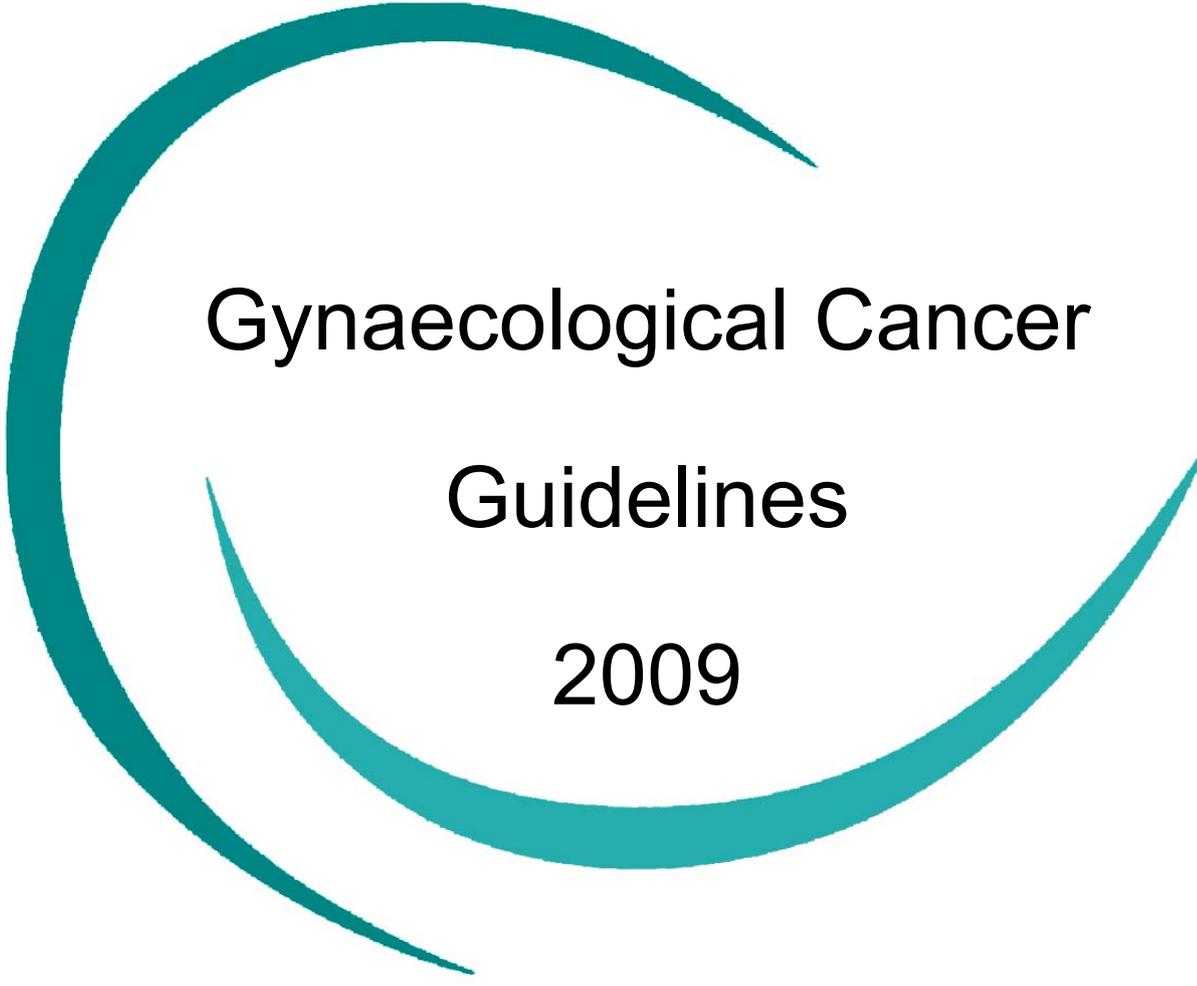


Best Clinical Practice

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Gynaecological Cancer

Guidelines

2009



Greater Metropolitan
Clinical Taskforce

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FOREWORD

Gynaecological Oncology Clinical Practice Guidelines were originally published in 2004 after many years of meetings 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, this group attracted a grant from the then Greater Metropolitan Transition Taskforce (GMITT) which provided for a coordinator, publishing and distribution of the document.

In addition to the disease sites, there are chapters on Pathology and Clinical Issues which includes clinical trials, familial aspects of gynaecological cancer, lymphoedema, palliative care, psychosocial care and vaginal stenosis.

In 2008 the Greater Metropolitan Clinical Taskforce (GMCT) formed a working group to review the chapters one at a time. In this version, now titled *Best Clinical Practice Gynaecological Cancer Guidelines 2009*, the Uterine Cancer chapter has been reviewed and updated. In Clinical Issues, the Palliative Care and Psychosocial Care sections remain, but are covered in greater depth in the GMCT's sister publication *Best Clinical Practice Gynaecological Cancer Palliative Care 2008*. All other chapters are the original versions which will be updated as they are reviewed.

The format of revised sections is different to the original document with standardised types of headings being used. It is important to note that the GMCT Review Group uses updated references in reviewed sections with the same rigour as the original document.

The guidelines are intended to be evidence-based wherever possible, but are not intended to be prescriptive. It is acknowledged that there is more than one approach to most clinical scenarios, but it is hoped that these guidelines, resulting as they do from many years of multidisciplinary cooperation, will bring some uniformity of approach, particularly with respect to radiation fields and doses, and chemotherapeutic protocols. It is also hoped that they may form the basis for collaborative research between institutions, particularly in relation to the less common tumours.

Thank you to all who have contributed to these guidelines:

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CERVICAL CANCER

STAGING OF CERVICAL CANCER

Staging of cervical cancer (Table 1.1) is based on clinical evaluation and must not be changed because of subsequent surgical findings. Where there is doubt as to which stage a particular cancer should be allocated, the earlier stage is mandatory.

Table 1.1 Carcinoma of the cervix uteri: FIGO nomenclature (Montreal, 1994)

FIGO stage	Extent of disease
Stage 0	Primary tumour cannot be assessed. No evidence of primary tumour. Carcinoma in situ.
Stage I	<p>The carcinoma is strictly confined to the uterus (extension to the corpus should be disregarded).</p> <p>Stage IA - Invasive cancer identified only microscopically. All gross lesions, even with superficial invasion, are stage IB cancers. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm, and no wider than 7 mm*.</p> <p>Stage IA1 – measured stromal invasion not greater than 3 mm depth, extension not greater than 7 mm.</p> <p>Stage IA2 – measured stromal invasion greater than 3 mm and not greater than 5 mm, extension not greater than 7 mm.</p> <p>Stage IB - Clinical lesions confined to the cervix or pre-clinical lesions greater than IA.</p> <p>Stage IB1 – clinical lesion no greater than 4 cm in size.</p> <p>Stage IB2 – clinical lesions greater than 4 cm in size.</p> <p>* The depth of invasion should not be greater than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, whether venous or lymphatic, should not alter the staging.</p>
Stage II	<p>The carcinoma extends beyond the cervix, but not to the pelvic wall or the lower third of the vagina.</p> <p>Stage IIA – no obvious parametrial invasion</p> <p>Stage IIB – obvious parametrial invasion</p>
Stage III	<p>The carcinoma has extended to the pelvic wall. On rectal examination there is no cancer-free space between the tumour and the pelvic wall. The tumour involves the lower third of the vagina. All cases with hydronephrosis or non-functioning kidney are included, unless known to be due to other causes.</p> <p>Stage IIIA – no extension to the pelvic, but involves the lower third of the vagina</p> <p>Stage IIIB – extension onto the pelvic wall and/or hydronephrosis or non-functioning kidney</p>
Stage IV	<p>The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to stage IV.</p> <p>Stage IVA – spread of growth to adjacent organs</p> <p>Stage IVB – spread to distant organs</p>

The following examinations are permitted for staging work-up:

- PV/PR examination – the size of the cervix is best determined by rectal exam and is also necessary to determine parametrial extension
- colposcopy
- cystoscopy, proctoscopy / sigmoidoscopy, IVP (optional for \geq 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)

Optional examinations such as CT, MRI or PET scans are of value for planning treatment. They may be useful in identifying macroscopic or microscopic nodal disease that is more extensive than anticipated clinically. The sensitivity and specificity of CT scan or MRI to rule out small nodal disease, particularly in the para-aortic chain where extended-field radiation therapy may offer a survival advantage, is somewhat limited (Scheidler et al, 1997), but PET scanning is much more useful in this regard.

Non-randomised studies of surgical staging have failed to demonstrate a survival benefit over clinical staging (Potter et al, 1993). Patients are likely to experience increased morbidity and mortality (Lagasse et al, 1980), particularly with trans-peritoneal dissection of the para-aortic lymph nodes (Weiser et al, 1989). 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 (Dargent et al, 2000a; Querleu et al, 2000; Vergote et al, 2002).

STAGE IA – MICROINVASIVE DISEASE

The following treatment recommendations (Figure 1.1) 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 where preservation of fertility is desired. Several series have reported recurrence rates comparable to radical hysterectomy, and encouraging live-born pregnancy rates (Roy et al, 1998; Covens et al, 1999; Dargent et al, 2000b; Shepherd et al, 2001; Schlaerth et al, 2003; Burnett et al, 2003). Most cases are in association with squamous cell carcinoma with maximum dimensions of < 2cm. Radical abdominal trachelectomy with pelvic lymphadenectomy may also be an option. These procedures are still considered investigational, and appropriate cases should be referred to tertiary referral centres specialising in laparoscopic surgery.

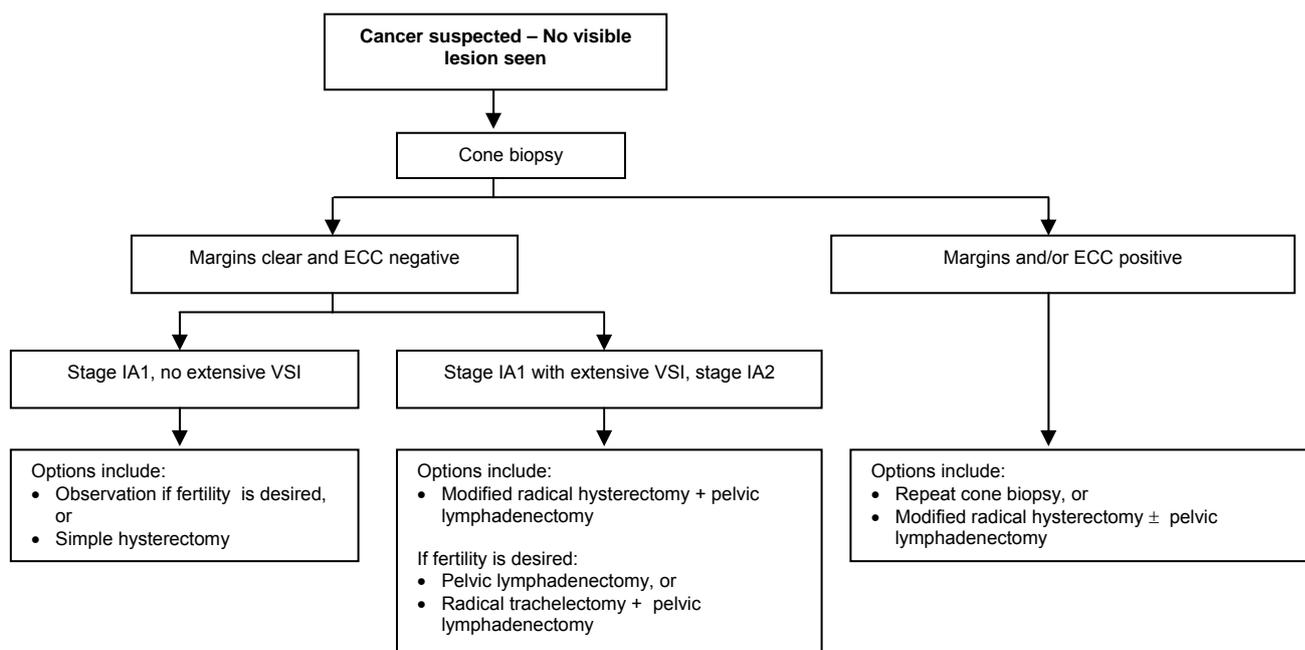


Figure 1.1 Management of microinvasive cervical cancer

STAGE IB and SELECTED STAGE IIA DISEASE

The following treatment recommendations (Figure 1.2) 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.

There is no high level of evidence to support the choice of either radical surgery or radiation therapy in the treatment of early-stage cervical cancer. Whilst overall disease-free survival is similar for both treatment modalities, the rates and types of complications differ (Landoni et al, 1997), with the combination of surgery and radiation therapy having greater subsequent morbidity than for either modality alone.

Optimal therapy for each patient should therefore take account of concurrent medical illness(es) and patient preference.

A randomised study comparing survival, relapse and morbidity between type II and type III radical hysterectomy in stage IB – stage IIA cervical cancer has found both to be equally effective; the former being associated with a lesser degree of late complications (Landoni et al, 2001). Radical trachelectomy and laparoscopic pelvic lymphadenectomy may be an option if fertility is desired (see previous section on microinvasive disease).

Results from five randomised phase III trials (Keys et al, 1999; Rose et al, 1999; Morris et al, 1999; Whitney et al, 1999, Peters et al, 2000) have shown an overall survival advantage for cisplatin-based chemotherapy given concurrently with radiation therapy. The patient populations in these studies included women with stage IB2 – stage IVA disease treated with primary radiation therapy, and women with stage I – stage IIA disease found to have poor prognostic factors (i.e. metastatic disease in pelvic lymph nodes, parametrial disease, or positive surgical margins). Although the trials vary somewhat in terms of stage of disease, radiation therapy dose, and chemo-radiation therapy schedule, they demonstrate a significant survival benefit for this combined approach with the risk of death from cervical cancer being decreased by 30% - 50%. Based on these results, concurrent cisplatin-based chemotherapy should be incorporated with radiation therapy in the treatment of women who require radiation therapy for the treatment of cervical cancer.

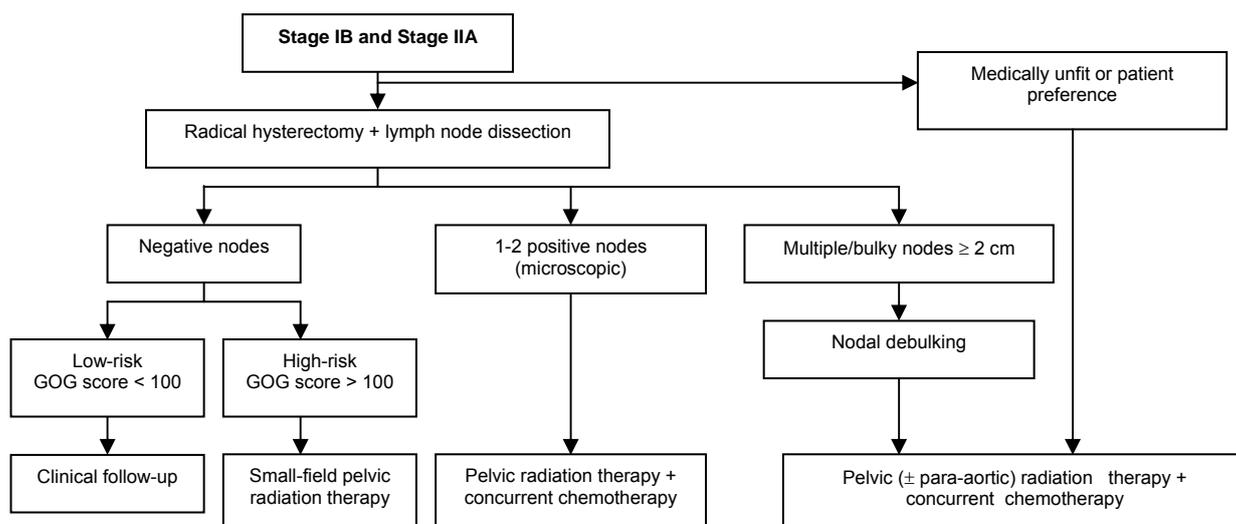


Figure 1.2 Management of early stage cervical cancer

High-Risk Node-Negative Disease

Approximately 15% of patients with negative nodes will develop recurrent disease, with approximately 75% of these recurrences being in the pelvis. The GOG scoring system (Delgado et al, 1990) (Table 1.2) is an attempt to quantify the clinico-pathologic risk of recurrence following radical hysterectomy. In this series of 645 patients, a GOG score of 120 gave a relative risk of recurrence of 40% at 3 years.

The GOG study by Sedlis et al (1999) evaluated the risks and benefits of adjuvant radiation therapy aimed at reducing recurrence in women with stage IB disease treated by radical hysterectomy and pelvic lymphadenectomy, with at least two of the following risk factors: outer-third stromal invasion; capillary lymphatic space invasion; and large clinical tumour diameter. Adjuvant whole pelvic radiation therapy following radical surgery was shown to reduce the number of recurrences at the cost of 7% grade 3 – 4 toxicity versus 2.2% in the no-further-treatment group.

In an attempt to reduce morbidity without compromising survival, a pilot study of small-field pelvic radiation therapy was undertaken at the Royal Hospital for Women (Kridelka et al, 1999). This showed a significantly improved survival, when compared with the GOG results. These findings were confirmed in a similar study undertaken more recently by Ohara et al (2003).

Extra-Uterine Disease (positive nodes, parametria or surgical margins)

The use of combined adjuvant chemotherapy and pelvic radiation therapy following primary surgery for extra-uterine disease has been shown to significantly improve both relapse-free and overall survival when compared to radiation therapy alone (Peters et al, 2000).

The role of extended-field (para-aortic) radiation therapy is controversial. The RTOG study (Morris et al, 1999) showed a survival advantage with pelvic radiation therapy and concurrent cisplatin compared to extended-field radiation therapy alone (although none of these patients had evidence of para-aortic nodal disease, demonstrated either by lymphangiography or retroperitoneal surgical staging). Information on the toxicity of extended-field radiation with concurrent cisplatin-based chemotherapy is limited. Such planned treatment may require dose-reduction of chemotherapy to allow completion of treatment.

Table 1.2 Relative-risk of recurrence after radical hysterectomy for stage I cervical cancer

	Variable	Relative-risk	
Depth of tumour penetration (mm)	<u>Superficial</u>	3 *	1.0
		4	3.0
		5	7.2
		6	14
		7	21
		8	26
	10	31	
	<u>Middle</u>	5	20
		6	22
		7	23
		8	25
		10	28
		12	32
	14	36	
	<u>Deep</u>	7	28
		8	30
		10	34
		12	37
		14	41
16		45	
* arbitrary reference	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	

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

For example, a 7 mm superficial tumour, measuring 2 cm, with VSI would be:

$$21 \times 1.9 \times 1.7 = 67.8$$

STAGE IB2 DISEASE

Bulky stage IB tumours (> 4 cm) are difficult to treat and, as such, there is no recommended standard therapy. Problems exist with both surgical and chemo-radiation treatment modalities. Treatment options include:

- primary chemo-radiation therapy
- primary surgery as for stage IB1
- neo-adjuvant chemo-radiation therapy followed by hysterectomy

Neo-adjuvant chemotherapy followed by radical surgery has emerged as a possible alternative to conventional chemo-radiation therapy for locally advanced disease. A number of phase III trials (Keys et al, 1999; Chang et al, 2000; Benedetti-Panici et al, 2002; Napolitano et al, 2003) have reported a survival benefit for patients with stage IB2 – stage II disease. Whilst these outcomes have not been compared to concurrent chemo-radiation therapy alone in a randomised controlled trial, the GOG study (Keys et al, 1999) comparing cisplatin, radiation therapy and adjuvant hysterectomy with radiation therapy alone followed by hysterectomy for bulky stage IB disease, suggests that the role of hysterectomy is doubtful given the superior result with the chemo-radiation therapy arm.

STAGE II – STAGE IVA

Treatment will depend on whether patients have locally advanced disease or bulky nodes on pre-operative CT scan (Figure 1.3).

Locally advanced disease

Results from two phase III trials (Rose et al, 1999; Whitney et al, 1999) report an overall survival benefit for cisplatin-based chemotherapy given concurrently with radiation therapy.

Treatment outcome has been shown to correlate with total duration of treatment (Fyles et al, 1992; Lanciano et al, 1992; Girinsky et al, 1993) and anaemia during treatment (Grogan et al, 1999). Attempts should be made to minimise treatment delays, and to maintain an adequate haemoglobin level (> 100 g/L) during treatment.

Bulky lymph nodes on pre-radiation therapy CT scan

Based on historical analysis, patients shown to have metastatic disease present on pre-treatment assessment have been found to have a poor prognosis. Investigational studies have been proposed to improve prognosis in this group.

Drawing an analogy to other cancer sites (e.g. head and neck), and consideration of radio-therapeutic principles, an investigational approach is to perform a pre-radiation therapy extra-peritoneal surgical debulking of all macroscopic lymph nodes followed by extended-field radiation therapy and brachytherapy (Hacker et al, 1995; Cosin et al, 1997).

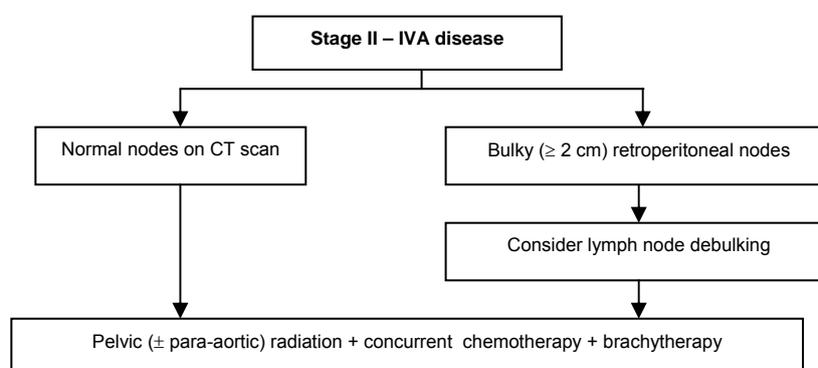


Figure 1.3 Management of advanced stage cervical cancer

ADVANCED / RECURRENT DISEASE

Treatment of advanced or recurrent disease will depend on previous treatment given, site or extent of recurrence, disease-free interval, and patient performance status at presentation (NIH, 1996) (Figure 1.4).

Some patients with recurrence will be highly treatable, whilst others can only be treated with palliative intent. Oncologists should assure patients that psychological support and adequate treatment of all symptoms, including pain, is part of the overall treatment plan.

Radiation therapy in combination with chemotherapy may cure 40% - 50% of patients with recurrence in the pelvis following radical surgery (Thomas et al, 1987).

Cisplatin-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. Response rates are consistently higher in patients with a good performance status and extra-pelvic disease, and lower in patients with a previously irradiated site.

The impact of chemotherapy on palliation and survival is unclear.

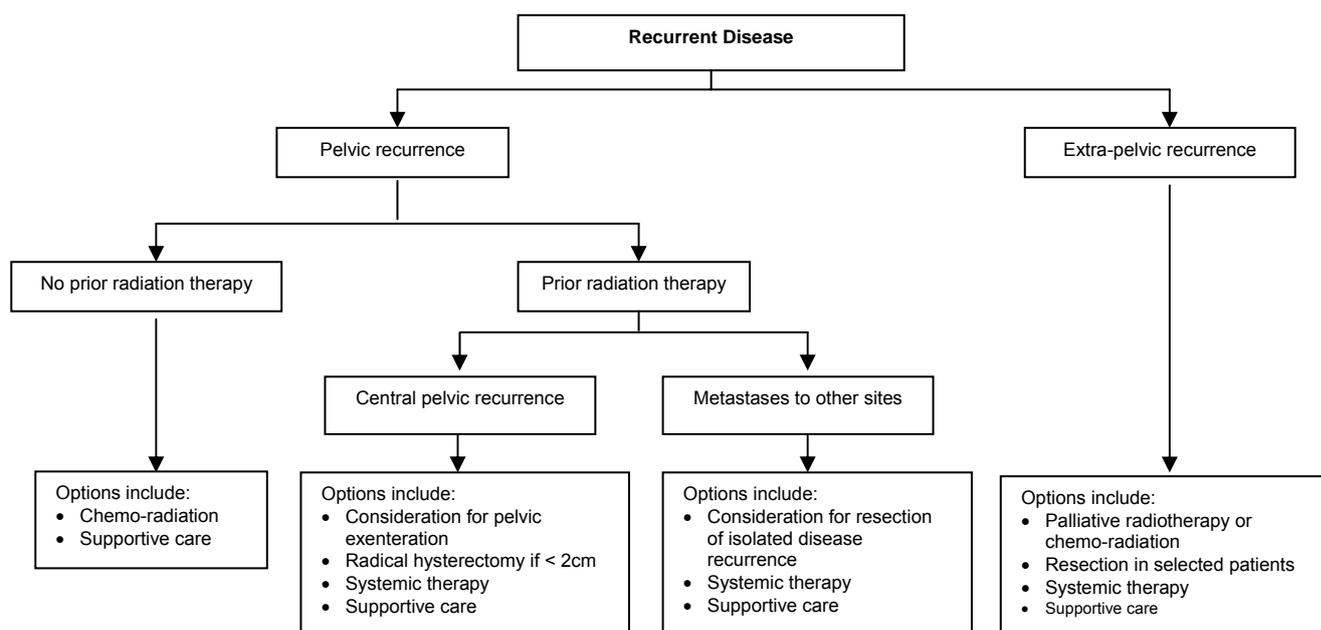


Figure 1.4 Management of recurrent cervical cancer

SMALL CELL CARCINOMA (neuroendocrine)

The literature suggests both poor survival and outcome for women with small cell carcinoma of the cervix – this is in line with small cell carcinomas arising in other sites (Perrin & Ward, 1995).

Patients should have:

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

Prior to treatment, patients should have the following investigations performed:

- FBC, EUC, LFTs, and LDH
- neurone-specific enolase
- CT scan of chest, abdomen and pelvis, and brain
- bone marrow examination

In the absence of randomised prospective trials, or established guidelines, the following investigational study treatment is suggested (Tables 1.3 and 1.4).

Table 1.3 Treatment schema for patients with small cell cervical cancer

Stage of disease	Treatment schema
Early stage disease (stage IB or stage IIA)	<ul style="list-style-type: none"> • Surgical resection (e.g. radical hysterectomy + pelvic lymphadenectomy) • 3 cycles chemotherapy • pelvic radiation therapy • further 3 cycles chemotherapy
Locally advanced disease	<ul style="list-style-type: none"> • 3 cycles chemotherapy • pelvic radiation therapy + brachytherapy • further 3 cycles chemotherapy
Metastatic / recurrent disease	<ul style="list-style-type: none"> • 2 cycles chemotherapy, then assess response • responders continue to maximum 6 cycles

Table 1.4 Chemotherapy regimen for patients with small cell carcinoma of the cervix

Day of cycle	Drug	Dose & route	Cycle frequency
1	Carboplatin	AUC 5	q3weekly
1 – 3	+ Etoposide	100 mg/m ²	

SPECIAL CIRCUMSTANCES

Inadvertent hysterectomy

Treatment options for patients discovered to have squamous cell carcinoma after simple hysterectomy include (Hacker, 2000):

- full pelvic radiation therapy
- radical surgery consisting of parametrectomy, upper vaginectomy, and pelvic lymphadenectomy

If there is gross lymphadenopathy demonstrated on radiological examination (≥ 2 cm), an extra-peritoneal lymphadenectomy should be performed followed by radiation therapy.

Re-operation should not be performed if there is evidence of metastatic disease, or there is an indication for post-operative radiation therapy on the basis of the hysterectomy specimen (eg. the surgical margins are not clear, and there is deep tumour infiltration or prominent lymph vascular space invasion).

Cancer arising in the cervical stump

Treatment of patients with cancer of the cervical stump is effective, yielding results comparable to those seen in patients with an intact uterus. Three large series (Miller et al, 1984; Barillot et al, 1993; Hellstrom et al, 2001) report similar results for loco-regional control and survival following pelvic radiation therapy and brachytherapy. Higher post-radiation therapy complication rates were reported than for patients with an intact uterus. This is most likely due to the event of previous surgery being conducted and the likelihood of compromised methods of delivering radiation therapy due to this surgery.

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

Cervical cancer in pregnancy

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

Treatment of invasive cancer during pregnancy depends on stage of disease and gestational age at diagnosis. The traditional approach is to recommend immediate treatment appropriate to the stage of disease when diagnosed before fetal maturity, and to delay treatment only if the cancer is detected in the third trimester. However, other reports suggest a deliberate delay to allow improved fetal outcome may be a reasonable option for patients with stage IA and early stage IB disease (Sood et al, 1996).

The clinical problem of cervical cancer in pregnancy requires attention to the health of the woman as well as the safety of the fetus. Ethical concerns, cultural and religious issues, and whether or not the patient wishes to continue with the pregnancy after being informed of the risks and benefits of treatment will influence appropriate treatment. Optimal counselling may require an interdisciplinary approach (ACOG, 2002).

RADIATION THERAPY FIELDS

Small-field external beam pelvic radiation therapy

Indications

- stage I or stage IIA following radical hysterectomy
- node-negative
- high-risk

Dosage

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

Field borders

AP volume borders

- superior – top of sciatic notch (S2 - S3 vertebra)
- inferior – bottom of obturator foramina
- lateral – 1 cm lateral to pelvic sidewall

Lateral volume borders

- anterior – 1 cm posterior to pubic tubercle
- posterior – ischial tuberosities

Standard-field (whole pelvis) external beam radiation therapy

Indications

Used in combination with brachytherapy as definitive treatment for non-metastatic disease

Dosage

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

Field borders

AP volume borders

- superior – lower border of L4-L5 vertebral junction
- inferior – inferior aspect of obturator foramina (where there is vaginal extension, the margin should be 3 cm below obvious disease)
- lateral – 2 cm lateral to the bony pelvic brim (corner blocks may be used to protect normal tissue)

Lateral volume borders

- anterior – outer edge of symphysis pubis
- posterior – will include the primary tumour and any extension of the disease posteriorly along the utero-sacral ligaments, as well as the pre-sacral nodes in front of S1 and S2 vertebra

Extended-field (para-aortic) external beam radiation therapy

Indications

High-risk para-aortic nodal involvement and/or the presence of histologically documented disease

Dosage

45 Gy in 1.6 Gy – 1.8 Gy fractions, delivered by four-field technique

Field borders

The para-aortic field is a “chimney” which extends from the superior edge of the standard pelvic field. The patient is supine.

AP volume borders

- superior – lower border of L1 vertebra (minimum)
- inferior – superior aspect of standard pelvic field
- lateral – tip of transverse process (8 cm)

Lateral volume borders

- anterior – approximately 4 cm in front of anterior edge of vertebral bodies
- posterior – 1 cm behind anterior edge of vertebral bodies

Brachytherapy

Low-dose-rate (LDR) or high-dose-rate (HDR) is given according to institutional availability, and preference.

There should be an emphasis on avoiding a prolonged interval (not > 2 weeks) between external beam radiation therapy and brachytherapy (Lanciano et al, 1993; Girinsky et al, 1993; Fyles et al, 1995).

Calculation of bladder dose and calculation or measurement of rectal dose is recommended. The dose should be in the range of 25 Gy – 35 Gy (LDR) at Point A. The optimum dose and dose per fraction using HDR is not yet well defined. Fraction sizes greater than 7.5 Gy should be avoided (Orton et al, 1991).

If the residual disease is too extensive for brachytherapy, or if it cannot be undertaken for some other reason, then a further 10 Gy may be given by reduced external beam fields.

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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.

Histological assessment of endometrial curettings **prior** to definitive surgery is necessary. All cases of proven or **suspected** malignancy should be referred to a Gynaecological Oncologist **prior** to surgery.

HISTOLOGICAL TYPES OF UTERINE CANCER

ENDOMETRIOID CARCINOMA

This accounts for 80% of cases of uterine cancer (¹). The risk factors for endometrioid uterine cancer are related to excessive unopposed oestrogen due to:

- obesity (often with diabetes and hypertension)
- hormone replacement therapy (unopposed oestrogen)
- anovulatory menstrual cycles, polycystic ovary syndrome
- oestrogen secreting tumours
- Tamoxifen usage of over 1-2 years (²)

Premalignant conditions may also 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 (³) 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 recent concept, exhibiting:

- a clonal aberration in endometrial glandular epithelial growth
- a high positive predictive value for the development of endometrial carcinoma

Confirmed cases should be treated by hysterectomy (⁴) (⁵)

Endometrioid Carcinoma:

- contains glandular elements that resemble those of non-neoplastic endometrium
- may demonstrate benign focal or morular squamous differentiation (up to 30%) and occasionally will be accompanied by a malignant squamous cell component
- may display focal mucinous differentiation (about 30%)
- may be predominantly or exclusively mucinous (10%)
- uncommonly may arise within endometriosis

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 (⁶)

Clear cell carcinomas:

- may metastasize distantly, even in early stage disease
- may arise within endometriosis

CARCINOSARCOMA

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

- be a form of metaplastic carcinoma, rather than a mixture of sarcoma and carcinoma (⁷)
- share epidemiological risk factors with endometrioid adenocarcinomas (obesity, hyperoestrogenism)
- exhibit clinical behaviour determined by the grade of the carcinomatous component
- exhibit patterns of spread similar to those of carcinomas rather than those of pure sarcomas (⁸)

LEIOMYOSARCOMA

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

- 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.

ENDOMETRIAL STROMAL SARCOMA

These are derived from the stroma of the endometrium and:

- may exhibit a propensity to produce tongues of tumour spreading within thick-walled lymphatic vessels
- were previously designated as low-grade endometrial stromal sarcomas

High grade, anaplastic lesions are designated “uterine sarcoma, NOS” as they are not recognisable as having endometrial stromal differentiation.

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 - 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. Lynch syndrome is due to an inherited defect in one of the mismatch repair (MMR) genes and the tumours have loss of the relevant MMR protein(s) when stained using immunohistochemistry (IHC)
- Women who have the Lynch syndrome (HNPCC) have up to a 40% lifetime risk of uterine cancer, a 10% lifetime risk of ovarian cancer and a 50 - 80% risk of colon cancer. They also have an increased risk of pancreatic, upper gastrointestinal and renal pelvis / ureter cancers
- Approximately 9% of women under 50 with endometrioid uterine cancer carry a mutation in a DNA mismatch repair gene, resulting in the Lynch syndrome⁽⁹⁾
- For this reason, a family history of bowel / uterine cancer *or* early onset (<50yo) *or* thin women with uterine cancer should arouse suspicion of Lynch syndrome and tumour. IHC for the MMR proteins is recommended to assist with the diagnosis
- Referral to a Family Cancer Clinic is recommended where suspicion of Lynch syndrome or other inherited syndromes is present. Genetic counselling and genetic testing may be appropriate

(See Section on Familial Aspects of Gynaecological Cancers)

PRINCIPLES OF MANAGEMENT

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

- endometrial sampling (office endometrial biopsy or curettage)
- consultation with a Gynaecological Oncologist where malignancy is proven or suspected (eg. longstanding vaginal bleeding and complex atypical endometrial hyperplasia on curettings)
- histological confirmation by an expert Gynaecological Pathologist with review by a Multidisciplinary Team (MDT)
- adjuvant treatment decisions should be tailored to the individual patient according to their risk of vaginal vault, pelvic, para-aortic or distant relapse
- **Preoperative Imaging** may be performed prior to referral to a Gynaecological Oncologist. This should include a chest X ray and CT scan of the abdomen and pelvis.

INITIAL TREATMENT

PRIMARY SURGERY

Primary surgery for uterine cancer is tailored to the histology, distribution of disease and patient characteristics. It should include 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 complete the surgical staging.

Laparoscopic hysterectomy, bilateral salpingo-oophorectomy and lymphadenectomy are currently compared to abdominal surgery in a randomised controlled trial. Single institution data suggest that this offers lower post-operative morbidity with similar recurrence rates.

PRIMARY RADIOTHERAPY

This is reserved for:

- women unfit for surgery due to medical comorbidities ⁽¹⁰⁾ ⁽¹¹⁾
- locally advanced disease, not suitable for primary surgery

Radiotherapy usually involves both external beam radiation and vaginal brachytherapy. Acceptable fractionation schemes have been published by The American Brachytherapy Society ⁽¹²⁾.

STAGING

2.1 Uterine cancers are surgically staged according to FIGO⁽¹³⁾

Stage	<u>Extent of disease</u>	Five-year survival by stage ⁽¹⁴⁾
Stage I	Ia – tumour limited to the endometrium	89%
	Ib – invasion to less than half of the myometrium	90%
	Ic – invasion to greater than half the myometrium	81%
Stage II	IIa – involvement of endocervical glands only	80%
	IIb – cervical stromal invasion	72%
Stage III	IIIa – tumour invades surface of uterus and/or ovaries, and/or positive peritoneal washings	63%
	IIIb – vaginal metastases	39%
	IIIc – metastases to pelvic and/or para-aortic lymph nodes	51%
Stage IV	IVa – tumour invades bladder and/or bowel mucosa	20%
	IVb – distant metastases including intra-abdominal and/or inguinal lymph nodes	17%

ADJUVANT TREATMENT

Adjuvant therapy is assigned on the basis of the estimated risk of recurrence.

ENDOMETRIOID CARCINOMA

Adjuvant Radiotherapy

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

Stage I

The risk factors for recurrence are:

- grades 2,3
- outer half myometrial invasion (Stage Ic)
- LVSI
- age >50y

Adjuvant radiotherapy should be considered for 2 or more risk factors ⁽¹⁵⁾.

Two randomised trials of adjuvant radiotherapy ⁽¹⁵⁾ ⁽¹⁶⁾ used pelvic external beam radiotherapy without vaginal brachytherapy. Approximately 75% of recurrences in the observational arm occurred in the vagina ⁽¹⁷⁾. The PORTEC-2 trial ⁽¹⁸⁾ shows that vaginal brachytherapy is equivalent to external beam radiotherapy in terms of survival. It is reasonable to treat properly staged medium-high risk Stage 1 patients with vaginal brachytherapy alone. However patients who have not been surgically staged and have Stage Ic, Grade 3 disease or higher should be considered for external beam radiotherapy and vaginal brachytherapy due to the 28% risk of lymph node metastases ⁽¹⁹⁾.

In these patients:

- vaginal brachytherapy alone reduces the risk of local recurrence although with a slightly higher risk of pelvic nodal recurrence ⁽¹⁸⁾
- pelvic radiotherapy reduces the risk of local recurrence by 72% with an absolute risk reduction of 6% ⁽²⁰⁾, but does not significantly improve disease free survival (DFS) or overall survival (OS)

Stage II

- adjuvant vaginal brachytherapy alone is suggested for node negative patients
- pelvic radiotherapy and vaginal brachytherapy is suggested for patients with unknown lymph node status

Stage III

Adjuvant radiotherapy is recommended for:

- Stage IIIa on basis of positive peritoneal cytology AND risk factors as per Stage I
- Stage IIIa on basis of adnexal involvement
- Stage IIIb and IIIc ⁽²¹⁾

Pelvic radiotherapy should be tailored to the distribution of involved lymph nodes. Whole abdominal radiotherapy is not recommended. Vaginal brachytherapy boost should be considered in patients with non-organ confined disease (ie. spread to adnexa, cervix) ⁽²¹⁾.

Adjuvant Chemotherapy

Adjuvant chemotherapy has been increasingly considered in recent years for serous, clear cell and high risk endometrioid cancers ⁽²²⁾ ⁽²³⁾ ⁽²⁴⁾.

Two recent studies have prompted some authorities to conclude that adjuvant chemotherapy should be considered in selected patients ⁽²⁵⁾ ⁽²⁶⁾.

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).

Carboplatin and Epirubicin are recommended as neither Taxanes nor granulocyte colony-stimulating factor are currently available on the PBS for this indication.

Suitable patients should be considered for the PORTEC-3 trial, which randomises patients with Grade 3 Stage I, Stage IIa and Stage III uterine malignancies to pelvic irradiation vs concurrent Cisplatin and radiotherapy followed by 4 cycles of Carboplatin and Paclitaxel.

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 (eg. lung metastases)

SEROUS AND CLEAR CELL CARCINOMA

Limited data shows:

- a higher recurrence in stage Ib/c than stage Ia ⁽⁶⁾
- 50% of recurrences have an extra-pelvic component
- the role of radiotherapy is not clear with a high rate of in-field and out-of-field failure ⁽²⁷⁾
- probable reduced vaginal vault recurrence with vaginal brachytherapy
- a trend to reduced recurrence with systemic chemotherapy ⁽²⁵⁾

Recommendations:

- adjuvant chemotherapy should be considered in all patients of Stage Ib and above ⁽⁶⁾
- patients with fully surgically staged Stage Ib-c disease should be considered for adjuvant vaginal brachytherapy
- all other unstaged patients and those with Stage II and III disease should be considered for pelvic RT or whole abdominal RT with vaginal brachytherapy ⁽²⁸⁾

The suggested chemotherapy regimen is combination Carboplatin and Cyclophosphamide given either as 6 cycles prior to radiotherapy or as “sandwich” therapy, q3 weekly for 3 cycles prior to radiotherapy and then another 3 cycles after RT. Taxanes are currently not approved on the PBS for these histological subtypes.

CARCINOSARCOMAS

Chemotherapy studies have documented some antitumour activity for Cisplatin, Doxorubicin, and Ifosfamide ⁽²⁹⁾.

Recommendations are therefore:

- consider adjuvant pelvic RT ⁽³⁰⁾ (+/- vaginal brachytherapy) for Stage I-III (as per endometrioid carcinoma)
- consider chemotherapy (Carboplatin and Epirubicin) for Stage Ib and above
Paclitaxel is not PBS listed for this indication.

LEIOMYOSARCOMA

These show:

- distant metastatic spread in apparently early stage disease
- chemoresistance and radiation resistance

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

ENDOMETRIAL STROMAL SARCOMA

These are:

- low grade by definition
- generally poorly responsive to radiotherapy
- generally poorly responsive to chemotherapy
- potentially responsive to high dose progestogens (eg. 200mg medroxyprogesterone acetate bd) or GnRH analogues ⁽³¹⁾

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

Link to Ci-SCAT for RT (and chemotherapy) protocols

www.treatment.cancerinstitute.org.au

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 (³²).

A suggested schema is:

- review visits 3-6 monthly for 3 years, then yearly to 5 years
- physical examination including examination of the supraclavicular nodes, abdomen and pelvis (with a speculum examination) at all visits
- no routine vaginal vault smears or imaging
- colposcopy and biopsy of any suspicious lesions
- advise patient to return for early review if any problems, such as bleeding, pain, bladder or bowel symptoms, become evident between scheduled visits (³³)

CURRENT CLINICAL TRIALS

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

RECURRENCE

Recurrent disease:

- commonly occurs within 3 years of diagnosis (³³)
- 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 (eg. FNA of suspicious lesions)
- performance status of the patient
- previous therapy and time to relapse

All cases should be considered by a MDT.

TREATMENT OF RECURRENCE

Radiation

Radiotherapy with intent to cure

Patients should be completely assessed to ensure there is no evidence of distant metastatic disease.

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 (³⁴)

Pelvic nodal recurrence:

- consider surgical debulking if nodal mass of ≥ 2 cm 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 (usually Cisplatin or liposomal Doxorubicin):

- has a response rate of approximately 20% in endometrioid carcinoma
- may give short term (months) relief of symptoms
- is reserved for metastatic disease not amenable to hormonal treatment or surgery
- is generally withheld until patients are symptomatic

Hormonal Therapy

Progesterone treatment is most useful for:

- low grade, progesterone receptor positive endometrioid tumours
- pulmonary metastases

Contraindications include:

- a history of thrombosis
- severe cardiac disease
- breast cancer

Progesterone therapy is also associated with weight gain which requires consideration in obese women.

Tamoxifen is occasionally used to treat recurrent endometrioid cancer.

Aromatase inhibitors have limited activity and may be considered second / third line therapy 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 therapy)
- 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 which 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 symptom, site of disease, previous treatment and patient factors.

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OVARIAN CANCER

CLASSIFICATION AND STAGING OF OVARIAN CANCER

More detailed guidelines on the management of epithelial ovarian cancer can be found in the CAN and NBCC publication endorsed by the NHMRC (2004).

Staging is based on findings at clinical examination and surgical exploration (Table 3.1 and Figure 3.1) (Heintz et al, 2001).

Table 3.1 Carcinoma of the ovary: FIGO nomenclature (Rio de Janeiro, 1988)

FIGO stage	Extent of disease
Stage I	Growth is limited to the ovaries. Stage IA – Growth is limited to one ovary; no malignant ascites; negative cytology; no tumour on the external surface; capsule intact Stage IB – Growth is limited to both ovaries; no malignant ascites; negative cytology; no tumour on the external surface; capsule intact Stage IC * - Tumour either stage IA or stage IB, but with tumour on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage II	Growth involving one or both ovaries with pelvic extension. Stage IIA – Extension of metastases to uterus and/or tubes Stage IIB – Extension to other pelvic tissues Stage IIC * - Tumour either stage IIA or stage IIB, but with tumour on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage III	Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes; superficial liver metastases; tumour limited to the true pelvis but with histologically-proven malignant extension to the small bowel or omentum. Stage IIIA – Tumour grossly limited to the true pelvis with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces. Stage IIIB – Tumour involving one or both ovaries with histologically confirmed implants on abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative. Stage IIIC – Abdominal implants greater than 2 cm in diameter, and /or positive retroperitoneal or inguinal nodes.
Stage IV	Growth involving one or both ovaries with distant metastases; if pleural effusion is present there must be positive cytology; parenchymal liver disease. * In order to evaluate the impact of prognosis of the different criteria for allotting cases to stage IC or stage IIC it would be of value to know if the source of malignant cells detected was peritoneal washings or ascites, and if rupture of the capsule was spontaneous or caused by the surgeon.

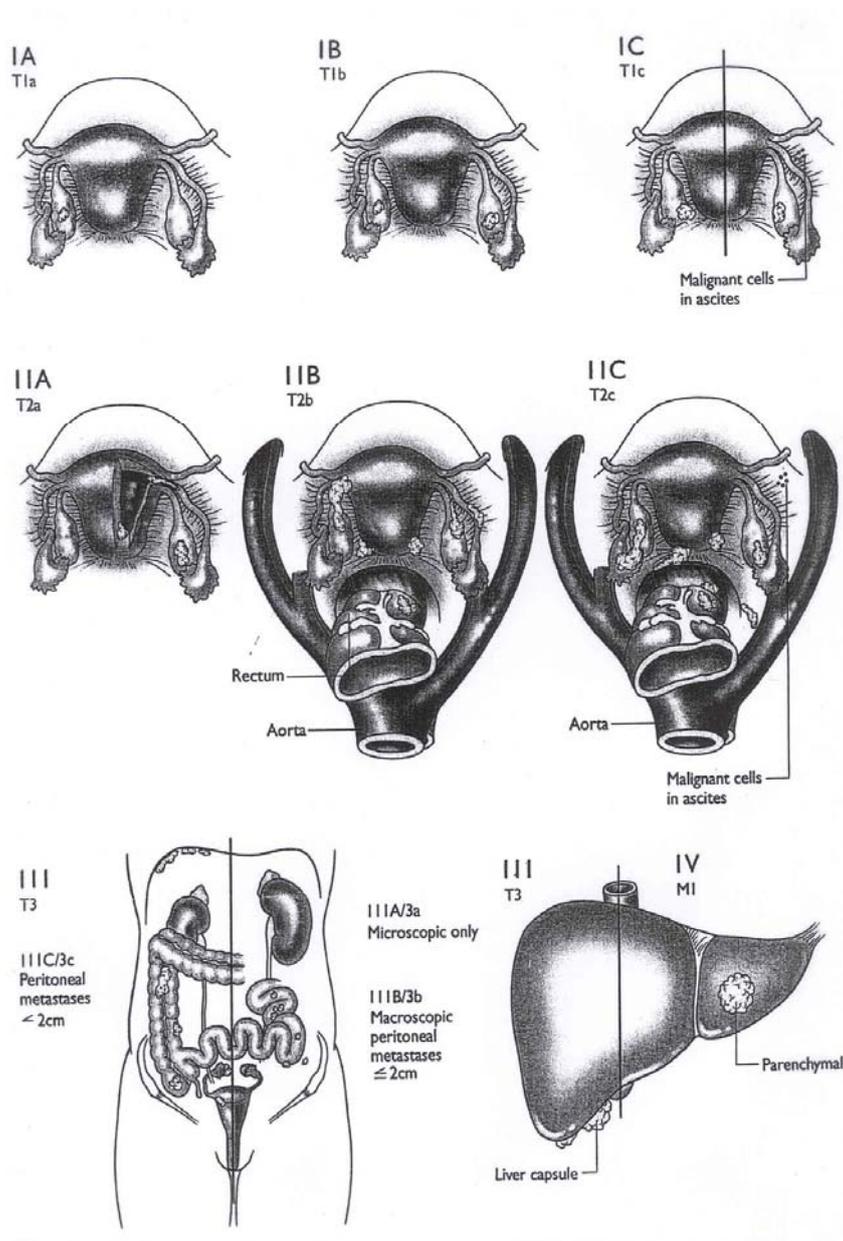


Figure 3.1 Carcinoma of the ovary: Staging of ovarian cancer: primary tumour and metastases (FIGO and TNM)

EPITHELIAL OVARIAN CANCER

Management of a pelvic mass

Epithelial ovarian cancer should be treated by a gynaecological oncologist in a hospital facility that has the necessary support and consultative services that will optimise the patient's outcome (e.g. pre-operative counselling, psycho-social support services, and intra-operative frozen section assessment). Any woman with a pelvic mass in association with the following features should be referred to a gynaecological oncologist for management (ACOG, 2002):

- raised serum CA 125 (or very raised [> 200 U/ml] in a pre-menopausal woman)
- ascites
- nodular or fixed pelvis
- any evidence of abdominal or distant metastases
- family history of one or more first-degree relatives with breast or ovarian cancer

The Risk of Malignancy Index (RMI) (Table 3.2) (Jacobs et al, 1990) in the presence of a pelvic mass may help determine which women would benefit from direct referral to a tertiary gynaecological oncology unit. It is generally accepted that an RMI cut-off value of 200 is used to discriminate benign from malignant ovarian masses.

Table 3.2 Risk of Malignancy Index for ovarian cancer

Criteria		Scoring system	Score
Menopausal status	<ul style="list-style-type: none"> • pre-menopausal • post-menopausal 	1 3	A (1 or 3)
Ultrasonic features	<ul style="list-style-type: none"> • multi-loculated • solid areas • bilaterality • ascites • metastases 	No features = 0 One feature = 1 > 1 feature = 3	B (0, 1 or 3)
Serum CA 125		Absolute level	C
Risk of Malignancy Index			A x B x C

Early stage disease and borderline tumours

All patients with early stage disease and borderline tumours should have comprehensive staging performed (Figure 3.2).

Surgical staging (Piver, Barlow & Lele, 1978; Young et al, 1983; Buchsbaum et al, 1989) should include:

- peritoneal washings for cytology
- exploration of all peritoneal surfaces including the diaphragm, bowel serosa, and Pouch of Douglas
- biopsy of any suspicious lesions
- infracolic omentectomy and peritoneal biopsies
- adequate sampling of pelvic and para-aortic lymph nodes

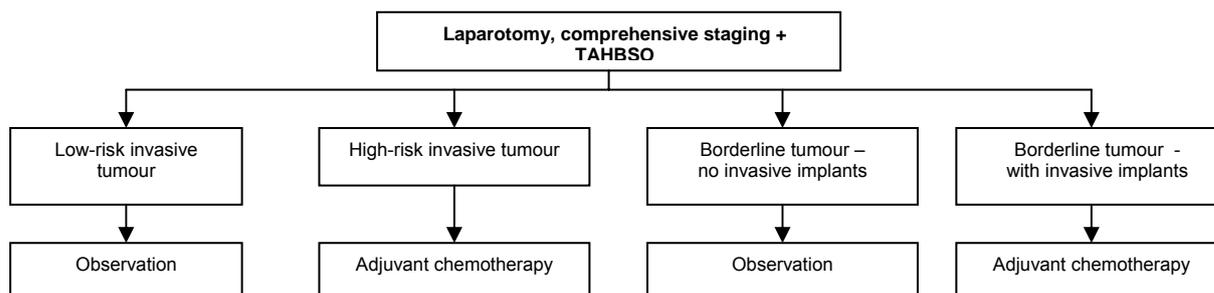


Figure 3.2 Management early stage epithelial and borderline ovarian tumours

Invasive tumours

The treatment of patients with early stage invasive disease is determined by the associated risk factors (Table 3.3) (Young et al, 1990).

Pre-menopausal women who wish to retain their fertility may have fertility-preserving surgery in association with close follow-up if they have early stage disease and favourable low-risk pathology (Zanetta et al, 1997; Duska et al, 1999; Schilder et al, 2002).

Adjuvant chemotherapy with a platinum agent is recommended for high-risk disease as it improves survival, and delays recurrence (Trimbos et al, 2003a; Trimbos et al 2003; Colombo et al, 2003). The commonly used treatment regimen of carboplatin and paclitaxel (Table 3.4) is used because of ease of administration, and acceptable side-effects.

Patients with apparent stage I disease who have not been adequately staged, and where re-exploration is not considered, should also be offered adjuvant chemotherapy.

Table 3.3 Risk associated with early invasive ovarian cancer

Risk	Risk factors
Low-risk	<ul style="list-style-type: none"> stage IA or stage IB G1 or G2
High-risk	<ul style="list-style-type: none"> All stage I, G3 tumours stage IC (does not include patients staged as IC by virtue of intra-operative rupture) stage IA or stage IB, and G1 or G2 in the presence of dense adhesions clear cell carcinoma incompletely staged, apparent early stage tumours

Table 3.4 Chemotherapy regimen for high-risk early stage ovarian cancer

Day of cycle	Drug	Dose & route	No. of cycles	Cycle frequency
1	Paclitaxel + Carboplatin	175 mg / m ² IV AUC 5 – 6 IV	4	q3 weekly

Borderline tumours

The management of borderline ovarian tumours should be based on expert histopathological review (Russell, 1979). The nature of any documented metastases should be clearly defined according to the criteria of Bell, Weinstock & Scully (1988).

In the absence of invasive implants there is no evidence of a benefit from adjuvant therapy (Trope et al, 1993; Seidman & Kurman, 2000). Patients with invasive implants should be treated with adjuvant chemotherapy (Figure 3.2).

Stage II - stage IV – Advanced disease

Patients with advanced stage disease are treated with a combination of cytoreductive surgery and chemotherapy (Figure 3.3).

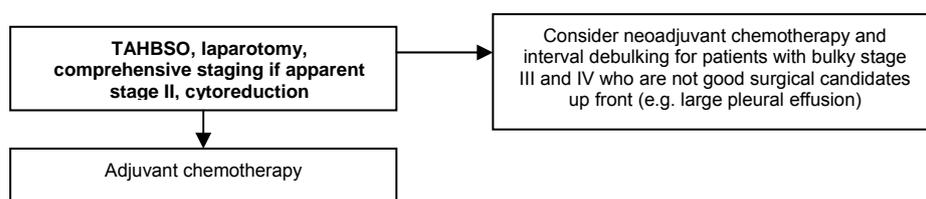


Figure 3.3 Management of advanced stage epithelial ovarian cancer

Primary cytoreductive surgery

The morbidity associated with cytoreductive surgery is generally well tolerated and offers three theoretical advantages (Venesmaa P & Ylikorkala O, 1991):

- improvement in physiological status of the patient by alleviating the nausea and early satiety often associated with a large omental mass, and decreasing the volume of ascites
- elimination of hypoxic areas of tumour, thereby improving the perfusion of the residual tumour nodules, and increasing the growth fraction of the tumour
- enhancement of the immunological competence of the patient

Primary cytoreductive surgery typically includes (Griffiths, 1975; Hacker et al, 1983; Hoskins et al, 1992; Farias-Eisner et al, 1993):

- total abdominal hysterectomy
- bilateral salpingo-oophorectomy
- omentectomy
- resection of metastatic lesions from the peritoneal surfaces or from the bowel

The goal of primary cytoreductive surgery should be to remove all, or as much as possible, macroscopic disease (Bristow et al, 2002). Optimal cytoreduction is usually defined as residual disease ≤ 2 cm.

Adjuvant chemotherapy

First-line chemotherapy (Table 3.5) ideally should include a platinum compound (Aabo et al, 1998; Covens et al, 2002). Whilst there is no evidence of any significant difference in progression-free or overall survival between carboplatin and cisplatin, the favourable toxicity profile and ease of administration of carboplatin has generally made it the drug of choice (duBois, Neijt & Thigpen, 1999; Ozols, 1999; Neijt et al, 2000).

The use of platinum, either in combination with paclitaxel or given sequentially, is supported by the results of three phase III trials (McGuire et al, 1996; Piccart et al, 2000; Muggia et al, 2000). The current recommended chemotherapy regimen is a combination of carboplatin and paclitaxel (Table 3.5).

Table 3.5 Chemotherapy regimen for advanced stage epithelial ovarian cancer

Day of cycle	Drug	Dose & route	No. of cycles	Cycle frequency
1	Paclitaxel + Carboplatin	175 mg / m ² IV AUC 5 – 6 IV	6	q3 weekly

The ICON trial (2000) suggested that single-agent carboplatin may produce similar survival rates to combination paclitaxel and carboplatin, but with reduced toxicity. This is worthy of consideration, particularly in elderly patients and those with a poor performance status.

Intra-peritoneal chemotherapy is an option supported by phase II trials for patients with small-volume residual disease following surgery, however, the reported benefits need to be balanced against the drawbacks of catheter-related morbidity, infection, and discomfort associated with treatment (Alberts et al, 1996; Armstrong et al, 2002). Intra-peritoneal chemotherapy is not recommended for patients who have significant intra-abdominal adhesions at the conclusion of their surgery as the adhesions may limit the distribution of chemotherapy within the abdomen.

Adjuvant radiation therapy

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

Neo-adjuvant chemotherapy

The following patients who are unfit for primary cytoreductive surgery may be considered for neo-adjuvant chemotherapy:

- histologically or cytologically confirmed adenocarcinoma
- UICC / ECOG performance status ≥ 3 (e.g. large pleural effusion)
- bulky extra-peritoneal disease.

Treatment involves combination chemotherapy with paclitaxel and carboplatin (Table 3.5). Interval debulking can be carried out after two or three cycles of chemotherapy if there has been a good clinical response, and improved performance status.

Second-look surgery

Second-look operations should only be undertaken in the context of a research setting.

Monitoring after primary therapy

A carefully programmed follow-up routine that includes history and examination should be provided at appropriate intervals by a gynaecological oncologist, medical oncologist, or specialist gynaecologist. A common practice is to advise no less than 3-monthly reviews for two years after initial treatment, then 4-monthly review for the next year, 6-monthly until 5 years before moving to annual review.

Serum CA 125 is an accurate predictor of relapse in those women who initially had a raised CA 125 at time of diagnosis (Jacobs & Bast, 1989; ESMO, 2001). Criteria for defining relapse and progression using CA 125 have been described (Rustin et al, 1996).

Imaging should not be done routinely outside a clinical trial setting, however, abdomino-pelvic CT scan or ultrasound should be performed if there is clinical or biochemical evidence of recurrence.

Persistent or recurrent disease

Salvage therapy is not curative for the overwhelming majority of patient who relapse. Therefore, the goals of follow-up and treatment need to incorporate quality of life considerations as an integral part of treatment planning.

Chemotherapy

Platinum-sensitive

Patients with a platinum-free interval of > 6 months should be considered for re-treatment with platinum (Rose et al, 1998; Cantu et al, 2002). Carboplatin-based combination chemotherapy may be superior to single-agent carboplatin in patients with 'platinum-sensitive' recurrent ovarian cancer (ICON and AGO Collaborators, 2003).

Platinum-resistant

For patients with platinum-resistant disease there are a number of treatment options including:

- other chemotherapeutic agents such as taxanes, topotecan, oral etoposide, liposomal doxorubicin, or gemcitabine
- consideration for phase I or II studies
- hormonal therapy such as tamoxifen

An argument can be made for not considering further treatment for patients falling into the following groups (Markman et al, 1996; ten Bokkel Huininkl et al, 1997; Rose et al, 1998; Gordon et al, 2001; O'Byrne et al, 2002):

- disease progression during treatment
- best response being stable disease only
- recurrence < 6 months following platinum therapy

Surgery

There is no routine place for surgery for patients who develop progressive disease during their initial chemotherapy (Berek et al, 1983; Hoskins et al, 1989).

Secondary cytoreduction will only benefit a small sub-set of highly selected patients with relapsed disease (Sharp et al, 1995; Tay et al, 2002). These include:

- patients with a long disease-free interval (> 2 years)
- patients in whom residual disease can be completely cleared

Surgery may be important for palliation (e.g. treatment of bowel obstruction where quality of life may be improved by the intervention).

Radiation therapy

Palliative radiation therapy may be appropriate for the treatment of selected patients (e.g. patients with brain metastases, PV/PR bleeding and other pelvic symptoms).

GERM CELL TUMOURS

It is important to limit the morbidity associated with surgery so as not to delay the commencement of chemotherapy. As these tumours are very chemo-sensitive, conservative or fertility-preserving surgery is indicated.

Initial surgery should include unilateral salpingo-oophorectomy, peritoneal cytology, and meticulous exploration of the abdomen and retro-peritoneal lymph nodes. If the contra-lateral ovary contains a cystic lesion it should be enucleated. Biopsy of a normal looking contra-lateral ovary is not indicated if the patient has a non-dysgerminomatous malignancy. The role of debulking advanced ovarian germ cell tumours is not defined.

Patients with stage IA dysgerminoma or stage IA, G1 pure immature teratoma, may be managed by surgery alone. All other patients with malignant germ cell tumours require chemotherapy. BEP chemotherapy (Table 3.6) is recommended (Williams et al, 1991). During chemotherapy oral contraceptives should be prescribed to prevent pregnancy and suppress ovarian function in order to reduce possible damage to the ovaries.

The role of second-look surgery remains controversial (Williams et al, 1991) but may be indicated for bulky nodes or where there was advanced disease initially.

After completion of therapy, all patients should be followed by serial tumour markers and examination. Most will resume normal menstrual function and normal reproductive function (Brewer et al, 1999)

Table 3.6 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	100 mg / m ² IV	3	q3 weekly
– 5	Cisplatin	20 mg / m ² IV		

SEX CORD STROMAL TUMOURS

Stage I – early disease

For younger women wishing to preserve their fertility, 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 (Malstrom et al, 1994; Pautier et al, 1997).

Adjuvant treatment is not considered necessary in stage I disease.

Stage II – stage IV – advanced disease

The appropriate treatment for advanced disease may be either radiation therapy or combination chemotherapy may be appropriate treatment (Wolf et al, 1999). While there is little data available, BEP chemotherapy (Table 3.6), as used for germ cell tumours, is recommended (Homesley et al, 1999).

Recurrent disease

Secondary cytoreduction may have a role if the disease appears localised and resectable, and the disease-free interval is greater than 12 months. Serum inhibin levels can be used in surveillance for recurrence (Jobling et al, 1994).

CLASSIFICATION AND STAGING OF FALLOPIAN TUBE CANCER

Staging is based on surgical findings at laparotomy.

Table 3.7 Carcinoma of the fallopian tube: FIGO nomenclature

FIGO stage	Extent of disease
Stage I	<p>Growth limited to the fallopian tubes</p> <p>Stage IA – Growth limited to one tube with extension into the submucosa and/or muscularis but not penetrating the serosal surface; no ascites.</p> <p>Stage IB – Growth limited to both tubes with extension into the submucosa and/or muscularis but not penetrating the serosal surface; no ascites.</p> <p>Stage IC – Tumour either stage IA or IB, but with tumour extension through or onto the tubal serosa; or with ascites present containing malignant cells or with positive peritoneal washings.</p> <p>* The staging system does not distinguish between microscopic foci or replacement of tubal epithelium by malignant epithelium and grossly evident masses in the tubal lumen that do not penetrate the wall beyond the epithelium. The former have not been reported to spread beyond the tube, whereas the latter can extend beyond the tube, recur, and be fatal. The "mucosa" presumably refers to the epithelium because involvement of the lamina propria component of the mucosa requires the staging of tumour as IA.</p> <p>** Because the fallopian tube has no submucosa, this designation presumably refers to the lamina propria</p>
Stage II	<p>Growth involving one or both fallopian tubes with pelvic extension</p> <p>Stage IIA – Extension and/or metastases to the uterus and/or ovaries.</p> <p>Stage IIB – Extension to other pelvic tissues.</p> <p>Stage IIC – Tumour either stage IIA or IIB, but with tumour extension through or onto the tubal serosa; or with ascites present containing malignant cells or with positive peritoneal washings.</p>
Stage III	<p>Tumour involving one or both fallopian tubes with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal glands. Superficial liver metastasis equals Stage III. Tumour appears limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum.</p> <p>Stage IIIA – Tumour grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.</p> <p>Stage IIIB – Tumour involving one or both tubes with histologically confirmed implants on abdominal peritoneal surfaces, none exceeding 2 cm. in diameter. Lymph nodes are negative.</p> <p>Stage IIIC – Abdominal implants greater than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.</p>
Stage IV	<p>Growth involving one or both fallopian tubes with distant metastases; if pleural effusion is present there must be positive cytology; parenchymal liver disease.</p>

The treatment of this disease is identical to that of epithelial ovarian cancer.

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. The role of cytoreductive surgery is unclear but extrapolation from the experience with epithelial ovarian cancer indicates that significant benefit might be expected, particularly if all the macroscopic disease can be resected.

Chemotherapy

Carboplatin and paclitaxel as per treatment for epithelial ovarian cancer.

It is unclear whether patients with disease confined to the fallopian tube (ie. stage IA, grade 1 or 2) benefit from adjuvant therapy.

Radiation therapy

The role of radiation therapy is unclear. There may be a role for whole abdominal radiation therapy with pelvic boost in properly selected patients.

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VULVAL CANCER

CLASSIFICATION AND STAGING OF VULVAL CANCER

Vulval cancer is staged by surgical and/or pathologic findings (Table 4.1).

Table 4.1 Carcinoma of the vulva: FIGO nomenclature (Montreal, 1994)

FIGO stage	Extent of disease
Stage 0	Carcinoma in situ, intra-epithelial carcinoma
Stage I	Lesions 2 cm or less in diameter confined to the vulva or perineum. No nodal metastases. Stage IA – lesions 2 cm or less in diameter confined to the vulva or perineum and with stromal invasion no greater than 1.0 mm. No nodal metastases. Stage IB – lesions 2 cm or less in diameter confined to the vulva or perineum and with stromal invasion greater than 1.0 mm. No nodal metastases. * The depth of invasion is defined as the measurement of tumour from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.
Stage II	Tumour confined to the vulva and/or perineum more than 2 cm in the greatest dimension, with no nodal involvement.
Stage III	Tumour of any size with: (i) adjacent spread to the lower urethra and/or vagina, or the anus, and/or (ii) unilateral regional groin node metastases.
Stage IV	Stage IVA – Tumour invades any of the following: upper urethra, bladder mucosa, rectal mucosa, pelvic bone, and/or bilateral regional node metastasis. Stage IVB – Any distant metastases including pelvic lymph nodes.

Carcinoma of the vulva is an uncommon tumour, representing about 4% of gynaecologic malignancies. It is predominantly a disease of postmenopausal women. Ninety percent of cancers are squamous in origin, while melanomas, adenocarcinomas, basal cell carcinomas, verrucous carcinomas, sarcomas, and other rare malignancies also occur. Most squamous carcinomas occur on the labia majora but the labia minora, clitoris, and perineum may also be primary sites.

Vulval intraepithelial neoplasia (VIN) III is a precursor lesion in some patients, and should be effectively treated by superficial excision, with or without laser therapy, when diagnosed (Jones & Rowan, 1994; Herod et al, 1996).

Treatment of invasive vulval cancer has evolved into an individualised multidisciplinary approach, and patients should be referred centrally to a gynaecological cancer centre where all relevant expertise is available (van der Velden et al, 1996; Rhodes, Cummins & Shafi, 1998).

SQUAMOUS CELL CARCINOMA OF THE VULVA

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

If the lesion is ≤ 2 cm in diameter and depth of stromal invasion is ≤ 1 mm on wedge biopsy, complete excision of the lesion must be undertaken to allow serial sectioning to properly assess the depth of invasion.

Investigations to assist diagnosis include:

- Pap smear of the cervix if cervix is still insitu
- colposcopy of the cervix and vagina because of the common association with other squamous intraepithelial lesions
- CT-scan of the pelvis and groins is often helpful 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 (Hacker, 2000). In considering treatment options, it is necessary to consider independently the most appropriate management of the primary lesion and groin lymph nodes.

Early stage disease

Management of primary lesion

In order to decrease psychosexual morbidity, a radical local excision rather than a radical vulvectomy is performed, and for localised lesions, this operation is as effective as radical vulvectomy in preventing local recurrence (Iversen, Abeler & Aalders, 1981; Hacker et al, 1984(a); Hacker & van der Velden, 1993; Farias-Eisner et al, 1994; Burke et al, 1995) (Figure 4.1).

Surgical removal should achieve lateral margins of at least 1cm, and the deep margin should be the inferior fascia of the uro-genital diaphragm, which is co-planar with the fascia lata and the fascia over the pubic symphysis (Heaps et al, 1990). If the lesion is close to the urethra, the distal 1-cm 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.

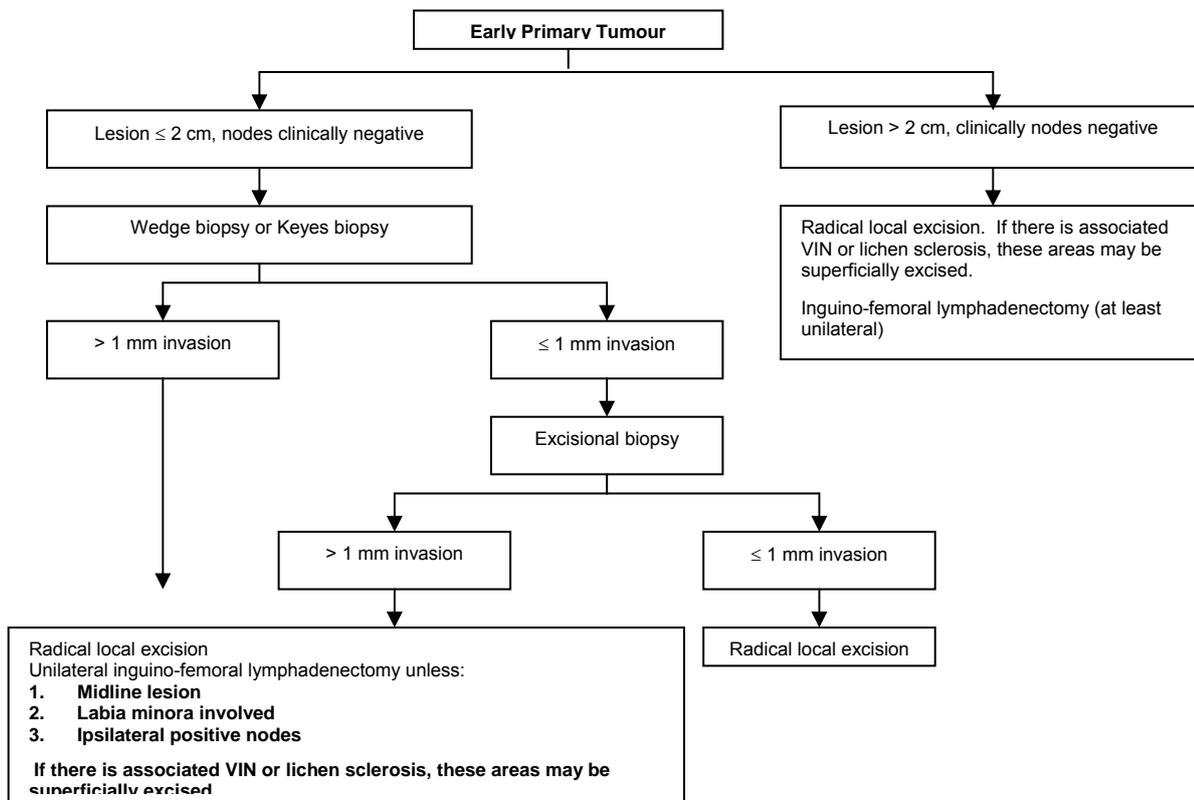


Figure 4.1 Management of early vulvar cancer

Management of groin lymph nodes

Recurrence in the groin carries a very high mortality so appropriate groin dissection is the single most important factor in reducing mortality from early vulvar cancer (Hacker, 2000).

Patients with T1 tumours and ≤ 1 mm stromal invasion have less than 1% risk of having lymph node metastases, and do not require groin dissection (Iversen, Abeler & Aalders, 1981; Hacker & van der Velden, 1993).

All patients with T2 lesions and all patients with T1 tumours with > 1 mm stromal invasion should have at least an ipsilateral inguinal-femoral lymphadenectomy.

The incidence of positive contralateral nodes in patients with lateral T1 tumours is $< 1\%$, so unilateral groin dissection is appropriate (Hacker, 2000). Bilateral groin dissection should be performed for midline tumours, and for those involving the anterior labia minora (Iversen & Aas, 1983). Large lateral tumours should probably also have bilateral dissection, particularly if the ipsilateral nodes are positive (Iversen & Aas, 1983).

Groin dissection

Both inguinal and femoral nodes should be removed, as inguinal node dissection alone is associated with a higher incidence of groin recurrence (Stehman et al, 1992a). The femoral nodes are situated medial to the femoral vein within the fossa ovalis. There is no need to remove the fascia lata to dissect the femoral nodes (Micheletti et al, 1990). Groin dissection may be safely performed through a triple incision approach to improve primary healing (Hacker et al, 1981). To avoid skin necrosis, all subcutaneous tissue above the superficial fascia must be preserved.

Groin dissection (with post-operative radiation for patients with positive groin nodes) was superior to groin irradiation in one randomised trial, although the depth dose may have been inappropriate in this study (Stehman et al, 1992b).

Management of patients with positive groin nodes

The Gynecologic Oncology Group demonstrated superior results for pelvic and inguinal radiation compared to pelvic node dissection for patients with grossly positive groin nodes, or more than one microscopically positive node (Homesley et al, 1986).

Subsequent studies have further emphasised the prognostic significance of the morphology of positive groin nodes, particularly the size of the metastasis and the presence or absence of extra-capsular spread (Origoni et al, 1992; Paladini et al, 1994; van der Velden et al, 1995).

Patients with one (and possibly two) micro-metastases (< 5 mm) do not require adjuvant radiation therapy.

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

- one macrometastasis (> 10 mm diameter)
- extracapsular spread
- two (possibly three) or more micrometastases

Radiation therapy

In most cases, fields should include the inguino-femoral nodes and at least the lower pelvic nodes (below the SI joints).

One of a variety of radiation techniques can be selected, depending on the patient's body habitus, and extent of disease. Combined photon and electron techniques are often used to treat the regional nodes without overdosing the femoral heads. However care must be taken to completely include both the superficial and deep inguinal lymph nodes. In most cases, CT-based treatment planning should be used to verify adequate coverage.

It is important to avoid under-dosage of inguinal nodes by high-energy photon beams. If electron beams are used, the energy must be sufficient to cover the femoral nodes. The dose of radiation is determined by the initial extent of regional disease and any known residual. After a groin dissection with microscopic inguinal metastases, 50 Gy in 1.8 - 2.0 Gy fractions is usually sufficient. If there are multiple nodes positive or if there is evidence of extracapsular extension, somewhat higher doses up to 60 Gy may be given to a reduced volume. Gross residual disease may require doses of 60 - 70 Gy.

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

It is desirable to determine the status of the groin nodes prior to planning the overall treatment (Hacker, 2000).

If there are no suspicious nodes palpable in the groin, bilateral inguino-femoral lymphadenectomy should be performed. If final histologic assessment reveals positive nodes,

adjuvant radiation to the groin and pelvis should follow the guidelines given for early stage disease.

If there are suspicious nodes in the groin, a pre-operative CT scan may help identify the extent of groin and pelvic lymphadenopathy (Figure 4.2). Resection of all enlarged groin nodes should be performed, and frozen section diagnosis obtained. If nodes are negative, full inguino-femoral lymphadenectomy should be performed.

If nodes are positive, a complete lymphadenectomy should probably be avoided because full groin dissection together with post-operative groin irradiation may result in severe lymphoedema. Only enlarged nodes from the groin and pelvis should be removed, and the patient given post-operative groin and pelvic radiation.

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 (Figure 4.3).

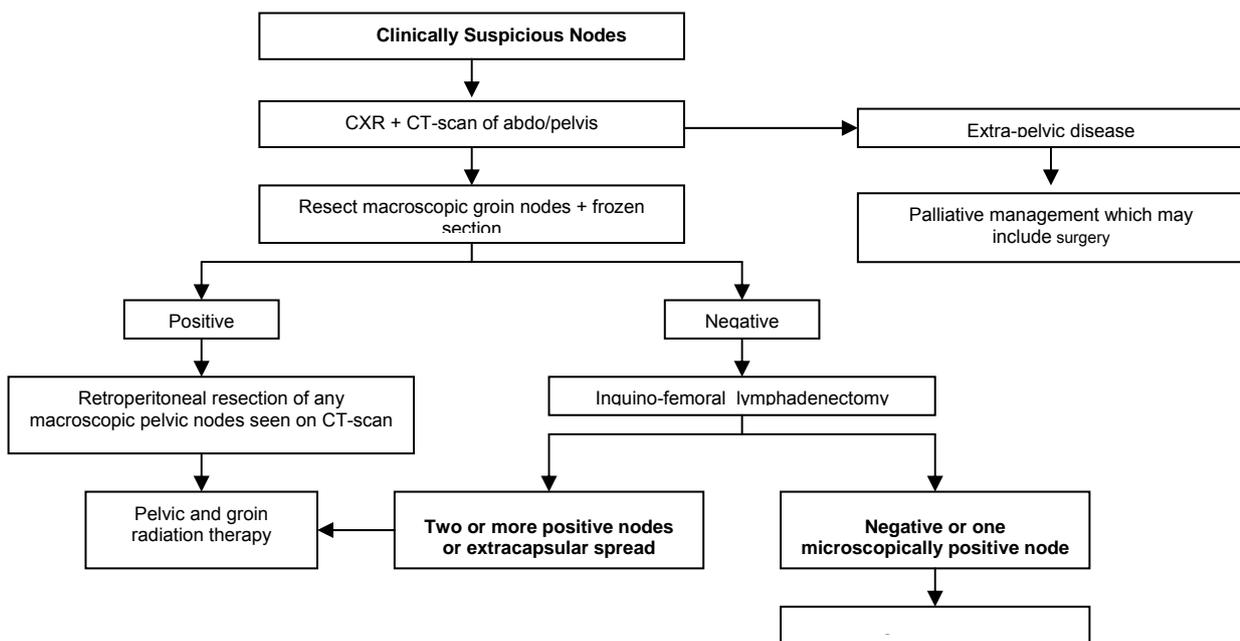


Figure 4.2 Management of clinically suspicious groin nodes in advanced vulval cancer

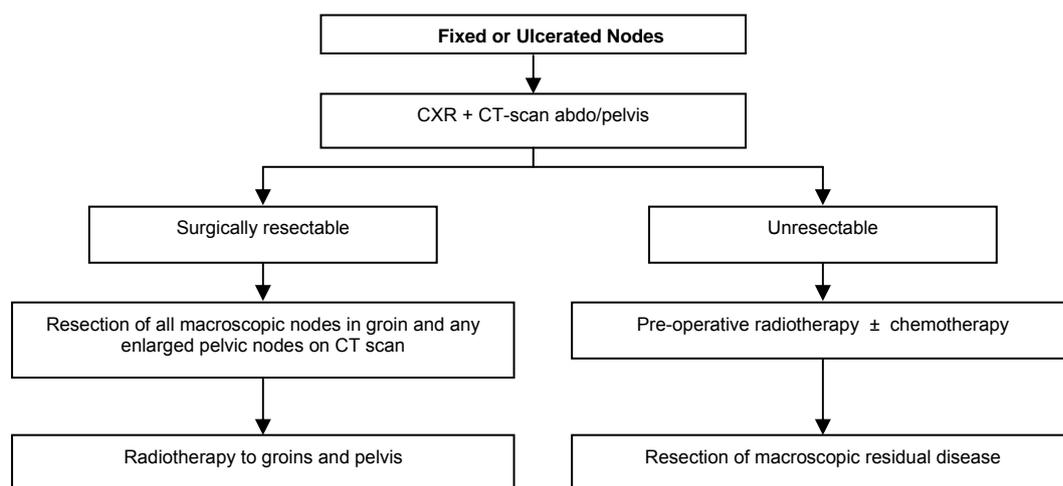


Figure 4.3 Management of clinically obvious groin nodes in advanced vulval cancer

Management of the primary tumour

Treatment of the advanced primary tumour should follow dissection of the groins. Groin and pelvic radiation should follow standard indications (Figure 4.4).

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 radiation therapy, followed by a more limited resection of the tumour bed (Hacker et al, 1984b; Boronow et al, 1987).

Chemo-radiation has been used, sometimes without need for surgical resection of the tumour bed (Thomas et al, 1989; Lupi et al, 1996; Landoni et al, 1996; Cunningham et al, 1997).

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.

Radiation therapy

If the groin nodes are positive and meet the requirements described earlier for adjuvant radiation, the initial radiation treatment fields should include the pelvis, inguinal nodes, and primary site, which are treated to a total dose of at least 50Gy.

Some clinicians prefer to treat in an open leg position but care must be taken to apply bolus to the vulva to avoid under-dosage of the skin.

Areas of gross disease are particularly high risk and are usually boosted with appositional fields of electrons selected to provide an adequate dose to the surface and at depth. Gross vulval disease probably requires 60 - 70 Gy to achieve local control, although investigators are currently exploring a wide variety of chemo-radiation schedules, and the relationship between dose and local control remains uncertain.

Close surgical margins

Post-operative radiation may be used for close surgical margins (< 5 mm), if the margins cannot be re-excised (Faul et al, 1997). Although local control is improved, overall survival is not significantly different because of the ability to salvage patients with local recurrence.

In some cases, the positive margin may be boosted with brachytherapy, although this technique requires experience to avoid an excessive risk of necrosis. Alternatively, the operative bed may be treated with an appositional electron field.

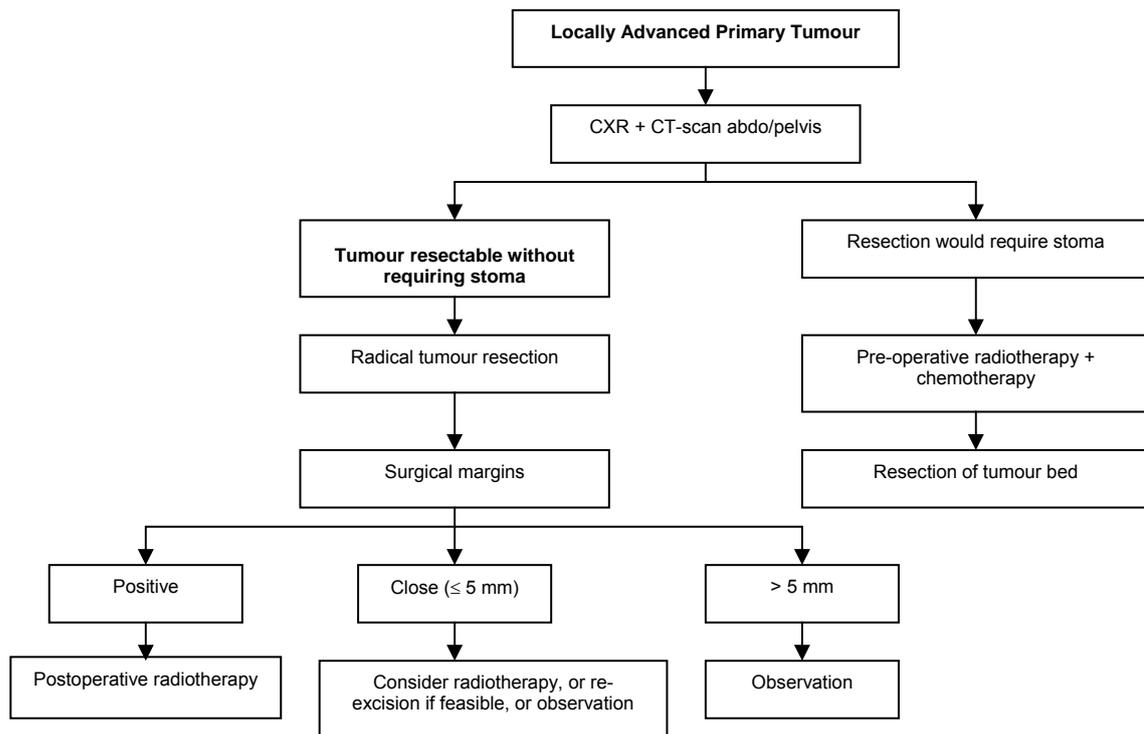


Figure 4.4 Management of primary tumour in advanced vulval cancer

VULVAL MELANOMA

Vulval melanoma is the second most common neoplasm of the vulva.

The majority of lesions involve the clitoris or labia minora. Any pigmented lesion on the vulva should be excised for diagnosis unless it has been known to be present and unchanged for some years.

In line with trends toward more conservative surgery for cutaneous melanomas, there is a trend toward more conservative resection of vulval melanomas (Rose et al, 1988; Trimble et al, 1992). Primary lesions should be treated by radical local excision, with margins around the lesion of at least 1-cm.

The role of node dissection is also controversial, but the Intergroup Surgical Melanoma Program has conducted a prospective, multi-institutional randomised trial of elective node dissection versus observation for intermediate thickness cutaneous melanomas (1 – 4 mm) (Balch et al, 1996). There were 740 patients entered into the trial, and elective node dissection resulted in a significantly better survival for patients 60-years of age or younger, patients with tumours 1 - 2 mm thick, and patients without tumour ulceration.

An ECOG trial of adjuvant high-dose interferon versus observation for 280 patients with stage IIB or III melanoma or regional nodal relapse has demonstrated significant prolonged relapse-free survival and overall survival for patients with positive nodal involvement (Kirkwood et al, 1996).

Consultation with a melanoma unit regarding adjuvant therapy is advised.

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. Adenoid cystic and adenosquamous variants have also been reported. In general, adenocarcinomas of the vulva occur a decade or so before most invasive squamous cancers. Frequently, diagnosis is made after resection of what is thought to be a persisting Bartholin's cyst.

Radical vulvectomy and bilateral groin dissection have been the standard approach for Bartholin gland carcinomas. However ipsilateral groin dissection and radical hemivulvectomy may be equally effective for early lesions (Copeland et al, 1986). Because these lesions are deep in the ischioanal fossa, surgical margins are more likely to be close, particularly for bulky lesions, and post-operative radiation to the vulva may decrease the likelihood of local recurrence (Copeland et al, 1986).

If the ipsilateral groin nodes are positive, bilateral groin and pelvic radiation may decrease regional recurrence.

For adenoid cystic lesions, radical local excision alone is the treatment of choice, with adjuvant local radiation recommended for positive margins or perineural invasion (Copeland et al, 1987).

PAGETS DISEASE OF THE VULVA

This is predominantly an intra-epithelial lesion, but in about 20% of cases, it may be associated with an underlying invasive adenocarcinoma (Fanning et al, 1999). The disease occurs predominantly in the post-menopausal population. Most patients will present with vulval discomfort and itching and on examination, an eczematoid-weeping lesion is often seen. Diagnosis is confirmed by biopsy, which usually will establish if one is dealing with an intra-epithelial or invasive lesion.

Intra-epithelial Paget's disease requires superficial local excision. It is difficult to obtain clear margins with this disease, as often the underlying histologic change will extend far beyond what is visible clinically. More recently, there has been a move to perform less radical resection for intraepithelial lesions, with re-excision at a later date should lesions become symptomatic or clinically visible. Lesions that involve or extend into the urethra or anus can be particularly difficult to manage, and may require laser therapy. If there is an underlying adenocarcinoma, the invasive component should be treated by radical local excision with margins of at least 1 cm. At least an ipsilateral inguinal-femoral lymphadenectomy should be performed for unilateral lesions with adjuvant radiation following the same indications as for squamous carcinomas.

WOUND CARE FOLLOWING VULVAL SURGERY

The major immediate morbidities following surgery for vulval cancer are wound infection, wound breakdown, and lymphocyst formation. Approximately 85% of patients undergoing en bloc operation will develop one of these complications. This can be reduced to approximately 44% by using separate groin incisions (Hacker, 2000).

The following may help to reduce post-operative wound complications:

- initial post-operative bedrest
- frequent perineal toilets whilst on bed rest
- frequent sitz baths once mobilising
- wound care following toileting
- keeping the perineum dry following wound care or showering (e.g. by using a hair dryer)

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VAGINAL CANCER

CLASSIFICATION AND STAGING OF VAGINAL CANCER

The vagina extends from the vulva upward to the uterine cervix. Cases should be classified as carcinoma of the vagina when the primary site of growth is in the vagina. Tumours present in the vagina as secondary growths from either genital or extra-genital sites should be excluded.

Staging is shown at Table 5.1. A growth that has extended to the portio and reached the area of the external os should always be allotted to carcinoma of the cervix. A growth limited to the urethra should be classified as carcinoma of the urethra. Tumours involving the vulva should be classified as carcinoma of the vulva (Beller et al, 2001).

Table 5.1 Carcinoma of the vagina: FIGO nomenclature (Rio de Janeiro, 1988)

FIGO stage	Extent of disease
Stage I	The carcinoma is limited to the vaginal wall.
Stage II	The carcinoma has involved the sub-vaginal tissue but has not extended to the pelvic wall.
Stage III	The carcinoma has extended to the pelvic wall.
Stage IV	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 IVA – Tumour invades bladder and/or rectal mucosa and/or direct extension beyond the true pelvis Stage IVB – Spread to distant organs.

Vaginal cancers are uncommon tumours comprising 1-2% of gynaecological malignancies (Peters et al, 1985). Over 97% are carcinomas. Evidence related to management and prognosis of vaginal cancer is based on retrospective series including two Australian series (Leung & Sexton, 1993; Foroudi, Bull & Gebiski, 1999).

Pre-treatment staging should include:

- EUA, cystoscopy
- chest X-ray
- abdominal/pelvic CT scan ± MRI pelvis

Therapeutic alternatives depend on:

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

Radiation therapy is generally regarded as the mainstay of treatment for this tumour (Ball & Berman, 1982). In a select group of patients with small, early stage tumours permitting clear surgical margins, surgery appears to be effective (Stock et al, 1995, Tjalma et al, 2001a).

The role of chemo-radiation is yet to be defined. Data from the management of other anogenital cancers has shown a survival benefit with the introduction of concurrent radiation therapy and chemotherapy. Chemotherapy has not been shown to be curative for advanced vaginal cancer, and there are no standard drug regimens.

In general the prognosis for all stages of vaginal cancer is worse than that for cervical and vulvar cancer (Hacker, 2000). This reflects the difficulty in optimal dose delivery of radiation therapy.

Possible poor prognostic factors in some but not all series include older patient age, advanced stage, large tumour size, distal or posterior vaginal location, nodal metastases, high grade and adenocarcinoma as against squamous cell carcinoma (Al-Kurdi & Monaghan, 1981; Houghton & Iversen, 1982; Peters et al, 1985; Kucera et al, 1985; Kirkbride et al, 1995; Chyle et al, 1996).

Lymph nodes

The lymphatic drainage of the vagina is complex. The lymphatic drainage of the upper vagina is to pelvic nodes, 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.
The risk of pelvic nodal involvement in surgically staged series is 6% – 14% for stage I and 26% – 32% for stage II (Al-Kurdi & Monaghan, 1981; Davis et al, 1991).

Pelvic nodal failure with whole pelvic radiation therapy varies from 5.5% – 18% (Foroudi et al, 1999, Chylke et al, 1996, Kirkbride et al, 1995; Stock et al, 1995).

Although one non-randomised series of 65 patients (Yeh et al, 2001) showed no difference in pelvic control between large pelvic radiation fields (treating up to the common iliac nodes) and small pelvic fields (treating up to the lower border of the sacro-iliac joints), all other series that delineate radiation therapy fields utilised have treated the entire pelvis.

- treatment of inguino-femoral nodes where there is involvement of the lower one third of the vagina (Chyle et al, 1996; Perez et al, 1999)

If the lower one third of the vagina was not involved, 0% of patients presented with inguinal node metastases in two series (Al-Kurdi & Monaghan, 1981; Stock et al, 1995); and in four series, 0% developed inguinal node recurrence (Houghton & Iversen 1982; Perez et al, 1999; Kirkbride et al, 1995; Chyle et al, 1996).

If the lower one third of the vagina was involved, 10% - 38% of patients have been reported as presenting with inguinal node metastases (Al-Kurdi & Monaghan, 1981; Stock et al, 1995), and 10% - 16% have been reported to develop inguinal node recurrence (Houghton & Iversen, 1982; Perez et al, 1999; Chyle et al, 1996).

STAGE I and STAGE II DISEASE

Superficial tumours < 0.5cm thick

Treatment options include:

- brachytherapy or interstitial therapy. Most radiation therapy series describe the selection of superficial, small-diameter lesions for treatment with brachytherapy alone, often reporting local control rates of between 90% - 100% (Leung & Sexton, 1999; Perez et al, 1999). However, small superficial stage I lesions are not identified in terms of size or thickness in these papers. Other large series have recommended external beam radiation therapy and brachytherapy to be used for patients with any stage disease beyond in-situ (Chyle et al, 1996)
- surgery dependent upon site and extent of tumour. Surgical options include:
 - wide local excision
 - radical hysterectomy with excision of upper vagina

Tumours > 0.5cm thick

Treatment options include:

- individualised radiation therapy by combination of external beam and either brachytherapy or interstitial therapy.
- surgery, dependent on site and extent of tumour. Surgical options may include:
 - partial vaginectomy ± radical hysterectomy
 - the role of surgical staging is yet to be identified. In a series of 301 patients, staging pelvic lymphadenectomy was associated with a higher 10-year complication rate (35% versus 11%, P = 0.004) but no improvement in outcome (Chyle et al, 1996)
 - resection of bulky lymph nodes > 2cm in diameter
 - ovarian transposition may benefit young patients prior to radiation therapy. and surgical staging prior to radiation therapy, although the role of surgical staging is yet to be identified

STAGE III and STAGE IV DISEASE

Treatment for advanced stage disease needs to be individualised.

Treatment options include:

- surgery, although this has a minimal role. Surgical options may include:
 - debulking of enlarged inguinal nodes > 2cm in diameter
 - ovarian transposition in younger women
 - exenterative surgery in those patients who present with a vesico-vaginal or recto-vaginal fistula
- radiotherapy – individualised depending on site and bulk of disease. Treatment results in this group of patients are unsatisfactory with 5-year survival figures of 40% for stage III, and 0% – 20% for stage IV disease (note that some series include inguinal node involvement as stage IV disease). Treatment for stage III disease follows similar principles to that used for stage IIB – IIIB cervix cancer with a combination of external beam radiation therapy and brachytherapy
- combined radiation and chemotherapy. Reports of combined radiation therapy and chemotherapy in advanced disease are few. One of the larger series from Princess Margaret Hospital (Kirkbride et al, 1995) failed to demonstrate any improvement using a combination of mitomycin-C and 5-fluorouracil as has been used for anal carcinoma. Given the improved outcome in patients with cervical cancer using a combination of platinum and radiation therapy, this represents a more obvious therapeutic alternative. Weekly cisplatin also has the advantage that, unlike mitomycin-C and 5-fluorouracil, mucosal toxicity is not likely to be accentuated, therefore treatment times are unlikely to be prolonged (Lee et al, 1994)

RECURRENT VAGINAL CANCER

Recurrence of vaginal cancer carries a poor prognosis. Treatment options will depend on prior treatment, site of recurrence, patient performance status and preferences. For those women with central recurrence and no evidence of distant metastases, exenterative surgery may be appropriate and offer the only chance of cure.

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

VAGINAL MELANOMA

Primary vaginal melanoma is rare accounting for less than 3% of vaginal cancers (Chung et al, 1980). Most knowledge of vaginal melanoma derives from case reports. The importance of prognostic factors is debated. Depth of invasion (important in cutaneous melanoma) has not been shown to be of significance, but size of tumour appears to be more relevant (Buchanan, Schlaerth & Kurosaki, 1998; Tjalma et al, 2001b).

Controversy surrounds optimal treatment of vaginal melanoma. No single therapeutic approach has a clear benefit. Treatment must be individualised and tailored to the size / extent of tumour (based upon examination and radiological examination) and the condition of the patient. Often a combination of surgery and radiation therapy is utilised. However, the prognosis of patients with primary vaginal melanoma is poor.

RADIATION THERAPY TECHNIQUES

Total radiation therapy treatment should be completed within 9 weeks (Yeh et al, 2001; Lee et al, 1994).

External-beam pelvic radiation therapy

External beam radiation therapy is usually given prior to brachytherapy to reduce tumour volume and render brachytherapy more effective.

The primary tumour, the vaginal apex and the introitus should be delineated with radio-opaque markers. CT scanning is preferable. The usual dose is 50Gy in 1.8Gy – 2Gy per fraction. Doses less than 50Gy have been found to be less effective (Perez et al, 1999).

Tumours not involving the lower 1/3 of the vagina

Target volume

- entire tumour, entire vagina, and pelvic lymph nodes

Technique

- four-field box with corner shielding and the patient prone, utilising a belly board.

Field borders

AP/PA

- superior – L5 – S1 junction
- inferior – cover the tumour with an inferior margin of 3 cm and the entire vagina
- lateral – 2 cm lateral to the bony pelvic brim (corner blocks can be used to protect normal tissues)

Lateral

- anterior – outer edge of symphysis pubis
- posterior – will include the primary tumour and any extension of disease posteriorly along the uter-sacral ligaments, as well as the pre-sacral nodes in front of S1 and S2
- superior - as for AP/PA fields
- inferior – as for AP/PA fields

Tumours involving the lower 1/3 of the vagina

Target volume

- entire tumour, the entire vagina, pelvic lymph nodes, and femoral and medial inguinal lymph nodes (Houghton & Iversen, 1982; Stock et al, 1995; Chyle et al, 1996; Perez et al, 1999).

Technique

- four-field box with corner shielding and the patient prone, utilising a belly board

OR

- two-fields, AP/PA with patient supine

Field borders

- four-field - as above, with the following alterations:
 - anterior – anterior field edge advanced to cover the inguinal lymph nodes
 - lateral – field edge can be expanded to the lateral edge of the acetabulum
- two-fields.
 - superior – L5 – S1 junction
 - inferior – covering the tumour with a 3 cm margin and the entire vagina
 - lateral – lateral edges of the acetabula (superior corner blocks may be used to protect normal tissues).
 - femoral head doses may be minimised by use of a wide AP field and narrow PA electron boost or by an anterior compensator.

Brachytherapy

Brachytherapy should follow external beam radiation therapy, aiming to give a combined tumour dose of at least 70Gy – 75Gy (Perez et al, 1999; Kirkbride et al, 1995; Peters et al, 1995; Fine et al, 1996). The total dose to the posterior bladder wall should not exceed 70Gy. The total dose to the anterior rectal wall should not exceed 60Gy – 65Gy.

High-dose-rate (HDR) brachytherapy is as effective and safe as low-dose-rate (LDR) brachytherapy (Kucera et al, 2001; Mock et al 2003). Planning must be individualised depending on the extent of disease, with either intracavitary or interstitial brachytherapy being required (Stock et al, 1992; Leung & Sexton, 1993). If brachytherapy is not possible, a conformal external beam radiotherapy boost should be considered.

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GESTATIONAL TROPHOBLASTIC DISEASE (GTD)

CLASSIFICATION AND STAGING OF GESTATIONAL TROPHOBLASTIC DISEASE

The staging and classification of gestational trophoblastic disease combines the basic anatomic staging of disease (Table 6.1) with the modified World Health Organisation risk factor scoring system (Kohorn, 2001) (Table 6.2).

Table 6.1 Anatomic FIGO staging for gestational trophoblastic disease (2000)

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, vaginal, broad ligament).
Stage III	Gestational trophoblastic tumour extends to the lungs with or without known genital tract involvement.
Stage IV	All other metastatic sites.

Table 6.2 Modified WHO scoring system for FIGO 2000 staging / scoring of gestational trophoblastic disease

	FIGO score			
Prognostic factors	0	1	2	4
Age	< 40 yrs	≥ 40 yrs	-	-
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	-
Interval months from index pregnancy	< 4	4 – 6	7 – 12	> 12
Pre-treatment β-hCG IU/L	< 10 ³	10 ³ - 10 ⁴	> 10 ⁴ - 10 ⁵	> 10 ⁵
Largest tumour size including uterus	< 3 cm	3 - 4 cm	≥ 5 cm	-
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

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 (eg. I:1, IV:15, or II:10).

Note: Hydatidiform mole and invasive mole should not be regarded as cancer (Paradinas, 1997). 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 β -hCG after hydatidiform mole evacuation and those who have trophoblastic metastases, have “trophoblastic neoplasia”.

In order to implement the FIGO 2000 staging/scoring system the following criteria for diagnosis need to be accepted (Kohorn, 2001; Kohorn, 2002):

Trophoblastic neoplasia after hydatidiform mole evacuation

- 4 values or more of plateau of β -hCG over at least 3 weeks; days 1, 7, 14 and 21
- rise of β -hCG of 10% or greater for 3-values or longer over at least 2 weeks; days 1, 7 and 14
- persistence of β -hCG 6 months after mole evacuation
- presence of histologic choriocarcinoma

Metastases

- Lung – 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 – CT or MRI (preferred)

Risk groups

- Low-risk group – score ≤ 6
- High-risk group – score ≥ 7

GESTATIONAL TROPHOBLASTIC DISEASE

The following treatment algorithm for gestational trophoblastic disease (Figure 6.1) has been adopted from Carney (2003).

Hydatidiform mole (complete and partial)

- evacuation of the mole by suction curettage
- post-operative surveillance with β -hCG assays:
 - weekly until 3 negative levels are obtained, then
 - monthly for 6 months
- contraceptive measures (OCP preferred, IUCD to be avoided) until β -hCG values have remained normal for 6 months

Abdominal hysterectomy with the mole in situ may be considered for patients desiring surgical sterilisation, but does not alter the need for follow-up.

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

In twin pregnancies with a viable fetus and a molar pregnancy, the pregnancy may be allowed to continue, after appropriate counselling of the risks to mother and fetus. This includes risk of

fetal demise of up to 60%, increased maternal obstetric complications and possible increased risk of persistent disease after delivery (Hancock & Tidy, 2002; RCOG, 2003).

Gestational trophoblastic neoplasia (GTN)

Indications for treatment include:

- 4 values or more of plateau of β -hCG over at least 3 weeks
- rise of β -hCG of 10% or greater for 3-values or longer over at least 2 weeks
- presence of histologic choriocarcinoma
- persistence of β -hCG 4-6 months after mole evacuation

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

Low-risk disease (WHO score ≤ 6)

- single-agent chemotherapy with methotrexate and folinic acid (Table 6.3) or actinomycin-D (Table 6.4)
- continue for 2-3 cycles beyond negative β -hCG
- surveillance then involves β -hCG every 2 weeks for 3 months, then monthly for 3 months. If β -hCG remains normal, check every 2 months for a further 6 months (Carney, 2003)
- contraception can be started during chemotherapy treatment and should be continued for at least 6 months and preferably one year

It is critical that treatment proceeds on an accurate schedule and in full dose. Dose reductions/delays promote emergence of drug resistance.

Alternate regimens (Table 6.5) may be considered if the above regimens are not convenient because of scheduling difficulties.

Salvage therapy following methotrexate

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 an β -hCG < 100 are often treated with actinomycin-D while those with higher levels are considered for EMA-CO (etoposide, methotrexate, actinomycin-D, vincristine, 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 (Lurain, 1998) (Table 6.6)
- repeat cycle every 2 weeks
- if necessary, use g-CSF to avoid treatment delays
- continue for 2-3 cycles beyond negative β -hCG

Follow-up

- early ultrasound in next pregnancy to confirm normal fetus
- histopathological examination of placenta after delivery
- β -hCG at 6 weeks post-partum.

Refractory disease

- combination chemotherapy with EMA-EP (Surwit & Childers, 1991) (Table 6.7)
- repeat cycle every two weeks
- continue for 2-3 cycles beyond negative β -hCG
- consider surgical resection of any lesion amenable to such an approach

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 (Soper, 1994; Jones, Wolchok & Lewis, 1996).

Brain metastases

Brain metastases in gestational trophoblastic disease present a significant risk of cerebral haemorrhage. Surgical resection should therefore be considered (Semple et al, 2004).

Intra-thecal methotrexate 12.5 mg (Rustin et al, 1989) and high dose IV methotrexate as part of EMA-CO may be given (Newlands et al, 2002).

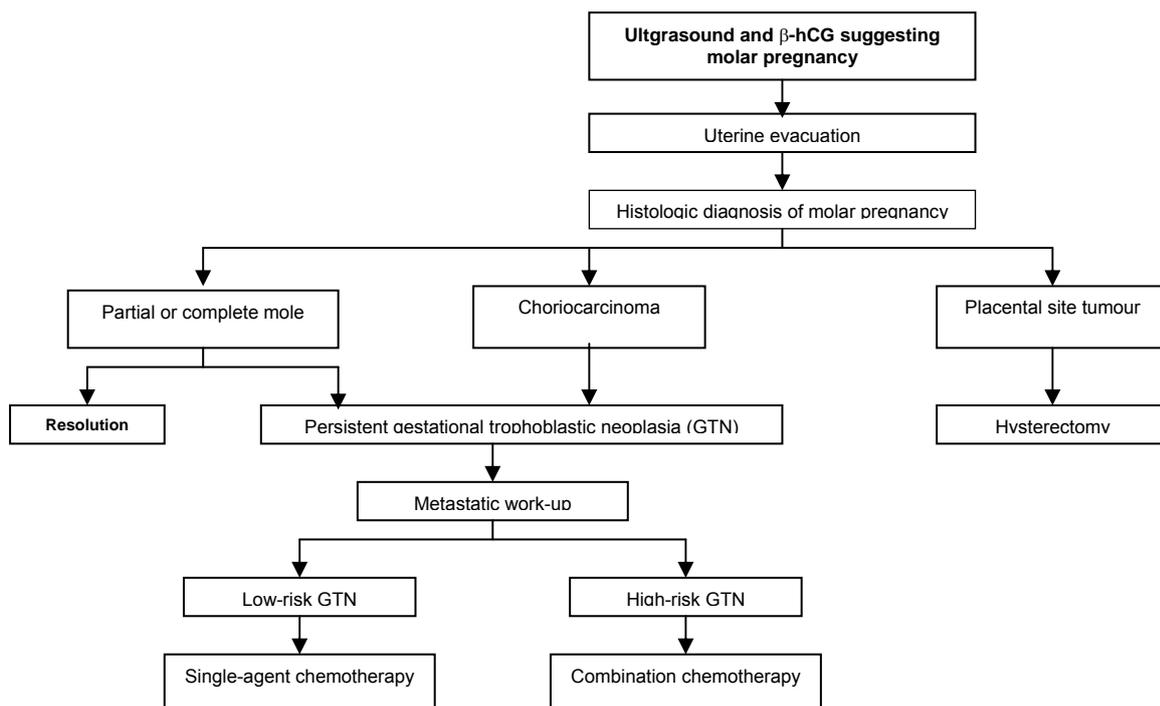


Figure 6.1 Diagnosis and treatment of gestational trophoblastic disease

Table 6.3 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	q2weekly
2, 4, 6, and 8	Folinic acid	0.1mg/kg IM or PO (24 hrs after methotrexate)	

Table 6.4 Actinomycin-D regimen for low-risk gestational trophoblastic neoplasia

Day of cycle	Drug	Dose & route	Cycle frequency
1	Actinomycin-D	1.25mg/m ² IV	Q2weekly

Table 6.5 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/m ² IM	Weekly
1 – 5	Actinomycin-D	0.5 mg IV	q2weeks

Table 6.6 EMA-CO regimen for high-risk gestational trophoblastic neoplasia

Day of Cycle	Drug	Dose & Route	Cycle Frequency
1	Etoposide + Actinomycin-D + Methotrexate	100 mg/m ² IV infusion over 30 mins 0.5 mg IV push 300 mg/m ² IV infusion over 12 hrs	q2weeks
2	Etoposide + Actinomycin-D + Folinic acid	100 mg/m ² 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/m ² IV push 600 mg/m ² IV	

Table 6.7 EMA-EP regimen for refractory gestational trophoblastic disease

Day of Cycle	Drug	Dose & Route	Cycle Frequency
1	Etoposide + Actinomycin-D + Methotrexate	100 mg/m ² IV infusion over 30 mins 0.5 mg IV push 300 mg/m ² IV infusion over 12 hrs	
2	Etoposide + Actinomycin-D + Folinic acid	100 mg/m ² 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	q2weeks
8	Etoposide + Cisplatin	100 mg/m ² IV infusion over 30 minutes 80 mg/m ² IV	

PLACENTAL SITE TROPHOBLASTIC TUMOUR

Diagnostic features include:

- rare form of gestational trophoblastic neoplasia
- β -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 (Papadopoulos et al, 2002)
- antecedent pregnancy in most cases is term delivery
- metastatic disease occurs at presentation in more than 30% of cases with recurrences occurring in 30% of all cases (Feltmate et al, 2002)
- MRI may be helpful in monitoring treatment (Feltmate et al, 2002)
- placental site trophoblastic tumour is excluded from new scoring system for gestational trophoblastic neoplasia as scoring does not correlate with outcome
- poor prognostic factors, which include:
 - mitotic count greater than 5 per 10 hpf (Feltmate et al, 2001)
 - greater than 2 years since antecedent pregnancy (Papadopoulos et al, 2002)
 - lung metastases (Papadopoulos et al, 2002)

Treatment for placental site trophoblastic tumour includes:

- hysterectomy as the treatment of choice for non-metastatic disease
- adjuvant therapy (EMA-PE) is indicated for patients with metastatic disease at presentation and may be indicated for patients with poor prognostic factors (Feltmate et al, 2001; Papadopoulos et al, 2002)
- surgery should be considered if resectable masses are present

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GYNAECOLOGICAL 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 (RCPA).

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 at all times the responsibility of the pathologist (RCPA, 2001).

The following pathology reporting, grading, and histologic types (Tables 7.1 – 7.13) have been adopted from the Gynecologic Oncology Group Virtual Hospital Pathology Manual, which can be downloaded from the Internet:

<http://vh.org/adult/provider/pathology/OBGYNoncology/>

CERVICAL CANCER

Anatomical pathology reporting

Table 7.1 Anatomical pathology variables for reporting cervical cancer

Macroscopic	
Specimen	<ul style="list-style-type: none"> • Uterine size and weight, size of cervix, adnexa (right and left), size of para-cervical tissue (R and L), and vaginal cuff size
Tumour	<ul style="list-style-type: none"> • Size (3 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)	<ul style="list-style-type: none"> • Size (range where applicable), size of largest metastasis, and number of nodes and pieces per cassette
Microscopic	
	<ul style="list-style-type: none"> • Histologic type (grade) • Associated CIN (grade) • 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 • Capillary – lymphatic space invasion • Status of para-cervical tissue (parametrial invasion) • Proximity to margins / or positive margins • Lower uterine segment • Vaginal involvement • Special stains • Metastatic sites (likely to be submitted separately) ie. lymph nodes positive / number nodes by site; extra-nodal extension • Other disease processes.

Histologic classification

Table 7.2 Histologic type and classification for cervical cancer

Major histologic type	Classification of histologic type
Epithelial	<ul style="list-style-type: none"> Squamous intraepithelial lesion (CIN 1 – 3; carcinoma in situ) Invasive squamous cell carcinoma (keratinising; non-keratinising; verrucous; warty; papillary; lymphoepithelioma-like)
Glandular	<ul style="list-style-type: none"> In situ lesion (endocervical glandular dysplasia, adenocarcinoma in situ) Invasive adenocarcinoma (mucinous; endometrioid; clear cell; serous; mesonephric; villoglandular)
Other invasive tumours	<ul style="list-style-type: none"> Adenosquamous (gland forming; large cell carcinomas with intracellular mucin) Glassy cell Adenoid basal Carcinoid Small cell Undifferentiated
Collision tumours	<ul style="list-style-type: none"> Mesenchymal (leiomyosarcoma; endocervical stromal sarcoma; sarcoma botryoides [embryonal rhabdomyosarcoma]; alveolar soft part sarcoma; endometrioid stromal sarcoma) Mixed epithelial and mesenchymal (adenosarcoma; malignant mixed mullerian tumours [carcinosarcoma]; Wilm's tumour) Miscellaneous malignancies (malignant melanoma; lymphoma and leukaemia; germ cell) Secondary tumours

Grading

Grading of invasive squamous cell carcinoma of the cervix is related to cell type and morphology, degree of differentiation, and tumour architecture; the grading for invasive adenocarcinoma is based on the degree of architectural differentiation, characterised by the amount of glandular formation (Table 7.3).

Table 7.3 Grading of squamous cell carcinoma and adenocarcinoma of cervix

Grade	Squamous cell carcinoma	Adenocarcinoma
Grade 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.
Grade 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 cribriform 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.
Grade 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.

UTERINE CANCER

Anatomical pathology reporting

Table 7.4 Anatomical pathology variables for reporting uterine cancer

Macroscopic	
Specimen	<ul style="list-style-type: none"> Size and weight of uterus, size of cervix, adnexa (R and L)
Tumour	<ul style="list-style-type: none"> Overall size (3 dimensions), location(s) involved, appearance, depth of invasion (from endometrial/myometrial junction), myometrial thickness (mm), endometrial thickness (non-tumour), serosal involvement, cervix involvement, and adnexal involvement.
Other findings	<ul style="list-style-type: none"> -
Lymph nodes (by site)	<ul style="list-style-type: none"> Size (range where applicable), size of largest metastasis, and number of nodes and pieces per cassette
Microscopic	
	<ul style="list-style-type: none"> Histologic type (include percentage if mixed epithelial types) FIGO grade Type of invasion (broad front, infiltrating finger-like, discontinuous) Multifocal invasion Maximum depth of invasion (mm) Capillary – lymphatic space invasion Total myometrial thickness at point of deepest invasion (mm) Lower uterine segment involvement (surface glandular or stromal) Endocervix involvement (surface glandular or stromal) Other organs involved Special stains Associated hyperplasia (simple, complex, atypical) Other disease processes Metastatic site(s) (may have been submitted separately) Lymph nodes positive / number of nodes by site Extra-nodal extension Washings

Histologic classification

Table 7.5 Major histologic type and classification of uterine cancers

Major histologic type	Classification of histologic type
Epithelial	<ul style="list-style-type: none"> Endometrioid (adenocarcinoma; adenocarcinoma with squamous differentiation) Serous adenocarcinoma (Note 1) Clear cell adenocarcinoma (Note 1) Mucinous adenocarcinoma (Note 2) Squamous cell carcinoma (Note 2) Mixed carcinoma Undifferentiated carcinoma
Non-epithelial	<ul style="list-style-type: none"> Endometrial stromal (stromal nodule; low-grade stromal sarcoma (Note 3); and high-grade stromal sarcoma (Note 4)) Smooth muscle tumour of uncertain malignant potential Leiomyosarcoma (epithelioid; myxoid) Mixed endometrial stromal and smooth muscle tumour Poorly differentiated (undifferentiated) endometrial sarcoma Other soft tissue tumours (homologous; heterologous)
Mixed epithelial, non-epithelial (Note 5)	<ul style="list-style-type: none"> Adenosarcoma (homologous; heterologous; with high grade stromal overgrowth (Note 6)) Carcinosarcoma – malignant mixed mesodermal tumour and malignant mixed Mullerian tumour (homologous; heterologous) Carcinofibroma
Miscellaneous	<ul style="list-style-type: none"> Sex cord-like tumours Germ cell neoplasms Neuroectodermal tumours Lymphoma

Grading

Table 7.6 Grading of uterine cancers

Grade	Histopathology and degree of differentiation
Grade 1 (G1)	5 % or less 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)	More than 50% of non-squamous or non-morular solid growth pattern

OVARIAN CANCER

Anatomical pathology reporting

Intra-operative consultation (eg. via frozen section) may be of value where clinical management decisions may be altered depending on the histological type. Ovarian tumours should be extensively sampled, one block for every 1-2cm diameter. Slides submitted should support the type of malignancy, the grade assigned, and the extent of disease. Intra-operative rupture should be noted. Documentation of tumour extent is necessary.

Table 7.7 Anatomical pathology variables for reporting ovarian neoplasms

Macroscopic	
Specimen (include identifying markers for each ovary)	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Overall size (3 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
Other findings	<ul style="list-style-type: none"> -
Identifiers (ink applied)	<ul style="list-style-type: none"> -
Lymph nodes (by site)	<ul style="list-style-type: none"> Size (range where appropriate), size of largest metastasis, number of nodes and pieces per cassette
Microscopic	
	<ul style="list-style-type: none"> 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)

Histologic classification

Table 7.8 Major histologic type and classification of tumours of the ovary

Major Histologic Type	Classification of Histologic Type
Epithelial	<ul style="list-style-type: none"> • Serous (benign; LMP; adenocarcinoma) • Mucinous (benign; LMP; adenocarcinoma) • Endometrioid (benign or LMP; Carcinosarcoma; malignant mixed mullerian tumour; adenosarcoma; endometrial stromal sarcoma) • Clear cell (benign; LMP; adenocarcinoma) • Brenner (benign; LMP; adenocarcinoma) • Transitional cell (papillary type; malignant Brenner-like) • Undifferentiated carcinoma
Sex cord stromal tumours	<ul style="list-style-type: none"> • Granulosa – Theca cell tumours • Sertoli-Leydig cell tumours • Gynandroblastoma • Sex cord-stromal tumour with annular tubules • Steroid cell tumours
Germ cell tumours	<ul style="list-style-type: none"> • Dysgerminomas • Endodermal sinus tumours • Embryonal carcinoma • Polyembryona • Choriocarcinoma • Teratomas (immature [solid]; mature [cystic]) • Mixed form
Mixed germ cell and sex cord-stromal tumours	<ul style="list-style-type: none"> • Gonadoblastoma • Other
Miscellaneous malignancies	<ul style="list-style-type: none"> • Sarcoma (soft tissue type) • Malignant lymphomas • Small cell carcinoma • Metastatic neoplasm • Other

Grading

Use of the Universal Grading System is recommended (Shimizu et al, 1998; Silverberg 2000; Ishioka et al, 2003).

The specific components of the score must be recorded as well as the final grade as the different components have different prognostic value depending on the stage.

Table 7.9 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 = 0.345mm ²] 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 or 7 = Grade 2 8 or 9 = Grade 3

Clear cell carcinoma – total score is not assessed as architecture is not prognostic.

Transitional cell carcinoma – total score is not assessed, as solid / glandular is not relevant.

Borderline tumours – not usually graded, although a carcinoma-in-situ sub-category is recognised.

VULVAL CANCER

Anatomical pathology reporting

Table 7.10 Anatomical pathology variable for reporting vulval cancer

Macroscopic	
Specimen	<ul style="list-style-type: none"> Overall size, anatomic landmarks identifiable, and orientation markers per surgeon
Tumour	<ul style="list-style-type: none"> Anatomic location, size (3 dimensions), configuration, extent of involvement (urethra, vagina, anus), and distance to margins (including nearest cutaneous, vaginal and deep)
Adjacent skin abnormalities	<ul style="list-style-type: none"> -
Identifiers applied by pathologist (ink)	<ul style="list-style-type: none"> -
Blocks submitted	<ul style="list-style-type: none"> -
Lymph nodes (by location)	<ul style="list-style-type: none"> Size (range where applicable), size of largest metastasis, and number of nodes and pieces per cassette
Microscopic	<ul style="list-style-type: none"> Histologic type Histologic grade Depth of invasion (where applicable) (Notes 7 & 8) Thickness of invasive tumour (Note 9) Multi-focal invasion Capillary – lymphatic space invasion Perineural invasion Margin involvement and/or distance to closest margin(s) Involvement of urethra, rectum, or vagina Adjacent disease(s) (skin, vagina, etc. such as lichen sclerosis, hyperpalsia) Lymph nodes (by site) Number of positive / number found Size of largest metastasis Extracapsular extension Cloquet's node (highest inguinal node) Other disease processes

Histologic classification

Table 7.11 Histologic classification of intraepithelial disorders of the vulva

Major histologic type	Classification of histologic type
Non-neoplastic epithelial disorders	<ul style="list-style-type: none"> • Lichen sclerosis • Squamous hyperplasia, not otherwise specified (Note 10) • Other dermatoses / 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	Squamous intraepithelial neoplasia <ul style="list-style-type: none"> • VIN I, VIN II, VIN III (severe dysplasia or carcinoma in situ [Note 11])

Table 7.12 Histologic classification of neoplasia of the vulva

Major histologic type	Classification of histologic type
	<ul style="list-style-type: none"> • Invasive squamous cell carcinoma (keratinising; non-keratinising; basaloid carcinoma; verrucous; warty carcinoma [condylomatous]) • Basal cell carcinoma • Adenocarcinoma
Bartholin gland carcinoma	<ul style="list-style-type: none"> • Squamous cell carcinoma • Adenocarcinoma • Adenoid cystic carcinoma • Adenosquamous carcinoma • Undifferentiated and other
Soft tissue sarcomas	<ul style="list-style-type: none"> • Embryonal rhabdomyosarcoma (sarcoma botryoides) • Leiomyosarcoma • Other
Other malignant tumours	<ul style="list-style-type: none"> • Malignant melanoma • Lymphomas • Others

Grading

Table 7.13 Grading of invasive squamous cell carcinoma of the vulva

Grade	Invasive Squamous Cell Carcinoma
Grade 1	No poorly differentiated component
Grade 2	Poorly differentiated (Note 12) component occupies $\leq 25\%$ of the total area of the tumour
Grade 3	Poorly differentiated component occupies $> 25\%$, but $\leq 50\%$ of the total tumour area
Grade 4	Poorly differentiated component occupies $> 50\%$ of the tumour area.

NOTES

1. Serous carcinoma and clear cell carcinoma should comprise more than 50% of a tumour before designated in those categories when they are mixed components.
2. To consider a tumour a primary SCC or mucinous carcinoma of endometrium, concurrent cervical carcinoma of same cell type must be absent.
3. Low-grade stromal sarcomas are cytologically and architecturally bland with evidence of infiltrative behaviour – classically < 10 mitoses / 10hpf
4. High-grade stromal sarcomas are cytologically poorly differentiated with infiltrative behaviour, necrosis, and atypical mitoses, classically > 10 mitoses / 10 hpf.
5. An epithelial sub-type must be at least 10% of the total volume to designate the tumour mixed.
6. Adenocarcinoma with high-grade stromal overgrowth should be specifically noted due to its poor prognosis.
7. Depth of invasion is the maximal stromal invasion measured from the point of origin of invasion to the greatest depth. As this measurement is subject to problems resulting in less consistency, thickness is the preferred measurement, though both may give useful information.
8. Microinvasion is not used in reference to vulval carcinoma. Superficial invasion terminology may be useful when combined with a specific measurement for clinical management.
9. 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.
10. 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.
11. VIN III encompasses Bowen's disease, erythroplasia of Querat, and carcinoma in-situ, simplex type. Bowenoid papulosis is not a histopathologic diagnosis, but a clinical presentation.
12. Poorly differentiated carcinoma is generally found at the epithelial stromal junction.

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CLINICAL ISSUES

CLINICAL TRIALS

Clinical trials are a critical part of the research process - they help move basic scientific research from the laboratory into treatments for people. The clinical trial can be used both to evaluate what effect an intervention has on the natural history of cancer (the explanatory approach) and also to determine the optimal therapy from the patient's perspective (the pragmatic approach) (cited in Simes, 1992).

Randomised controlled trials (phase III) provide the least biased method of assessing a treatment thus providing the best level of evidence of treatment outcome. There are four phases of clinical trials (Table 8.1)

Classification of Clinical Trials

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

Recruitment and retention of trial participants

Where possible and appropriate, all patients who are eligible for a clinical trial should be offered the opportunity to participate.

The general public is largely unaware of clinical trials as a treatment / prevention option, or are misinformed about the clinical trial process (Harris Interactive, 2001). Less than 5% of eligible new cancer patients participate in clinical trials (Kelly, Ghazi & Caldwell, 2002). Possible reasons include socio-economic factors as well as patient- and clinician-based barriers.

A systematic review of the literature conducted by Prescott et al (1999) identified a number of barriers to participation in clinical trials (Table 8.2) but was unable to identify any strategies that had been proven to be effective in improving recruitment of patients to clinical trials.

A large study conducted by Sateren et al (2002) examined the impact of socioeconomic factors on accrual to National Cancer Institute sponsored cancer treatment trials. Overall the highest observed accrual was observed in suburban areas, and with higher socioeconomic levels. Furthermore, the number of oncologists and the presence of approved cancer programs were both significantly associated with increased accrual. The authors suggest that ongoing partnership with professional societies may be an effective approach to strengthen accrual to clinical trials.

On a more positive note, however, many patients participating in clinical trials find certain aspects of their participation appealing (Slevin et al, 1995). These include:

- contribution to research knowledge and benefits to humanity
- more likely to be treated by doctors with a special interest
- greater chance of obtaining new treatments
- progress is monitored more closely
- likely to obtain more information about the condition

Table 8.2 Barriers to participation in randomised controlled trials

Clinician-based barriers	Patient-based barriers
<ul style="list-style-type: none"> • Time constraints • Lack of staff and timing • Worry about the impact on doctor-patient relationship • Concern for patients • Loss of professional autonomy • Difficulty with the consent procedure • Lack of rewards and recognition 	<ul style="list-style-type: none"> • Additional procedures and appointments • Additional travel problems and cost • Patient preferences for a particular treatment (or no treatment) • Worry about uncertainty of treatment or trials • Concerns about information and consent • Protocol causing a problem with recruitment • Clinician concerns about information provision to patients

Possible ways to avoid losing patients enrolled on a trial include:

- only register “reliable” patients onto a trial, especially if long-term follow up is required
- give patients adequate information about the study at the time of informed consent, including an explanation of the importance of follow up even if study medication has been discontinued
- obtain alternative follow up contact information from the patient (eg. GP and relative/friend not living with the patient)
- reminder phone calls or letters to patients prior to follow up appointments – target those patients known to be poor attenders
- maintain the profile of the trial amongst patients (eg. newsletter, information sessions)
- provide positive feedback to patients

Protection of trial participants

Participant rights and safety must be protected at all times. This is done through:

- informed consent - the doctrine of informed consent contains four requirements (Lebacqz & Levine, 1997):
 - that the patient should be capable of giving consent
 - that consent should be freely given
 - that patients should be given all information relevant to their decision to agree
 - that patients should understand that information. The NHMRC guidelines in Australia state that patients should receive “sufficient” information although what constitutes “sufficient” is difficult to define and remains controversial

- two review panels that approve a clinical trial protocol before it begins - scientific review panel and human research ethics committee (HREC)
- monitoring, which continues during the trial, by the HREC, data and safety monitoring boards and federal agencies

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
- The Cancer Council Australia
- State and Territory Cancer Councils
- Database of Cancer Research in Australia (CARA)

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FAMILIAL ASPECTS OF GYNAECOLOGICAL CANCERS

More detailed guidelines on the familial aspects of gynaecological cancer can be found in *Familial Aspects of Cancer: a Guide to Clinical Practice* (1999). This document can be downloaded from the National Health and Medical Research Council website: <http://www.nhmrc.health.gov.au>.

Genes associated with ovarian cancer

Up to 10% of all epithelial ovarian cancers, and a higher proportion of early onset cases, are thought to be due to gene mutations (Table 8.3) (Stratton et al, 1997). Gene mutation carriers have at least a 10-fold increased risk of ovarian cancer.

Table 8.3 Known genes responsible for hereditary ovarian cancer

Syndrome	Gene	Chromosome	Risk of other cancer
Hereditary breast/ovarian cancer	BRCA1	17q	Female breast, prostate
	BRCA2	13q	Female breast, male breast, prostate, pancreas
Hereditary non-polyposis colorectal cancer	DNA mismatch repair gene (HNPCC)	Various	Colorectal, other gastrointestinal, endometrial, renal tract

Female carriers of BRCA1 gene mutations have an estimated lifetime risk of ovarian cancer that may be as high as 60% (Easton, Ford & Bishop, 1995), and in BRCA2 as high as 40% (Anonymous, 1999).

Carriers of HNPCC gene mutation have a 70-90% lifetime risk of developing any cancer. Women carriers have a lifetime risk of up to 40% for developing endometrial cancer, and up to 10% for ovarian cancer (Vasen et al, 1996).

Risk categories and management guidelines

A comprehensive family history is essential in estimating risk of ovarian cancer. A family history of breast cancer and of some other types of cancer should be taken into account and, if present, referral to a cancer genetics service may be appropriate.

The two risk categories (Tables 8.4 and Table 8.5) apply to women without breast or ovarian cancer (NHMRC, 1999).

First-degree relatives include parents, siblings and children. Second-degree relatives include aunts, uncles, nieces, nephews and grandparents.

Issues for consideration

Vaginal bimanual pelvic examination, although simple, is not specific or sensitive enough to detect ovarian cancer and is therefore not recommended as a screening method (Grover & Quinn, 1995).

CA125 is increased in only 20-25% of patients with Stage I ovarian cancer (Friedlander & Tucker, 1997). Benign (and frequently pre-menopausal) conditions such as fibroids, endometriosis, pelvic inflammatory disease, and pregnancy can elevate CA125 substantially. In pre-menopausal women, specificity is only 94.5% (Einhorn et al, 1992) and, whilst frequently done, should generally not be recommended as a surveillance test for this group of women. The sensitivity and specificity of colour flow Doppler has been reported as 96.4 and 99.8% respectively (Jacobs et al, 1993). The addition of trans-vaginal ultrasound to CA125 measurement increases specificity close to 100% and gives a positive predictive value of 27% (Einhorn et al, (ibid); 1993).

A number of cohort studies have demonstrated that prophylactic oophorectomy provides a significant lifetime reduction in the risk of developing ovarian cancer for women who are BRCA 1 or BRCA2 mutation carriers (Rosen et al, 2004). Since primary peritoneal carcinoma may still occur despite prophylactic oophorectomy (Tobacman et al, 1982), indefinite follow-up using annual CA125 might be considered. The use of HRT to manage the symptoms of surgical menopause should be done with caution as many aspects of the effects of HRT on breast cancer risk in mutation carriers is still unclear (Garber & Hartman, 2004).

Oral contraceptive use has been shown to reduce the incidence of ovarian cancer in one study (Narod et al, 1998), but not another (Modan et al, 2001). However, there is some evidence that that this may increase the risk of early onset breast cancer in BRCA1 mutation carriers, but not BRCA2 carriers (Narod et al, 2002).

Table 8.4 Category 1 - Women at, or at most, moderately above average risk of developing ovarian cancer

Risk factors	<p>The lifetime risk of ovarian cancer is 1 in 100 (for most women in this group), but not more than 1 in 30. Risk is no more than 3-fold higher than the population average. This group covers more than 99% of the population and comprises women with:</p> <ul style="list-style-type: none"> • No confirmed family history of ovarian cancer; or • One first- or second-degree relative diagnosed with ovarian cancer at any age (provided the family is not of Ashkenazi Jewish ancestry*); or • One second-degree relative diagnosed with ovarian cancer at any age; or • Two first- or second-degree relatives diagnosed with ovarian cancer, but on different sides of the family (ie. one on each side of the family) <p>* Genetic susceptibility to ovarian and breast cancer is more common in people of Ashkenazi Jewish ancestry.</p>
Management	<ul style="list-style-type: none"> • Reassure women that the risk is at, or at most, moderately above the average risk for the general population and that more than 97% of women in this group will not develop ovarian cancer • Advise women about current best practice for the early detection of cancers for the population. • Advise women to visit their general practitioner promptly with any health changes. <p>The efficacy of ovarian cancer screening is unproven (Mackey & Creasman, 1995). Screening the general population for epithelial ovarian cancer cannot be justified on the basis of its prevalence and inadequate sensitivity of the available tests (NIH, 1995).</p>

Table 8.5 Category 2 - Women at potentially high risk of developing ovarian cancer

Risk factors	<p>The lifetime risk of ovarian cancer is from 1 in 30 up to 1 in 3, or possibly higher if shown to have a high-risk mutation. The risk may be more than 3-fold higher than the population average. This group comprises less than 1% of the female population and comprises women with:</p> <ul style="list-style-type: none"> • One first-degree relative with epithelial ovarian cancer in a family of Ashkenazi Jewish ancestry. • Two first- or second-degree relatives on the same side of the family diagnosed with epithelial ovarian cancer, especially if one or more of the following features occurs on the same side of the family <ul style="list-style-type: none"> • Additional relative(s) with breast or ovarian cancer • Breast cancer diagnosed before the age of 40 • Bilateral breast cancer • Breast and ovarian cancer in the same woman • Breast cancer in a male relative. • Three or more first- or second-degree relatives on the same side of the family diagnosed with any cancers consistent with HNPCC: colorectal cancer (particularly if diagnosed before the age of 50), endometrial cancer, ovarian cancer, gastric cancer, and cancers involving the renal tract • Member of a family in which the presence of a high-risk ovarian cancer gene mutation has been established.
Management	<ul style="list-style-type: none"> • Advise women that there is a potentially high risk of developing ovarian cancers and perhaps other cancers such as breast cancer, but that the majority of women in this group will not develop ovarian cancer. • If the woman wishes to clarify her genetic risk or that of her family, or wishes to consider risk-reducing surgery, discuss referral to a specialist family cancer clinic for advice, appropriate counselling and management. • Because early detection may be important, and because bilateral salpingo-oophorectomy has been proven to reduce the risk of ovarian and breast cancer in women with a mutation in BRCA1 and BRCA2 (Struwing et al, 1995; Rebbeck et al, 1999), advise women to see a gynaecological oncologist. An appropriate individualised surveillance program may include: <ul style="list-style-type: none"> • Visiting their general practitioner promptly with any health changes • Trans-vaginal ultrasonography (the age at which this could commence may depend on the family history and if a high-risk ovarian cancer gene mutation has been identified) • CA125 measurement • Surveillance relevant to other cancers (eg. attending for clinical breast examination in line with NBCC policy and mammography or other surveillance if the family history is consistent with HNPCC). • Discuss possible participation in a relevant approved clinical trial. <p>* There is no evidence that transvaginal ultrasonography and CA125 reduce mortality from ovarian cancer, but they may be considered for women who have not undergone risk-reducing salpingo-oophorectomy.</p>

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LYMPHOEDEMA

Diagnosis and incidence of lymphoedema

The diagnosis of lymphoedema is often based on clinical criteria alone as there are no commonly accepted definitions – the limited number of studies published to date report various limb circumference criteria and methods of measuring excess fluid (Logan, 1995). In any case, lymphoedema is a progressive condition with the following components:

- excess protein in interstitial fluid
- oedema
- chronic inflammation

Lower leg lymphoedema (LLL) is a major source of morbidity for women who have surgery and/or radiation therapy to lymph nodes as part of treatment for a gynaecological cancer. Ryan et al (2003a) recently reported on almost 500 women treated over a 5-year period. Clinically diagnosed LLL occurred in 18% of women. 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. 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. Pelvic lymphadenectomy was associated with a 20% risk.

Management of lymphoedema

There are no treatments available to prevent lymphoedema. The aims of treatment are to relieve problems with pain and oedema, and to improve skin and tissue texture (Ryan et al, 2003b). The cornerstones of treatment are:

- education
- exercise
- simple massage
- multi-layer bandaging initially (Badger, Peacock & Mortimer, 2000)
- containment hosiery

As a general guide, women who are at risk of developing LLL should be:

- provided with information both pre- and post-operatively about the risks and early signs and symptoms
- provided with information about skin care and exercise
- referred to a qualified, specialised therapist to effect early management

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PALLIATIVE CARE

The comprehensive **Best Clinical Practice Gynaecological Cancer Palliative Care 2008** resource is available from the Greater Metropolitan Clinical Taskforce GO Secretariat.

Definition and key principles of 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 radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.”
(adapted from WHO, 2003)

Integration of patient care from diagnosis

Palliative care is patient-centred and acknowledges the patient and family or social unit as the focus of care. Responsibility for palliative care is shared by all concerned in diagnosis, investigation, treatment and review of patients. Early recognition and treatment of problems and use of preventive measures when problems may reasonably be predicted can limit the ultimate severity of pain or other symptoms. This implies the need for the “lead clinician” to clearly identify, and reassess, the goals of treatment throughout a course of illness; and to recognise when specialists in palliative medicine, or nursing, or other dimensions of palliative care should be involved (Berek & Hacker, 2000; Doyle et al, 2004).

The mixed management or parallel model of care favoured by end-of-life authorities in the USA (Field & Cassel, 1997) (Fig. 1) reflects the reality and ideal of end-of-life care; therapies are not rigidly divided as seen in earlier “transitional” models of care. It allows ongoing efforts to extend life while still preparing for future care needs, and when appropriate, for approaching death.

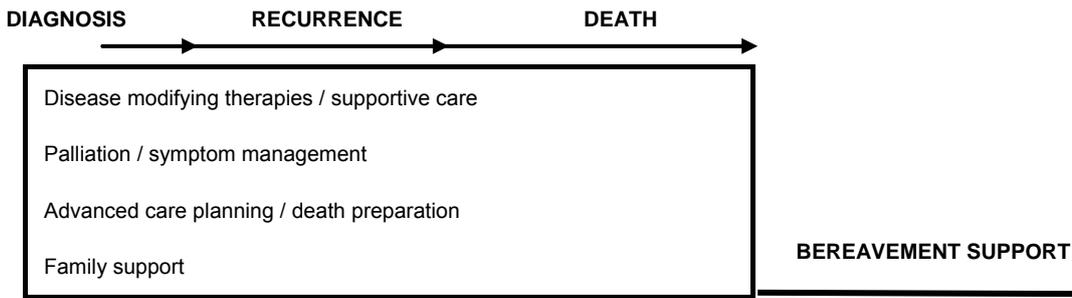


Figure 8.1 Model for mixed management of an eventually fatal illness

Patients require frequent assessment regarding their symptom relief, personal and family support, and care issues. This should be undertaken at every admission, clinic visit, or outpatient treatment visit by whoever is involved in the patient's care. Where needs are identified, referral should be made to the health professional with the most appropriate skill to meet that need.

Care should also be monitored so that: a) patients with poorly controlled symptoms; b) deaths in circumstances compromising patient dignity; c) partners/friends/family with gross distress, are noted and relevant resources mobilised or care procedures modified.

Care must be taken with regard to cultural issues, especially when approaching communication of prognosis.

The following will facilitate discussion with patients (NBCC & NCCI, 2003):

- clear determination of goals by lead clinician
- collaboration and coordination between all health professionals involved in the patient's care
- allocation of adequate time for discussion with the patient and provision of a private environment
- eliciting the patient's understanding of her illness, her concerns and goals before discussing specific clinical decisions
- involvement of the patient in controlling the situation, eg "if I have bad news, who would you like to be here with you?" and "if I have bad information or news what information do you need or want?"
- open and honest presentation of information about changes in the cancer, treatment efficacy and, where requested, prognosis
- inquiry into the patient's understanding of palliative care and emphasise its role throughout illness including how palliative care might apply to this particular patient in her unique situation
- explicit statement of non-abandonment – providing a clear message to the patient that they will receive optimal care and will not be abandoned and that the current treating team will be available for the duration of the illness, for consultation and/or further active treatment if appropriate

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PSYCHOSOCIAL CARE

The comprehensive **Best Clinical Practice Gynaecological Cancer Palliative Care 2008** resource is available from the Greater Metropolitan Clinical Taskforce GO Secretariat.

The following summary has been taken from the clinical practice guidelines for psychosocial care (NBCC & NCCI, 2003). These guidelines can be downloaded from the National Health and Medical Research Council website: <http://www.nhmrc.gov.au>

Further information for health professionals can be found at the Gynaecological Cancer Psychosocial Support Service website: <http://www.gynaecancersupport.org.au>

Incidence of psychosocial morbidity associated with a cancer diagnosis

“Many people diagnosed with cancer face practical, emotional and psychological demands in addition to their physical treatment. These psychosocial needs are significant, and frequently go undetected and unmet. Up to 66% of people with cancer experience long-term psychosocial distress (Zabora et al, 2001): up to 30% experience clinically significant anxiety problems (Bodurka-Bevers et al, 2000), and prevalence rates for depression range from 20% - 35% (Dean, 1987; Jacobsen, Bovbjerg & Redd, 1993; Jenkins, Carmody & Rush, 1998).” “Some studies report clinical depression in up to 40% of patients with progressive disease in palliative care (Bukberg, Penman & Holland, 1984).”

“The experience of cancer may continue to have an emotional impact on some people long after their initial diagnosis. Residual concerns about recurrence and fear of checkups may last for many years after the original diagnosis. The diagnosis of recurrence causes significant distress.”

“Many people report inadequate information to guide decision-making, and others are disadvantaged because of a lack of knowledge about practical support, even when such services are available.”

The impact on families of those with cancer is considerable with stress levels experienced by partners reported as comparable to, or higher than, that of patients themselves (Baider & Denour, 1999). Children of parents with cancer are also susceptible to stress and in need of support (Compas et al, 1994; Welch, Wadsworth & Compas, 1996).

Psychosocial support

There is an increasing body of evidence that psychological therapies improve emotional adjustment and social functioning, and reduce both treatment- and disease-related distress in patients with cancer (Devine & Westlake, 1995, Sheard & Maguire, 1996; Meyer & Mark, 1995).

As a minimum standard of care, gynaecological oncology units should:

- establish mechanisms for the routine assessment of patients' psychosocial well-being (NSW Health, 2003)
- provide a range of support services to address the information, support and sexual adjustment needs of patients and their families
- refer patients early for specialist psychosocial support (eg. clinical psychologist, social worker, and liaison psychiatrist) when risk factors or symptoms of distress become evident.

The NBCC and NCCI guidelines provide generic evidence-based recommendations about:

- the provision of information
- the integration of quality-of-life issues into the care of patients with cancer
- minimising the social, and psychological impact of cancer on patients and their family
- strategies for the identification and management of patients experiencing significant emotional distress

Summary statements with level I and level II evidence cover:

- general interactional skills
- discussing prognosis
- discussing treatment options: providing information and choice
- preparing patients for potentially threatening procedure and treatment
- emotional and social support
- ensuring continuity of care
- support towards the end of life
- exploring and responding to specific concerns through a range of interventions (eg. cognitive behavioural techniques, family and couples therapy, relaxation techniques)
- types and benefits of specialised care
- treatment of anxiety and depression

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VAGINAL STENOSIS

Diagnosis and incidence of vaginal stenosis

The vagina is the most common site of late toxicity of brachytherapy for the treatment of gynaecological cancer (MacLeod et al, 1999). Few authors define vaginal stenosis adequately and those who do, define it inconsistently (eg. vaginal shortening, agglutination, adhesions, fibrosis or stenosis). Whilst reports of incidence vary between 2% and 90%, many women develop some degree of stenosis within 4-6 weeks of completing brachytherapy (Hartman & Diddle, 1972; Flay & Matthews, 1995). 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.

Vaginal shortening is reported as being greater for women with cervical cancer than for those with endometrial cancer (Bruner et al, 1993) and more common in those undergoing radiotherapy and surgery for cervical cancer than those undergoing radiotherapy alone (Flay & Matthews, 1995). Women undergoing hysterectomy for endometrial cancer, with the addition of external beam radiotherapy combined with brachytherapy, have been found to have greater toxicity than for brachytherapy alone (MacLeod et al, 1999). The severity of stenosis appears to be related to a higher dose per fraction of brachytherapy, an increased number of fractions and a smaller diameter (≤ 20 mm) of the brachytherapy applicator (Sorbe & Smeds, 1990; Nori et al, 1994; Nunns et al, 2000).

Prevention and management of vaginal stenosis

It is generally accepted that vaginal stenosis may be prevented by regular sexual intercourse or the use of vaginal dilators, although there is some evidence that sexual intercourse alone does not prevent it (Decruze, Guthrie & Magnani, 1999). Currently 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) (Lancaster, 2003 in press).

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. There is evidence that compliance increases when a dedicated staff member provides specific information and instructions about dilator use.
- encouraged to commence using vaginal dilators as soon as comfortably possible, and certainly within 4 weeks of completing brachytherapy. 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) (Lancaster, 2004). By promoting daily use, it is hoped that in the long term women will use the dilator at least 2-3 times a week.
- encouraged to use the dilator daily for a minimum of 3 years and if possible, indefinitely and
- assessed for toxicity and have this documented at clinical follow-up. The use of topical oestrogen cream has proposed benefits for women being treated with brachytherapy for cervical cancer (Denton & Maher, 2003), but remains controversial for women with endometrial cancer.

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QUICK REFERENCES

COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

The National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) are used for collecting treatment-related adverse event data to facilitate the evaluation of new cancer therapies, treatment modalities, and supportive measures (NCI, 1999; NCI, 2003).

Definitions

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 9.1) with more than 200 individual adverse events.

Table 9.1 CTCAE adverse event categories

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

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 9.2).

Table 9.2 CTCAE grading of adverse events

Grade	Criteria
Grade 1	Mild adverse event
Grade 2	Moderate adverse event
Grade 3	Severe adverse event
Grade 4	Life-threatening or disabling adverse event
Grade 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 radiation therapy.

Grading is based on specific clinical criteria that usually require evaluation by a clinician.

Note: Disease progression or signs and symptoms definitely related to disease should not be graded.

Several sources of information for adverse event grading may be encountered.

- *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 9.3) 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 9.3 CTCAE scale of attribution of causality

Scale	Attribution
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).

References

National Cancer Institute, Cancer Therapy Evaluation Program. *Common toxicity criteria manual* Version 2.0, June 1999. <http://ctep.cancer.gov/>

National Cancer Institute, Cancer Therapy Evaluation Program. *Common terminology criteria for adverse events (CTAE)* Version 3.0, June 2003. <http://ctep.cancer.gov/>

DIFFERENTIATION OF HYSTERECTOMY TYPES

Table 9.4 Classes of hysterectomy for cervical cancer

Type I	Simple or extra fascial hysterectomy. Removal all cervical tissue but no parametrium
Type II	Modified radical hysterectomy Removal of more para-cervical tissue than type I while still preserving the blood supply to the distal ureters and bladder. The medial half of the cardinal ligament is removed.
Type III	Radical hysterectomy Wide radical dissection of the parametrial and para-vaginal tissues. The uterine artery is ligated at its origin from the internal iliac artery.
Type IV	Extended radical hysterectomy Complete removal of all peri-ureteral tissue, a more extensive excision of peri-vaginal tissues and when indicated, excision of the internal iliac vessels along that part of the pelvic wall.
Type V	Partial exenteration Removal of central recurrent cancer involving portions of the distal ureter or bladder. A reimplantation of the ureter is then performed.

Reference

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FRANCO ITALIAN GLOSSARY FOR REPORTING COMPLICATIONS OF TREATMENT OF GYNAECOLOGICAL CANCER

Table 9.5 *Franco Italian general grading system for complications*

Grade	Complications
Grade 0	Absence of complications or acute reversible symptoms or signs which do not modify the planned course of treatment.
Grade 1	Mild complications – these complications are mildly disabling and may cause some functional impairment.
Grade 2	Moderate complications – both obvious symptoms and signs are present resulting in intermittent or persistent interference with normal activity
Grade 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.
Grade 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 9.6 *Franco Italian complications by organ system and grade*

GASTROINTESTINAL – Rectum	
Grade 1	<ul style="list-style-type: none"> Any acute symptoms of proctitis interrupting treatment for more than 10% of the planned treatment time or lasting more than two 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 Immediately repairable intra-operative injury Haemorrhoids provoked by treatment of the cancer
Grade 2	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Recto-vaginal fistula Rectal stenosis requiring surgery
GASTROINTESTINAL – Sigmoid colon	
Grade 1	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Sigmoid fistula Sigmoid bleeding requiring surgery Sigmoid obstruction requiring surgery
GASTROINTESTINAL – Colon (other than sigmoid)	
Grade 1	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 & 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

URINARY – Bladder and urethra

- 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 ($<10^5$) and/or 4 episodes of acute cystitis per year
 - Cystocele 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 ($>10^5$) 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
 - Cystocele 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 (eg. 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 (sides(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

Reference

Chassagne D, Sismondi P, Horiot JC, et al. A glossary for reporting complications of treatment in gynaecological cancers, *Radiotherapy & Oncology* 1993; 26:195-202.

KARNOFSKY RATING SCALE and ECOG PERFORMANCE STATUS

The Karnofsky Rating Scale (Karnofsky, 1948) and GOG/ECOG Performance Status (Oken, 1982) (Table 9.7) 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.

Table 9.7 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, eg. 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

References

Karnofsky DA, Abelmann WH, Craver LF, Burchenal. The use of nitrogen mustards in the palliative treatment of cancer. *Cancer* 1948; 1:634-656.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5:649-655.

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. 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) (Therasse, 2000). The following definitions and criteria (Table 9.8) have been abstracted from the RECIST Quick Reference.

Table 9.8 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 < 20 mm with conventional techniques or < 10 mm with spiral CT scan.

Baseline documentation of target and non-target lesions

- All measurable lesions up to a maximum of 5 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically)
- A sum of the longest diameter (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 through-out follow up

Response criteria for target and non-target lesions

(Table 9.9 and Table 9.10)

Table 9.9 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.

Table 9.10 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

Reference

Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumours. *J Natl Cancer Institute* 2000; 92:205-16. <http://www3.cancer.gov/bip/RECIST.htm>

RTOG / EORTC RADIATION MORBIDITY SCORING

Radiation therapy toxicities

In reporting toxicity associated with radiation therapy, it is necessary to differentiate between acute and late morbidity (NCI, 1999):

- acute morbidity is defined as those events that occur from day 1, or commencement of radiation therapy, through day 90
- late radiation effects are defined as those effects that first occur 90 days or more after initiation of radiation therapy

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 Table 9.11 and Table 9.12

Table 9.11 Grading acute radiation morbidity for most common tissue sites during/following treatment for gynaecological cancer

	Grade 1	Grade 2	Grade 3	Grade 4
Skin	<ul style="list-style-type: none"> • Follicular, faint or dull erythema • Eplation • Dry desquamation • Decreased sweating 	<ul style="list-style-type: none"> • Tender or bright erythema • Patchy moist desquamation • Moderate oedema 	<ul style="list-style-type: none"> • Confluent, moist desquamation other than skin folds • Pitting oedema 	<ul style="list-style-type: none"> • Ulceration • Haemorrhage • Necrosis
Lower GI (includes pelvis)	<ul style="list-style-type: none"> • Increased frequency or change in quality of bowel habits not requiring medication • Rectal discomfort not requiring analgesics 	<ul style="list-style-type: none"> • Diarrhoea requiring parasympatholytic drugs • Mucous discharge not necessitating sanitary pads • Rectal and/or abdominal pain requiring analgesics 	<ul style="list-style-type: none"> • Diarrhoea requiring parenteral support • Severe mucous or blood discharge necessitating sanitary pads • Abdominal distension (flat plate radiograph demonstrates distended bowel loops) 	<ul style="list-style-type: none"> • Acute or sub-acute obstruction • Fistula • Perforation • GI bleed requiring transfusion • Abdominal pain on tenesmus requiring decompression or diversion
Genito-urinary	<ul style="list-style-type: none"> • Frequency of urination or nocturia twice pre-treatment habit • Dysuria, urgency not requiring medication 	<ul style="list-style-type: none"> • Frequency of urination or nocturia which is less frequent than every hour • Dysuria, urgency, bladder spasm requiring local anaesthetic 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Haematuria requiring transfusion • Acute bladder obstruction secondary to clot passage • Ulceration • Necrosis

Table 9.12 Grading late radiation morbidity for common tissue sites following treatment for gynaecological cancer

	Grade 1	Grade 2	Grade 3	Grade 4
Bladder	<ul style="list-style-type: none"> Slight epithelial atrophy Minor telangiectasia (microscopic haematuria) 	<ul style="list-style-type: none"> Moderate frequency Generalised telangiectasia Intermittent macroscopic haematuria 	<ul style="list-style-type: none"> Severe frequency and dysuria Severe generalised telangiectasia (often with petechiae) Frequent haematuria Reduction in bladder capacity (<150 ml) 	<ul style="list-style-type: none"> Necrosis Contracted bladder (capacity <100 ml) Severe haemorrhagic cystitis
Bowel	<ul style="list-style-type: none"> Mild diarrhoea Mild cramping Bowel movement <5 times daily Slight rectal discharge or bleeding 	<ul style="list-style-type: none"> Moderate diarrhoea and colic Bowel movement >5 times daily Excessive rectal mucous or intermittent bleeding 	<ul style="list-style-type: none"> Obstruction or bleeding requiring surgery 	<ul style="list-style-type: none"> Necrosis Perforation Fistula
Vagina	<ul style="list-style-type: none"> Partial stenosis or shortening but less than complete occlusion 	<ul style="list-style-type: none"> Complete occlusion Telangiectasis with frequent bleeding 	<ul style="list-style-type: none"> Radionecrotic ulcer 	<ul style="list-style-type: none"> Fistula to bladder, bowel or peritoneal cavity

Reference

National Cancer Institute (NCI), Cancer Therapy Evaluation Program. *Common toxicity criteria manual* Version 2.0, 1999. <http://www.rtog.org/members/toxicity>

USEFUL WEBSITES

Organisation	Address
Altavista (search engine)	http://www.au.altavista.com
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.ahrdma.com.au
Australian Institute of Health and Welfare (AIHW)	http://www.aihw.gov.au
Australian Society of Gynaecological Oncologists (ASGO)	http://www.users.bigpond.com/asgo
Canadian Cancer Society (CCS)	http://www.cancer.ca/ccs
CancerBACUP	http://www.cancerbcup.org.uk
Cancer Council NSW (CCNSW)	http://www.nswcc.org.au
Cancer Nurses Society of Australia (CNSA)	http://www.cnsa.org.au
Centre for Evidence Based Medicine, Oxford	http://www.admin.ox.uk/oxro/
Doctors Reference Site	http://www.dreref.com.au
Eastern Cooperative Oncology Group (ECOG)	http://www.ecog.dfci.harvard.edu
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.igo.org
International Union Against Cancer (UICC)	http://www.uicc.ch
Google (Australia)	http://www.google.com.au
Gynecologic Oncology Group (GOG)	http://www.gog.org
Gynaecological Cancer Psychosocial Support Service	http://gynaecancersupport.org.au
Journal of the American Medical Association (JAMA)	http://www.jama.ama-assn.org
Journal of Clinical Oncology (JCO)	http://www.jco.org
Journal of the National Cancer Institute (Cancer Spectrum) (JNCI)	http://www.jncicancerspectrum.oupjournals.org
Medscape Hematology-Oncology	http://www.medscape.com/hematology-oncologyhome
Memorial Sloan-Kettering Cancer Centre	http://www.mskcc.org
National Cancer Control Initiative (NCCI)	http://www.ncci.org.au
National Cancer Institute (NCI)	http://www.nci.nih.org
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
New England Journal of Medicine, (The) (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	http://www.cancer.med.upenn.edu
Overcome	http://www.ovacome.org.uk
Radiation Therapy 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://www.sgo.org

The Cancer Institute NSW

<http://www.swog.org>

The Lancet

<http://cancerinstitute.org.au>

Therapeutic Goods Administration (TGA)

<http://www.thelancet.com>

World Health Organisation (WHO)

<http://www.health.gov.au/tga>

Yahoo! Health

<http://www.who.int>

OTHERS

<http://www.dir.yahoo.com/health>

NOTES