Chapter 8
Cervical Cancer Staging

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Abstract Cervical cancer (CC) is an important cause of morbidity and mortality worldwide in female populations. Because the prognosis and management of these patients depends on proper staging, emphasis must be placed on ensuring that health care professionals are perfectly familiar with current standards. Cervical Cancer staging is still achieved clinically. In some cases, it relies on surgical staging and diagnostic imaging tools that have widely progressed to improve their ability to detect tumor foci and distant site extensions. A section about preinvasive lesions is included in this chapter as a preamble to invasive lesions, which are the topic of the present text.

Keywords Cervical cancer • Staging • Clinical profile • Prognosis • TNM • FIGO • Physical examination

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J.G. de la Garza-Salazar et al. (eds.), *Cervical Cancer*,
DOI 10.1007/978-3-319-45231-9_8

8.1 Uterine Cervix Preinvasive Lesions

HPV infection precedes the CC carcinogenic process (as discussed in a previous chapter). Most invasive lesions are preceded by an intraepithelial lesion or a Cervical Intraepithelial Neoplasia (CIN). Most CIN develop in the cervix transformation zone, which is located in the squamo-columnar junction between the endocervix columnar epithelium and the ectocervix squamous epithelium. This area is called the transformation zone because it undergoes a columnar epithelial metaplasia process toward the external cervical orifice in response to different factors, including pH and hormonal changes, throughout a woman's life. CIN's form a spectrum comprising a neoplastic cell continuum according to observed changes in the cytoplasm, the loss of nuclear polarity, pleomorphism, and mitosis. They are divided into CIN 1, in which only the inferior one-third of the epithelium is affected; CIN 2, in which the lesion extends up to the middle one-third of the epithelium, and CIN 3, in which the lesion has extended through the entire thickness of the epithelium [1].

The mean time to a CIN 3 or in situ carcinoma development from the moment of an initial HPV16 infection is between 7 and 12 years, whereas in a high risk HPV-positive CIN 1, the development time is 6 years [2].

The most widely used CC screening study is still cervical-vaginal cytology. It is important to disclaim the notion that colposcopy is not a screening method because it requires an extensive amount of resources and preparation to be adequately performed. However, all cytological abnormalities must be further analyzed by colposcopy. The goal is to reveal aberrations that can guide biopsy collection with the aim of ruling out invasive cancer [3].

8.2 Treatment of Premalignant Lesions

Low grade squamous intraepithelial lesions (LG-SILs) and atypical squamous epithelium of undetermined significance (ASE-US).

Because LG-SILs can spontaneously resolve within less than 24 months, women diagnosed with LG-SIL may be kept under surveillance, with periodic cytological exams every 6 months [4]. Recent recommendations include the use of a "co-assay", in which the results of a high-risk HPV detection test are combined with (e.g.: hybrid capture) a cytological test because the combination results in sensitivity that reaches 90–100% [5] and better predicts the development of high grade lesions or cancer.

In the case of a negative high-risk HPV test but a LG-SIL-coherent cytology, it is recommended that the test be repeated after 1 year. If at that time the cytology shows AS-EUS, a larger lesion, or the presence of a high-risk HPV virus, a colposcopy and guided biopsy are performed. Conversely, if both tests yield negative results, no cytological propagation is observed, and the high risk-HPV virus test is also negative, both tests can be repeated in 3 years [6].

In contrast, in postmenopausal women, LG-SIL cases can be assessed by performing a co-assay within 6 months or directly proceeding to perform a colposcopy and a biopsy. If the HPV test yields negative results for the presence of high-risk viruses or no lesions are identified in colposcopy, the co-assay is performed 1 year later. If the result is AS-EUS or higher, colposcopy is performed, otherwise, routine screens are performed [7].

In patients with CIN1 according to biopsy results in which this finding is preceded by a cytological determination of LG-SIL or AS-EUS, the co-assay must be performed after 1 year. If both are negative, routine screens are performed. If CIN 1 persists for 2 years, it is acceptable to either continue with surveillance or treat the lesion. Both ablation and scission can be used, but the former treatment implies a satisfactory colposcopy. In cases in which the second assessment shows CIN 2 or higher, the lesion must be treated.

In patients with CIN 2 preceded by LG-SIL or AS-EUS, the follow-up protocol is more intense. It includes a diagnostic scission procedure, and during follow-up, the co-assay is performed once every 1 or 2 years. If patients show normal results in successive assays, they return to 3 year follow-up [8].

Current recommendations suggest performing a colposcopy when the examination shows an ASC-US, LG-SIL, H-ASC and Atypical Glandular Cells (AGC) and when there is a positive HPV test. After LG-SIL cytology and an inadequate colposcopy or positive endocervical curettage, an excisional procedure is recommended to achieve a more accurate diagnosis and treatment protocol. Any CIN 2 or CIN 3 histological diagnosis based on a cervical biopsy must be followed by excision of the transformation zone unless the patient is pregnant [7].

In cases in which a malignant macroscopic lesion is identified in the cervix uteri, it is necessary to perform a staging procedure, that corresponds to the magnitude of the disease. It is also important to know the signs and symptoms that are presented in invasive disease.

8.3 Clinical Profile and Physical Examination

All women with precursor lesions or in situ carcinoma are asymptomatic, although there may be clinical manifestations that are associated with the disease because of the presence of concomitant infections. In invasive cancer cases, as dissemination progresses, signs and symptoms begin to appear. The most frequent sign is transvaginal hemorrhage, which is most often post-coital, intermenstrual, or postmenopausal. Moreover, tumor necrosis produces serosanguinous smelly fluid.

These types of symptoms appear early in exofitic tumors of the ectocervix. However, in endocervical tumors, the manifestations are subtle, even in advanced disease. This underscores the importance of perfect endocervical canal sampling, during which the sample is obtained prior to the cytology [9].

In locally advanced and metastatic stages, the patient may lose weight and have inguinal and/or supraclavicular lymph node enlargement. A bad smell can also be

perceived as a result of postcoital bleeding. Bladder or rectal invasion result in the appearance of fistulae, hematuria and hematochezia, pelvic pain, sciatic nerve region pain, leg edema, lumbar pain, and, in the presence of extension to the contiguous viscera, sacral plexus affection and lymphatic, vascular or uretral obstruction.

It is worth mentioning that exploration is more difficult in postmenopausal women because lesions are frequently located in an endocervical location and the uterine cervix is atrophic and not easy to visualize. Furthermore, vaginal examinations are more difficult in these patients because of atrophia, the loss of elasticity, and a reduction in patient complaint.

After an inspection, a bimanual exploration is performed to evaluate the shape, dimensions, and mobility of the uterus, including the uterine cervix and parametria. The uterus may be enlarged because of endometrial infiltration, uterine collection, or the presence of concomitant miomatosis and the possible coexistence of anexial involvement. If the uterus is fixed, it is certain to be because of tumor infiltration towards the pelvic wall. To evaluate its extension towards the parametria, bladder, and rectum, it is necessary to perform a careful rectovaginal exploration: the right side of the pelvis (parametrium) is palpated with the right hand, and the left side is palpated with the left hand (introducing the middle finger through the rectum and the index finger through the vagina [9]). When a parametrium is involved, it is usually irregular, nodular and painful at touch.

During the physical examination, it is important to explore the lympho-porting areas. If, during the exploration of the supraclavicular or inguinal region, any suspicious increase in the volume of lymph nodes is noticed, fine needle aspiration biopsy can reasonably rule out metastatic disease.

Additional analyses can be useful for accurate staging, and, in some cases, laboratory results can be prognostic (e.g., hemoglobin). It is important to keep in mind that these tools provide only more precise information that is difficult to obtain through physical examination.

A very important prognostic factor that can differ across clinicians during exploration is tumor size. Hence, confirmation by a qualified expert is crucial, mainly during the early stages of the disease, because tumor size, depth of invasion, and stromal involvement are correlated with each other [9].

In clinical stages II, III, and IV, poor prognostic indicators include the presence of the disease in the pelvic nodes, a growth in the size of the primary tumor, low hemoglobin levels, and functional status.

8.4 Clinical Staging

In cervical cancer, stage assigning is based on clinical data. Experience is required for staging to be reproducible and reliable. Thus, CC clinical staging rules are based on gynecological clinical explorations that are performed by an expert, preferably while the patient is under anesthesia (although this depends on the health center). The initially assigned clinical stage should be maintained and remain unchanged despite subsequent new discoveries even in cases of recurrence [10].

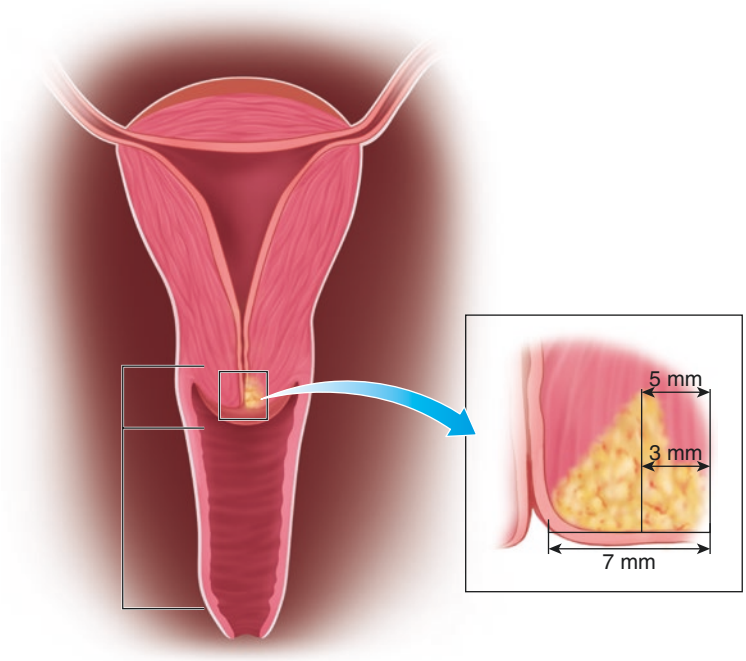


Fig. 8.1 Stage Ia1: There is a cancerous area of 3 millimeters (mm) or smaller in depth, and 7 mm or smaller in length. Stage Ia2:There is a cancerous area larger than 3 mm but not larger than 5 mm in depth, and 7 mm or smaller in length

The currently used staging system is the one that was adopted by the International Federation of Gynecology and Obstetrics (FIGO). It should be taken into consideration that the staging system is useful only for comparative purposes and must not be taken as an indication of norms. Each clinical case must be individually considered and supported by imaging methods before proposing the best treatment plan. According to the FIGO, clinical exploration is the gold standard for CC staging. Tumor diameter, vaginal infiltration, and tumor extension to parameters and septi (e.g., the vesicovaginal septum and rectovaginal septum) represent the morphological parameters that should be considered during CC staging, as follows:

In 2009, FIGO revisited CC staging and established the following [11]:

Stage 0: In situ carcinoma, intraepithelial carcinoma.
Stage I: Carcinoma strictly limited to the cervix (Fig. 8.1).

Stage Ia: Invasive cancer identified only in microscopy, stromal invasion is no more than 5 mm deep and 7 mm wide.
Stage Ia1: Stromal invasion <3 mm deep and <7 mm in extension or width.
The incidence of lymphatic nodal metastasis in stage IaI is 0.1–2.6%, in most cases, it is less than 1% [12].

Stage Ia2: Stromal invasion >3 mm but <5 mm in depth and <7 mm in extension. In this stage, the risk of metastasis to pelvic and para-aortic lymph nodes ranges from 0 to 9.7% [13].

The depth of the invasion must not be more than 5 mm from the base of the epithelium and the surface of the glands from which they originate. The involvement of the vascular, venous of lymphatic space must not alter staging.

Stage Ib: Lesions clinically confined to the cervix or preclinical lesions larger than stage Ia2.

Stage Ib1: Lesions clinically visible but no larger than 4 cm.

The risk of nodal pelvic or para-aortic metastasis in stage Ib1 ranges from 10% to 22% [14].

Stage Ib2: Clinically visible lesions are larger than 4 cm (Fig. 8.2).

Stage II: The Carcinoma has extended further than the uterus but not to the pelvic wall or the inferior one-third of the vagina.

Stage IIa: Engagement of two thirds of the superior part of the vagina without affecting the parametrium.

Stage IIa1: Clinically visible lesion <4 cm in its largest dimension.

Stage IIa2: Clinically visible lesion >4 cm in its largest dimension (Fig. 8.3).

Stage IIb: Parametrium infiltration without affecting the pelvic wall.

Pelvic lymph node metastasis is generally 10–27% in stage II, and para-aortic lymph node involvement occurs in 7–25% of stage II cases [12]. Other authors claim that in stage IIb, the incidence of para-aortic node involvement is 19.8% [15] (Fig. 8.4).

Stage III: Involvement of the inferior third of the vagina or extension to the pelvic wall. In a rectal examination, no cancer-free space is observed between the tumor and the pelvic wall. All hydronephrosis and non-functioning kidney are included unless they can be attributed to other causes.

Stage IIIa: Involvement of the inferior third of the vagina but extension no to the pelvic wall.

Stage IIIb: Extension towards the pelvic wall and hydronephrosis or a non-functioning kidney (Fig. 8.5).

Nodal involvement in this stage extends to the pelvic nodes in as many as 43% and to the para-aortic nodes in 7–25% of cases [12]. Other authors argue that in stage III, nodal affection is usually up to 27.5% [15].

Stage IV: Extension out of the pelvis or a clinically invasion of bladder mucosa or rectum.

Stage IVa: Tumor involves bladder or rectal mucosa.

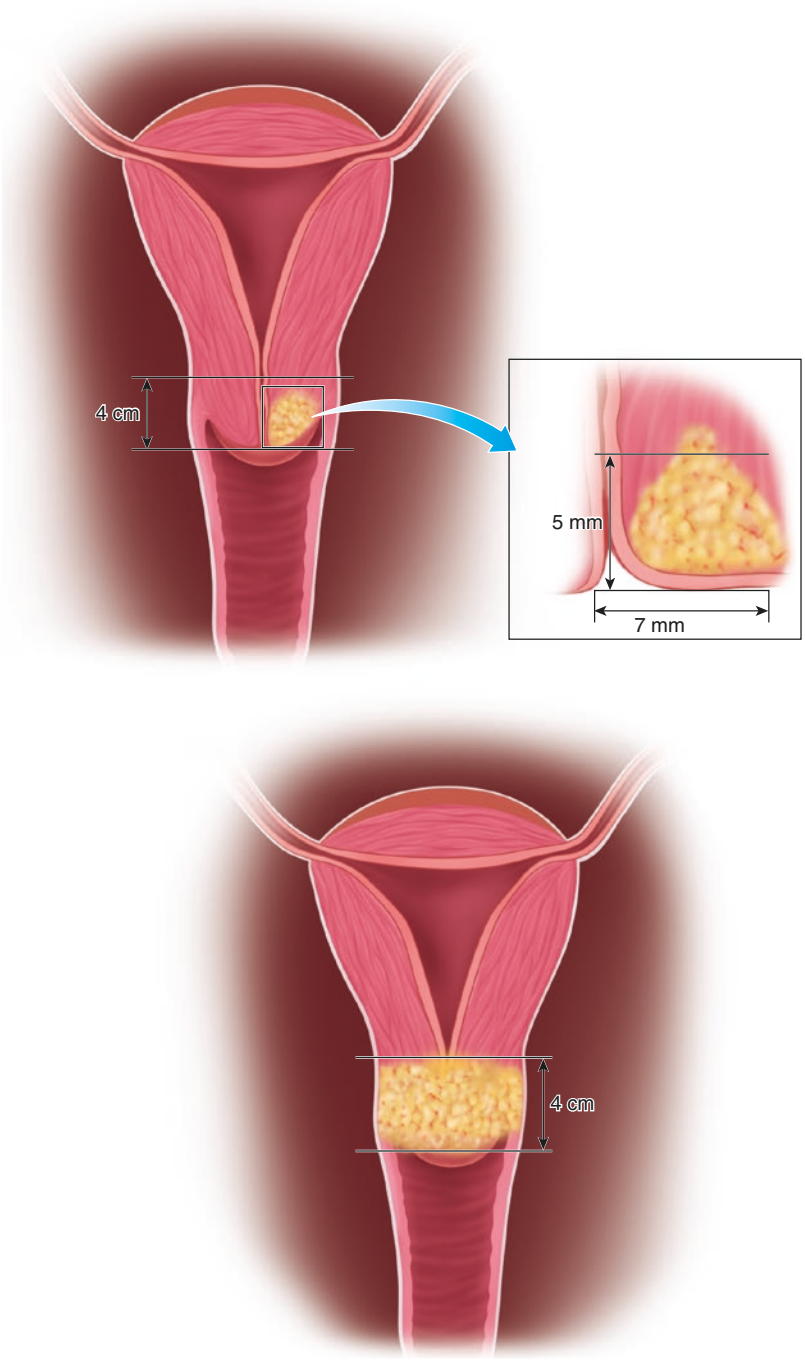


Fig. 8.2 CC stages Ib1-Ib2: Ib1 tumor less than 4 cm and Ib2 tumor greater than 4 cm

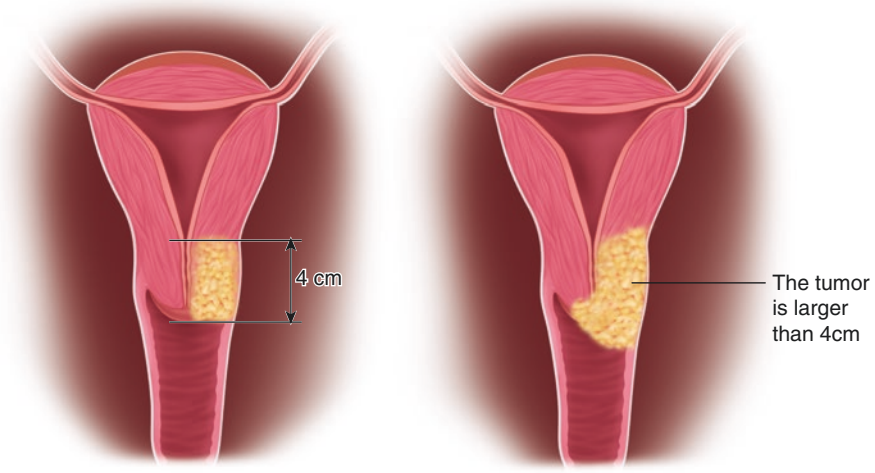
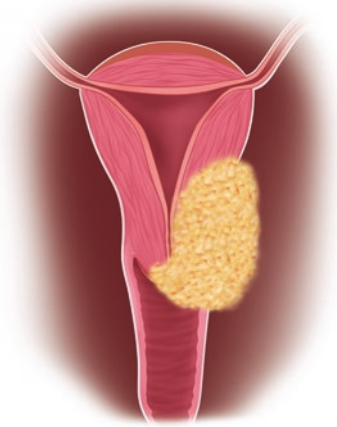


Fig. 8.3 Stages IIa1-IIa2. The tumor has not spread to the tissue next to the cervix, also called the parametrial area.

Fig. 8.4 CC stages IIb. The tumor has spread to the parametrial (tissue surrounding the uterus) area.



Stage IVb: Distant metastasis or disease outside the true pelvis (Fig. 8.6).

Nearly 5–35% of CC patients will develop metastasis to the lungs. Some other common metastasis sites are the bones (16%), liver (3%) and intestines. Bone affection happens via hematic dissemination, and small intestine affection can occur as a result of the direct extension of the para-aortic nodes or via peritoneal dissemination [16].

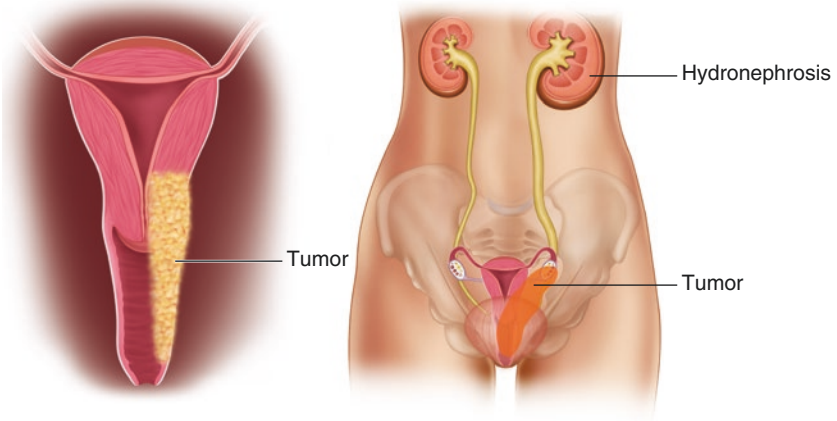


Fig. 8.5 CC stages IIIa. The tumor involves the lower third of the vagina, but it has not grown into the pelvic wall. IIIb. The tumor has grown into the pelvic wall and/or causes hydronephrosis or nonfunctioning kidneys.

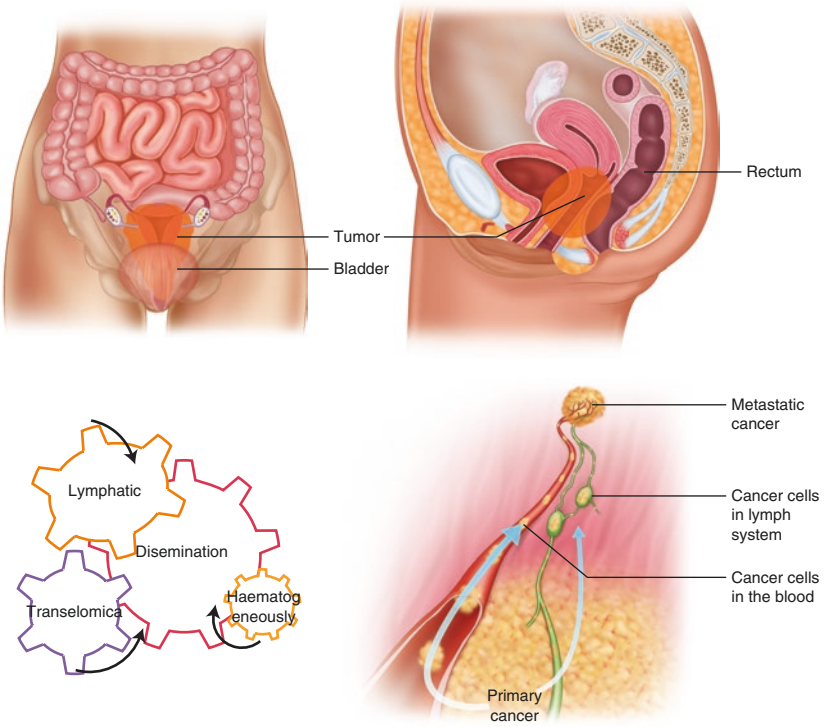


Fig. 8.6 CC stages IVa and Ivb. The tumor has spread to the mucosa (lining) of the bladder or rectum and grown beyond the pelvis.

8.5 Surgical Staging

When performing surgical treatment, histopathological findings can affect CC staging. Thus, the TNM nomenclature, which was approved by the American Joint Committee on Cancer (AJCC) and is in its 7th edition, is generally used.

The cases must be classified as CC if the primary site of origin is the cervix. All histologic types are included. The grade is determined according to the widely used methods, but the grade does not affect staging.

The nomenclature includes the following:

Tx = The primary tumor cannot be assessed.
T0 = No evidence of a primary tumor.
Tis = In situ carcinoma.

- T1 = Cervical carcinoma confined to the uterus.
  - T1a = Invasive carcinoma diagnosed by microscopy only.
  - T1a1 = Stromal invasion of 3 mm or less in depth and 7 mm or less in horizontal extension.
  - T1a2 = Stromal invasion of more than 3 mm but less than 5 mm with a horizontal extension of 7 mm or less.
  - T1b = Clinically visible lesion confined to the cervix or microscopically visible but larger than T1a/Ia2.
  - T1b2 = Clinically visible lesion of 4 cm or less at its largest part.
- T2 = Cervical carcinoma that invades further than the uterus but not towards the pelvic wall or the inferior one-third of the vagina.
  - T2a = Tumor without invasion to the parametria.
    - T2a1 = Clinically visible lesion of 4 cm or less in its largest part.
    - T2a2 = Clinically visible lesion of more than 4 cm in its largest part.
  - T2b = Tumor with invasion into the parametria.
- T3 = Tumor is extended to the pelvic wall or involves the inferior one-third of the vagina, and/or causes hydronephrosis or a dysfunctional kidney.
  - T3a: The tumor involves the inferior one-third of the vagina without extending to the pelvic wall.
  - T3b: Tumor has extended to the pelvic wall and/or causes hydronephrosis or a non-functioning kidney.
- T4 = The tumor invades the bladder or rectum mucosa or it extends further than the true pelvis.

Nx = Regional lymphatic nodes cannot be evaluated.
N0 = There is no metastasis to regional lymphatic nodes.
N1 = Metastasis to regional lymphatic nodes.

M0 = No distant metastasis.

M1 = Distant metastasis (including peritoneal extension, the supraclavicular, mediastinal, or para-aortic nodes, and the lungs, liver, or bones).

In most clinical scenarios, the first treatment is defined by the clinical stage, while the pathological stage is useful for direct adjuvant therapy, whether it includes radiotherapy or chemotherapy.

The pathologic classification of TNM does not replace the TNM clinical classification but instead provides additional information mostly related to local and distant recurrence and reveals the presence of hidden residual disease or micrometastases, at the beginning of presentation [17].

Cervical cancer is disseminated through the lymphatic system. Hence, the first place where metastases appear is the pelvic lymph nodes, followed by the para-aortic nodes. Laparotomy and laparoscopy are the most widely used methods for nodal evaluation in CC, given that they have similar sensitivities. The most important survival prognosis factor is a nodal status [18].

8.6 Imaging Studies

Although the FIGO staging system does not include imaging to stage CC, committees promote the use of these imaging techniques to allow for the determination of prognostic factors, such as tumor size, parametrial involvement or pelvic wall involvement, and adjacent organ invasion or lymphatic node metastasis [19]. These are valuable for determining a treatment plan, but must not be used to modify the initial clinical stage of the patient.

In has been shown that transrectal ultrasound is superior to MRI for detecting tumor after biopsies because it calculates volume with a higher precision and evaluates parametrial invasion. The role of the ultrasound has improved as a result of the advent of novel technologies and the implementation of high frequency transducers that allow a higher quality image to be obtained. The advantages of ultrasound over MRI are that the former has a lower cost, is less invasive and faster to be performed, more availability, and does not require contrast, unlike MRI. However, ultrasound is operator-dependent, and interpretation of ultrasound data is therefore variable [20].

CT- scan (Computed Axial Tomography) has a sensitivity of 32–80% in the evaluation of CC and a parametrial invasion sensitivity of 17–100% with a mean of 64% in CC. Specificity is 50–100%, with a mean of 81%. The VPP to evaluate nodal involvement is 51–65%, with a VPN of 86–96% and a sensitivity of 31–65% [21]. However, Innocenti et al. reported that transvaginal ultrasound had a higher sensitivity for detecting parametrial infiltration than surgical staging (78% vs 50%, $p = 0.06$) [22, 23].

Excretory urography is the only imaging tool that is recommended for diagnosing ureteral obstruction according to the FIGO. It is mandatory for all patients except those in early stages IA1 to IB1. Its use requires intestinal preparation, proper renal

function, and the use of contrast agents, and it is thus a very expensive method that is more time-consuming and takes a longer time to yield results than other methods. Nonetheless, no recent studies have supported the use of the ultrasound as an alternative imaging tool for detecting ureteral obstructions or hydronephrosis [24].

The advantages of the pyelogram are that it allows for an intermediate visualization of the whole urinary system, the urinary tract and the parenchyma, and presents the possibility of allowing the identification of interrelationships, such as those between the cup and the renal papilla, ureter alterations or those in the ureteric mucosa, and the presence of fistulae [25]. Its disadvantages include the following: it uses ionizing radiation and contrast, it is more expensive than ultrasound, its precision depends on renal function, it has a low definition for observing minimal lesions, and it provides a poor characterization of renal masses. Generally, this imaging method is not indicated for CC patients because ultrasound, CT-scan and MRI provide a better evaluation and higher precision [25].

Chest X-ray is used to evaluate pleural effusions and metastatic disease to the lung parenchyma in stage IVB patients. Although it does not have the specificity of chest CT-scan, it has a lower cost and is available in more hospital units [21].

In 2015, Devine proposed a CC staging system that was based on MRI findings, as follows [26]:

Stage I: Tumors in microinvasive stage IA are not observed in MRI, although they can be detected as early reinforcement foci in dynamic contrast images.

Stage II: Tumor invasion towards the vagina can be observed as T2 hyperintensity. It interrupts the vaginal walls, which are normally hypointense. It is important to keep in mind that physical exploration is more precise than MRI for observing vaginal fornices, and MRI is superior to gynecological exploration for detecting parametrial invasion (sensitivity, 69% and specificity, 93%). The precision of physical exploration is 50%.

Stage III: The internal obturator, the levator ani, and the piriform muscles show hyperintense infiltration when a tumor is involved.

Stage IV: When there is invasion into adjacent organs, a separation plane loss can be observed in the fat between the cervix and the bladder or the rectum. The abnormally high signal intensity in the vesical wall is an indicator of tumor involvement, but is confirmed with cystoscopy as a bullous edema.

When extrapelvic retroperitoneal lymph node enlargements are identified using CT or MRI, a guided biopsy is recommended to confirm the findings and better planning the treatment regimen.

The sensitivity (66.6%) and specificity (98%) of MRI are higher than the rates for gynecological exploration for local disease, also has a 50% sensitivity and 96.8% specificity to detect metastasis to the pelvic nodes, and 66.6% sensitivity and 100% specificity for paraortic nodes [27]. Detecting metastasis to lymph nodes using MRI is based upon size, including a 1 cm or larger axis diameter. Larger nodes are generally reactive, while smaller ones can contain neoplastic activity microscopic foci.

PET and PET/CT are the most accurate diagnostic methods that can be used to evaluate exptrapelvic disease in locally advanced CC. Their high rate of true-positive results suggests that surgical staging is unnecessary when using PET-CT, when there is high uptake in the para-aortic nodes. The para-aortic node involvement false positive rate is 12%, and these cases are mainly attributed to nodal disease of 5 mm or less. If we only consider the patients with pelvic uptake, the para-aortic node false negative rate is 22% [28] However, when evaluating hepatic metastasis, there is a higher sensitivity and specificity in PET/MRI or even MRI over PET/CT [29]. In spite of its actual importance, surgical staging of the retroperitoneal nodes is highly relevant because it allows us to more accurately detect pelvic or para-aortic metastases , improving survival rates when more radical treatment is advised.

In 2004, 531 new cases of invasive cancer were registered in the INCan's records. The resulting clinical stage distribution was as follows: CSI: 19%, CSII: 40%, III: 24%, IV: 5%, and 11%. Patients were not classified according to any previous treatment. These results show that there is a tendency to diagnose in less advanced stages, thanks to screening and prevention methods that have recently gained recognition.

8.7 Conclusions

Cervical Cancer staging is performed in a clinical setting because it requires basic tools that can be used in any hospital clinic throughout the world. Proposing a universal classification system would allow the establishment of a common language for the international medical community. However, histopathological staging is necessary to widen the available sources of information and to assess patient prognoses. Imaging methods are mainly helpful in patients in advanced disease stages or patients who are recurrent. Hence, it is important to plan more accurate therapeutic strategies as a function of each patient's stage.

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