RADIATION THERAPY OF CANCER OF THE CERVIX: A CORRELATION OF RADIOBIOLOGY WITH CLINICAL PRACTICE*

by

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In addition to the suffering of the individual patient, cervical cancer has an impact on the social system in that it strikes women in relatively young age groups and strongly affects family structures. In India it accounts for approximately 30% of all cancers in women. The specific incidence figures in India are not precisely known, but from the data of the Cancer Registry of the International Cancer Centre in Kanyakumari, the annual incidence of uterine cancer, which in this country is predominently cervical, is approximately 200 per 100,000 for women over the age of 21; that is one new case per 500 women per year. Although this figure may seem small in relation to the morbidity for all the other diseases striking the population of India, particularly among the poorer socio-economic classes, the impact of this disease on the young family can be devastating. This is particularly true because of the unfortunate tendency of these patients to present themselves to the physician rather late in the development of this disease. In fact, three quarters of the patients presenting at the clinic of the Christian Medical College Hospital in Vellore with invasive carcinoma of the cervix were staged in Groups III and IV. The situation in the rest of India is probably not too dissimilar. Cervical cancer is predominantly a disease of the lower socio-economic group and it is this group which everywhere has the least availability of medical services and, where they are available, is least likely to subject itself to preventive examination and most likely to delay the seeking of medical attention after symptoms develop. Thus, although we can and must continue to stress the importance of the preventive aspects of this almost wholly preventable disease and to promote campaigns for the early diagnosis of this almost wholly curable disease in its early stages, the practical problems of dealing with the large reservoir of clinically invasive cervical cancer cases remain.

First, let it be stated that the main cause of treatment failure in all stages is the inability to cure the disease locally, that is, intrapelvically. The number of cases dying of distant metastases with the pelvis clear of disease is extremely small. Epidermoid

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carcinoma of the cervix, as carcinomas go, is a relatively well behaved, reasonably orderly, progressing disease, that probably has an average history of several years from the malignant transformation of a single cell or a group of cells to the exodus of the host. Local invasion followed by regional lymphatic metastases precedes by a reasonable length of time the seeding of cells by hematogenous routes. It is thus a tremendous challenge for those modalities equipped to deal with regionally localized disease to improve their ability to sterilize intrapelvic cancer. These modalities include radiation therapy, surgery and regional chemotherapy.

A total hysterectomy with a generous vaginal cuff has a reasonably good chance of curing some patients with very early disease but is likely to fail where the tumour infiltrates submucosally down the vagina and laterally along the paracervical tissues and lymphatics.

It is for this reason that Wertheim promoted the radical hysterectomy operation. This is designed to remove these tissues along with lymph nodes along the major pelvic vessels. Even here the operation is not complete in that lymphatic vessels and nodes wrapped around the major vessels cannot be removed en bloc, but in fact are only partially dissected out. Therefore, even a Wertheim hysterectomy cannot be curative when lymphatic spread has occurred to inaccessible nodes within the pelvis.

These factors, along with the morbidity attached to this operation in even the best hands, have served to continue the use of radiation as the main therapeutic modality in most parts of the world. Why is radiation effective, where is it ineffective, and how can radiation therapy be improved? The following is a discussion of some basic points of radiation biology that have significance in the better understanding of the use of radiation therapy in the treatment of cervical cancer.

The Statistical Concept of Cell killing by Radiation.

Cells, normal and malignant, are killed primarily by means of chromosomal damage. A portion of a chromosome, being hit by a unit of radiation, usually sustains a break (Fig. 1).

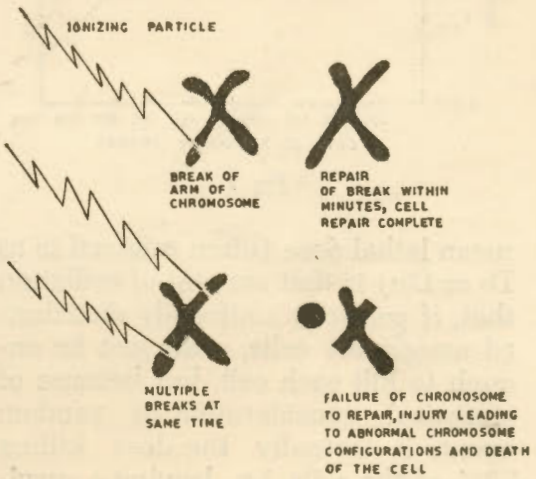

Fig. 1

Repair processes within the nucleus usually repair the break rapidly. However, if several such events occur rapidly within the same cell the repair mechanism may become saturated and permanent damage results which leads to the inability of the cell to divide further, although it may remain intact until it dies of "old age". We call this action on cell division "repro-

ductive" or "genetic" death as opposed to "metabolic" or "morphological" death when a cell is destroyed by, say, heat. The kinetics of reproductive death by radiation can be graphically plotted as shown in Fig. 2. The

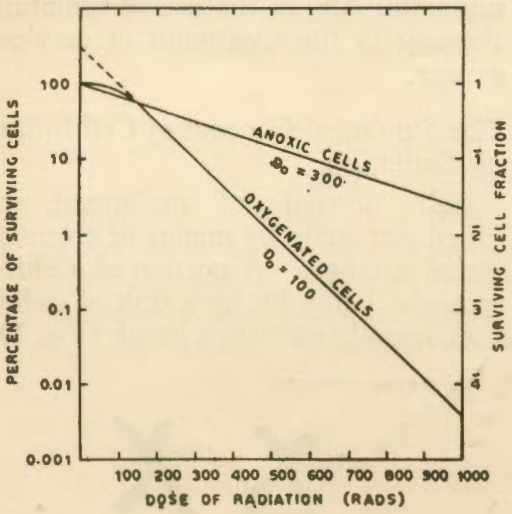

Fig. 2

mean lethal dose (often referred to as D_0 or D_{37}) is that amount of radiation that, if perfectly uniformly distributed among the cells, will just be enough to kill each cell, but because of statistical consideration of random events is actually the dose killing 73% of the cells, i.e., leaving a surviving percentage of 37%. This dose for most mammalian well oxygenated cells lies between 100 and 150 rads.* Thus, for a single dose of 500 rads, 99% of the cells are destroyed; for a single dose of 1000 rads 99.999% of the cells are destroyed. With this remarkable sensitivity, why does not radiation easily destroy all regionally limited cancers and for that matter destroy normal tissues completely at the usual doses given in radiation therapy?

Three important factors are responsible:

I. Cell Number

We assume that it takes just one cancer cell remaining in the body to regrow the cancer. From the previous cell survival curve the statistics of the percentage of surviving cancer cells after low doses of radiation are dramatic. Take the example of a tumour of just 1 cm in diameter. It probably contains one million (10^6) cancer cells. To destroy every cell with radiation requires a single dose of at least 1500 rads which gives a surviving fraction of 10^{-7}, in other words, this gives a 9 in 10 chance that every cell is destroyed and should give a cure rate of 90% for a series of tumours of this size. 1700 rads, with a surviving fraction of 10^{-8} gives a 99% cure rate probability. However, this is not found in practice because of the following factor:

II. Cellular Oxygenation

Fig. 3 shows a cross-section of a minute tumour measuring only 1 millimeter in diameter. In the center is a necrotic zone. At the rim of this necrotic zone are undoubtedly tumour cells that are on the verge of death because of anoxia through competition for available oxygen from the surrounding blood vessels. Now, it has been found that anoxic or severely hypoxic cells are more radio-resistant than well-oxygenated cells by a factor of about 2.5. That

*The rad is that unit of ionizing radiation that yields 100 mgs of energy when absorbed in 1 gram of the substance in question.

is to destroy 10 anoxic cells takes 3850 rads instead of 1500 rads for well-oxygenated cells, in other words, over twice as much radiation. Clinically we know that a 1 cm tumour can be destroyed in over 90% of the cases with a dose of about 2500 rads —this clinical finding confirms the laboratory data and indicates that tumours have a mixture of well-oxygenated and poorly-oxygenated, but nevertheless viable cells. Now, the factor which permits us to often selectively destroy these cells can be described under the following heading.

III. Cell Kinetics

As previously described, all mammalian cells, tumour or normal, have a similar radiosensitivity except for the influence of oxygen. Therefore, the surrounding normal tissues are equally sensitive or often even more sensitive to radiation than the tumour cells. However, these normal cells have an enormous capacity to respond to radiation injury by increased rates of cell division and cell migration from the periphery into the radiated zone. These dynamic processes result in rapid repopulation of the tumour site by fibroblasts, endothelium, and epithelium. This process is aided by delivering the radiation dose in small increments over a long period of time; it is probable that many tumour cells, particularly the anoxic radioresistant cells, are more slowly dividing and have, therefore, a smaller capacity to repair radiation injury as compared to the more rapidly dividing cells. This fractionated or protracted radiation enhances the ratio of destruction to normal tissue destruction and permits the outstanding functional and cosmetic results that can sometimes be obtained with radiation therapy (Fig. 4).

How does all this affect the problem of Cervical Cancer?

The present rationale is to use an internal radiation source, such as radium or radiocobalt, in the form of uterine and vaginal applicators to locally radiate the cancer. The anatomical situation of cervical cancer has made the use of internal radiation uniquely feasible. The two most important attributes are low dose rates and geometry. As previously described, it is the dose rate factor which permits a selective destruction of tumour cells. In addition, the rapid fall-off dose rate from the source of radiation on the basis of the inverse-square law allows the surrounding important vital structures such as the bladder and rectum to be relatively spared. In fact, in good hands the late morbidity from radiation for Stage I and II cervical carcinoma is no more than 5%.

However, in the case of a more extensive tumour or a very bulky stage I or stage II, a very strong rationale exists to deliver external radiation first. In fact, on several points it seems desirable to give external radiation to all patients immediately after the diagnosis of carcinoma of the cervix has been made. These are:

1. Immediate stopping of further tumour cell division. Every additional tumour cell requires more radiation to give an equally good

chance of cure. It has been calculated for some large tumours that every day of delay in treatment costs at least an additional 500 rads of radiation, an additional dose that often cannot be afforded from the standpoint of normal tissue tolerance.

2. Significant sterilization of cells that may be dislodged during pelvic examination and radium insertion.

3. Reduction of the bulk of the tumour so that radiation from radium with its rapid fall-off, is more effective. In fact, radium (or cobalt) should probably not be used primarily in the case of any tumour over 4 cm in maximum diameter. External radiation should be given first to reduce the bulk.

4. Sterilization of nests of tumour cells in regional lymphatics. The dose to destroy microscopic islands of cells is quite small.

From these considerations I advocate the following programme:

1. Immediate cobalt-60 therapy to the entire pelvis to a dose of at least 1000 rads in 1 week as soon as the biopsy report is made.

2. In the case of a very early carcinoma, stage 1a in young women, or in those with fibroids or pelvic inflammatory disease staged up to early II a, to carry out Wertheim hysterectomy. At this time, examination under anaesthesia and cystoscopy should also be performed in all cases.

3. In all others to continue for an additional 2000 rads. In stages I b & II a to insert radium within 1 week at a low dose rate for 1 or 2 sessions to maximum of 7000 milligram hours. In II b, III and IV to continue to 4000 rads and evaluate for tumour shrinkage—if adequate, to insert radium—if not, to wait 2 weeks and continue external radiation to a total dose of 6000 rads—then again evaluate for radium. In selected cases of III and IV with anterior extension into bladder, to perform anterior exenteration 3 weeks after completion of external radiation.

4. Postoperative radiation should be reserved for those cases where positive nodes have been demonstrated. In such cases radiation of the para-aortic nodes is indicated.

All the above procedures presuppose that the patient has been placed in the best possible nutritional and haematological condition, a problem which is not easy to achieve, particularly in India. But anaemia and local sepsis both probably enhance tumour anoxia, making the job of radiation even more difficult.

The best immediate future in the treatment is an improved mutual understanding of the role of radiation and surgery and the judicious combination of these modalities in the more advanced cases. A certain percentage of massive disease cases in Stage IV, although they may be regionally localized, are not curable no matter what the approach; chemotherapy may be the best palliation for such cases.

At the very least, we can reduce the unnecessary morbidity of the presently cureable stages of cervical cancer (Fig 5) from poor radiation therapy and injudicious surgery. The California data indicate that indiscriminate surgery has lowered the cure rate and has enhanced the mor-

bidity, particularly from ureterovesical injury.

Summary

1. Cervical cancer is a preventable disease; but in India it is and will continue for a long time to be a significant treatment problem.

2. Cervical cancer kills the patient largely by local and regional extension as compared to breast cancer, where distant metastases are the usual causes of death.

3. The role of local and regional radiation therapy should be based on logical principles of modern radiobiology.

4. The important principles discussed include:

A. The exponential slopes of cell killing by radiation.

B. The importance of cell number in tumours.

C. The radiosensitivity of anoxic and oxygenated tumour cells.

D. The cell kinetics of normal and malignant cell populations.

5. By utilizing these principles in a rational way the optimum selection of treatment modalities for different stages of cervical cancer can be made. Local radiation with radium or cobalt^{60} applicators, external radiation with megavoltage beams, and surgery should thus be usually employed in combination for particular treatment problems.

See Figs. on Art Paper II