INVASIVE CERVICAL CANCER

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INCIDENCE AND MORTALITY

- Cancer of the uterine cervix is the third most common gynecologic cancer diagnosis and cause of death among gynecologic cancers in the United States.
- Unfortunately, in countries that do not have access to cervical cancer screening and prevention programs, cervical cancer remains the second most common type of cancer (17.8 per 100,000 women) and cause of cancer deaths (9.8 per 100,000) among all types of cancer in women.

- Globally, cervical cancer accounted for an estimated 530,000 new cancer cases worldwide and for 275,000 deaths in 2008.
- Eighty-six percent of new cervical cancer cases will be seen in developing countries. Worldwide, the mortality rate from cervical cancer is 52 percent.
- Global incidence and mortality rates depend upon the presence of screening programs for cervical precancer and cancer and of human papillomavirus vaccination, which are most likely to be available in developed countries.
- Due to these interventions, there has been a 75 percent decrease in the incidence and mortality of cervical cancer over the past 50 years in developed countries

AGE DISTRIBUTION

- Worldwide in 2008, the cumulative risks of developing cervical cancer and of cervical cancer mortality by age 75 years were: developed countries (0.9 percent incidence/0.3 percent mortality) and developing countries (1.9 percent/1.1 percent)

RISK FACTORS

- Early onset of sexual activity – compared with age at first intercourse of 21 years or older, the risk is approximately 1.5-fold for 18 to 20 years and two-fold for younger than 18 years
- Multiple sexual partners – compared with one partner, the risk is approximately two-fold with two partners and three-fold with 6 or more partners
- A high-risk sexual partner (eg, a partner with multiple sexual partners or known human papillomavirus infection)
- History of sexually transmitted infections (eg, Chlamydia trachomatis, genital herpes)

- History of vulvar or vaginal squamous intraepithelial neoplasia or cancer (HPV infection is also the etiology of most cases of these conditions)
- Immunosuppression (eg, human immunodeficiency virus infection)
- Cervical cancer is less common in sexual partners of circumcised males
- Early age at first birth (younger than 20 years old) and increasing parity (3 or more full term births) are also associated with an increased risk of cervical cancer, these are also likely due to exposure to HPV through sexual intercourse

RISK FACTORS

- Low socioeconomic status is associated with an increased risk of cervical cancer.
- In the United States, cervical cancer incidence and mortality is higher in nonwhite than in white women
- Oral contraceptive use has been reported to be associated with an increased risk of cervical cancer.
- In contrast to squamous cell cancer of the cervix, cigarette smoking is **not** associated with a significantly increased risk of adenocarcinoma of the cervix compared to nonsmokers (squamous cell carcinoma: RR 1.50, 95% CI 1.35–1.66; adenocarcinoma: RR 0.86, 95% CI 0.70–1.05).
- Genetics —There is no well-established model of a genetic basis for cervical cancer. Population studies have shown an increased incidence of cervical cancer within families. such familial clustering had been attributed to shared environmental exposures and risk factors.

PATHOGENESIS AND HISTOPATHOLOGY

- Subtypes HPV 16 and 18 are found in over 70 percent of all cervical cancers.
  1. Squamous cell carcinoma – HPV 16 (59 percent of cases); 18 (13 percent); 58 (5 percent); 33 (5 percent); 45 (4 percent)
  2. Adenocarcinoma – HPV 16 (36 percent); 18 (37 percent); 45 (5 percent); 31(2 percent); 33 (2 percent)
- the distribution of histologic types is:
  1. Squamous cell carcinoma – 69 percent
  2. Adenocarcinoma (including adenosquamous) – 25 percent
  3. Other histologies – 6 percent

Histopathology of cervical cancer

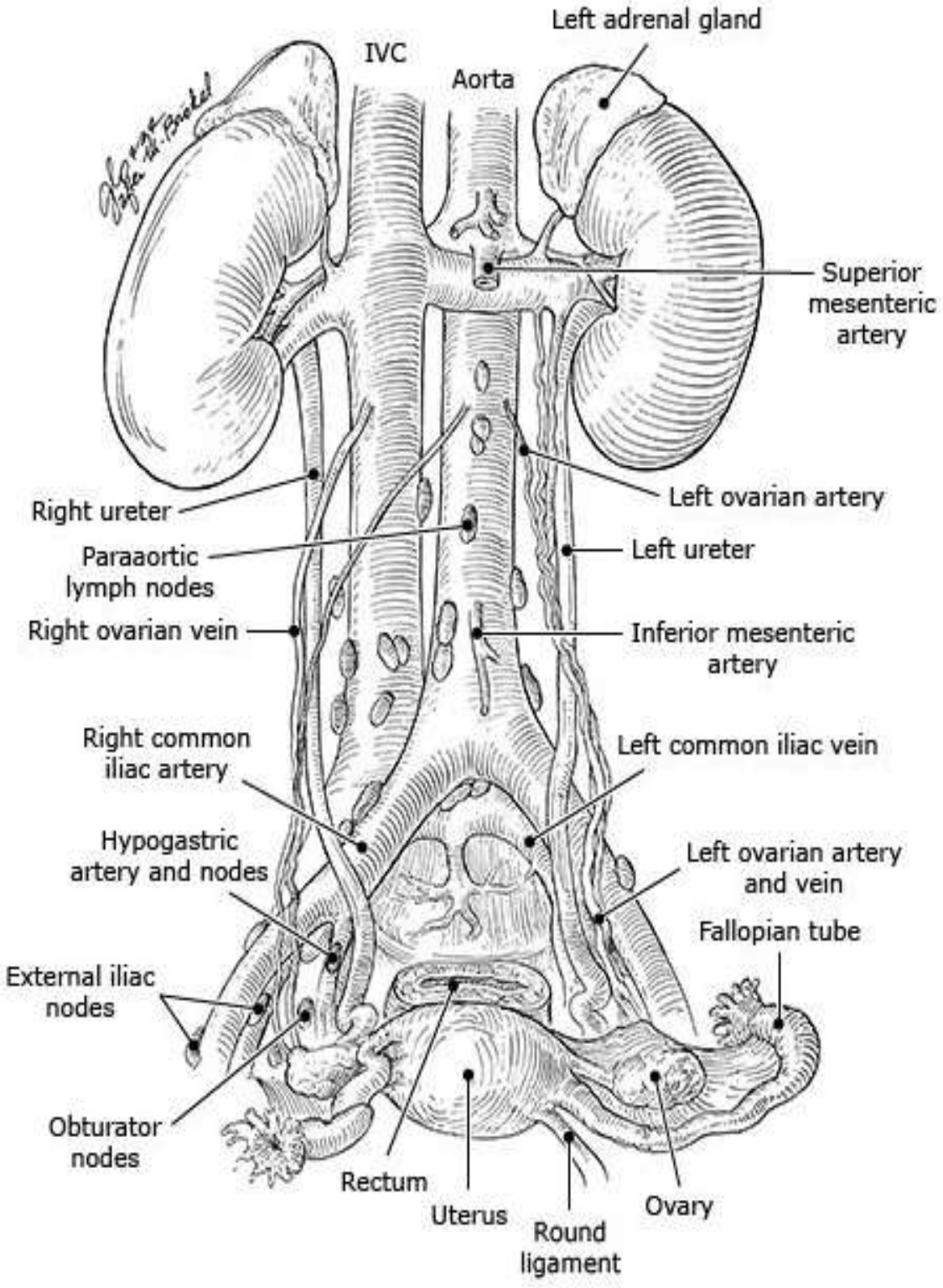
A. Squamous cell carcinoma
Large cell, keratinizing squamous cell carcinoma
Large cell, non-keratinizing squamous cell carcinoma
Verrucous carcinoma
Papillary squamous and transitional cell carcinoma
Lymphoepithelioma-like carcinoma
B. Adenocarcinoma
Mucinous, endocervical variant
Mucinous, intestinal type, signet ring variant
Mucinous, adenoma malignum (minimal deviation variant)
Mucinous, villoglandular adenocarcinoma (well differentiated)
Endometriod type
Clear cell type
Papillary serous type
Mesonephric type
C. Adenosquamous carcinoma
D. Adenoid cystic carcinoma
E. Neuroendocrine (carcinoid, small cell, large cell)
F. Undifferentiated carcinoma
G. Mixed epithelial and mesenchymal tumors

ROUTES OF SPREAD

- Cervical cancer can spread by direct extension or by lymphatic or hematogenous dissemination.
- Direct extension may involve the uterine corpus, vagina, parametria, peritoneal cavity, bladder, or rectum.
- Ovarian involvement by direct extension of cervical cancer is rare; ovarian metastases occur in approximately 0.5 percent of squamous cell carcinomas and 1.7 percent of adenocarcinomas.
- The most common sites for hematogenous spread are the lungs, liver, and bone; the bowel, adrenal glands, spleen, and brain are less frequent sites

- Historically, obturator lymph nodes were thought to be the most frequent site of nodal metastases in women with cervical cancer .
- It was also thought that lymphatic spread advanced in an orderly fashion from the lymph nodes on the pelvic sidewall to the common iliac, and then the paraaortic group . However, subsequent studies, including those utilizing the sentinel lymph node mapping technique, emphasize that any of the pelvic lymph node groups, and even paraaortic lymph nodes, may contain the first draining lymph node and may be the first site of nodal metastasis.
- The distribution of sites of nodal metastasis were: external iliac (43 percent), obturator (26 percent), parametrial (21 percent), common iliac (7 percent), presacral (1 percent), and paraaortic (1 percent).

Female pelvic and paraaortic lymph nodes



CLINICAL MANIFESTATIONS

- Early cervical cancer is frequently asymptomatic, underscoring the importance of screening. The most common symptoms at presentation are:
  1. Irregular or heavy vaginal bleeding
  2. Postcoital bleeding
- Some women present with a vaginal discharge that may be watery, mucoid, or purulent and malodorous
- Advanced disease may present with pelvic or lower back pain, which may radiate along the posterior side of the lower extremities.
- Bowel or urinary symptoms, such as pressure-related complaints, hematuria, hematochezia, or vaginal passage of urine or stool, are uncommon and suggest advanced disease.
- In asymptomatic women, cervical cancer may be discovered as a result of cervical cancer screening or incidentally, if a visible lesion is discovered upon pelvic examination.

DIAGNOSIS

- Physical examination:
  - Visualization of the cervix upon speculum examination may reveal a normal appearance or a visible cervical lesion; large tumors may appear to replace the cervix entirely. Any lesion that is raised, friable, or has the appearance of condyloma should be biopsied, regardless of previous benign cervical cytology results
  - A thorough pelvic examination including rectovaginal examination with assessment of tumor size and vaginal or parametrial involvement is required for staging cervical cancer.
- Cervical cytology
- Cervical biopsy and colposcopy

STAGING SYSTEMS

- FIGO system — The International Federation of Gynecology and Obstetrics (FIGO) collaborated with the International Union Against Cancer (IUCC) to formulate the most recent version of the FIGO system for cervical cancer. The FIGO staging system is largely based upon physical examination and a limited number of endoscopic diagnostic procedures and imaging studies. The FIGO system is used more commonly than the TNM system.
- TNM system — The American Joint Committee on Cancer and the IUCC created a TNM classification system that is parallel to the FIGO system. Clinical TNM staging is based upon the same staging procedure as FIGO staging. The "T" stages correspond to the FIGO stages with the exception of carcinoma in situ. The TNM system designates this Tis, but FIGO no longer includes stage 0. The TNM system also includes a pathologic staging system (pTNM) to be used for women who undergo surgical treatment or in whom cervical cancer is discovered incidentally after hysterectomy. The AJCC advises that the results of the pathologic evaluation should not be allowed to change the clinical stage, but be recorded separately as the pathologic stage.

Staging cervical cancer (TNM and International Federation of Gynecology and Obstetrics [FIGO])

Primary tumor (T)

TNM categories	FIGO stages	Definition
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis*		Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a •	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm in depth with a horizontal spread 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion or involvement of the lower one-third of the vagina [1,2]
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension with involvement of less than the upper two-thirds of the vagina
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension with involvement of less than the upper two-thirds of the vagina
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)

Regional lymph nodes (N)

TNM categories	FIGO stages	Definition
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis

Distant metastasis (M)

TNM categories	FIGO stages	Definition
M0		No distant metastasis
M1	IVB	Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone)

STAGING PROCEDURE

- Standard staging procedure International Federation of Gynecology and Obstetrics (FIGO) guidelines allow the following examinations for establishing the stage of cervical cancer, but it is not mandatory to perform all of these tests on every patient.

1. Physical examination
2. Pelvic examination – speculum, bimanual, and rectovaginal examination for palpation and inspection of the primary tumor, uterus, vagina, and parametria
3. Examination for distant metastases – palpation of groin and supraclavicular lymph nodes; examination of the right upper quadrant
4. Cervical biopsy
5. Colposcopy with directed cervical biopsy
6. Endocervical curettage

7. Conization
8. Endoscopy
9. Hysteroscopy
10. Cystoscopy
11. Proctoscopy
12. Imaging studies
13. Intravenous pyelogram (IVP) – evaluation for urinary tract obstruction; in many centers computed tomography or magnetic resonance imaging is used instead.
14. Imaging with a plain chest radiograph and radiograph of the skeleton – evaluation for metastases

LABORATORY EVALUATION

- Routine evaluation —Women with cervical cancer should have a complete blood count, liver and renal function tests, and urinalysis to determine systemic effects and the impact of potential metastatic disease. In addition, they should have routine preoperative or pretreatment testing.
- Tumor markers —The use of tumor markers for monitoring therapy or detecting recurrence in cervical cancer is investigational.
- A number of serum markers have been investigated for their utility in assessing prognosis, monitoring response to therapy, and detecting recurrence; none has achieved widespread acceptance. The most commonly used are serum squamous cell carcinoma (SCC) antigen, tissue polypeptide antigen, CEA, CA-125, and CYFRA 21-2
- Many of these markers are elevated in a significant proportion of patients with more advanced stage disease, and they correlate with disease activity.
- CA-125 levels are elevated in only 13 to 21 percent of women with cervical squamous cell cancer, but may be a better tumor marker for those with adenocarcinoma.

SURGICAL EVALUATION OF LYMPH NODES

- Women treated with radical hysterectomy for cervical cancer also undergo assessment of pelvic and paraaortic lymph nodes. In addition, lymph node sampling is performed in some women treated with primary chemoradiation. Although the finding of positive lymph nodes does not alter the FIGO stage, surgicopathologic results impacts treatment planning in up to 43 percent of cases.
- Lymph node dissection — Lymph node dissection debulks enlarged nodes, which may have a therapeutic benefit, and provides information for treatment planning (to individualize the radiotherapy field)
- The evaluation procedure can be performed via laparotomy or laparoscopy through a transperitoneal or extraperitoneal approach.
- Extraperitoneal and laparoscopic approaches to staging (including extraperitoneal laparoscopic) are associated with reduced morbidity
- Sentinel lymph node biopsy — Sentinel lymph node biopsy for women with cervical cancer appears promising, but is still investigational.

MANAGEMENT OF EARLY STAGE CERVICAL CANCER

- Women are defined as having early stage cervical cancer if their cancer was diagnosed on microscopic examination (stage IA) or they have a clinically visible lesion confined to the cervix measuring less than 4 cm (stage IB1)
- Intermediate-risk disease
  1. Presence of lymphovascular space invasion (LVSI) plus deep one-third cervical stromal invasion and tumor of any size
  2. Presence of LVSI plus middle one-third stromal invasion and tumor size ≥2 cm
  3. Presence of LVSI plus superficial one-third stromal invasion and tumor size ≥5 cm
  4. No LVSI but deep or middle one-third stromal invasion and tumor size ≥4 cm
- High-risk disease
  1. Positive surgical margins
  2. Pathologically confirmed involvement of the pelvic lymph nodes
  3. Microscopic involvement of the parametrium

MANAGEMENT OF EARLY STAGE CERVICAL CANCER

- For women with early stage cervical cancer, we suggest a modified radical hysterectomy with pelvic lymphadenectomy rather than primary chemoradiation. It's suggested to reserve primary RT for women who are not candidates for primary surgery due to medical comorbidities or poor functional status.
- For women with microinvasive disease (stage IA1) who have no evidence of intermediate-risk or high-risk features, It's suggested to perform conization or extrafascial hysterectomy rather than radical hysterectomy
- For women of reproductive age who wish to preserve their fertility and have a lesion size ≤2 cm and no lymph node metastases, uterus-preserving surgery is a reasonable treatment option.
- For women with early stage cervical cancer with intermediate-risk features (ie, lymphovascular invasion, cervical stromal invasion, or tumor is ≥4 cm), It's suggested to give adjuvant RT rather than chemoradiation
- For women with early stage cervical cancer with high-risk features (ie, positive surgical margins, pathologically involved pelvic nodes, or positive involvement of the parametria), we recommend adjuvant chemoradiation rather than RT alone, It's suggested to give adjuvant RT be administered with single-agent cisplatin rather than the combination of cisplatin plus 5-FU

Types of hysterectomy

Subtotal/supracervical
Subtotal/supracervical hysterectomy. The uterus is removed. The superior portion of the cervix is amputated, the remainder of the cervix is conserved. Intrafascial hysterectomy is a subtype of subtotal hysterectomy in which the uterosacral ligaments are conserved. [1]
Class I [2]
Extrafascial hysterectomy. The fascia of the cervix and lower uterine segment, which is rich in lymphatics, is removed with the uterus.
Class II
Modified radical hysterectomy. The uterine artery is ligated where it crosses over the ureter and the uterosacral and cardinal ligaments are divided midway towards their attachment to the sacrum and pelvic sidewall, respectively. The upper one-third of the vagina is resected.
Class III
Radical hysterectomy. The uterine artery is ligated at its origin from the superior vesical or internal iliac artery. Uterosacral and cardinal ligaments are resected at their attachments to the sacrum and pelvic sidewall. The upper one-half of the vagina is resected.
Class IV
Radical hysterectomy.The ureter is completely dissected from the vesicouterine ligament, the superior vesical artery is sacrificed, and three-fourths of the vagina is resected.
Class V
Radical hysterectomy. There is additional resection of a portion of the bladder or distal ureter with ureteral reimplantation into the bladder.

MANAGEMENT OF LOCALLY ADVANCED CERVICAL CANCER

- Locally advanced cervical cancer is defined as:

1. disease confined to the cervix with a clinically visible tumor >4 cm (stage IB2)
2. disease that invades beyond the uterus, but involves less than the upper two-thirds of the vagina (stage II)
3. disease that extends to the pelvic sidewall, involves the lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney (stage III)
4. or disease that extends to the rectum or bladder, or beyond the true pelvis (stage IVA)

- For women with locally advanced cervical cancer, it's recommend to give primary chemoradiation rather than primary surgery or radiation therapy (RT). It's suggested to give weekly cisplatin during RT rather than combination chemotherapy (eg, cisplatin plus 5-FU) during RT
- Women who are poor candidates for primary chemoradiation include women with acute or chronic pelvic inflammatory disease, a coexisting pelvic mass, or women who are not candidates for optimal radiation therapy (due to anatomic considerations or concerns about compliance), It's suggested to perform a primary modified radical hysterectomy

PATTERNS OF RECURRENCE

- After either radical hysterectomy or radiation therapy for early stage disease, the predominant site of disease recurrences is local (ie, at the vaginal apex) or regional (ie, pelvic sidewall). The risk of persistent or recurrent pelvic disease increases with more advanced initial disease stage
- Retrospective studies have reported the following distribution of anatomic sites of recurrence :
  1. Central (ie, vaginal apex or pelvis without side wall involvement) – 22 to 56 percent
  2. Pelvic sidewall – 28 to 37 percent
  3. Distant metastases or multiple recurrence sites – 15 to 61 percent
- The location and frequency of distant metastases are:
  1. Lung – 21 percent
  2. Bone –16 percent
  3. Paraaortic nodes –11 percent
  4. Abdominal cavity – 8 percent
  5. Supraclavicular nodes – 7 percent

POSTTREATMENT SURVEILLANCE

- Careful clinical evaluation is the most important component of the follow-up for patients with cervical cancer (a review of systems and physical examination with particular attention to the supraclavicular and inguinal lymph nodes, as well as rectovaginal and abdominal examinations).
- It's suggested to perform evaluations on the following schedule depending on disease extent:
  1. For high-risk disease (advanced stage, treated with primary chemotherapy/radiation therapy or surgery plus adjuvant therapy), every three months for the first two years, every six months for years 3 and 5, and then annually.
  2. For low-risk disease (early stage, treated with surgery alone, no adjuvant therapy), every six months for the first two years, then annually.

- It's suggested to do annual cervicovaginal cytology rather than at every follow-up visit for all patients except for those who have undergone pelvic RT, in whom we eliminate cytologic examination as a component of posttreatment).
- It's suggested not to do pursuing surveillance radiographic imaging (chest x-ray, positron emission tomography (PET)/computed tomography (CT), magnetic resonance imaging) unless a recurrence is suspected
- It's suggested not to use assays of SCC antigen, PET scans, pelvic ultrasound, intravenous pyelography (IVP), or MRI as a routine component of the posttreatment surveillance strategy in asymptomatic patients.

MANAGEMENT OF RECURRENT OR METASTATIC CERVICAL CANCER

- Following treatment of early stage cervical cancer, distant metastases or multiple recurrence sites develop in 15 to 61 percent of cases, usually within the first two years of completing treatment.
- Recurrent cervical cancer presents as disease isolated to the pelvis (locoregional recurrence) or with disease involving other organs or outside the pelvis. If a vaginal recurrence is suspected, the area of concern should be biopsied to prove recurrent disease

- All patients suspected of recurrent disease should undergo positron emission tomography (PET)/computed tomography (CT) for evaluation of local and distant disease.
- For patients with a local recurrence, It's suggested to do surgical resection if they are appropriate surgical candidates based on tumor recurrence, age, and comorbidities.
- In select patients, surgical resection may present a curative option. Patients who are not surgical candidates should receive chemoradiation, if they have not been previously undergone pelvic or intravaginal radiation.

- For women presenting with disease limited to the nodes (ie, para-aortic and/or supraclavicular nodes), some experts prefer to treat with systemic chemotherapy. Others prefer to administer radiation therapy (RT) (with or without chemotherapy). A choice between them depends on institutional practice and patient preferences. For women presenting with isolated metastatic disease (ie, to the lung or liver), we suggest surgical resection if they are appropriate candidates).
- These patients may achieve a sustained clinical remission following resection of disease. For women with recurrent cervical cancer, those who are not surgical candidates, and those who present with metastatic disease, It's suggested to give first-line treatment with chemotherapy plus bevacizumab rather than chemotherapy alone

CERVICAL CANCER SURVIVAL

Survival by FIGO stage for patients with cervical cancer: 1999 to 2001 FIGO statistics

FIGO stage	Number of patients	Overall survival, percent		
		One year	Two years	Five years
IA1	829	99.8	99.5	97.5
IA2	275	98.5	96.9	94.8
IB1	3020	98.2	95.0	89.1
IB2	1090	95.8	88.3	75.7
IIA	1007	96.1	88.3	73.4
IIB	2510	91.7	79.8	65.8
IIIA	211	76.7	59.8	39.7
IIIB	2028	77.9	59.5	41.5
IVA	326	51.9	35.1	22.0
IVB	343	42.2	22.7	9.3

- Stage is the most important prognostic factor, followed by nodal status. Outcomes are worse for women with involved pelvic or para-aortic nodes.