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Cervical cancer – pre-therapeutic investigations and clinical staging "versus" surgical staging

CARLOS F. DE OLIVEIRA, M.D., PH.D.,
FERNANDO MOTA, M.D., PH.D.

Gynaecological Service, University Hospital, Coimbra

ABSTRACT Accurate staging of cervical cancer is essential for optimising the results of therapy, because therapy and prognosis vary considerably with the stage. It has been agreed that the staging of a cervical cancer is predominantly a clinical process. Pelvic examination under anaesthesia is indispensable when evaluating the parametria. Cervical cancer generally spreads via local and then regional lymphatics. Lymph node status is crucial in terms of prognosis and therapy of cervical cancer, although it is not incorporated in the FIGO staging classification. The major techniques for evaluating lymph node status include lymphangiography, CT-scan, ultrasonography, MRI and PET. There is a difference in the incidence of pelvic lymph node metastasis comparing stage IB (10-15%), IIA (10-25%) and IIB (25-40%). The obturator group is the most frequently involved. Available studies suggest that the obturator nodes are the primary and sentinel nodes in cervical carcinoma. The preliminary data showed that in early stages, the sentinel node was bilateral in 96% of cases and the sensitivity of the method was 100%. The identification rate was about 80%. The incidence of paraaortic nodes is different according to clinical stages: IB (5-15%), IIB (15-30%) and IIIB (30-45%). The value of surgical staging in the management of cervical cancer is controversial. Pre-treatment surgical staging in patients with cervical cancer has some important benefits: 1. it is the most sensitive and specific of all modalities for the identification of lymph node metastases, 2. it is possible to resect enlarged tumour-containing lymph nodes improving clinical outcome, 3 according to the true extent of the disease, it is possible to modify therapy, 4. it identifies patients with poor prognostic factors, 5. it allows disease downstaging, 6. it increases survival. However, those opposed to the routine use of pre-treatment surgical staging in cervical carcinoma argue that: 1. only a small number of patients can benefit from extended field treatment (±10%), 2. there is significant morbidity associated with the surgical procedure, 3. there is an increased risk of radiation injury after staging laparotomy, 4. there is the possibility of delaying the initiation of radiotherapy. Laparoscopic staging has been proposed as an alternative to laparotomy with a high sensitivity and specificity. Laparoscopy has several advantages, such as minimal invasion, little adhesion formation and quick recovery of the patient in comparison with laparotomy.

Key words staging, cervical cancer, preoperative investigations, surgery, laparoscopy

Address correspondence to:

Carlos F. de Oliveira, M.D.
Gynaecological Service
University Hospital of Coimbra
3049 Coimbra Codex, Portugal
Phone (351 39) 400 400 Fax (351 39) 721 478
E-mail de.oliveira@mail.telepac.pt

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

CLINICAL STAGING It is agreed that the staging of a cervical cancer is predominantly a clinical process, preferably with the patient anaesthetised. It cannot be changed later if findings with operation or subsequent treatment reveal further disease, since this "upstaging" of patients would produce an erroneous improvement in the results of treatment of early-stage disease.

CLINICAL EXAMINATION AND COMPLEMENTARY PROCEDURES The great majority of patients have a normal general physical examination. However, the inguinal lymph nodes may be palpated, particularly if the lower third of the vagina is 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 should be carried out to look for ascites or hepatomegaly. The aetiology of a pleural effusion or a swollen leg should be investigated. All these conditions may be due to metastatic disease.

Examination of the vulva and perineum may identify an in situ or a cancerous lesion. The relationship between the

Table 1. FIGO staging of carcinoma of the cervix uteri (Montreal, 1994)

Preinvasive carcinoma		
Stage 0		Carcinoma in situ, cervical intraepithelial neoplasia
Invasive carcinoma		
Stage I		The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
	IA	Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions – even with superficial invasion – are T1B/stage IB
	IA1	Stromal invasion ≤3 mm in depth and 7.0 mm or less in horizontal spread
	IA2	Stromal invasion >3 mm and <5 mm with a horizontal spread <7.0 mm
	IB	Clinically visible lesions limited to the cervix or pre-clinical cancers greater than stage IA
	IB1	Clinically visible lesions ≤4 cm
	IB2	Clinically visible lesions >4 cm
Stage II		The carcinoma extends beyond the uterus but not to the pelvic wall or to the lower third of the vagina
	IIA	No obvious parametrial involvement
	IIB	Obvious parametrial involvement
Stage III		The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumour and the pelvic wall. The tumour involves the lower third of the vagina. All cases with hydronephrosis or non-functioning kidney (unless known to be due to another cause)
	IIIA	Tumour involves lower-third of the vagina, with no extension to the pelvic wall
	IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage IV		The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum
	IVA	Spread of the tumour to adjacent organs
	IVB	Spread to distant organs

urethral orifice and an eventual lesion in the lower third of the vagina should be recorded. All suspicious lesions should be biopsied to confirm the diagnosis of metastasis.

At speculum examination, the cervix may appear entirely normal if the cancer is very small (subclinical) or located in the endocervix. Moreover, for patients with suspected early invasive cancer based on Papanicolaou (Pap) test results and a normal-appearing cervix, colposcopy is mandatory to 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 contour; ulcerated, friable and yellow-orange epithelium; large and severe or complex colposcopic abnormalities; and extension of these abnormalities into the canal.

The incidence of cervical adenocarcinomas is increasing. Sometimes the adenocarcinoma appears as a papillary lesion on the cervix. However, they generally develop within the canal when, initially, the ectocervix appears totally normal. 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 conization is necessary. Furthermore, punch biopsies are not sufficient for the definitive diagnosis of microinvasive cervical cancer and, again, a conization is indicated to assess correctly the depth and the horizontal extent of microinvasion.

The lesion on the ectocervix may be exophytic with a cauliflower-like appearance, irregular, variable in size, sometimes with a firm elevated margin and haemorragic. The lesion may 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 tends to show little visible ulceration or exophytic mass but 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 is developing inside the canal. After the examination of the cervix, the vaginal walls and particularly the vaginal fornices should be 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 the evaluation of 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. Tumour volume and the size and consistency of the cervix can be estimated by vaginal palpation. Endophytic or infiltrative cervical cancers can be suspected by the stone-hard consistency of the cervix on palpation. Infiltrative vaginal lesions can also be detected during this procedure and are often missed during vaginal inspection.

Transrectal palpation under anaesthesia is indispensable to evaluate the parametria. Are they soft/elastic or nodular/invaded by

the tumour? Is there tissue fixation onto the pelvic wall? Sometimes a nodular/invaded uterosacral ligament may be felt. An enlarged pelvic lymph node may be palpated. The gynaecologist can evaluate the softness, mobility or, in contrast, the invasion of rectum. The eventual invasion of the rectovaginal space can also be detected by inserting the index finger in the vagina and the middle finger in the rectum. According to our data (1), the pelvic examination under anaesthesia showed a sensitivity of 40% (5.3-85.4), a specificity of 90% (55.5-99.7), a positive predictive value of 66.7% (9.4-99.2) and a negative predictive value of 75% (42.8-94.5).

FIGO STAGING The current staging system of the International Federation of Gynaecology and Obstetrics – FIGO for cervical carcinoma (Montreal, 1994) is presented in *Table 1*. This classification applies only to carcinoma, and there should be histological confirmation of the disease. When there is doubt concerning the stage to which a cancer should be assigned, the earlier stage should be chosen. Other important FIGO guidelines for cervical cancer staging will be described. 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 treatment decisions in the future. 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 between 1 and 5 mm. It is argued that there is a significant difference in terms of recurrences, vascular invasion and survival between the two histopathologic entities (2). The purpose of this classification is to identify a group of patients who are not at risk of lymph node metastases or recurrences and who may be treated conservatively.

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. At 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 non-functioning kidney due to stenosis of the ureter by cancer allows a case to be 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 into 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.

AUXILIARY STUDIES FOR STAGING The procedures necessary for staging cervical cancer and the acceptable auxiliary studies that will improve the clinical evaluation are listed in *Table 2*.

INTRAVENOUS PYELOGRAM Frequently this exam is normal. However, double ureters can be found, and their position determined; this is of utmost importance during surgery. The finding of a pelvic kidney will be taken into account when delineating the pelvic fields for radiotherapy.

Sometimes alterations can be found involving the ureters, bladder or kidneys, particularly in advanced cervical cancers.

Table 2 Pre-therapeutic investigations

Clinical examination	General physical examination
	Genital examination
	Bimanual rectovaginal examination (under anaesthesia)
Procedures	Colposcopy
	Biopsy
	Endocervical curettage
	Conization
Auxiliary studies	Intravenous pyelogram
	Cystoscopy
	Rectosigmoidoscopy
	Barium enema
	Chest x-ray
	Skeletal x-ray
Optional studies	Lymphangiography
	Computerised axial tomography
	Ultrasonography
	Magnetic resonance imaging
	Radionucleotide scanning
	Positron emission tomography

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 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 exam is helpful to define the integrity/invasion of the bladder. Careful inspection of the mucosa of the bladder – along with trigone and ureter orifices – should be undertaken. A normal pink bladder mucosa may be the site of erythema or leucoplakia. 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 to confirm the diagnosis. It should be remembered, though, that submucosal invasion of the bladder may be missed by cystoscopy.

RECTOSIGMOIDOSCOPY This is only useful when the tumour invades posteriorly and when 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 the lumen being stenosed by extension of the cervical tumour to the muscularis layer. Biopsies should be performed.

BARIUM ENEMA Colon contrast studies are only warranted in advanced disease and when clinically indicated. *Shingleton et al.* (3) reported that only 1 out of 340 patients with stage I and II cervical cancer had an abnormality due to the tumour, compared to 7.5% of 212 patients with stage III and IV disease. Barium enema can detect small serosal implants to adjacent bowel (4).

CHEST X-RAY (POSTERO-ANTERIOR AND LATERAL) Although pulmonary metastases are uncommon, they should be ruled out. In advanced disease, lung metastases are present in approximately 5% of the cases that would otherwise be stage III or IVA. Chest X-ray is also useful to the anaesthetist in evaluating the cardio-respiratory status of the patient.

SKELETAL X-RAY This exam is unproductive because bone metastases are rare and frequently are symptomatic.

OPTIONAL STUDIES FOR STAGING Optional studies, whose information is not allowed by FIGO to change the clinical stage, are also presented in *Table 2.* The findings of the optional studies are not used for assigning the FIGO stage because the techniques involved are not uniformly available throughout the world, and because the interpretation of their results is variable. However, the information provided by these optional studies may be used in planning therapy.

It is obvious that none of the previously described procedures and techniques will yield information on the most common metastatic pathway of cervical cancer, the lymphatic system. Knowledge of the lymph node status, among others, is useful in planning a therapeutic programme for the patient. Thus, lymphangiography (LAG), ultrasonography (US), and more recently computerised axial tomography (CT-scan), magnetic resonance imaging (MRI), positron emission tomography (PET) and even fine-needle lymph node aspiration have been employed. It should be emphasised that the results of these investigations will not change the patient's reported stage, but may change her treatment and individualised treatment programme as appropriate to the patient's stage and disease. Furthermore, the results of the imaging modalities highlight the limitations of the clinical staging.

LYMPHANGIOGRAPHY At least theoretically very important, since lymphangiography is the only examination where the internal architecture of lymph nodes will be observed. Its use raises some controversies because 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, along with blockage or asymmetry of pelvic and paraaortic lymph nodes, is particularly suggestive of nodal invasion (5). *Piver et al.* (6) reported that lymphangiography can detect 78% of histopathologycally documented invasion. *Fuchs and Rosenberg* (7) showed 87% of accurate diagnosis, 1.5% of false positivity and 12% of false negativity. The main factors that contribute to these rates are: congenital absence of some lymph nodes; some pelvic and paraaortic nodes are not opacified; inflammation, which along with tuberculosis or endometriosis may induce false positive results; and the size of the metastases should be 5 to 10 mm in diameter to be visible (8).

Lymphangiography has, however, its merits. It has been shown to be of prognostic value in stage III. Overall 5-year survival is 58 versus 17% when comparing negative and positive lymphangiographic findings (7). Similar conclusions were reported by *Hammond et al.* (9) for cervical cancers in stages IB to IIIB. Moreover, suspect paraaortic nodes may be sampled during surgery, or radiotherapeutic fields may be extended to involve these areas.

A Gynaecologic Oncology Group study (GOG-63) reported by *Heller et al.* (10) showed for lymphangiography a sensiti-

vity of 78.6%, a specificity of 73% and the percentage of false-negative findings were 8.2%. *Table 3* presents the results of this study concerning the paraaortic (PAN) and the pelvic (PLN) lymph nodes.

Table 3. Results of lymphangiography used to evaluate paraaortic and pelvic lymph nodes (10)

Lymphangiography	Paraaortic lymph nodes +	Pelvic lymph nodes+
Positive	56/44 (79%)	185/50 (27%)
Negative	56/12 (21%)	185/135 (73%)
Unsatisfactory	64/8	200/15

COMPUTERISED AXIAL TOMOGRAPHY (CT-SCAN) Parametrial (particularly 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 (11). 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, as well as allowing the study of the liver and urinary system (12). A recent study has shown that the positive predictive value of CT-scan in predicting bladder invasion is 60%, with a negative predictive value of 100% (13). 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 to monitor therapy.

Although it cannot detect invasion of normal-sized lymph nodes, especially pelvic nodes, this technique has a fair specificity and sensitivity of about 70 to 80% in identifing abnormal paraaortic lymph nodes (12-14). *Table 4* shows the results of the GOG protocol 63 (10) concerning CT-scan.

Table 4. Results of computerized axial tomography used to evaluate paraaortic and pelvic lymph nodes (10)

Computerized axial tomography	Paraaortic lymph nodes +	Pelvic lymph nodes+
Positive	61/21 (34%)	192/8 (4%)
Negative	61/40 (66%)	192/184 (96%)
Unsatisfactory	64/3	200/8

ULTRASONOGRAPHY The genito-urinary system and the lymphatic system can be explored using this technique. Furthermore, it can be useful to the patient with leg oedema to differentiate lymphatic obstruction from deep vein thrombosis. The use of transvaginal and/or transrectal probes considerably increases the sensitivity of ultrasonography in evaluating the tumour volume and its local spread (parametria, bladder), which can be used to monitor treatment. In addition, hydronephrosis may not only be detected but also followedup during radiotherapy. The sensitivity of ultrasonography is, however, lower than lymphangiography and CT-scan to detect lymph nodes *(Table 5)*. Sonography is also operator-dependent, and is unlike to give objective and reproducible data for tumour classification.

Table 5. Results of ultrasonography used to evaluate paraaortic and pelvic lymph nodes nodes (10)

Ultrasonography	Paraaortic lymph nodes+	Pelvic lymph nodes+
Positive	54/10 (19%)	160/2 (1%)
Negative	54/44 (81%)	160/158 (99%)
Unsatisfactory	64/10	200/40

MAGNETIC RESONANCE IMAGING (MRI) MRI seems promising as a means of evaluating parametrial involvement, with a sensitivity of 85 to 92%. For parametrial involvement, we found a sensitivity of 80% (28.4-99.5), a specificity of 80% (44.4-97.5), a positive predictive value of 66.7% (22.3-95.7) and a negative predictive value of 88.9% (51.7-99.7) (1). Its sensitivity to evaluate the vesicovaginal space has been reported to be between 75 to 85% (12). Precise measurements of cervical tumours (depth of stromal invasion and tumour volume), and therapy monitoring are obtained using this technique, particularly in advanced stages, but in stage IB as well(15). For stromal invasion, we found an accuracy of 100% (1). Even high resolution MRI for diagnosing pelvic lymph node metastases has been reported to have only a 68% sensitivity and 78% specificity (16). *Table 6* shows the results of MRI in the staging of carcinoma of the uterine cervix, compared with the pathological findings at surgery, in order to assess the accuracy of MRI in the evaluation of disease extent (17).

Table 6. Results of MRI used to evaluate parametria and nodes (17)

MRI	Parametria	Nodes
Sensitivity	71%	38%
Specificity	87%	84%
Accuracy	85%	76%

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 provides a means to study the nature of a suspect lesion located in the parametrium or lymph nodes, and confirm 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 designing optimal radiation treatment portals.

To evaluate tumour volume, parametrial and vesicovaginal extension, MRI is superior to CT-scan and sonography, either as pre-therapeutic investigation or in follow-up assessment (12-19). 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 (18). 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.

POSITRON EMISSION TOMOGRAPHY (PET) Positron emission tomography scanning is a novel technique for the study of malignancies. *Rose et al.* (20) undertook a prospective study to evaluate PET scanning in detecting paraaortic nodal metastasis in patients with locally-advanced cervical cancer. The role of PET imaging is defined, in part, by the radiopharmaceuticals used. One of these, 2-[18F] fluoro-2-deoxy-D-glucose (FDG) is useful in oncology, because many tumours have high glycolitic rates. Cervical cancers have a high avidity for FDG. *Table 7* shows the results of PET-FDG.

Table 7. Results of PET-FDG used to evaluate lymph nodes in locallyadvanced cervical cancer (20)

PET-FDG	Paraaortic lymph nodes	Pelvic lymph nodes
Sensitivity	75%	100%
Specificity	92%	100%
PPV	75%	100%
NPV	92%	100%

PPV positive predictive value NPV negative predictive value

LYMPH NODE STATUS Cervical cancers generally spread via local and then regional lymphatics. It is conceivable that distant metastases may occur due to failure to treat involved lymph nodes adequately. An early-stage tumour considered curable by surgery may be better treated by radiotherapy or chemotherapy in the presence of lymph node metastases. In advanced stages, radiotherapy to the pelvis may be insufficient when paraaortic lymph nodes are also invaded (21). Lymph node status is crucial in terms of prognosis and therapy of cervical cancer, although it is not incorporated in the FIGO staging classification.

PELVIC NODES *Table 8* shows the results of a *French* (22) and a *Japanese study* (23) on the incidence of pelvic node metastases in patients with cervical cancer stages I and II. There is a difference in the incidence of pelvic lymph node metastasis comparing stage IB and stages IIA and IIB. The obturator group was the most frequently involved: 18% (French study) and 19% (Japanese study). On the other hand, common iliac nodes were involved in 4 and 9%, external iliac nodes in 11 and 4%, and parametrial node involvement was found in 5 and 9%, respectively.

Table 8. Incidence of pelvic node metastases in stages I and II

Stages	*Michel et al.* (22)	*Sakuragi et al.* (23)
IB	299/51 (17%)	96/11 (12%)
IIA	26/3 (12%)	15/4 (27%)
IIB	96/24 (25%)	97/38 (39%)

Table 9 shows the parametrial and pelvic lymph node involvement according to clinical stages I and II (24). In this study parametrial node involvement was correlated to the involvement of the pelvic nodes. The pelvic nodes were negative in 74 and positive in 26% of patients with negative parametrial nodes. Conversely, the pelvic nodes were positive in 81 and negative in 19% of patients with positive parametrial nodes.

Table 9. Parametrial and pelvic lymph node involvement according to clinical stage I and II (24)

Stages	Parametrial nodes	Pelvic lymph nodes
IB	15/132 (11%)	36/132 (27%)
IIA	1/8 (13%)	2/8 (25%)
IIB	47/219 (22%)	89/219 (41%)

In stage III, the incidence of pelvic lymph node metastasis is variable and greater than in stages I and II: 55% for *LaPolla et al.* (25) and 66% for *Downey et al.* (26).

Table 10 shows the incidence of paraaortic lymph node metastasis according to pelvic node involvement (23). When pelvic nodes were negative, the incidence of paraaortic lymph node metastasis was 0.5 to 1%. When pelvic nodes were positive, the incidence of paraaortic lymph mode metastasis varied from 28% (multiple positive pelvic nodes) to 32% (bilateral positive pelvic nodes) and 37% (common iliac positive nodes). According to the data of this study, the incidence of positive paraaortic metastasis increased from 5% (one pelvic node involved) to 17% (2 or 3 pelvic nodes involved) or to 46% (more than 4 pelvic nodes involved).

Table 10. Incidence of paraaortic lymph node metastasis according to pelvic lymph node involvement in stages I and II (23)

Pelvic lymph nodes	Negative	Positive
Multiple*	1/179 (0.6%)	8/29 (28%)
Bilateral*	1/183 (0.5%)	8/25 (32%)
Common iliac	2/189 (1%)	7/19 (37%)

*excluding common iliac lymph node

Downey et al. (26) reported the overall 5-year survival according to the pelvic nodal status in patient's stages I, II and III: negative pelvic nodes 81%, positive pelvic nodes with only microscopic metastasis 64%, positive pelvic nodes with macroscopic resected metastasis 52%, and positive pelvic nodes with macroscopic unresected metastasis 0%.

Concerning the resection of bulky positive lymph nodes in patients with cervical carcinoma stages I, II and III submitted to radical hysterectomy, *Hacker et al.* (27) reported that the survival for patients with completely resected bulky pelvic and common iliac nodes was comparable to that for patients with micrometastasis. The study suggests that every effort should be made to identify patients with cervical cancer who have bulky positive lymph node metastasis, and to remove these nodes surgically prior to radiation therapy. The risk factors associated with pelvic lymph node metastasis include capillary-lymphatic space involvement, depth of invasion, parametrial involvement and tumour size (10, 23).

The results of previously mentioned studies suggest that the obturator nodes are the primary and sentinel nodes in cervical carcinoma, since they are the first to be colonised by cancer cells. In a prospective study conducted by *Echt et al.* (28), the sentinel lymph node was found in 15.4% (2/13) of cervical cancer patients. Moreover, *Dargent et al.* (29) tried to identify the sentinel node in early-stage cervical cancer using laparoscopy. The preliminary results showed that the sentinel node was bilateral in 96% of cases and the sensitivity of the method was 100%. The identification rate was 76.5% and increased when the injection of a dye solution was done in the four quadrants of the cervix in addition to the lateral fornices.

PARAAORTIC NODES *Table 11* shows the incidence, in different series (10, 25, 30-32), of paraaortic lymph node involvement according to clinical stage.

Table 11. Literature data showing the incidence of paraaortic metastasis according to clinical stages

Stages	*Lagasse et al.* (30)	*LaPolla et al.* (25)	*Heller et al.* (10)	*Cosin et al.* (31)	*Holcomb et al.* (32)
IB	6%	-	-	16%	-
IIB	32%	15%	21%	12%	13%
IIIB	31%	38%	32%	41%	32%
IVA	33%	33%	13%	33%	50%

Cosin et al. (31) showed that in a group of 266 patients with cervical carcinoma who underwent extraperitoneal pelvic and paraaortic lymphadenectomy prior to receiving radiotherapy, lymph node metastases were detected in 50% of patients. The disease-free survival at 5 and 10 years for patients without lymph node metastases was 75 and 68%, respectively. This was significantly better than the survival rate for patients who had resected microscopically positive pelvic and/or paraaortic lymph nodes (43 and 35%, respectively), as well as that for patients who had macroscopically positive pelvic and/or paraaortic lymph nodes that were resected completely at the time of surgery. Moreover, all patients who had unresected lymph nodes recurred and died before 3 years. In contrast, *Kim et al.* (33) did not show a statistically significant advantage in survival when excising grossly involved paraaortic lymph nodes. Long-term survival among women with grossly involved, unresected paraaortic metastases was uncommon.

Table 12 Locally advanced cervical carcinoma: recurrence patterns in pre-treatment laparotomy group versus clinical staging group (32)

Group	None	Pelvic	Distant	Persistent disease	Total
Laparotomy	33 (43%)	3 (4%)	14 (19%)	26 (34%)	76
Clinical	38 (25%)	13 (9%)	13 (9%)	87 (57%)	151
Total	71 (31%)	16 (7%)	27 (12%)	113 (50%)	227

Table 12 outlines the recurrence patterns for two different groups of patients, the first undergoing pre-treatment laparotomy and the second undergoing only clinical staging (32). The median survival of patients in the first group was statistically longer than that of patients in the second group, 29 months versus 19 months. Multivariate analysis controlling for both stage and age showed that pre-treatment staging laparotomy is a significant predictor of survival in patients with locally advanced cervical carcinoma.

The *GOG* (34) evaluated the patterns of recurrence in cervical cancer metastatic to paraaortic lymph nodes. *Table 13* shows the sites of recurrence.

Table 13. Sites of recurrence following treatment of cervical carcinoma with periaortic metastases (34)

Site of recurrence	Number of cases	%
None	33	34
Pelvic	21	22
Vagina	4	4
Distant	26	27
Local and distant	4	4
Unspecified	8	8

Table 14. Recurrence patterns by lymph node groups (34)

Lymph node group	Pelvic recurrence	Distant recurrence
Negative lymph node	6 (5%)	12 (10%)
Microscopic resected lymph node	4 (11%)	7 (20%)
Macroscopic resected lymph node	9 (13%)	12 (17%)
Unresectable lymph node	0	6 (86%)

Cosin et al. (31) correlated lymph node status and recurrence patterns, which is summarised in *Table 14. Sakuragy et al.* (23) demonstrated that the size of the tumour can predict the presence of paraaortic lymph node metastases (≤2 cm 2%; ≥4 cm 16%). *Podczaski et al.* (35) estimated the survival of patients with or without paraaortic nodal involvement as assessed by pre-treatment laparotomy. Patient survival was adversely affected by the presence of paraaortic nodal metastases. Two- and five-year actuarial survivals for patients with paraaortic nodal involvement were 35 and 27%, respectively. In contrast, patients without paraaortic node metastases had 2- and 5-year actuarial survival rates of 72 and 50%, respectively.

INTRAPERITONEAL DISEASE The presence of intraperitoneal disease is one of the major factors to predict patient survival (35). The incidence of intraperitoneal disease was recorded in different studies as varying between 6 (35), 10 (25) and 12% (32). The *GOG study* (10) included pelvic cytology as a protocol requirement. This information revealed that paraaortic nodes were positive when washings were positive 44% of the time. Pelvic nodes were positive when washings were positive in 60% of the cases.

The concept of ovarian preservation at the time of radical hysterectomy for stage IB squamous cell cancers of the cervix is well established. Concerning the adenocarcinoma, the percentage of ovarian metastases varies according to some clinical features. *Natsume et al.* (36) performed a retrospective study of patients treated for cervical adenocarcinoma to identify pathologic factors associated with ovarian metastasis. The incidence of ovarian metastases was more frequent in stage II (19%) than in stage IB (2.5%). No patients with stromal invasion up to the inner two-thirds had ovarian metastases. By contrast, 20.8% of patients with outer one-third stromal invasion and 2.5% with parametrial invasion had ovarian metastases. A significantly higher incidence of ovarian metastases was also observed in patients with lymph node metastases (25%) than in patients without lymph node metastases (6.5%). Multivariate analysis, however, found only deep stromal invasion to be an independent risk factor for ovarian metastases.

SURGICAL STAGING

STAGING LAPAROTOMY The value of surgical staging in the management of cervical cancer is controversial because the information obtained may only benefit a limited number of patients (approximately 10%). However, surgical staging for cervix cancer is the most exact means of determining disease extent which can be used to optimise treatment. Pre-treatment staging laparotomy consists of intraperitoneal exploration with pelvic and paraaortic lymph node sampling. The retroperitoneal space can be reached by a transperitoneal incision or by extraperitoneal access. In both cases, lymph node biopsies, resection of bulky positive lymph nodes or lymphadenectomy is possible. Moreover, intraperitoneal exploration is always carried out and consists of inspection, palpation of viscera and lymph nodes. Cytological washings and biopsy of any suspicious lesions should be performed.

Pre-treatment surgical staging in patients with cervical cancer has some important benefits: 1. it is the most sensitive and specific of all modalities for the identification of lymph node metastases, 2. it is possible to resect enlarged tumour-containing lymph nodes improving clinical outcome, 3. according to the true extent of the disease it is possible to modify therapy, 4. it identifies patients with poor prognostic

Table 15. Staging laparotomy – complications

Complications	Number of cases (%)	Approach	Authors
Pulmonary embolus	2/276 (0.7)	Extra	*Cosin et al.* (31)
	2/89 (2)	Extra	*Holcomb et al.* (32)
	0/43	Extra/Trans	*Kim et al.* (33)
	2/44 (5)	Trans	*LaPolla et al.* (25)
	0/34	Extra	
Venous/arterial injury	0/276	Extra	*Cosin et al.* (31)
	0/21 (19)	Trans	*Kim et al.* (33)
	0/16 (12)	Extra	
	4/44 (9)	Trans	*LaPolla et al.* (25)
	4/34 (12)	Extra	
	4/155 (3)	Trans	*Podzarski et al.* (35)
	0/104	Extra	

Extra extraperitoneal Trans transperitoneal

Table 16. Staging laparotomy – complications

Complications	Number of cases (%)	Approach	Authors
Deaths	3/276 (3)	Extra	*Cosin et al.* (31)
	1/89 (1)	Extra	*Holcomb et al.* (32)
	0/43	Extra/Trans	*Kim et al.* (33)
	1/44 (2)	Trans	*LaPolla et al.* (25)
	0/34	Extra	
Intestinal	20/276 (7)	Extra	*Cosin et al.* (31)
	4/21 (19)	Trans	*Kim et al.* (33)
	2/16 (12)	Extra	
	6/33 (18)	Extra	*Hacker et al.* (27)
	3/51	Trans	*Podzarski et al.* (35)
	3/104	Extra	

Extra extraperitoneal Trans transperitoneal

factors, 5. it allows disease downstaging and 6. it increases survival.

However, the limitations should not be neglected: 1. only a small number of patients can benefit from extended field treatment, 2. there is important morbidity associated with the surgical procedure, 3. there is an increased risk of radiation injury after staging laparotomy and 4. there is the possibility of delaying radiotherapy.

Tables 15 and *16* show the complications of staging laparotomy in different studies (25, 27, 31-33, 35). According to these data, it is not very clear if there is a significant difference in terms of complications between the transperitoneal

Table 17. Staging laparotomy – complications (25)

Complications	Transperitoneal	Extraperitoneal
Intraoperative	6/44 (14)	5/43 (12)
Early postoperative	9/44 (20)	4/43 (9)
Late postoperative	4/44 (9)	1/43 (2)
No complications	38/44 (86)	31/43 (72)

Table 18. Comparision of clinical staging with the results of surgical staging (30)

Clinical stage	Patients with less advanced stage	Patients with more advanced stage	Total patients
IB	0	35 (24%)	143
IIA	0	12 (55%)	22
IIB	3	28 (49%)	58
IIIA	0	1 (50%)	2
IIIB	3	27 (44%)	61
IVA	0	2 (67%)	3
IVB	0	0	1
Total	6 (2%)	105 (36%)	290

incision or the extraperitoneal access. However, the data of *LaPolla et al.* (25) comparing the different access to the retroperitoneal space *(Table 17)* shows a decreased number of complications when the extraperitoneal access is used.

STAGING LAPAROSCOPY Considering the improvements of laparoscopy, gynaecological surgeons increasingly use this technique for staging and treatment of patients with cervical cancer. Gynaecological malignancies were not suitable to laparoscopic management until the technique of paraaortic lymphadenectomy became possible. Laparoscopic staging has been proposed as an alternative to laparotomy. *Possover et al.* (21) evaluated the lymph node status by laparoscopy in 84 patients with cervical cancer and reported a sensitivity of 92.3%, a specificity of 92.9%, a positive predictive value of 70.6% and a negative predictive value of 98.5%. Laparoscopy has several advantages, including minor trauma, little adhesion formation, decreased blood loss, better recognition of tumour and more rapid recovery of the patient in comparison with laparotomy.

Concerning the number of lymph nodes removed laparoscopically, *Possover et al.* (21) reported 31.1 pelvic nodes and 10.9 paraaortic lymph nodes, *Fowler et al.* (37) 23.5 pelvic nodes, and, in patients who underwent radical hysterectomy, *Childers et al.* (38) reported that 91% of pelvic and paraaortic nodes were removed at the time of laparoscopy.

CLINICAL STAGING "VERSUS" SURGICAL STAGING The GOG study reported by *Lagasse et al.* (30) shows that the comparison of clinical stage with results of operative evaluation revealed less advanced disease in 2% of patients. In 36% of patients, either the local tumour was more advanced than predicted clinically or there were metastases involving the pelvic or paraaortic lymph nodes *(Table 18)*.

The data from *LaPolla et al.* (25) indicated that in 80 patients with stage IIB or greater disease, 34% showed more advanced disease at surgical staging and 14% showed less advanced disease *(Table 19)*. The patients with more advanced disease had either peritoneal, omental or lymph node metastases. Patients with operative findings demonstrating less tumour than clinical examination had chronic pelvic inflammatory disease, endometriomas, fibroids or benign ovarian tumours.

Table 19. Comparision of clinical staging with the results of surgical staging (25)

Clinical stage	Patients with less advanced stage	Patients with more advanced stage	Total patients
IIB	4 (10%)	14 (36%)	39
IIIA	0	0	1
IIIB	7 (19%)	12 (32%)	37
IVA	0	1 (33%)	3
Total	11 (14%)	27 (34%)	80

By means of surgical staging, a substantial proportion of patients with cervical cancer has been found to have disease outside the usual fields of treatment. It remains to be demonstrated if improved survival in these patients can be achieved by more aggressive treatment in randomized trials.

REFERENCES

1. Jorge AFM. Estadiamento dos tumores uterinos por Ressonância Magnética. Thesis. Serviço de Ginecologia dos Hospitais da Universidade de Coimbra. Coimbra, 1995.

2. Burghard E, Ostor A, Fox H. The new FIGO definition of cervical cancer stage IA: a critique. Gynecol Oncol 1997; 65:1-5.

3. Shingleton HM, Fowler WC, Koch GG. Pretreatment evaluation in cervical cancer. Am J Obstet Gynecol 1971; 110:385-389.

4. Gedgaudas RK, Kelvin FM, Thompson WR, et al. The value of the preoperative barium-enema examination in the assessment of pelvic masses. Radiology 1983; 146:609-613.

5. Leman M, Park R, Barham D. Pretreatment lymphangiography in carcinoma of the uterine cervix. Gynecol Oncol 1975; 3:354-360.

6. Piver MS, Wallace S, Castro JR. The accuracy of lymphangiography in carcinoma of the uterine cervix. Am J Roentgenol 1971; 3:278-283.

7. Fuchs WA, Rosenberg GS. Lymphography in carcinoma of the cervix. Acta Radiol 1975; 16:353-361.

8. Koelher PR, Wohl GT, Schaffer B. Lymphangiography, A survey of its current status. Am J Roentgenol 1964; 92:1216-1223.

9. Hammond JA, Herson J, Freedman RS, et al. The impact of lymph node status on survival in cervical carcinoma. Int J Rad Oncol Biol Phys 1981; 7:1713-1718.

10. Heller PB, Malfetano JH, Bundy BN et al. Clinical-pathologic study of stage IIB, III and IVA carcinoma of the cervix: extended diagnostic evaluation for paraaortic node metastases - a Gynecologic Oncology Group Study. Gynecol Oncol 1990; 38:425-430.

11. Villasanta V, Whittley NO, Haney PJ, et al. Computed tomography in invasive carcinoma of the cervix: an appraisal. Obstet Gynecol 1983; 62: 218-224.

12. Darbois Buthiau D, Dargent D. Cancer du col utérin. In: Buthiau D, Khayat D, eds. Scanner et IRM en cancérologie. Berlin, Springer Verlag, 1995: 279-290.

13. Sundborg MJ Taylor RR, Mark J, et al. Cystoscopy after computed tomography scan to identify bladder invasion in cervical cancer. Obstet Gynecol 1998; 92:364-366.

14. Brenner DE, Whitley NO, Prempee T, et al. An evaluation of the computed tomographic scanner for the staging of carcinoma of the cervix. Cancer 1982; 50:2323-2328.

15. Rubens D, Thornbury JR, Angel C, et al. Stage IB cervical carcinoma: comparision of clinical, MR and pathologic staging. Am J Rad 1988; 150:135-138.

16. Hawighorst H, Schoenberg SO, Knapstein PG, et al. Staging of invasive cervical carcinoma and of pelvic lymph nodes by high resolution MRI with a phased-array coil in comparison with pathological findings. J Comp Ass Tomog 1998; 22:75-81.

17. Greco A, Mason P, Leung WL, et al. Staging of carcinoma of the uterine cervix: MRI-surgical correlation. Clin Radiol 1989; 40:401-405.

18. Scheidler J, Hricak H, Yu KK, et al. Radiological evaluation of lymph node metastases in patients with cervical cancer. A meta-analysis. JAMA 1997; 278:1096-1101.

19. Cobby M, Browning J, Jones A, et al. Magnetic resonance imaging, computed tomography and endosonography in the local staging of carcinoma of the cervix. Br J Radiol 1990; 63:673-679.

20. Rose PG, Adler LP, Rodriguez M, et al. Positron emission tomography for evaluation paraaortic nodal metastases in locally advanced cervical cancer before surgical staging: A surgical-pathologic study. J Clin Oncol 1999; 17:41-45.

21. Possover M, Krause N, Kuhne-Heid R, et al. Value of laparoscopic evaluation of paraaortic and pelvic lymph nodes for treatment of cervical cancer. Am J Obstet Gynecol 1998; 178:806-810.

22. Michel G, Morice P, Castaigne D, et al. Lymphatic spread in stage IB and II cervical carcinoma: anatomy and surgical implications. Obstet Gynecol 1998; 91:360-363.

23. Sakuragi N, Satoh C, Takeda N, et al. Incidence and distribution pattern of pelvic and paraaortic lymph node metastasis in patients with stages IB, IIA and IIB cervical carcinoma treated with radical hysterectomy. Cancer 1999; 85:1547-1554.

24. Girardi F, Lichtenegger W, Tamussino K, et al. The importance of parametrial lymph nodes in the treatment of cervical cancer. Gynecol Oncol 1989; 34:206-211.

25. LaPolla JP, Schlaerth JB, Gaddis O, et al. The influence of surgical staging on the evaluation and treatment of patients with cervical carcinoma. Gynecol Oncol 1986; 24:194-206.

26. Downey GO, Potish RA, Adcock LL, et al. Pre-treatment surgical staging in cervical carcinoma: Therapeutic efficacy of pelvic lymph node resection. Am J Obstet Gynecol 1989; 160:1055-1061.

27. Hacker NF, Wain GV, Nicklin JL. Resection of bulky positive lymph nodes in patients with cervical carcinoma. Int J Gynecol Cancer 1995; 5:250-256.

28. Echt ML, Finan MA, Hoffman MS, et al. Detection of sentinel lymph nodes with lymphazurin in cervical, uterine and vulvar malignancies. South Med J 1999; 92:204-208.

29. Dargent D, Martin X, Roy M, et al. Identification of a sentinel node with laparoscopy in cervical cancer. Abstract Book SGO 2000, San Diego, Abstract 44, pp 128.

30. Lagasse LD, Creasman WT, Shingleton HM, et al. Results and complications of operative staging in cervical cancer: experience of the Gynecologic Oncology Group. Gynecol Oncol 1980; 9:90-98.

31. Cosin JA, Fowler JM, Chen MD, et al. Pretreatment surgical staging of patients with cervical carcinoma. The case for lymph node debulking. Cancer 1998; 82:2241-2248.

32. Holcomb K, Abulafia O, Matthews RP. The impact of pretreatment staging laparotomy on survival in locally advanced cervical carcinoma. Eur J Gynaecol Oncol 1999; 20:90-93.

33. Kim PY, Monk BJ, Chabra S, et al. Cervical cancer with paraaortic metastases: significance of residual paraaortic disease after surgical staging. Gynecol Oncol 1998; 69:243-247.

34. Berman ML, Keys H, Cresman W, et al. Survival and patterns of recurrence in cervical cancer metastatic to periaortic lymph nodes. Gynecol Oncol 1984; 19:8-16.

35. Podczaski ES, Palombo C, Manetta A, et al. Assessment of pretreatment laparotomy in patients with cervical carcinoma prior radiotherapy. Gynecol Oncol 1989; 33:71-75.

36. Naysume N, Aoki Y, Kase H, et al. Ovarian metastasis in stage IB and II cervical adenocarcinoma. Gynecol Oncol 1999; 74:255-258.

37. Fowler JM, Carter JR, Carlson JW, et al. Lymph node yield from laparoscopic lymphanenectomy in cervical cancer: a comparative study. Gynecol Oncol 1993; 51:187-192.

38. Childers JM, Hatch K, Surwit EA. The role of laparoscopic lymphadenectomy in the management of cervical carcinoma. Gynecol Oncol 1992; 47:38-43.