



CARCINOMA OF THE CERVIX

Worldwide, cervical carcinoma is the second most common cancer among women. This cancer and the precancerous changes of the cervix are now largely viewed as a spectrum of sexually transmitted diseases given the initiating role of the venereally transmitted Human Papillomavirus (HPV) identified in over 90% of cases worldwide. While the Papanicolaou test has been confirmed as a cost-effective screening device, it is underutilized in non-industrialized countries, as well as in the developed countries. In the United States, cervical cancer incidence and mortality has reduced by 70% due to pap smears, but remains the sixth leading cause of cancer death, trailing lung, breast, colorectal, ovarian, and endometrial malignancies.

Colombia	42 per 105 women
Costa Rica	26
German DR, India	22
China, Singapore	19
Japan, England, France	11
US Hispanic	30
US Black	10
US White	7
Israel, Shanghai	4
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The incidence among Caucasian US women plateaus in the third decade at about 10/100,000, and remains at the same rate throughout life. Among Hispanic US women, it increases with age up to 40 per 105 women into the seventh decade before it plateaus, with an average of 30 per 105 women.

HUMAN PAPILLOMA VIRUS AND OTHER RISK FACTORS

Since the late 1980's cervical cancer has been formally recognized as a sexually transmitted disease following venereal Human Papilloma virus transmission. The association of HPV and cervical cancer is strong, consistent and well established, confirming HPV as the central etiologic factor for cervical cancer. Among 1008 cervical cancer samples from 22 countries around the world, 96% contained at least one of 26 HPV types, with HPV 16 in 50% of samples and HPV 18 in 14%.

HPV's are 55-nm, non-enveloped, icosahedral, doublestranded DNA virion in a closed

circle of 8,000 base pairs. There are more than 100 types of HPV, with over 35 infecting the anogenital tract. The group III mucosotropic HPV's consist of three types:

Low risk for cancer: #6, 11, 42-44 –seen in 20% LGSIL and no HGSIL

Intermediate risk: #31, 33, 35, 51, 52 –seen in 23% HGSIL and no cancers

High risk for malignancy: #16, 18, 45, 46 –seen in 53% HGSIL and 74% cancers

The virus infects the cells in the basal layer of the epithelia in breaks in the skin of susceptible hosts to which the virus is exposed. The virus can then:

1. Stabilize as a circular virion and remain latent for years, killing a few cells (koilocytosis) in the process.
2. It can replicate HPV's that induce the proliferation of the epithelium into a wart or thickening (acanthosis).
3. It can become integrated into the host genome, which interrupts control of oncoproteins. The uncontrolled overproduction of viral proteins E6 and E7 seem to impact the host growth-regulatory proteins p53 and pRb of the surface epithelial cells and appears to have been incorporated into the host human cellular genome when dysplasia is stimulated.

An estimated 30% – 40% Americans carry HPV, yet little attention is paid to prevention of this epidemic. While 30% of HPV infections are clinically recognizable as genital warts, fully 70% of HPV infections are subclinical, and without symptomatology. Transmission rates are highest between ages 16 to 25, and decrease by age 35, highest among immunosuppressed and pregnant women.

Unprotected genital to genital contact is the highest risk behavior for transmission. Therefore, those who partner with men, be they male or female, are at highest risk of receiving the virus. While the HPV has been described as transmissible by sexual contact between female partners, this is rare.

While most infections of the .9 to 44 per 105 women who are infected with HPV will clear the viral infection spontaneously, it is estimated that 15-35% of these women continue to harbor the virus and develop a high-grade dysplasia within 2 years. It is not known which mechanisms enable some women to clear the infection, but only a small percent of women with HPV develop cervical cancer.

The risk factors for progression of cervical dysplasia to cervical carcinoma comprise three categories: the exposure to *initiating* HPV, the exposure to cancer promoting agents, and the health of one's *immune* system.

Exposure to *initiating* HPV:

1. Venereal exposure to HPV at an early age (first intercourse during teenage years) increases risk of incorporation of the HPV into the metaplastic cell genome.

2. The number of lifetime male sexual partners also increases probability of exposure to HPV.
3. Intercourse with males who have had multiple partners, a sexually transmitted disease, penile carcinoma, or a prior partner with cervical carcinoma, all of which significantly increase exposure to virulent types of HPV.
4. HPV prevalence among women with lower levels of education and lower income has also been observed.

Cancer promoting risk factors include:

1. Cigarette smoking.
2. Poor nutrition. Poor nutrition and low intake of anti-oxidant fruits and vegetables have been associated with higher risk for developing cervical dysplasia and carcinoma. Vitamin A, C and folic acid measurements revealed higher levels in healthy controls than cervical cancer patients.

Immunosuppression due to:

1. Intrinsic immunosuppressive disorders such as lupus or rheumatoid arthritis
2. HIV infection,
3. Transplant medication, or chronic steroid use increases the risk for persistent HPV infection and predispose to development of premalignant cervical dysplasias and cervical cancer.

While use of oral contraceptives has been implicated as a risk factor for cervical carcinoma, detailed studies suggest that it is not the hormonal influence that imparts risk, but rather the fact that oral contraceptive users have more sexual experiences and are less likely to use spermicidal creams. Such creams can have a virucidal effect.

PREVENTION AND RISK MODIFICATION

Techniques that reduce exposure to HPV reduce exposure to cancer promoters, and which enhance immune status can prevent HPV infection, and reduce cancer rates. Monogamy or celibacy, and consistent use of barrier contraceptive methods are critical in reducing rates of cervical carcinoma. Condom use, which effectively reduces HIV transmission, should be encouraged among all individuals at risk. Many sex and AIDS education programs have significant effects on adolescent sexual risk-taking behavior, delaying the initiation of intercourse, reducing the frequency of intercourse, reducing the number of sexual partners, or increasing the use of condoms or other contraceptives. Such programs have the potential to reduce exposure to unintended pregnancy and sexually transmitted disease, including HPV infection. These programs should be replicated widely in U.S. schools. Safer sex techniques and regular pap smears, if used by all individuals, could theoretically reduce the incidence of cervical cancer by about 95%.

Vitamin C has been associated with a reduced risk of cervical cancer.

The Papanicolaou smear, or Pap test, has been shown to effectively recognize the noninvasive precursors of cervical carcinoma. The Papanicolaou smear (pap test) has reduced cervical cancer rates to less than one quarter of the rate one half century ago.

However, patient noncompliance, inadequate sample collection, and inaccurate pathologic interpretation are the most common causes for failure of early detection. Pap testing should be performed yearly; starting either at age 18 or after sexual activity begins. The abnormal pap requires colposcopic (magnified) visual examination of the cervix with biopsy of any lesion and areas of concern. This divides patients into three categories:

Atypical cells of uncertain significance – requires observation by repeat pap smears.
LGSIL – includes koilocytes and mild dysplasia, which can regress and do not require immediate treatment.

HGSIL – includes moderate and severe dysplasias, and requires treatment.

Treatment of the precursor lesions by acid, laser ablation, freezing, or loop surgical excision can adequately prevent the development of cervical malignancy. Most treatments have a 60-90% success rate and may require repeated efforts.

Low grade dysplasia- 62% regress without treatment,
22% persist as mild dysplasia,
16% become malignant within 7-8 years.

High grade dysplasia-66% become malignant within 10 years.

Closer surveillance of high-risk women such as those with HIV, those on immunosuppressive medications, pregnant women and those with immunosuppressive diseases is indicated. Substance abuse, including cigarettes, drugs and alcohol, confers a significantly lower treatment success rate for dysplasia and poorer survival from carcinoma than that observed for women who are not substance abusers. Women with dysplasia should be cautioned to discontinue all smoking.

SYMPTOMS OF INVASIVE CANCER

Irregular or postmenopausal bleeding and a new discharge are the most common symptoms experienced by over 90% of patients. The bleeding can be an exaggeration of the menstrual cycle duration or intensity, or occur after physical perturbation such as after sexual activity or douching. Discharges can range from profuse non-odorous mucous to foul watery and purulent. Any new bleeding or discharge in a post-menopausal woman requires gynecologic work up to rule out an occult malignancy in the reproductive tract.

DIAGNOSIS OF CANCER

Examination of the cervix with a primary carcinoma will usually immediately reveal an exophytic friable lesion, but occasionally only cervical erythema or ectropion is observed, with Pap smear data similarly showing only inflammatory atypia. Occult endocervical carcinoma, endometrial carcinoma, or even Fallopian tube or ovarian carcinoma can present in this subtle fashion. A biopsy of any suspicious change of the

ectocervix or endocervix and a detailed pelvic examination, with emphasis on the rectovaginal portion should be performed. Further work up consisting of endocervical curettage, endometrial suction aspiration, and possibly CA-125 with transvaginal sonography is indicated.

PATHOPHYSIOLOGY OF CANCER

Cervical dysplasia is considered a clonogenic event starting in most cases at the squamo-columnar junction at the basement membrane, replacing the normal epithelium. Left untreated, locally invasive growth proceeds through the basement membrane into the stroma, expanding the cervix with an exophytic mass or, with endophytic growth, into the classic barrel-shaped cervix. Once invasion into the stroma is deeper than 3.0 mm, the tumor can access the lymphatic ducts and spread to the pelvic nodes in up to 15% of cases (Stage I). Growth in the cervical stroma will proceed with cancer cells spreading in either or both of two directions: superficially along the cervical epithelium and down the vaginal wall, or interstitially along fascial planes resulting in direct spread laterally into the parametrium (Stage II). This advance of tumor growth enables more cells to access the lymphatics resulting in about 30% of patients having positive pelvic lymph nodes. Further growth into the parametrium typically blocks the ureter as it encroaches toward the boney pelvic sidewall (Stage III) and is associated with about 60% of lymph node positivity. Distant spread of cancer is possible with rare patients exhibiting growth into the bladder or rectum, liver, lung or brain (Stage IV).

Approximately 77% of cervical carcinomas are squamous in origin, with the majority being large cell non-keratinizing. Adenocarcinoma comprises 11% of cervical malignancies, and offers a slightly lower survival, possibly attributed to its frequent endophytic growth pattern, which can grow for a longer time before symptoms develop. 2.5% are adenosquamous, and 8% are not classified. Small cell carcinoma of neuroendocrine origin and other rare histotypes occur in only 3% to 5% of cases.

The important favorable prognostic features of cervical carcinoma include younger age, lower stage, smaller lesion size, absence of lymphatic ductal and nodal involvement, lower grade of differentiation, minimal depth of invasion in the cervical stroma, non-smoking status.

CANCER STAGING

The staging schema for cervical carcinoma replicates the natural history of the disease. Standards for staging have been defined and are maintained by an international board of cooperative Gynecologists, the Federation Internationale Gynecologic Obstetrica, (FIGO) which last revised the standard in 1994, as presented below. (Table 1) Only physical examination findings and a few widely available radiographic tests, the intravenous pyelogram and chest x-ray, are permitted in assigning the FIGO stage. The physical exam is performed in detail, and can include cystoscopy or proctosigmoidoscopy, as needed. Findings from more sophisticated or invasive radiographic investigations, such as computed tomography (CT) or magnetic resonance imaging (MRI), can sometimes provide clinically useful information, but they cannot be used to assign or to change the patient's FIGO stage. Cystoscopy and proctoscopy typically have limited value and are thus omitted in early stage, small lesion cases, but are necessary and occasionally positive in more advanced disease. Once the FIGO

staging has been assigned, it does not ever change. The value of the additional information from MRI or CT can, however, be used to direct and influence modes of therapy. Surgical staging using laparoscopy or by extraperitoneal "laparotomy," has not been shown to provide a survival benefit, and should be performed only in investigational study protocols.

TABLE 1. FIG O Staging of Carcinoma of the Cervix Uteri, 1994

Preinvasive Carcinoma

Stage 0 Carcinoma in situ, intraepithelial carcinoma

Invasive Carcinoma

Stage I Carcinoma strictly confined to the cervix (extension to the corpus is disregarded).

Stage Ia1 Lesions detected microscopically that can be measured as no greater than 3mm deep and 7mm wide. Minimal microscopically evident stromal invasion. (.2-1.2% die)

Stage Ia2 The depth of invasion is between 3- 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates, and less than 7 mm wide. (1.7% die)

Stage Ib1 Lesions up to 4.0 cm diameter.

Stage Ib2 Lesions larger than 4.0 cm diameter.

Stage II The carcinoma extends beyond the cervix but has not extended onto the wall. The carcinoma involves the vagina, but not the lower third.

Stage IIa No obvious parametrial involvement.

Stage IIb Obvious parametrial involvement.

Stage III The carcinoma has extended onto the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or nonfunctioning kidney.

Stage IIIa No extension to the pelvic wall, only involvement of the lower third of the vagina.

Stage IIIb Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney.

Stage IV The carcinoma has extended to the mucosa of the bladder or rectum.

Stage IVa Spread of the growth to adjacent organs, biopsy confirmed.

Stage IVb Spread to distant organs.

*The diagnosis of Stage Ia1 and Stage Ia2 is based on microscopic examination of removed tissue, preferably a cone, which includes the entire lesion. Vascular space involvement, either venous or lymphatic, does not change the staging but must be recorded because it may affect treatment decisions in the future.

THERAPY

The working assumption about microinvasive carcinomas is that there is only negligible risk of spread beyond the cervix and that local, nonradical therapy is needed.

The diagnosis, staging and treatment planning for microinvasive cervical carcinoma are undertaken following an adequate cone biopsy with pathologically clear endocervical and ectocervical, and deep stromal margins. A small biopsy or endocervical curettage is not adequate to rule out the presence of a deeply invasive disease process or to ensure the safety of conservative therapy. Likewise, a simple hysterectomy is not performed to diagnose, stage and treat because in most cases it is unnecessary, and in others it is inadequate therapy. Treatment by conservative observation, simple hysterectomy, or radical hysterectomy is determined only after detailed pathologic analysis of the cone specimen.

FIGO Stage Ia1 – lesions under 3mm

With Stage IA1, invasion under 3mm, there is a 1.9% chance of nodal involvement, and a death rate of .5%. Lesions in which invasion is only minimally microscopically evident can be treated with a cone biopsy only, and conservatively followed with endocervical and ectocervical pap testing every three months for two years. There is no specific need for hysterectomy for patients who have Stage Ia1 disease and negative margins. If an internal margin is involved with only dysplasia which is clearly distant from the invasive process, further local ablational therapy may be needed in about one third of cases, mandating a follow-up pap in two to three months to determine need for repeat therapy. However, if there is a dysplastic margin that is in the vicinity of the invasive focus, a repeat cone or local excisional therapy is indicated to confirm microinvasion.

Management of Stage Ia1 disease is individualized. In those patients with lesions that have less than 3 millimeters of invasion and do not have high-risk histology, or lymphatic space involvement, an adequate cone is sufficient if fertility is still desired or if hysterectomy is medically high risk. This subset of patients requires close observation, consisting of clinical exams every three months for the next two years that include endocervical and separate ectocervical assessment. Otherwise, a simple extrafascial hysterectomy can be performed.

Patients in Stage Ia1 with lymph vascular space invasion should be treated with a radical hysterectomy and bilateral pelvic lymphadenectomy. A Type II radical hysterectomy in which the ureter is mobilized laterally for a medial parametrial dissection can be performed in these cases because there is a lower rate of morbidity compared with the Type III radical hysterectomies in which the parametrium is ligated far laterally. Because the ovaries are almost never involved by cervical squamous or adenocarcinoma, oophorectomy should be performed only when indicated for independent indications.

Stages Ia2, Ib1 and IIa

With Stage IA2, invasion under 5mm, there is a 7.8% chance of nodal involvement, and a death rate of 2.4%. When a lesion invades deeper than 3.0 mm, a type III radical hysterectomy with pelvic and low periaortic lymphadenectomy or radical radiotherapy is

indicated. Primary surgical therapy is generally reserved for the slender, patient who is a good medical risk for radical pelvic surgery, and has a small lesion less than 4 cm in maximal diameter. If the patient is not an ideal medical risk for surgery then radical pelvic radiation should be provided. When the surgeon or radiation therapist is less than optimally experienced in Gyn Oncology, the surgery is usually less than radical, and the dose of radiation is usually less than maximal, sacrificing cure rates either way.

The surgery is performed through a midline or Maylard incision, or ideally, laparoscopically. Oophorectomy is not necessary. If grossly enlarged pelvic nodes are identified, the procedure should be terminated in favor of the equally curative pelvic radiotherapy. Completing the radical hysterectomy in such cases does not add to the cure rate because central disease is so well treated with radiotherapy. More importantly, it is useful to leave the uterus in place to serve as conduit for the intracavitary brachytherapy portion of the radiotherapy which critically boosts the external beam parametrial dose by some 1500 cGy.

Should the final pathology report reveal two or more positive pelvic nodes, outer third of the cervix, parametrial or vaginal margin involvement or proximity, chemoradiotherapy is indicated.

Any patient who is not an ideal surgical candidate should be treated with definitive chemoradiotherapy, employing cisplatin chemotherapy with external beam radiotherapy and two intracavitary implants. The external beam sterilizes the region and shrinks the primary disease so that brachytherapy can then eradicate residual central and parametrial disease. Ongoing research to optimize survival probability is looking at use of interstitial needle insertion for patients with asymmetric parametrial disease after external beam.

The chemotherapy should be administered before the radiotherapy. Most studies show that CDDP, the most active cytotoxic agent for metastatic or recurrent disease, works by inhibiting repair of sublethal radiation damage, and by sensitizing hypoxic cells to radiation damage. Weekly administration of CDDP at 25mg/m² works by interfering with repair of radiation damage, and is minimally myelosuppressive. Prolonged continuous infusion of 5-FU at 1g/m² daily for four days every three weeks provides maximal effectiveness.

Stages Ib2

Patients with larger Stage I lesions, > 4 cm, or a large barrel shaped cervix, are more likely to have either positive pelvic lymph nodes and microscopic parametrial disease. Chemoradiation is indicated as primary therapy (82% with CDDP/RT vs. 68% RT alone, GOG). Consideration for an extrafascial hysterectomy should be given if the cervical lesion fails to dramatically regress.

Stages IIb to IVa

Extended field pelvic radiation is the mainstay of therapy for any large or advanced cervical carcinoma (RTOG). Survival from advanced stage cervical carcinoma has nearly doubled in the last two decades because of advances in radiation dosing and machinery. While FIGO staging is entirely clinical, a CT scan of the abdomen is performed on patients with disease beyond the cervix in order to tailor the radiation

therapy to provide precise dose delivery and maximize survival. Distant disease must also be ruled out by examining the aortic nodal chain first. In patients with no suspicious aortic adenopathy by CT, further evaluation to rule out occult adenopathy is performed by extraperitoneal or laparoscopic paraaortic lymph node sampling. The GOG reported that 21% of well-staged IIB and 31% of IIIB cancer patients had metastasis to the aortic nodes. A retroperitoneal approach to pretherapy surgical staging and absence of previous surgery are associated with reduced incidence (11.5% vs. 3.9%, GOG) of subsequent radiation therapy complications.

If the aortic nodes are radiographically suspicious for spread of disease, they should be removed before chemoradiation as possible. Some studies have suggested higher cure probabilities with removal of enlarged nodes (Downey et al, 1989). Alternatively, a fine-needle aspiration is used to confirm disease presence. For these patients, the upper limits of the pelvic radiation field from the L4-5 interspace should be narrowed and extended superiorly to the diaphragm. Microscopic and macroscopic metastases in this region both confer a 5-year survival of about 12-25%, with most patients failing distantly. When aortic adenopathy is suspected, a CT scan of the chest should be obtained. If mediastinal or lung disease is identified and histologically confirmed, treatment should proceed as described for Stage IVb.

Patients with negative aortic nodes and non-bulky pelvic nodes are treated with chemotherapy and whole pelvic fourfield external beam radiation and one or two intracavitary or interstitial applications of cesium. Cisplatin was added to radiation treatments as of 2000 for an improvement in survival probability (63% with CDDP/RT vs. 47% RT at 5 years, GOG)(73% % with CDDP and 5FU vs. 58 RT only, RTOG). Unexpectedly some of these studies showed that even distant failures are reduced by chemotherapy with radiotherapy. In 2004, the GOG investigated use of Topotecan 75 mg/m² on days 1-3 and Cisplatin 50 mg/m² on day 1 of every three weeks, finding that overall (27 v. 13%) and complete (10 v. 3%) responses were higher than with Cisplatin alone for recurrent disease. Additionally progression during therapy was lower (28 v. 37%) with the doublet chemosensitizer. Median survival time was longer (9.4 v. 6.5 months). Those patients who recurred within 6 months of therapy did most poorly compared to women recurring in later months.

High-dose rate intracavitary radiation therapy for carcinoma of the uterine cervix has gradually found wider acceptance. However, treatment results have been equivalent for high dose and low dose rate techniques, with a slightly higher complication rate for the high dose rate group

Rectovaginal fistulas may develop during or after completion of pelvic radiotherapy, especially in patients with bulky parametrial or central disease. Fecal diversion by end colostomy will offer control and can be done with minimal interruption of the radiotherapy. Vesicovaginal fistulas can develop in patients with anterior spread of tumor along the vesicouterine septum. Percutaneous nephrostomies can divert the urinary stream although they are not always effective. Formation of a new bladder should usually be delayed until completion of radiotherapy, once local disease control has been ascertained.

Stage IVb

The goal in patients with distant metastases or recurrent disease is palliative.

Combination chemotherapy trials using bleomycin, cisplatin and ifosfamide, offer an overall tumor response rate of over 60%, but cures are rare. Rapid-course high dose external beam pelvic radiotherapy, with or without systemic chemosensitizing chemotherapy can be given depending upon the patient's desire. Urinary or fecal diversion should be performed in the least invasive manner possible in an attempt to alleviate specific symptoms.

RECURRENT DISEASE

Recurrent disease develops in nearly half of women with cervical carcinoma, and carries a poor prognosis. Of those who recur most become clinically apparent within the first two years after therapy. Therefore follow-up clinical exams and tumor marker assessment are indicated every three months for the initial two years, and every four to six months until five years. Yearly post-treatment chest x-ray has been advocated, but does not offer a survival advantage.

Site, timing and size of recurrence are important predictors of successful therapy, with small apical cervical lesions presenting after one year carrying the best prognosis. Prior to beginning any new therapy, thorough evaluation of the extent of the recurrence is essential. Magnetic resonance imaging (MRI) has the highest resolution of neoplastic lesions in a radiated field and should be routinely performed.

Patients initially treated by radical hysterectomy with pelvic recurrence should have pelvic radiotherapy with a sensitizer, and be considered for extended field. Patients with recurrent disease previously treated with radiotherapy, even after a radical hysterectomy, are evaluated for exenterative surgery.

The mortality rate from exenteration is 3% to 5%, with a surgical morbidity rate over 60%. Five-year survival rates from the institutions where exenterations are frequently performed are as high as 60%. Therefore, careful patient selection for this morbid procedure is necessary. Pre-operative evaluation with pelvic and abdominal MRI, chest x-ray, bone scan, and occasionally lymphangiogram and directed fine-needle aspiration, are indicated. Patients whose disease appears clinically and radiographically localized to the central pelvis should then be explored for exenteration. Parametrial fixation of the central tumor does not preclude successful exenteration, as many of these patients will have lateral planes of dissection free of tumor. Some surgeons have combined intra-operative radiation therapy for close or positive lateral pelvic margins with some success. However, large (5 cm or larger) recurrences, lateral pelvic wall disease, hydroureter, bladder/rectal involvement and nodal disease remain poor prognostic indicators reducing survival probabilities to 15-30%.

Careful intra and retroperitoneal exploration is performed with intra-operative examination of peritoneal cytology in cases with adenocarcinoma. However, up to 60% of these patients will be found to have intraperitoneal or distant disease and not qualify for exenteration. If the recurrence is confined to the pelvis, the exenteration proceeds with removal of the bladder, upper or total vagina, and, depending on the anatomy of the post-surgical pelvis and the recurrence, the rectum is removed as well. Total pelvic exenteration can now be performed in conjunction with simultaneous neovagina, genitourinary and gastrointestinal reconstruction with minimal morbidity. The development of the continent urinary diversion, with primary anastomosis of the

rectosigmoid helps to make such extensive surgery less disfiguring and disabling.

A subset of patients has been identified with such small central recurrence that only radical hysterectomy was performed. In these few cases, cure rates similar to exenteration were observed. Urinary fistula was one complication that occurred more frequently because the bladder was irradiated. Further research is ongoing, focusing on selecting patients for less radical procedures, minimizing operative morbidity, and maximizing post-operative functional and cosmetic effects, while maintaining the highest possible survival rates.

CERVICAL CARCINOMA DURING PREGNANCY

Dysplasia diagnosed during pregnancy used to be treated with cone biopsy, but now even carcinoma in situ is observed during pregnancy by colposcopic examinations every few months, reserving treatment until after delivery.

The occurrence of cervical carcinoma during pregnancy does not carry a poorer prognosis. Small lesions identified after 20 weeks of pregnancy can be observed during the gestation, planning combined delivery with radical extirpation or delayed radiation therapy. Very early stage cancers have had delay of therapy of 16 to 20 weeks with good results. Larger lesions and higher stage tumors should usually proceed to radiotherapy, with focus on the survivability of the mother, as reports confirm that delay for large lesions can be fatal.

PROGNOSIS

Overall, about half of patients with cervical carcinoma are cured. The 5-year survival rates are highest for early, small lesions approximating 90%. However, the prognosis is 75% for all Stage I patients because some Stage I cancers are large or have nodal mets. Stage II tumor, invading the parametrium or upper vagina, confers a 5-year survival of 55%. Once the tumor spreads outward to the sidewall or ureter, or down the vagina, Stage III, about 35% will survive. Less than 5% are cured with disease invading the bladder, rectum or with distant spread, Stage IV.

Practical Summary of 2005 ACOG Practice Bulletin: Management of Abnormal Cervical Cytology and Histology

Screening: Start at age 21 or 3 years after coitarche, annually, until age 30. No HPV screening before age 30. After age 30, if last 3 annual paps negative, screen every 2-3 years with HPV assay until age 70 or after hysterectomy, unless prior CIN, HIV or immunosuppression.

Pap -, HPV -: Repeat pap yearly under age 30, every 3 years after age 30 if no prior CIN or immunosuppression. Stop at 70 if all negative.

Pap -, HPV +: Repeat both in 6-12 months (4% risk of cancer), no colpo. If ASC and HPV -, repeat in one year. If HPV still positive or any CIN do colpo (80% of women may carry HPV, most clear it but 10-30% get dysplasia. Young are likely to clear in <2years. Smoking doubles risk of cancer.)

Age under 30 years: risk of cancer almost zero. Virus is highly likely to clear. If ASC, LSIL or HPV+: If no visible lesion, repeat pap in 6 and 12 months or just test HPV in 12 months. Can follow CIN 1, 2 similarly. Do not screen with HPV assay.

ASC (.2% risk of cancer, 6-12% risk of dysplasia) Repeat pap at 6 months **OR** immediate colpo **OR** do HPV test:

- If ASC and HPV – (55% will be-, 2% risk of dysplasia): repeat pap and HPV in one year.
- If +HPV colpo then. If HPV + (25% will have dysplasia): colpo.

ASC-H (70% HPV+, 10-90% have dysplasia), **LSIL** (15-30% have dysplasia), **HPV+** (13% become CIN 2,3) colpo, ECC, Bx:

- If Bx is Negative or CIN I (60% will regress,) Pap in 6 and 12 months, **OR** pap and HPV at 12 months, **OR** treat by excision or ablation. If any follow-up pap or HPV is positive: Repeat colpo.
- Unsatisfactory colpo for ASC-H or ASC-NOS x 2: leep cone.
- Untreated CIN 1 follow-up: pap at 6 and 12 months, with colpo for any higher lesion, **OR** HPV test at 12 months, and colpo if positive.
- Bx shows CIN 2 (40% regress), or CIN 3 (not seen to regress): excise or ablate.
 - If positive margin: 10% recur. Pap, ECC and HPV test in 6 months by ECC brush.
 - If negative margin: pap and HPV in 6 months, then yearly if normal.
- Follow up after treatment: Pap + HPV test in 6 and then yearly if both neg. Repeat colpo for any ASC or higher.

Post-Colpo follow-up:

- **No lesion seen and ECC- with ASC-H, LSIL, or ASC-and-HPV +** repeat pap and HPV in 12 months. Annual pap if HPV-. Recolpo if HPV +.
- **LSIL:** conservative follow-up preferred repeat pap and HPV at 12 months. Annual pap if HPV-. Recolpo if HPV +.

- **HSIL:** treat lesions and do pap and HPV assay at 6 months. Annual pap if HPV-. Recolpo if HPV +.

HSIL pap: (70% have dysplasia; 2% cancer; time from HSIL to cancer is 8-12 years).

Do ECC and colposcopy of cervix and vagina:

- No colpo findings or Bx only CIN 1 (35% with real dysplasia): re-review pap or do large cone if unsatisfactory colpo.
- Age under 30 and no lesion seen, ECC negative: re-colpo in 6 months with Pap and HPV test.
- Biopsy, ECC and plan ablation **OR** excisional leep all lesions, with post treatment ECC.
- If cone for SIL has + margin (12% recur): repeat pap and HPV in 3 months
- Follow up after treatment: Pap + HPV in 6 and 12 months, no colpo.
- Hysterectomy for Gyn indications and recurrent lesion or if unable to resect.

AGC NOS (40% have SIL, 2% have AIS, 1% cancer) Most have no visible lesion. Do ECC and Colpo.

- Endometrial Bx for all AEC, all AGC over age 35, and for any age with bleeding, obesity, oligo-ovulation.
- If negative ECC, no lesion: Pap + ECC every 6 months for two years.
- If negative ECC, no lesion, and HPV-: Pap + HPV at 12 months, only once.
- If AGC NOS x 2: cone.

AGC favor lesion (90% have SIL) -> colpo, ECC (are insensitive), and HPV test.

- If negative ECC and no lesion: Do surgical cone.

AIS (50% have SIL, 40% have cancer) -> surgical cone + post-ECC and Endometrial Bx

- AIS with negative margins pap, HPV test, ECC every 6 months until hysterectomy after fertility is complete. (25% recur, 2% new cancer)
- AIS with positive margins (80% residual lesion) re-cone until negative, then above.
- If invasion: plan radical hysterectomy.

Pregnant women with ASC, LSIL, CIN 2, 3 Colpo. Goal is to rule out cancer. Biopsy only lesions suspicious for invasion. Consider excision of cancer lesion. If no cancer or if unsatisfactory visualization of SCJ or lesion, colpo every 3 months. Recolpo and treat 8-10 wks

post-partum. Do not treat during pregnancy. No ECC during pregnancy.

ECC brush is equal to ECC sharp curettage. ECC brush must be negative prior to all ablations, and for all unsatisfactory colpo views.