

ADVANCES IN CERVIX CANCER

by: Gil Lederman, M.D.

There have been significant advances in treatment of cervix cancer. Historically these include the use of PAP smear for early diagnosis. Early diagnosis has produced a fall in incidence of high stage cancers. In fact, cancers diagnoses have decreased as pre-cancerous lesions are more commonly detected and successfully treated by gynecologists and gynecologic oncologists. Other advances include those of surgery and radiation.

Surgery is used for relatively localized cervix cancer while radiation can be used for localized as well as advanced states of cervix cancer.

The role of chemotherapy has always remained a question mark. Some have strongly advocated its use while others have pointed to lack of controlled or randomized studies. Recently a combined effort led by Morris et al, evaluated the use of radiation alone compared to radiation plus chemotherapy.

Appearing as the lead article in the prestigious New England Journal of Medicine authors state that 13,700 women in the United States are diagnosed with invasive cervix cancer and more than a third will eventually die of the disease.

Noted is that cervix cancer affects minority groups and women of low socio-economic status in greater proportions thought due to less access to screening programs such as the PAP smear for cervix cancer.

With a large cervical cancer mass at diagnosis or pelvic lymph nodes involved, usually radiation is administered. This radiation includes both external beam as well as brachytherapy (radiation delivered directly into the cervix and its surrounding tissues).

Some studies had reported apparent improved success when pelvis and the draining abdominal lymph nodes sites (so called the periaortic area) were treated with radiation. Other studies have explored the use of chemotherapy sequenced with radiation.

The failing of prior studies is the lack of control arm. This means studies do not compare two similar groups of patients treated in different ways - yet one group receiving the considered "standard of care." Historically, studies have been only single arm. Thus, it had been left for physicians and patients to make the comparison.

At the beginning of this decade a group of radiation doctors decided to compare pelvic and periaortic lymph node radiation only to pelvic radiation administered with concurrent chemotherapy.

Women included had locally advanced cervix cancer of the so-called Stage IIB through IVA. This meant the cancer was locally confined to the cervix and the associated areas to some degree. Stage IIB involves the tissues around the uterus while III included cancer extending to the pelvic side wall or lower part of the vagina. Stage IVA is cervix cancer that has spread to include the bladder or rectum.

Women were excluded if they had cancer beyond the pelvic area or spread to the periaortic lymph nodes. Also women with prior cancers were not allowed to participate as were those who could not take chemotherapy.

Prior chemotherapy or radiation also disallowed entry to this study.

How were patients treated? Patients received external beam radiation of either anterior or posterior (from the front and back side) using high energy beams or the four field technique (from the front, back, right and left side) of a more modest energy. For patients who received either radiation alone or with chemotherapy, specific details of the radiation were included so as to create a uniform standard of care.

Radiation dose to the pelvic lymph nodes and periaortic lymph nodes was 4500 rad given in daily dosages of 180 rad. Rad is a measurement of radiation dose. The radiation isotopes placed within and about the cervix included Cesium 137 or Radium 226.

Usually the first endocavitary treatment was performed before or during external beam radiation. The subsequent brachytherapy was performed within two weeks after completing pelvic radiation.

For patients receiving combination of chemotherapy and radiation together, chemotherapy included intravenous administration of Cisplatin. Cisplatin was given in a dose of $75\text{mg}/\text{m}^2$ over four hours followed 4000mg of Fluorouracil per metered squared over four days. Giving chemotherapy this way accounts for differences in patients' size. Larger patients receive greater doses.

The patients who were given the chemotherapy from the first through the fifth radiation day. The patients were followed on a regular basis with blood tests and physical exam.

After treatment, the patients were followed on a routine basis. If persistent or recurrent cancer was questioned a biopsy was performed to make the diagnosis.

Overall, 403 patients were entered into this study from September 1990 to November 1997. Two hundred and one were randomly allocated to radiation and chemotherapy while 202 received radiation only. Fifteen patients, after

randomization, were disqualified. Of 388 patients, 195 received combined treatment while 193 had radiation only.

Moderate and severe side effects were more commonly seen in those receiving chemotherapy and radiation together than radiation alone. These were described as limited or self-resolving. The authors describe no difference in late side effects within the two groups.

At the time of follow-up, 76% of the patients in the combined chemotherapy/radiation group were alive while 63% of those receiving radiation only were alive. Thirteen patients in the combined modality group were alive but with recurrent cancer compared to 32 patients in the radiation group.

The authors noted that overall survival was better among those receiving radiation and chemotherapy together than those who had radiation alone. The numbers show the difference to be 73% compared to 58% respectively.

Furthermore, 76% were alive and free of cancer at five years when both chemotherapy and radiation was used but only 40% in the radiation group. Having cancer spread later beyond the pelvic area occurred in 14% of those who received chemotherapy/radiation and in 33% of those who received radiation only. Local recurrences occurred in 19% if chemotherapy and radiation was used and in 35% if radiation only was used.

The authors did note that "there was no significant difference in overall survival between treatment groups among patients who had Stage III or IVA disease, although the study was not designed to have a significant number of patients in the sub-groups to test for statistically significant difference. For patients with Stage III or IVA disease, the five year disease free survival rates were 58% in a combined group and 38% in the radiotherapy group."

Most likely, larger numbers of patients would have made this significantly statistically as the numbers appear dramatically different.

Researchers concluded "There is now significant evidence to recommend that woman with locally advanced cervix cancer confined to the pelvis receive pelvic radiation concomitantly with treatment of Cisplatin and Fluorouracil. Further studies are needed to define the optimum regimen for these agents and to evaluate other combinations. The role of extended field radiation with chemotherapy must also be defined."

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