

Invasive Cervical Carcinoma

Christopher Kramer, M.D.

- I. Introduction
 - A. Careful clinical assessment of the anatomic extent of cancer spread at the time of presentation, with an examination under anesthesia by the oncologist, has led to individualization of treatment
 - B. The impact of newer diagnostic methods in tumor detection are under study
 1. Lymphangiography
 2. Laparotomy and lymph node biopsy
 3. Ultrasound
 4. Computerized axial tomography (CAT)
 - C. The high cure rate in cervical cancer can be credited to early detection and widespread use of cytologic screening
 - D. Through the decades, cytopathological diagnosis has converted a debilitating and deeply invading tumor into a highly curable noninvasive or microinvasive malignancy

II. Epidemiology and Etiology

- A. Epidemiology
 1. Invasive cancer of the cervix incidence ranks fourth and is comparable to that of lung cancer in women. Twenty thousand new cases of invasive cervix cancer occur in the United States each year.
 2. The incidence is much higher in low socioeconomic groups, and includes
 - a. Blacks
 - b. Puerto Ricans
 - c. Mexicans
 - d. Other immigrant populations
 3. Women at risk include
 - a. First marriage at an early age
 - b. Early age at first coitus
 - c. Large number of sexual partners
 - d. High parity
 - e. Poor medical attention postpartum
 - f. Marital divorce and separation
 - g. Prostitution
 - h. A background of emotional unhappiness and depression
 - i. Inadequate personal hygiene
 4. Low-risk groups
 - a. Nuns
 - b. Women in other religious orders
 - c. Jews
 - d. Country women

The incidence of invasive squamous cell carcinoma of the cervix has declined because of the pap smear. The problem with the pap smear is that it, of course, can have problems of false negativity because of sampling, processing and interpretation. You must always keep that in mind. The Bethesda system which was supposed to make things simpler, seems to make things more complicated and I think in many respects very ambiguous. They constantly report ASCUS, atypical squamous cells of undetermined significance.

B. Etiology

1. Herpesvirus type 2 (HSV-2) and the genital wart virus are prime suspects for carcinomas involving the lower genital tract on females
 - a. A close association has been found between HSV-2 infection and cervical neoplasia in cytohistopathologic and seroepidemiologic studies
 - b. Prospective studies show that women with genital herpetic infection are at an increased risk of developing cervical neoplasia

III. Detection and Diagnosis

A. Clinical detection

1. Early detection is clinically uncommon due to a lack of clinical signs or symptoms in the intraepithelial stage
 - a. Routine surveillance techniques are required to detect these early lesions. The cytologic (Pap) smear has proven to be the most easily applied, economical, and effective techniques yet devised
 - b. Cytological screening is a mandatory part of any preventive medical program and should be done regularly after women begin sexual activity, at whatever age
 - (1) This screening is generally done yearly
 - (2) The optimal sample should include both a cervical scraping and a sample from the cervical canal obtained using either an external aspirator or a cotton-tipped applicator stick
2. Occult asymptomatic lesions should be suspected if any abnormality of the cervix is visualized by speculum exam. A cervical Pap smear and/or colposcopic examination with a directed biopsy should be done
3. Overt manifestations include
 - a. Any abnormal vaginal bleeding (1) intermenstrual bleeding (2) Postcoital bleeding
 - b. Foul vaginal discharge
 - c. Pelvic pain, leakage of urine or feces from the vagina
 - d. Anorexia and weight loss are often signs of advanced disease

B. Diagnostic procedures

1. Cytologic interpretation
 - a. The cytology report is given as a narrative statement of the nature of the lesion to be anticipated
 - b. A numerical classification from Class I to V is often used, and should be accompanied by a narrative statement

The problem is that ASCUS is because of inflammation sometimes, because of some atypicality that is not a dysplasia, some frank invasion where they can't interpret it closely. One of the things that you should be concerned about with ASCUS is that where you need the pap smear the most is with an invasive squamous cell carcinoma of the cervix and the highest false negativity rate is with an invasive squamous cell carcinoma of the cervix. The reason is the malignant tumor grows so rapidly that it outgrows its blood supply. Hence, you get necrotic cells and you get inflammation. With those necrotic cells and that inflammation, you will sometimes get an atypical cell. So it behooves you to look at those patients carefully.

I think that the fallacy in the thinking about the pap smear is that the pap smear is diagnostic. It is not. It is a screening test. It is excellent as a screening test. It is also not accurate. The pap smear is only 50% accurate so you have to be extremely cautious.

If there is something that is suspicious, biopsy it. Don't be afraid to do that. Even if you don't have a colposcope. Now, obviously a colposcope will help but just doing a biopsy is very important. There is another very important caveat in dealing with cervical carcinoma and that is that 15% of cervical carcinomas are adenocarcinomas. Adenocarcinomas do not lend themselves well to an accurate diagnosis with the pap smear. The reason is that they don't have the squames they have got. You have got to look at actual tissue on that in order to get that.

If that cervix is suspicious, it bleeds on touch, it just looks a little too big, biopsy it. It is not going to hurt that patient to biopsy them.

The human papilloma virus. The problem with the human papilloma virus is that although it is definitely associated with dysplasia and carcinoma *in situ*, I do not believe that it is a causative agent. If you look at the simple statistics, and that is that there is only about 12-13,000 invasive carcinomas of the cervix per year, the papilloma virus is now in the millions.

What has happened is that as the population began to do pap smears from the '40s to the '50s where we had 50,000 invasive squamous cell carcinomas of the cervix per year and 43,000 died, in 1996, we only had about 12-13,000 with about 3,500 dying which is going from an 85% mortality clear down to a 25% mortality.

However, what has happened is that pap smear has picked up the carcinoma *in situ*. Now, the story about the HPV is that there were no statistics on the HPV prior to the '60s and then it was 600,000 and now it is in the millions. So you have to ask yourself, if the HPV is now in the millions and the invasive carcinomas have gone down and the carcinoma *in situ* added with the invasive carcinomas are no greater than they were in the 1940s, there is something that is just not exactly correct when they tried to pin down the HPV as being the definite cause of the carcinoma.

The leader of female malignancies is not the female pelvic malignancies. It starts, of course, with breasts. Then cervical

- (1) Class I: normal
 - (2) Class II inflammation
 - (3) Class III: dysplasia
 - (4) Class IV: carcinoma in situ (CIS)
 - (5) Class V: invasion
2. Transformation zone and colposcopy
 - a. Cervical intraepithelial neoplasia (CIN) begins in the transformation zone (T zone), that area of the cervix in which native columnar epithelium is replaced by squamous epithelium
 - b. The T zone is readily accessible for evaluation both by cytology and colposcopy
 - c. Colposcopy provides a well lighted, 10- to 15-fold magnified stereoscopic view of the cervix
 3. Colposcopy is not recommended as a screening technique.
 - a. Cytology is the screening method of choice
 - b. Three percent acetic acid is applied to the cervix to accentuate the topographic and vascular alterations which are found in neoplastic epithelium
 - c. These changes help to direct the colposcopist to biopsy the most abnormal area
 - d. In many cases, colposcopically directed biopsy can give an accurate diagnosis prior to definitive therapy.
 4. Colposcopy is extremely useful, but a conization must be performed if
 - a. There is no colposcopically visible lesion and the abnormal tissue is thought to be in the endocervical canal
 - b. The entire lesion cannot be seen with the colposcope
 - c. The patient is considered an inappropriate candidate, ie, one deemed unreliable for follow-up
 - d. When a diagnosis of microinvasion is made on colposcopic biopsy
 - e. Colposcopically directed biopsies fail to explain the cytology
 5. Directed biopsy: endocervical curettage
 - a. A complete evaluation should include a carefully performed endocervical curettage above the cervical biopsy

IV. Classification

- A. Clinical varieties
 1. Cervical intraepithelial neoplasia (CIN)
 - a. Dysplasia
 - (1) Mild
 - (2) Moderate

carcinoma, as I've said, has been a success story because it went from 50,000 and dropped clear down to about 13,000 but you've still got that carcinoma in situ to deal with. Then, of course, the next one that comes up is a uterine carcinoma and then after that is your ovarian carcinoma and then your vulvar carcinomas.

Invasive squamous cell carcinoma is predominantly seen in the younger patients. The 15-34 age group has about 2,600 and the 34-54 has only about 1,200 overall.

The other thing that you have to appreciate is, and there was a case just recently in which the patient had a little bit of bleeding, was postmenopausal. The doctor couldn't figure out what it was and fortunately he got biopsies up into that endocervix. That squamocolumnar junction is certainly the point, hypothetically, that causes the invasive carcinoma to start. What happens is that the transformation zone which is the place wherein the cervix turns out, you get an ectropion. Then you get a squamous cell metaplasia to lay down and either a virus or a chemical or some process that causes that immune system to go awry and that is where you get your dysplasias to start to go through the mild-moderate-severe dysplasia carcinoma in situ microinvasion and invasive carcinoma. But as the patient gets older, that is going to go up the canal. Again, in using the colposcope, you've got to watch out because you are not going to be able to see up that canal and you may have to take that person to outpatient surgery to do a good adequate biopsy if you are suspicious that they've got some type of a process going on there.

The pap smear can pick up slides from anywhere including occasionally picking up psammoma bodies, of all things, from an ovarian carcinoma. So it can pick those up sometimes and don't ignore them because they are there somewhere. On the other hand, the colposcope helps you to appreciate exactly where that lesion is. That is to say that you must follow the premises of a colposcopic biopsy satisfactory components. That is that you must be able to see the entire lesion, you must be able to see the squamocolumnar junction, then endocervical curettage must be negative or at least complementary to what that pap smear is and the pap smear and the diagnosis must be coordinated correctly.

The squamous epithelium is. Only 0.24 mm. Just below, in less than 1 mm, you've already got vascular and lymphatic channels. For reasons that aren't clearly understood, that basement membrane is certainly a barrier for the disease to progress beyond this and it will stay there for a long, long period of time. I have seen patients have evidence of carcinoma in situ that has been there for 15-20 years. But once it becomes invasive and breaks that basement membrane, all bets are off. That is an urgent problem and it needs to be taken care of as quickly as possible.

Also, as you will see, the amount of cells that can be contained in a cubic millimeter is quite dramatic. With any malignancy, the cells can double logarithmically in three weeks time. So you certainly want to understand that there is a certain urgency to get on with the diagnosis. There are big arguments about how far do you have to go before you've got frank invasion. You can see that in a given patient, you can have frank invasion just less than 1 mm below. On the other hand, by definition and

(3) Severe

- b. The various degrees of intraepithelial neoplasia are distinguished by the extent to which the full thickness of the epithelium is composed of undifferentiated neoplastic cells
- c. CIN forms a continuum, beginning with mild dysplasia (grade 1) through CIS (grade 3), and ending with invasive carcinoma
- d. Patients with the earlier stages of CIN (the dysplasias), may have one of three courses
 - (1) Regression
 - (2) Persistence
 - (3) Progression to CIS or invasive carcinoma
- e. The risk of progression to more significant disease increases with decreasing differentiation

2. CIS

- a. CIS or CIN grade 3 (stage 0) is widely accepted as a precursor of invasive carcinoma. This is based upon two general types of evidence
 - (1) The finding of CIS and invasive carcinoma simultaneously in the Sallie cervix
 - (2) The development of invasive carcinoma in patients after a diagnosis of CIS without treatment

3. Microinvasive carcinoma

- a. Microinvasive carcinoma (stage Ia) of the cervix represents the earliest transition of a CIS, presenting no threat of metastasis. Frankly invasive carcinoma may spread from the cervical stroma to adjacent tissues and lymphatics

4. Invasive carcinoma

- a. Grossly invasive carcinoma of the cervix varies considerably in its appearance, depending upon the nature of its growth pattern and mode of regional spread
- b. Invasive carcinoma is frank invasion when the cervical stroma is penetrated >3 mm of depth from the basement membrane
 - (1) Exophytic lesions originating on the portio vaginalis often grow to form large friable polypoid masses
 - (2) They may be small, but if very large they form a "bulk" lesion, which may reach enormous proportions and fill the entire pelvis
 - (3) This type needs special consideration for therapy
- c. Infiltrative tumors tend to show little visible ulceration, but may present as a stony, hard cervix

how you would treat this patient remains different because statistically you will see there is only about a 1% chance in microinvasion of a patient having a lymphatic space involved.

The types of invasive carcinomas of the cervix run the gamut. The most frequent, of course, are the squamous cell, keratinizing, non-keratinizing and the small cell. The small cell is, of course, a special category that is highly malignant that will grow very, very rapidly and also as you will see has many more cells in it. The next most common group, of course, is the adenocarcinomas. Virtually 85% of the carcinomas of the cervix are the squamous cell carcinoma and only 15% represent the adenocarcinomas. The adenocarcinomas are a little bit more difficult to diagnose. On the other hand, they respond to treatment almost equally.

With the large cells, you've got a population of over 275,000 when you've got 1 mm of invasion up to approximately a million and then it goes to 3 million when you are at 3 mm worth of invasion. Whereas if you are starting with the small cell, you've got 700,000 that goes up to over a million and then even higher than that when you've got 3 mm of invasion.

There have been great arguments about whether or not you need to treat microinvasion more aggressively versus invasive carcinoma. We have run the gamut from 1 mm to 3 mm to currently saying that 5 mm is frank invasion. I am here to tell you today though that if you've got 3 mm of invasion, I would treat that patient as if they've got frank invasion because you don't know what is in that specimen that is going to come out. A compromise would be to do at least a modified radical where there is some ambiguity and then once you've got that specimen out, you can take a look at that and have your pathologist do a frozen section.

Microinvasion. A small amount has gone below the basement membrane. I would be very comfortable to treat that patient in a very conservative manner with a conization, if my margins were free and clear and I didn't have vascular and lymphatic space involvement and I did not have multiple foci of this throughout the area. Something greater than that, I would do a cone in some circumstances, but I would be very selective and I would get a gynecologist involved to make that disposition before I did something like that. Certainly once that patient has reached their child bearing capacity, I would get on with doing definitive therapy.

Microinvasion, as you will see by definition, is going to be less than 3 mm and the overall node incidence is only 1.2%. That is a good composite study of almost 700 patients all together. In that circumstance, certainly in a patient that wants to retain her child bearing capacity, you could consider to treat her in a more conservative manner. But that patient needs extremely close follow-up with pelvic examination and pap smears every three months along the way.

The criteria for the classification in the treatment of microinvasive disease is the depth of invasion and also the confluence. The depth of invasion, of course, as I said to you should be less than 3 mm although today you will find that they will allow you to go to 5 mm in the staging category of microinvasion. Confluence is in a horizontal plane. The lesion shouldn't be any greater than 7 mm. There should not be any

- d. These endophytic-type lesions, when they reach sizes >5 cm, are considered to be "barrel-shaped" and also need special consideration for therapy.

B. Route of spread

1. Carcinoma of the cervix spread patterns include direct contiguity, lymphatic invasion, and rarely, blood-borne metastases
2. The tumor may invade into
 - a. The vaginal mucosa, extending microscopically, beyond visible or palpable disease
 - b. The myometrium of the lower uterine segment and corpus, particularly lesions originating in the endocervix
 - c. The paracervical lymphatics, and from there to the most commonly involved lymph nodes. These have been previously described as primary and secondary groups
 - (1) primary spread group
 - (a) Parametrial nodes are the small lymph nodes, traversing the parametria
 - (b) Paracervical or ureteral nodes are located above the uterine artery where it crosses the ureter
 - (c) Obturator: surrounding the obturator vessels and nerves
 - (d) Internal iliac nodes course along the hypogastric (internal iliac) vein near its junction with external iliac groups
 - (e) Sacral nodes
 - (2) Secondary spread group
 - (a) Common iliac nodes
 - (b) Inguinal nodes consist of the deep and superficial femoral lymph nodes
 - (c) Para-aortic nodes

C. Anatomic staging of the International Federation of Gynecology and Obstetrics

Table 1
Cervix Uteri

| <u>Stage</u> | <u>0</u> | <u>(TIS)</u> | <u>CIS</u> |
|--------------|----------|--------------|--|
| Stage | I | (T1) | Carcinoma confined to cervix |
| | IA | (T1a) | Microinvasive carcinoma |
| | | (T1b) | All other cases of stage I |
| Stage | II | (T2) | Cancer extends beyond cervix, but not to Pelvic wall or lower vagina |
| | IIA | (T2a) | No obvious parametrial involvement |
| | IIB | (T2b) | Obvious parametrial involvement |
| Stage | III | (T3) | Cancer to pelvic wall or lower vagina, or ureteral obstruction |

endolymphatic or vascular space involvement although a positive endolymphatic space involvement does not necessarily equal a positive lymph node involvement. When there is a single focus of disease, that makes you more comfortable in treating that than multicentricity in two or three quadrants and, of course, the surgical margins are extremely important to look at.

That is why in doing your cone, you should be extremely careful and I would be a little bit cautious with this thing called the LEEP that is being pushed. I have seen invasive carcinoma looped and leaped and that is the wrong thing to do. I have seen people think that it is simple to do but then you've got a cervix that has got a tremendously strong consistency. So there you are, the thing is not high enough and then you go around the thing and then you also get a char effect with this LEEP. So cold knife cone is still a very, very good procedure to use. Do your cone where you can really see what you are doing, use 0.25% Xylocaine with 1:400,000 epinephrine. That 0.25% Xylocaine with 1:400,000 epinephrine will virtually give you a bloodless cone and if you've got good traction sutures at 3 and 9 o'clock and you pull that down and you circumscribe your cone with a #15 blade and then you use an #11 blade which is like a dagger blade to shape your cone, you will be able to have a good cone in virtually all specimens.

A good cone. Should be at least 2 cm to 2.5 cm across on the base of the diameter and the hypotenuse should be at least 1.5 cm going up on that. The specimen itself should be handled very carefully so that you get at least 15-20 blocks and about 60-80 sections before you are satisfied that cone diagnosis is a good diagnosis.

One other thing that we have used that we have found extremely helpful in doing the cones is to take a 4 x 8 cm Surgicel, take a gram of Avitene, wrap that in a ball and that while that is an expensive thing, put that as a pledget up against that cone that has been carved out, tie it loosely with your traction sutures in place and I am here to tell you that you will not see post cone bleeding if you do that properly. We have used that for a number of years and have virtually not seen any post cone bleeding using that technique.

If there are multiple foci of microinvasion and the depth is less than 3 cm, the microinvasion does not involve the lymphatic spaces and the margins are okay, that is the patient that you could treat in a conservative manner. Any patient that falls out of that category should be treated with at least a modified radical to a radical hysterectomy. A modified radical, as we will show you later, doesn't go quite as far to the pelvic side wall and the patients tolerate that procedure extremely well and you still have the option to go get nodes at that point in time after you've gotten that specimen out.

You could do the simple cone or the extrafascial hysterectomy. A single focus of microinvasion, depth less than 3 cm, no endolymphatic invasion and the surgical margins are free and clear.

Ironically enough, whether you treat a patient that has frank invasive carcinoma with radiation therapy or with surgical therapy, the results are very close to equal. The problem, of course, comes in the fact that patients beyond stage IIA are not

| | | | |
|-------|------|-------|--|
| | IIIA | (T4a) | No extension of pelvic wall |
| | IIIB | (T3b) | Extension to one or both pelvic walls, or ureteral obstruction |
| Stage | IV | (T4) | Carcinoma beyond true pelvis or invading bladder or rectum |
| | IVA | (T4a) | Spread to adjacent organs |
| | IVB | (T4b) | Spread to distant organs |

D. Uniform TNM classification

1. Nodes

- a. NX: not possible to assess regional nodes
- b. NO: no evidence of regional node involvement
- c. N1: evidence of regional node involvement
- d. N3: fixed or ulcerated regional nodes
- e. Na: juxtaregional node involvement

2. Distant metastasis (M)

- a. MX: not assessed
- b. Me: no (known) distant metastasis
- c. M 1: distant metastasis present
- d. Specify:

3. Specify sites according to the following notations:

- a. Pulmonary: PUL
- b. Bone marrow: MAR
- c. Osseous: OSS
- d. Pleura: PLE
- e. Hepatic: HEP
- f. Skin: SKI
- g. Brain: BRA
- h. Eye: EYE
- i. Lymph nodes: LYM
- j. Other: OTH

IV. Postsurgical classification

A. Residual tumor (R)

1. Types

- a. R0
 - (1) No residual tumor
 - (2) Totally resected
- b. R1
 - (1) Microscopic residual only
 - (2) Confined to tumor bed
- c. R2
 - (1) Macroscopic tumor residual
 - (2) Specify

2. Once clinical staging has been done, the patient remains in the same stage, irrespective of later changes or outcome following

surgical candidates by in large for definitive therapy. However, as you will see, patients that are stage IIB, IIIA, IIIB and even IVA are candidates, pre-radiotherapy, for surgical staging. The reason, as you will see, is that this clinical staging is fraught with a lot of errs because it does not take into consideration para-aortic nodes. If you treat a patient with radiotherapy, first of all, you are not going to have that disease treated until you are almost five to six weeks into therapy whereas with surgical therapy, it is very definitive and you are getting the treatment done right away. Plus you are able to assess the extent of disease. So, for patients that have Stage I with some exceptions and IIA, we would recommend a radical hysterectomy in virtually all of them. Now, if a patient has a tumor that is 6-7 cm, in that situation we would probably opt to do surgical staging on that patient and then go on with radiation therapy so that you can really know whether or not you need to treat that patient with both pelvic and para-aortic lymph nodes at that same time. Certainly, in stage IIB and IIIB there is no question about that.

Now, surgical therapy does several things for you. It allows you to preserve the ovaries because once you've gotten to 2,000 gray or 2,000 rad, you have lost the ovaries. So in a patient that is in her reproductive years, anywhere up to an age of 45 or certainly at least age 40, you would like to preserve those ovaries. Even if you have to give radiation therapy, you can move those ovaries with surgical therapy. You can move them by unhooking them from the utero-ovarian ligament and bringing them back up to the rib cage or on the posterior side in the gutter so that they are well above the iliacs so that you then can radiate that patient safely and protect those ovaries at the same time. Plus, when you use radiation therapy, your vaginal elasticity goes to pot, your vaginal mucosa dries. So again that is why in a younger aged patient, we would prefer to do surgery as opposed to radiation therapy where we can.

Staging is a confusing conglomerate that continues to evolve and change. The problem with staging is that theoretically it is not supposed to change once you stage that patient clinically. But as you will see again, clinical staging is fraught with a lot of errs. Carcinoma situ is pretty clear. There is no question about that. The microinvasion is minimal stromal invasion and as we've said, IAI means it is just minimal, IAII means that it goes down to a depth but it doesn't exceed a depth of 5 mm and it doesn't have a confluence of greater than 7 mm. The thing that also is confusing is it doesn't make any difference supposedly whether you measure from the depth of the gland or from the top of the epithelium in staging that. Any patient then that is greater than that, in that IAII category then is bumped up to the stage IB category.

The problem with the IB category is that it takes all-comers. It takes patients that have 1 cm disease up to as many as 6, 7, and I've seen them as big as 12 cm disease. Obviously, that is not a stage I patient although from the staging, it is categorized as that. Stage IIA means that you are involving the cervix and the vaginal fornix. Stage IIB is one or both perimetria and stage IIIA is down to the lower third of the vagina, stage IIIB is out to the pelvic side wall, stage IVA involves the bladder or the rectum but not out of the pelvis and stage IVB is beyond that.

There is also one other exception in the clinical staging of stage I. That is that if a patient has an IVP and they do need to have

treatment or other procedures

- a. With the new diagnostic and screening methods in use today, the clinical population of female patients with advanced disease is rapidly decreasing
- b. Approximately 80% of carcinoma of the cervix is diagnosed in the preinvasive or early invasive stages:

B. Histopathology

1. Carcinoma of the uterine cervix is squamous in about 90% of the cases and is generally moderately undifferentiated
 - a. <10% of cervical lesions are adenocarcinomas
 - b. These probably have a radiosensitivity similar to that of squamous carcinomas
 - c. Mixed carcinomas of both squamous and adenocarcinoma types occasionally occur, and both types are invasive
 - d. Sarcomas also occur but are extremely rare and hold the poorest prognosis
2. Grading is rarely of value in predicting overall outcome. The most acceptable is that of Reagan and Wentz: who have correlated outcome with type and size of cells

Table 2

5-Year Survival 1

| | |
|---|------|
| I Keratinizing carcinoma | 45.1 |
| II Large cell nonkeratinizing carcinoma | 77.6 |
| III Small cell carcinoma | 17.0 |

VI. Staging Work-up

- A. The staging system is clinically diagnostic, with emphasis on
 1. Examination under anesthesia
 2. Examination by both the gynecologist and radiation therapist
- B. Patients with CIS are not subject to a complete tumor survey; diagnostic studies are done as indicated, and colposcopy may be helpful to rule out invasive carcinoma
- C. For invasive carcinoma
 1. Recommended procedures
 - a. Hemogram
 - b. Liver chemistries, BUN
 - c. Chest x-ray, skeletal survey, IV pyelogram
 - d. Cystoscopic exam
 - e. Sigmoidoscopic exam, barium enema (for patients over 50 years of age or when indicated by symptoms or physical findings)

that in the staging criteria and she has a hydronephrosis, then that patient is bumped up to a stage IIIB. What you need to understand about staging is that you need it to categorize patients but it doesn't predict prognosis and it doesn't tell you how to treat the patient. If anything, what you need to do in an ambivalent situation is to stage down and treat up. The reason is because you're not exactly sure and you are far better off to stage up rather than to stage down in treating that patient.

The important thing is to understand that the disease grows first by direct contiguity, meaning that it can go down the cervix into the vagina, down the uterosacral ligament, out the perimetrium per cervical tissues or up into the myometrium. Supposedly, it is not supposed to make any difference, certainly with staging when it goes clear up into the myometrium. I am sure it does in the overall prognosis of the patient. The second way that it travels, of course, is once it has inundated that endocervical stroma, it is into those vascular and lymphatic channels and it can take a walk in that way as well.

Predominantly, they go to the external iliac and to the internal iliac nodes and then to a lesser degree to the obturator, the common iliac and the presacral nodes and then to a lesser degree to the para-aortic nodes. These are autopsy studies that shows the disease can virtually go anywhere. It can take a walk clear down to the tibia. It can take a walk clear up into the brain. I have even seen it in the ophthalmicus of the brain in a given patient.

In the early '70s, the staging clinically was challenged by a number of universities. What they basically show that with stage IB, you had about a 5.6% incidence of positive para-aortic nodes. Stage IIA and IIB jumped clear up to as high as 15-25% depending upon which study you read and in stage III, you are up to 30% or better with the lymph nodes that are already into the para-aortic nodes. This is the reason that I've strongly said to you that I feel that any patient that is going to undergo radiation therapy that is stage II, III or IV should undergo a surgical staging prior to that treatment. That can be done in a retroperitoneal approach by virtue of making a hockey-like incision from the midclavicular line down to the rib cage and literally going through the external-internal oblique transverse sales fascia and then rolling the peritoneum over. You can get access to the para-aortic nodes in that way and safely take out those para-aortic nodes and even go under the peritoneum, over the aorta to the opposite side and get the nodes on the opposite side as well.

Today, also it can be done laparoscopically in institutions.

Your problem, of course, is that you say, "Why not the CAT scan?" the CAT scans specificity is such that anything that is less than 1 cm, they can't really tell you whether there is anything that is suspicious or not.

In approaching a radical hysterectomy to treat these patients, the anatomy is fairly clear that the infundibulopelvic with the ovarian artery and vein clearly parallels that ureter. That ureter is most commonly found on the medial leaf of the broad ligament until it gets down to the uterine artery. The second part of that ureter, though, dips into that dense fibroconnective tissue of the ureteric tunnel and then comes out just before it

- f. Biopsy is required to establish bladder or rectal involvement as well as suspicious pulmonary nodules
- 2. Optional and investigative procedures
 - a. Lymphangiograms are often useful in determining the spread of disease to the para-aortic lymph nodes. Unfortunately, the incidence of false-negatives varies from 20--50%
 - b. Needle biopsy techniques can be utilized to confirm positive nodes
 - c. Prestaging laparotomy has been recommended in major cancer treatment centers; approximately one-third of the advanced cases of cervical carcinoma already had disease beyond the pelvis

V. Principles of Treatment

A. General

- 1. The treatment of carcinoma of the cervix depends upon the extent of disease
- 2. Surgery, radiotherapy (RT), and combinations of the two modalities have given the best results for cervical cancer
- 3. Chemotherapy and immunotherapy have no proven role in the primary treatment of cervical carcinoma.

B. Surgery

- 1. This may include one of the following procedures
 - a. Cryotherapy
 - b. Catheterization
 - c. Conization
 - d. Vaginal hysterectomy
 - e. Simple extrafascial total abdominal hysterectomy
 - f. Modified radical abdominal hysterectomy
 - g. Radical abdominal hysterectomy with a bilateral deep pelvic node dissection
 - h. Bilateral salpingo-oophorectomy is elective, depending upon the patient's age, menstrual history, and findings at surgery.
- 2. The choice of treatment depends upon the stage of disease
- 3. Pretreatment laparotomy and paraaortic node biopsy may be used to evaluate some patients with advanced cervical carcinoma, ie, stages IIb, III, and IIIb
- 4. Pelvic exenterative surgery is usually reserved for recurrent disease

C. Radio therapy

- 1. RT is generally used in treatment of invasive cervical carcinoma
- 2. Treatment plans usually include
 - a. Intracavitary irradiation to deliver a high dose to the central tumor
 - b. Supervoltage external beam therapy to insure adequate

enters into the bladder. That is the reason why you have to, in order to do a radical hysterectomy, go to the bifurcation of the common external-internal neck artery, take that interiliac and travel down to the bifurcation of the superior vesicle on the uterine artery and then pluck out that uterine artery. You need to lift that uterine artery up over that ureter and then you are able to unroof the ureter and deflect it laterally in caudad and be able to get the paracervical, parametrial and uterosacral ligaments as you will see in the other slides.

Now this shows how well the planes are between the vesicle vaginal portion of that cervix. If you will get midway between the bladder and that lower uterine segment, that is a free plane and as long as you stay out of the bladder pyramids which are either side of this, this place right in here, is avascular. So if you take that down at that point, you are able to see that properly and then later on you can come back and get those bladder pyramids.

You have a nice free space also posteriorly in that cul-de-sac that is relatively avascular. The vascularity again is more laterally so if you go right in the center, you are able to get good tissue planes on that.

In getting the uterosacral ligaments, this shows it in terms of a modified radical that is midway between but you can see the juxtaposition to the ureter and the reason why you have to unroof that ureter and get it deflected laterally and caudad. Whereas, with a radical hysterectomy, you are coming clear out to the lateral pelvic side wall with the uterosacral ligaments. Now, in the cardinal ligaments, again, it is even more important that you get that ureter unroofed because you can see in the modified radical you are very close to the ureter whereas with the radical hysterectomy, you are clear over to the side wall of the pelvis.

In taking the vagina, in a modified radical hysterectomy, you are just below the cervix and getting the fornix. In a radical hysterectomy, you are lower than that - almost halfway down that vagina.

Radiation therapy. There are some very important things that you need to appreciate and that is you need to deliver no less than 156 rads per day in order to get an adequate treatment of that patient. Currently today, the standard machines are at about 180 rads. The linear accelerators of today are really much more accurate delivery systems.

The standard for stage IB is that you are really trying to treat that central part because you have very little chance, only about a 10-15% chance of nodes being involved in that stage IB so they are giving 2,000 of external and then they are giving approximately 8,000 to a minimum of 6,000 of intracavitary. The thing that you need to appreciate and help your patient to understand is that when they are getting the intracavitary, because of the principle of the inverse square law, basically you've got your highest dose at the point source. One centimeter away is half the dose. Two centimeters it is one-fourth of the dose, three centimeters it is one-ninth of the dose, four centimeters is one-sixteenth of the dose and five centimeters is one-twenty-fifth of the dose. That 5 cm component is where the nodes are so you can see where you fall off a great deal when you are out towards the pelvic side wall with the intracavitary.

treatment to the node-bearing areas

- c. Para-aortic node irradiation by external treatment has been added in those cases where the nodes are positive
3. Treatment is planned individually to conform to each patient's distribution of disease and anatomic variations
- D. Chemotherapy and immunotherapy. There are no completely effective agents known
- E. Treatment by stage
 1. Dysplasia (mild and moderate)
 - a. Because a large number of CIN 1 and CIN 2 lesions regress (62% and 33%), or persist (24% and 49%), and only a small number progress to CIN 3 (13% and 18%), many authors feel that this condition can and should be followed with serial cytology and follow-up exams every 6 months
 - b. Cryotherapy and electrocoagulation have also been used increasingly
 - c. However, at the present time, these modalities should be regarded as clinical investigations in progress
 2. Severe dysplasia (CIS)
 - a. Patients with severe dysplasia or CIS are most effectively treated by total abdominal hysterectomy with a wide vaginal cuff
 - b. The decision to remove the ovaries at the same time depends on the patient's
 - (1) Age
 - (2) Menopausal status
 - (3) Disease stage of the ovaries
 3. Some patients may be treated less radically by cervical conization and frequent follow-up exams with Pap smears every 3 months
 - a. Patients desiring further child-bearing and who can be carefully followed
 - b. Reliable patients who can be carefully followed
 4. Stage Ia (microinvasive) carcinoma
 - a. At present, it is felt that only a total abdominal hysterectomy with a wide vaginal cuff (modified radical hysterectomy) is necessary with up to 1 mm depth of invasion
 - b. Because of a risk of lymph node involvement (3-7%), patients with > 3 mm of invasion in this category should be treated the same as Stage Ib
 - c. Between 1- and 3-mm invasion, there is dispute over how much treatment is necessary
 5. Stage Ib
 - a. Radical RT and hysterectomy are probably equally effective in

When you are dealing with a patient that is a IIB, you now have got stuff into the perimetria so now you want to get a higher external dose and therein they will deliver 4,000 on that patient and they will deliver it at 180 rad per week for approximately four and a half weeks, Because 180 rads is 900 per week and four weeks would be 3,600 and you've got to bring it up a couple of more days to get that 4,000 on that. Then you go to your intracavitary and you do it two times with that. Those intracavitaries will last for approximately 24-48 hours on two occasions.

When you are dealing with a IIIB disease, you most often have bulky disease that extends clear out to the pelvic side wall and hence you up the dose externally to approximately 5,000 and then you come back in with approximately 4,000 intracavitary in that situation.

Then there is also the palliative approach. When we are dealing with a bulky patient, i.e. a patient that has a cervical carcinoma that measures greater than 5 cm, we will often use a combination of chemotherapy using cis-platinum or mitomycin-C and 5-FU for a five day treatment and we do it in several different ways. In some protocols, we will treat them with combined chemo on week 1 and 5 and in some protocols we will treat them on weeks 1 and then 3 and 5 on that. There have been dramatic responses in that and I suspect that when the protocols mature that are currently being looked by the GYN-oncology group that there may be a more standardized approach to doing that more commonly. Because certainly the combination chemotherapy and radiation therapy seems to be tolerated well and at the same time these patients get a very dramatic result with shrinkage of the tumor.

The other thing you need to keep in mind is that with radiation therapy you have immediate, you have ongoing and you have delayed side effects. Those delayed side effects can go up to a year and a half or greater. The risk of a severe radiation side effect today is about the same as surgery. Somewhere between 1 and 3%. Most commonly, patients will get problems with radiation cystitis and some radiation enteritis and sometimes radiation proctitis but they are usually not of any severe degree.

After a patient has been successfully treated for invasive carcinoma of the cervix, those patients need to be followed for life. We see those patients every three months. Often times we see them with the referring doctor on alternate visits. We get a pelvic examination and a pap smear on those patient on each and every visit. At six month intervals, we get an IVP and a chest x-ray for the first two years and then we go to four months at the third year in our institution and then we go to six months thereafter for life.

You have to have a high index of suspicion that these patients when they come in with some type of symptomatology that there is a possibility that the disease is back. One of the problems with recurrent cervical carcinoma is that when you go to look for it, it is hard to find. Part of the reason is because you get like a shotgun effect of pellets all over the doggone place so when a patient complains of leg edema or of pain in the buttocks area, look out. There may well be small bits of disease that have actually gone into that area and are extremely hard to find in a way so you have to just watch that patient. In those patients, we would get a bone scan as well as a CAT scan

treating the stage I cervical carcinoma

- b. Radical hysterectomy and pelvic node dissection is one basic method of treatment and may be favored for the young patients
- c. Ovaries are not removed unless the patient is postmenopausal or the ovaries are abnormal
- d. In elderly patients or those with serious medical complications, RT is recommended. This should include external supervoltage therapy and intracavitary radium

6. Stages IIa and IIb

- a. RT and surgery as outlined for stage Ib can be used
- b. For stage IIa, this surgical treatment should be limited to young, otherwise healthy women; all others are treated by RT
- c. For stage IIb, pretreatment laparotomy for assessment of para-aortic nodes is being recommended in some large cancer treatment centers. This investigative procedure is followed by the appropriate RT to include external and intracavitary irradiation with para-aortic fields as indicated.
- d. Para-aortic involvement is found in approximately 15 % of all cases in stage II. It is unknown whether para-aortic extended field RT will increase the survival rate

7. Stages IIIa and IIIb

- a. RT is the method for all cases in this stage
- b. Pretreatment laparotomy is recommended in major cancer treatment centers unless the patient's condition does not warrant laparotomy.
- c. Para-aortic nodes have been found to be positive in approximately 35-50% of several series of stage III cervical carcinoma.

8. Stage IV

- a. RT is the basic method of treatment
- b. Occasionally, where the disease is limited to the pelvis and the is primarily anterior or posterior, pelvic exenteration and removal of the internal genitalia, bladder and/or rectum may be used as primary therapy

9. RT is mainly by external therapy to the whole pelvis in those few cases where the detectable disease is limited to the pelvis. Beyond that, the patient receives individual attention regarding additional therapy

F. Special considerations of/for treatment

1. Cervical stump lesions that result from invasive carcinoma developing in a patient previously treated by a subtotal hysterectomy for benign disease
 - a. Are becoming less common
 - b. Present special difficulties both for surgical and RT techniques,

and you need to get a CAT scan of the chest-abdomen-pelvis. For some reason, my GYN colleagues, very often when they are thinking about female pelvic malignancies, they either start just at the pelvis or they do the abdomen and the pelvis and they forget the chest. Because you have got to look there to make certain that there is not something going on especially when you are talking about recurrent disease.

Now there is a small group of patients that have recurrent disease that are still salvageable. By in large, a patient that has this set of symptomatology is in big trouble and these patients are going to have to go to some type of a chemotherapeutic regimen that today still is not as successful as we would like. When a patient has evidence of central recurrence by virtue of a biopsy done at this point and after the patient has undergone that complete workup to include that chest x-ray, that IVP, that CAT scan of the chest, abdomen and pelvis, then that patient needs an expiration. The first thing you've got to do an expiration is make certain there is nothing in the upper abdominal area of the patient or up in the liver which most probably would have been picked up on the CAT scan. The way you follow through on that is if the CAT scan looks positive, prove it. Stick a needle in. The next thing you've got to do is evaluate the para-aortic lymph nodes and then after the para-aortic lymph nodes, you've got to evaluate the pelvic nodes and then lastly, you've got to evaluate to see that you can get around the entire thing before you commit that patient to an exenteration.

In doing an exenteration, if that patient has disease that is all anterior, you can get by with an anterior exenteration which means that you spare the colon and rectum and they don't end up with a colostomy. In a patient that has disease that is going posteriorly, you can sometimes spare the bladder and just do a posterior exenteration and they will end up with just a colostomy. In a total pelvic exenteration, these patients will end up, of course, with a urinary conduit as well as a colostomy. Some of the things that have happened current day that have helped to get a greater longevity for these patients is the colon urinary conduit as opposed to the small bowel conduit. The other thing that is very good today is a Kock pouch where they don't even have to wear a bag and you can use a segment of the small bowel and make a pouch out of that. With the way that pouch is designed, it has the same qualities of a colon conduit and that is that you don't get reflux back up into the kidneys whereas when you are using an ileal conduit, you do get into problems with reflux up into the kidneys.

The other thing that is done is that the omentum is taken off from the hepatic flexure all the way across to the splenic flexure which retains its blood supply at that point and that whole omentum is brought down and is laid across that pelvis and that makes a big difference in the overall morbidity and mortality of these patients.

When you look at radiation therapy and you look at patients that have surgical therapy, your overall chance of having a patient that you can treat successfully with an exenteration only amounts to about 5-6% of those patients that have been previously treated.

but in general can be treated the same as stage Ib, either surgically or by RT

- c. Special radium applicators or intravaginal therapy, utilizing low voltage cone techniques may be required
2. The bulky or "barrel-shaped cervix is better treated by a combination of RT and simple extrafascial hysterectomy. This group represents a high risk of central recurrence, and combination therapy has reduced the incidence of recurrence from as high as 20 % to 3 % in one center
3. Pregnancy
 - a. CIS requires a satisfactory colposcopic diagnosis or conization
 - (1) The patient may be safely followed with serial cytology on a monthly basis during the remainder of the pregnancy
 - (2) Vaginal delivery is safe, and definitive therapy as outlined above can be carried out postpartum
 - b. Invasive carcinoma has a sense of urgency
 - (1) Although pregnancy does not seem to alter the course or prognosis significantly, vaginal delivery can disseminate disease via the cervical venous sinusoids
 - (2) The dissemination is due more to the delay from diagnosis to treatment than the specific act of delivering through an invasive cervix
 - (3) In the first and second trimester, the patient should be treated as for nonpregnant stage
 - (4) In the third trimester, when the fetus is viable, a C-section should be performed followed by the appropriate therapy.
 - (5) Although surgery is preferred, patients can also be treated by RT as outlined above
 - (6) For advanced stages, this requires a hysterectomy followed by RT
4. Persistence or recurrence
 - a. Defined as active malignant disease
 - (1) Up to 6 months posttherapy: persistence
 - (2) Beyond 6 months posttherapy: recurrence
 - b. Requires special evaluation and individualization, to include
 - (1) Repeat staging survey
 - (2) Scalene node biopsy
 - (3) Possible laparotomy if the disease appears to be centrally recurrent
 - c. With central recurrence, pelvic exenteration is considered a curative procedure
 - d. If there is tumor beyond the pelvis or noncentral recurrence, then chemotherapy is indicated

The incidence of recurrence after radiation therapy is only 1.5% in stage I, about 5% in stage IIB and about 17% in more aggressive IIIB category of patients.

The survival with a pelvic exenteration only approaches about 33%. The reason why you don't take these cases lightly is because there is also about a 13-15% overall mortality with this group of patients. About a 30% overall survival in over 1,500 patients and a 12.5% overall mortality.

Chemotherapy. The best agents are 5-FU, cis-platinum and the mitomycin-C and to a lesser degree bleomycin is effective. The combination of cis-platinum and 5-fluorouracil is extremely well tolerated. So is mitomycin C and 5-FU. It will put those patients into remission for a period of time. The problem with bleomycin is that very often these patients will get pulmonary toxicity over a period of time. The problem with the Adriamycin therapy is that these patients get into problems with cardiotoxicity.

- (1) At present, the best remission rates (45-50% have been vincristine 1.4 mg/m²; 2-4 hours prior to high-dose methotrexate 250-500 mg/m² . Followed in 24 hours by citrovorum rescue factor IV and then oral dosages six times
 - (2) This therapy requires adequate renal function (creatinine clearance of 50-75 cc/minute) and good hydration
 - (3) Hypogastric arterial refusion of chemotherapy has also been tried
- e. In cases of recurrence following surgery, each case must be evaluated in light of findings on tumor survey and physical examination. The treatment may be either RT or surgery
5. Complications of therapy
- a. Mortality, (1-2%) and morbidity (2-5%) figures from both modalities in competent hands are about equal
 - b. Surgical complications
 - (1) ureteric fistulae occur in 1%
 - (2) Those complications, especially with a radical hysterectomy and lymphadenectomy, include
 - (a) Lymphocyst
 - (b) Ureteral or vesical fistulae
 - (c) Atonic bladder with urinary retention
 - (d) Pyelonephritis
 - (e) Hemorrhage
 - (f) pulmonary emboli
 - (g) Wound infection
 - (h) Dehiscence
 - (i) Infection
 - (3) Postoperative morbidity has been reported in some series as high as 15%, but with modern operative techniques, can be reduced to 5%
 - c. RT complications
 - (1) Have been reduced from 8.2% to 1.5% with the development of modern RT techniques
 - (2) RT complications include
 - (a) Immediate side effects
 - i. Usually mild and transient
 - ii. Include
 - Anorexia
 - Nausea
 - Weight loss
 - Diarrhea
 - Dysuria

- Cystitis
- iii. Delayed side effects include
 - Subcutaneous fibrosis
 - Hemorrhagic cystitis
 - Ureteral stricture (rare)
 - Large or small bowel injury, (eg, proctitis, sigmoiditis, partial small bowel obstruction more commonly than large bowel injury)
 - Occasional retrovaginal, vesicovaginal, or enterocutaneous fistulae
 - Vault necrosis

G. Results and prognosis

1. When comparing surgical and RT results, it should be noted that in all surgical series, there is selectivity
 - a. RT has a wider range of patient applicability
 - b. Unfortunately, there is no controlled series available wherein surgery or RT has been randomly assigned to patients with stage I lesions in the same clinic
 - c. Treatment results have to be compared by equally competent surgical and RT teams in different institutions
2. Surgical therapy for invasive cervical carcinoma is only applicable for stages I and n.

H Clinical investigations

1. For localized stages I and II: Treatment results by RT and/or surgery are excellent
2. For advanced stages III and IV
 - a. This site is accessible and evaluable and therefore a prime target for testing combinations of RT and chemotherapy in the setting of unresectable local regional disease with distant metastases a late development
 - b. Some agents are still being evaluated
 - (1) Radiosensitizers (electron affinity agents)
 - (2) Hydroxyurea
 - (3) Hyperbaric oxygen breathing
 - c. Para-aortic nodal irradiation is another approach under study, as well as the addition of immunostimulation with *Corynebacterium parvum*