Staging classifications and clinical practice guidelines of gynaecologic cancers

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I would like to thank L Zigliani and KF Tam
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Staging classifications and clinical practice guidelines of gynaecologic cancers

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Preface

The second edition of the Good Practice Guidelines on Gynaecologic Cancers was a collaborative effort between FIGO and the International Gynecologic Cancer Society. Both organisations put women's health and combat female cancers as their priority objectives. Though the style and presentation of the revised guidelines on individual cancers may differ from the first edition, the same purpose of offering consensus guidelines to clinicians in combating female cancers is the same. In the revised edition, the guidelines are based on strongest available evidence which varies from topic to topic. The evidence has been graded as follows:

A – randomised controlled trial
B – prospective (cohort) study with a comparison group
C – retrospective follow up study
D – cross sectional study

However, guidelines on breast cancer have not been revised. It is envisaged that with increase in knowledge and progress in the management of cancers, a third edition may be needed in future. In the mean time, based on current evidence, these guidelines could serve as a good reference where adaptation to local use could be based on.

Hextan YS Ngan
Chairman of FIGO Committee on Gynecologic Oncology

For the first time, the International Gynecologic Cancer Society (IGCS) has been invited to collaborate with FIGO in the development of treatment guidelines for gynaecologic malignancies. The final product is the result of input from many specialists in both organisations. They are not intended to be absolute guidelines, but rather to represent a reasonable synthesis of the current literature for each disease site. Patient management always needs to be individualised, taking into account a patient's general medical condition, her cultural environment, and the available expertise and technology.

It is envisaged that these guidelines will need to be revised at least every 3 years or earlier, should any landmark clinical trial results become available.

Neville F Hacker
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Principles of Cancer Staging

The major task faced by a clinician having made a diagnosis of cancer is to determine the most effective therapy and formulate a prognosis for the patient. In order to optimally manage a cancer, both the extent of the disease and knowledge of its biology are essential. The extent of the disease is generally expressed in terms of its stage. The major purpose of staging that has been agreed upon internationally is to offer a classification of a cancer's extent so as to provide a method of conveying ones clinical experience to others for the comparison of treatment methods without confusion or ambiguity.

Cancer staging is central to the modern management of cancer patients. Cancer is also a biologic continuum and a dynamic process, which is artificially compartmentalised by staging systems. It is clear, however, that the phases or substages must have clinical relevance. Cancer staging systems should also be evidence-based and they should be user friendly. Staging systems need to be based on the best available knowledge at hand and this implies that the changes will occur over time based upon the development or the acquisition of new knowledge.

It also follows that the acquisition of this knowledge is facilitated by the use of staging system insofar as staging will help with knowledge creation by facilitating clinical research, producing new data on similar groups of patients and also by integrating this new data about similar patients from diverse sources. Staging also helps knowledge dissemination by providing a common international language for information sharing and facilitates the teaching of both new and established health care workers.

Gynaecologists have a long and proud tradition of using staging systems for female cancers, dating back to the League of Nations staging system for cervical cancer, first published in 1920. In 1954 FIGO assumed the patronage of the Annual Report on the Treatment of Gynecological Cancer. With it also came the responsibility for overseeing the staging of gynaecological cancers, which were at the heart of the Annual Report data and information system. Since that time the FIGO Committee on Gynecologic Oncology has made several modifications to the various staging systems for gynaecological cancer, most notably those for cervix and endometrial cancer. 1954 also saw the UICC set up a committee on clinical stage classification

and applied statistics, which had as its aim the extension of the general technique of classification of cancer at all sites by anatomical extent of the disease using the TNM system.

The FIGO system of classification was originally based on clinical examination, essentially of the anatomical extent of disease. Over the years all staging systems for gynaecological cancers, with the exception of cervical cancer, have moved from a clinical basis to one of a surgical pathological nature.

Stage I has generally been referred to as early stage disease, where the lesions would appear to be confined to the organ of origin. Stage II is a general description of disease that has extended locally beyond the site of origin to involve adjacent organs or structures. Stage III then represents more extensive involvement and stage IV representing clearly metastatic disease. The basic stages are then generally classified into substages, which are usually a reflection of specific prognostic factors within a given stage.

Tumour classifications may be based on many systems. For example, the anatomical site of the disease and the clinical and pathological extent of disease. Similarly the histologic type and grade of tumours, as well as age of patient and the duration of signs and symptoms are all known to have an influence on the outcome of disease and have all been used in various staging systems. The TNM system describes the anatomical extent of disease based on the assessment of three primary components. T refers to the extent of the primary tumour, N to the presence or absence and extent of regional lymph node metastases, and M the presence or absence of distant metastases. The TNM system is also further classified into two groups. The cTNM system, which is essentially a pretreatment clinical classification based on evidence acquired before treatment from physical examination, imaging, biopsy, endoscopy, surgical exploration and other relevant examinations. The pTNM system is the other subgroup and is based on postsurgical histopathological classification. This uses evidence acquired before treatment once again, supplemented or modified by the additional evidence acquired from surgical and from pathological examination. After assigning T, N, M and/or pT, pN and pM categories, these items may then be grouped into stages. The classification system and stage grouping, once established, must remain unchanged in medical records. Clinical stage is

essential to select and evaluate therapy, while the pathological stage provides the most precise data to estimate prognosis and calculate end results. The FIGO and TNM classifications are virtually identical. The TNM Prognostic Factor Project Committee has graciously agreed to defer to all questions regarding staging of gynaecological cancer to the FIGO Committee on Gynecologic Oncology.

In conclusion, any good staging system must have three basic characteristics. It must be valid, reliable, and above all, it must be practical. Validity means that the staging system must allow for the creation of groups of cases, that experience similar outcomes at the same time reflecting a full range of possible presentations for each type of cancer. Also over time, the system in order to retain its validity must be flexible so that it can adapt to important changes in medical care.

A reliable staging system should ensure that identical cases would always be assigned to the same stage category. It should be unambiguous; it should be based as far as possible on measurement quantities that have been evaluated objectively. The system should also not be subject to frequent changes until sufficient data and information is obtained to warrant such changes.

Finally, a practical staging system must be suitable for day to day use in a wide range of clinical environments and must not require diagnostic procedures that are not readily available to most practitioners or extraordinary expertise or knowledge regarding a particular malignancy.

Principles Governing the Development of Good Practice Guidelines

The following basic concepts and principles were used to produce these clinical practice guidelines.

Definition:

Clinical practice guidelines (CPG) or good practice guidelines (GPG) are systematically developed statements to assist health care practitioners and providers in making decisions about appropriate care for patients in specific clinical circumstances.

Purpose:

The purpose of CPG's may vary depending on ones perspective; eg a

clinician may see them as a method of improving patient outcomes. Administrators and other societal authorities may see them as helpful in viewing distribution and allocation of health funding and appropriated (related) resources.

Objectives:
The objectives of CPG should be a way of reducing inappropriate variation in clinical practice. This may also serve to prevent resource limitations from adversely affecting patient care and may also be used as ways of influencing health care providers to incorporate new strategies into the clinical care of their patients based on new scientific evidence.

Statement:
Clinical practice guidelines should always be based on evidence. However, high levels of evidence are not always available for certain situations. A distinction must be made between Evidence and Beliefs. CPG must also consider benefits versus harm versus evidence. In terms of belief care needs to be taken because patient advocacy movements may grasp these items and use them for their own personal agendas and at times what patients want may be markedly different from what the evidence might show or what might be appropriate treatment.

Guideline Development:
- Guidelines capture evidence and/or beliefs at a point in time and therefore they will need to change in the future.
- Guidelines should consider social and cultural differences.
- Guidelines should be enabling and not prescriptive in nature.
- One needs to be careful that physician-created guidelines are not taken over by third parties and made mandatory. This we wish to avoid.
- Anything that is mandatory should not be called a guideline. It might be better termed recommendation.
- Guidelines should offer rather than saying “one should treat”.

Concerns:
a) Many groups are developing guidelines and it is difficult not to produce guidelines that may not be in conflict with some other body.
b) Guidelines should not be too rigid so as to actually hamper physician decision-making freedom.
c) Legal implications and the threat of medicolegal action need to be considered if one is practising outside of so called guidelines.
d) Individuals may be unaware that guidelines actually exist for particular scenarios.

Cancer of the Vulva

1.1 Staging

1.1.1 Anatomy.
Cases should be classified as carcinoma of the vulva when the primary site of growth is in the vulva. Tumours present in the vulva as secondary growths, from either a genital or extra-genital site, have to be excluded. Malignant melanoma should be separately reported and staged according to the system for cutaneous melanomas. A carcinoma of the vulva that extends into the vagina should be considered as a carcinoma of the vulva. There must be histologic confirmation of the cancer.

1.1.1.1 Nodal stations.
The inguinal and femoral nodes are the primary sites of regional spread.

1.1.1.2 Metastatic sites.
Involvement of pelvic lymph nodes (external, hypogastric obturator and common iliac) are considered distant metastases.

1.1.2 Surgical staging classification.
Vulvar cancer has been surgically staged since 1988. The final diagnosis is dependent upon thorough histopathologic evaluation of the operative specimen (vulva and lymph nodes). Various modifications have been made with a subdivision of Stage I in 1994.

1.1.2.1 Regional lymph nodes (N).
- NX – Regional lymph nodes cannot be assessed;
- NO – No regional lymph node metastasis;
- N1 – Unilateral regional lymph node metastasis;
- N2 – Bilateral regional lymph node metastases.

1.1.2.2 Distant metastasis (M).
- MX – Distant metastasis cannot be assessed;
- M0 – No distant metastasis;
- M1 – Distant metastasis.

Table 1: Carcinoma of the Vulva – Staging

FIGO Stages		TNM Categories
	Primary tumour cannot be assessed	TX
	No evidence of primary tumour	T0
0	Carcinoma in situ (preinvasive carcinoma)	Tis
I	Tumour confined to vulva or vulva and perineum, 2 cm or less in greatest dimension	T1
IA	Tumour confined to vulva or vulva and perineum, 2 cm or less in greatest dimension and with stromal invasion no greater than 1.0 mm*	T1a
IB	Tumour confined to vulva or vulva and perineum, 2 cm or less in greatest dimension and with stromal invasion greater than 1.0 mm*	T1b
II	Tumour confined to the vulva or vulva and perineum, more than 2 cm in greatest dimension	T2
III	Tumour invades any of the following: lower urethra, vagina, anus and/or unilateral regional node metastasis	T3
IV		T4
IVA	Tumour invades any of the following: bladder mucosa, rectal mucosa, upper urethral mucosa; or is fixed to bone and/or bilateral regional node metastases	
IVB	Any distant metastasis including pelvic lymph nodes	

* *The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial dermal papilla, to the deepest point of invasion.*

Table 2: Carcinoma of the Vulva – Stage grouping

FIGO Stage	UICC		
	T	N	M
0	Tis	N0	M0
IA	T1A	N0	M0
IB	T1B	N0	M0
II	T2	N0	M0
III	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4	Any N	M0
IVB	Any T	Any N	M1

1.1.2.3 Histopathologic types.
Squamous cell carcinoma is the most frequent form of cancer of the vulva. Malignant melanoma is the second most common tumour and should be reported separately. Other histopathologic types are:

adenocarcinoma underlying Paget's disease of vulva, verrucous carcinoma, Bartholin gland carcinoma, adenocarcinoma not otherwise specified (NOS), basal cell carcinoma.

- Histopathologic grades (G).
- Gx – Grade cannot be assessed;
- Gl – Well-differentiated;
- G2 – Moderately differentiated;
- G3 – Poorly or undifferentiated.

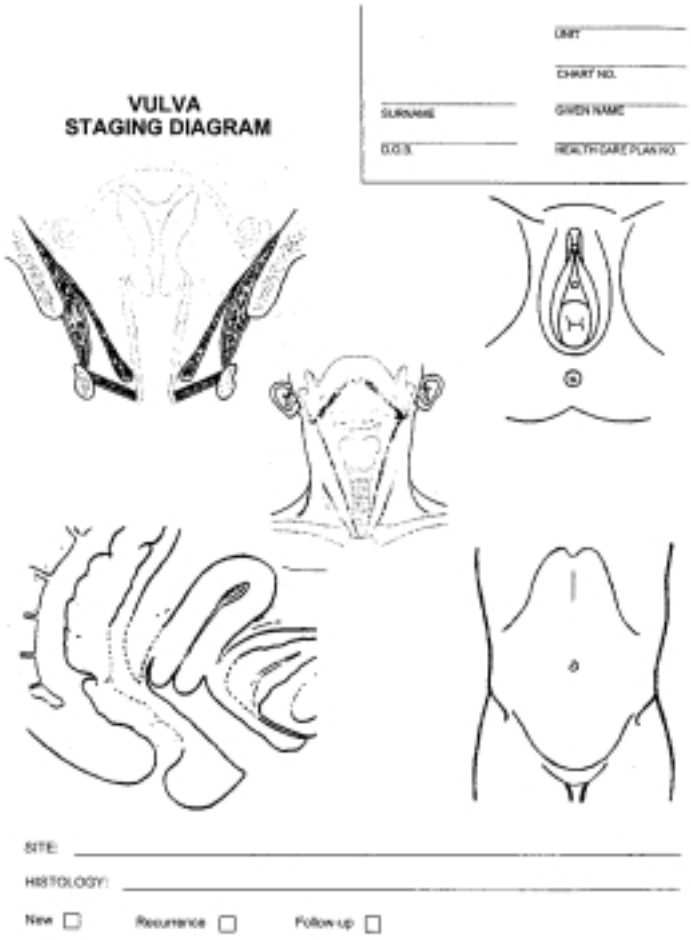


Figure 1: Vulvar Staging Diagram

1.2 Introduction
Carcinoma of the vulva is an uncommon tumour, representing about 4% of gynaecologic malignancies. Because of the relatively small experience of individual institutions, randomised trials of therapeutic

approaches are uncommon, and most studies are based on retrospective clinico-pathologic reviews.

It is predominantly a disease of postmenopausal women, the age specific incidence increasing with increasing age. The external location of the vulva should prompt early presentation, but traditionally significant delays in diagnosis have been common with this cancer.

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.

Vulvar intraepithelial neoplasia (VIN) tends to occur in younger women and may be associated with similar lesions of the cervix and vagina. VIN III is a precursor lesion in some patients, and should be effectively treated by superficial excision, with or without laser therapy, when diagnosed.[1,2]

Treatment of vulvar 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.[3,4] **Level of evidence B.**

1.3 Screening

There is no screening procedure for vulvar cancer. However patients with a past history of cervical or vaginal cancer should have inspection of the vulva, with or without colposcopic examination, as part of their regular follow-up.[5] Patients with lichen sclerosis or a past history VIN III should also be kept under regular surveillance.

1.4 Squamous Cell Carcinoma

1.4.1 Presenting Symptoms

Vulvar cancer may be asymptomatic, but most patients present with a vulvar lump or ulcer. There is often a long standing history of pruritus, which may be due to associated vulvar dystrophy. Bleeding or discharge is an occasional presenting symptom, and patients with advanced disease may present with a lump in the groin.

1.4.2 Diagnosis

Diagnosis should be confirmed by biopsy prior to definitive treatment. A wedge biopsy under local anaesthesia in the office is usually sufficient. The biopsy should include some surrounding skin and 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 or less 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. The Committee on Gynecologic Oncology of FIGO measures depth of stromal invasion from the epithelial-stromal junction.[6]

1.4.3 Investigations

1. Pap smear of the cervix if cervix is still in situ
2. Colposcopy of the cervix and vagina, because of the common association with other squamous intraepithelial lesions.
3. A CT scan of the pelvis and groins is often helpful to detect any enlarged lymph nodes in the groins or pelvis.
4. Routine full blood count, biochemical profile and chest x-ray preoperatively.

1.4.4 Clinical Practice Guidelines

The clinical findings should be recorded on a staging diagram (eg Fig 1). The material in Tables 1 and 2 is usually listed on the reverse side of the diagram.

1.4.5 Treatment

1.4.5.1 Treatment of vulvar intraepithelial neoplasia (VIN) or carcinoma in situ

Various treatment modalities are available for treating intraepithelial lesions of the vulva. Initial assessment should consist of multiple biopsies to ensure that the lesion is entirely intraepithelial. Patients with multifocal lesions should have biopsies taken from several lesions. Once the diagnosis has been established local excision of the superficial vulvar epithelium with a 0.5-1.0-cm margin is considered adequate for lesions of the lateral aspect of the vulva. Lesions involving the labia minora may also be treated by local excision but may respond favourably to laser vaporisation or ablation. Laser treatment

of the hair-bearing skin of the vulvar epithelium will usually produce depigmentation and destruction of hair follicles with subsequent loss of hair growth. Laser is also appropriate for clitoral lesions. Large lesions may be treated with a skinning vulvectomy and split thickness skin graft. **Level of evidence C.**

1.4.5.2 Invasive vulvar cancer

Management of vulvar cancer must be individualised. There is no standard operation and the emphasis is on performing the most conservative operation consistent with cure of the disease.[7]

In considering treatment options, it is necessary to consider independently the most appropriate management of

1. the primary lesion
2. the groin lymph nodes

1.4.5.2.1 Microinvasive vulvar cancer (Stage IA)

Stage IA carcinoma of the vulva is defined as a single lesion measuring 2 cm or less in diameter with a depth of invasion of 1.0 mm or less, the depth being measured from the epithelial-stromal junction of the most adjacent superficial dermal papilla to the deepest point of invasion. Lesions of this extent should be managed with wide local excision. If the local resection reveals features that are unfavourable (neural or vascular invasion), consideration should be given to more radical excision. Groin dissection is not necessary for lesions of this type.[8,9] **Level of evidence C.**

1.4.5.2.2 Early vulvar cancer

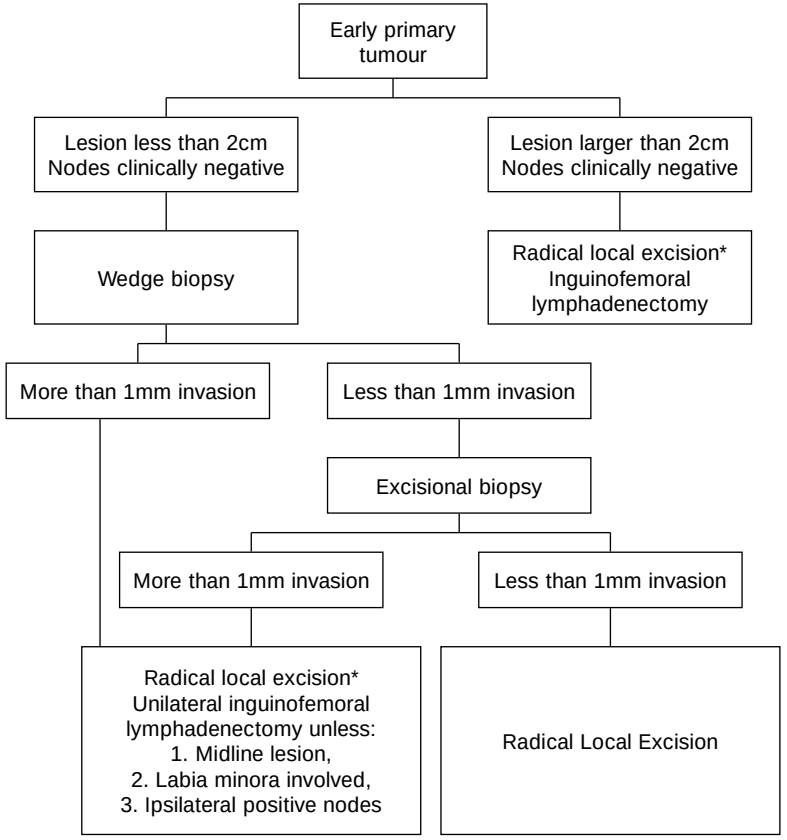
Tumors confined to the vulva without clinically suspicious lymph nodes may be considered early.

1.4.5.2.2.1 Management of the primary lesion (Figure 2)

In order to decrease psychosexual morbidity, a more conservative operation than radical vulvectomy usually is indicated. The procedure may be called a radical local excision, and for localised lesions, this operation is as effective as radical vulvectomy in preventing local recurrence.[8,9,10,11,12]

Surgical removal should achieve lateral margins of at least 1 cm, and the deep margin should be the inferior fascia of the urogenital

Figure 2: Management of early vulvar cancer



**If there is associated VIN or lichen sclerosis, these areas may be superficially excised.*

diaphragm, which is coplanar with the fascia lata and the fascia over the pubic symphysis[13].

If the lesion is close to the urethra, the distal 1 cm of the urethra may be resected without jeopardizing urinary continence.

If there is associated VIN or lichen sclerosis, these areas may be superficially excised to control symptoms and to exclude other areas of superficial invasion. **Level of Evidence B.**

1.4.5.2.2.2 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.[7]

All patients with T2 lesions and all patients with T1 tumours with > 1mm stromal invasion should have at least an ipsilateral inguinofemoral lymphadenectomy. **Level of Evidence B.**

The incidence of positive contralateral nodes in patients with lateral T1 tumours is < 1%, so unilateral groin dissection is appropriate for such lesions.[7]

Bilateral groin dissection should be performed for midline tumours, and for those involving the anterior labia minora.[14] Large lateral tumours should probably also have bilateral dissection, particularly if the ipsilateral nodes are positive.[14] **Level of Evidence C.**

1.4.5.2.2.3 Groin dissection

It is recommended that both inguinal and femoral nodes be removed, as inguinal node dissection alone is associated with a higher incidence of groin recurrence.[15] **Level of Evidence A.** 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.[16]

Groin dissection may be safely performed through a triple incision approach as this may improve primary healing.[17] **Level of Evidence B.** Alternately, an enbloc approach may be used, particularly for clitoral or periclitoral lesions. To avoid skin necrosis, all subcutaneous tissue above the superficial fascia must be preserved.

Groin dissection (with postoperative 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.[18]

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.[19] **Level of Evidence A.**

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 extracapsular spread.[20, 21, 22]

Patients with one (and possibly two) micrometastases (<5mm) 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. **Level of Evidence C.**

1.4.5.2.2.4 Radiation fields and doses

In most cases, fields should include the inguinofemoral 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.

It is important to avoid underdosage of superficial inguinal nodes by high energy photon fields. If electron beams are used, the energy must be sufficient to cover the deep inguinal nodes.

In most cases, CT – based treatment planning should be used to verify adequate coverage.

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 positive nodes 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.

The role of concurrent chemotherapy in this setting is unknown.

1.4.5.2.3 Advanced vulvar cancer

Patients with T3 or T4 primary tumours or bulky positive groin nodes

are considered to have advanced vulvar cancer. For such patients, multimodality treatment planning is particularly important.

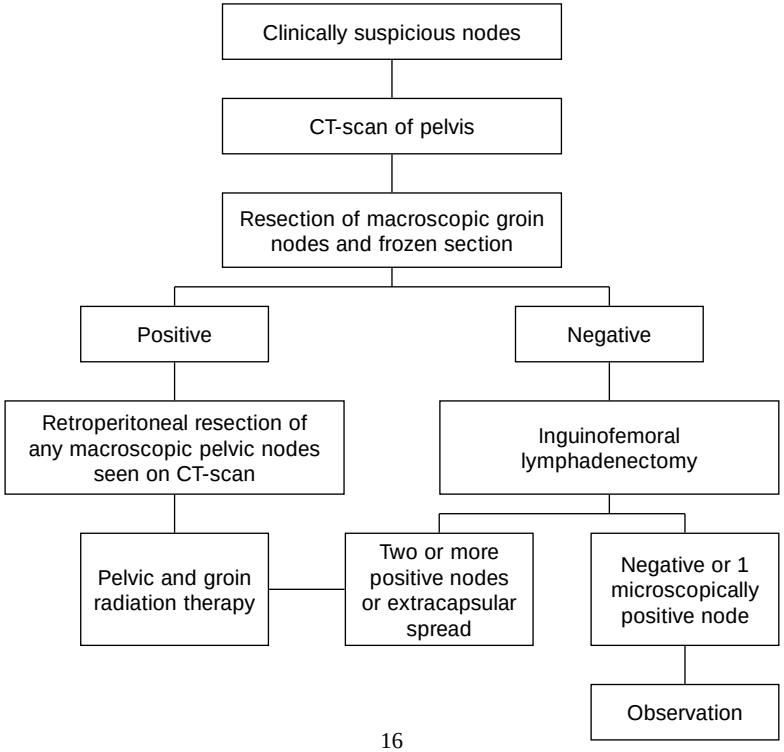
1.4.5.2.3.1 Management of the groin lymph nodes

It is desirable to determine the status of the groin nodes prior to planning the overall treatment.[7]

If there are no suspicious nodes palpable in the groin, bilateral inguinofemoral 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 preoperative CT scan may help identify the extent of groin and pelvic lymphadenopathy (Figure 3).

Figure 3: Management of clinically suspicious groin nodes



Resection of all enlarged groin nodes should be performed, and frozen section diagnosis obtained.

If nodes are negative, full inguinal – 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, 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). **Level of Evidence C.**

Figure 4: Management of clinically obvious groin nodes:

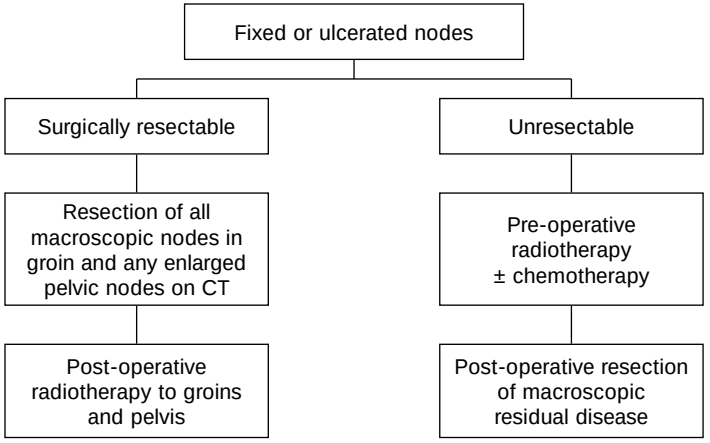
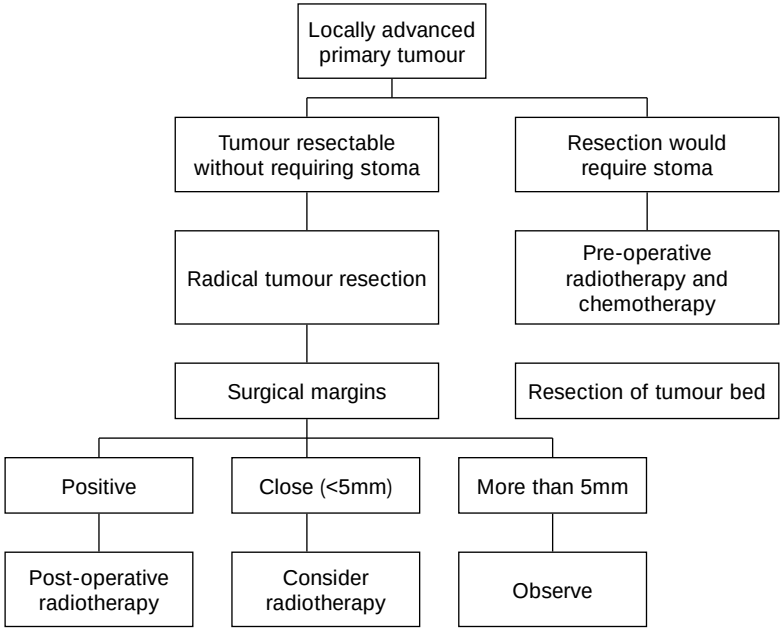


Figure 5: Management of advanced primary tumour*



(Treatment should follow dissection of the groins. Groin and pelvic radiation should follow standard indications)

1.4.5.2.3.2 Management of the primary tumour (Figure 5)
This should follow dissection of the groins.

If it is possible to resect the primary lesion with clear surgical margins and without sphincter damage leading to urinary or fecal 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.[23, 24]

Chemoradiation has been used, sometimes without need for surgical resection of the tumour bed.[25, 26, 27, 28]

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.

1.4.5.2.3.3 Radiation Protocol
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. Care must be taken to adequately cover the inguinal nodes.

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

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

1.4.5.2.3.4 Close surgical margins
Post-operative radiation may be used for close surgical margins (<5mm), if the margins cannot be re-excised.[29] 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. **Level of Evidence C.**

1.5 Special situation

1.5.1 Vulvar melanoma
Vulvar melanoma is the second most common neoplasm of the vulva. The majority of lesions involve the clitoris or labia minora. The Clark or Breslow modifications to the micro staging system should be used for the staging of vulvar melanoma rather than the more common TNM/FIGO system. These systems measure the depth of invasion in terms of the descriptive histology of the skin.

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

vulvar melanomas.[30,31] 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, multinstitutional randomised trial of elective node dissection versus observation for intermediate thickness cutaneous melanomas (1-4 mm).[32] 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.

1.5.2 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 generally occur a decade or so before most invasive squamous cancers of the vulva. 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.[32] Because these lesions are deep in the ischiorectal 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.[33]

If the ipsilateral groin nodes are positive, bilateral grin 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. **Level of Evidence C.**

1.5.3 Paget's Disease

This is predominantly an intraepithelial lesion, but on occasion it may be associated with an underlying invasive adenocarcinoma. The disease occurs predominantly in the menopausal or postmenopausal population. Most patients will present with vulvar discomfort and itching and on examination an eczematoid-weeping lesion is often

seen. Diagnosis is usually confirmed by biopsy and usually will establish if one is dealing with an intraepithelial or invasive lesion.

Intraepithelial Paget's disease requires superficial local excision. It is difficult to obtain clear margins with this disease, as often the underlying histologic change will seem to 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 inguinofemoral lymphadenectomy should be performed for unilateral lesions with adjuvant radiation following the same indications as for squamous carcinomas. **Level of Evidence C.**

1.6 Pathology

The surgical specimen should be correctly orientated and photographed. The photograph should be used to indicate the origin of tissue blocks.

The size of the specimen should be measured and the dimensions of any visible tumour measured.

The macroscopic tumour-free surgical margins should be measured.

Sections are taken through the tumour to measure tumour depth.

Sections should be taken from urethral, anal and vaginal resection margins.

Lymph nodes should be carefully dissected out and the site from which they are removed recorded. A full cross-section of each lymph node should be embedded.

The following histological points should be noted:

a. Tumour type:
   keratinizing
   basaloid
   bowenoid

b. Depth of invasion
   Should be measured from the epithelial-stromal junction of the

adjacent dermal papilla to the deepest point of invasion by the tumour.

c. Tumour grade
Noted, but not proven to be prognostically significant.

d. Histological measurement of tumour free margins and statement as to whether tumour is completely excised.

e. Presence or absence of vascular space invasion

f. Nature of the adjacent non-malignant squamous epithelium
VIN
Lichen sclerosus
Squamous hyperplasia
HPV associated changes

g. Sites and number of nodes examined and number of positive nodes. Presence or absence of extracapsular spread.

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Cancer of the vagina

2.1 Staging

A description of the staging classification for primary vaginal carcinoma is detailed in Table 1 and its stage grouping in Table 2.[1]

Table 1: Carcinoma of the Vagina: FIGO staging

Stage O	Carcinoma in situ; intraepithelial neoplasia grade 3
State I	The carcinoma is limited to the vaginal wall
Stage II	The carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall
Stage III	The carcinoma has extended to the pelvic wall
Stage IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum; bullous oedema as such does not permit a case to be allotted to Stage IV
IVA	Tumour invades bladder an/or rectal mucosa and/or direct extension beyond the true pelvis
IVB	Spread to distant organs

FIGO, International Federation of Obstetrics and Gynecology

2.1.1 Anatomy

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 the growth is in the vagina. Tumours present in the vagina as secondary growths, from either genital or extra-genital sites should be excluded. 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. There should be histologic verification of the disease.

Table 2: Carcinoma of the Vagina – Stage Grouping

FIGO Stage	UICC		
	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
	T3	N1	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1

2.1.1.1 Nodal stations

The upper two-thirds of the vagina is drained by lymphatics to the pelvic nodes, with the lymphatics paralleling the course of the uterine artery and the vaginal artery to the obturator, hypogastric and external iliac nodes. The lower third of the vagina drains to the inguinal-femoral nodes. Some lesions may drain via pararectal lymphatic channels.

2.1.1.2 Metastatic sites

The most common sites of distant spread include the lungs, liver, and bony skeleton. The rules for staging are similar to those for carcinoma of the cervix.

2.1.1.3 Histopathologic types

Squamous cell carcinoma is the most common type of cancer occurring in the vagina. Infrequently an adenocarcinoma may occur.

2.1.1.4 Histopathologic grades (G)

- Gx – Grade cannot be assessed;
- Gl – Well differentiated;
- G2 – Moderately differentiated;
- G3 – Poorly or undifferentiated.

2.1.1.5 Regional lymph nodes (N)

- NX – Regional lymph nodes cannot be assessed;
- NO – No regional lymph node metastasis;

- Nl – Pelvic or inguinal lymph node metastasis.

2.1.1.6 Distant metastasis (M)

- MX – Distant metastasis cannot be assessed;
- MO – No distant metastasis;
- Ml – Distant metastasis.

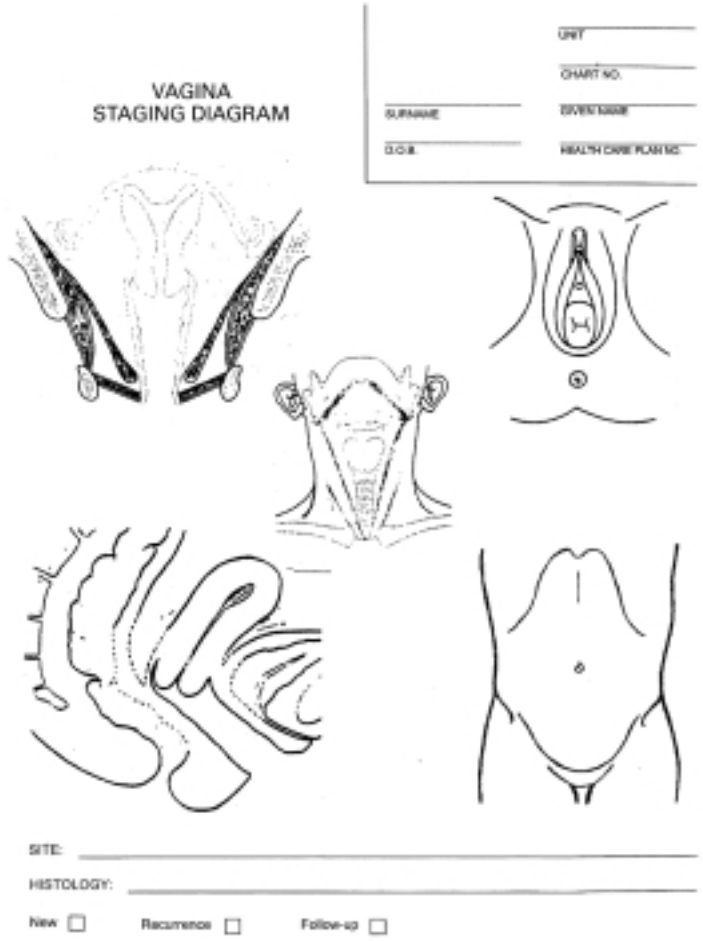

Figure 1: Vaginal Staging Diagram

2.2 Introduction

Carcinoma of the vagina is the rarest of primary gynaecological neoplasms and is responsible for less than 1% of gynaecological malignancies. The vagina, however, can be a common site of metastatic disease by either direct extension of cervical or vulvar tumours or through metastatic lymphatic or vascular deposits as seen in endometrial and gestational trophoblastic disease.

Up to 30% of patients with primary vaginal carcinoma have a history of in situ or invasive cervical cancer treated at least 5 years earlier.[2-4] Some vaginal cancers are preceded by vaginal intraepithelial neoplasia (VAIN), although the true malignant potential of VAIN is not known.[5,6] Prior pelvic radiation has also been considered a possible cause of vaginal cancer.[7,8]

Most vaginal cancers occur in postmenopausal or elderly women. Histologically, approximately 95% of primary vaginal cancers are squamous cell lesions. Metastatic tumours in the vagina can also occur from non-gynaecological sites such as the urinary bladder, urethra or periurethral glands and rarely breast or lung cancer.

2.3 Screening

Routine screening for vaginal cancer following hysterectomy for benign disease is not cost effective, but women with a history of cervical intraepithelial or invasive neoplasia are at increased risk, and should be followed with regular pap smears.[9]

2.4 Vaginal intraepithelial neoplasia (VAIN)

For patients with an abnormal pap smear and no gross abnormality, vaginal colposcopy and use of Lugol's iodine to stain the vagina are necessary. Excision of colposcopically abnormal areas is usually necessary under anaesthesia. This is particularly true for lesions involving the vaginal vault, where occult carcinoma may be found in up to 28% of patients with VAIN.[10]

Treatment of VAIN is individualised and depends on the extent, location and general medical condition of the patient. Numerous treatment methods, ranging from the various methods of local tissue destruction or ablation through to more extensive surgery and including total vaginectomy, as well as intracavitary radiotherapy have been used to treat VAIN. Selection of appropriate treatment is usually

based on a careful study of several factors, including the general medical condition of the patient, histology of the lesion, and location and extent of disease, as well as the experience and expertise of the treating surgeon with the specific treatment methods. The proximity of the urethra, bladder and rectum to the vaginal epithelium is an important factor to be considered, particularly when local destructive or surgical excision methods are used. Damage or injury to these structures can occur with possible fistula formation, particularly when the patient has had prior radiation therapy.

The use of topical 5-fluorouracil (5-FU) is a relatively simple ambulatory treatment, which does not require anaesthesia or complicated equipment[11]. This approach may be especially valuable for patients with widespread or multifocal lesions, which would require extensive surgical procedures. Side effects with this therapy during treatment are usually minimal and the medication is usually well tolerated by patients.

Laser vaporisation with a CO2 laser is an effective treatment for VAIN.[12] This technique generally requires local or general anaesthesia.

Excisional procedures either with electrosurgical loops or a scalpel excision have also been used to treat VAIN. Surgical excision is particularly appropriate for vault lesions. Also on occasion, total vaginectomy and split thickness skin grafting may be necessary to treat extensive lesions that involve virtually the entire length of the vaginal tube and where other conservative methods have been unsuccessful. **Level of Evidence C.**

2.5 Invasive carcinoma

Most patients present with painless vaginal bleeding and discharge, and definitive diagnosis can usually be made by biopsy of a gross lesion detected on speculum examination. This can often be done in the office, but may be facilitated by examination under anaesthesia.

2.5.1 Treatment

Patients should all be referred to tertiary referral units, because of the limited experience with these lesions. All treatment must be individualised, and will vary depending on the stage of disease and the site of vaginal involvement.

For most patients, it is important to try to maintain a functional vagina.

2.5.1.1 Surgery

Surgery has a limited role because of the close proximity of the bladder and rectum, but may be useful in the following situations:

(1) In patients with Stage I disease involving the upper posterior vagina.

If the uterus is still in situ, radical hysterectomy, upper vaginectomy to achieve clearance of at least 1 cm, and pelvic lymphadenectomy may be performed, while if hysterectomy has been previously performed, radical upper vaginectomy and pelvic lymphadenectomy may be appropriate.

(2) In young patients who require radiation

Pre-treatment laparotomy may allow ovarian transposition, surgical staging and resection of any bulky positive lymph nodes.

(3) In patients with Stage IVA disease, particularly if a recto-vaginal or vesico vaginal fistula is present.

Primary pelvic exenteration is a suitable treatment option for such patients, either combined with pelvic lymphadenectomy or pre-operative radiation.

(4) Groin dissection should be considered if a tumour invades the lower one-third of the vagina. Some Stage I patients maybe amenable to primary surgery, which will usually require partial resection of the vulva as well. **Level of Evidence C.**

2.5.1.2 Radiation Therapy

Radiation therapy is the treatment of choice for most patients with vaginal cancer, and comprises an integration of teletherapy and intracavitary/interstitial therapy.

Selected cases of Stage I and II lesions can be treated adequately with intracavity radiation alone.[13,14] For larger lesions, treatment is usually started with approximately 5000 cGy external radiation to shrink the primary tumour and treat the pelvic nodes.

Intracavitary treatment follows. There is improved local control with total tumour doses of at least 7000cGy.[13,15]

If the lower one-third of the vagina is involved, the groin nodes should be treated or dissected. **Level of Evidence C.**

There is limited reported experience with chemo-radiation for vaginal cancer.[14] However in view of the problem with control of the central disease, the concurrent use of 5-fluorouracil and/or Cisplatin may be appropriate. **Level of Evidence D.**

2.5.2 Prognosis

Recent reports have indicated 5-year survival rates comparable to cervical cancer.[13,14] A study from the Princess Margaret Hospital in Toronto of 138 patients reported 5-year cause-specific survival rates of 77% for Stage I/II and 56% for Stage III/IV.

2.6 Special situations

2.6.1 Adenocarcinoma

Approximately 9% of primary vaginal carcinomas are adenocarcinomas, and they affect a younger age group, regardless of whether or not exposure to diethylstilbestrol (DES) in utero has occurred.

Adenocarcinomas may arise in areas of vaginal adenosis in DES exposed patients, in Wolffian rest elements, peri-urethral glands, and foci of endometriosis.

2.6.1.1 Screening

A young woman exposed to DES in utero should be initially seen when she begins to menstruate, or at approximately 14 years of age. The entire vagina and cervix should be inspected and palpated, and a pap smear taken.[16]

2.6.1.2 Treatment

In general, adenocarcinomas are treated in a similar manner to squamous lesions. In young patients, every effort should be made to preserve vaginal and ovarian function. This may necessitate reconstruction of the vagina, or pre-radiation ovarian transportation.

2.6.1.3 Prognosis

Prognosis for clear cell carcinomas of the vagina is generally good, with an overall survival of 78%.[17] Survival for non-clear cell adenocarcinomas is significantly worse than for squamous cancer.[13]

2.6.2 Vaginal Melanoma

Malignant melanomas of the vagina are rare, and almost all cases occur in white women.[18] They most commonly occur in the distal vagina, particularly on the anterior vaginal wall.[18,19]

Most are deeply invasive and radical surgery has been the mainstay of treatment, often involving some type of pelvic exenteration.

Recently, more conservative local excisions have been used, with comparable survival rates reported.[18,20]

Radiation therapy may be effective in selected cases, and high-dose fractions (>400 cGY) may field better response rates.[21]

Overall 5 year survival is about 10%. **Level of Evidence C.**

2.6.3 Sarcoma botryoides

Sarcoma botryoides is a highly malignant tumour of the rhabdomyoblasts. These neoplasms are found in infants and children and usually present with discharge, bleeding or a visible mass at the introitus.

In the past, exenterative surgery was used for these lesions, but survival was poor. More recently, conservative surgery has been used in conjunction with pre-operative or post-operative chemotherapy and radiotherapy with significantly improved survival. Most reported chemotherapeutic experience has been with Vincristine, Actinomycin D and Cyclophosphamide (VAC).[22,23]

If the lesion is small and can be resected with organ preservation, surgery should be the initial approach. For bulkier lesions, pre-operative chemo or radiotherapy should be given.

Extended radiotherapy fields are not recommended as they may produce significant developmental problems with the bony pelvis by destroying or interfering with growth centres in these structures.

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Cancer of the Cervix Uteri

3.1 Staging

3.1.1 Anatomy

3.1.1.1 Primary site. The cervix is the lower third of the uterus. It is roughly cylindrical in shape, projects through the upper, anterior vaginal wall and communicates with the vagina through an orifice called the external os. Cancer of the cervix may originate on the vaginal surface or in the canal.

3.1.1.2 Nodal stations. The cervix is drained by preureteral, postureteral, and uterosacral routes into the following first station nodes: parametrial, internal (obturator - hypogastric), external iliac, presacral, and common iliac. Para-aortic nodes are second station and are considered metastases.

3.1.1.3 Metastatic sites. The most common sites of distant spread include the aortic and mediastinal nodes, the lungs and skeleton.

3.1.2 Rules for classification

3.1.2.1 Clinical-diagnostic staging. Staging of cervical cancer is based on clinical evaluation; therefore, careful clinical examination should be performed in all cases, preferably by an experienced examiner and under anaesthesia. The clinical staging must not be changed because of subsequent findings. When there is doubt as to which stage a particular cancer should be allocated, the earlier stage is mandatory. The following examinations are permitted: palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and X-ray examination of the lungs and skeleton. Suspected bladder or rectal involvement should be confirmed by biopsy and histologic evidence. Conization or amputation of the cervix is regarded as a clinical examination. Invasive cancers so identified are to be included in the reports. Findings of optional examinations, e.g. lymphangiography, arteriography, venography, laparoscopy, ultrasound, CT scan and MRI, are of value for planning therapy but, because these are not generally available and the interpretation of results is variable, the findings of such studies should not be the basis for changing the clinical staging. Fine needle aspiration (FNA) of scan-detected suspicious lymph nodes may be helpful in treatment planning.

3.1.2.2 Postsurgical treatment -pathologic staging. In cases treated by surgical procedures, the pathologist's findings in the removed tissues can be the basis for extremely accurate statements on the extent of disease. The findings should not be allowed to change the clinical staging, but should be recorded in the manner described for the pathologic staging of disease. The TNM nomenclature is appropriate for this purpose. Infrequently it happens that hysterectomy is carried out in the presence of unsuspected extensive invasive cervical carcinoma. Such cases cannot be clinically staged or included in therapeutic statistics, but it is desirable that they be reported separately.

As in all gynaecological cancers, staging is determined at the time of the primary diagnosis and cannot be altered, even at recurrence.

Only if the rules for clinical staging are strictly observed will it be possible to compare results among clinics and by differing modes of therapy.

3.1.3 Staging classification

3.1.3.1 Notes about the staging. Stage 0 comprises those cases with full-thickness involvement of the epithelium with atypical cells but with no signs of invasion into the stroma.

The diagnosis of both Stage lal and la2 should be based on microscopic examination of removed tissue, preferably a cone biopsy, which must include the entire lesion. The depth of invasion should not be > 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The second dimension, the horizontal spread, must not exceed 7 mm. Vascular space involvement, either venous or lymphatic, should not alter the staging, but should be specifically recorded because it may affect treatment decisions in the future. Larger lesions should be staged as Ib. As a rule, it is impossible to clinically estimate if a cancer of the cervix has extended to the corpus. Extension to the corpus should therefore be disregarded.

A patient with a growth fixed to the pelvic wall by a short and indurated, but not nodular, parametrium should be allotted to Stage IIB. It is impossible, at clinical examination, to decide whether a smooth and indurated parametrium is truly cancerous, or only inflammatory. Therefore, the case should be placed in Stage III only if the

Table 1: Carcinoma of the Cervix Uteri – Staging

FIGO Stages		TNM Categories
	Primary tumour cannot be assessed	TX
	No evidence of primary tumour	T0
0	Carcinoma in situ (preinvasive carcinoma)	Tis
I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)	T1
IA	Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions – even with superficial invasion – are Stage IB/T1b	T1a
IA1	Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread	T1a1
IA2	Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less[a]	T1a2
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2/T1a2	T1b
IB1	Clinically visible lesion 4.0 cm or less in greatest dimension	T1b1
IB2	Clinically visible lesion more than 4 cm in greatest dimension	T1b2
II	Tumour invades beyond the uterus but not to pelvic wall or to lower third of the vagina	T2
IIA	Without parametrial invasion	T2a
IIB	With parametrial invasion	T2b
III	Tumour extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or non-functioning kidney	T3
IIIA	Tumour involves lower third of vagina no extension to pelvic wall	T3a
IIIB	Tumour extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney	T3b
IVA	Tumour invades *mucosa* of bladder or rectum and/or extends beyond true pelvis[b]	T4
IVB	Distant metastasis	M1

[a] *Note: The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.*

[b] *Note: The presence of bullous edema is not sufficient to classify a tumour as T4.*

parametrium is nodular to the pelvic wall or if the growth itself extends to the pelvic wall.

The presence of hydronephrosis or non functioning kidney resulting from stenosis of the ureter by cancer permits a case to be allotted to Stage III even if, according to other findings, the case should be allotted to Stage I or Stage II.

The presence of bullous oedema, as such, should not permit a case to be allotted to Stage IV. Ridges and furrows into the bladder wall should be interpreted as signs of submucous involvement of the bladder if they remain fixed to the growth at rectovaginal examination. Finding malignant cells in cytologic washings from the urinary bladder requires further histological confirmation in order to be considered for Stage IVA.

Table 2: Carcinoma of the Cervix Uteri – Stage Grouping

FIGO Stage	UICC		
	T	N	M
0	Tis	N0	M0
IA1	T1a1	N0	M0
IA2	T1a2	N0	M0
IB1	T1b1	N0	M0
IB2	T1b2	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
IIIA	T3a	N0	M0
IIIB	T1	N1	M0
	T2	N1	M0
	T3a	N1	M0
	T3b	Any N	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1

3.1.3.2 Regional Lymph Nodes (N)

- NX – Regional lymph nodes cannot be assessed
- N0 – No regional lymph node metastasis
- N1 – Regional lymph node metastasis

3.1.3.3 Distant Metastasis (M)

- MX – Distant metastasis cannot be assessed

- M0 – No distant metastasis
- M1– Distant metastasis

3.1.4 Histopathology

Cases should be classified as carcinomas of the cervix if the primary growth is in the cervix. All histologic types must be included. Grading by any of several methods is encouraged, but is not a basis for modifying the stage groupings. When surgery is the primary treatment, the histologic findings permit the case to have pathologic staging, as described above. In this situation, the TNM nomenclature may be used. All tumours are to be microscopically verified.

3.1.4.1Histopathologic types

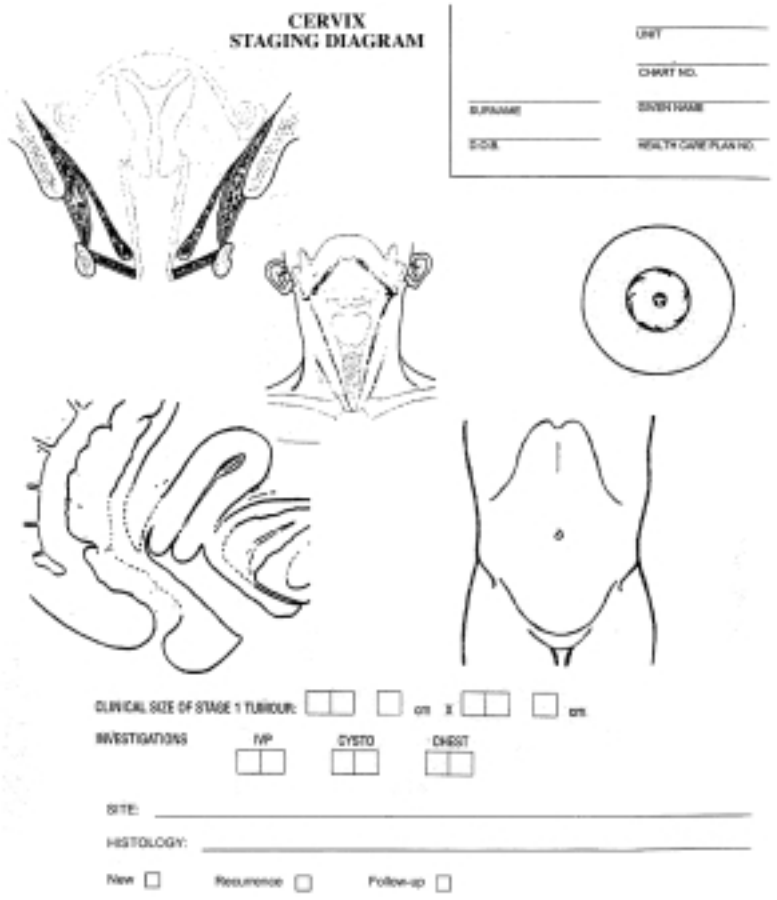
- Cervical intraepithelial neoplasia, Grade III
- Squamous cell carcinoma in situ
- Squamous cell carcinoma
  - Keratinizing
  - Nonkeratinizing
  - Verrucous
- Adenocarcinoma in situ
- Adenocarcinoma in situ, endocervical type
- Endometrioid adenocarcinoma
- Clear cell adenocarcinoma
- Adenosquamous carcinoma
- Adenoid cystic carcinoma
- Small cell carcinoma
- Undifferentiated carcinoma

3.1.4.2 Histopathologic grades (G)

- Gx – Grade cannot be assessed;
- G1 – Well differentiated;
- G2 – Moderately differentiated;
- G3 – Poorly or undifferentiated.

3.2 Introduction

World-wide, cervical cancer is second only to breast cancer as the most common female malignancy in both incidence and mortality. More than 80% of new cases are diagnosed in economically disadvantaged people.



Carcinoma of the uterine cervix grows locally and may extend in continuity to the paracervical tissues and to the pelvic organs, spread to regional lymph nodes, and only later metastasize to distant structures.

Squamous carcinoma and adenocarcinoma are the most frequent histologic types.

3.3 Cervical Screening

Data from many countries have shown that screening with cervical cytology reduces the incidence and mortality from cervical cancer.

Principles:

1. The purpose of a cervical screening programme is to reduce the incidence and mortality of cervical cancer.
2. Cervical screening should be population based with wide coverage (aim for at least 80% coverage of the population).
3. Cervical cytology is the most used method of screening.

3.3.1 Screening guidelines

3.3.1.1 Age group to be screened

This depends on the particular age distribution of deaths from cervical cancer and may be "country specific". Deaths from cervical cancer are rare before age 25. Women can be discharged from the screening programme at the age of 65 if they have had two negative smears in the previous 10 years.

3.3.1.2 Frequency of screening

There is a higher incidence of women developing an interval cancer if the time from the previous smear is extended beyond 3 years.

3.3.1.3 Management of cervical cytology results

Recommendations for management after a cervical smear:

1. Routine recall: for a reportedly normal smear
2. Repeat smear:
   - i if smear is inadequate, repeat in three months.
   - ii for mild dyskaryosis or borderline nuclear changes, repeat in six months. The six-month recommended repeat interval allows for possible resolution of changes. After three such smears colposcopy is recommended.
3. Refer for colposcopy: For moderate or severe dyskaryosis, query invasive disease or query glandular neoplasia.

3.4 Management of Cervical Cancer

3.4.1 Microinvasion

The diagnosis of Stage IA1 or Stage IA2 disease can only be made on

the basis of a cone biopsy with negative margins, or on a trachelectomy or hysterectomy specimen. If the margins of the cone biopsy are positive for CIN III or invasive cancer, a second cone biopsy should be performed or the patient treated as for Stage IB1 disease.[1]

Colposcopy should be performed to exclude any associated vaginal intraepithelial neoplasia (VAIN) before undertaking definitive treatment.

3.4.1.1 Stage IA1

The recommended management is total abdominal or vaginal hysterectomy.[2] If there is any associated VAIN, an appropriate cuff of vagina should be removed.

If fertility is desired, observation after cone biopsy is appropriate, with Pap smear follow up at four months, 10 months, and then annually if both previous smears are negative. **Level of Evidence B.**

3.4.1.2 Stage IA2

There is a definite potential for lymph node metastasis in patients with Stage IA2 disease, so pelvic lymphadenectomy should be included in the treatment protocol.[3,4]

The recommended treatment is modified radical hysterectomy (Type 2) and pelvic lymphadenectomy. If there is no lymph vascular space invasion, consideration may be given to extrafascial hysterectomy and pelvic lymphadenectomy. **Level of Evidence C.**

If fertility is desired, options are:

i large cone biopsy plus extra-peritoneal or laparoscopic pelvic lymphadenectomy, or

ii radical trachelectomy and extra peritoneal or laparoscopic pelvic lymphadenectomy.[5]

3.4.1.3 Follow up:

Should be mainly with Pap smears and should be annually after two normal smears at four and 10 months.

3.4.2 Invasive carcinoma

3.4.2.1 Initial Evaluation

For the patient with a visible lesion, biopsy should be done to confirm the diagnosis. Initial evaluation includes clinical examination (if necessary under anaesthesia), and colposcopy of the vagina to exclude

VAIN. Relevant clinical symptoms should be investigated, and the bladder and rectum may be evaluated by cystoscopy and sigmoidoscopy if symptomatic. Chest x-ray and renal evaluation (which may consist of renal ultrasound, IVP, CT or MRI) are mandatory. CT and/or MRI may provide some information on nodal status.

3.4.2.2 Stage IB1, IIA < 4 cm

Early stage cervical cancer (IB1, IIA < 4cm) has a good prognosis and can be controlled with surgery or radiotherapy.[6,7] **Level of Evidence A.**

The treatment of choice will depend on the availability of resources, the oncologist involved, and the age and the general health of the patient. It is desirable to have multidisciplinary consultation where possible and patients should be informed about the therapeutic alternatives, including their toxicity and the expected outcomes.

Morbidity is usually higher when both surgery and radiation are combined. In order to minimize morbidity, primary therapy should avoid the planned use of both radical surgery and radiation therapy. **Level of Evidence A.**

3.4.2.2.1 Surgery

The standard surgical treatment of stage IB1/IIA (< 4 cm diameter) is modified radical or radical abdominal hysterectomy (Class II and Class III according to Piver Rutledge classification) and pelvic lymphadenectomy.

In younger patients, the ovaries may be preserved and suspended outside the pelvis if post-operative radiation is likely to be given.

A vaginal radical hysterectomy and laparoscopic pelvic lymphadenectomy may be done in particular cases.[8,9] **Level of Evidence C.**

3.4.2.2.2. Radiotherapy

The standard radiation treatment of stage IB1/IIA (< 4 cm diameter) is external pelvic irradiation plus brachytherapy. Suggested doses, including both external beam radiation and LDR brachytherapy, are 80-85 Gy to point A and 50-55 Gy to point B. The dose of external pelvic radiation should be 45 to 50 Gy in 180 to 200 cGy fractions. Using HDR brachytherapy, doses should be defined according to biological equivalence.

3.4.2.2.3 Adjuvant therapy post surgery

The risk of recurrence after radical surgery is increased with the presence of positive nodes, positive parametria, or positive surgical margins. Adjuvant concurrent chemoradiation (using 5FU + Cisplatin or Cisplatin alone) improves survival compared with pelvic irradiation alone in such patients.[10] **Level of Evidence A.**

Risk is also increased in those with uninvolved nodes but large tumour volume, capillary – like space (CLS) involvement, and outer one-third invasion of the cervical stroma. Adjuvant whole pelvic irradiation reduces the local failure rate and improves progression-free survival compared with patients treated with surgery alone.[11] **Level of Evidence A.**

Two groups have reported comparable tumour control with decreased morbidity using a small field of pelvic radiation, designed to cover the vaginal vault and parametrial tissues.[12,13] The upper border on this field extends to about S_{1-2} rather than L_5-S_1. **Level of Evidence C.**

3.4.2.3 Stage IB2 – IIA (> 4 cm)

Options for primary therapy include:

1) Primary chemoradiation[14]
2) Primary radical hysterectomy and bilateral pelvic lymphadenectomy, which usually needs to be followed with adjuvant radiation
3) Neoadjuvant chemotherapy (three rapidly delivered courses of platinum based chemotherapy) followed by radical hysterectomy and pelvic lymphadenectomy +/- adjuvant post-operative radiation or chemoradiation.[15]

3.4.2.3.1 Concurrent chemoradiation

The most commonly used treatment is external beam radiation plus intracavitary brachytherapy with concurrent weekly platinum chemotherapy. Suggested doses of radiation should be 85 to 90 Gy to point A and 55 to 60 Gy to point B. Cisplatin is given in a dose of 40 mg per m^2 weekly during external beam therapy. In patients with positive common iliac or paraaortic nodes, extended field radiation should be considered.[16,17] Little data are yet available on the toxicity associated with concurrent chemotherapy and extended field irradiation. **Level of Evidence A.**

3.4.2.3.2 Primary surgery and probable adjuvant radiation

Primary radical hysterectomy offers the advantage of allowing proper surgical staging, while simultaneously removing the primary tumour, thereby obviating the need for brachytherapy.[18] It also allows resection of any bulky positive lymph nodes, which are less likely to be sterilized with primary radiation.[19]

Because these tumours are bulky by definition, adjuvant radiation is more likely to be necessary. Patients at particular risk of local recurrence are those with extensive CLS involvement and those with invasion to the outer third of the cervical stroma.[20] The high-risk node-negative patients may be treated by whole pelvic[11] or small field pelvic[12,13] radiation. Patients with positive common iliac or para aortic nodes may be treated by extended field radiation[16,17] with or without chemotherapy. **Level of Evidence C.**

3.4.2.3.3 Neoadjuvant chemotherapy followed by radical hysterectomy and pelvic lymphadenectomy

Data from randomised trials would suggest that neoadjuvant platinum based chemotherapy prior to definitive surgery is associated with better results than primary radiation.[15,21] There are no data available to compare the results of concurrent chemoradiation with those of neoadjuvant chemotherapy followed by surgery. **Level of Evidence B.**

The chemotherapy used in the Buenos Aires study was as follows:[15]

Cisplatinum 50 mg/m^2 IV in 15 minutes on day 1

Vincristine 1 mg/m^2 IV push on day 1, and

Bleomycin 25 mg/m^2 by continuous infusion over six hours on days 1-3.

The regime is repeated at 10-day intervals for three cycles.

Table 3: Management of Advanced Cervical Cancer

Stages:	Stage IIB – IVA
Staging:	Examination under general anaesthesia Chest x-ray Optional CT scan of abdomen and pelvis Renal imaging
Radiation technique:	A. Primary target Tumour + uterus B Secondary target Pelvic lymph nodes and common iliac lymph nodes Field technique: 4 field Field borders for external irradiation A. Tumour determined by palpation and CT scan (if available) + 2 cm margin B. A-P fields: Lateral: 2 cm lateral to the bony margin of pelvis Superior: Between L_5 and S_1 Inferior: 2 cm below the obturator foramen (or 2 cm below lower extent of clinical tumour) C. Lateral fields: Anterior = individually determined by tumour Posterior = individually determined by tumour Primary target: External irradiation 50 Gy/5-6 weeks + LDR intracavitary boost 30-35 Gy point A (for IIB-IVA, 35-40 Gy) Secondary target: External irradiation 50 Gy/5 Weeks **Total treatment time: 6-7 weeks**
Concurrent chemotherapy:	Cisplatin 40 mg/m^2 every week during external irradiation

3.4.2.4 Advanced cervical cancer

3.4.2.4.1 Definition

Includes stage IIB, stage III and IVA.

3.4.2.4.2 Primary treatment

Standard primary treatment is irradiation given as a combination of external radiation and intracavitary brachytherapy with concurrent chemotherapy.[14,22] **Level of Evidence A.**

Primary pelvic exenteration may be considered for Stage IVA disease not extending to the pelvic sidewall, particularly if a vesicovaginal or rectovaginal fistula is present. **Level of Evidence C.**

3.4.2.4.3 Irradiation dose and technique

Doses and field technique are given in Table 3. Irradiation should be given by an appropriate energy causing a uniform dose distribution (± 5%) within the primary and secondary target volume. The target volume should be determined by clinical examination and CT-scanning when possible. The field technique should consist of at least four fields. Brachytherapy may be given as high or low dose rate. The standard treatment is external beam radiation plus intracavitary brachytherapy concurrent with platinum based chemotherapy. Cisplatin is given weekly during the external beam therapy at a dose of 40 mg/m^2. Suggested doses of radiation should be 85 to 90 Gy to point A and 55 to 60 Gy to point B. In patients with positive common iliac or paraaortic nodes extended field radiation should be considered.[16,17,23] **Level of Evidence C.**

3.4.2.5 Stage IVB or recurrent disease

3.4.2.5.1 Background

Recurrence may be pelvic, distant or both. As the bulk of the primary pelvic tumour increases, the proportion of patients with disease recurrent or persistent in the pelvis as the only site of failure increases compared with the proportion developing distant metastases.

The majority of recurrences occur within two years of diagnosis and the prognosis is poor with most patients dying as a result of uncontrolled disease.[24] The median duration of survival is seven months.

Symptoms of recurrent/metastatic cervical cancer may include pain, leg swelling, anorexia, vaginal bleeding, cachexia and psychological problems among others.

The coordinated efforts of a team of professionals are optimal; this may include gynaecologic oncologists, radiation and medical oncologists, palliative care physicians, specialised nursing staff, psychologists, and possibly stomaltherapists. Relief of pain and other symptoms, along with comprehensive support for the patient and her family, are paramount.

3.4.2.5.2 Management of patients who relapse after primary treatment

Treatment decisions should be based on the performance status of the patient, the site of recurrence and/or metastases, the extent of metastatic disease and the prior treatment.

3.4.2.5.2.1 Locally recurrent cervical cancer following radical surgery

Guidelines – Locally Recurrent Cervical Cancer Following Surgery	**Level of Evidence**
Radiation therapy is indicated in patients with locally recurrent cervical cancer following radical surgery	C
Concurrent chemotherapy with either Fluorouracil and/or Cisplatin with radiation should be considered and may improve outcome	B
Pelvic exenteration may be an alternative (particularly if a fistula is present) to radical radiotherapy and concurrent chemotherapy in selected patients without pelvic sidewall involvement.	C

3.4.2.5.2.2 Therapeutic options for local relapse after primary surgery

Relapse in the pelvis following primary surgery may be treated by either radical radiation or pelvic exenteration. Radical irradiation (+/- concurrent chemotherapy) may cure a substantial proportion of those with isolated pelvic failure after primary surgery.[25]

Radiation dose and volume should be tailored to the extent of disease. Fifty Gray in 180 cGy fractions should be delivered to microscopic disease and using field reductions 64 to 66 Gy should be delivered to the gross tumour volume.

Where disease is metastatic or recurrent in the pelvis after failure of primary therapy and not curable, a trial of chemotherapy with palliative intent or symptomatic care is indicated. Cisplatin is the single most active agent for the treatment of cervical cancer.[26,27]

The expected median time to progression or death is three to seven months.

3.4.2.5.2.3 Local recurrence following definitive (radical) radiation

Guideline – Local Recurrence Following Prior Radiotherapy	Level of Evidence
Selected patients with resectable recurrences should be considered for pelvic exenteration	C

The only potentially curative treatment after primary irradiation is pelvic exenteration. Patients should be selected carefully; those with resectable central recurrences that involve the bladder and/or rectum without evidence of intraperitoneal or extra pelvic spread and who have a dissectable tumour-free space along the pelvic sidewall are potentially suitable. The triad of unilateral leg oedema, sciatic pain and ureteral obstruction almost always indicates unresectable disease on the pelvic sidewall, and palliative measures are indicated.

The prognosis is better for patients with a disease-free interval greater than six months, a recurrence 3 cm or less in diameter, and no sidewall fixation[28-31]. The five-year survival for patients selected for treatment with pelvic exenteration is in the order of 30 – 60% and the operative mortality should be < 10%.

In carefully selected patients, a radical hysterectomy may be performed. Suitable patients are mainly those whose central tumour is not more than 2 cm in diameter[32].

3.4.2.5.2.4 The role of systemic chemotherapy in Stage IVB or recurrent metastatic cervical cancer

Guidelines – Systemic Chemotherapy in Metastatic Cervical Cancer	Level of Evidence
Cisplatin is the single most active agent to treat cervical cancer	B
The response rate (31%) with 100 mg/m^2 Cisplatin is higher than that with 50 mg/m^2 (21%) but not associated with any improvement in progression-free or overall survival.[27]	B
Response rates to chemotherapy are consistently higher in patients with good performance status and extra pelvic disease and low in previously irradiated sites.	C
The impact of chemotherapy on palliation and survival is unclear	C

3.4.2.6 Distant metastases

Local treatment with radiation therapy is indicated to sites of symptomatic involvement in patients with metastatic disease for alleviation of symptoms including pain arising from skeletal metastases[33], enlarged paraaortic or supraclavicular nodes, and symptoms associated with cerebral metastases[34].

In view of the shortened life expectancy of patients with metastatic cervical cancer, palliative radiotherapy should be given via larger fractions over shorter periods of time than conventional radical courses of treatment[35].

Appendix 1 FIGO Staging

Stage	Characteristics
0	Carcinoma in situ, intraepithelial carcinoma; cases of stage 0 should not be included in any therapeutic statistics for invasive carcinoma
I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)
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 taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging)
IA1	Measured invasion of stroma no greater than 3 mm in depth and no wider than 7 mm
IA2	Measured invasion of stroma > 3 mm and no greater than 5 mm in depth and no wider than 7 mm
IB	Clinical lesions confined to the cervix or preclinical lesions > IA
IB1	Clinical lesions no greater than 4 cm in size
IB2	Clinical lesions > 4 cm in size
II	The carcinoma extends beyond the cervix, but has not extended onto the pelvic wall; the carcinoma involves the vagina, but not as far as the lower third
IIA	No obvious parametrial involvement
IIB	With parametrial involvement
III	The carcinoma has extended onto 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 a hydronephrosis or nonfunctioning kidney should be included, unless they are known to be due to other causes
IIIA	No extension onto the pelvic wall, but involvement of the lower third of the vagina
IIIB	Extension onto the pelvic wall or hydronephrosis or nonfunctioning kidney
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

(1) FIGO staging is based on clinical data (clinical examination and colposcopy), chest x-rays, IVP, biopsy and D&C.
(2) Cystocopy and sigmoidoscopy may be used for clinical stage (bladder and/or rectal mucosal biopsy).
(3) Lymphangiogram, CT, MRI, laparotomy, laparoscopy cannot be used for clinical staging.
(4) Pathological IVP defines a cancer as stage IIIB.
(5) Paracervical, parametrial, hipogastric, obturator, internal, external and common iliac, presacral and sacral are the regional nodes.

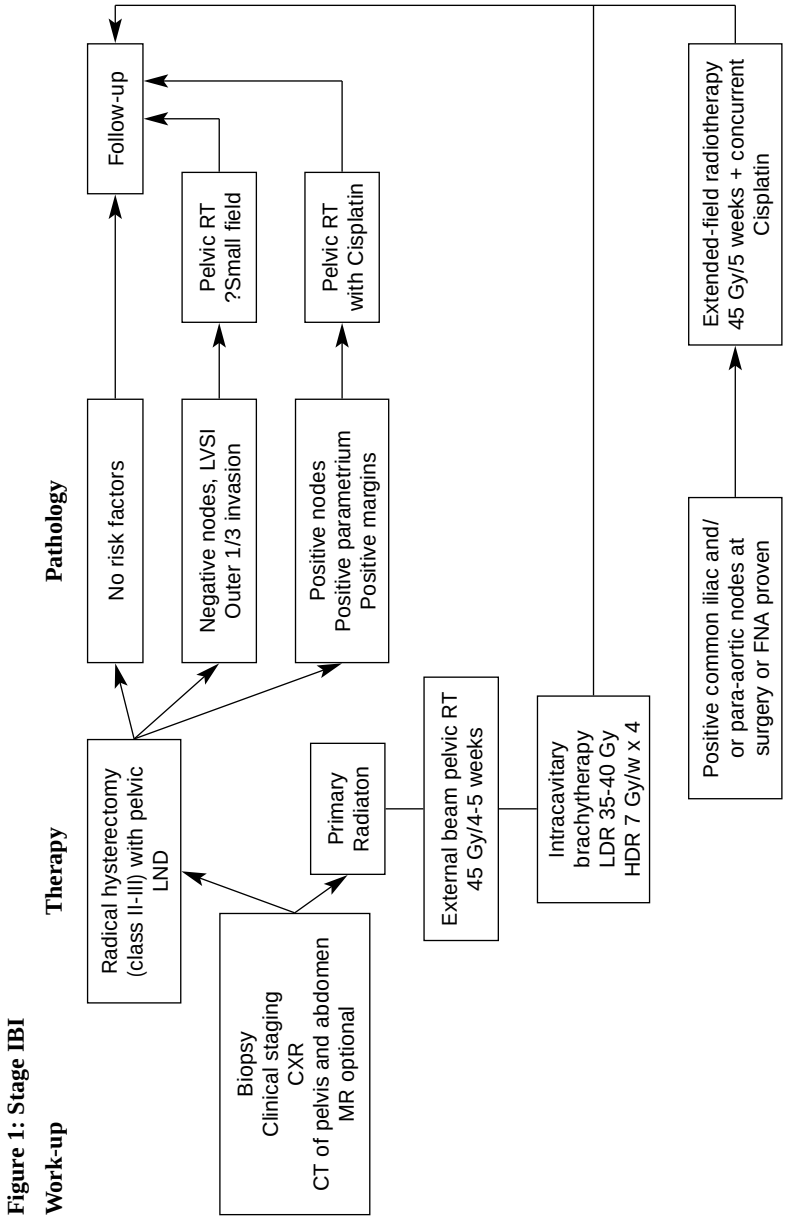


Figure 1: Stage IBI

Figure 2: Stage IB2 and IIA

°Neoadjuvant chemotherapy: 3 courses of platinum-based chemotherapy
Technique: 4 fields. Field borders for ext. irradiation. A: Tumour determined by palpation and CT scan + 2 cm margin. B: A-P fields:* ***Laterally: 2 cm lateral to bony margin of pelvis. Superior: Between L_5 and S_1. Inferior: 2 cm below the obturator foramen. Posterior = individually determined by tumour.*
The role of neoadjuvant CT followed by class II-III radical hysterectomy and pelvic lymphadenectomy (+ adjuvant concurrent CT/RT) remains to be further defined.

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Cancer of the Corpus Uteri

4.1 Staging

4.1.1 Anatomy

4.1.1.1 Primary site. The upper two-thirds of the uterus above the level of the internal cervical os is called the corpus. The fallopian tubes enter at the upper lateral corners of a pear-shaped body. The portion of the muscular organ that is above a line joining the tubouterine orifices is often referred to as the fundus.

4.1.1.2 Nodal stations. The major lymphatic trunks are the uteroovarian (infundibulo-pelvic), parametrial, and presacral, which drain into the hypogastric, external iliac, common iliac, presacral, and paraaortic nodes.

4.1.1.3 Metastatic sites. The vagina and lungs are the common metastatic sites.

4.1.2 Rules for classification

The FIGO Committee on Gynecologic Oncology, following its meeting in 1988, recommended that endometrial cancer be surgically staged. There should be histologic verification of grading and extent of the tumour.

4.1.3 Notes about the staging

4.1.3.1 Histopathology – degree of differentiation. Cases of carcinoma of the corpus should be grouped with regard to the degree of differentiation of the adenocarcinoma as follows:

- G1: ≤ 5% of a nonsquamous or nonmorular solid growth pattern.
- G2: 6-50% of a nonsquamous or nonmorular solid growth pattern.
- G3: > 50% of a nonsquamous or nonmorular solid growth pattern.

Table 1: Carcinoma of the Corpus Uteri – Staging

FIGO Stages		TNM Categories
	Primary tumour cannot be assessed	TX
	No evidence of primary tumour	T0
0	Carcinoma in situ (preinvasive carcinoma)	Tis
I	Tumour confined to the corpus uteri	T1
IA	Tumour limited to endometrium	T1a
IB	Tumour invades up to less than half of myometrium	T1b
IC	Tumour invades to more than one half of myometrium	T1c
II	Tumour invades cervix but does not extend beyond uterus	T2
IIA	Endocervical glandular involvement only	T2a
IIB	Cervical stromal invasion	T2b
III	Local and/or regional spread as specified in IIIA, B, C	T3 and/ or N1
IIIA	Tumour involves serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings	T3a
IIIB	Vaginal involvement (direct extension or metastasis)	T3b
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes	N1
IVA	Tumour invades bladder mucosa and/or bower *mucosa*[a]	T4
IVB	Distant metastasis (excluding metastasis to vagina, pelvic serosa, or adnexa, including metastasis to intra-abdominal lymph nodes other than para-aortic and/or inguinal nodes)	M1

[a] *Note: The presence of bullous oedema is not sufficient evidence to classify a tumour as T4*

4.1.3.2 Regional Lymph Nodes (N)

- NX – Regional lymph nodes cannot be assessed
- N0 – No regional lymph node metastasis
- N1 – Regional lymph node metastasis

4.1.3.3 Distant Metastasis (M)

- MX – Distant metastasis cannot be assessed
- M0 – No distant metastasis
- M1 – Distant metastasis

Table 2: Carcinoma of the Corpus Uteri – Stage Grouping

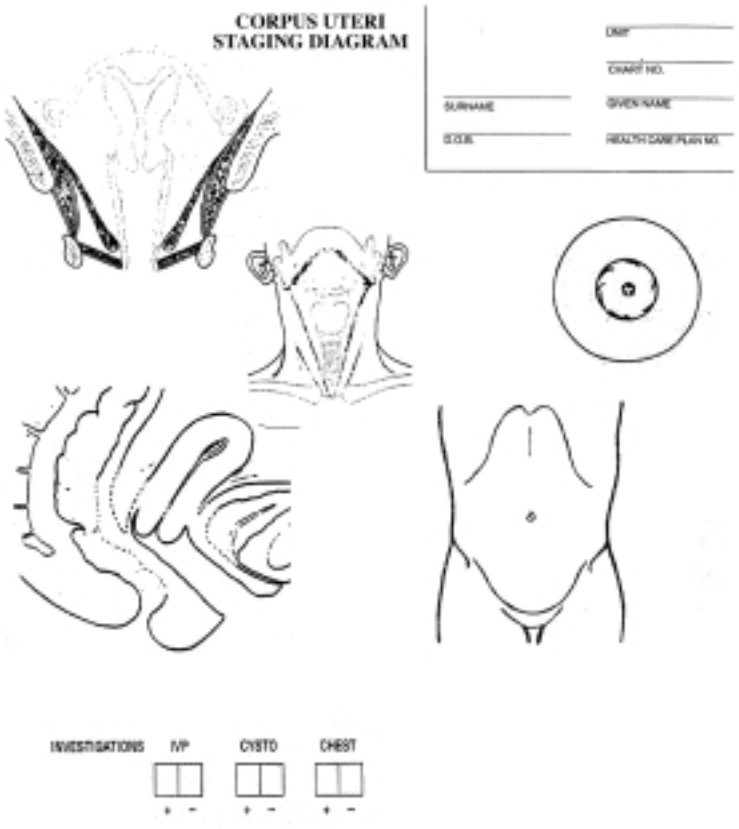
FIGO Stage	UICC		
	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
IC	T1c	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC	T1	N1	M0
	T2	N1	M0
	T3a	N1	M0
	T3b	N1	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1

4.1.3.4 Notes on pathologic grading

- Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a Grade l or Grade 2 tumour by 1.
- In serous and clear cell adenocarcinomas, nuclear grading takes precedent.
- Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

4.1.3.5 Rules related to staging

- Corpus cancer is now surgically staged, therefore procedures previously used for determination of stages are no longer applicable (e.g. the findings of fractional curettage to differentiate between Stage I and Stage II).
- It is appreciated that there may be a small number of patients with corpus cancer who will be treated primarily with radiation therapy. In these cases, the clinical staging adopted by FIGO in 1971 would still apply, but designation of that staging system would be noted.
- Ideally, width of the myometrium should be measured along with the depth of tumour invasion.



4.1.4 Histopathology (according to WHO/ISGP[a] classification)
All tumours are to be microscopically verified.
The histopathologic types are:

- Endometrioid carcinoma
  - Adenocarcinoma
  - Adenocanthoma (adenocarcinoma with squamous metaplasia)
  - Adenosquamous carcinoma (mixed adeno carcinoma and squamous cell carcinoma)
- Mucinous adenocarcinoma
- Papillary serous adenocarcinoma

- Clear cell adenocarcinoma
- Adenosquamous carcinoma
- Undifferentiated carcinoma
- Mixed carcinoma

[a] = International Society of Gynecological Pathology

4.1.4.1 Histopathologic grades (G)

- Gx – Grade cannot be assessed;
- G1 – Well differentiated;
- G2 – Moderately differentiated;
- G3 – Poorly or undifferentiated.

4.2 Introduction

In developed countries, where deaths from cervical cancer have been reduced by up to 50% because of screening, endometrial cancer ranks alongside ovarian cancer as the leading types of gynaecological cancer. The incidence of endometrial cancer rises from 2 per 100,000 women per year under the age of 40 years to 40-50 per 100,000 women per year[1] in the 6th, 7th and 8th decades. Attention has been drawn to the fact that deaths from endometrial cancer in the United States doubled between 1988 and 1998[2], probably due to a combination of increased life expectancy and an epidemic of obesity, which predisposes to this disease.

The aetiology of endometrial cancer is unclear, although endometroid carcinoma is thought to progress through a premalignant phase of intraendometrial neoplasia in a large proportion of cases.[3] Other forms such as papillary serous and clear cell carcinoma probably arise as a result of a sequence of poorly understood genetic mutations; we know, for example, that mutant p53 commonly stains positive in papillary serous carcinoma.

Until recently there was very little research on which to base clinical practice guidelines, but the last 10 years have seen greater interest in endometrial cancer clinical trials. Although its early presentation following postmenopausal bleeding results in a generally good prognosis, the view that endometrial cancer is a straightforward disease is erroneous; stage for stage, it is no less dangerous than ovarian cancer. As such it requires to be treated by tightly governed protocols and where appropriate by expert multidisciplinary teams.

There is no means of effective screening available in endometrial cancer, although certain high risk groups such as those with Lynch type 2 syndrome can undergo endometrial surveillance by hysteroscopy and biopsy. Following presentation, ultrasound is an effective first test with a high negative predictive value when the endometrial thickness is less than 5 mm. In one of the largest studies undertaken, there was a negative predictive value of 96% amongst 1168 women in whom the results of transvaginal ultrasound were correlated with an endometrial biopsy obtained by curettage.[4] When a biopsy is required this can be obtained usually as an office procedure using a number of disposable instruments developed for the purpose. In certain cases hysteroscopy may be helpful, and with flexible instruments can also be done without recourse to general anaesthesia. If cervical stenosis or patient tolerance does not permit an office procedure, then curettage under anaesthesia is necessary. Individuals whose pelvic examination is unsatisfactory may also be evaluated with transvaginal or abdominal ultrasound to rule out concomitant adnexal pathology.

Following a histopathologic diagnosis of endometrial carcinoma, the next stage in management is to determine the degree of risk for metastatic disease, to determine the local extent of the tumour, and, by the significant proportion with comorbidity, to assess perioperative risk, anticipating surgery as the mainstay of treatment.

As a minimum the pathology report should indicate both the tumour type and the degree of differentiation. A chest x-ray, full biochemistry and blood count are routine. A serum CA-125 may be of value in advanced disease for follow-up. Evaluation for metastasis is indicated particularly in patients with abnormal liver function tests, and clinical findings such as parametrial or vaginal tumor extension. In certain situations, cystoscopy and/or barium enema may be helpful, if direct extension to bladder or rectum is suspected.

In order to evaluate the risk of nodal metastases some preoperative evaluation of myometrial invasion is desirable to be considered along with the endometrial pathology.

4.3 Prognostic tumour characteristics for high risk

The recommended histopathological criteria for determining poorer prognosis are as follows:

Tumour grade 3 (poorly differentiated)
Deep myometrial invasion (FIGO stage 1C)
Lymphvascular channel involvement
Positive peritoneal cytology
Serous papillary tumour
Clear cell tumours
Cervical involvement (stage II)

Although ultrasound can be employed for this purpose, the most accurate means of assessing both depth of disease and cervical involvement is MR scanning. CT and MR are equivalent in terms of evaluating nodal metastases, but neither is good enough to replace surgical lymph node assessment.[5-10]

Non surgical staging for endometrial cancer where extrauterine disease exists, is inherently inaccurate, particularly in respect of small node involvement, intraperitoneal implants, and adnexal metastasis. Furthermore, it is widely accepted that a curettage specimen may underclassify the tumour when the hysterectomy specimen has been fully examined. Up to 20% of tumours may have a worse histologic grade and occasionally different tumour type based on the hysterectomy specimen.

4.4 Surgical staging procedure for endometrial cancer

In 1988, the FIGO system changed from clinical to surgical staging for endometrial cancer. Since that recommendation, considerable debate has ensued as to what constitutes an internationally acceptable approach. A generally recommended protocol would be that the abdomen should be opened with a vertical midline abdominal incision and peritoneal washings taken immediately, from the pelvis and abdomen, followed by careful exploration of the intra-abdominal contents. The omentum, liver, peritoneal cul-de-sac and adnexal surfaces should be examined and palpated for any possible metastases, followed by careful palpation for suspicious or enlarged nodes in the aortic and pelvic nodal areas. The standard surgical procedure should be an extrafascial total hysterectomy with bilateral salpingo-oophorectomy. Adnexal removal is also recommended even if the adnexa appear normal as they may contain micrometastases. Vaginal cuff removal is not necessary nor is there any benefit from excising parametrial tissue in the usual case. If cervical stromal involvement is

demonstrated pre-operatively or if unsuspected cervical involvement is noted and can be encompassed by a modified radical hysterectomy, then this may be the most appropriate action in experienced hands.

Although mandated through the staging system, lymphadenectomy of the pelvis and para-aortic areas remains controversial. Selective node sampling is of dubious value as a routine; complete lymphadenectomy being reserved for cases with high-risk features. Many individuals with endometrial cancer are obese or elderly, with other medical problems, and clinical judgment is required to determine if additional surgery is warranted. Any deeply invasive tumour or radiological suggestion of positive nodes are definitely indications for retroperitoneal lymph node evaluation with removal of any enlarged or suspicious lymph nodes. If these nodes are positive on frozen section, further node dissection may be unnecessary unless clinically positive nodes can be excised with minimal risk to the patient.

Indications for aortic node sampling would include suspicious aortic or common iliac nodes, grossly positive adnexa, grossly positive pelvic nodes and high grade tumours showing full thickness myometrial invasion. Patients with clear cell, papillary serous or carcinosarcoma histologic subtypes are also candidates for aortic node sampling. The uterine tissue and any nodes should be cut up and examined as described in Appendix 1.

4.5 Who should perform the surgery?

Low risk tumours will have positive nodes in less than 5% cases (well differentiated and <1/2 myometrial invasion) and do not require full surgical staging. These women can generally be safely operated on by a general gynaecologist, but those at greater risk of extrauterine disease who require lymphadenectomy should be referred to a specialist gynaecological oncologist. This triaging of women can be done most effectively by a thorough pre-operative assessment, paying particular attention to the pathology and to radiological features.

4.6 Is lymphadenectomy therapeutic?

Although required for accurate staging, whether lymphadenectomy has any therapeutic benefit is as yet unproven. One case control study has suggested that it may[11] and another showed a good prognosis even in node positive women[12], but randomised trials are essential in order

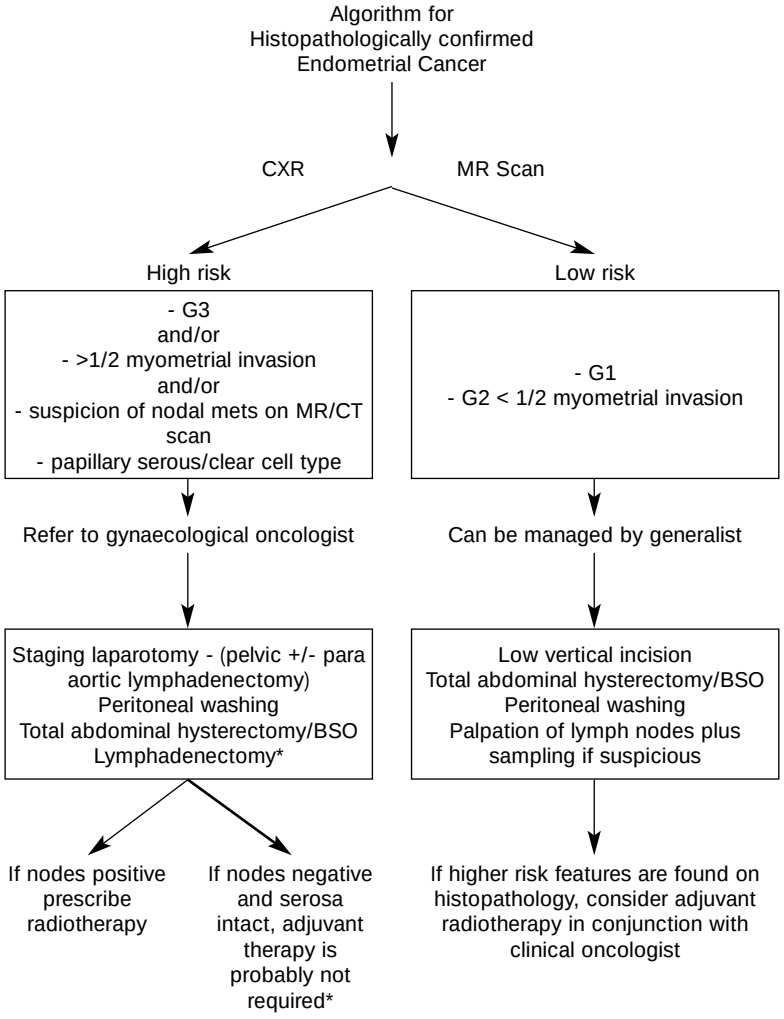
to prove this. In the UK, the ongoing MRC ASTEC trial is randomising all women who are undergoing surgery for presumed stage 1 endometrial cancer to pelvic lymphadenectomy or no lymphadenectomy.

Laparoscopically assisted vaginal hysterectomy is permitted, for surgeons experienced in this technique in low grade disease, but would need to be converted to an open procedure if unexpected metastases are identified. It can be accompanied by a laparoscopic lymphadenectomy, if surgical staging is to be undertaken.

4.7 Adjuvant Radiotherapy

Historically, two basic approaches have been adopted regarding the use of radiotherapy in the initial management of endometrial carcinoma. The earlier approach was to administer preoperative irradiation followed by surgery. More recently, findings at laparotomy are used to determine the need for radiotherapy in a purely adjuvant setting following definitive surgery.

In Europe it has been common practice to base the need for adjuvant radiotherapy on risk determined by grade of tumour and myometrial invasion. In North America and Australia the decision is generally based more on whether surgical staging has excluded extrauterine disease and hence the risk of recurrence. The argument is that rationalising the use of radiotherapy in this way reduces morbidity and maintains survival rates. A recent case series has indicated excellent results for stage 1 endometrial cancer, in which external radiation was avoided in node negative women. In this series only 6.9% received radiotherapy[13]. It is worthwhile reviewing the evidence on which decisions regarding adjuvant radiotherapy can be robustly based. Low risk disease does not require adjuvant radiotherapy as demonstrated in a Danish cohort study of low risk women, with a 96% 5 year survival[14]. A seminal Norwegian trial[15] indicated 20 years ago that overall survival was not improved by adjuvant external beam therapy, although it did reduce the risk of pelvic recurrence. The trial included 621 women with all categories of FIGO stage 1 disease and all women had vaginal brachytherapy. The failure to improve overall survival was due to a higher risk of distal metastases in women who had had brachytherapy. Another important trial from the Netherlands (PORTEC) has recently been reported[16] in which 715 women with



**Randomised trials are needed to provide conclusive evidence regarding the clinical effectiveness of lymphadenectomy and adjuvant radiotherapy in the presence of high risk factors.*

either grade 1 (outer 1/2), all grade 2 or grade 3 (inner 1/2) were randomised after surgery (without lymphadenectomy) to pelvic radiotherapy or no further treatment. This trial again showed a significant reduction in the 5-year vaginal and pelvic recurrence rates after RT (4% in the RT group vs 14% in the control group), but without any survival benefit. Endometrial carcinoma related death rates were 9% in the RT group and 6% in the control group. Survival after relapse was significantly better for patients in the control group. Most recurrences were located in the vagina, with a survival after vaginal recurrence of 69% at 3 years (both groups combined). RT and patient age <60 years were the significant favourable prognostic factors for locoregional relapse, while grade 3 histology and age ≥60 years were significant predictive factors for endometrial carcinoma related deaths.

As has already been stated, the MRC ASTEC trial is currently randomising women undergoing surgery for stage 1 endometrial cancer to pelvic lymphadenectomy or no lymphadenectomy. Following surgery, high risk cases are again randomised to receive external beam radiotherapy independent of the lymph node status. High risk is based on histopathological criteria without exclusion. This will include higher risk disease than the PORTEC Trial.

The published data suggest that adjuvant radiotherapy is not indicated in the presence of low or intermediate risk stage 1 disease. This would certainly include a) all G1 tumours without serosal involvement, and G2 < 50% myometrial invasion. In higher risk women in whom full surgical staging has excluded extrauterine disease, radiotherapy is of uncertain benefit and many would reserve external beam radiotherapy in these women for pelvic recurrence. Others would advocate adjuvant radiotherapy for the very high risk cases such as G3 tumours, > 50% myometrial invasion. With regard to vaginal brachytherapy, this is used far less routinely than used to be the case, however it is advisable in the presence of cervical involvement.

4.8 Progestogen therapy

This has been widely prescribed in the past, but a meta-analysis of 6 randomised trials involving a total of 3,339 women has shown no survival benefit for adjuvant progestogen therapy in endometrial

cancer[17]. A subsequently published randomised trial of 1012 women also failed to demonstrate any survival benefit[18].

4.9 Stage II

Patients with clinically occult Stage II disease are generally managed in a similar fashion as patients with Stage I disease.

Surgical treatment can be used as a primary treatment for clinically overt cervical involvement; a Wertheim type radical hysterectomy with bilateral pelvic lymphadenectomy and selective aortic node dissection should be performed. If this approach is to be used, pre-operative MR scanning is advisable to ensure local resectability without bladder involvement. If surgery is not considered feasible initially, full pelvic radiotherapy and intracavitary brachytherapy, followed by adjunctive hysterectomy, with selective lymphadenectomy of the aortic pelvic nodes, may be employed.

4.10 Stage III

Patients with Stage III endometrial carcinoma, by virtue of vaginal parametrial extension, are best treated by pelvic irradiation after thorough metastatic work-up. Once therapy is complete, exploratory laparotomy is advised on those patients whose disease seems to be resectable. Extended field radiation therapy or systemic therapy with cytotoxic medications or hormones is warranted in the presence of extrapelvic metastases, depending on the patient's condition. If an individual is in a clinical Stage III category, because of adnexal mass or involvement, as noted on ultrasound, these individuals should undergo surgery without preoperative radiotherapy, to determine the nature of the mass and to perform surgical pathological staging. In many instances cytoreductive surgery can be carried out and if the uterus is resectable then hysterectomy and adnexectomy should be performed. In some instances, rather than metastases to the ovary, one may find that the patient has a primary lesion of both the endometrium and also of the ovary after histologic examination of the removed tissue.

4.11 Stage IV

Patients with evidence of extrapelvic metastases are usually managed with systemic chemotherapy or hormonal therapy. Local irradiation may be beneficial, particularly in brain or bone metastases and occasionally pelvic radiotherapy may help in providing local tumour control and prevent bleeding or complications from local disease.

4.12 Special considerations

4.12.1 Diagnosis post-hysterectomy

Diagnosis of endometrial carcinoma post-hysterectomy can present some difficult management problems, particularly if the adnexae had not been removed. This situation most often arises following vaginal hysterectomy for pelvic prolapse. Recommendations for further post-operative therapy are based on known risk factors for extrauterine disease related to the histologic grade and depth of myometrial involvement. Individuals with grade 3 lesions, deep myometrial invasion, or LVS invasion are candidates for additional surgery to remove the adnexa and to complete surgical staging. Alternately, the empiric use of external beam radiation to the pelvis may be used. Patients with a grade 1 or 2 lesion with minimal myometrial invasion and no LVS involvement generally require no further therapy.

4.12.2 Medically inoperable patient

Morbid obesity and severe cardiopulmonary disease are the general reasons a patient with endometrial carcinoma is usually thought to be medically inoperable. Uterine brachytherapy can achieve cure rates in excess of 70% and may be combined with external beam radiotherapy in the presence of prognostic factors suggesting a high risk of involved nodes.

For patients with a well-differentiated lesion and contraindications to general anaesthesia and unsuited for radiotherapy, high-dose progestins may be used.

4.12.3 Diagnosis in the young woman

The diagnosis of endometrial carcinoma during the reproductive years should be made with caution, since this malignancy is uncommon in women < 35 years and intraendometrial carcinoma may be confused with severe atypical hyperplasia in these situations. In these women consideration should be given to an oestrogen related underlying condition such as granulosa cell tumour, polycystic ovaries or obesity. Atypical hyperplasia can be treated successfully with progestins, and the decision to use progestins in these situations may be

appropriate if preservation of fertility is the highly desirable clinical factor. Equivocal lesions should be examined by an experienced pathologist. If carcinoma is confirmed, hysterectomy with adnexal removal remains the treatment of choice. When uncertainty remains regarding the presence of true carcinoma, the ultimate decision rests with the patient and the patient should undergo thorough counselling and documentation if a conservative approach is followed.

4.12.4 Positive peritoneal cytology

The presence of positive peritoneal cytology, which is often a difficult diagnosis, given the malignant appearance of reactive mesothelial cells, should only be made after a thorough cytopathology review. Management in this situation is controversial if no other features of extrauterine disease have been documented at the time of surgical staging, because insufficient data exist regarding recurrence risk and treatment results.

4.13 Follow-up

The conventional reasons for follow up of treated cancer patients are accepted and involve providing reassurance, diagnosing early recurrence and collecting data. A range of protocols for following up women with endometrial cancer exists but the evidence base in endometrial cancer does not provide much support for follow up in terms of improving survival. One prospective[19] and several retrospective studies[20-23] internationally have addressed follow up. Overall, very few recurrences were identified as a direct result of clinic review and neither recurrence free nor overall survival were improved in these cases compared with those detected at clinical presentation. A Canadian study[22] concluded that the use of routine follow up Pap smears and chest x-rays was probably not cost effective. In non-irradiated patients, a strong case can be made for regular follow up to detect vaginal recurrence at the earliest opportunity, given the high salvage rate following radiotherapy[24].

4.14 Recurrence

Localised recurrences are managed preferentially by surgery, irradiation, or a combination of the two. Large lesions should be excised, if feasible, with isolated pelvic recurrence of any grade being potentially curable if it occurs more than 1 or 2 years after initial therapy. In this setting, extended or radical surgery may be justified if the patient has already received prior irradiation. The results of pelvic exenteration in properly selected cases of this sort are similar to those obtained in cervical cancer. Patients with non-localised recurrent tumours may be candidates for progestin therapy (medroxyprogesterone acetate 50-100 mg tid or megestrol acetate 80 mg two to three times per day). The progestin therapy is continued as long as the disease is static or in remission. Maximum clinical response may not be apparent for 3 or more months after initiating therapy. Chemotherapy with cisplatinum, taxol and adriamycin has been recommended for patients with advanced or recurrent disease, non-amenable to cure by surgery and/or radiotherapy.

4.15 Recommendations for practice

1. Preoperative assessment by endometrial pathology is required to differentiate between tumours at low and high risk of lymph node metastasis, and imaging can be useful in determining depth and cervical involvement and suspicion of involved nodes. **Level of Evidence C.**
2. Outside clinical trials, lymphadenectomy should be performed for staging only in high risk cases. There is little evidence to support a therapeutic benefit, but it may be used to select women with positive nodes for radiotherapy. **Level of Evidence C.**
3. There is evidence that adjuvant radiotherapy is not effective in women with low or moderate risk endometrial cancer in terms of overall survival, though it does reduce the rate of pelvic recurrence. **Level of Evidence A.** It is certainly indicated in cases with positive nodes and in advanced stage disease. Outside clinical trials, most would advocate its use in the presence of high risk prognostic factors to ensure pelvic control. For surgically staged patients with negative nodes, vaginal brachytherapy may be recommended in higher risk cases.
4. There is no evidence to support the use of adjuvant hormone therapy (progestogen). **Level of Evidence A.**
5. High risk and advanced stage endometrial cancer should be managed where possible by gynaecological oncologists as part of a multidisciplinary specialist team. **Professional consensus**.
6. Randomised trials are required to demonstrate the effectiveness of

chemotherapy in both node positive primary and in recurrent disease.

Appendix 1 – Pathology

Endometrial Biopsy

Tissue from an endometrial biopsy (curettage or outpatient sampler) should be embedded in its entirety. A single Haematoxylin and Eosin section is often sufficient for diagnostic purposes. The pathologist should attempt to provide details of the tumour type and grade. Bearing in mind the likelihood of a discrepancy between the grade of tumour in the initial sample and that in the final specimen (Lampe et al 1995, Stoval et al 1991) the pathologist may prefer to grade the tumour as well, moderately or poorly differentiated rather than providing a formal FIGO grade. The pathologist should include details of additional tumour subtypes and myometrial, cervical or lymphovascular invasion in his report if these are identified.

In addition to providing data on which the patient's post-operative management is based, pathological examination of the resection specimen provides an opportunity to audit the above.

Hysterectomy Specimen

The pathologists approach to the resection specimen will be heavily dependent upon local practice. In many units the specimen will be cut up in the fresh state and blocks taken for frozen section examination. In those units where intra-operative consultations are not usual, fixation can be facilitated by removing the cervix with a transverse incision about 25 mm above the external os, incising the uterine corpus along the anterior midline and inserting gauze or tissue paper. The fixative should be changed at least once in the first 24 hours and the specimen container rinsed out to facilitate fixation. The cervix should not be incised in the midline prior to cut up since this distorts the specimen.

Macroscopic examination and cut up of the specimen should include a record of its weight, dimensions and those of any accompanying adnexae. The specimen should be sectioned at three to five mm intervals using parallel slices in either the sagital or transverse plane and carefully examined for evidence of carcinoma.

The configuration of the carcinoma (polypoid or flat), its length, thickness and the number of slices involved (which when multiplied by their estimated thickness, can be translated into an estimate of its width) should be recorded. The depth of myometrial invasion and the width of uninvolved myometrium should be measured. These measurements should be repeated for each plane of the myometrium invaded by tumour (ie: anterior, posterior, left and right lateral walls and fundus). The involvement of lower uterine segment (uterine isthmus) and left and right cornua should be recorded.

The macroscopic estimate of the depth of myometrial invasion will accord with the histological assessment in almost 90% of cases provided the assessment is confined to an estimate of involvement of the inner or outer half (Doeving et al 1989, MK Heatley, personal observation). One or more blocks should be taken through the full thickness of the tumour and uninvolved myometrium. If the myometrium is too thick to fit into one cassette, two should be used. A frozen section study has shown that one (or occasionally two) blocks provide a correct indication of the extent of myometrial invasion in over 90% of cases (Atad et al 1994). It is recognised however, that more extensive histological assessment is desirable if histotechnology resources permit. A histological assessment of the depth of invasion is desirable because pathologists may experience difficulty in determining the true extent of myometrial invasion if, eg, there are associated conditions such as adenomyosis (Jacques et al 1998). It is also desirable to assess the background endometrium to establish if hyperplasia is present (Beckner et al 1985).

Histological examination

The extent to which the specimen is examined histologically will be best determined locally depending upon the availability of histotechnology resources. At a minimum, blocks should be selected to allow adequate FIGO staging for each patient (FIGO 1989). In the case of the uterine specimen, the usual blocks of cervix (midline from the anterior and posterior lips) should suffice unless there is associated cervical pathology. A transverse block from the junction of cervix and uterine isthmus should be processed to exclude or document tumour involvement at this position. It is often possible to identify this junction, since an admixture of cervical and endometrial glands can be

visualised on macroscopic examination of parallel slices from the cut end of the uterus or previously amputated cervical stump.

Blocks of fallopian tube (to exclude intraluminal tumour extension), ovary (to exclude metastatic or synchronous endometrioid neoplasia) and suspicious serosal lesions should be sampled. Many pathologists routinely examine the cornua histologically since myometrial invasion at these locations represents the point at which the tumour extends closest to the serosa and may upstage the tumour from a stage 1b to a 1c lesion.

Reports should include:

- tumour type with details of minor components
- grade
- depth of myometrial invasion
- width of tumour free myometrium
- presence or absence of lymphatic invasion
- involvement of cervical epithelium or stroma.

Other samples which may be recovered include ascitic fluid or peritoneal washings for cytological assessment and tissue from the vagina, bladder, bowel, peritoneum or lymph nodes. If a tumour deposit is macroscopically identifiable, it may be sufficient to sample the tumour only. If no tumour is macroscopically identifiable, it is usually necessary to sample all the submitted tissue histologically to confirm or exclude its presence.

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Cancer of the Fallopian Tube

5.1 Staging

5.1.1. Anatomy

5.1.1.1. Primary Site

The fallopian tube extends from the posterior superior aspect of the uterine fundus laterally and anteriorly to the ovary. Its length is approximately 10cm. The lateral end opens to the peritoneal cavity.

5.1.1.2. Metastatic sites

Carcinoma of the Fallopian tube metastasizes in three manners:

- Intraperitoneal seeding with peritoneal implants even with intact tube
- To the regional lymph node including the para-aortic nodes and pelvic lymph nodes
- Direct extension to the surrounding organs[1]

5.1.2. Descriptive aspects

The fallopian tube is a hollow viscus. Disease is often incidentally found at laparotomy or presents as an adnexal mass. Fallopian tube should be staged surgically with a histological confirmation of disease. This includes carcinoma in situ. Tumour extension into the submucosa or muscularis and to and beyond the serosal can therefore be defined. These facts, together with the laterality, in addition to the presence or absence of ascites, must also be taken into consideration.[1]

5.1.3. Surgical staging classification

Staging for the fallopian tube is by surgical pathological system. Operative findings prior to tumour debulking may be modified by histopathologic as well as clinical or radiologic evaluation. The most common staging system used is the FIGO staging system.[5] However, it is useful to know the UICC TMN staging system (See Table 1 and 2).

5.1.4. Histopathologic types

More than 90% of fallopian tube carcinoma is papillary serous adenocarcinoma. Other tumours include clear cell carcinoma and endometriod carcinoma. All these are treated essentially the same. Rare types include sarcoma, germ cell tumours and lymphoma.[1,4]

5.1.4.1 Histopathologic grades

- Gx – Grade cannot be assessed
- G1 – Well differentiated (Papillary)
- G2 – Moderately differentiated (Papillary-alveolar)
- G3 – Poorly differentiated (Alveolar-medullary)[1,4,15]

Table 1: Carcinoma of the fallopian tube – Staging

FIGO		TNM
	Primary Tumour cannot be assessed	TX
0	No evidence of primary tumour	T0
	Carcinoma in situ (pre-invasive carcinoma)	Tis
I	Tumour confined to fallopian tubes	T1
IA	Tumour limited to one tube, without penetrating the serosal surface; no ascites	T1a
IB	Tumour limited to both tubes, without penetrating the serosal surface; no ascites	T1b
IC	Tumour limited to one or both tubes, with extension onto/ through the tubal serosa; or with positive malignant cells in the ascites or positive peritoneal washings	T1c
II	Tumour involves one or both fallopian tubes with pelvic extension	T2
IIA	extension and/ or metastasis to uterus and/or ovaries	T2a
IIB	extension to other pelvic organ	T2b
IIC	IIB/C with positive malignant cells in the ascites or positive peritoneal washings	T2c
III	Tumour involves one or both fallopian tubes with peritoneal Implants outside the pelvis and /or positive regional lymph nodes	T3 and/orN1
IIIA	Microscopic peritoneal metastasis outside the pelvis	T3a
IIIB	Macroscopic peritoneal metastasis outside the pelvis 2 cm Or less in greatest dimension	T3b
IIIC	Peritoneal metastasis more than 2cm in greatest dimension And/or positive regional lymph nodes	T3c and/orN1
IV	Distant metastasis beyond the peritoneal cavity	M1

Table 2: Carcinoma of the fallopian tube – Stage grouping

FIGO Stage	T	UICC N	M
IA	T1a	N0	M0
IB	T1b	N0	M0
IC	T1c	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
IIC	T2c	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC	T3c	N0	M0
	Any T	N1	M0
IV	Any T	Any N	M1

Regional Nodes (N)

Nx Regional lymph nodes cannot be assessed
N0 No Regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastasis (M)

Mx Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Table 3: Diagnostic criteria

Pathologic criteria for primary fallopian tube malignancy
1. The tumor arises from the endosalpinx
2. The histologic pattern reproduces the epithelium of tubal mucosa
3. There is transition from benign to malignant epithelium is found
4. The ovary and endometrium are either normal or with a tumour smaller than tumour in the tube.

Level of Evidence A.

5.2 Overview

Carcinoma of the fallopian tube is a rare malignancy. It forms between 0.1% to 1.8% of all gynaecological cancers diagnosed and the annual incidence of 3.6 per million women in the USA has not changed much in the past years. More than 60% of fallopian tube cancer occurs in post-menopausal women. Predisposing factors have been studied, but there have been no consistent factors identified. However, the similarities in the age group, association with low parity, and frequent infertility status, suggest that the etiology may be similar to ovarian carcinoma. Indeed, studies have demonstrated similar genetic abnormalities as in ovarian cancer, such as c-erb, p53, k-ras mutations, as well as a recent possible association with BRCA 1 and BRCA 2.[1,9,10]

5.3 Screening

Fallopian tube carcinoma is a rare entity. There is no recommendation for screening.[1,4,5,11]

5.4 Diagnosis

5.4.1. Pre-operative

Abnormal vaginal bleeding is the most common presenting complaint and it is present in more than 50% of patients. This may be associated with watery vaginal discharge, vague lower abdominal pain, distention, and pressure. 10% of patients present with *'hydrops tubae profluens'*, a palpable pelvic mass that resolves during examination associated with watery vaginal discharge. More than 50% of patients present with Stage I or Stage II disease, most likely due to its pattern of presentation. Although it has been diagnosed as incidental finding during pap smear and during CA 125 screening (as part of a randomised control trial), Pap smear and CA 125 cannot be recommended as screening modalities. However, CA125, being raised in a significant percentage of patients, acts as an adjunctive to transvaginal ultrasonography, CT or MRI scan.[1,2,4]

The fallopian tubes' close proximity to the ovary and the uterus makes it difficult sometimes to identify the true primary. This is particularly so in the advanced stages. The most widely accepted and therefore most commonly used diagnostic criteria for the diagnosis of primary fallopian tube carcinoma is shown in Table 3. It was first developed by Hu and later modified by Sedlis.[1,4,12,13]

5.4.2. Staging laparotomy

Retrospective analyses have suggested that advanced stages at presentation and the presence of residual tumour at the end of treatment

with chemotherapy are associated with poorer prognosis. Therefore careful surgical staging at presentation is paramount in the treatment of early fallopian cancer. For advanced disease, there should also be optimal removal of the primary tumour and involved adjacent organs.[1-6,8] The following must be performed through a midline incision:

- Careful evaluation of the entire abdomino-pelvic cavity to delineate extent of disease
- Total abdominal hysterectomy and bilateral salpingo-ophorectomy
- Sampling of the pelvic and para-aortic lymph nodes
- Infracolic omentectomy
- Washings of the peritoneal cavity
- Biopsies of any suspicious areas including the abdominal and pelvic peritoneum
- Appendectomy

In the rare event that a patient is young and wishes to retain fertility, limited surgery can be considered for carcinoma in-situ only, after detailed evaluation and careful discussion. However, this limited approach is not encouraged in view of high incidence of bilateral involvement. In established cancer, there is no role for conservative surgery.[1,2,5]

5.5. Clinical Practice Guidelines

5.5.1. Management of fallopian tube adenocarcinoma

Since the first reported case in 1847, there have only been 1,500 cases documented in the literature. Further, retrospective reviews have been hampered with non-uniform clinical and surgical staging, non-central pathological reviews, and lack of diagnostic criteria. As more retrospective reviews were reported, especially after the wide acceptance of the FIGO staging, it became apparent that the histology, prognostic indicators and survival seem to mirror that of ovarian cancer. The only exception seems to be that firstly, stage for stage, patients with early stage fallopian carcinoma has a poorer prognosis. Secondly, that fallopian tube carcinoma had a significant rate of lymph node metastases rate. In view of the similarities with ovarian cancer and the impracticality of performing prospective randomised trials in a relatively rare cancer, the management of fallopian tube carcinoma has been essentially that of ovarian cancer.[1-4-8] Surgical staging, which is extremely pertinent, has been outlined above. The guidelines for post-operative management are also essentially identical to those of ovarian cancer.

5.5.1.1. Chemotherapy regimes

The success of the paclitaxel and platinum combination in ovarian cancer has led to greater usage of this combination in fallopian cancer. Many retrospective reviews seem to suggest that this regime is superior to historical controls using a combination of alkylating agent with platinum. It is therefore the view of many clinicians that chemotherapy for ovarian cancer should be acceptable for fallopian cancer in the absence of prospective studies.[1-4,6-18] For chemotherapy regimes please refer to ovarian cancer regimes.

5.5.1.2. Management of Early disease

5.5.1.2.1. Management of Carcinoma in situ

Patients should undergo laparotomy with resection of the tumour as outlined above. There is no recommendation for adjuvant therapy for carcinoma in-situ of the fallopian tube after primary surgical therapy.[1,2,5]

5.5.1.2.2. FIGO Stage I and Stage II

Patients with early stage disease should undergo surgical staging. Patients with a final histology of adenocarcinoma in situ or Stage I grade I tumour do not require postoperative adjuvant chemotherapy. For all other patients, they should be considered for adjuvant platinum based chemotherapy. Patients whose diagnosis was incidental (i.e. patients who underwent surgery for benign condition, and histology specimen contained malignancy) should undergo repeat surgical staging and optimal debulking should there be residual tumour. These patients should then receive adjuvant platinum based chemotherapy.[1-3,14-18] **Level of Evidence C.**

5.5.1.3. Management of Advanced disease

5.5.1.3.1 FIGO Stage III

All carcinoma is taken to be adenocarcinoma unless otherwise stated

and platinum based chemotherapy regimes are as per ovarian cancer. Patients who have undergone surgical debulking should be considered for adjuvant platinum based chemotherapy.[1-3,14-17] Patients who have not undergone optimal debulk at initial diagnosis because of medical contraindications should receive platinum based chemotherapy followed by re-evaluation. After 3 cycles of chemotherapy, at the time of evaluation, these patients can be considered for second look and secondary cytoreduction should there be any residual tumour. However, this practice has not been validated with any prospective trial in fallopian tube cancer. **Level of Evidence C.**

5.5.1.3.2. FIGO Stage IV

- Patients with distant metastases should have the primary site of disease confirmed histologically.
- As much tumour as possible should be resected at laparotomy, and a symptomatic pleural effusion should be drained preoperatively.
- Patients who are of adequate performance status should receive platinum based chemotherapy, as per ovarian cancer. For other patients too ill to receive chemotherapy, symptomatic treatment should be offered. **Level of Evidence C.**

5.5.2. Management of Choriocarinoma of the Fallopian tube

This entity is extremely rare, but has been reported in tubal pregnancy and also associated with in-vitro fertilisation. Patients should be treated as for uterine choriocarcinoma, which is curable, with primary surgery followed by chemotherapy according to the prognostic factors. In this case, conservative surgery can be considered for limited disease if fertility is to be preserved.[19-21] **Level of Evidence D.**

5.5.3. Management of Germ Cell Tumours of the Fallopian tube

These are extremely rare in the fallopian tube. However, they do occur in young women with fertility potential, and although highly curable, they tend to progress rapidly. Therefore, it is pertinent to diagnose and treat early. Treatment is with primary surgery followed by chemotherapy according to the prognostic factors. Limited conservative surgery should be considered for disease of all stages if fertility is to be preserved. Chemotherapy protocols are as ovarian germ cell tumours.[1,2] **Level of Evidence D.**

5.5.4. Management of Sarcoma of the Fallopian tube

Tubal sarcomas are extremely rare lesions. Most sarcomas histologically are classified as mixed Mullerian tumours. Treatment again is with primary surgery and chemotherapy as per sarcoma of uterine origin.[23-25] **Level of Evidence D.**

5.5.5. Management of miscellaneous rare histologies

The fallopian tube is not exempted from other rare tumours such mucosa related (MALT) lymphoma.[26] Treatment is with primary surgery and systemic chemotherapy. The chemotherapy protocols are directed by the individual histologies. **Level of Evidence D.**

5.5.6. Follow up

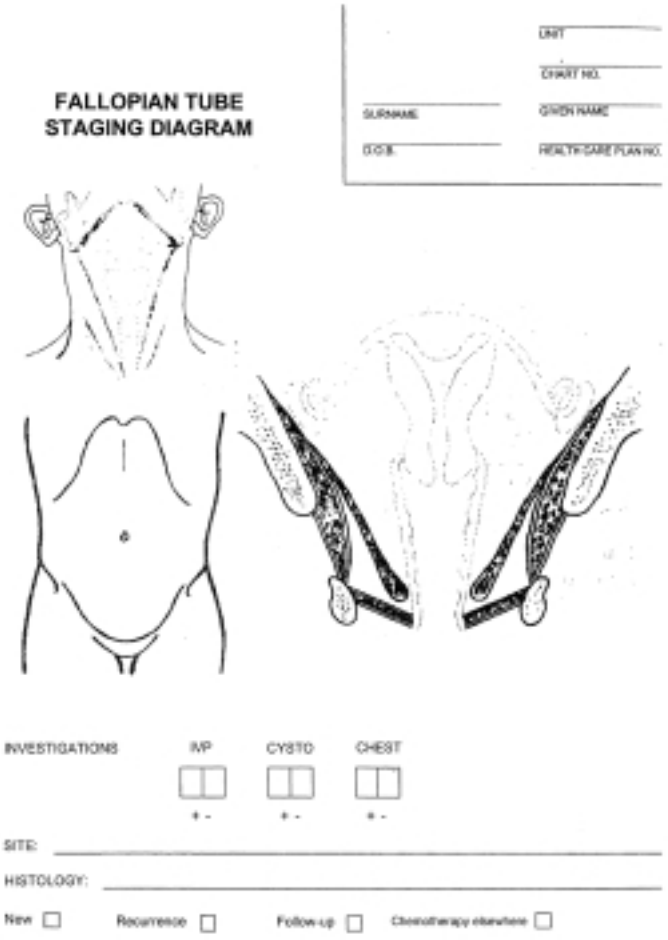
There is no evidence to show that intensive clinical monitoring in asymptomatic women has any positive impact on overall survival or on the quality of life. Nonetheless, early diagnosis of recurrence after a prolonged progression free interval is thought to offer the best results. The objectives of follow up are as follows:

- Determination of the patient's immediate response to the treatment employed;
- Early recognition and prompt management of any treatment-related complications, including any psychological sequelae;
- Early detection of persistent or recurrent disease;
- Collection of data regarding the efficacy of treatment;
- For patients with early disease, to serve as an opportunity for screening for breast cancer, and for patients treated with conservative surgery, to serve as an opportunity for screening for cervical cancer

In general, during the first year following treatment, patients should be seen every three months with a gradual increase in intervals to every four to six months and annually after the fifth year. At each follow up, the patient should have her history retaken; complete physical examination (including breast, pelvic and rectal examination) performed to exclude any clinical signs of recurrence. The serum CA125 titer may also be checked at regular intervals, especially if it was raised at primary diagnosis, although the literature in this area is unclear as to the impact of such a practice on survival. Radiological tests such as ultrasonography of the pelvis, CT scans or MRI scans

should only be performed when the clinical findings or the tumour markers suggest possible recurrence.[5-7] **Level of Evidence D.**

All patients with an intact cervix should receive a regular pap smear. All patients above the age of 40 should undergo a yearly routine mammogram, as should younger patients with a strong family history of breast cancer.



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Cancer of the Ovary

6.1. Staging

6.1.1. Sites of Ovarian Cancer

6.1.1.1 Primary site

The ovaries are a pair of solid oval-shaped organs, 2-4 cm in diameter, that are connected by a peritoneal fold to the broad ligament and by the infundibulopelvic ligament to the lateral wall of the pelvis.

6.1.1.2. Nodal drainage

The lymphatic drainage occurs by the utero-ovarian, infundibulopelvic, and round ligament trunks and an external iliac accessory route into the following regional nodes: external iliac, common iliac, hypogastric, lateral sacral, para-aortic nodes and, occasionally, to the inguinal nodes.[1,5]

6.1.1.3. Metastatic sites

The peritoneum, including the omentum and pelvic and abdominal viscera, is the most common site for seeding. This includes the diaphragmatic and liver surfaces. Pleural involvement is also frequent. Other extra peritoneal or extra pleural sites are relatively uncommon but can still occur.[1,5]

6.1.2. Rules for classification

Although CT scans can delineate the intra-abdominal spread of disease to a certain extent, ovarian cancer should be staged surgically. There should be histological confirmation of the disease. Operative findings, prior to tumour debulking, determine the stage and therefore the prognosis of the patient.[1,5,8]

Chest X-rays serve as a screen for pleural metastases. As extra-pulmonary and extra-peritoneal metastases are infrequent, there is no requirement for other radiological evaluation unless symptomatic. Serum CA 125 titer are useful in determining response to chemotherapy, although it is does not contribute to staging.

6.1.2.1. Evaluation of surgical staging

If the pre-operative suspicion is malignancy, the laparotomy should

be performed via a midline incision. The following should be performed for adequate staging:[1,8]

- Careful evaluation of all peritoneal surfaces
- 4 washings of the peritoneal cavity: diaphragm, right and left abdomen, pelvis
- Infracolic omentectomy
- Selected lymphadenectomy of the pelvic and para-aortic lymph nodes
- Biopsy and/or resection of any suspicious lesions, masses and any adhesions
- Random blind biopsies of normal peritoneal surfaces, including that from the undersurface of the right hemidiaphragm, bladder reflection, cul-de-sac, right and left paracolic recesses, and both pelvic sidewalls
- Total abdominal hysterectomy and bilateral salpingo-oophorectomy
- Appendectomy for mucinous tumors

6.1.2.2. Postsurgical treatment – pathologic staging

The biopsies taken as outlined above would form the basis of staging. However, any other suspicious area, such as pleural effusion, and rare but obvious involvement of extra pulmonary or pleural and extra peritoneal sites must be biopsied.[1,8]

6.1.2.3. Federation of Gynecologists and Obstetrics (FIGO) staging

The most commonly utilised staging system is the FIGO system modified in 1988. It is based on findings made mainly through surgical exploration as outlined above. See Table A for the complete FIGO staging.[1,3,4] However, it is also useful to be aware of the equivalents within the UICC TMN classification (See Table 1, and Table 2)

Table 1: Carcinoma of the ovary-Staging

FIGO		TNM
	Primary Tumour cannot be assessed	TX
0	No evidence of primary tumour	T0
I	Tumour confined to ovaries	T1
IA	Tumour limited to one ovary, capsule intact No tumour on ovarian surface No malignant cells in the ascites or peritoneal washings	T1a
IB	Tumour limited to both ovaries, capsules intact No tumour on ovarian surface No malignant cells in the ascites or peritoneal washings	T1b
IC	Tumour limited to one or both ovaries, With any of the following Capsule ruptured, tumour on ovarian surface, Positive malignant cells in the ascites or positive peritoneal washings	T1c
II	Tumour involves one or both ovaries with pelvic extension	T2
IIA	Extension and/ or implants in uterus and/or tubes No malignant cells in the ascites or peritoneal washings	T2a
IIB	Extension to other pelvic organ No malignant cells in the ascites or peritoneal washings	T2b
IIC	IIA/B with positive malignant cells in the ascites or positive peritoneal washings	T2c
III	Tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph nodes metastasis	T3 and/or N1
IIIA	Microscopic peritoneal metastasis beyond the pelvis	T3a
IIIB	Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension	T3b
IIIC	Peritoneal metastasis beyond pelvis more than 2cm in greatest dimension and/or regional lymph nodes metastasis	T3c and/or N1
IV	Distant metastasis beyond the peritoneal cavity	M1

Note: Liver capsule metastasis is T3/ Stage III, liver parenchymal metastasis M1/ Stage IV. Pleural effusion must have positive cytology.

Table 2: Carcinoma of the ovary – Stage grouping

FIGO Stage	T	UICC N	M
IA	T1a	N0	M0
IB	T1b	N0	M0
IC	T1c	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
IIC	T2c	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC	T3c	N0	M0
	Any T	N1	M0
IV	Any T	Any N	M1

Regional Nodes (N)

Nx Regional lymph nodes cannot be assessed
N0 No Regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastasis (M)

Mx Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis (excluding peritoneal metastasis)

6.1.3. Histopathologic classification

Majority of ovarian cancer is of the epithelial origin. The task forces of FIGO endorse the histological typing of epithelial ovarian tumours as presented in the WHO publication n.9 in 1971. It is recommended that all ovarian epithelial tumours be subdivided according to a simplified version.[2]

Epithelial ovarian neoplasms are classified as follows:

- Serous tumours
- Mucinous tumours
- Endometrioid tumours
- Clear cell tumours
- Brenner tumours
- Undifferentiated carcinomas
  - This group of malignant tumours is of epithelial structure but

they are too poorly differentiated to be placed in any other group.

- Mixed epithelial tumours
  - These tumours are composed of two or more of the five major cell types of common epithelial tumours. The types are usually specified.
- Cases with intraperitoneal carcinoma in which the ovaries appear to be incidentally involved and not the primary origin should be labelled as extra-ovarian peritoneal carcinoma.

Epithelial tumours of the ovary are also further subclassified by grading. This is important because histological grading is proportional to prognosis. This grading system does not apply to non-epithelial tumours.

- Gx – Grade cannot be assessed
- G1 – Well differentiated
- G2 – Moderately differentiated
- G3 – Poorly differentiated

Non-epithelial malignancy, although more uncommon, is also extremely important. These include granulosa cell tumours, germ cell tumours, sarcomas and lymphomas. They shall be discussed as separate entities.

6.2. Introduction

Malignant tumours of the ovaries occur at all ages. Major histologic types occur in different age groups. For women less than 20 years old of age, germ cell tumours constitute the majority of cases while epithelial ovarian cancers (EOC) are primarily seen in women older than 50 years.

EOC is a relatively common disease in the USA. The lifetime risk of a woman in the United States to develop ovarian cancer is approximately 1 in 70. Approximately 23% of gynaecologic cancers are ovarian in origin, but 47% of all deaths from cancer of the female genital tract occur in women with ovarian cancer. Overall, epithelial ovarian cancer accounts for 4% of all new cancer diagnoses and 5% of all cancer related death.

The overall incidence of EOC varies from 9 to 17/100,000 and is the highest in industrialised countries with the exception of Japan. However, this incidence rate increases proportionately with age. The

largest number of patients with epithelial ovarian cancer is found in the age group 60-64.

Established risk factors for EOC are essentially reproductive and genetic in nature. Women who have never had children are twice as likely to develop this disease. High risk has also been associated with women of low parity. First pregnancy at an early age, early menopause and the use of oral contraceptives have been associated with lower risks of ovarian cancer.[1]

EOC is a clonal disease that arises from a single cell in more than 90% of cases. Multiple genetic changes must occur in the ovarian surface epithelium (OSE) to produce malignant transformation. Repeated rupture and repair (ovulation) of the OSE provides this opportunity for genetic aberrations. Hereditary factors are implicated in approximately 5% of all ovarian cancers. So far, the syndromes that have been identified are:[6-7]

1. The Breast-Ovarian Cancer Syndrome, linked to an inherited mutation in the BRCA 1 and the BRCA 2 genes (site-specific Ovarian Cancer Syndrome);
2. Type II Lynch Syndrome, which also includes colon, breast, endometrial and prostate cancer in affected individuals.

6.3. Screening

To date no cost effective screening program for any ovarian cancer has been established. Studies using CA 125, ultrasonography of the pelvis and pelvic examination have not produced an acceptable level of sensitivity and specificity in women of normal risks. Patients with a strong family history of epithelial ovarian cancer, especially of the syndromes described above, should consult a genetic counselor to stratify their risks, and when appropriate, be placed on prospective screening trials.[1] Presently there are no screening studies for non-EOC.

6.4. Diagnosis

The success of treatment depends on early diagnosis. However, the ability to achieve early diagnosis remains an unsolved problem. The clinician must be mindful of the different neoplasms that occur in different age groups in order to have a high index of suspicion. Borderline tumours occur most commonly in the perimenopausal age

group. For younger patients, tumour markers such as human gonadotropin (hCG) and a-fetoprotein (AFP) are mandatory to exclude germ cell tumours.

EOC in its early stages does not usually produce symptoms or signs that would alert the clinician to this diagnosis. Approximately two-thirds of all EOC are Stage III or Stage IV at diagnosis. Symptoms that include vague abdominal pain or discomfort, menstrual irregularities, dyspepsia and other mild digestive disturbances, which may only be been present for a few months, is usually the presenting complaint. Therefore, a high index of suspicion is required for all women between the ages of 40 to 69. As the disease progresses, the ascites, abdominal distention and discomfort generally worsen and may be associated with respiratory symptoms from increased intra-abdominal pressure or from the transudation of fluid into the pleural cavities. Abnormal uterine or vaginal bleeding is uncommon as a symptom or sign of disease.

A detailed medical history must be taken to ascertain possible risk factors, history of other cancers and history of cancer in the family. Then a complete physical examination, including breast, pelvic and rectal examination must be performed. A pap smear is also usually performed at the same time.[1]

Prior to surgery a chest radiograph should be taken to screen for pulmonary and pleural metastases while a CT scan of the abdomen and pelvis should be performed to delineate the extent of intra-abdominal disease or the presence of another primary. However, in the absence of extra-abdomino-pelvic disease, radiological scanning does not replace surgical staging with laparotomy. Barium enema is also indicated should symptoms suggest possible bowel cancer. Tumour markers should including CA 125 and carcinoembryonic antigen (CEA) should be considered. With a high CA 125, the most common diagnosis would be EOC. However, a stomach or colon primary can, in advanced metastatic stages, mimic ovarian cancer. A current mammogram should also be considered as patients are frequently in the age group where breast cancer is prevalent.

6.4.1. Staging laparotomy and surgical management

Generally, the prognosis of all ovarian tumours are independently affected by the following:[1,9,14]

- Stage of the cancer at diagnosis;
- The histological subtype and grading;
- The volume of residual disease

Of the three, the most important are the stage and the volume of residual disease. This holds true regardless of the histological diagnosis.

A thorough staging laparotomy is therefore the most important part of early management. Upon entering the abdominopelvic cavity through a midline incision, the peritoneal fluid should be sent for cytology. In the absence of ascites, irrigation should be performed and washings should be sent for cytology.

The laparotomy should then proceed with a detailed examination of the contents including all the peritoneal surfaces. In addition to all the suspicious sites, random biopsies from the peritoneal reflection of the bladder, the posterior cul-de-sac, both paracolic gutters, subdiaphragmatic surfaces and both pelvic sidewalls should be taken. The primary tumour, if limited to the ovary, should be examined to look for capsular rupture. All obvious sites of tumour must be removed wherever possible in addition to total hysterectomy and bilateral salpingo-oophorectomy. Further, the omentum, pelvic and para-aortic lymph nodes should also be removed for histological examination. This procedure allows for accurate staging of early disease and has the objective of optimal debulking of advanced disease.

In younger women fertility is an issue. In these patients, the prognosis according to the extent of the tumour should be discussed, and conservative surgery can be considered with informed consent.[1, 15] Conservative surgery should require the following:

- Laparotomy assessment as outlined above in section 6.1.2.1, except total hysterectomy and bilateral salping-oophorectomy;
- Intraoperative finding of unilateral ovarian involvement with capsule intact (stage Ia);
- Normal examination of the opposite ovary (without wedge biopsy)

Only then, conservative surgery can preserve the intact ovary and the uterus for future reproduction.

6.5. Clinical Practice Guidelines

6.5.1. Management of patients in the reproductive age group with a suspicion of cancer diagnosis

Clinical judgement is a major factor in surgical decision-making and this is the most pertinent in the approach to a pelvic mass in the young, reproductive age group of women. In the past, the options are essentially limited to either laparotomy with assessment and removal, or observation; the latter being assisted with regular pelvic ultrasonography. The advancement in laparoscopic technique has provided another option for evaluation and potential treatment.

However, if the suspicion is strong for malignancy, open laparotomy is indicated. In the presence of good surgical skills, laparoscopy is more appropriate if the suspicion is more for benign disease in a young lady, where the tumour markers (including human gonadotropin and a-feto protein) are normal.

The following factors, which point to the presence of a malignancy, are useful in the clinical assessment of masses and can serve as a guide but it is by no means comprehensive:

- Age of the patient (young for germ cell, older for EOC)
- Bilaterality
- Fixed or solid masses
- Ascites
- Ultrasonographic finding of complex masses in the ovary
- CT finding of metastatic nodules
- Elevated tumour markers

The subsequent management of the patient should then match the postoperative diagnosis.[1]

6.5.2. Management of epithelial ovarian cancer (EOC)

6.5.2.1. Early stage

About a quarter of patients will present with apparent Stage I or Stage II disease. Although the preliminary radiological findings may seem to corroborate with clinical findings of early disease, it is imperative that these patients still undergo a thorough surgical staging. The details of the staging laparotomy have been outlined above. For patients with obviously limited disease (Stage Ia), who desire to retain their reproductive potential, a wedge biopsy of the contralateral unaffected ovary is not recommended as it can affect the subsequent fertility.

The prognosis of adequately staged patients with Stage Ia and Stage Ib Grade I cystadenocarcinoma is extremely good such that adjuvant chemotherapy would not provide further benefits. For higher grade tumours and for patients with Stage Ic, adjuvant platinum based chemotherapy should be considered, although this practice remains controversial. All patients with Stage II disease should receive adjuvant chemotherapy. The number of cycles of chemotherapy has also not been clarified but usually between 3-6.[1,11-13] **Level of Evidence A.**

6.5.2.2. Advanced stage

Three quarters of all patients with ovarian cancer present with Stage III or IV disease. In these patients, they are usually quite symptomatic from the intra-abdominal disease. This may affect the performance status and fitness for surgery. However, as mentioned above, one of the most critical prognostic indicators in patients with advanced stage ovarian cancer is the volume of residual disease. Therefore, all patients whose medical condition and fitness for surgery permits should undergo primary surgical laparotomy with maximal attempt at optimal cytoreduction.[1,8]

In certain patients whose primary cytoreduction is considered suboptimal, interval debulking may be considered after three cycles of systemic chemotherapy.[1,18] This also applies to patients who could not, in lieu of physical fitness, undergo primary cytoreduction prior to chemotherapy.

Patients who have had cytoreduction should receive adjuvant chemotherapy.[1,17] For systemic chemotherapy, a combination of a paclitaxel or docetaxel with carboplatin is the first choice. Docetaxel is considered because of its favourable neurotoxicity profile.[19] See 6.5.2.3. for chemotherapy regimes.

At the end of six cycles of chemotherapy, maintenance chemotherapy with paclitaxel has been shown to improve disease free interval but not overall survival.[25] However, this treatment must only be offered if a patient achieves complete response to treatment, and understands the aim of treatment and its potential toxicities.

The role of intraperitoneal chemotherapy remains controversial. The results for the current Gynecologic Oncology Group trial con-

cerning frontline intra-peritoneal chemotherapy are pending. **Level of Evidence A.**

6.5.2.3. Chemotherapy for EOC

The following chemotherapy regimes are recommended for the treatment of ovarian cancer:[16,19,20]

- Paclitaxel 175mg/m^2 over 3 hours/ Carboplatin AUC 6 over 1 hour
- Docetaxel at 75m/m^2 over 1 hour/ Carboplatin AUC 5 over 1 hour

For the above two regimes the dose of the carboplatin is based on Calvert's formula using creatinine clearance calculated with the mathematical formula, not using the EDTA method.

The following chemotherapy schedules can also be considered:

- Paclitaxel 135mg/m^2 over 24 hours/ Cisplatin 75mg/m^2 over 6 hours
- Paclitaxel 175mg/m^2 over 3 hours/ Cisplatin 75mg/m^2 over 6 hours

6.5.2.4 Consideration for second look operation

There have been many trials studying the benefits of second look operations. Patients who had residual disease at the end of chemotherapy treatment seem to benefit from second look surgery while patients who were optimally debulked at initial diagnosis did not benefit. This strategy in the management of advanced ovarian cancer is therefore not considered standard.[21-24] Patients should be offered second look laparotomy only as part of eligibility criteria for clinical trials. **Level of Evidence C.**

6.5.2.5 Follow up for malignant EOC

There is no evidence to show that intensive clinical monitoring in asymptomatic women has any positive impact on overall survival or on the quality of life. Nonetheless, early diagnosis of recurrence after a prolonged progression free interval is thought to offer the best results. The objectives of follow up are as follows:

- Determination of a patient's immediate response to the treatment employed;
- Early recognition and prompt management of any treatment-related complications, including any psychological sequelae;
- Early detection of persistent or recurrent disease;

- Collection of data regarding the efficacy of any treatment and the complications associated with those treatments;
- For patients with early disease, to serve as an opportunity to screen for breast cancer, and for patients treated with conservative surgery, to serve as an opportunity for screening for cervical cancer

In general, during the first year following treatment, patients should be seen every three months with a gradual increase in intervals to every four to six months and annually after the fifth year. At each follow up, the patient should have her history retaken; complete physical examination (including breast, pelvic and rectal examination) performed to exclude any clinical signs of recurrence. The CA125 may also be checked at regular intervals. It is unclear as to the utility of such a practice on survival impact.[10] Radiological tests such as ultrasonography of the pelvis, CT scans or MRI scans should only be performed when the clinical findings or the tumour markers suggest possible recurrences. **Level of Evidence C.**

All patients with intact cervix should receive a regular pap smear. All patients above the age of 40 should undergo a yearly routine mammogram, as should younger patients with a strong family history of breast cancer. **Level of Evidence A.**

6.5.2.6 Management of relapsed EOC

The majority of patients treated for advanced EOC will unfortunately relapse. Many studies have looked at stratifying these patients for treatment. It is evident from these data that patients who had a disease free interval of at least 6 months can be considered platinum sensitive patients. Patients whose disease free interval is less than 6 months can be considered platinum refractory. Trials have also shown that the longer the platinum free interval, the higher the response rate to further platinum, as well as non platinum treatment.[1,26]

For patients who are considered platinum sensitive there are two options. One option is to enroll in clinical trials looking at enhancing the efficacy of carboplatin treatment with other cytotoxics or non-cytotoxic agents. The other option is to receive single agent carboplatin or cisplatin. The favourable toxicity profile of carboplatin makes it a more preferred choice. There are no randomised studies to

suggest combination therapy is superior to single agent platinum in terms of overall survival.

Patients with localised recurrences after a long disease free interval may benefit from a secondary cytoreduction. Repeat cytoreduction for this group of patient has hitherto been controversial. A recent Gynecologic Oncology Group trial studying the strategy of repeat cytoreduction versus no repeat cytoreduction for patients with long disease free interval, prior to chemotherapy has been completed. Results are awaited.

For patients who are considered platinum refractory there are also two options. The first option is to enroll in available clinical trials. The second option is further non-platinum chemotherapy. There are quite a number of choices for chemotherapy: liposomal doxorubicin[27]; topotecan[27]; etoposide[28,29] and gemcitabine[30,31] have all shown a response ranging between 10-15%, either as a single agent or in combination. The hitherto lack of quality of life and palliative index measurements in salvage chemotherapy treatment of these patients makes it difficult to recommend the best option. It is important to bear in mind the function of the bone marrow in the dosing of chemotherapy in patients who have had many lines of chemotherapy.

The optimal management of a patient with refractory ovarian cancer requires a careful assessment the patient's physical, mental and spiritual condition. It is pertinent to identify any physical condition that may immediately affect this patient's survival or quality of life so that adequate appropriate treatment can be given. Such physical conditions include systemic infections, intestinal obstruction, ascites, pleural effusion, and unusual metastases to organs such as the brain, liver or bone.

The treatment of an asymptomatic patient with recurrent disease based on tumour marker alone is difficult. Close observation or hormonal therapy with agents such as Tamoxifen can be considered.[32]

It is important that the patient understands that chemotherapy responses do not necessarily translate into meaningful survival prolongation. Often improvement in quality of life and optimisation of functionality become the goals of treatment. Any therapy that may compromise the latter goals may not be justified. At these difficult times, it is of utmost importance to involve the patient's friends, family and loved ones in the decision-making. **Level of Evidence C.**

6.5.3 Management of epithelial cancer of low malignant potential (borderline tumour)

Compared to obviously malignant neoplasms, these borderline tumours tend to affect a younger population. They constitute 15% of all EOC. Nearly 75% of these are Stage I at the time of diagnosis. The following can be said for these tumours:

- The diagnosis must be based on the original tumour
- Extensive sectioning of the neoplasm is necessary to rule out truly invasive characteristics.
- The prognosis of these tumours is extremely good, with a 10- year survival of about at 95%
- Lesions that behave in a malignant fashion usually have an indolent course
- There are occasional spontaneous regression of peritoneal implants
- Early stage, serous histology, and younger age patients at diagnosis are associated with a more favourable prognosis
- Although gross residual disease after primary laparotomy is associated with poorer prognosis, mortality from the disease remains unusual

The cause of death has been determined to be benign complications of disease (e.g., small bowel obstruction), complications of therapy, and only rarely malignant transformation. The mainstay of treatment is primary surgical staging and cytoreduction. For patients with Stage I disease that still desire to have children, and who have stage I disease, conservative surgery with unilateral oophorectomy can be considered after intra-operative inspection of the contralateral ovary to exclude involvement. For patients with only one ovary, or bilateral cystic ovaries, a partial oophorectomy can be considered to retain fertility. For all other patients, total hysterectomy and bilateral salpingo-ophorectomy is recommended with maximal cytoreduction.

Optimally cytoreduced patients in all stages of disease should receive only expectant treatment without adjuvant chemotherapy, provided the metastases are also borderline tumours histologically. There have been no prospective studies that suggest benefit of adjuvant chemotherapy. A small percentage of patients may benefit from chemotherapy. These are patients in whom the histological specimens reveal of invasive implants or the peritoneal surfaces or omentum.

Patients who develop a rapid recurrence of intraperitoneal disease require chemotherapy. Such patients probably had undetected invasive cancers.

For patients with slow recurrence of the disease, especially after a long disease free interval, it is widely practised to repeat optimal cytoreduction and post-operative observation, leaving chemotherapy for only the seemingly rapidly progressing tumours.

Follow up of patients with no evidence of disease is as those of malignant EOC, but less frequent intervals are appropriate. If the contralateral ovary has been retained, it should be followed by transvaginal ultrasonography, at least on an annual basis.[1,33-35] **Level of Evidence C.**

6.5.4 Management of granulosa cell tumour

Granulosa cell tumours account for about 70% of sex-cord stromal tumours, and 3-5 % of all ovarian neoplasm. There are two types of granulosa cell tumour: the juvenile and the adult type. Due to the high oestrogen production, the juvenile type presents with sexual preciosity, while the adult type may present with postmenopausal bleeding. Because the presenting symptoms are usually prominent, and the tumours are usually slow growing, the majority of patients are diagnosed with Stage I disease. The peak incidence is in the first postmenopausal decade.

The nature of these tumours, like those of borderline tumours, is generally slow growing with a tendency to late recurrence. Stage at diagnosis is the most important prognostic indicator. Others of significance include age of patient, tumour size, and histological features. It follows then, that, again like most ovarian tumours, adequate cytoreduction is the mainstay of treatment. However, again since we see this tumour in patients with reproductive potential, conservative surgery can be considered for limited Stage I disease.

The infrequency of disease, and its protracted course has resulted in the lack of prospective studies. There is no evidence that adjuvant chemotherapy or radiotherapy improves the results obtained with good surgery alone for Stage 1 disease. However, some clinicians advocate adjuvant chemotherapy for Stage II and Stage III disease[36]. This strategy is based on small studies. It is recommended that should there be a clinical trial, patients should be enrolled.

Follow up is clinical. Further studies are required to confirm if inhibin is a useful tumour marker. **Level of Evidence C.**

6.5.5 Management of Germ cell tumours

6.5.5.1 Introduction

This group of ovarian tumours consists of a variety of histologically different entities that are all derived from the primitive germ cells of the embryonic gonad. Malignant germ cell tumours represent a relatively small proportion of all ovarian tumours. Prior to advances in chemotherapy, the prognosis for these aggressive tumours was poor. Over the past decade, new chemotherapeutic regimes have made germ cell tumours among the most highly curable cancers.

6.5.5.2 Presentation

The highest incidence of germ cell tumour occurs in the second and the third decades of life. It is frequently diagnosed by finding a palpable abdominal mass in a young lady who complains of abdominal pain. The following are the symptoms of germ cell tumours in order of frequency:[37]

- Acute abdominal pain
- Chronic abdominal pain
- Asymptomatic abdominal mass
- Abnormal vaginal bleeding
- Abdominal distention

6.5.5.3 Histological Classification

The classification of germ cell tumours of the ovary is important for prognostication and for treatment with chemotherapy. Germ cell tumours are simply classified as below:[2]

- Germ cell tumours
  - Dysgerminoma
  - Non-dysgerminoma (Embryonal cancer)
    - Embryonal differentiation
      - Mixed
      - Mature
      - Immature
    - Extraembryonal differentiation
      - Choriocarcinoma

– Endodermal sinus tumour (yolk sac tumour)
– Extraembryonal carcinoma

6.5.5.4 Diagnosis, staging and surgical management
Germ cell tumours are staged the same as epithelial ovarian cancer. The treatment is dependent not only on the stage. Dysgerminoma is the equivalent of seminoma in testicular cancer. It is exquisitely chemotherapy and radiotherapy sensitive. The cure rate is high irrespective of the stage of the neoplasm. The other histologies are really equivalent to non-seminomas in testicular cancer. The aggressiveness of the disease is dependent on the type, the most aggressive being endodermal sinus and choriocarcinoma. With chemotherapy, they are also highly curable.[37,38,39,44,45]

As chemotherapy can cure the majority of patients even with advanced disease, conservative surgery is standard in all stages of all germ cell tumours. By conservative surgery, it means full laparotomy with careful examination and detailed biopsies of all suspicious area with limited cytoreduction thereby avoiding major morbidity. The uterus and the contralateral ovary intact if they are normal. Only then, can the patient be considered adequately staged and properly prognosticated. Wedge biopsy of a normal ovary is not recommended as it defeats the purpose of conservative therapy by causing possible infertility. Patients who received conservative surgery with the preservation of one ovary may retain acceptable fertility rates despite adjuvant treatment with chemotherapy. There has also been no report of higher adverse obstetric outcome or long-term unfavourable sequelae in the offspring.[37,46,47,48,49]

Second look surgery is of no proven benefit except in a minority of patients whose tumour was not completely resected at the initial surgical procedure and who had teratomatous elements in their primary tumour. Surgical resection of residual masses detected by clinical examination or by radiographic procedures may be beneficial as such masses may contain mature teratoma or residual tumour.[37,41,42,43]

6.5.5.5 Post operative management and follow up of dysgerminoma
Patients with Stage Ia disease may be observed after surgery. A small portion of patents may recur, but they can be treated successfully at the time of recurrence with a high rate of cure.[37] This applies to

patients who have been completely staged. Incompletely staged patients with presumed Stage Ia disease or those with higher stage disease should receive adjuvant chemotherapy treatment. For any stage beyond Stage Ia, chemotherapy should be given. Radiotherapy for early stages is probably as effective as an adjuvant treatment but concerns with ovarian failure makes it undesirable for patients with an intact ovary. However, for patients with any contraindication for chemotherapy, radiotherapy remains an effective option.

Dysgerminoma is extremely sensitive to chemotherapy, and treatment with chemotherapy cures the majority of patients even with advanced disease. The recommended chemotherapy regime is etoposide 100mg/m2 per day for 5 days with cisplatin 20mg/m2 per day for 5 days, with or without bleomycin at 10U per day for day 1/8/15 (EP or BEP; various schedules of bleomycin are utilised). When there is bulky residual disease, it is common to give 3 to 4 courses of combination BEP chemotherapy. As BEP chemotherapy is associated with a lower relapse rate and shorter treatment time[38], it is preferred compared to an older regime VAC[39], a combination of vincristine, dactinomycin, and cyclophosphamide given in an adjuvant setting. Other tested chemotherapy regimes include combinations of ifosfamide and doxorubicin; vinblastine, ifosfamide and cisplatin; cyclophosphamide, doxorubicin and cisplatin. All patients who do not respond to standard therapy are candidates for clinical trials. **Level of Evidence B.**

All patients should have lactate dehydrogenase (LDH) and human gonadotropin (bHCG) performed as to monitor the treatment. All patients treated with chemotherapy may be followed up with medical history, physical examination and tumour markers (LDH, bHCG) every 1-2 monthly for year 1, every 2 months for year 2, every 3 months for year 3, every 4 months for year 4, every 6 months for year 5, and once a year subsequently. Although tumour markers are important, radiological imaging is also pertinent, especially for patients whose tumour markers were not raised at diagnosis. CT scans should be performed as clinically indicated.

Patients who did not receive chemotherapy should be followed up more closely. 90% of relapse in patients treated with chemotherapy usually occurs within the first two years after primary diagnosis. At

relapse, these patients can be successfully treated.[37] **Level of Evidence D.**

6.5.5.6 Post operative management and follow up of non-dysgerminoma

With chemotherapy, these tumours are also highly curable, even with advanced disease. Patients with Stage Ia Grade I immature teratoma, or mature teratoma have very good prognosis and should only be observed after primary conservative surgery. Patients with Stage I Grade II immature teratoma also have very good prognosis. It is controversial whether adjuvant chemotherapy adds any further overall survival benefit in this subgroup of patients. All other patients with higher stage and higher-grade tumours should receive postoperative adjuvant chemotherapy.[37]

The recommended chemotherapy regime is etoposide 100mg/m2 per day for 5 days with cisplatin 20mg/m2 per day for 5 days, with or without bleomycin at 10U per day for day 1/8/15 (EP or BEP; various bleomycin schedules are utilised). When there is bulky residual disease it is common to give 3 to 4 courses of combination chemotherapy and 2 additional courses after achieving serological remission. As BEP chemotherapy is associated with a lower relapse rate and shorter treatment time[38], it is preferred compared to an older regime VAC,[39] a combination of vincristine, dactinomycin, and cyclophosphamide given in an adjuvant setting.

Patients who do not respond to BEP may still attain a durable remission with cisplatin/vinblastine/ifosfamide (VIP) as salvage therapy.[40] Newer potential treatments include an ifosfamide combination or high-dose chemotherapy and autologous marrow rescue. Although the role of secondary cytoreductive surgery for patients with recurrent or progressive ovarian germ cell tumours remains controversial, it may have some benefit for a select group of patients, particularly those with immature teratoma. After maximal effort for surgical cytoreduction, chemotherapy should be considered. All patients who do not respond to standard therapy are candidates for clinical trials. **Level of Evidence B.**

All patients should have lactate dehydrogenase (LDH), a-feto protein (AFP), and human gonadotropin (bHCG) performed as to monitor the

treatment. All patients treated with chemotherapy should be followed up with medical history, physical examination and appropriate tumour markers every 1-2 month for year 1; every 3 months for year 2; every 4 months for year 3; every 4 months for year 4; 6 monthly for year 5; and yearly subsequently. CT scans should be performed as clinically indicated.

Patients who did not receive chemotherapy should be followed up more closely. Relapses in patients usually occur within the first two years after diagnosis.[37] **Level of Evidence D.**

6.5.6 Management of Sarcoma of the Ovary

Primary sarcoma of the ovary is a rare entity that occurs primarily in post menopausal patients. Nevertheless, an accurate diagnosis and differentiation from other types of primary ovarian cancer is important, as the prognosis is generally poor. There are two types of sarcoma. Mixed mullerian tumours (MMTs), the more common of the two are defined by the presence of both carcinomatous and sarcomatous components. Pure sarcomas are rarer. They can be categorised as stromal cell sarcomas, fibrosarcomas, leiomyosarcomas, neurofibrosarcomas, rhabdomyosarcomas, chondrosarcomas, angiosarcomas, and liposarcomas.

Patients with early stage disease have survival advantage compared to those with advanced stage disease. The role of histological subtype and residual disease as prognostic indicators are controversial, although many studies suggest that larger volume of residual disease is associated with shorter survival. Different chemotherapeutic regimes have been reported with wide ranging response rates. Platinum based regimes seem to have the better outcome compared to non-platinum regimes. The overall prognosis remains poor. The rarity of this entity prohibits any prospective randomised trials to test the efficacy of any treatment strategy.

Despite the absence of more concrete data it is still recommended that patients with ovarian sarcomas undergo complete surgical staging with optimal cytoreduction if possible. In the absence of a trial of adjuvant chemotherapy, patients should receive platinum based chemotherapy postoperatively.[50]

The follow up schedule is recommended as for EOC. However, the

benefit of surveillance with CA 125 is unknown. **Level of Evidence C.**

6.5.7 Management of Primary Lymphoma of the Ovary (POL)

Primary lymphoma of the ovary is also rare. The majority of lymphomas that involves the ovary usually do so as part of a systemic disease. Therefore, when the diagnosis of ovarian lymphoma is made it is pertinent to exclude systemic disease. Fox and Langley had proposed a three point diagnostic criteria making this entity even rarer. The criteria are as follows:

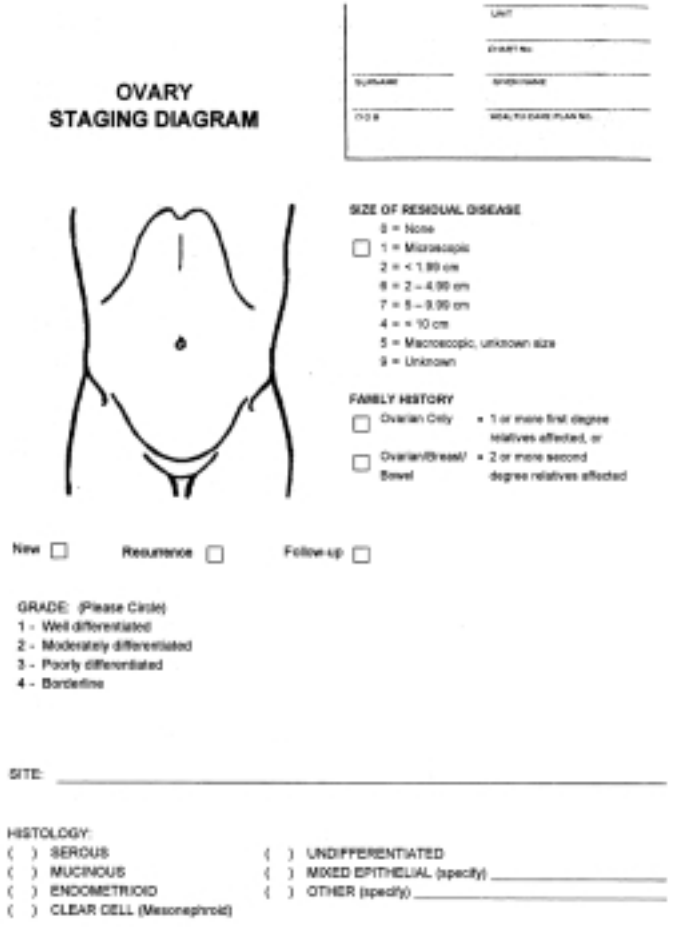
- At the time of the diagnosis, the lymphoma is clinically confined to the ovary and full investigations fail to reveal evidence of lymphoma elsewhere. A lymphoma can still be considered as ovarian primary if spread has occurred to immediately adjacent lymph nodes or if there has been direct spread to infiltrate immediately adjacent structures
- The peripheral blood and bone marrow should not contain any abnormal cells
- If further lymphomatous lesions occur at sites remote from the ovary then at least several months should have lapsed between the appearance of ovarian and extraovarian lesions.

Recent studies have shown that benign lymphoid tissue can be found in up to 50% of normal ovaries. It is therefore possible that POL may have arisen from malignant transformation of these benign aggregates. POL has a propensity to metastasize to the contralateral ovary and intraperitoneally. Diagnosis requires excisional or incisional biopsy following by appropriate fixation to allow accurate subclassification. Fine needle biopsies of masses will not be adequate for this purpose. Diffuse large cell non Hodgkin's lymphoma has been reported to be the commonest subtype although the rarity of POL as a whole prohibits a detailed understanding of the significance of the subclassifications.

One entity that demands greater attention is ovarian involvement in Burkitts lymphoma in countries where Burkitts disease is endemic. Enlargement of one or both ovaries is the second most common form of presentation after involvement of the jaw.

Treatment of POL after surgical removal is no different from treatment of lymphoma elsewhere in the body. It requires systemic

chemotherapy according to the histological subtype. Such patients should be managed and followed up in conjunction with hemato-oncologists. Prognosis is usually good, depending on the histological subtype.[51-52] **Level of Evidence D.**



OVARY
STAGING DIAGRAM

UNIT
SURNAME
FORENAME
D.O.B.

SIZE OF RESIDUAL DISEASE
0 = None
1 = Microscopic
2 = < 1.99 cm
6 = 2 – 4.99 cm
7 = 5 – 9.99 cm
4 = > 10 cm
5 = Macroscopic, unknown size
9 = Unknown

FAMILY HISTORY
Ovarian Only
Ovarian/Breast/ Bowel
= 1 or more first degree relatives affected, or
= 2 or more second degree relatives affected

New ☐ Recurrence ☐ Follow-up ☐

GRADE: (Please Circle)
1 - Well differentiated
2 - Moderately differentiated
3 - Poorly differentiated
4 - Borderline

SITE: _____

HISTOLOGY:
( ) SEROUS
( ) MUCINOUS
( ) ENDOMETRIOID
( ) CLEAR CELL (Mesonephroid)
( ) UNDIFFERENTIATED
( ) MIXED EPITHELIAL (specify) _____
( ) OTHER (specify) _____

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Trophoblastic Disease

7.1 Introduction

Before 1969 metastatic choriocarcinoma was nearly invariably fatal, whereas most patients are now cured and usually retain reproductive function. The basis for this dramatic change is earlier diagnosis, the ability to precisely measure human chorionic gonadotrophin (hCG) and the availability of effective chemotherapy. Trophoblastic disease needs to be treated by, or at least in consultation with, physicians experienced in the management of this disease spectrum. The morbidity and mortality is 9 times higher when the inexperienced physician treats such patients.

Precise follow-up of patients and precise monitoring using a reliable assay of hCG is essential to good results. The protocol presented here will help outline these principles.

7.1.1 Definitions:

The term Gestational Trophoblastic Neoplasia (GTN) replaces the terms chorioadenoma destruens, metastasizing mole and choriocarcinoma. These were pathologic diagnoses. While histologic verification is desirable it is not essential for the clinical classification we now use. Hydatidiform mole is gestational trophoblastic disease GTD). Nine to twenty per cent of patients with complete hydatidiform mole go on to have gestational trophoblastic neoplasia. This may be chemical only or associated with evidence of invasive mole. If the process is confined to the uterus, it is termed non-metastatic trophoblastic neoplasia. If metastases are demonstrated in the lung or vagina and/or in brain, liver, kidney or elsewhere, the diagnosis is that of metastatic gestational trophoblastic neoplasia. Besides post-molar trophoblastic neoplasia, trophoblastic tumor may also follow abortion (30 %) or normal pregnancy (20 %). Placental site trophoblastic tumor (PSTT) is a variant of GTD but should be classified separately as it has a distinct clinical presentation and its course and management differs from GTD. Non-gestational trophoblastic disease is choriocarcinoma of the ovary or testis.

7.1.2 Etiology Of Hydatidiform Mole

Our perspectives of the pathophysiology of hydatidiform mole and trophoblastic neoplasia have also become significantly focused. The

distinction between complete mole and classical mole has been validated by genetic analysis and DNA fingerprinting. Complete mole occurs in one in 1500 pregnancies in the USA but still in 1 in 400 pregnancies in Korea, Indonesia and among Native Americans in the United States! With complete mole, the chromosomal material from the ovum is lost and the genetic material in the conceptus is paternally derived. Fertilization of this "empty" ovum by one sperm results in a 46XX androgenic conceptus. Fertilization may be by 2 sperms giving an XX or XY androgenic conceptus. A YY fertilization will not develop beyond a few cell embryo. With complete mole no fetus develops from this androgenic fertilization. The placenta develops hydatidiform changes and trophoblastic hyperplasia, resulting in mole with a 9% - 20% chance of subsequent neoplasia.

Partial mole is being increasingly recognized as a cause of fetal loss. Many first trimester abortions are associated with triploidy and are in fact partial moles when examined histologically and confirmed by flow cytometry. Clinically there is high hCG, a fetus is present that is abnormal and there are hydatidiform changes in the placenta. Early pregnancy pre-eclampsia may occur and there is usually less trophoblastic hyperplasia than with a complete androgenic mole. The incidence of trophoblastic sequelae is 4%.

It should be noted that hydatidiform degeneration is a sign of a poorly functioning early placenta and may occur with spontaneous abortion without trophoblastic hyperplasia.

The diagnosis of metastatic gestational trophoblastic neoplasia in a patient who has not had a hydatidiform mole may be difficult. All physicians need to be aware that any female patient of reproductive years who has an obscure disease may have choriocarcinoma. This applies particularly to women presenting with cerebrovascular accidents or persistent pneumonia. All such patients need to have an hCG.

7.2 Diagnosis, Evacuation and Follow-up after Evacuation of Hydatidiform Mole

Ultrasound examination of the first trimester uterus and particularly vaginal colour Doppler flow ultrasound, has made possible the detection of abnormalities of early pregnancy. The diagnosis of hydatidiform mole is nearly always made by ultrasound. After mole evacuation, patients are followed closely with weekly beta-hCG. The

diagnosis of gestational trophoblastic neoplasia is made on the basis of an elevated beta-hCG plateau or rising hCG titers over a period of several weeks. Histologic choriocarcinoma and/or the appearance of metastases with a persistently raised serum hCG level is an absolute indication for chemotherapy.

Physical examination and investigations such as chest x-ray, ultrasound, CT scanning, or MRI of the brain, chest, abdomen and pelvis particularize the type of disease present. Gestational trophoblastic neoplasia responds excellently to chemotherapy and even with extensive high risk metastatic disease a mortality of 90% has been converted to a cure rate of 92% or better.

Hydatidiform mole should be treated by evacuating the uterus. The patient must then be followed by serial weekly hCG titers to undetectable levels. In the 20% of patients in whom the levels of hCG remain elevated, several courses of chemotherapy may be required. In general, patients are no longer treated for moles with prophylactic chemotherapy as this exposes 80% to unnecessary chemotherapy. Prophylactic or rather adjuvant chemotherapy (i.e. not one course, but several courses to nondetectable hCG) should only be offered to patients who cannot be followed.

7.2.1 hCG Assays, Nicked hCG, Phantom hCG

A reliable assay for total hCG is central to the management of patients with trophoblastic disease. The assay must measure **all portions of the hCG molecule particularly free beta subunit, nicked hCG and hyperglycosylated hCG**. Several commercial assay kits do not measure free beta subunit or nicked hCG or differentially recognised hyperglycosylated hCG. Physicians treating patients with trophoblastic disease must ensure that the laboratory used provides accurate assay results, otherwise false low values may result in inappropriate management.

In the last few years we have also encountered patients who have positive serum pregnancy tests but have no trophoblastic disease and in fact no pregnancy associated events. These patients' serum contains heterophillic antibody that reacts with the antibody of certain assay kits to give (false) positive hCG results. This is called phantom hCG.

The presence of real hCG may easily be confirmed and phantom

hCG ruled out by performing an hCG immunoassay or by demonstrating the similar presence of hCG in serum and in urine. When there is doubt the US hCG Reference Laboratory should be consulted (larry@hcglab.com)

7.2.2 Pathology

The histologic diagnosis of both complete and partial hydatidiform mole is well recognized. If there is doubt in distinguishing between partial mole and complete mole flow cytometry may be helpful and is now a well established technique. The major current difficulty is the recognition of tissue obtained from the uterus at 4 to 8 weeks gestational age as hydatidiform mole. The criteria for making the diagnosis of these early moles, made possible by the earlier ultrasound diagnosis of the hydatidiform mole, have been extensively described by Paradinas. It is important to realize that the classical features may not yet be present and that fetal membrane and even fetal erythrocytes may still be present.

The histologic diagnosis of placental site tumor may also be difficult on curettage material and may require the expertise of a gynaecologic pathologist with extensive experience in this refined area of gynaecologic pathology. This becomes particularly important when hysterectomy is indicated in young nulliparous women in whom this diagnosis is believed to be present.

7.3 Detailed Discussion of Trophoblastic Disease Management

7.3.1 Hydatidiform Mole

7.3.1.1 Diagnosis of hydatidiform mole

1. History
2. Clinical examination
3. Ultrasound examination preferably with Vaginal Colour Doppler Flow Ultrasound
4. Radiologic examination by magnetic resonance imaging or CT scan is indicated only when ultrasound examination is inconclusive.
5. Serum hCG levels are helpful.

Note: Bleeding or excess vomiting in the first trimester merits ultrasound examination to allow a positive diagnosis of mole, multiple pregnancy or fetal abnormality. “No fetal heart or high hCG above 80,000 mlU/ml equals mole.”

7.3.1.2 Required Studies for Patients with Hydatidiform Mole

1. Clinical examination including neurological examination, eye fundus examination and blood pressure.
2. Chest x-ray
3. Blood count with platelet count, BUN, creatinine and liver function tests on admission. Blood group and hold clot. Thyroid function tests may be indicated. Clinical thyrotoxicosis is very rare. PT, PTT, prothrombin, fibrinogen, if clinically indicated,
4. Serum hCG immunoassay. A specimen of serum for hCG should be obtained (1) prior to and (2) one day after the evacuation of the mole before the patient leaves the hospital.
5. Digital oximetry, blood gases, and lung scan are mandatory if there is suspicion of pulmonary embolization or pulmonary metastases which are not demonstrable by chest x-ray.

7.3.1.3 Management of Hydatidiform Mole

The hydatidiform mole is surgically evacuated as soon as possible after diagnosis. If necessary the patient is stabilised after the diagnosis is established. If hematologic, thyroid or pulmonary problems are present these are treated: the essential principle is mole evacuation. Evacuation should be done by suction curettage with accompanying syntocinon infusion plus ergonovine if necessary. The cervix may be dilated gently and slowly. With complete mole, a 9 mm or 10 mm suction curettage usually suffices and greater dilatation of the cervix is usually not necessary. A careful, “light” sharp curettage should be performed following the suction procedure to ensure the uterus has been completely evacuated. Hydatidiform moles of gestational size greater than 16 weeks should be evacuated at the Trophoblast Center because of the risk of pulmonary embolization of molar tissue.

Hysterectomy may be done in patients who have finished childbearing.

If the patient wishes to retain her uterus she should be allowed to do so as hysterectomy does not improve the prognosis. **RHOGAM SHOULD BE GIVEN IF INDICATED.**

7.3.1.4 Management Post-Evacuation

1. The patient is followed by weekly hCG measurements until hCG becomes undetectable. Anaemia or infection is treated if present. When the hCG becomes undetectable, two further specimens are obtained at weekly intervals. Subsequently, the patient is tested monthly for six months and then at two monthly intervals for a further six months to insure that the hCG levels remain undetectable.
2. AN ASSAY FOR hCG SENSITIVE TO 2 mlU/ml OR LESS, IS ESSENTIAL FOR FOLLOW-UP. The assay must be able to detect all portions of the hCG molecule.
3. The patient is given reliable contraception, preferably in the form of the pill. If the fall in hCG was logarithmic the patient may be allowed to become pregnant after 6 months of follow-up. If there is very slow fall in hCG post-mole, a longer wait is indicated. It is useful to obtain an ultrasound scan early during the subsequent pregnancy and to follow hCG early in that next pregnancy to document its normalcy. hCG should also be followed to negative levels after delivery of that baby.
4. Please note that patients with a uterus four weeks larger than dates and with theca lutein cysts have a 50% chance of trophoblastic sequelae.

7.3.2 Gestational Trophoblastic Neoplasia
Principal

Gestational trophoblastic neoplasia (GTN) follows hydatidiform mole (60%), previous miscarriage/abortion (30%), normal pregnancy or ectopic gestation (10%). GTN most commonly follows hydatidiform mole as a persistently elevated hCG titer. There may also be continuing and recurring bleeding after mole. Metastatic gestational trophoblastic neoplasia will frequently manifest itself by symptoms from the metastases, such as intracranial neoplasia or “pneumonia.”

7.3.2.1 Diagnosis of post-molar GTN

The diagnosis of gestational trophoblastic neoplasia is made on the basis of elevated hCG levels supported, if possible, but not necessarily by histologic or radiologic evidence. If, after mole, hCG remains elevated, falls and becomes elevated again, therapy is instituted.

Management should only be undertaken by an experienced team: mortality outside a trophoblastic center is much greater than morbidity in a center.

7.3.2.2 Management of gestational trophoblastic neoplasia
Required Studies

1. Clinical examination: (watch for the vaginal metastasis)
2. Serial weekly hCG measurements on serum
3. Complete blood count and platelets. PT, PTT, fibrinogen, BUN, creatinine, liver function tests.
4. Chest x-ray
5. Brain, MR (or CT) scan when there is any suspicion of cerebral metastases.
6. Liver CT scans when indicated. A whole body CT scan is normally done in patients who have lung metastases.
7. Curettage should be done if there is uterine bleeding. Biopsies may be obtained from accessible sites. THERE IS GRAVE DANGER OF HEMORRAGE AT THE BIOPSY SITE.
8. Magnetic resonance imaging when indicated.
9. T4, thyroid studies when indicated.
10. Selective scanning using anti hCG antibody linked to radioactive iodine or indium may be done if there is persistent chemotherapy resistant disease.

7.3.2.3 Staging

7.3.2.3.1 The Staging of Gestational Trophoblastic Neoplasia by The International Federation of Obstetricians and Gynecologists (FIGO).

In 2000 FIGO recommended a clinical staging of gestational trophoblastic tumors and requested that such cases should be reported to the Annual Report of Gynecologic Tumors. For this purpose the definitions of the clinical stages of gestational trophoblastic tumours are:

FIGO Staging

Stage I Gestational trophoblastic tumors strictly confined to the uterine corpus.

Stage II Gestational trophoblastic tumors extending to the adnexa or to the vagina, but limited to the genital structures.

Stage III Gestational trophoblastic tumors extending to the lungs, with or without genital tract involvement.

Stage IV All other metastatic sites.

According to FIGO, hydatidiform mole should be registered but not be staged as Stage 0 because if hCG persists and the patient requires chemotherapy restaging would be required. Such restaging transgresses the basic principle of any staging system. Patients with hydatidiform mole are placed on record but staging only applies to trophoblastic neoplasia.

Cases which do not fulfill the criteria for any given stage should be listed separately as unstaged. It should be realized that most cases of low risk metastatic disease are comprised by Stage 3, while the high risk group of metastatic tumors first described by Hammond is the group that comes under Stage 4.

7.3.2.3.2 A Modified WHO Scoring System has been combined with The FIGO Staging.

FIGO in 2000 accepted the World Health Organization scoring system based on prognostic factors that were first devised by Prof. Kenneth Bagshawe. The score values for the risk factors will be 1,2 and 4. Blood groups will not be used in the scoring system. Liver metastases will be given a score of 4. The cut off score for low risk and high risk neoplasia was ratified by the June 2002 FIGO Cancer Committee announcement. A score of 6 or less is low risk disease treatable by single agent chemotherapy. A score of 7 or greater is high risk disease that requires combination chemotherapy. Medium risk disease has been eliminated.

FIGO (WHO) Risk Factor Scoring with FIGO Staging	0	1	2	4
Age	< 40	≥ 40		
Antecedent Pregnancy	Hydatidiform Mole	Abortion	Term	
Interval Months From Index Pregnancy	< 4	4 - 6	7 - 12	> 12
Pretreatment hCG Milli Iu/Ml	$<10^3$	10^3 - 10^4	$>10^4$ - 10^5	> 10^5
Largest Tumor Size including Uterus		3 - 4 cm	≥5 cm	
Site of Metastases Including uterus		spleen kidney	gastrointestinal tract	brain liver
Number of Metastases Identified		1 - 4	5 - 8	> 8
Previous Failed Chemotherapy			Single Drug	Two Or More Drugs

This combining of the modified WHO risk factor scoring system with the FIGO staging was accepted by the FIGO Cancer Staging and Nomenclature Committee in September 2000 and ratified in June 2002 with the FIGO announcement (see bibliography). It is now part of the FIGO staging and scoring system for gestational trophoblastic neoplasia.

7.3.2.3.3 The Agreed Criteria To Diagnose Gestational Trophoblastic Neoplasia (GTN) include:

1) At least 4 values of persistently elevated hCG plateau (days 1,7,14 and 21) or longer or sequential rise of hCG for two weeks (days 1,7,14) or longer. The actual values of hCG are left to the discretion of individual physicians.
2) Lung metastases are diagnosed by chest x-ray.

7.3.2.4 Treatment of Gestational Trophoblastic Neoplasia (Trophoblastic Tumor)

7.3.2.4.1 Gestational Nonmetastatic Trophoblastic Neoplasia, Low Risk Metastatic Neoplasia (lung metastases only) in patients who have gestational trophoblastic neoplasia for less than 4 months and whose hCG value is less than 40,000 mlU/ml hCG. WHO score 6 or less. FIGO Stage I, II, and III.

1. Drug schedules: single agent chemotherapy:
   (a) Methotrexate 0.4 mg/kilo IM for 5 days, repeated every 2 weeks. This is one of the original protocols used in GTD and is still used at Yale. It is the standard protocol at the Brewer Trophoblast Center in Chicago. It is associated with a 10% primary failure rate.
   (b) Methotrexate with Leucovorin rescue (Table 1). Methotrexate 1.0 mg per kg im every other day for 4 doses with leucovorin 0.1 mg per kilo 24 hours after each dose of Methotrexate. This is a widely used protocol in the United Kingdom and the United States but has a 20% - 25% primary failure rate.
   (c) Methotrexate 50 mg per M^2 im given weekly. This regimen is associated with a 30% primary failure rate. If this occurs Methotrexate 0.4 mg/kilo IM for 5 days may be administered or the medication may be changed to Actinomycin-D 12 mcg/k for 5 days.
   (d) Actinomycin-D, 1.25 mg per M^2 given every 2 weeks. This protocol carries a 20% primary failure rate. It is an alternative to the pulsed weekly methotrexate protocol (c).
   (e) Actinomycin-D, 12 micrograms per kilo IV daily for 5 days, repeated every 2 weeks. This protocol is an alternative to the 5 day MTX protocol. It may be used with patients who have hepatic dysfunction. It carries an 8% primary failure rate.
   (f) Methotrexate 250 mg infusion over 12 hours. This is the MTX portion of the EMA-CO protocol. It is associated with a 30% primary failure rate.

NOTE: ACTINOMYCIN-D CAUSES SEVERE SLOUGH IF INFILTRATED AND MUST BE INJECTED VIA A NEW FREE RUNNING INTRAVENOUS INFUSION. IF ANY EXTRAVASATION DOES OCCUR, THE AREA SHOULD BE INFILTRATED WITH 100 mg HYDROCORTISONE AND 2 CC OF 1% XYLOCAINE.

The primary failure rate of the "pulsed" regimens is significantly greater than that of single agent 5 day courses because of insufficient drug exposure to cells in the S phase of replication. For example the primary failure rate of the 5 day Actinomycin course is 8% compared with 20% with the pulsed Actinomycin-D 1.25 mg per M^2.

2. Repeat complete blood count, platelets, creatinine, BUN and SGOT are obtained on first day of each course.
3. At least one course, and usually two to three courses of chemotherapy should be given beyond first negative hCG level particularly if the fall of hCG is slow or there has been extensive disease.

7.3.2.4.2 High Risk Gestational Trophoblastic Neoplasia (Tumor) Definition. FIGO Stages I, II, II with WHO score 7 or greater or Stage IV.

Experience has shown that single-agent chemotherapy leads to poor results in these patients. Patients with high-risk disease are now treated with the combination chemotherapy EMA-CO as primary therapy. EMA-CO is Etoposide, Methotrexate with Leucovorin rescue and Actinomycin, given on day 1 and 2 and Cyclophosphamide and Vincristine (Oncovin) are given on day 8. This combination has been found to be far more acceptable and less toxic than MAC chemotherapy (Methotrexate, Actinomycin and Cytoxan: originally C was Chlorambucil). The Bagshawe II regimen has now been superseded by EMA-CO. However several centers are returning to the use of MAC because of the risk of leukaemia with EMA-CO used for more than 6 courses.

The patient is closely monitored and courses of EMA-CO are repeated sequentially until remission is obtained. Neupogen is usually given to sustain white cells.

7.4 Chemotherapy "For The Road"

Three further courses of chemotherapy, at least the first of which will be combination therapy, are given beyond the first non-detectable hCG value. A negative hCG value implies that the number of malig-

nant cells present in the body is less than 10^7. It does not mean the disease at that time is completely eradicated.

Certain metastatic sites may require special therapy. For example, brain lesions are treated with an increased dose of Methotrexate to 1 gm per m^2 in the EMA-CO protocol. With this relatively high dose of methotrexate the urine must be maintained alkaline. Depending on the size and number of brain metastases patients may be treated with 25 to 30 grey whole brain irradiation or excisional surgery. Patients with liver metastases may be treated with 20 grey liver radiation or hepatic artery infusion. Both with brain and liver metastases, the radiation serves to prevent catastrophic hemorrhage more than controlling the trophoblastic disease.

Patients resistant to EMA-CO or recurring after previous multiagent chemotherapy may be treated by the EMA-EP (EP-EMA) protocol: this is EMA alternating with etoposide and platinum. On occasion EMA-PA (P=cis-platinum, A=adriamycin) may be used.

For EMA-EP resistant cases Taxol with Cisplatin alternating with Taxol-Etoposide or Taxol-5-FU or iphosphamide, cisplatinium etoposide (ICE) or vinblastine etoposide cisplatin (BEP) have been used.

7.4.1 Surgery For Chemotherapy Resistant and Persistent Metastases

Metastases to lung, liver, brain or other sites that do not regress with chemotherapy may be amenable to surgical extirpation.

7.4.2 Pregnancy After Metastatic Trophoblastic Disease

Patients need to wait for twelve months after ceasing chemotherapy before undertaking pregnancy.

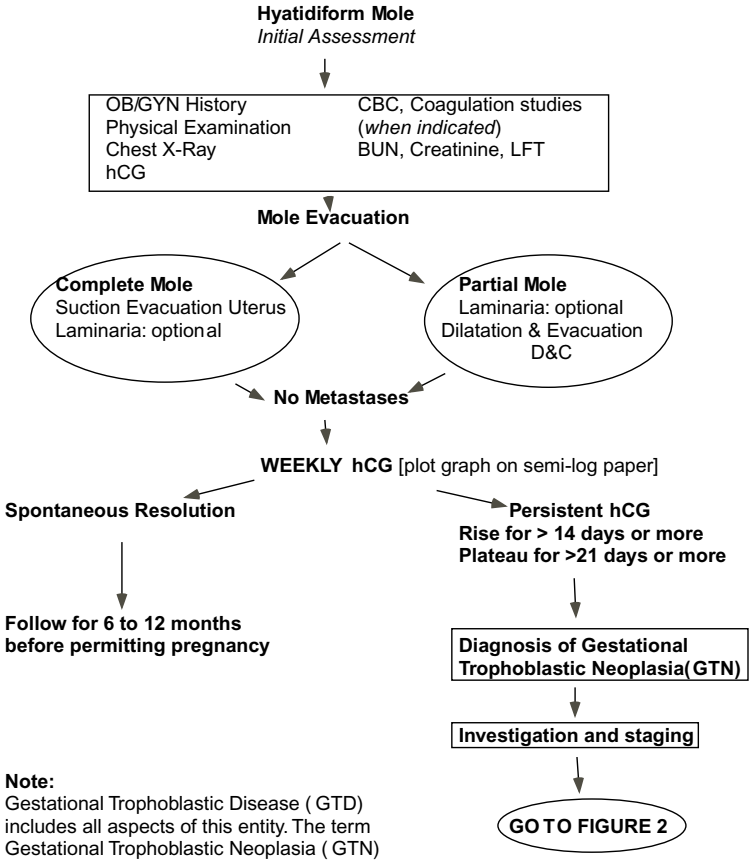
7.4.3 Placental Site Trophoblastic Tumour

Placental Site Trophoblastic Tumor should be separated from Gestational Trophoblastic Tumor such as hydatidiform mole and choriocarcinoma. It should be treated by a trophoblastic center. Tumor load with Placental Site Trophoblastic Tumor is not reflected by hCG and while hPL may be seen immunohistochemically it is rarely detectable in serum. Patient management with both chemotherapy and surgery requires individualisation.

7.5 Trophoblastic Patient Record

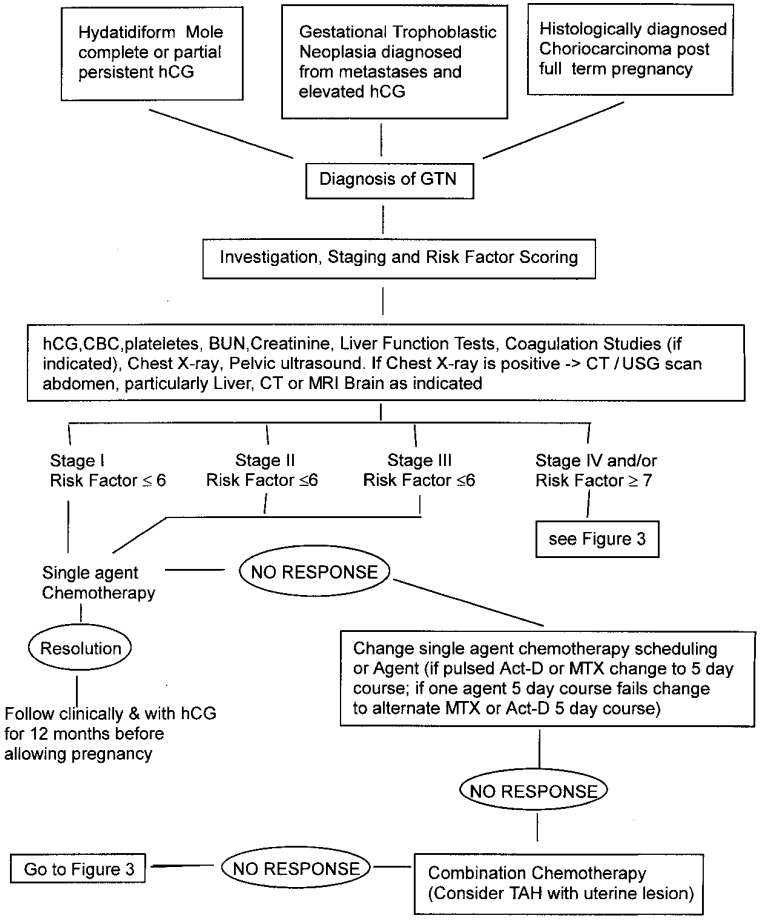
Physicians treating trophoblastic disease are urged to maintain an active record of weekly hCG measurements on semi-log graph paper. Treatment events such as chemotherapy and radiologic investigations are recorded on the same record.

Guidelines for the Management of Gestational Trophoblastic Disease: Figure 1

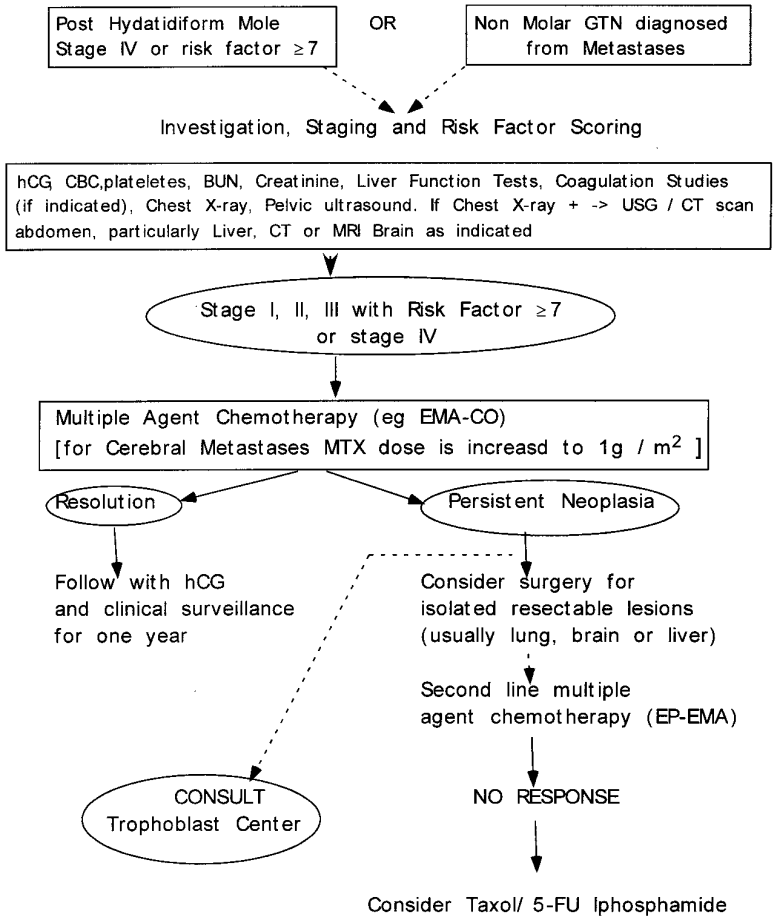


Note:
Gestational Trophoblastic Disease (GTD) includes all aspects of this entity. The term Gestational Trophoblastic Neoplasia (GTN) is reserved for entities that require chemotherapy and replaces invasive mole malignant GTD and other such terms. Choriocarcinoma is a pathologic term: PSTT is classified separately

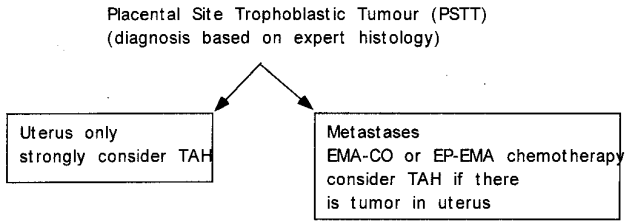
Guidelines for the Management of Trophoblastic Neoplasia: Figure 2



Guidelines for the Management of Trophoblastic Neoplasia: Figure 3



Guidelines for the Management of Trophoblastic Disease: Figure 4



Appendix

Chemotherapy Protocols

Single Agent Chemotherapy Protocols for Low Risk Trophoblastic Neoplasia. WHO Score 6 or less.

1. Methotrexate 0.4 mg/kg daily for 5 days given IM.2
2, Methotrexate-Citrovorum Factor Rescue Protocol

DAY	THERAPY
1	CBC, PLATELET COUNT, SGOT MTX, 1 mg/kg, im
2	CF, O.1 mg/kg, im
3	MTX, 1 mg/kg, im
4	CF, O.1 mg/kg, im
5	MTX, 1 mg/kg, im
6	CF, O.1 mg/kg, im
7	MTX, 1 mg/kg, im
8	CF, O.1 mg/kg, im

CBC = COMPLETE BLOOD COUNT
MTX = METHOTREXATE
CF = CITROVORUM FACTOR RESCUE

3. Methotrexate 50 mg/kg given weekly by 1M injection.
4. Actinomycin 12 mcg/per kilogram daily for 15 days.
5. Act-D 1.25 mg per M2 given every two weeks. (Pulsed Act D)
6. Methotrexate 250 mg infusion over 12 hours.

Suggestions for the Management of Primary Failure of single agent chemotherapy in Low Risk GTN (Risk Factor Score ≤ 6)

If pulsed single agent chemotherapy, either Methotrexate 50mg/M^2 or Actinomycin 1.25 mg/M^2 or Methotrexate with leucovoran rescue do not effect response it may be worthwhile to use the same agent given as a 5 day course; ie Methotrexate 0.4 mg per kg daily for 5 days or Actinomycin 12 microgm/Kg daily for 5 days, before switching to the alternate agent. The failure of pulsed single agent chemotherapy is thought to be associated with insufficient time of exposure of cells in cycle during the relatively brief time effective levels are present in the circulation. This practice may avoid having to give multi agent chemotherapy in such a situation in more then 50% of these patients.

Current Multi-Agent Chemotherapy for High-Risk GTN, EMA-CO WHO Score 7 or greater

Etoposide (VP-16), Methotrexate, Actinomycin D, alternating weekly with Cyclophosphamide and Oncovin (vincristine)
EMA-CO is administered on a weekly basis with anticipated cycling between each course of 14 days.

Day 1 (A) Actinomycin D 500 micrograms IV push new IV.
Etoposide 100 mg/m^2 over 30-50 minutes
Methotrexate 100 mg/m^2 IV infusion over 1 hour and then
Methotrexate 200 mg/m^2 IV infusion over 12 hours by pump.

Day 2 (A) Actinomycin D 500 micrograms IV push new IV
Etoposide 100 mg/m^2 over 30-50 minutes
Folinic Acid 15mg IV push Q 6 hours for 8 doses beginning 24 hours after Methotrexate bolus. Some physicians administer the folinic acid Q 12 hours for 4 doses orally 15 mg commencing 24 hours after commencing methotrexate.

Day 8 (B) Vincristine (Oncovin) 1 mg/m^2 IV
Cyclophosphamide 600 mg/m^2 IV.

NOTE:
1. Neupogen may be administered. **Note that this must be started**

24 hours after day 2 chemotherapy and then be stopped 24 hours before CO.

2. If the creatinine is greater than 2.0 creatinine clearance should be done prior to therapy and should be 50 or more.
3. Cycles are repeated on day 15 of cycle.
4. Chemotherapy is administered when WBC is greater than 3000 per cc. Granulocytes are greater than 1500 per cc. Platelets are greater than 100,000 and a Grade 3 gastrointestinal infection and mucositis morbidity has cleared. If toxicity necessitates a delay in course B for longer than 6 days, course A is recycled.

Combination Chemotherapy for Trophoblastic Neoplasia with Brain Metastases – EMA-CO with High Dose Methotrexate

For GTN with brain metastases the EMA-CO protocol is modified. The dose of MTX is increased to 1000 mg per m^2 (one gram per m^2). The MTX infusion is given over 24 hours. The urine must be kept alkaline with a measured pH of greater than 7.5 at all times by administration of bicarbonate IV. Urinary volume and pH must be followed assiduously.

If Neupogen is given, it needs to be given commencing 24 hours after the last chemotherapy and ceasing 24 hours prior to the next planned chemotherapy.

Combination Chemotherapy for High Risk Trophoblastic Neoplasia Resistant to EMA-CO or recurring after Combination Chemotherapy

The majority of trophoblast centres use EP-EMA (EMA-CO) under such circumstances. EMA is administered in the standard way and etoposide and platinum are substituted for CO. This is a more demanding and more toxic regimen. The following schedule is taken from the Charing Cross protocol as they have had the most experience and the greatest success.

Combination Chemotherapy for EMA-CO Failure in Trophoblastic Neoplasia: EP-EMA

Cisplatin is given on Day 1 by infusion of 80 mgm/kg in 1 liter by infusion pump over 12 hours. Etoposide 100 mg/m^2 is given over 1 hour. Day 8 – EMA is given in standard doses **but the second day Actinomycin-D and etoposide are omitted**. The cycle is repeated every 15 days.

Neupogen is commenced 24 hours after first methotrexate infusion and stopped 24 hours before day 8 platinum. It is recommenced 24 hours after stopping platinum and stopped 24 hours before next EMA. The timing of Neupogen has to be carefully planned.

Alternate Combination Chemotherapy for High Risk GTN: Methotrexate, Actinomycin, Cyclophosphamide (MAC) Protocol for High Risk GTN. This regimen has been largely superceded by EMA-CO

DAY	THERAPY
Day1	CBC, platelet count, SGOT
	Compazine, 25 mg, IM, PO or PR
	MTX, 1.0 mg/kg. IM
	ACT-D, 12 mcg/kg, stat IV
	Cyclophosphamide, 3 mg/kg, stat IV
Day2	CBC, platelet count
	Compazine, 25 mg, IM, PO or PR
	Leucovorin, 0.1 mgm/kg. IM
	ACT-D, 12 mcg/kg, stat IV
	Cyclophosphamide, 3 mg/kg, stat IV
Day 3, 4, 5, repeat day 1&2	
Day 6	CF, 0.1 mg/kg, IM
Day 7	CBC, platelet count, SGOT
	MTX, 1.0 mg/kg. IM
Day 8	CF, 0,1 mg/kg, IM

Courses are repeated every 2 weeks or as soon as white cells and platelet recover.

Bagshawe 9-Day Multi-Agent Chemotherapy

This Protocol has been reported to be more toxic than MAC and will probably be used only in exceptional circumstances. However several trophoblast centres use it for high-risk disease as initial therapy because of the leucemogenic association of EMA-CO

Bleomycin, Etoposide, Cisplatin (BEP) for Chemotherapy Resistant Gestational Trophoblastic Neoplasia and for Primary Ovarian Germ Cell Tumor

Etoposide 100 mg IV in 500 ml N saline over 1 hour Days 1, 2, 3, 4

Cisplatin 100 mg/m^2 day one IV continuous infusion x 24 hours with NSx6 at 250 ccs/hr; add 20 mEgn KCl and 2 mg $MgSO_4$ to each of last 2 liters.

Bleomycin 10 units per m^2 per day for 3 days; days 2,3 and 4; IV continuous infusion for 96 hours.

Give day 1, VP-16 prior to cisplatin. Give day 2, VP-16 as part of cisplatin post hydration; then complete post-hydration (concurrent with 1st bleomycin infusion) with D5/NS at 150 ml/hr for 11 hours. Give day 3, and 4 VP-16 prior to starting 2nd and 3rd Bleomycin infusion. Kytril, Compazine and Benadryl are given with these medications.

Validity of Studies on which The Protocols are based

In an age of evidence based medicine very few of the chemotherapy protocols used to treat trophoblastic disease have undergone the rigors of a prospective randomised study. No study fulfills a Cochrane category I or II for clinical studies. The evidence on which management of Trophoblastic Neoplasia (GTN) is presently based throughout the world fulfills only a Cochrane category III. This applies to all the management protocol in this document.

Consultation

Physicians wishing for consultation concerning case management should contact their nearest Trophoblast Center early rather than late following mole evacuation. A list of telephone numbers and e-mail addresses will be found on the web at: www.isstd.org. The bibliography provides an overview of the present situation. Those wishing to have a more detailed outline may get in touch with one of the Trophoblast Centers.

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Examples of Figo 2002 Staging:Scoring

Please see pages 8 and 9 for risk score analysis

1. Low Stage:Low Score

Forty-five year old patient requiring chemotherapy 6 weeks after hydatidiform mole. The hCG was 900 milli IU/ml. There were no metastases. The FIGO Stage : Score is **I : 1**.

2. High Stage:High Score

40 year old patient, 7 months after full term pregnancy who presents with lung (4 Mets), brain (1 met; 5 cm size), liver (2 mets) and kidney (one met each) metastases with an hCG of 42,000 milli IU/ml. This patient is FIGO Stage **IV : 18**.

3. High Stage:Low Score:

20 year old patient, who presents 8 weeks post-hydatidiform mole with one metastasis to the lung and one to one kidney (4 cm in size) with an hCG of 800 mlU/ml. The FIGO Stage : Score is **IV:4**

4. Low Stage:High Score

Patient, aged 44, is 8 months post miscarriage, has uterine bleeding and by ultrasound is found to have a 9 cm mass in the uterus. D & C shows histologic choriocarcinoma. The hCG is 18000 milli IU/ml and there is also a 5 cm nodule in the vagina. Single agent chemotherapy with methotrexate has failed. There are no other metastases. The FIGO: Stage Score for this patient is **II : 10**

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Nippon Medical School
Tokyo
Japan

J Soper
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USA

Cancer of the Breast

8.1 Staging

8.1.1 Anatomy

8.1.1.1 Primary Site

The breast is situated on the anterior chest wall and is composed of glandular tissue with a dense fibroareolar stroma. The glandular tissue consists of approximately twenty lobes, each of which terminates in a separate excretory duct in the nipple.

8.1.1.2 Regional Lymph Nodes

Lymphatic drainage of the breast is via three major pathways: axillary, transpectoral and internal mammary. The intramammary lymph nodes are considered with the axillary lymph nodes for staging purposes. Metastases to other lymph nodes, including supraclavicular cervical and contralateral internal mammary nodes are considered distant metastases (M1).

1) Axillary

Interpectoral nodes and lymph nodes along the axillary vein and its tributaries may be divided into the following levels:

i) Level I (low-axilla): Lymph nodes that are lateral to the lateral border of the pectoralis minor muscle.
ii) Level II (mid-axilla): Lymph nodes which lie between the medial and the lateral borders of the pectoralis minor muscle and the interpectoral (Rotter's) lymph nodes).
iii) Level III (apical axilla): Lymph nodes medial to the medial margin of the pectoralis minor muscle, including those designated as subclavicular, infraclavicular, or apical.

2) Internal mammary

Internal mammary lymph nodes in the intercostal spaces along the edge of the sternum in the endothoracic fascia. Any other lymph node metastasis is coded as a distant metastasis (M1) and includes supraclavicular, cervical or contralateral internal mammary lymph nodes.

8.1.1.3 Metastatic sites

All distant visceral sites are potential sites for metastases. The major

sites of involvement are bone, lung, brain and liver. Metastatic disease has been found in almost every remote site.

8.2 Rules for classification

8.2.1 Clinical Staging

Clinical staging includes physical examination with careful inspection and palpation of the skin, mammary gland itself and lymph nodes (axillary, supraclavicular and cervical), as well as pathological examination of the breast or other tissues, and imaging to establish the actual diagnosis of breast cancer. The extent of tissues examined pathologically for clinical staging is less than that required for pathologic staging. Appropriate operative findings are also elements of clinical staging including the size of the primary tumour and chest wall invasion and the presence or absence of regional or distant metastases.

8.2.2 Pathological staging

Pathological staging will include all of the data used for clinical staging and surgical resection as well as pathological examination of the primary carcinoma, including not less than excision of the primary cancer with no tumour in any margin of resection by gross pathological examination. The case may be included in the pathologic stage if there is only microscopic but not gross involvement at a resection margin. Lesions with a resection margin, on gross examination, are coded as TX because the extent of the primary tumour cannot be assessed. Resection of at least the lower axillary lymph nodes (level I) should be carried out. Such a resection ordinary will include six or more lymph nodes.

8.3 TMN Classification

The clinical measurement used for classifying the primary tumour (T) should be the one that provides the most accurate information (e.g. physical examination or mammogram). Pathologically the tumour size for classification is a measurement of the invasive component. Lesions that show a large in situ component (e.g. 3-4 cm) and a small invasive component (e.g. 0.5 cm) are classified as T1a.

8.4 Definition of TMN

8.4.1 Primary Tumour (T)

Definitions for classifying the primary tumour (T) are the same for clinical and for pathologic classification. The telescoping method of classification can be applied. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic, are used, the examiner can use the telescoped subsets of T1. (See Table 1).

Table 1: Breast cancer pre-treatment clinical classification

TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Tis	Carcinoma in situ; intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no tumour	
T1	Tumour 2 cm or less in greatest dimension	
	T1a	0.5 cm or less in greatest dimension
	T1b	More than 0.5 cm but not more than 1 cm in greatest dimension
	T1c	More than 1 cm but not more than 2 cm in greatest dimension
T2	Tumour more than 2 cm but not more than 5 cm in greatest dimension	
T3	Tumour more than 5 cm in greatest dimension	
T4	Tumour of any size with direct extension to chest wall or skin	
	T4a	Extension to chest wall
	T4b	Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
	T4c	Both (T4a and T4b)
	T4d	Inflammatory carcinoma (See the definition of inflammatory carcinoma in the introduction)

Note: Paget's disease associated with a tumour is classified according to the size of the tumour.

8.4.2 Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed (e.g., previously removed)

N0 No regional lymph node metastasis

N1 Metastasis to movable ipsilateral axillary lymph node(s)

N2 Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures

N3 Metastasis to ipsilateral internal mammary lymph node(s). (See Table 2).

Table 2: Breast cancer post-surgical classifications

Pathologic Classification (pN)

pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis
pN1	Metastasis to movable ipsilateral axillary lymph node(s)
pN1a	Only micrometastasis (none larger than 0.2 cm)
pN1b	Metastasis to lymph node(s), any larger than 0.2 cm
pN1bi	Metastasis in one to three lymph nodes, any more than 0.2 cm and all less than 2 cm in greatest dimension
pN1bii	Metastasis to four or more lymph nodes, any more than 0.2 cm and all less than 2 cm in greatest dimension
pN1biii	Extension of tumour beyond the capsule of a lymph node metastasis less than 2 cm in greatest dimension
pN1biv	Metastasis to a lymph node 2 cm or more in greatest dimension
pN2	Metastasis to ipsilateral axillary lymph nodes that are fixed to one another or to other structures
pN3	Metastasis to ipsilateral internal mammary lymph node(s)

8.4.3 Distant metastasis (M)

MX Presence of distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis (includes metastasis to ipsilateral supraclavicular lymph node(s))

8.5 Introduction

Carcinoma of the female breast represents one of the most frequent malignant tumours in women, in both developing and industrialised nations. In recent years there has been an increased emphasis on the diagnosis of breast cancer through instructions in breast self examination, regular physical examinations by the patient's physician, and the use of mammography. This activity, coupled with extensive public education, is leading to earlier diagnosis of disease in a sizable proportion of women with breast cancer and should lead to better overall survival and prognosis.

One result of earlier diagnosis has been the increasing number of

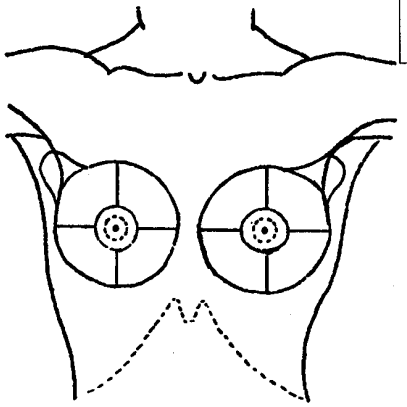
BREAST STAGING DIAGRAM

UNIT

CHART NO.

SURNAME GIVEN

D.O.B. HEALTH CARE PLAN NO.



NOTE

1. "Central area" as shown by solid circle around the areola is defined as a 3 cm radius from edge of the nipple.
2. Indicate scars on Staging Diagram.

Tumour palpable ☐ Tumour not palpable ☐

Size of breast tumour _____ cms

Measured by (a) Mammogram _____ (b) Caliper _____ (c) Other _____

Right breast ☐ Left breast ☐

I.C.D.-0

Anatomical Subsite _____

Pathological Diagnoses _____

PATIENT REFERRED: for initial planned management ☐ recurrence or metastatic disease ☐ post treatment follow-up ☐ post treatment unknown ☐

BASED ON: Assessment ☐ Questionnaire ☐ Other ☐

CLINICAL - I0 I II III IV Unknown

TNM PRE-TREATMENT CLINICAL CLASSIFICATION (1997)

T -	TX	Tis	T0	T1	T1mic	T1a	T1b	T1c	T2	T3	T4	T4a	T4b	T4c	T4d
N -	NX		N0	N1	N2	N3									
M -	MX		M0	M1											

TNM POST-SURGICAL HISTOPATHOLOGICAL CLASSIFICATION (1997)

BASED ON: Pathology Review ☐ Other ☐

pT -	pTX	Tis	pT0	pT1	pT1mic	pT1a	pT1b	pT1c	pT2	pT3	pT4	pT4a	pT4b	pT4c	pT4d
pN -	pNX		pN0	pN1	pN1a	pN1b	pN1bi	pN1bii	pN1biii	pN1biv	pN2	pN3			
pM -	pMX		pM0	pM1											

DISTANT METASTASES

	Clinical	Path
Pulmonary	☐	☐
Osseous	☐	☐
Hepatic	☐	☐
Brain	☐	☐
Marrow	☐	☐
Other	☐	☐
Distant Lymph Nodes	☐	☐

Completed by: _____ Date: _____

Diagnosis/Stage amended to: _____

By: _____ Date: _____

Reason: _____

women seen with in situ disease. This has led to a reevaluation of both the risk to these individual women and the subsequent recommendations for management of in situ disease while still conserving the breast. Wide local excision, followed by radiation therapy, produces survival and local control, which is equivalent to that obtained with mastectomy so that breast conservation is now considered standard therapy for most women with operable breast cancer. Adjuvant systemic therapy has also been demonstrated to reduce the risk of cancer recurrence and improve survival in women with breast cancer. Adjuvant chemotherapy for younger women and tamoxifen for women over the age of 50 should be offered to all but the lowest risk women. The role of combined chemotherapy and tamoxifen is still evolving. For patients with locally advanced disease, early use of systemic and local regional therapies may be helpful. In the management of metastatic disease patients the major objective should be to reduce and possibly prevent morbidity with an emphasis on the quality of life for that individual.

8.6 Screening

Approximately one in nine women, living to the age of 90, will eventually be diagnosed as having breast cancer. Mammography for screening is directed towards women at high risk. Risk factors for breast cancer, apart from hereditary factors (i.e. two or more first degree relatives), include obesity, advancing age, early menarche, late menopause, nulliparity, delayed age of first birth and alcohol consumption.

Women are encouraged to perform regular breast self examination (BSE). For premenopausal women this is best done in the week following the menstrual period and for post menopausal women a specific day of the month should be chosen. The examination should include inspection of the breast and palpation of the breast and axilla. In order to perform adequate BSE the patient should be provided with the proper instruction as to the correct technique and the manner in which this should be performed.

8.7 Screening Mammography

Individuals under the age of 40, with a strong family history of breast cancer (i.e. two or more family members), should participate in

screening programs if available. Genetic counselling and testing, if available, may also be of benefit in individuals at high risk for hereditary breast cancer. In these situations, annual screening mammography is recommended. Women between the ages of 40 and 50 should also attend on an annual basis. In women aged 50 to 74, research has shown that 25% fewer breast cancer deaths can be expected in women if they have regular screening mammograms between the age of 50 and 69. To achieve this rate, at least 70% of eligible women in this age group must have regular screening mammography. Currently, we would recommend that women aged 50 to 74 have a screening mammogram at least every 24 months. Women aged 75 to 79 should have screening mammograms every two years as the incidence of breast cancer increases with age.

The use of ultrasound or thermography as screening methods are not recommended as these techniques do not have the sensitivity or specificity of mammography at this time.

8.8 Hereditary breast cancer

A women with a sister or mother with bilateral breast cancer would be at a four-fold risk of breast cancer; if the case were postmenopausal or a nine-fold risk; if the case was premenopausal she would be at an even higher risk if in addition to the family history she met any of the following criteria: family history of ovarian cancer, male breast cancer or Ashkenazi Jewish heritage.

8.9 Clinical practice guidelines

8.9.1 Management of a breast abnormality

8.9.1.1 Mass detected by mammogram only

In the case of a discrete mass lesion noted on examination may benefit from ultrasound examination to help distinguish between a cystic and a solid lesion. If the lesion is thought to be cystic it may be aspirated under ultrasound control and material sent for cytologic interpretation.

Solid masses found on ultrasound can be managed either by fine needle aspiration, stereotactic cord needle biopsy or open surgical biopsy guided by fine wire localization.

8.9.1.2 Fine calcifications noted on mammogram
When this abnormality is identified and if the opinion of the diagnostic radiologist is such that the appearance is suspicious, stereotactic core needle biopsy or open biopsy is required. If the finding is thought to be less suspicious then a follow-up mammogram in 4-6 months may be recommended.

8.9.1.3 Palpable mass
All palpable masses require biopsy assessment. A mammogram may also be helpful in the assessment of a palpable mass to evaluate the rest of the breast tissue and also to assess the contralateral breast. A normal mammogram should not be a cause for delay in biopsy in these situations.

8.9.1.4 Cystic lesion
It is thought that if a lesion is cystic, it should be aspirated and if the cyst disappears following the aspiration and the fluid is free of blood then biopsy is not necessary. If, however, the cyst occurs repeat aspiration may be done. Cytologic examination of the fluid is usually not helpful.

8.9.1.5 Solid lesions
Any solid lesion needs to be assessed with either a fine needle aspiration, stereotactic core needle biopsy or open surgical biopsy.

8.9.2 Pre-operative investigations
Investigations that are recommended to determine the presence or absence of blood-borne metastatic disease prior to definitive surgical management include bilateral mammography, CBC, liver enzymes including alkaline phosphatase, chest x-ray. A bone scan is not ordinary recommended for clinical stage T1, T2 and N0 cancers since asymptomatic patients are unlikely to have a positive bone scan due to metastatic disease. Tumours that are greater than 5 cm or where there is palpable axillary lymph nodes or an elevated alkaline phosphatase, a bone scan should be carried out in these situations. If the liver enzymes are elevated then ultrasound of the liver should also be performed.

8.9.3 Handling the surgical specimens
To assist treatment planning, sufficient detail must be obtained from

a pathology report and as a minimum should include the following information: orientation, type and size of the specimen, size of the invasive cancer measured in mm, type of invasive carcinoma, grade of invasive carcinoma, presence or absence of lymphatic-vascular or neural space invasion, type, grade and extent of in situ carcinoma indicating the distance that the in situ carcinoma extends beyond any invasive carcinoma that may be present, multifocality of either the invasive or in situ component, relationship of the cancer to the marked resection margins, number of nodes sampled and the number of nodes involved, the presence or absence and extent of any extranodal spread of carcinoma in axillary fat, and oestrogen receptor status.

8.9.4 Hormone receptor levels
The oestrogen receptor status of breast cancer can be determined by immunocytochemical staining of tissue specimens or aspirates. When possible it is preferable to submit the specimens, unfixed, immediately to pathology for selection of the most appropriate technique for handing each individual specimen. Immunocytochemical staining is the standard technique to test for oestrogen receptors. It can be performed on fresh or frozen tissue, scrapings obtained from the surface of small lesions, and from aspirates with reliable results. Oestrogen receptor staining may also be a useful technique in evaluating metastasis in patients with unknown primaries in whom the possibility of metastatic breast carcinoma is in the differential diagnosis.

8.9.5 Tumour management based on TMN classification

8.9.5.1 Paget's disease of the breast
Surgical excision remains the standard management for Paget's disease of the nipple or breast. In selected patients partial mastectomy may be offered if this will lead to a satisfactory cosmetic result when the lesion is completely excised. A sample of underlying breast tissue will be removed with the nipple to assess if any associated invasive or in situ component is present.

8.9.5.2 Ductal carcinoma in situ
Detailed mammographic examination of the breast to obtain a preoperative assessment of the extent of the lesion is required for ductal

carcinoma in situ (DCIS). For patients treated with breast conservation close cooperation and communication is required between the surgeon, radiologist/mammographer and pathologist to ensure that local therapy has been adequate.

The larger the focus of DCIS the higher the chance of a focus of microinvasive disease. Therefore an axillary lymph node dissection may be appropriate in patients with DCIS greater than 5 cm in diameter.

Total mastectomy remains an option for patients with DCIS, however recent evidence has demonstrated that radiotherapy reduces incidence of subsequent in situ and invasive breast recurrences. Currently, adjuvant radiotherapy is recommended with women with DCIS tumours greater than 1 cm in diameter or comedocarcinoma who are interested in breast conservation and in any patient who has a resection but in whom close margins (less than 5 mm) is present.

Women with well differentiated DCIS less than 1 cm in diameter, with complete radiographic and pathologic excision of the lesion, may be managed by wide local excision alone.

Those women with very diffuse areas of DCIS (greater than 5 cm or greater than or equal to 1/4 of the breast on mammography) have a substantial risk of recurrence even after excision and radiotherapy, and for these patients mastectomy is generally recommended. Tamoxifen or other adjuvant systemic therapy is not currently recommended, however when the results of controlled trials are available with this agent tamoxifen may be subsequently recommended in an adjunctive setting.

8.9.5.3 Lobular carcinoma in situ

Authorities would regard lesions of this type as having a high risk for development of an infiltrating carcinoma in either or both breasts. It would appear that the risk for subsequent carcinoma is not confined to the segment of breast tissue involved by the in situ change. The risk to each breast is approximately equal and approaches 15% within 10-15 years. Patients may be given the option of either careful follow-up, or on occasion bilateral mastectomy with or without immediate or delayed reconstruction.

8.9.5.4 Stage I or II invasive cancer

Partial or total mastectomy combined with level I and level II axillary node dissection is recommended. Axillary nodal status is still the most powerful predictor for the need for adjuvant therapy.

8.9.5.5 Partial mastectomy, axillary dissection and radiation therapy

This combination is the standard treatment for patients with tumour less than 5 cm, providing that the tumour is unifocal and is sufficiently small in relationship to the size of the breast, in that wide local excision with a margin of normal tissue is possible and results in a reasonable cosmetic effect. In addition there should be no contraindication to radiotherapy. Removal of skin is a major factor affecting the cosmetic outcome in such cases. In general it is not necessary to remove skin unless it is involved by tumour. The cavity of the local excision should also be marked with small metallic hemoclips to help in localizing the area for subsequent radiotherapy should this prove to be necessary.

Even with pathologically negative margins, 25-40% of women treated with partial mastectomy alone will recur in the breast within 5-10 years. Therefore all patients treated by partial mastectomy and axillary dissection should be reviewed regarding the need for radiation therapy to the breast.

8.9.5.6 Modified radical mastectomy

This traditional method of surgical management is equivalent to breast conservation. When a modified radical mastectomy is performed the scar should be located with appropriate consideration of the site of the primary tumour but at the same time recognizing that some patients will desire breast reconstruction. The extent of the scar and any drains should be medial to the midaxillary line and above the sixth rib. Modified radical mastectomy is the treatment of choice if there are multiple tumours in a single breast and the size of the tumour is such that removal of the primary tumour with an adequate margin of normal tissue will lead to considerable distortion of the breast. Modified radical mastectomy is also the treatment of choice if there are absolute or relative contraindications to radiation therapy. Also elderly patients may find surgery easier than a partial mastecto-

my and node dissection and the subsequent three to five weeks of daily radiation therapy. In addition, modified radical mastectomy is also the treatment of choice in patients who are not available for follow-up and if the patient is not interested in breast conservation.

8.9.5.7 Radical mastectomy

The classic radical mastectomy procedure is rarely indicated today, although for tumours which are tethered to the underlying pectoral fascia over a small area, extension of the modified radical mastectomy to include removal of some portion of the underlying muscle is not infrequently performed. Classical radical operation may be indicated in an occasional patient where an adequate margin cannot be otherwise accomplished.

8.9.5.8 Locally advanced tumours

These tumours are generally regarded as inoperable. Occasional exceptions may occur in patients with large breasts and mobile T3 lesions without palpable nodes (T3, N0, M0). In these patients modified radical mastectomy may well be the treatment of choice.

Surgery after chemotherapy and radiotherapy may be helpful in the prevention of local recurrence. These patients should be assessed for operability after response to therapy and a metastatic work-up repeated prior to considering modified radical mastectomy. This excludes patients with initial supraclavicular node involvement. Failure to respond to the initial chemotherapy is not an indication for surgery. Local control is not enhanced by operating on inoperable patients as cutting through tumour may actually worsen the prospects for local control by producing massive involvement through the tissue planes of the axilla.

These patients also have a high risk of widespread micrometastatic disease and chemotherapy may help eradicate micrometastasis and improve the local regional results of radiation therapy. A variety of intensive chemotherapy regimens are available but a standard commonly employed treatment would consist of six courses of cyclophosphamide, doxorubicin (adriamycin) and 5-fluorouracil (this is the CAF regimen).

Radiation therapy is usually given after the course of chemotherapy, however if the patients fail to show any improvement in their local

condition following the third course of chemotherapy then chemotherapy should be discontinued and local regional radiotherapy instituted. Radiotherapy is given to the whole of the breast and the lymph node areas. A boost dose to the site of the primary lesion is usually given. A dose to the axilla is also increased by approximately 10% if bulky axillary involvement was present.

Tamoxifen, 20 mg PO daily for five years, starting approximately four weeks after the completion of chemotherapy, should be offered to all patients with locally advanced tumours except patients under the age of 50 with oestrogen receptor negative tumours.

8.9.6 Special situations

8.9.6.1 Inflammatory breast cancer

Inflammatory breast cancer usually presents with rapid development of swelling redness in the classic peau d'orange (skin oedema) which may be mistaken for an infection and treated with antibiotics before the correct diagnosis is suspected. A mass is often palpated and the breast may be diffusely involved. Mammogram may show a discrete mass but often there is only diffuse increase in the density and skin thickening. Although the diagnosis is primary clinical, a distinctive pathological finding is the involvement of dermal lymphatic vessels by tumour cells which in turn produce the skin erythema and oedema.

Inflammatory breast cancer is the most aggressive form of malignant disease at this site with a medial survival of 18-24 months irrespective of intensive combined modality treatment. Surgery is not generally advised as initial treatment apart from diagnostic biopsy. Patients who do not show clinical evidence of metastatic disease and who do not develop such evidence during treatment, mastectomy is considered after the completion of chemotherapy and radiation therapy. Chemotherapy and radiation are combined using cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) every three weeks for six treatments. This is then followed by radiation to the breast, chest wall and regional lymph nodes. If the response to chemotherapy is poor after the initial six weeks, chemotherapy should be discontinued and radiation therapy given at that time. Tamoxifen, 20 mg daily for five years, is recommended for all

patients except for those under the age of 50 who have oestrogen receptor negative tumours.

8.9.6.2 Local regional recurrence

Local regional recurrence may follow prior treatment with modified radical mastectomy or partial mastectomy, node dissection or radiation therapy. Local regional recurrence generally carries a poor prognosis but approximately 15% of patients will be long-term survivors after further local regional therapy. Metastatic disease and extensive local recurrence are incurable and the major aim of therapy is palliation. There is no evidence to suggest that early or aggressive treatment of recurrent or metastatic disease will add to survival. Occasionally preventing or eliminating impending or otherwise inevitable problems may be an indication for treatment in the asymptomatic patient. On occasion, with asymptomatic patients, local radiation may be given to the involved area if one is dealing with a solitary metastasis.

8.9.6.3 Carcinoma of the breast in pregnancy

Breast cancer is the most common tumour occurring in women during their reproductive years, so the combination of breast cancer and pregnancy is not uncommon but does produce special management problems. It is extremely important to assess the potential for cure in an individual patient and both the welfare of the patient and the foetus needs to be evaluated.

Definitive treatment of breast cancer during the first trimester of pregnancy may endanger the foetus and therefore therapeutic abortion may be recommended. The treatment of the malignancy will then proceed as in the nonpregnant patient. Individuals who decline termination should be treated by modified radical mastectomy. No adjuvant radiation therapy or chemotherapy should be given during pregnancy.

During the second trimester the breast cancer can be adequately treated surgically without pregnancy termination. Modified radical mastectomy is the treatment of choice without immediate radiation and chemotherapy.

During the third trimester, foetal maturity should be assessed by standard techniques. Consideration should be given to inducing

labour as soon as foetal viability is present. Initial treatment by modified radical mastectomy is appropriate and as soon as feasible following delivery. The patient should receive additional treatment as for the non-pregnant state. (See Table 3).

Table 3: Histopathologic Type

The histologic types are the following:
Carcinoma, NOS (not otherwise specified)
Ductal
Intraductal (in situ)
Invasive with predominant intraductal component
Invasive, NOS (not otherwise specified)
Comedo
Inflammatory
Medullary with lymphocytic infiltrate
Mucinous (colloid)
Papillary
Scirrhous
Tubular
Other
Lobular
In situ
Invasive with predominant in situ component
Invasive
Nipple
Paget's disease, NOS (not otherwise specified)
Paget's disease with intraductal carcinoma
Paget's disease with invasive ductal carcinoma
Other
Undifferentiated carcinoma

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