 disease.(49)

Two randomised trials of adjuvant radiotherapy used pelvic external beam radiotherapy without vaginal brachytherapy and approximately 75% of recurrences in the observational arm occurred in the vagina.(48, 50) The PORTEC-2 trial showed that vaginal brachytherapy is equivalent to external beam radiotherapy in terms of survival.(51) It is reasonable to treat properly staged medium-high risk Stage I patients with vaginal brachytherapy alone. However patients who have not been surgically staged and have apparent Stage IB, Grade 3 disease or higher should be considered for external beam radiotherapy due to the 28% risk of lymph node metastases.(52)

Conversely, a number of studies have demonstrated equivalent survival outcomes with observation alone in intermediate risk patients (PORTEC–1, DEMCA) with improved quality of life scores compared to external beam radiotherapy. In these patients:

- vaginal brachytherapy alone reduced the risk of local recurrence, although with a slightly higher risk of pelvic nodal recurrence(51)
- pelvic radiotherapy reduced the risk of local recurrence by 72% with an absolute risk reduction of 6, but did not significantly improve disease free survival (DFS) or overall survival (OS)(53).

Stage II

- Adjuvant vaginal brachytherapy alone is suggested for node negative patients, although small field pelvic RT is an option.
- Pelvic radiotherapy is suggested for patients with unknown lymph node status.

Stage III

Adjuvant chemotherapy can be considered for stage 3 endometrial carcinoma of all types based on GOG–122.(54)

Whether additional radiotherapy is beneficial is currently the subject of randomised trials (e.g. GOG–258(55)). Treatment decisions need to balance toxicity and potential benefit.

Adjuvant chemotherapy

Adjuvant chemotherapy has been increasingly considered in recent years for serous, clear cell and high risk endometrioid cancers.(54, 56, 57)

Two studies have prompted some authorities to conclude that adjuvant chemotherapy should be considered in selected patients.(54, 58) In addition, Cochrane reviews have confirmed the superiority of adjuvant chemotherapy over adjuvant radiotherapy in advanced endometrial cancer.(59) For early stage high risk cancer, there is evidence of superiority of chemotherapy alone vs. radiation alone and this may be considered an option in high risk cases.(60)

The demonstrated toxicity of chemotherapy and design limitations of these studies should be taken into account when considering adjuvant chemotherapy (which should be evaluated by a MDT).

Node positive patients may be considered for concurrent chemoradiation followed by four cycles of carboplatin and paclitaxel (PORTEC–3 Protocol). The PORTEC–3 trial showed increased disease free survival but no increase in overall survival in these patients.(61)

Stage IV

The options for these patients include:

- hormonal treatment:
  - Provera 100–200mg bd
  - Tamoxifen 20mg daily
- palliative pelvic and/or intracavitary (vaginal) radiotherapy
- palliative chemotherapy (generally reserved for distant symptomatic disease (e.g. lung metastases))
- cytoreductive surgery.

Cytoreductive surgery may be considered in selected cases where optimal cytoreduction (to <1cm) is likely to be achievable, as this is associated with improved survival based on retrospective studies.(62, 63) In these cases consideration needs to be given to the potential for significant risk of morbidity or mortality given the limited evidence of survival benefit.

Serous and clear cell carcinoma

Limited data show:

- a higher recurrence in stage IB than earlier stage disease(32)
- 50% of recurrences have an extra-pelvic component(64)
- the role of radiotherapy is not clear with a high rate of in-field and out-of-field failure(65)
- probable reduced vaginal vault recurrence with vaginal brachytherapy(66)
- a trend to reduced recurrence with systemic chemotherapy(54).

It is recommended that:

- adjuvant chemotherapy should be considered in all patients with Stage IA (myoinvasive) and above(32)
- patients with fully surgically staged Stage I disease should be considered for adjuvant vaginal brachytherapy
- all other unstaged patients and those with Stage II and III disease should be considered for adjuvant treatment.

A commonly used chemotherapy regime is combination carboplatin and paclitaxel, given either as six cycles prior to radiotherapy or as 'sandwich' radiotherapy, q3 weekly for three cycles prior to radiotherapy and then another three cycles after radiotherapy.

Carcinosarcoma

Chemotherapy studies have documented some antitumour activity for cisplatin, doxorubicin, and ifosfamide.(67) It is recommended to: consider adjuvant pelvic RT (+/– vaginal brachytherapy) for Stage I–III (as per endometrioid carcinoma), and consider chemotherapy for Stage IA (myoinvasive) and above.

Leiomyosarcoma

This type of cancer shows distant metastatic spread in apparently early stage disease and chemoresistance and radiation resistance.

Patients should have a CT scan of the chest, abdomen and pelvis to detect metastatic disease. As treatment is palliative it is usually symptom-directed.

Endometrial stromal sarcoma

This type of cancer is:

- usually low grade
- generally poorly responsive to radiotherapy
- generally poorly responsive to chemotherapy
- potentially partly responsive to high dose progestogens (e.g. 200mg medroxyprogesterone acetate bd) or GnRH analogues(68) or anti-oestrogen therapies.

Decisions for treatment should be based on surgical stage, tumour grade, patient age and co-morbidities. This also applies to undifferentiated sarcomas (NOS).

Surveillance and follow up

There are no studies providing unequivocal evidence for follow-up regimes. An analysis of 16 retrospective studies suggested that 70% of recurrences were symptomatic and that only 0–4% of recurrences in asymptomatic women were detected by vaginal vault smears.(69) Low-risk patients may be suitable for follow up shared between the GP and the treating team.(70)

A suggested protocol is:

- review visits every three months for the first year, followed by four monthly and then six monthly visits in the second and third years. Annual visits may be performed in the fourth and fifth years.
- perform physical examination including examination of the supraclavicular nodes, abdomen and pelvis (with a speculum examination) at all visits
- do not perform routine vaginal vault smears or imaging studies, as they have not been shown to improve outcomes(69)
- colposcopy and biopsy any suspicious lesions
- advise the patient to return for early review if any problems (such as bleeding, pain, bladder or bowel symptoms) become evident between scheduled visits.(71)

Clinical trials

Some women may wish to participate in a clinical trial. Refer to the Australia New Zealand Gynaecological Oncology Group (ANZGOG) website (www.anzgog.org.au) for information on current uterine cancer trials.

Recurrence

Recurrent disease commonly occurs within three years of diagnosis.(71) It may occur at the vaginal vault, which is often curable with radiation treatment in women who have not previously had pelvic radiation.

Recurrent disease requires reassessment of the:

- histology of the initial and (if possible) recurrent disease
- distribution of recurrent disease (local, regional and distant), using a combination of examination (under anaesthesia if necessary), imaging (CT/PET, MRI as indicated) and pathology/cytology (e.g. fine needle aspiration (FNA) of suspicious lesions)
- performance status of the patient
- previous treatment and time to relapse.

All cases should be considered by a MDT.

Treatment of recurrence

Radiotherapy

Patients to be treated with radiotherapy with cureative intent should be completed assessed to ensure there is no evidence of distant metastatic disease.

Recurrence site	Information
Vaginal vault/central pelvic recurrences	Treat with whole pelvic radiotherapy + vaginal vault brachytherapy in radiation-naive patients. Salvage rates of 70–80% have been documented.(72)
Pelvic nodal recurrence	Consider surgical debulking if nodal mass of >2cm diameter. Treat with whole pelvic radiotherapy +/– boost to area of recurrence.

Palliative radiotherapy

Palliative radiotherapy may be used for:

- uncontrolled bleeding in a patient with incurable disease
- visceral obstruction due to recurrent tumour
- pain secondary to bone or nerve involvement.

Individualise radiation doses depending on performance status of patients, metastatic disease burden and symptomatic site.

High dose pelvic radiotherapy (50Gy) may be appropriate for palliation of pelvic symptoms in good performance status patient with low extra-pelvic disease burden.

Chemotherapy

Chemotherapy is reserved for metastatic disease not amenable to hormonal treatment or surgery, and is generally withheld until patients are symptomatic.

It may give short term (months) relief of symptoms, has a response rate of approximately 20–50% in endometrioid carcinoma. Limited recent data has shown a much higher response rate with the inclusion of bevacizumab.(73)

Hormonal treatment

- Progesterone treatment is most useful for low grade, progesterone receptor-positive endometrioid tumours and pulmonary metastases. Contraindications include a history of thrombosis, severe cardiac disease and breast cancer. Progesterone treatment is also associated with weight gain, which requires consideration in obese women.(74)
- Tamoxifen is occasionally used to treat recurrent endometrioid cancer.
- Aromatase inhibitors have limited activity and may be considered second or third line treatment for patients in whom chemotherapy is contraindicated.

Surgery

Surgery may be used in selected cases for isolated recurrence, providing:

- examination and imaging (including PET scans) shows no evidence for multiple sites of disease
- other modalities of treatment are not feasible (radiation, hormonal treatment)
- the patient has good performance status
- clinical data have been considered by a MDT.

Surgery should be tailored to minimise morbidity but may entail:

- laparotomy and resection of an isolated mass
- pelvic exenteration with faecal and/or urinary diversion in rare circumstances.

Palliative care issues

Problems that may require palliative care input include:

- vaginal bleeding
- pain (including neuropathic pain from nerve involvement)
- bladder and bowel symptoms
- fistula (bowel or bladder)
- ureteric obstruction
- ascites
- rarely, respiratory or neurological symptoms.

Treatment is targeted to the symptom, taking into account the site of disease, previous treatment and patient factors.

Ovarian, fallopian tube and primary peritoneal cancer

Serous carcinoma is the most common histological subtype of epithelial ovarian, tubal or peritoneal carcinoma. Most cases appear to originate from the fimbrial end of the fallopian tube, based on immunohistological studies.(75) These carcinomas will be regarded as a single entity in this chapter.

Other histological types of ovarian, tubal or peritoneal cancers (e.g. mucinous, endometrioid) are less common and often a lower stage at diagnosis. Refer to the Cancer Australia Clinical practice guidelines on the management of women with epithelial ovarian cancer(76).

The key histological features of ovarian /tubal/peritoneal carcinomas are:

- histological cell type
- the presence of precursor lesions in the fallopian tubes (serous tubal intraepithelial carcinoma (STIC) lesions)
- involvement of contralateral ovary, peritoneum, omentum, bowel
- lymph node metastases where lymph node sampling has been performed.

Further information

For information about ovarian cancer anatomical pathology reporting, histologic type and grading, see Gynaecological pathology.

Classification and staging of ovarian and fallopian tube cancer

Staging of ovarian and fallopian tube cancer is based on findings at clinical examination and surgical exploration.(77, 78)

Table 5. FIGO ovarian, fallopian tube, and peritoneal cancer staging system [2014]

FIGO Stage	Extent of disease	
Stage I	**Tumour confined to ovaries or fallopian tube(s)**	
	Stage IA	Tumour limited to one ovary (capsule intact) or fallopian tube: no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
	Stage IB	Tumour limited to both ovaries (capsule intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
	Stage IC	Tumour limited to one or both ovaries or fallopian tubes, with any of the following:
	Stage IC1	Surgical spill
	Stage IC2	Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
	Stage IC3	Malignant cells in the ascites or peritoneal washings
Stage II	**Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer**	
	Stage IIA	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
	Stage IIB	Extension to other pelvic intraperitoneal tissues

FIGO Stage	Extent of disease	
Stage III	**Tumour involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/ or metastasis to the retroperitoneal lymph nodes**	
	Stage IIIA1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven)
	Stage IIIA1(i)	Metastasis up to 10mm in greatest dimension
	Stage IIIA1(ii)	Metastasis more than 10mm in greatest dimension
	Stage IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without metastasis to the retroperitoneal lymph nodes
	Stage IIIB	Macroscopic peritoneal metastasis beyond the pelvis up to 2cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
	Stage IIIC	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)
Stage IV	**Distant metastasis excluding peritoneal metastases**	
	Stage IVA	Pleural effusion with positive cytology
	Stage IVB	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Source: International Federation of Gynaecology and Obstetrics(79)

Early stage ovarian and fallopian tube cancer

At least 85% of cancers previously thought to originate in the ovary are now known to originate in the fallopian tube. (80) Ovarian and fallopian tube cancers are treated similarly, with single agent or combination chemotherapy.

Stage I

Suboptimally staged and high risk early stage ovarian cancer (stage IB–IC [not 1C1] grade 2, any grade 3 or stage IC [not 1C1] clear cell histology) should be offered adjuvant chemotherapy.(81)

Adjuvant chemotherapy is usually a platinum-based doublet (i.e. carboplatin and paclitaxel). This is largely based upon indirect evidence that it improves outcomes when administered as adjuvant treatment for more advanced disease.(82)

There is a paucity of data regarding the ideal number of cycles of treatment as adjuvant treatment patients with early stage ovarian cancer. Women treated for early stage serous carcinoma with six cycles of chemotherapy had lower rates of recurrence but no improvement in overall survival and increased toxicity, compared with three cycles.(83, 84)

Stage II–IV

Chemotherapy is recommended for all patients with Stage II–IV epithelial ovarian cancer, either after primary debulking or as neoadjuvant chemotherapy. The standard of care is combination carboplatin/paclitaxel (IV) every three weeks for an average of six cycles.

Intraperitoneal and dose-dense regimens can also be considered, although both approaches may be associated with an increased toxicity.(85) The use of intraperitoneal chemotherapy has declined due to the logistics of administration and increased risk of toxicity, despite level 1 evidence of long-term survival benefits in selected optimally-debulked stage III ovarian cancer patients.(86)

For patients who develop an allergy to or do not tolerate paclitaxel, the combination of docetaxel/carboplatin or pegylated liposomal doxorubicin (PLD)/carboplatin can be considered as an alternative.

Targeted therapy

The addition of bevacizumab to carboplatin and paclitaxel improves progression-free survival in patients with advanced ovarian cancer with poor prognostic features, such as stage IV cancers or suboptimally debulked tumours. (87) Bevacizumab may be given after completion of the carboplatin/paclitaxel chemotherapy phase.

Uncertainty remains about the dose and the duration of therapy.

Trials with other targeted agents and extended therapy with bevacizumab are ongoing.

Maintenance therapy

Maintenance therapy with chemotherapy or immunotherapy after the completion of frontline platinum-paclitaxel chemotherapy has not been proven to benefit the outcome of patients with advanced ovarian cancer.(88)

Only the antiangiogenic agent bevacizumab has been shown to achieve a small incease in overall survival in women with suboptimally debulked stage III or stage IV disease at diagnosis.(88)

Adjuvant radiotherapy

Whole abdominal radiotherapy (WART) may be appropriate for highly selected patients. Those most likely to benefit from WART are those with Stages I–III disease having no macroscopic disease in the upper abdomen at surgery and small macroscopic disease (<1 cm) in the pelvis.

One trial has shown a survival advantage in patients with Stage IC clear cell ovarian cancer who have adjuvant whole abdominal radiation.(89) There is however, risk of significant toxicity in some patients.

Neo-adjuvant chemotherapy (NACT)

NACT refers to a regime whereby patients receive three cycles of chemotherapy prior to surgery, followed by further chemotherapy after surgery. The goal of NACT is to reduce perioperative morbidity and mortality.

NACT is an option for patients who have significant medical comorbidities and/or where optimal surgical debulking is unlikely.

NACT with surgical debulking after three cycles has been shown to result in similar median survival to patients treated with primary surgery followed by adjuvant chemotherapy.(90) A subanalysis of the data suggested a possible survival benefit of primary surgery over NACT in patients with stage 3C or less. Patients with bulky Stage IIC or Stage IV disease may do better with NACT than primary surgery.

New and evolving strategies such as dose-dense treatment and the safety and feasibility of incorporating bevacizumab into the neo-adjuvant setting are being studied.(91)

BRCA mutations

Germline BRCA mutations are more common in women with serous ovarian carcinoma compared with other histological subtypes and are present in about 17% of women with high-grade serous carcinomas.(92)

Six to eight percent of these tumours have somatic BRCA mutations. Tumours with a BRCA mutation have defective DNA repair and a higher response to treatment with a PARP inhibitor and platinum-based chemotherapy.(92)

Women with non-mucinous ovarian, fallopian and primary peritoneal cancers should be offered an appointment with a geneticist/genetic counsellor, or offered genetic testing using Medicare/Mainstreaming as described in the Indications for genetic testing section.

Clinical trials

Women with ovarian cancer may be offered entry into the INOVATe study. INOVATe is a research study funded by the Cancer Institute NSW to 2020, offering intensive molecular charcteristation of ovarian carcinomas, including next-generation multigene mutation testing, gene copy number alterations, altered gene and protein expression and analysis of homologous recombination DNA repair deficiency (HRD), depending on available tumour tissue samples.

This information contributes to the selection of the most appropriate clinical trials for patients, when current treaments are no longer effective, and will ultimately contribute to the development of precision treatment for ovarian cancer.

Monitoring after primary treatment

Follow-up including symptom review and examination should be provided at appropriate intervals by a gynaecological oncologist, medical oncologist or specialist gynaecologist. This is usually three monthly for two years after initial treatment, then six monthly until five years before moving to annual review.

Measurement of CA125 at routine review does not improve overall survival as early treatment of rising CA125 does not improve outcome in otherwise asymptomatic women(93) Despite this information, some patients continue to want to CA125 measurements, and this can be done at the clinician's discretion.

Imaging should not be routinely performed outside a clinical trial setting. Abdomino-pelvic CT scans or PET scans should be performed if there is clinical or biochemical evidence of recurrence.

PET-CT scans may reveal sites of disease not visible on CT scans and are most useful for selecting patients suitable for secondary debulking surgery.

Persistent or recurrent disease

As salvage treatment is not curative for the overwhelming majority of patients, follow-up and further treatment needs to incorporate quality of life considerations into planning.

Highly selected patients may be considered for secondary surgery, which has been shown to result in a survival benefit in several retrospective studies.(94–96)

Patients who are candidates for secondary cytoreductive surgery generally have:

- demonstrated that they have platinum sensitive disease, i.e. have suffered a recurrence beyond six months after completion of primary treatment
- limited sites of disease so that a complete gross resection can be achieved(97); and
- no evidence of ascites(98, 99).

Second and third line chemotherapy

Platinum sensitive

Disease progression after six months (and especially after 12 months) of the last dose should be treated with carboplatin +/– paclitaxel/gemcitabine/doxorubicin.

Platinum resistant/refractory

Treatment for platinum-refractory (progression during treatment or within four weeks of the last dose) or resistant disease (progression within six months of the last dose) should be focused on maintaining or improving quality of life and control of symptoms.

Chemotherapy should be selected based on toxicity, clinical situation of the patient and convenience of administration. Single-agent chemotherapy in this setting is preferred as combination chemotherapy increases toxicity.(100) Dose-dense delivery of a platinum agent can be considered, as well as hormonal therapy such as tamoxifen or an appropriate clinical trial.

Targeted therapy

Bevacizumab may be combined with carboplatin/gemcitabine followed by maintenance treatment for first-line treatment of platinum-sensitive relapse. Treatment should continue until disease progression or disease toxicity is demonstrated. This increases progression free survival (PFS), but not overall survival (OS).(100) Note that at the time of publication, bevacizumab is not PBS listed for this indication.

Bevacizumab in combination with either PLD weekly paclitaxel or topotecan may be given for patients with platinum-resistant relapse who have received two or fewer chemotherapy regimens. Trials have shown an augmentation of the chemotherapy response, improved PFS and improvement in quality of life with bevacizumab, but no OS benefit.(101) Note that at the time of publication, bevacizumab is not on the PBS for this indication.

Olaparib is available on the PBS as maintenance treatment for gBRCA 1, 2 mutation positive high grade serous ovarian cancer, and fallopian tube cancer, primary peritoneal cancer after a partial or complete response to a platinum-based chemotherapy regimen for relapse. Patients must have received at least two previous platinum containing regimens.

Germ cell tumours

Conservative, fertility sparing surgery is indicated if a germ cell tumour is suspected from imaging and tumour markers and confirmed on intraoperative frozen section. Initial surgery should include:

- unilateral salpingo-oophorectomy
- peritoneal cytology
- meticulous exploration of the abdomen and retro-peritoneal lymph nodes.

Contralateral cystic lesions should be removed with cystectomy and ovarian conservation. Biopsy of a normal looking contra-lateral ovary is not indicated.

The role of debulking advanced ovarian germ cell tumours is not defined, however there is some evidence that maximal cytoreduction may be of benefit.(102)

Patients with stage IA dysgerminoma or stage IA low or high grade immature teratoma may be managed by surgery alone. All other patients with malignant germ cell tumours require chemotherapy. BEP chemotherapy is recommended – see Table 6. During chemotherapy, oral contraceptives should be prescribed to prevent pregnancy and suppress ovarian function in order to reduce possible damage to the ovaries.

Second look surgery is reserved for patients with teratoma elements.

After completion of treatment, all patients should be followed by serial tumour markers and examination. Most will resume normal menstrual function and normal reproductive function.

Table 6. BEP chemotherapy regimen for patients with germ cell tumours

Day of cycle	Drug	Dose and route	No. of cycles	Cycle frequency
1	Bleomycin	30 units IV	12	Weekly
1–5	Etoposide +	100mg/ m2 IV	3–4	Q3 weekly
1–5	Cisplatin	20mg/ m2 IV		

Sex cord stromal tumours

Stage I – early disease

For younger women wishing to preserve their fertility, a unilateral salpingo-oophorectomy and fractional D&C may be all that is required. In post-menopausal women, a total abdominal hysterectomy and bilateral salpingo-oophorectomy is recommended.

Adjuvant treatment is not considered necessary in stage I disease.(103)

Stage II–IV – advanced disease

Women with stage II–IV disease are at increased risk of recurrence, therefore adjuvant therapy is generally recommended. While there are little data, BEP chemotherapy is an active combination in the first line setting. However more recent studies suggest that taxanes in combination with carboplatin is a more tolerable alternative.(104)

Recurrent disease

Data to support the optimal management of recurrent disease are lacking. If the disease appears to be easily resectable then low quality data suggest that secondary cytoreduction may provide a survival advantage.(105, 106) In some patients resection of a granulosa tumour recurrence may provide significant symptomatic relief and therefore may be considered. Increasing serum inhibin levels are highly specific for recurrence.(107)

Systemic therapy for recurrent disease is usually platinum based, either BEP or carboplatin/paclitaxel.(108) In some cases, particularly adult type granulosa cell tumours, leuprolide acetate, tamoxifen or aromatase inhibitors are also effective. Megestreol acetate has also been shown to have activity in the recurrent setting.(109) Given the paucity of data however, enrolment into appropriate clinical trials should be considered.

Surgery

Patients should undergo total abdominal hysterectomy and bilateral salpingo-oophorectomy. If there is no evidence of gross tumour spread, a full staging operation should be performed.

Patients with metastatic disease should have as much tumour debulked as is possible. Extrapolation from experience with epithelial ovarian cancer indicates that significant benefit might be expected with radical debulking, particularly if all the macroscopic disease can be resected.

Chemotherapy

Use carboplatin and paclitaxel as per treatment for epithelial ovarian cancer.

It is unclear whether patients with disease confined to the fallopian tube (i.e. stage IA, grade 1 or 2) benefit from adjuvant therapy and decisions regarding treatment should be based on clinical judgement.

Radiotherapy

The role of radiotherapy is unclear. Treatment of isolated nodal recurrence may be considered.

Vulval cancer

Carcinoma of the vulva is an uncommon tumour, representing about 4% of gynaecologic malignancies. Squamous cell carcinomas account for approximately 85% of these cancers, while melanomas, adenocarcinomas, basal cell carcinomas, verrucous carcinomas, sarcomas, and other rare malignancies also occur.(110)

Vulval melanoma is the second most common neoplasm of the vulva.(110)

Vulval cancer terminology

Vulvar intraepithelial neoplasia (VIN) is a precancerous cellular abnormality of the vulva that is confined to the epithelium. HSIL (previously known as VIN 2 or VIN 3) refers to to a histologic high grade squamous intraepithelial lesion. LSIL refers to a low-grade squamous intraepithelial lesion.

The key histological features are:

- histological cell type
- tumour dimension (microscopic and macroscopic)
- depth of invasion
- lymphovascular space invasion
- surgical margins
- lymph node metastases where surgically staged.

Further information

For information about vulval cancer anatomical pathology reporting, histologic type and grading, see Gynaecological pathology.

HSIL should be treated with excision or laser therapy when diagnosed.(111, 112) Treatment of invasive vulval cancer should occur in a gynaecological cancer centre where all relevant expertise is available.(113)

Classification and staging of vulval cancer

Vulval cancer is staged by surgical and/or pathologic findings.

Table 7. Carcinoma of the vulva: FIGO nomenclature

FIGO Stage	Clinical/Pathological Findings	
Stage I	**Tumor confined to the vulva**	
	Stage IA	Lesions ≤2cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0mm*, no nodal metastasis
	Stage IB	Lesions >2cm in size or with stromal invasion >1.0mm*, confined to the vulva or perineum, with negative nodes
Stage II	**Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes.**	
Stage III	**Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino-femoral lymph nodes**	
	Stage IIIA	(i) With 1 lymph node macrometastasis (≥5 mm), or (ii) 1–2 lymph node micrometastasis (es) (<5 mm)
	Stage IIIB	(i) With 2 or more lymph node macrometastases (≥5 mm), or (ii) 3 or more lymph node micrometastases (<5mm)
	Stage IIIC	With positive nodes with extracapsular spread

FIGO Stage	Clinical/Pathological Findings	
Stage IV	Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures	
	Stage IVA	Tumor invades any of the following: (i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or (ii) fixed or ulcerated inguino femoral lymph nodes
	Stage IVB	Any distant metastasis including pelvic lymph nodes

Source: International Federation of Gynecology and Obstetrics (79)

Squamous cell carcinoma of the vulva

Diagnosis should be confirmed by a 4mm Keyes punch biopsy under local anaesthesia prior to definitive treatment. The biopsy should include underlying stroma. It is preferable to not excise the entire lesion, as it makes it more difficult to plan the definitive excision.

If the lesion is ≤2cm in diameter and depth of stromal invasion is ≤1mm on wedge biopsy, complete excision of the lesion with adequate surgical margins must be undertaken.

Investigations to assist diagnosis include:

- cervical screening test of the cervix if cervix is still in situ
- colposcopy of the cervix and vagina (because of the common association with other squamous intraepithelial lesions)
- CT scan of the pelvis and groins to detect any enlarged lymph nodes in the groins or pelvis, particularly in the presence of palpable groin nodes
- routine full blood count, biochemical profile and chest x-ray (CXR) pre-operatively.

In treating vulval cancer, there is no standard operation. The emphasis is on performing the most conservative operation consistent with cure of the disease.(114) The primary lesion and groin nodes should be considered separately in considering treatment options.

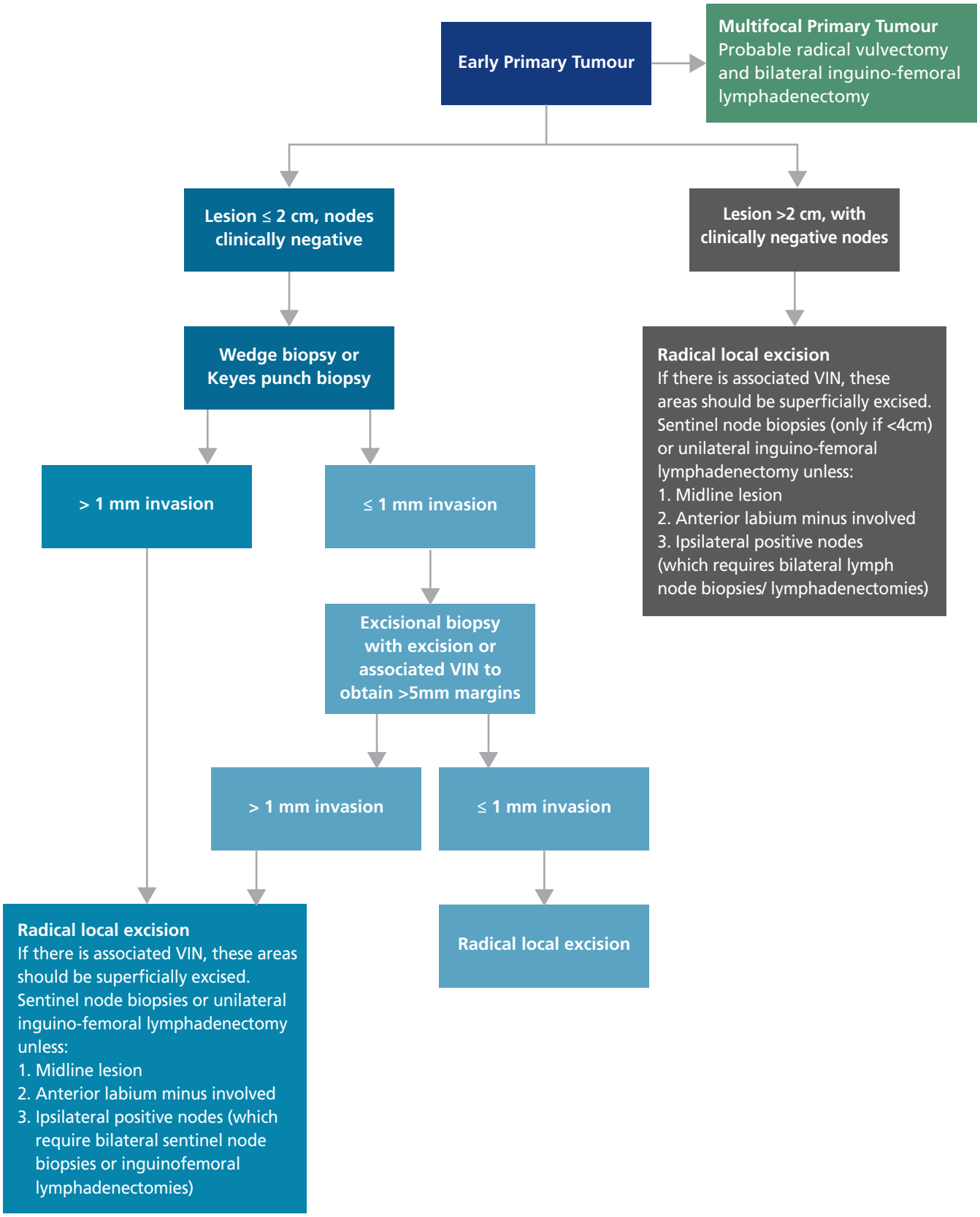
Early stage disease

Management of primary lesion

A radical local excision rather than a radical vulvectomy is as effective in preventing disease recurrence for localised lesions (see Figure 5).(115, 116)

Surgical removal should achieve lateral margins of at least 1cm, and the deep margin should be the inferior fascia of the uro-genital diaphragm.(117) If the lesion is close to the urethra, the distal 1cm of the urethra may be resected without jeopardising urinary continence. Any associated VIN should be superficially excised to control symptoms and to exclude other areas of superficial invasion.

Figure 5. Management of early vulval cancer



Management of groin lymph nodes

Patients with T1 tumours and ≤1mm stromal invasion have less than 1% risk of having lymph node metastases, and do not require sentinel lymph node biopsies or groin dissection.(114)

Patients with T1 tumours with >1 mm stromal invasion should have at least a sentinel lymph node biopsy or an ipsilateral inguinal-femoral lymphadenectomy.(114) Patients with tumours over 4 cm in diameter should undergo full lymphadenectomy. Both inguinal and femoral nodes should be removed.

Bilateral groin dissection or sentinel node biospies should be performed for midline tumours, and for those involving the anterior labia minora.(118) Bilateral dissection should also be considered for large lateral tumours, particularly if the ipsilateral nodes are positive.(118)

Lymphatic mapping

Sentinel lymph node dissection reduces the incidence of lower limb lymphoedema, but false negative biopsies occur in 2-3% of patients, similar to recurrence rates with complete lymphadenectomy.(119) Sentinel node mapping should be conducted within the clinical registry.

Management of patients with positive groin nodes

Patients with one (and possibly two) micro-metastases (<5mm) after a complete lymphadenectomy do not require adjuvant radiotherapy.

If the contralateral groin nodes have not been dissected, ultrasonic surveillance of these nodes may be prudent for the first 6–12 months.(114)

Patients should receive bilateral pelvic and groin irradiation for the following indications:

- one macrometastasis (>5mm diameter)
- extracapsular spread
- ≥3 micrometastases.

Radiotherapy

Radiation fields should include the inguino-femoral nodes and at least the lower pelvic nodes (below the sacroiliac joint).

After a groin dissection with microscopic inguinal metastases, 50Gy in 1.8–2.0Gy fractions is usually sufficient. If there are multiple nodes positive or if there is evidence of extracapsular extension, higher doses up to 60Gy may be given to a reduced volume. Gross residual disease may require doses of 60–70Gy.

Chemotherapy

The role of concurrent chemotherapy in this setting is unknown.

Advanced stage disease

Patients with T3 or T4 primary tumours or bulky positive groin nodes are considered to have advanced vulval cancer. For such patients, multimodality treatment planning is particularly important.

Management of the groin lymph nodes

The status of the groin nodes should be determined prior to planning treatment.(114)

Groin nodes should be managed as per early vulval cancers. If there are ulcerated or fixed groin nodes, a pre-operative CT scan of pelvis and groins may help identify the extent of groin and pelvic lymphadenopathy. If the nodes are resectable, any enlarged nodes from the groin and pelvis should be removed. If they are unresectable, they should be biopsied to confirm the diagnosis then treated with primary radiation. When feasible, the nodes should be resected following the radiation (see Figure 6).

Figure 6. Management of clinically suspicious groin nodes in advanced vulvar cancer

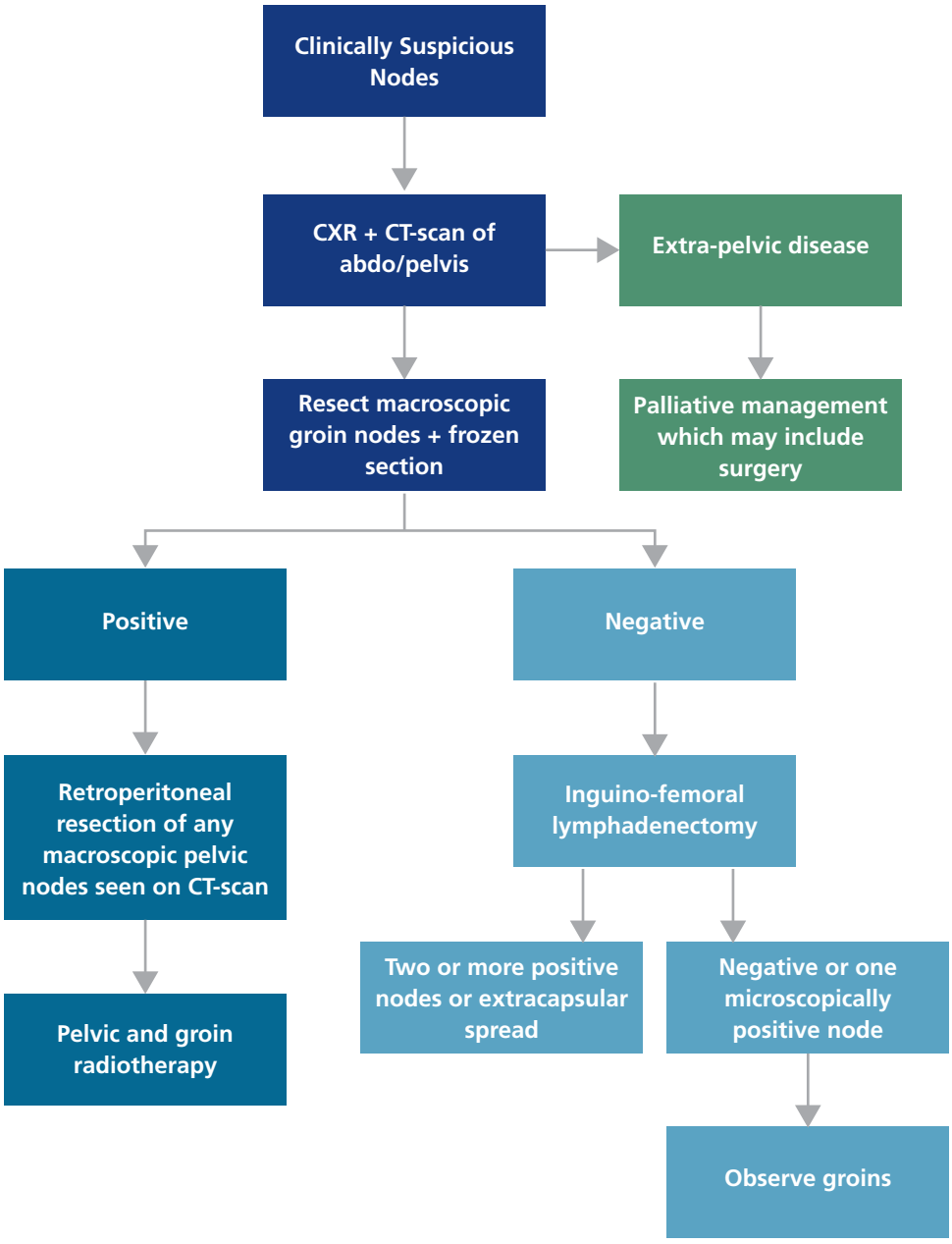
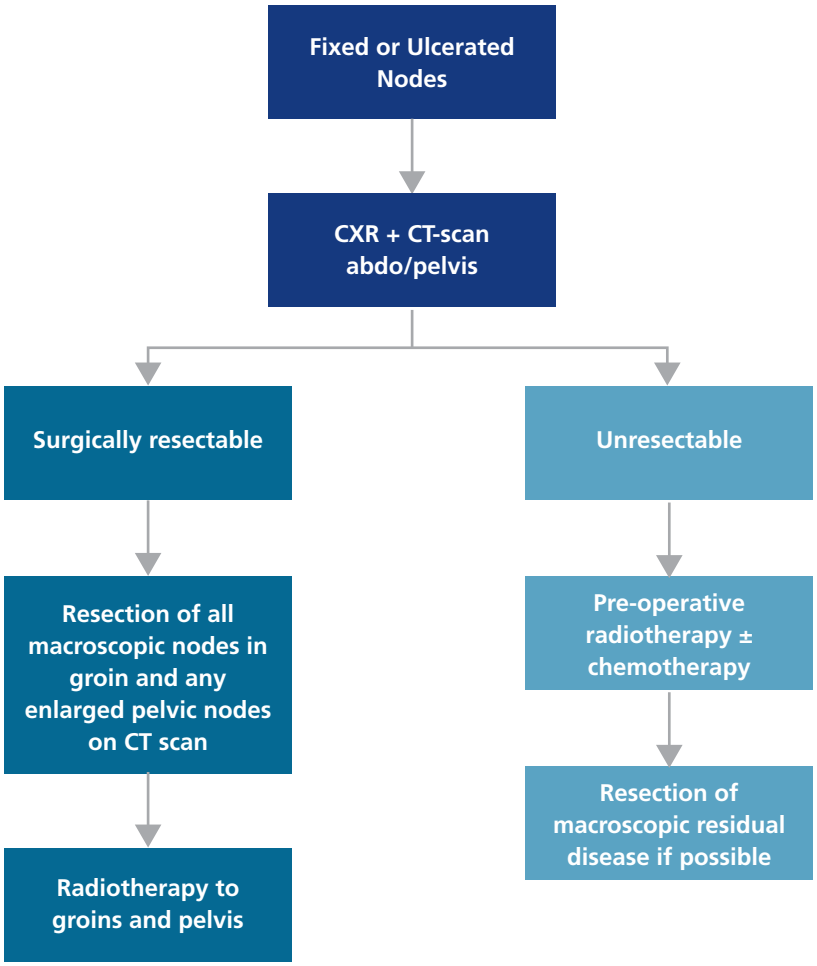


Figure 7. Management of clinically obvious groin nodes in advanced vulvar cancer



Management of the primary tumour

Treatment of the advanced primary tumour should follow dissection of the groin. Groin and pelvic radiation should follow standard indications (see Figure 6).

If it is possible to resect the primary lesion with clear surgical margins and without sphincter damage leading to urinary or faecal incontinence, primary surgical excision is desirable.

If primary surgery would result in the need for a bowel or urinary stoma, it is preferable to employ primary radiotherapy, followed by a more limited resection of the tumour bed.(120, 121) Chemoradiation has been used, sometimes without need for surgical resection of the tumour bed.(122, 123) The groin nodes and pelvis may need to be included in the treatment field depending on the status of the groin nodes, as determined initially.

Radiotherapy

Radiotherapy fields should include the pelvis, inguinal nodes and primary site, which are treated to a total dose of at least 50Gy. Areas of gross disease are particularly high risk and are usually boosted. Gross vulval disease requires 60–70Gy to achieve local control.

Close surgical margins

Post-operative radiation may be used for close surgical margins (<5mm), if the margins cannot be re-excised.(124) Although local control is improved, overall survival is not significantly different.(124)

Vulval melanoma

Primary vulval melanoma lesions should be treated by radical local excision, with margins around the lesion of at least 1cm.

The role of node dissection is also controversial. Lymph node dissection has been shown to result in significantly better survival for patients:

- ≤60 years
- with tumours 1–2mm thick
- without tumour ulceration.

Sentinel node biopsy is an alternative strategy but nodal recurrence in sentinel node negative patient has been documented.(125)

It is advised to consult with a melanoma unit regarding adjuvant therapy and the potential for participation in cutaneous melanoma clinical trials.

Bartholin gland cancer

Cancers arising in the Bartholin gland may be either transitional or squamous types arising from the duct, or an adenocarcinoma from the gland itself.

Surgical margins are likely to be close, particularly for bulky lesions. Postoperative radiation to the vulva may decrease the likelihood of local recurrence.(126) If the ipsilateral groin nodes are positive, bilateral groin and pelvic radiation may decrease regional recurrence.(126)

For adenoid cystic lesions, radical local excision alone is the treatment of choice, with adjuvant local radiation recommended for positive margins or perineural invasion.(127)

Paget's disease of the vulva

Paget's disease may be associated with an underlying adenocarcinoma in 20% of cases.(128)

Clinically, it appears as an an eczematoid-weeping lesion. Diagnosis is confirmed by biopsy. Clear margins may not be obtained as the disease extends beyond the visible abnormality. Paget's disease often recurs over subsequent years. Topical imiquimod cream (5%) may be used to treat recurrences but further investigation is required. (129, 130)

Wound care following vulval surgery

Recommended nursing care includes:

- **frequent perineal toilets**
- **patient education for regular vulval care and wound care after toileting**
- **drying the perineum following wound care or showering.**

Vaginal cancer

Vaginal cancers are uncommon tumours comprising only 2–3% of gynaecological malignancies and 0.15% of cancer overall.(131) HPV appears to be a risk factor in younger but not older patients.(131)

Classification and staging of vaginal cancer

Cases should be classified as carcinoma of the vagina only when the primary site of growth is in the vagina. Tumours located in the vagina as secondary extensions or metastases from other genital or extra-genital sites should not be regarded as primary vaginal cancer.

Table 8. FIGO nomenclature for carcinoma of the vagina

FIGO Stage	Extent of disease
Stage I	The carcinoma is limited to the vaginal wall
Stage II	The carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall
Stage III	The carcinoma has extended to the pelvic wall
	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum; bullous oedema as such, does not permit a case to be allotted to Stage IV.
Stage IV	**Stage IVA** – Tumour invades bladder and/or rectal mucosa and/or direct extension beyond the true pelvis
	Stage IVB – Spread to distant organs

Source: International Federation of Gynecology and Obstetrics(79)

Management

Pre-treatment staging should include:

- examination under anesthesia (EUA), representative biopsy, colposcopy and cystoscopy
- Chest CT or CXR, abdominal/pelvic CT scan with intravenous contrast
- MRI pelvis with vaginal hydrophilic gel with protocoled sequence acquisitions (Smith & Gormly, 2008; Griffin et al, 2008)
- FDG-PET (to aid locoregional treatment strategy and if there is clinical concern for metastatic disease).

Therapeutic alternatives depend on:

- the stage, size and location of the lesion
- the presence or absence of the uterus
- whether there has been prior pelvic radiation
- the medical status of the patient.

Radiotherapy is generally regarded as the mainstay of treatment for vaginal cancer.(132, 133)

Surgery appears to be effective in a select group of patients with small, early stage tumours where clear surgical margins can be achieved without exenterative procedures.(134)

The role of chemoradiation is yet to be defined. Chemotherapy is likely to be beneficial for more advanced and lymph node positive vaginal cancer, but there are no randomised trials.(135)

Prognosis

In general the prognosis for all stages of vaginal cancer is worse than that for cervical and vulvar cancer.(136)

Possible poor prognostic factors in some series include:(137)

- older patient age
- pre-treatment haemoglobin
- advanced stage cancer
- large tumour size
- prior hysterectomy
- distal or posterior vaginal location
- nodal metastases
- high histological grade
- non-squamous cell carcinoma subtypes.

Lymph nodes

The lymphatic drainage of the upper vagina is to pelvic nodes (iliac and pre-sacral), and the lower one third of the vagina is to the inguino-femoral nodes and to pelvic nodes.

In managing nodes, consideration should be given to:

- treatment of pelvic lymph nodes in all patients with invasive disease(136)
- treatment of inguino-femoral nodes where there is involvement of the lower one third of the vagina.

Stage I and Stage II disease

Superficial tumours <0.5cm thick

Dependent on the location of the tumour and patient age, treatment options include:

- high dose-rate brachytherapy (HDRB) intra-cavity and/or interstitial therapy. Pre-treatment colposcopic mapping with use of implanted fiducial markers and MRI planning are recommended to optimise this strategy.
- surgery dependent upon site and extent of tumour. Surgical options include wide local escision or radical hysterectomy with excision of the upper vagina.

Tumours >0.5cm thick

Dependent on the location of the tumour, treatment options include:

- individualised radiotherapy by combination of external beam and HDR BTs (as with superficial tumours <0.5cm thick)
- surgery, dependent on site and extent of tumour. Surgical options may include:
  - partial vaginectomy ± radical hysterectomy
  - resection of bulky lymph nodes >2cm in diameter
  - ovarian transposition may benefit young patients prior to radiotherapy and surgical staging prior to radiotherapy, although the role of surgical staging is yet to be identified.

The role of surgical staging is yet to be defined.

Stage III–IV disease

Treatment for advanced stage disease needs to be individualised based on patient age and co-morbidity score. Treatment options include:

- surgery for debulking of enlarged inguinal nodes >2cm in diameter, ovarian transposition in younger women or exenterative surgery in those patients who present with a vesico-vaginal or recto-vaginal fistula
- radiotherapy, individualised depending on site and bulk of disease
- a combination of external beam radiotherapy and brachytherapy, for treatment of stage III disease (following similar principles to that used for stage IIB–IIIB cervix cancer)
- combined radiation and chemotherapy.

Recurrent vaginal cancer

Recurrence of vaginal cancer is associated with a poor prognosis and treatment goals are likely to be palliative.(138)

Treatment options will depend on prior treatment, site of recurrence, patient performance status, patient expectation and preferences. For those women with central recurrence and no evidence of distant metastases, exenterative surgery may be appropriate and offers the only chance of cure.(139) In woman with prior radiation history, re-irradiation may be possible using stereotactic IMRT techniques or sophisticated HDRB at centres with appropriate expertise.(139)

There are no chemotherapeutic options shown to offer any survival advantage but this may offer some palliative benefit.

Consider enrolment in appropriate clinical trials of novel systemic agents, including targeted molecules and immune-oncology.

Vaginal melanoma

Primary vaginal melanoma is rare. Depth of invasion (important in cutaneous melanoma) has not been shown to be of significance as most vaginal melanomas are deeply invasive. The size of tumour appears to be more relevant.(140)

Controversy surrounds optimal treatment of vaginal melanoma. No single therapeutic approach has been shown to have a clear benefit. Treatment must be individualised and tailored to the size and extent of tumour (based upon examination and radiological examination) and the condition of the patient. A combination of surgery and radiotherapy is often utilised. The prognosis of patients with primary vaginal melanoma remains poor.

Radiotherapy

Techniques

- Total radiotherapy treatment including brachytherapy should be completed within 50 days to mirror standards-of-care in cervical cancer.(e.g. EMBRACE Protocol 2008)(141)
- Consideration should be given to include weekly intravenous cis-platinum (35–40mg/m2) in selected individuals during EBRT.
- Image-fusion of simulation (planning) CT datasets with appropriate MRI sequences and FDG-PET to aide gross tumour volume (GTV) and clinical target volume (CTV) delineation.
- Vaginal CT contrast should be considered in all patients at time of simulation.

If available to be placed during EUA, fiducial marker seeds demarcating the 'GTV at diagnosis' (a GEC-ESTRO concept for cervical cancer outlined in the EMBRACE protocol(142)) should be correlated with other imaging findings and used to aide cone-beam CT soft-tissue matching during IMRT.

External beam pelvic radiotherapy

- External beam radiotherapy is usually given prior to brachytherapy to reduce tumour volume and render brachytherapy more effective. EBRT can be used as an adjuvant therapy following surgery, as part of primary therapy in locally advanced disease, or for secondary therapy/palliation in recurrent or metastatic disease.
- Radiation technique and doses are important to maximise cancer control while limiting normal tissue toxicity.
- Interruption in EBRT should be minimised. Adequate dosing is crucial and can be accomplished with either 3D conformal approaches or IMRT, dependent on the facility and radiation oncologist competence.
- Doses range from 50–50.4Gy in 1.8–2 Gy fractions for adjuvant therapy to 59.4–64.8Gy in 1.8 Gy fractions (or 55–60Gy in 25 fractions) for unresectable disease using a conformal or highly conformal intensity modulated techniques.(141)
- Acute effects during EBRT (e.g. diarrhoea, bladder irritation, fatigue, mucocutaneous reaction) can be further accentuated by concurrent chemotherapy. The impact of the toxicities can be ameliorated (for example, using local skin care or symptomatic medications), and breaks in EBRT should be avoided or minimised. Side effects generally resolve several weeks after completion of radiotherapy.
- Post-operative adjuvant EBRT should be initiated as soon as adequate healing is achieved, preferably within 6–8 weeks.

Brachytherapy

Brachytherapy should follow external beam radiotherapy, aiming to give a combined total dose of at least 80–85Gy (a/b 10Gy) using the EMBRACE concepts.(141) In the event either technically or clinically high dose rate (HDR) brachytherapy is not a feasible treatment option, a highly conformal (intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT)) EBRT boost should be considered.

Gestational trophoblastic disease

Gestational trophoblastic disease (GTD) includes a range of tumours that follow a pregnancy. The preceding pregnancy may be intrauterine or ectopic and may or may not progress to term. The pregnancy may have been many years before diagnosis of GTD.

It is rare, with an estimated frequency of approximately 1.7 per 1000 deliveries.(143)

GTD includes abnormal products of conception (hydatiform moles, classified as partial or complete, choriocarcinomas) and placental site tumours. Molar pregnancies may regress spontaneously but are generally highly responsive to chemotherapy. Treatment is based upon the histopathology, regression of ß-hCG level, staging and FIGO score (see Table 10). See Figure 8 for a treatment algorithm for gestational trophoblastic disease.

Terminology

Hydatidiform mole and invasive mole should not be regarded as cancer. Trophoblastic disease should be regarded as the collective name for hydatidiform mole and trophoblastic neoplasia. Those patients requiring chemotherapy or excisional surgery because of persistence of ß-hCG after hydatidiform mole evacuation and those who have trophoblastic metastases have 'trophoblastic neoplasia'.

Classification and staging of gestational trophoblastic disease

The staging and classification of gestational trophoblastic disease combines the basic anatomic staging of disease (Table 9) with the modified World Health Organization risk factor scoring system (Table 10).(144)

Table 9. Anatomic FIGO staging for gestational trophoblastic disease

FIGO Stage	Extent of disease
Stage I	Disease confined to the uterus
Stage II	Gestational trophoblastic tumour extends outside the uterus but is limited to the genital structures (adnexae, vagina, broad ligament)
Stage III	Gestational trophoblastic tumour extends to the lungs with or without known genital tract involvement
Stage IV	All other metastatic sites

Source: FIGO Committee on Gynecologic Oncology(145)

Table 10. Modified WHO scoring system for FIGO 2009 staging/scoring of gestational trophoblastic disease

	FIGO score			
Prognostic factors	0	1	2	4
Age (years)	<40	≥40	–	–
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	–
Interval months from index pregnancy	<4	4–6	7–12	>12
Pre-treatment ß–hCG IU/L	<103	103–104	>104–105	>105
Largest tumour size including uterus	<3 cm	3–4cm	≥5cm	–
Site of metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Number of metastases identified	0	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	Two or more drugs

Source: FIGO Committee on Gynecologic Oncology(145)

The identification of an individual patient's stage and risk score is expressed by allotting a Roman numeral to the stage and an Arabic numeral to the risk score separated by a colon (e.g. I:1, IV:15, or II:10). A low-risk group is scored ≤6 and high-risk group is scored ≥7.

In order to implement the FIGO 2000 staging/scoring system the following criteria for diagnosis need to be accepted.(144, 146)

Routine repeat-evacuation after the diagnosis of a molar pregnancy is not warranted.

In twin pregnancies with a viable foetus and a molar pregnancy, the pregnancy may be allowed to continue, after appropriate counselling of the risks to mother and foetus. This includes risk of foetal demise of up to 60%, increased maternal obstetric complications and possible increased risk of persistent disease after delivery.(147, 148)

Hydatidiform mole (complete and partial)

Treat with:

- evacuation of the mole by suction curettage
- contraceptive measures (OCP preferred, IUCD to be avoided) until ß–hCG values have remained normal for six months
- post-operative surveillance with ß–hCG assays:
  - weekly until three negative levels are obtained, then
  - monthly for six months for a complete mole.

Persistent molar pregnancy

- Persistent molar pregnancy is defined as:
- four values or more with a plateau of ß–hCG over at least three weeks; i.e. days 1, 7, 14 and 21
- rise of ß–hCG of 10% or greater for 3–values or longer over at least 2 weeks; days 1, 7 and 14
- persistence of ß–hCG 6 months after mole evacuation
- presence of histologic choriocarcinoma.

Women with stable or rising ß–hCG levels should undergo staging for metastases including:

- **Lung – chest X-ray (CXR)** is adequate and CT scan is acceptable. CXR is used to count the number of metastases for risk score assessment
- **Intra-abdominal – CT** scanning is preferred although many institutions may still use ultrasound for liver metastases
- **Brain – MRI** (preferred) or CT scan.

Treatment is based on the FIGO score (Table 10).

Gestational trophoblastic neoplasia (GTN)

Indications for treatment include:

- four values or more of plateau of ß–hCG over at least three weeks
- rise of ß–hCG of 10% or greater for 3–values or longer over at least two weeks
- presence of histologic choriocarcinoma
- persistence of ß–hCG 4–6 months after mole evacuation.

Hysterectomy may be considered as primary treatment of non-metastatic GTN for older patients who have completed childbearing as it may decrease the need for, or the duration of, chemotherapy. It does not alter the requirement for ongoing follow-up monitoring of ß–hCG.

Low-risk disease (WHO score ≤6)

- Administer single-agent chemotherapy with methotrexate and folinic acid (Table 11) or actinomycin–D (Table 12).
- Continue for three cycles beyond negative ß–hCG.
- Surveillance then involves ß–hCG every two weeks for three months, then monthly for three months. If ß–hCG remains normal, check every two months for a further six months.(149) Some centres vary the way this surveillance is carried out, but a total of 12 months is required.
- Contraception can be started during chemotherapy treatment and should be continued for at least 6 months and preferably one year.

About 20% of patients will need to switch to second line chemotherapy following initial methotrexate due to drug resistance or toxicity. As a guide, patients with a ß–hCG <100 are often treated with actinomycin–D while those with higher levels are considered for EMA–CO (etoposide, methotrexate, actinomycin–D, vincristine and cyclophosphamide).

High-risk disease (WHO score ≥7)

High-risk refers to patients whose disease is not likely to be cured by single-agent chemotherapy, and who are at the highest risk of treatment failure. These patients should only be treated in tertiary referral centres where expertise is available in the management of such patients.

Treatment involves combination chemotherapy with EMA–CO (Table 14), with a repeat cycle every two weeks. Continue for 3 cycles beyond negative ß–hCG. If necessary, use g–CSF to avoid treatment delays.

Follow-up involves:

- early ultrasound in the next pregnancy to confirm normal foetus
- histopathological examination of placenta after delivery
- ß–hCG at six weeks postpartum.

Refractory disease

Treat refractory disease with combination chemotherapy with EMA–EP (Table 15), with a repeat cycle every two weeks. Continue for three cycles beyond negative ß–hCG.

Consider surgical resection if it is feasible and consistent with the patient's wishes.

Extra-uterine metastases

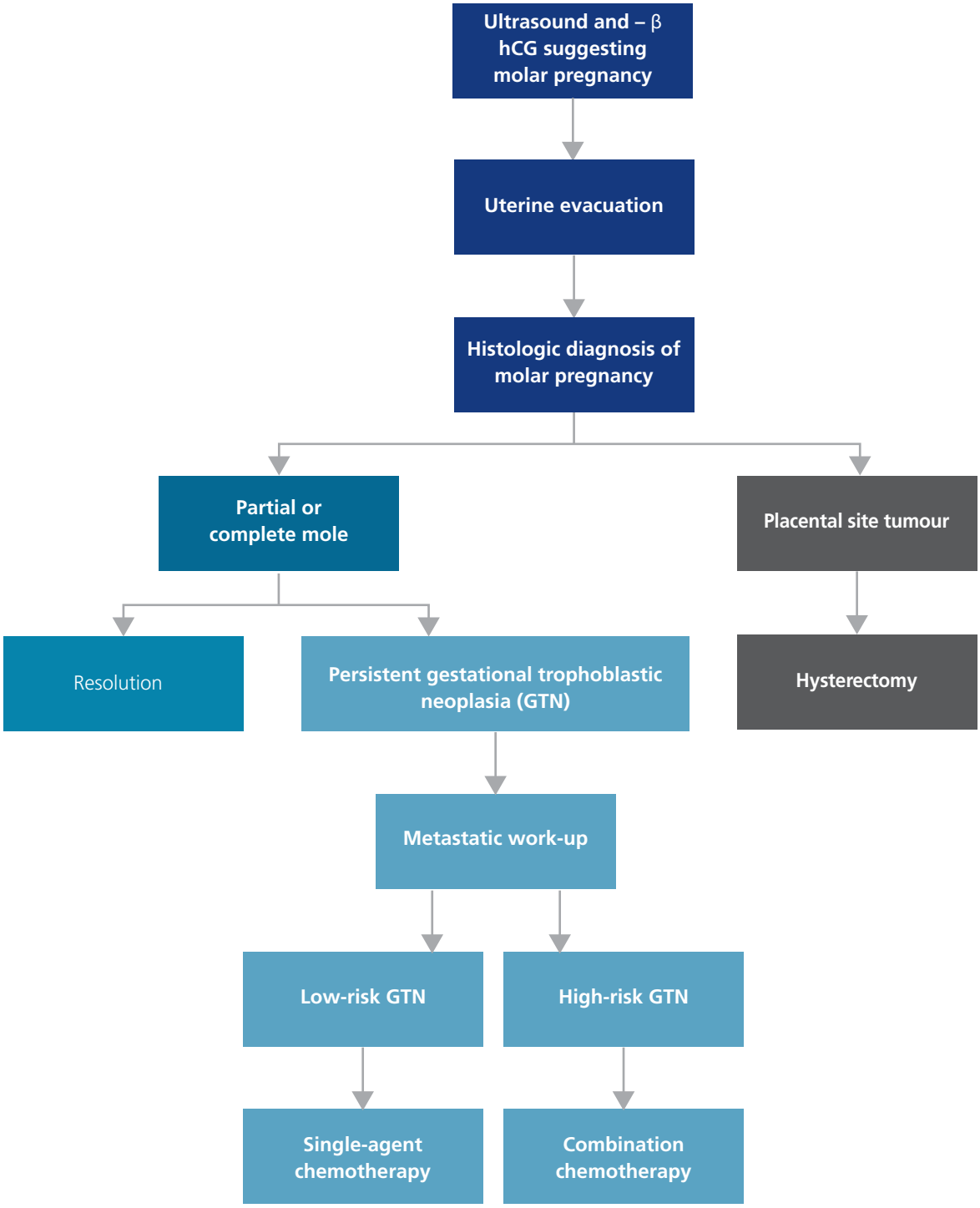
Adjuvant surgery such as hysterectomy and thoracotomy in conjunction with chemotherapy may be of use in selected patients for removing foci of persistent or recurrent high-risk gestational trophoblastic tumours.

Brain metastases

Brain metastases in gestational trophoblastic disease present a significant risk of cerebral haemorrhage. Surgical resection should therefore be considered.(150)

Intrathecal methotrexate (12.5mg) and high dose IV methotrexate as part of EMA–CO may be given.(151)

Figure 8. Diagnosis and treatment of gestational trophoblastic disease



Adapted from: Carney 2003(149)

Table 11. Methotrexate/folinic acid regimen for low-risk gestational trophoblastic neoplasia

Day of cycle	Drug	Dose & route	Cycle frequency
1, 3, 5, and 7	Methotrexate +	1mg/kg IM	
2, 4, 6, and 8	Folinic acid	0.1mg/kg IM or PO (24 hrs after methotrexate)	q2weekly

Table 12. Actinomycin–D regimen for low-risk gestational trophoblastic neoplasia

Day of cycle	Drug	Dose & route	Cycle frequency
1	Actinomycin–D	1.25mg/m2 IV	Q2weekly

Table 13. Alternate drug regimens for low-risk gestational trophoblastic neoplasia

Day of cycle	Drug	Dose & route	Cycle frequency
1 – 5	Methotrexate	0.4 ug/kg/d IM or IV	q2weeks
1	Methotrexate	50 mg/m2 IM	Weekly
1 – 5	Actinomycin–D	0.5 mg IV	q2weeks

Table 14. EMA–CO regimen for high-risk gestational trophoblastic neoplasia

Day of cycle	Drug	Dose & route	Cycle frequency
1	Etoposide + Actinomycin–D + Methotrexate	100 mg/m2 IV infusion over 30 mins 0.5 mg IV push 300 mg/m2 IV infusion over 12 hrs	q2weeks
2	Etoposide + Actinomycin–D + Folinic acid	100 mg/m2 IV infusion over 30 minutes 0.5 mg IV push 15 mg IM or PO every 12 hours for 4 doses starting 24 hours after start of methotrexate	
8	Vincristine + Cyclophosphamide	1 mg/m2 IV push 600 mg/m2 IV	

Table 15. EMA–EP regimen for refractory gestational trophoblastic disease

Day of cycle	Drug	Dose & route	Cycle frequency
1	Etoposide + Actinomycin–D + Methotrexate	over 30 mins 0.5 mg IV push 300 mg/m2 IV infusion over 12 hrs	q2weeks
2	Etoposide + Actinomycin–D + Folinic acid	100 mg/m2 IV infusion over 30 minutes 0.5 mg IV push 15 mg IM or PO every 12 hours for 4 doses starting 24 hours after start of methotrexate	
8	Vincristine + Cyclophosphamide	100 mg/m2 IV infusion over 30 minutes 80 mg/m2 IV	

Placental site trophoblastic tumour

This is a rare form of gestational trophoblastic neoplasia. In more than 30% of cases, metastatic disease is present at diagnosis, and recurrences occur in 30% of all cases.(152)

Placental site trophoblastic tumour is excluded from the scoring system for GTN. Poor prognostic factors include:

- mitotic count greater than 5 per 10 hpf(153)
- greater than two years since antecedent pregnancy(154)
- lung metastases(154).

ß–hCG production is usually low and not a reliable marker of disease, but may be used to monitor response to treatment or as a marker for recurrence.(154)

In most cases, the antecedent pregnancy is term delivery.

Treatment for placental site trophoblastic tumour includes:

- hysterectomy for non-metastatic disease
- adjuvant therapy (EMA–PE) for patients with metastatic disease at presentation, and may be indicated for patients with poor prognostic factors (153, 154)surgery should be considered if resectable masses are present.

MRI may be helpful in monitoring treatment. Feltmate, 2002 #157}

Gynaecologic pathology

Role of the pathologist

To maximise the usefulness of the information provided by the pathologic examination, the treating clinician should work closely with the pathologist in providing all the clinically relevant information. The pathologist should be accredited by The Royal College of Pathologists of Australasia.

The correct handling of specimens submitted for morphological assessment is critical; when in doubt, consult the pathologist. The management of macroscopic examination and dissection of tissue specimens, including the selection of tissue for microscopic examination, is the responsibility of the pathologist at all times and must follow clearly defined RCPA standards and guidelines.(155)

The following pathology reporting, grading, and histologic types (Tables 16–27) have been adapted from WHO 2014 and current RCPA reporting guidelines.(35)

Cervical cancer

Anatomical pathology reporting

Table 16. Anatomical pathology variables for reporting cervical cancer

Macroscopic	
Specimen	Uterine size and weight, size of cervix, adnexa (right and left), size of para-cervical tissue (R and L), and vaginal cuff size
Tumour	Size (three dimensions), location, appearance, depth of invasion/thickness of cervical wall, para-cervical involvement, corpus involvement, vaginal cuff involvement, distance from tumour to vaginal margin, other sites involved, other findings, identifiers (ink) applied, and blocks submitted
Lymph nodes (by site)	Size (range where applicable), size of largest metastasis, and number of nodes and pieces per cassette
Microscopic	**Histologic type and grade**
	Associated intraepithelial lesion CIN (grade) e.g. LSIL – CIN 1 Maximum depth of invasion from base of the surface epithelium (mm) Thickness of cervical wall at deepest invasion (mm) Maximum extent of linear invasion (mm) Multi-focal invasion Lymphatic space invasion Status of para-cervical tissue (parametrial invasion) Proximity to margins or positive margins Lower uterine segment Vaginal involvement Special stains and immunohistochemistry Metastatic sites (likely to be submitted separately) i.e. lymph nodes positive /number nodes by site; extra-nodal extension Other disease processes

Source: FIGO 2014(79)

Histologic classification

Table 17. Histologic type and classification for cervical cancer

Major histologic type	Classification of histologic type (Kurman et al 2014)
Squamous	Low grade squamous intraepithelial lesion (LSIL – CIN 1) High grade squamous intraepithelial lesion (HSIL – CIN 2 or 3) Invasive squamous cell carcinoma (keratinising; non-keratinising; basaloid; verrucous; warty; papillary; lymphoepithelioma-like)
Glandular	Adenocarcinoma in situ (AIS) Invasive adenocarcinoma (usual type; mucinous; endometrioid; clear cell; serous; mesonephric; villoglandular)
Other epithelial tumours	Adenosquamous Glassy cell Adenoid basal Adenoid cystic Neuroendocrine Undifferentiated
Rare tumours	Mesenchymal (leiomyosarcoma; sarcoma botryoides [embryonal rhabdomyosarcoma]; alveolar soft part sarcoma; angiosarcoma; malignant peripheral nerve sheath tumour; endometrioid stromal sarcoma) Mixed epithelial and mesenchymal (e.g. adenosarcoma; carcinosarcoma) Miscellaneous malignancies (malignant melanoma; lymphoma and leukaemia; germ cell) Secondary tumours

Source: FIGO(35), World Health Organization(156)

Grading

Grading of cervical carcinomas is often included in pathology reporting, but has a considerable subjective component.

The grade of tumour is not required for the Gynecological Oncology Group (GOG) score used to assess the need for adjuvant therapy. The WHO position(156) on grading squamous cell carcinoma is:

"Grading is based on the degree of nuclear pleomorphism, size of nucleoli, mitotic frequency and necrosis, of all which correlate with growth rate, may convey some degree of prognostic information related to tumour sensitivity to chemotherapy or radiotherapy. Based on the extent of squamous differentiation, tumours may be graded as well, moderately or poorly differentiated, or perhaps more reliably into low-grade and high-grade."

Table 18. Historical guide: Grading of squamous cell carcinoma and adenocarcinoma of cervix

Grade	Squamous cell carcinoma	Adenocarcinoma
1	Cell type is typically keratinising large cell. The majority of cells (>75%) are well differentiated. Mitotic activity is infrequent. Tumour architecture includes papillary and solid exophytic types; the borders are pushing with cohesive cells.	The tumour contains well-formed regular glands with papillae. The cells are elongated and columnar with uniform oval nuclei; there is minimal stratification (fewer than three cell layers in thickness). Mitotic figures are infrequent.
2	Cell type is usually non-keratinising large cell. Approximately 50% of the cells are well differentiated; fewer cells show individual keratinisation. Mitotic activity is increased. The tumours have infiltrative borders; obscuring inflammation is more common.	The tumours contain complex glands with frequent bridging and cribiform formation. Solid areas are more common, but these make up less than half of the tumour. The nuclei are more rounded and irregular; micronucleoli are present. Mitoses are more frequent.
3	Cell type is commonly a small cell. The cells have basophilic cytoplasm with high nuclear to cytoplasmic ratios. Cell and nuclear size are uniform. Fewer than 25% of the cells are differentiated. Mitotic activity is abundant, and abnormal mitoses are present. The tumours are typically infiltrative, with individual malignant cells at the borders.	The tumour contains sheets of malignant cells; few glands (<50%) are discernible. The cells are large and irregular with pleomorphic nuclei. Occasional signet cells are present. Mitoses are abundant, with abnormal forms. Desmoplasia is pronounced, and necrosis is common.

Note: This is a historical guide and it is not necessary to assign a grade in current reporting.

Source: Parra-Herran(157)

Uterine cancer

Anatomical pathology reporting

Table 19. Anatomical pathology variables for reporting uterine cancer

Macroscopic	
Specimen	Uterine size and weight, size of cervix, adnexa (right and left), size of para-cervical tissue (R and L), and vaginal cuff size
Tumour	Size (three dimensions), location, appearance, depth of invasion/thickness of cervical wall, para-cervical involvement, corpus involvement, vaginal cuff involvement, distance from tumour to vaginal margin, other sites involved, other findings, identifiers (ink) applied, and blocks submitted
Lymph nodes (by site)	Size (range where applicable), size of largest metastasis, and number of nodes and pieces per cassette
Microscopic	**Histologic type and grade**
	Associated intraepithelial lesion CIN (grade) e.g. LSIL – CIN 1 Maximum depth of invasion from base of the surface epithelium (mm) Thickness of cervical wall at deepest invasion (mm) Maximum extent of linear invasion (mm) Multi-focal invasion Lymphatic space invasion Status of para-cervical tissue (parametrial invasion) Proximity to margins or positive margins Lower uterine segment Vaginal involvement Special stains and immunohistochemistry Metastatic sites (likely to be submitted separately) i.e. lymph nodes positive /number nodes by site; extra-nodal extension Other disease processes

Source: FIGO 2014(79)

Histologic classification

Table 20. Major histologic type and classification of uterine cancer

Major histologic type	Classification of histologic type
Epithelial[i]	Endometrioid adenocarcinoma (adenocarcinoma with squamous differentiation; villoglandular; secretory) Serous carcinoma[ii] Clear cell adenocarcinoma Mucinous adenocarcinoma[i] Squamous cell carcinoma[i] Neuroendocrine tumours Mixed carcinoma Undifferentiated carcinoma Dedifferentiated carcinoma
Non-epithelial	Endometrial stromal (e.g. stromal nodule; low-grade stromal sarcoma[iii]; and high-grade stromal sarcoma[iv]) Smooth muscle tumour of uncertain malignant potential (STUMP) Leiomyosarcoma (epithelioid; myxoid) Undifferentiated uterine sarcoma Miscellaneous mesenchymal tumours (e.g. rhabdomyosarcoma, PEComa)
Mixed epithelial, non-epithelial	Adenosarcoma (with sarcomatous overgrowth)[v] Carcinosarcoma
Miscellaneous	Sex cord-like tumours (e.g. uterine tumour resembling ovarian sex tumour) (Kurman et al 2014) Germ cell neoplasms Neuroectodermal tumours Lymphoma

Source: World Health Organization(156)

Grading

Table 21. Grading of uterine cancer

Grade	Histopathology and degree of differentiation
Grade 1 (G1)	≤5% of non-squamous or non-morular solid growth pattern
Grade 2 (G2)	6–50% of non-squamous or non-morular solid growth pattern
Grade 3 (G3)	>50% of non-squamous or non-morular solid growth pattern

Source: World Health Organization(156)

i An epithelial sub-type must be at least 5% of the total volume to designate the tumour mixed.

ii To consider a tumour a primary SCC or mucinous carcinoma of endometrium, concurrent cervical carcinoma of same cell type must be absent.

iii Low-grade stromal sarcomas are cytologically and architecturally bland with evidence of infiltrative behaviour – classically <10 mitoses/10hpf.

iv High-grade stromal sarcomas are cytologically poorly differentiated with infiltrative behaviour, necrosis, and atypical mitoses, classically >10 mitoses/10 hpf.

v Adenosarcoma with sarcomatous overgrowth should be specifically noted due to its poor prognosis.

Ovarian cancer

Anatomical pathology reporting

Intra-operative consultation (e.g. via frozen section) may be of value where clinical management decisions may be altered depending on the histological type.(158)

Ovarian tumours should be extensively sampled, with one block for every 1–2cm diameter.(156) Slides submitted should support the type of malignancy, grade assigned and the extent of disease.

Intra-operative rupture should be noted.

Documentation of tumour extent is necessary.

Table 22. Anatomical pathology variables for reporting ovarian neoplasms

Macroscopic	
Specimen (include identifying markers for each ovary)	Size and weight, colour, condition of capsule, cut surface appearance, estimate % cystic/% solid tumour, papillary growth pattern (if present, estimate %), and other organs grossly involved
Tumour	Overall size (three dimensions), location(s) involved, appearance, depth of invasion (from endometrial/myometrial junction), myometrial thickness (mm), endometrial thickness (non-tumour), serosal involvement, cervix involvement, adnexa involvement
Lymph nodes (by site)	Size (range where appropriate), size of largest metastasis, number of nodes and pieces per cassette
Microscopic	**Histologic type and grade**
	Histologic type Histologic grade Invasion Capsular / surface involvement Capillary – lymphatic space involvement Special stains Metastatic sites (likely to be submitted separately) Location of positive sites (lymph nodes positive/number of nodes; size of largest metastasis; extra-nodal extension)

Source: Royal College of Pathologists and Australasia(159)

Histologic classification

Table 23. Major histologic type and classification of tumours of the ovary

Major histologic type	Classification of histologic type
Epithelial	Serous (benign; borderline/low malignant potential (LMP); high-grade carcinoma; low-grade carcinoma) Mucinous (benign; borderline/LMP; carcinoma) Endometrioid (benign; borderline/LMP; carcinoma) Clear cell (benign; borderline/LMP; carcinoma) Brenner (benign; borderline/LMP; carcinoma) Seromucinous (benign; borderline/LMP; carcinoma) Undifferentiated carcinoma
Mixed epithelial/ mesenchymal	Adenosarcoma Carcinosarcoma
Sex cord stromal tumours	Granulosa – Theca cell tumours Sertoli-Leydig cell tumours Gynandroblastoma Sex cord-stromal tumour with annular tubules Steroid cell tumours
Germ cell tumours	Dysgerminomas Endodermal sinus tumours Embryonal carcinoma Polyembryona Choriocarcinoma Teratomas (immature [solid]; mature [cystic]) Mixed form
Mixed germ cell and sex cord-stromal tumours	Gonadoblastoma Other
Miscellaneous malignancies	Small cell carcinoma, hypercalcemic type Small cell carcinoma, pulmonary type Mesothelioma Malignant lymphomas Metastatic neoplasm

Source: The Royal College of Pathologists of Australasia(160)

Grading

For serous carcinoma of ovary, the subtype high-grade or low-grade must be recorded, in recognition of the distinct biological behaviours and molecular profiles of these tumours.(161, 162)

It is now recognised that the origin of most cases of high-grade serous carcinoma is the fallopian tube.(163) There are recommendations for assigning site of origin in a range of circumstances.(163)

Use of the universal grading system may be an adjunct to recording low grade versus high grade serous adenocarcinoma, as well as a guide to behaviour of mucinous and endometrioid carcinomas. If the universal grading system has been used, the specific components of the score must be recorded as well as the final grade.

Table 24. Universal grading system for ovarian cancer

Feature	Score
Architectural pattern (predominant)	Glandular =1 Papillary = 2 Solid = 3
Nuclear pleomorphism	Slight =1 Moderate =2 Marked =3
Mitotic activity (mitotic figures per 10 high-power fields [1 hpf = 0.345mm2] in most active region)	0–9 =1 10–24 =2 >25 =3
Grade (total score is obtained by adding the three values obtained for the features above	3–5 = Grade 1 6–7 = Grade 2 8–9 = Grade 3
Clear cell carcinoma – total score is not assessed as architecture is not prognostic. **Borderline tumours** – not usually graded, although a carcinoma in situ subcategory is recognised.	

Source: The Royal College of Pathologists of Australasia(164)

Vulval cancer

Anatomical pathology reporting

Table 25. Anatomical pathology variable for reporting vulval cancer

Macroscopic	
Specimen	Overall size, anatomic landmarks identifiable, and orientation markers per surgeon
Tumour	Anatomic location, size (three dimensions), configuration, extent of involvement (urethra, vagina, anus), and distance to margins (including nearest cutaneous, vaginal and deep)
Tumour	Size (range where applicable), size of largest metastasis, and number of nodes and pieces per cassette
Microscopic	
	Histologic type Histologic grade Depth of invasion (where applicable)[vi] Thickness of invasive tumour[vii] Multi-focal invasion Lymphatic space invasion Perineural invasion Margin invdolvement and/or distance to closest margin(s) Involvement of urethra, rectum, or vagina Adjacent disease(s) (skin, vagina, etc. such as lichen sclerosis, hyperplasia) Lymph nodes (by site) Number of positive/number found Size of largest metastasis

Source: The Royal College of Pathologists of Australasia(165)

vi Microinvasion is not used in reference to vulval carcinoma. Superficial invasion terminology may be useful when combined with a specific measurement for clinical management. Tumour thickness is the measurement of tumour from the surface (including intra-epithelial disease) to the deepest stromal invasion. Measurement is preferably with an ocular micrometer.

vii When lichen sclerosis and squamous hyperplasia occur together, both should be reported. When hyperplastic lesions fulfil diagnostic criteria for specific dermatoses, they should be designated such.

(165)Histologic classification

Table 26. Histologic classification of intraepithial disorders of the vulva

Major histologic type	Classification of histologic type
Non-neoplastic epithelial disorders	Lichen sclerosis Squamous hyperplasia, not otherwise specified Other dermatoses or dermatitis
Mixed non-neoplastic and neoplastic epithelial disorders	When lichen sclerosis or squamous hyperplasia is associated with vulval intra-epithelial neoplasia (VIN), both diagnoses should be reported
Intraepithelial neoplasia	Low grade squamous intraepithelial lesion (LSIL) High grade squamous intraepithelial lesion (HSIL) (note 10) Differentiated-type vulvar intraepithelial neoplasia

Table 27. Histologic classification of neoplasia of the vulva

Major histologic type	Classification of histologic type
	Invasive squamous cell carcinoma (keratinising; non-keratinising; basaloid carcinoma; verrucous; warty carcinoma [condylomatous]) Basal cell carcinoma Adenocarcinoma (e.g. Paget disease; od sweat gland type; of intestinal type)
Bartholin gland carcinoma	Squamous cell carcinoma Adenocarcinoma Adenoid cystic carcinoma Adenosquamous carcinoma Undifferentiated and other
Soft tissue sarcomas	Embryonal rhabdomyosarcoma (sarcoma botryoides) Leiomyosarcoma Other
Other malignant tumours	Malignant melanoma Lymphomas Others

Grading

Grading has traditionally followed an empirical system used in SCC of any site. It is based on a summation of the amount of extra- and intracellular keratinisation, degree of nuclear atypia and mitotic count.

While empirical grading is commonly performed, it is of disputed value as a prognostic indicator. One problem is that keratin production is used as a grading criterion despite there being little prognostic difference between keratin-rich (keratinising) and keratin-poor (basaloid) carcinoma. While grading may work in an experimental

Clinical issues

Clinical trials

Clinical trials are a critical part of improving outcomes in patients with gynaecological cancer. Where possible and appropriate, all patients who are eligible for a clinical trial should be offered the opportunity to participate.

Table 8.1 Classification of clinical trials by objective

Phase	Objective
Phase I	Attempts to determine whether or not a treatment is safe
Phase II	Usually single-group studies that attempt to determine whether or not the trial drug has any positive treatment effect on the disease
Phase III	Randomised controlled trials where a new drug is compared against the best standard therapy
Phase IV	Usually post-marketing surveillance studies

Further information for patients, clinicians and other health professionals about clinical trials can be obtained from:

- Australia New Zealand Gynaecological Oncology Group (ANZGOG)
- National Health and Medical Research Council (NHMRC) Clinical trials Centre
- Cancer Council Australia or state and territory Cancer Councils
- Database of Cancer Research in Australia (CARA).

Familial aspects of gynaecological cancers

Heritable mutations may contribute to the development of some gynaecological cancers. For example, BRCA 1 and BRCA 2 contribute to 10–20% of ovary, fallopian tube and primary peritoneal cancers; Lynch Syndrome is associated with uterine and ovarian cancers. There are also other less common genetic causes (e.g. Peutz-Jeghers syndrome and Cowden syndrome).

Identification of affected patients or family members can allow:

- targeted treatment with novel chemotherapy agents, such as PARP inhibitors
- screening and preventative strategies for syndrome associated cancers.

Consider the histopathology, age at diagnosis and family history. Abnormal mismatch repair gene protein immunohistochemistry may indicate the possibility of Lynch syndrome.

Refer to Cancer Australia's Familial Risk Assessment – Breast and Ovarian Cancer (FRA–BOC) online tool designed by Cancer Australia to assess risk and need for referral. See: https://canceraustralia.gov.au/clinical-best-practice/gynaecological-cancers/familial-risk-assessment-fra-boc.

Indications for referral to a family cancer clinic

It may be appropriate to refer the patient to a family cancer clinic, although in some centres the genetic testing of women with ovarian cancer may be done by gynaecological oncology teams after appropriate training.

Cancer Institute NSW (EviQ) has nationally agreed guidelines which have indications for referral of:

- individuals with concerns about a family history of breast cancer(166)
- individuals with concerns about a family history of endometrial cancer(167)
- individuals with concerns about a family history of ovarian cancer(168).

The NSW Health Centre for Genetics Education has a list of family cancer clinic clinics – see http://www.genetics.edu.au/Genetics-Services/family-cancer-services

Medicare rebate

There is a Medicare rebate for breast/ovarian cancer related genetic testing dependent on defined criteria. Refer to item numbers 73295, 73296 and 73297.

Indications for genetic testing

- For women with high grade non-mucinous invasive epithelial ovarian cancer aged <70, testing of BRCA1/2 is recommended even in the absence of family history. Refer to EviQ for the relevant indications for testing.(168)
- Consideration for testing for other cancer genetic syndromes related to gynaecological cancer (e.g. Peutz-Jeghers syndrome, Cowden syndrome) is available on EviQ, but best done through a family cancer clinic.

Management of woman at increased risk of gynaecological cancer

Nationally agreed guidelines for risk management for unaffected women at increased risk of gynaecological cancer due to a BRCA1/2 mutation(169) or due to Lynch syndrome(170) are available at EviQ.

Cancer Australia has published detailed guidelines about the management of women at increased risk of ovarian cancer.(171) The key point is that ovarian cancer surveillance is not recommended for women at high or potentially high risk. Evidence shows that ultrasound or CA125, singly or in combination, is not effective at detecting early ovarian cancer. For women with a BRCA gene mutation, risk-reducing bilateral salpingo-oophorectomy reduces the risk of pelvic serous cancer, and reduces cancer related and all-cause mortality.

Lymphoedema

Diagnosis and incidence of lymphoedema

Lymphoedema is the accumulation of excess fluid in the body caused by obstruction of the lymphatic drainage mechanisms.(172) Lymphoedema is a progressive chronic condition with the following components:

- excess protein in interstitial fluid
- oedema
- chronic inflammation.

The diagnosis of lymphoedema is often based on clinical criteria alone, with various assessment and limb volume measurement methods available.(173)

The incidence of secondary lymphoedema following treatment for cancer in Australia is unknown and it is likely that its prevalence is underestimated.(174) Lower leg lymphoedema (LLL) is a major source of morbidity for women who have surgery and/or radiotherapy to lymph nodes as part of treatment for a gynaecological cancer. Conservative treatment approaches should be used as appropriate to reduce the risk of secondary lymphoedema.

Ryan et al (2003) reported clinically diagnosed LLL in 18% of women.(175) Of those who developed LLL, 71% did so within 6 months of surgery, the majority of these (53%) within 3 months, and 84% did so by 12 months. (175) This is much sooner than commonly believed. The number developing LLL following vulvectomy and lymph node dissection for vulvar cancer (60%) was significantly greater than for any other type of surgery.(175)

Pelvic lymphadenectomy was associated with a 7–18% risk.(175)

Management of lymphoedema

There are no treatments available to prevent lymphoedema. Management involves decongesting the reduced lymphatic pathways in order to reduce the size of the limb.(172)

Best practice management of lymphoedema involves a holistic, multidisciplinary approach that includes:

- education
- exercise/movement and elevation
- swelling reduction and maintenance
- skin care
- risk reduction
- pain and psychosocial management(173).

Conservative lymphoedema treatment, including complex physical therapy, manual lymph drainage, compression, bandaging, elevation and massage, is associated with volume reductions and improvements in quality of life.(174)

Women who are at risk of developing LLL should be:

- provided with education both pre- and post-operatively about the risks, early signs and symptoms
- provided with information about skin care and exercise
- encouraged to participate in healthy lifestyle behaviours
- referred to a qualified, specialised therapist for early management.

Vaginal stenosis

Vaginal stenosis is the narrowing and/or loss of flexibility of the vagina, and it occurs as a side effect of radiotherapy and/or genital surgery. The vagina is the most common site of late toxicity of brachytherapy for the treatment of gynaecological cancer. Many women develop some degree of stenosis within 4–6 weeks of completing brachytherapy. This can result in long-term sexual dysfunction and painful vaginal examinations for patients, and the inability of clinicians to perform an adequate clinical examination.(176)

Topical oestrogen cream

The use of topical oestrogen cream has proposed benefits for women being treated with brachytherapy for cervical cancer, but remains controversial for women with endometrial cancer.(177)

Vaginal stenosis may be prevented by the use of vaginal dilators. There is wide variation in the practice recommendations made by individual clinicians and radiation oncology centres across Australian (i.e. recommendation to use dilators, time to initiate use, frequency of use, insertion time, duration of use and the provision of information).(178)

As a general guide, all women undergoing vaginal brachytherapy should be:

- provided with information about the development of vaginal stenosis
- instructed in the use of vaginal dilators, regardless of their reported levels of sexual activity
- encouraged to start using the vaginal dilator as soon as comfortably possible, within four weeks of completing brachytherapy
- encouraged to use the dilator daily for a minimum of three years and if possible, indefinitely
- assessed for toxicity, with this documented at clinical follow-up.

Pain or discomfort may be present with initial dilator use. A narrow diameter dilator (1.5–2cm) is recommended to break down early adhesions. As discomfort decreases, the diameter of the dilator can be gradually increased up to 3cm to minimise the late effects of collagen formation and circumferential fibrosis.

There is little consensus on insertion time of dilators, with reports varying from 2–20 minutes (median 5–10 minutes).(178) By promoting daily use, it is hoped that in the long term women will use the dilator at least 2–3 times a week.

Psychosocial care

For clinical information about psychosocial care, refer to:

- the Cancer Australia Clinical practice guidelines for the psychosocial care of adults with cancer (2003) or associated summary card.(179) The guidelines provide an evidence-based guide to the detection and management of psychosocial issues for patients diagnosed with cancer.
- Recommendations for the identification and management of fear of cancer recurrence in adult cancer survivors, a guideline to assist in making management recommendations and providing care for improved patient outcomes(180)
- Clinical guidance for responding to suffering in adults with cancer, about the conceptualisation and assessment of suffering in the cancer context, and therapies or interventions that may help alleviate suffering.(181)

For consumer resources, refer to Cancer Australia. The Cancer: how are you travelling? brochure provides information about the emotional and social impact of cancer for people diagnosed with cancer, their family and friends.(182)

There is also a resource about intimacy and sexuality for women with gynaecological cancer, which supports women (and their partners) in understanding and addressing issues of intimacy and sexuality following the diagnosis and treatment of gynaecological cancer.(183)

Additional information

K. Hodgkinson and J. Gilchrist (eds), The Psychosocial Care of Adults with Cancer: A Health Professional's Guide on What to Say and Do, Melbourne, Ausmed Publications, 2008.

Hobbs K, Smith K. Psychosocial and spiritual care, in T. Lancaster and K. Nattress (eds) Gynaecological Cancer Care: A Guide to Practice, Melbourne, Ausmed Publications, 2005.

Palliative care

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

Palliative care:

- provides relief from pain and other distressing symptoms
- affirms life and regards dying as a normal process
- intends neither to hasten or postpone death
- integrates the biological, psychosocial and spiritual aspects of patient care
- offers a support system to help the family cope during the patient's illness and in their own bereavement
- uses a team approach to address the needs of the patients and their families, including bereavement counselling, if indicated
- will enhance quality of life, and may also positively influence the course of illness
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiotherapy, and includes those investigations needed to better understand and manage distressing clinical complications.(184)

Some women with gynaecological cancer may require palliative care from the day of diagnosis if their disease is already not amenable to curative treatment. Others may require palliative care at a later time when disease progression produces troublesome symptoms.

It is recommended to refer to the Greater Metropolitan Clinical Taskforce GO Secretariat's Best Clinical Practice Gynaecological Cancer Palliative Care (2008) resource, available from the Agency for Clinical Innovation (ACI).(185)

Principles in the care of women with advanced gynaecological cancer

Palliative care should:

- aim to enhance quality of life
- provide symptom relief, attention to personal needs
- provide care planning
- include a pervasive, sound, ethical instinct guiding key clinical decision-making
- include assessment of each problem, differentiating between disease related problems and acute problems with an easily reversible cause.

Appendix 1. Common terminology criteria for adverse events

The National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) is used for collecting treatment-related adverse event data to facilitate the evaluation of new cancer therapies, treatment modalities, and supportive measures.(186)

- **Toxicity** – Toxicity is not clearly defined by regulatory organisations. The term is generally used for an adverse event that is possibly, probably or definitely related to the agent or treatment.
- **Adverse event** – Any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An adverse event is a term that is a unique representation of a specific event for medical documentation and scientific analysis.
- **Dose-limiting adverse event** – This is determined by the individual protocol, not the CTCAE. Although it would be convenient to assume that all Grade 3 events represent dose limiting toxicities, this is not appropriate. Acceptable adverse events vary with the patient population and the anticipated outcome of the treatment. More severe adverse events may be acceptable with a potentially curative regimen than with a palliative treatment.
- **Adverse event categories** – The primary organisation of the CTCAE v3.0 (NCI, 2003) is based on patho-physiological and anatomical categories to facilitate location of adverse events. There are 28 categories of adverse events (Table 28) with more than 200 individual adverse events.

Table 28. CTCAE adverse event categories

CTCAE adverse event categories			
Allergy/immunology	Death	Infection	Pulmonary/upper respiratory
Auditory/ear	Dermatology/skin	Lymphatics	Renal/genitourinary
Bone/blood marrow	Endocrine	Metabolic/laboratory	Secondary malignancy
Cardiac arrhythmia	Gastrointestinal	Musculoskeletal/soft tissue	Sexual/reproductive function
Cardiac general	Growth and Development	Neurology	Surgery/intra-operative injury
Coagulation	Haemorrhage/bleeding	Ocular visual	Syndromes
Constitutional symptoms	Hepatobiliary/pancreas	Pain	Vascular

Source: National Cancer Institute(186)

Grades (general definitions)

For each adverse event, grades are assigned and defined using a scale from 1 to 5. Specific criteria for each grade are included for each adverse event.

Table 29. CTCAE grading of adverse event

Grade	Criteria
1	Mild adverse event
2	Moderate adverse event
3	Severe adverse event
4	Life-threatening or disabling adverse event
5	Death related to adverse event

Most adverse events and grading criteria are applicable to any treatment modality and should be used to classify adverse events regardless of which modality causes the adverse event unless otherwise specified.

When an adverse event occurs in a multimodality therapy, it should be graded using the most relevant description of an adverse event whether it is one from the standard list or one that is specifically for radiotherapy.

Grading is based on specific clinical criteria that usually require evaluation by a clinician. Disease progression or signs and symptoms definitely related to disease should not be graded.

There can be several sources of information for adverse event grading:

- **Patient diaries** – Many investigators require patients to maintain a record of any symptoms or abnormalities they experience during a course of therapy. These diaries are most often discussed when the patient comes into the clinic for the next treatment. The interviewer grades adverse events reported at each visit.
- **History and physical exam** – It has been demonstrated that adverse events will not be identified unless appropriate questions are asked and necessary examination performed. It is necessary to develop interviewing techniques to elicit important adverse event information from patients. Review of systems should be performed as part of the medical history. When symptoms or signs are elicited, more specific questions will be required.
- **Clinical emergencies** – Sometimes, serious adverse events are encountered. These are usually graded and recorded at the time of the event. When additional information becomes available later, it must be recorded and grading changes may be necessary.

Scale for attribution of causality

To ensure that treatment-related conditions are distinguished from disease-related conditions, attribution of causality (Table 30) is a critical though often difficult first step in grading adverse events (NCI, 1999). For each event, the attending clinician in conjunction with the research nurse who examined and evaluated the patient should assign the attribution.

Adverse events must be documented and graded if there is any probable, possible, or definite relationship to the agent. Adverse events that are definitely related to disease should not be graded.

If an adverse event is caused by a combination of treatment and disease, the adverse event should be graded as it is observed with no adjustment.

Table 30. CTCAE scale of attribution of causality

Grade	Criteria
5 = Definite	The adverse event is clearly related to the investigational agent(s)
4 = Probable	The event is likely to be related to the investigational agent(s)
3 = Possible	The adverse event may be related to the investigational agent(s)
2 = Unlikely	The adverse event is doubtfully related to the investigational agent(s)
1 = Unrelated	The adverse event is clearly not related to the investigational agent(s)

Appendix 2. Franco Italian glossary for reporting complications of treatment of gynaecological cancer

Table 31. Franco Italian general grading system from complications

Grade	Criteria
0	Absence of complications or acute reversible symptoms or signs which do not modify the planned course of treatment
1	**Mild complications** – these complications are mildly disabling and may cause some functional impairment
2	**Moderate complications** – both obvious symptoms and signs are present resulting in intermittent or persistent interference with normal activity
3	**Severe complications** – any acute or chronic symptoms or signs that are life threatening either per se or because of the treatment required, and any permanent and severe tissue and/or organ damage.
4	Documented evidence that death is due to the primary treatment, or to the complication of treatment, or to the treatment of complication(s). This applies to each organ system in the following tables.

Table 32. Franco Italian complications by organ sytem and grade

Gastrointestinal – Rectum	
Grade 1	Any acute symptoms of proctitis interrupting treatment for more than 10% of the planned treatment time or lasting >2 weeks after the completion of treatment
	Mild or occasional rectal bleeding with or without mucosal hyperaemia and/or oozing of blood and/or telangiectasia
	Rectocele not requiring treatment
	Haemorrhoids provoked by treatment of the cancer
Grade 2	Rectal bleeding requiring blood transfusion and/or hospitalisation
	Pain and/or tenesmus associated with rectal stenosis demonstrated on barium enema or proctoscopy
	Rectocele requiring surgical treatment
	Ribbon-like stools associated with rectal stenosis demonstrated on barium enema or proctoscopy
	Persistent symptoms or signs of rectal origin requiring iterative medical and/or dietary treatment
Grade 3	Recto-vaginal fistula
	Rectal stenosis requiring surgery

Gastrointestinal – Sigmoid colon	
Grade 1	Narrowing of the lumen with mild constipation
	Mild or occasional bleeding considered to be of sigmoid colon origin
	Immediately repairable intra-operative injury
Grade 2	Intermittent periods of diarrhoea and constipation considered to be of sigmoid origin with or without string-like stools
	Bleeding considered to be of sigmoid origin requiring blood transfusion or hospitalisation
	Necrotic ulceration
Grade 3	Sigmoid fistula
	Sigmoid bleeding requiring surgery
	Sigmoid obstruction requiring surgery
Gastrointestinal – Colon (other than sigmoid)	
Grade 1	Minor reversible symptoms or signs thought to be of colonic origin
	Mild occasional bleeding thought to be of colonic origin
	Immediately repairable intra-operative injury
Grade 2	Intermittent symptoms or signs of colonic origin requiring medical treatment
	Bleeding of colonic origin requiring blood transfusion or hospitalisation
	Necrotic ulceration without need for surgery
Grade 3	Fistula
	Bleeding requiring surgery
	Colonic obstruction requiring surgery
Gastrointestinal – Small bowel	
Grade 1	Post-operative obstruction settling on conservative treatment
	Immediately repairable intra-operative injury
	Signs and symptoms of possible late injury without malabsorption
Grade 2	Symptoms and signs of malabsorption confirmed radiologically and/or biochemically, not requiring surgery
	Clinical and/or radiological evidence of chronic obstruction, not requiring surgery
	Any symptoms or signs requiring surgery resulting in normal bowel functions and normal activity
Grade 3	Chronic obstructions and/or malabsorption resulting in Karnofsky score equal or less than 40% (WHO 3, 4 performance status scale) and/or weight loss of more than a quarter of normal body weight
	Any symptoms or signs requiring surgery not resulting in normal bowel functions and/or normal activity

Gastrointestinal – Stomach and duodenum	
Grade 1	Nausea and/or vomiting despite anti-emetic therapy
	Immediately repairable intra-operative injury
Grade 2	Vomiting with severe fluid and electrolyte unbalance
	Symptoms and signs of gastric or duodenal ulceration within the irradiated fields confirmed radiologically and/or endoscopically, not requiring surgery
	Stress ulcer not requiring surgery
Grade 3	Any ulcer directly or indirectly related to treatment which require surgery
Gastrointestinal – Non-specific abdominal signs and/or symptoms	
Grade 1	Any acute digestive symptoms interrupting treatment for more than 10% of the planned overall treatment time or lasting more than 2 weeks after the completion of treatment
	Persistent or intermittent abdominal symptoms and/or signs considered to be related to treatment without interfering with normal activity
Grade 2	Persistent or intermittent abdominal symptoms and/or signs considered to be related to treatment interfering with normal activity
Grade 3	There are no G3 in this section
Gastrointestinal – Non-specific abdominal signs and/or symptoms	
Grade 1	Any acute symptoms of cystitis interrupting treatment for more than 10% of the planned overall treatment time or lasting more than 2 weeks after the completion of treatment
	Mild or occasional haematuria with or without mucosal hyperaemia and/or telangiectasia
	Stress incontinence, minor and/or occasional incontinence
	Any symptoms or signs of abnormal bladder functions lasting for more than 2 weeks and less than 6 months with residual volume of less than 100 cc and without bacteriuria (<105) and/or 4 episodes of acute cystitis per year
	Cystocoele not requiring treatment
	Immediately repairable intra-operative injury
Grade 2	Haematuria requiring blood transfusion and/or hospitalisation and/or intra vesical therapy
	Postural incontinence
	Any symptoms of bladder dysfunction lasting > 6 months with residual volume of 100 cc or more or with bacteriuria (>105) and/or 4 episodes of acute cystitis per year
	Immediate or early post-operative vesico-vaginal fistula with complete healing and normal function after treatment
	Urethral stenosis requiring repetitive dilatations
	Cystocoele requiring surgery
	Permanent urinary retention from bladder or urethral origin requiring either a temporary catheterisation lasting at least one day or minor surgical manoeuvres on urinary tract
Grade 3	Haematuria requiring major surgery or embolisation
	Total incontinence
	Permanent urinary retention requiring either long-term catheterisation or major surgery
	Early or late vesico-vaginal fistula with permanent anatomical and/or functional damage
	Urethral stenosis requiring surgery

Urinary – Ureters (side/s should be specified)	
Grade 1	Urinary symptoms associated with radiological evidence or ureteric dilatation in the absence of hydronephrosis and lasting more than 6 months
	Immediately repairable intra-operative injury
Grade 2	Immediate or late post-operative uretero-vaginal fistula with subsequent adequate renal function after treatment and not requiring surgery
	Ureteral stenosis requiring surgery with subsequent normal renal function
Grade 3	Uretero-vaginal fistula* and/or ureteral stenosis with subsequent inadequate renal function, or which resulted in a non-functioning kidney, or which required either nephrectomy or permanent nephrostomy * Any complex fistula (e.g. uretero-vesico-vaginal) should be quoted at each site of involvement
Vascular – (side/s should be specified)	
Grade 1	Thrombophlebitis settling on medical treatment
	Symptomatic or asymptomatic lymphocele resolving spontaneously
	Permanent or intermittent leg oedema not interfering with normal activity
	Immediately repairable intra-operative injury
Grade 2	Thrombophlebitis requiring surgery
	Lymphocele requiring drainage
	Intermittent or permanent leg oedema interfering with normal activity
	Permanent or intermittent claudication of the lower limb(s)
	Pulmonary embolism without functional sequelae after medical treatment
Grade 3	Any vascular damage requiring major surgery
	Life-threatening pulmonary embolism occurring during treatment of disease and/or treatment of complications, and/or resulting in permanent functional damage
	Lymphocele resulting in non-functioning kidney requiring major surgery
	Severe leg oedema resulting in Karnofsky score equal to or less than 40% (WHO 3 or 4 degree)

Cutaneous	
Grade 1	Any acute radiation induced skin reaction interrupting treatment for more than 10% of the planned overall treatment time or lasting more than 2 weeks after the completion of treatment
	Asymptomatic radiation-induced cutaneous and/or subcutaneous fibrosis
	Abdominal wound infection or haematoma requiring minor surgery and/or nursing care for more than 4 weeks
	Abdominal wound dehiscence not requiring surgery
Grade 2	Symptomatic radiation-induced cutaneous and/or subcutaneous fibrosis
	Symptomatic skin oedema within the irradiated field(s)
	Symptomatic keloid scar requiring treatment
	Abdominal wound dehiscence requiring surgery
	Telangiectasia
Grade 3	Radiation-induced cutaneous and/or subcutaneous fibrosis requiring surgery
	Radionecrosis
Uterus – Vagina – Vulva	
Grade 1	Any acute symptoms of vulvo-vaginitis interrupting the treatment for more than 10% of the planned overall treatment time or lasting more than 2 weeks after the completion of the treatment
	Vaginal narrowing and/or shortening to half or less than half the original dimensions
	Mild dyspareunia
	Asymptomatic vaginal or vulval oedema with or without telangiectasia
	Uterine perforation or pyometra or haematometra not requiring surgery
	Immediately repairable vaginal tear
Grade 2	Vaginal narrowing and/or shortening to more than half the original dimensions
	Moderate dyspareunia
	Symptomatic vulval oedema and/or telangiectasia and/or fibrosis
	Uterine perforation or pyometra or haematometra requiring exploratory laparotomy or drainage surgery
	Repeated infectious vaginitis
Grade 3	Complex vaginal stenosis
	Severe dyspareunia
	Vulval and/or vaginal and/or uterine necrosis requiring surgery
	Post-treatment peritonitis or uterine perforation requiring major surgery

Pelvic soft tissues	
Grade 1	Fibrosis limited to the inner half of one or both parametria
	Pelvic abscess or haematoma draining spontaneously
Grade 2	Fibrosis limited to the inner half of one or both parametria
	Pelvic abscess or haematoma draining spontaneously
	Fibrosis involving at least one parametrium as far as the pelvic side wall, and/or asymptomatic frozen pelvis
	Pelvic abscess or haematoma requiring surgical drainage
Grade 3	Symptomatic frozen pelvis
	Peritonitis or haematoma requiring laparotomy
Bone (side/s should be specified)	
Grade 1	Radiological signs of bony sclerosis or fracture within the irradiated field(s) with or without pain, but without functional impairment
Grade 2	Radiological signs of bony sclerosis or fracture within the irradiated field(s) with pain and functional impairment, but not requiring surgery
Grade 3	Clinical symptoms and/or radiological signs of bony sclerosis and/or necrosis and/or fracture requiring surgery
Peripheral nerves (side(s) should be specified)	
Grade 1	Neurological sensory symptoms in the absence of signs with or without mild functional impairment
Grade 2	Neurological sensory symptoms with moderate functional impairment, and/or neurological sign(s) with or without moderate functional impairment
Grade 3	Neurological symptoms and signs with marked trophic changes and/or severe functional impairment
Haemopoietic tissue Impairment is quantified according to the WHO criteria. The haemopoietic complications are graded according to the clinical consequences.	
Grade 1	Any acute haemopoietic impairment interrupting treatment for more than 10% of the planned overall treatment time
Grade 2	Any haemopoietic impairment causing definitive interruption of the planned treatment with subsequent haematological recovery
Grade 3	Persistent haematological toxicity equal or above the level of any WHO grade 2

Appendix 3. Karnofsky rating scale and GOG/ECOG performance status

The Karnofsky Rating Scale(187) and GOG/ECOG Performance Status(188) are used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine the appropriate treatment and prognosis.(189)

Table 33. Karnofsky Rating Scale and ECOG Performance Status

Rate	Karnofsky Rating Scale	Grade	ECOG/GOG Performance Status
100	Normal with no complaints or evidence of disease	**0**	Fully active, able to carry out all pre-disease performance without restriction.
90	Able to carry on normal activity but with minor signs of illness present.		
80	Normal activity but requiring effort. Signs and symptoms of disease more prominent.	**1**	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.
70	Able to care for self, but unable to work or carry on other normal activities.		
60	Able to care for most needs, but requires occasional assistance.	**2**	Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Considerable assistance and frequent medical care required; some self-care possible.		
40	Disabled; requiring special care and assistance.	**3**	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled; hospitalisation required but death not imminent.		
20	Extremely ill; supportive treatment and/or hospitalisation required.	**4**	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
10	Imminent death		
0	Dead	**5**	Dead

Appendix 4. Response evaluation criteria for solid tumours (RECIST)

Definitions

RECIST is a set of published rules that define when cancer patients improve ('respond'), stay the same ('stable'), or worsen during treatments.(190) The criteria were published by an international collaboration including European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the USA, and the National Cancer Institute of Canada Clinical Trials Group (NCIC).(190)

The following definitions and criteria have been abstracted from the RECIST Quick Reference.

Table 34. RECIST definitions of extent of disease

Extent of Disease	Definition
Measurable disease	The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology
Measurable lesions	Lesions that can be accurately measured in at least one dimension with the longest diameter ≥ 20 mm using conventional techniques or ≥10 mm with spiral CT scan
Non-measurable lesions	All other lesions, including small lesions (longest diameter <20mm with conventional techniques or <10mm with spiral CT scan

Source: RECIST(190)

Baseline documentation of target and non-target lesions:

- All measurable lesions up to a maximum of five lesions/organ and 10 lesions in total, representative of all involved organs should be identified as 'target lesions' and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with longest diameter [LD]) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the LD for all target lesions should be calculated and reported as the baseline sum LD. The baseline sum LD is used as the reference by which to characterise the objective tumour.
- All other lesions (or sites of disease) should be identified as "non-target lesion" and should be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow up.

Response criteria for target and non-target lesions

Table 35. RECIST criteria for measuring response of target lesions

Response	Criteria
Complete response (CR)	Disappearance of all target lesions
Partial response (PR)	At least a 30% decrease in the sum LD of target lesions, taking as reference the baseline sum LD
Progressive disease (PD)	At least a 20% increase in the sum of target lesions, taking as reference the smallest sum LD recorded since treatment started or the appearance of one or more new lesions
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment regime started

Source: RECIST(190)

Table 36. RECIST criteria for measuring response of non-target lesions

Response	Criteria
Complete response (CR)	Disappearance of all non-target lesions and normalisation of tumour marker level
Incomplete response/ Stable disease (SD)	Persistence of one or more non-target lesions(s) and/or maintenance of tumour marker level above normal limits
Progressive disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Source: RECIST(190)

Appendix 5. Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer radiation morbidity scoring

Radiotherapy toxicities

In reporting toxicity associated with radiotherapy, it is necessary to differentiate between acute and late morbidity.

- Acute morbidity is defined as those events that occur from day one, or commencement of radiotherapy, through day 90.
- Late radiation effects are defined as those effects that first occur 90 days or more after initiation of radiotherapy.

There are 14 acute and 17 late morbidity organ tissue categories graded from 0 (no morbidity) to 5 (death). The 1–4 grading for the most common tissue categories relating to the radiation treatment of gynaecological cancers are shown in Tables 37–38.

Table 37. Grading acute radiation morbidity for most common tissue sites during/following treatment for gynaecological cancer

	Grade 1	Grade 2	Grade 3	Grade 4
Skin	Follicular, faint or dull erythema Epilation Dry desquamation Decreased sweating	Tender or bright erythema Patchy moist desquamation Moderate oedema	Confluent, moist desquamation other than skin folds Pitting oedema	Ulceration Haemorrhage Necrosis
Lower GI (includes pelvis)	Increased frequency or change in quality of bowel habits not requiring medication Rectal discomfort not requiring analgesics	Diarrhoea requiring parasympatholytic drugs Mucous discharge not necessitating sanitary pads Rectal and/or abdominal pain requiring analgesics	Diarrhoea requiring parenteral support Severe mucous or blood discharge necessitating sanitary pads Abdominal distension (flat plate radiograph demonstrates distended bowel loops)	Acute or sub-acute obstruction Fistula Perforation GI bleed requiring transfusion Abdominal pain on tenesmus requiring decompression or diversion
Genito-urinary	Frequency of urination or nocturia twice pre- treatment habit Dysuria, urgency not requiring medication	Frequency of urination or nocturia which is less frequent than every hour Dysuria, urgency, bladder spasm requiring local anaesthetic	Frequency with urgency and nocturia hourly or more frequently Dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic Gross haematuria with/without clot passage	Haematuria requiring transfusion Acute bladder obstruction secondary to clot passage Ulceration Necrosis

Table 38. Grading late radiation morbitity for common tissue sites following treatment for gynaecological cancer

	Grade 1	Grade 2	Grade 3	Grade 4
Bladder	Slight epithelial atrophy Minor telangiectasia (microscopic haematuria)	Moderate frequency Generalised telangiectasia Intermittent macroscopic haematuria	Severe frequency and dysuria Severe generalised telangiectasia (often with petechiae) Frequent haematuria Reduction in bladder capacity (<150 ml)	Necrosis Contracted bladder (capacity <100 ml) Severe haemorrhagic cystitis
Bowel	Mild diarrhoea Mild cramping Bowel movement <5 times daily slight rectal discharge or bleeding	Moderate diarrhoea and colic Bowel movement >5 times daily Excessive rectal mucous or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis Perforation Fistula
Vagina	Partial stenosis or shortening but less than complete occlusion	Complete occlusion Telangiectasis with frequent bleeding	Radionecrotic ulcer	Fistula to bladder bowel or peritoneal cavity

Appendix 6. Useful websites

Organisation	Website
American Cancer Society (ACS)	http://www.cancer.org
American Society of Clinical Oncology (ASCO)	http://www.asco.org
Australian Bureau of Statistics (ABS)	http://www.abs.gov.au
Australian Department Health and Aging (ADHA)	http://www.health.gov.au
Australian Health and Research Data Managers Association (AHRDMA)	http://www.aihw.gov.au
Australian Institute of Health and Welfare (AIHW)	http://www.aihw.gov.au
Australian Society of Gynaecological Oncologists (ASGO)	http://www.asgo.net.au/index.html
Canadian Cancer Society (CCS)	http://www.cancer.ca
CancerBACUP	http://patient.info/leaflets/cancerbacup.htm
Cancer Council NSW (CCNSW)	https://www.cancercouncil.com.au
Cancer Nurses Society of Australia (CNSA)	http://www.cnsa.org.au
Centre for Evidence Based Medicine, Oxford	http://www.cebm.net/
Doctors Reference Site	http://www.drsref.com.au
Eastern Cooperative Oncology Group (ECOG)	http://ecog-acrin.org
European Organisation for Research & Treatment of Cancer (EORTC)	http://www.eortc.be
Food and Drug Administration (FDA)	http://www.fda.gov
International Federation of Gynecology and Obstetrics (FIGO)	http://www.figo.org
International Union Against Cancer (UICC)	http://www.uicc.ch
Gynecologic Oncology Group (GOG)	http://www.gog.org
Journal of the American Medical Association (JAMA)	http://jamanetwork.com/journals/jama
Journal of Clinical Oncology (JCO)	http://www.jco.org
Journal of the National Cancer Institute	https://academic.oup.com/jnci/issue
Medscape Hematology-Oncology	http://www.medscape.com/hematology-oncologyhome
Memorial Sloan-Kettering Cancer Center	http://www.mskcc.org
National Cancer Institute (NCI)	https://www.cancer.gov
National Cancer Institute of Canada (NCIC)	http://www.ncic.cancer.ca
National Health and Medical Research Council (NHMRC)	http://www.nhmrc.gov.au
National Institutes of Health (NIH)	http://www.nih.gov
The New England Journal of Medicine (NEJM)	http://www.content.nejm.org

NHMRC Clinical Trials Centre (CTC)	http://www.ctc.usyd.edu.au
NSW Health	http://www.health.nsw.gov.au
Oncolink	https://www.oncolink.org
Overcome	http://www.ovacome.org.uk
Radiotherapy Oncology Group (RTOG)	http://www.rtog.org
Royal Australian and New Zealand College of O&G (RANZCOG)	http://www.ranzcog.edu.au
Society of Gynecologic Oncologists (SGO)	http://www.sgo.org
Southmost Oncology Group (SWOG)	http://vvww.swog.org
The Cancer Institute NSW	https://www.cancerinstitute.org.au
The Lancet	http://www.thelancet.com
Therapeutic Goods Administration (TGA)	https://www.tga.gov.au
World Health Organization (WHO)	http://vvww.who.int

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