Staging and pretherapeutic investigations

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Abstract. *– An overview on the staging of carcinoma of the cervix uteri is presented. The importance of a clinical examination under anaesthesia is emphasised. The complementary procedures and accepted auxiliary examinations for cancer staging are analysed. A summarised description of the optional investigations that can improve clinical staging is also presented. It is stressed that cervical cancer staging does not limit treatment strategies which must be tailored to the disease on an individual basis.*

Keywords: clinical examination, CT scan, cystoscopy, intravenous pyelogram, lymphangiography, rectosigmoidoscopy, staging, ultrasonography.

Introduction

Accurate cervical cancer staging (assessing the extent of the disease) is necessary for the selection of appropriate treatment modalities and for planning their sequence. Staging is also important, not only as a means of evaluating treatment strategies within one institution, but also because it provides a means of comparing results from different institutions throughout the world. It should therefore be done as uniformly as possible. Accurate staging is also essential in optimising the results of therapy, because therapy and prognosis vary considerably from stage to stage. However, staging does not limit treatment modalities, and therapy can be tailored to the architecture of the tumour in each patient.

Clinical staging

It is agreed that staging of cervical cancer is a predominantly clinical process, preferably with the patient anaesthetised. It cannot be changed later if findings at operation or subsequent treatment reveal further disease, since this "upstaging" of patients would produce erroneous improvements in the results of treatment of early-stage disease. The pretherapeutic investigations that can be used for staging cervical cancer are presented *(table I)*.

■ Clinical examination and complementary procedures

The great majority of patients will have a normal general physical examination. However, the inguinal lymph nodes should be palpated, particularly if the lower third of the vagina has been invaded. Supraclavicular lymph nodes should also be palpated since they can be the site of distant metastases, even in apparently early-stage cervical cancers. Abdominal palpation is carried out to look for ascites or hepatomegaly. The aetiology of a pleural effusion or a swollen leg is investigated. All these conditions may be evidence of metastatic disease.

Table I. Pretherapeutic investigations.

Clinical examination	General physical examination Genital examination Bimanual rectovaginal examination (under anaesthesia)
Procedures	Colposcopy Biopsy Endocervical curettage Conisation
Auxiliary examinations	Intravenous pyelogram Cystoscopy Rectosigmoidoscopy Chest X-ray Skeletal X-ray
Optional investigations	Lymphangiography Computerised axial tomography Ultrasonography Magnetic resonance imaging Radionucleotide scanning Laparoscopy

Examination of the vulva and perineum may rarely identify an in situ or cancerous lesion. The relationship between the urethral orifice and an eventual lesion in the lower third of the vagina is recorded. All suspicious lesions should be biopsied to confirm the diagnosis of metastases.

At speculum examination, the cervix may appear entirely normal if the cancer is very small (subclinical) or located in the endocervix. For patients with suspected early invasive cancer based on Papanicolaou (Pap) test results and a normal-appearing cervix, colposcopy is mandatory and will identify the most suspicious area to be biopsied. Colposcopic findings suggestive of early cervical cancer are: atypical blood vessels (abnormal in size, shape, calibre, direction), irregular surface contours, an ulcerated, friable and yellow-orange epithelium, large and severe or complex colposcopic abnormalities, and their extension into the canal.

The incidence of cervical adenocarcinomas is increasing, accounting for about 20% of cervical neoplasms. Sometimes the adenocarcinoma appears as a papillary lesion on the portio. However, it generally develops within the canal when the ectocervix appears totally normal, at least initially. In these circumstances, an endocervical curettage is mandatory as the final step of a careful colposcopic examination.

Punch biopsies are adequate for the confirmation of a clinically obvious cancer. However, if the diagnosis cannot be established conclusively with biopsy or endocervical curettage, diagnostic conisation is necessary. Furthermore, punch biopsies are not sufficient for the definitive diagnosis of microinvasive cervical cancer and again a conisation is indicated to correctly assess the depth and horizontal extent of microinvasion involvement as well as vascular penetration.

The lesion on the ectocervix can be exophytic with a cauliflower-like appearance; irregular; variable in size; sometimes with a firm, elevated margin; and haemorrhagic. The lesion can also be ulcerated with an indurated base, in which case the cervix and eventually the vaginal fornices may be replaced by a necrotic crater. Sometimes an infiltrating tumour shows a little visible ulceration or exophytic mass but it is perceived as a stone-hard cervix on palpation. As the tumour develops, a gross cervix may be found (the so-called "barrel-shaped cervix") when a squamous cell carcinoma involves the whole cervix or an infiltrative endocervical tumour develops inside the canal. After examination of the cervix, the vaginal walls and particularly the vaginal fornices are carefully inspected to look for suspicious lesions. Biopsies should be performed.

■ Pelvic examination under anaesthesia

This step of the evaluation, carried out by at least one, generally two, experienced oncologists, is fundamental for the staging of cervical cancer since the true extent of the cancer may be underestimated if rectovaginal examination under anaesthesia is omitted. This examination is indispensable for evaluating the extension of the tumour towards the vaginal fornices, down the vagina, laterally into the parametria, anteriorly into the vesicovaginal space, or posteriorly into the uterosacral ligaments. Vaginal palpation will specify tumour volume, as well as the size and consistency of the cervix. Endophytic or infiltrative cervical cancers can be suspected due to a stone-hard consistency of the cervix upon palpation. Infiltrative vaginal lesions can also be detected during this procedure, but are often missed during vaginal inspection.

Transrectal palpation under anaesthesia is indispensable in evaluating the parametria:

– Are they soft/elastic, or nodular and invaded by the tumour? The tumour is often secondarily infected. It is, therefore, sometimes impossible to know how much of the

fixation and thickening in the parametria are due to tumour or to inflammatory reaction. Preliminary antibiotic and anti-inflammatory treatment can be prescribed.

– Is the invasion unilateral or bilateral?

– Is there tissue fixation onto the pelvic wall? Sometimes a nodular/invaded uterosacral ligament can be felt. An enlarged pelvic lymph node can be palpated. The gynaecologist will evaluate softness and mobility or invasion of the rectum. The eventual invasion of the rectovaginal space can also be detected by inserting the index finger into the vagina and the middle finger into the rectum.

Laboratory investigations

A general biological evaluation using clinical as well as an array of laboratory tests is performed in order to evaluate patient general health, and any metabolic, renal or cardiorespiratory functions which may contraindicate surgery. In addition, haemoglobin levels should be determined and anaemia corrected. Abnormal liver function tests may indicate metastases in this organ. Hypercalcemia may denote advanced disease with bone involvement.

The tumour marker SCC ("squamous cell carcinoma") should be determined prior to any therapy and if elevated, may be a useful marker in assessing response to therapy. Increased serum levels are found in 50% to 75% of locally advanced cancers, and the titer value correlates to stage, tumour volume and prognosis. In adenocarcinomas of the cervix, preoperative measurement of the tumour marker CA125 should be obtained.

Auxiliary examinations for staging

The necessary procedures for staging cervical cancer and the acceptable auxiliary examinations to improve clinical evaluation are listed *(table I)*. Optional investigations, the information from which is not allowed by FIGO to change the clinical stage, are also presented. The findings of the optional investigations are not used in assigning the FIGO stage because the techniques involved are not uniformly available throughout the world, and interpretation of their results is variable. However, the information provided by these optional investigations may be used in planning therapy.

■ Intravenous pyelogram

This examination is frequently normal. However, double ureters can be found and their position determined which is of utmost importance during surgery. The finding of a pelvic kidney must be taken into account when delineating the pelvic fields for radiotherapy. Abnormalities can sometimes be found involving the ureters, bladder or kidneys, particularly in advanced cervical cancers. Any deviation, angulation, rigidity or obstruction of the ureters should be recorded, since they may be directly invaded by the regional spread of the tumour (especially in the vicinity of the bladder), or an adenopathy may compress or deviate them.

Hydronephrosis, secretion retardation or a non-functioning kidney may be present. The bladder may show an encroachment evoking compression, or an irregularity and/or rigidity suggesting invasion by the tumour.

■ Cystoscopy

Cystoscopy is seldom productive in evaluating stage I and II cervical cancer patients. However, this examination is helpful in defining the integrity/invasion of the bladder.

Careful inspection of the mucosa of the bladder, as well as trigone and ureter orifices should be undertaken. A normal, pink bladder mucosa may be the site of erythema or leucoplasia. Single or multiple exophytic growths, granulations, ulcerations, and localised oedema may all be hallmarks of invasion of the bladder mucosa. Biopsies of these suspicious areas are necessary in confirming the diagnosis. It should be remembered, though, that submucosal invasion of the bladder may be missed by cystoscopy.

■ Rectosigmoidoscopy

This is useful only when the tumour invades posteriorly and the rectovaginal space is infiltrated. It allows the observation of rectal and lower colon mucosae that may be normal or congestive, fixed, showing friable and bloody vegetations, or its lumen may be stenosed by extension of the cervical tumour to the muscularis layer. Biopsies should be performed.

■ Chest X-ray (posteroanterior and lateral)

Although pulmonary metastases are uncommon, they need to be ruled out. In advanced disease, lung metastases are present in approximately 5% of cases that would otherwise be stage III or IVa. Chest X-ray is also useful to the anaesthetist for evaluating the cardiorespiratory status of the patient.

■ Skeletal X-ray

This examination is unproductive because bone metastases are rare and frequently symptomatic.

The FIGO staging system

The current staging system of the International Federation of Gynaecology and Obstetrics (FIGO) for cervical carcinoma is presented [5] *(table II)*. This classification applies only to carcinoma, and there should be histological confirmation of the disease. When there is doubt in deciding on a stage, the earlier stage should be chosen. The diagnosis of both stages Ia1 and Ia2 should be based on microscopic examination of removed tissue, preferably a cone, which must include the entire lesion. 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 to the deepest point of invasion. 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 recorded as it may affect future treatment decisions. Lesions of greater size should be staged as Ib. As a rule, it is impossible to estimate clinically whether a cancer of the cervix has extended to the corpus. Extension to the corpus should therefore be disregarded.

Some authors support the subdivision of stage Ia into "early stromal invasion" (i.e. microscopic epithelial neoplastic buds which emanate from the base of a carcinoma in situ), and "microinvasion" to a depth of between 1 and 5 mm. It is argued that there is a significant difference in terms of recurrence, vascular invasion, and survival between the two histopathological entities [3]. The purpose of this classification is to identify a group of patients who are not at risk for lymph node metastases or recurrence and who may be treated conservatively.

Table II. FIGO staging of carcinoma of the cervix uteri.

Pre-invasive Carcinoma	
Stage 0	Carcinoma in situ, intraepithelial carcinoma (these cases should not be included in any therapeutic statistics).
Invasive Carcinoma	
Stage I	Carcinoma strictly confined to the cervix (textension to the corpus should be disregarded).
	Stage Ia Pre-clinical carcinomas, i.e. those diagnosed only by microscopy.
	Stage Ia1 Lesions with ≤ 3 mm invasion.
	Stage Ia2 Lesions detected microscopically that can be measured. Depth of invasion of > 3 to 5 mm. Horizontal spread must not exceed 7 mm.
	Stage Ib Lesions invasive > 5 mm.
	Stage Ib1 Lesions ≤ 4 cm.
	Stage Ib2 Lesions > 4 cm.
Stage II	Carcinoma extends beyond the cervix but not onto the pelvic wall. Carcinoma involves the vagina, but not the lower third.
	Stage IIa No obvious parametrial involvement.
	Stage IIb Obvious parametrial involvement.
Stage III	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 hydronephrosis or non-functioning kidney (unless known to be due to another cause).
	Stage IIIa No extension to the pelvic wall.
	Stage IIIb Extension onto the pelvic wall and/or hydronephrosis or non-functioning kidney.
Stage IV	Carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum.
	Stage IVa Spread of the tumour to adjacent organs.
	Stage IVb Spread to distant organs.

A patient with a tumour fixed to the pelvic wall by a short and indurated but not nodular parametrium should be assigned to stage IIb. On clinical examination, it is impossible to decide whether a smooth, indurated parametrium is truly cancerous or only inflammatory. Therefore, the case should be assigned to stage III only if the parametrium is nodular to the pelvic wall or the tumour itself extends to the pelvic wall. The presence of hydronephrosis or a non-functioning kidney, due to stenosis of the ureter by cancer, means that a case is allotted to stage III even if, according to other findings, it should be assigned to stage I or II.

The presence of a bullous oedema, as such, should not permit a case to be assigned to stage IV. Ridges and furrows in the bladder wall should be interpreted as signs of submucous involvement of the bladder if they remain fixed to the tumour on palpation (i.e. examination from the vagina or the rectum during cystoscopy). Finally, a cytological finding of malignant cells in washings from the bladder requires further examination and a biopsy specimen from the mucosa of the bladder.

Optional investigations

It is obvious that none of the previously described procedures and techniques yields information on the commonest metastatic pathway of cervical cancer: the lymphatic

system. Knowledge of lymph node status, among others, is useful in devising a therapeutic programme for the patient. Thus, lymphangiography, ultrasonography, and, more recently, computerised axial tomography, magnetic resonance imaging, and even fine-needle lymph node aspiration are employed.

It must be emphasised that the results of these investigations will not change the patient's reported stage, but may change her treatment, i.e. an individualised treatment programme, appropriate to the patient's stage and disease. Furthermore, the results of the imaging modalities highlight the limitations of the clinical staging.

■ Lymphangiography

Since lymphangiography is the only examination where the internal architecture of the lymph nodes will be observed, it is, at least theoretically, very important, but it causes some controversy. It is a fairly difficult study, has low sensitivity although excellent specificity, and its role in the future management of patients with cervical cancer is questionable for some oncologists. Sensitivity is lowest with small metastases, and even large nodal deposits can be missed.

A radiotransparent image in an enlarged node is particularly suggestive of nodal invasion, as are blockage or asymmetry of pelvic and para-aortic lymph nodes [11]. Piver et al [12] reported that lymphangiography can detect 78% of histopathologically documented lymph node invasion. Fuchs and Rosenberg [7] showed 87% accurate diagnoses, with 1.5% false positive and 12% false negative results. The main factors that contribute to these rates are: the congenital absence of some lymph nodes, some pelvic and para-aortic nodes are not opacified, inflammation and the size of the metastases (they need to be 5 to 10 mm in diameter to be visible [6]). Tuberculosis or endometriosis can also induce false positive results. Lymphangiography has its merits, however. It has been shown to be of prognostic value in stage III. The overall 5 year survival rate was 58% versus 17%, comparing negative and positive lymphangiographic findings [7]. Similar conclusions were reported by Hammond et al [8] for cervical cancers in stages Ib to IIIb. Moreover, suspect para-aortic nodes can be sampled during surgery, or radiotherapeutic fields extended to involve these areas.

■ Computerised axial tomography (CT scan)

Parametrial (especially its inner third) and vaginal invasion are often undetected. False positive results are also common, since it is difficult to differentiate invasion from inflammation, prior radiation or infection [19]. In contrast, CT scan in advanced cervical cancer (stages IIb to IV) seems capable of improving clinical findings by defining the tumour volume accurately, evaluating adjacent structures for contiguous involvement and also allowing the study of the liver and urinary system [6]. A recent study has shown the positive predictive value of CT scan in predicting bladder invasion to be 60%, with a negative predictive value of 100% [17]. CT scan can allow direct visualisation of the ureters, retroperitoneum, pelvic sidewalls, and adenopathies. The bowel can be opacified and vascular structures enhanced with contrast. For all these reasons, CT scan is of value in monitoring therapy.

Although it cannot detect invasion of normal sized lymph nodes, especially pelvic nodes, this technique has a fair specificity and sensitivity (about 70% to 80%) in identifying abnormal para-aortic lymph nodes [2, 6]. Optimally, positive nodes should be documented by fine-needle aspiration or surgical excision because the CT scan has a 5% to 10% false positive rate [1].

■ Ultrasonography

The genito-urinary and the lymphatic systems can be explored by this technique. It is also useful for patients with leg oedema, in differentiating lymphatic obstruction from deep vein thrombosis. The current use of transvaginal and/or transrectal probes has considerably increased the sensitivity of ultrasonography when evaluating tumour volume and its local spread (parametria, bladder), and can be used to monitor treatment. In addition, hydronephrosis may not only be detected but also followed up during radiotherapy. The sensitivity of ultrasonography is, however, lower than that of lymphangiography and CT scan in detecting lymph nodes. Sonography is also operator-dependent, and is unlikely to give objective and reproducible data for tumour classification.

■ Magnetic resonance imaging (MRI)

MRI seems promising in evaluating parametrial involvement, with a sensitivity of 85% to 92%. Its sensitivity in evaluating the vesicovaginal space has been reported to be between 75% and 85% [6]. Precise measurements of cervical tumours (depth of stromal invasion and tumour volume), and therapy monitoring are obtained particularly in advanced stages, but also in stage Ib [15]. Even high resolution MRI for diagnosis of invaded pelvic lymph nodes has been reported to have only a 68% sensitivity and 78% specificity [9].

■ Comparison of optional investigations

Compared to MRI, CT scan permits effective visualisation of the thorax and upper abdomen. Another advantage of CT scan over MRI is the availability of bowel contrast and visualisation of the urinary tract and hepatic metastases. Unlike MRI, CT scan and sonography-guided fine needle aspiration biopsy provide a means of studying the nature of a suspect lesion located in the parametrium or lymph nodes and of confirming tumour recurrence. However, MRI has a greater capacity than CT scan to discriminate between cancer and normal cervical and uterine tissue. Hence, MRI is more useful in the design of optimal radiation treatment portals.

To evaluate tumour volume, parametrial and vesicovaginal extension, MRI is superior to CT scan and sonography, both in pretherapeutic investigation and in follow-up assessment [4, 6]. It is generally accepted that nodal involvement is better evaluated by lymphography followed by CT scan. However, the results of a recent meta-analysis showed no statistically significant difference comparing lymphography, CT scan and MRI in the evaluation of lymph node metastases [16]. When a recurrence is suspected, a CT scan should be performed. Eventually, as a second-line examination, MRI may also help to differentiate between fibrosis and relapse of disease.

■ Laparoscopy

Considering the discordance ranging from 30% to 70% between clinical staging and findings during surgery [18, 20], laparoscopy can improve cervical cancer staging. Unsuspected or inconspicuous intraperitoneal, adnexal or liver metastases may be diagnosed. Intraperitoneal biopsies and washings can be carried out and discriminate between inflammation and invasion. Moreover, laparoscopic evaluation and sampling of pelvic and para-aortic lymph nodes have been reported to have a sensitivity and specificity of about 92% in identifying disease [14] and this may change the primary therapy offered to the patient.

Surgical and pathological staging

Some factors (e.g. absence or presence and level of lymph node metastases, or subclinical parametrial extension) which have prognostic significance and affect the selection and sequencing of treatment modalities are not taken into account in clinical staging.

Surgical staging of patients with cervical cancer shows that a proportion have extrapelvic lymph node metastases lying outside conventional radiation fields. Treatment with extended volume radiation fields can result in salvaging some of these patients [13]. However, surgical staging may delay initiation of radiation and increase treatment complications (e.g. deep vein thrombosis, pulmonary embolus, bowel obstruction). Furthermore, the novel and more accurate imaging techniques can spare cervical cancer patients the potential morbidity and mortality of surgical staging.

After surgery, the pathological findings in the removed specimens can form the basis for very precise evaluation of the extent of the disease: pathological staging. These findings should not alter the clinical staging but should be recorded, to help management of the patient and as valuable prognostic parameters.

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Invasive carcinoma of the cervix

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