

Changing Concepts of Cancer Biology, Diagnosis and Treatment

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Cancer is the number two killer in the United States and will probably account for some 400,000 deaths in 1982. The lung has now achieved the dubious distinction of being the most common site of cancer in men and causes the most deaths. Cancer of the colon and rectum is the second most common cancer in both males and females combined, whereas carcinoma of the breast and uterus predominate in women.

The incidence of most cancers has been rising rather slowly over the past several decades for reasons that are not clear, possibly because of increasing contamination of our environment by chemical carcinogens, air pollution, and prescription drugs. In males lung cancer has dwarfed the incidence of most of the other tumors; even in females there is an ominous recent sharp angling of the curve upward. Carcinoma of the stomach and carcinoma of the cervix have markedly declined during the past several years, but the reason for this is unclear. Perhaps the decline may be related to some dietary factor which has been eliminated due to better techniques for preserving or preparing meat.

It is useful to examine the anticipated five-year cancer survival rates for specific sites taken from the Surveillance Epidemiology End Results Group of the National Cancer Institute. Many localized cancers, particularly those of the bladder, breast, colon, larynx, prostate and uterus, show prolonged survival times. The notable exception is the lung with a five-year survival of only 23%, even if the tumor is localized at the time of surgery. The American Cancer

Society purports to indicate that this means tumors should be detected earlier. An alternative explanation is that those tumors which remain localized are biologically less malignant and grow more slowly, and therefore have a greater likelihood of being found at a time when they have not yet spread.

What is not emphasized is that for prostatic neoplasms and lung cancer, probably 80–85% of the tumors are disseminated when first discovered, so that the localized cancers are in the distinct minority. Once a tumor has been disseminated, the chances for prolonging survival are greatly diminished.

During the past five years there have been no substantially new modalities of therapy. In some areas our surgical techniques are already extremely refined while in other areas they continue to evolve, as in the currently expanding use of microsurgery in pituitary, pineal, ocular, and laryngeal tumors. There has been a proliferation of endoscopists, and it is now a rare endobronchial, colonic, or jejunal lesion that manages to escape direct visual inspection through the endoscope before it is removed.

Substantial advances have been made in diagnostic radiology, particularly in the areas of CT scanning and ultrasound. Radiotherapeutic techniques have gradually evolved as well. Treatment planning is better because of newer computer-simulated models. The high-voltage linear accelerator and the use of newer heavy particles, such as the neutron and photon beams, have also given a higher therapeutic index in specific problems.

The cumulative impact of these refine-

ments in surgery, radiology, and chemotherapy has been substantial. For example, in radiotherapy there has been great improvement in survival for those who have tumors that are both radiosensitive and tend to be localized. There is little question that we have markedly improved the therapeutic index in retinoblastoma, testicular carcinoma, Hodgkin disease, and have improved the situation in head and neck cancer, as well as prostate, bladder, ovary, and tonsil cancer.

More striking is that a number of cancers, particularly congenital trophoblastic tumors, Burkitt lymphoma, testicular neoplasms, Wilms tumor, and neuroblastoma are now being cured routinely by chemotherapy. Hodgkin disease has been heavily affected by appropriately used radiation therapy and chemotherapy, sometimes in combination. Survival of patients with Hodgkin disease in 1979 is probably greater than 50% for all tumors. Chemotherapy is also generally agreed to be useful for palliation of prostatic carcinoma and breast carcinoma as well as chronic lymphocytic leukemia, lymphosarcoma, and acute myeloblastic leukemia.

We have not changed survival times of patients with the more common solid tumors to any extent despite the progress we have made in controlling the fluid tumors of leukemia and lymphoma. Little progress has been made in prolonging survival of patients with solid organ tumors, particularly those of the lung, colon, and genitourinary tract which are the most common and which far outnumber leukemias and lymphomas. Nevertheless, a great deal of progress has been made during the past decade.

We have learned much about the biological behavior of human tumors, some from animal experimentation and some from carefully designed cooperative clinical trials. There are two important concepts which have had considerable impact: first, the concept of micrometastases and their relationship to tumor burden, particularly in breast cancer; and second, differences in biologic aggressiveness among histologically-similar types of cancer as exemplified by Hodgkin disease.

With respect to the concept of total tumor burden and micrometastases, it should first be stressed that all tumors, when discovered, are actually in a fairly late stage of their growth. If we assume that a tumor begins as a single cell and continues doubling and growing ex-

ponentially, it has already divided approximately 30 times to reach a size of about 10^8 or 10^9 cells and a weight of about one gram. A one-cm tumor nodule is probably at the limit of detection either by palpation or x-ray.

Treatment may accomplish any of several goals. An effective treatment may shrink the tumor drastically, perhaps by a factor of a thousand, but unless every cell is destroyed, it is almost certain that the tumor will recur. If the recurrent tumor tends to follow the same kinetics as the earlier tumor, its rate of growth will be the same. This is usually the case except in the case of metastatic tumors; such tumors usually grow faster. In general, the more substantial the response, the longer the survival.

In some instances effective treatment, such as hormonal therapy, may drive the tumor into a state of dormancy or quiescence, so that its rate of growth is changed, but at some later point when it resumes autonomous growth, it will again grow at a rate similar to the rate it exhibited initially or even faster.

Many chemotherapists have spoken of eradication of the last tumor cell. We now know that this is somewhat naive and may perhaps apply to one or two tumors in which most all the cells are actively growing and are susceptible to a chemotherapeutic agent. In the most common solid tumors such as those of the lung, breast, and colon, only a portion of the cells are in cycle and are susceptible to chemotherapy at any one time.

It is likely that many tumors continually shed cells into the circulation, and the cells that are shed must be counted in the total tumor burden. There was an experiment which was performed in mice in which an implanted mammary carcinoma was allowed to grow to the size of 700 mg. At that time surgery was performed, and all visible tumor was excised. Nevertheless, it was clear that there must have been micrometastases at sites distant from the resection because with large tumors essentially no mice remained tumor free one month after surgery.

There is a striking parallelism between this experiment and a similar study performed in humans where the tumor burden was simply measured by the number of positive lymph nodes found during surgery in patients with breast carcinoma. As the number of positive nodes increased, the ten-year survival of these patients fell drastically. A number of surgeons claim that

patients with higher numbers of positive lymph nodes do poorly because the nodes act as a secondary focus of disease and that more extensive operations should be performed.

If this thesis were correct, then there should be clearly demonstrable differences between patients that had different types of operations. The newer operation that is now being performed is a simple or total mastectomy in which just the breast is removed, but the contents of the axilla are not taken (they may be biopsied but are not removed), and the pectoralis muscle is also preserved. This is to be compared with a standard radical mastectomy in which the entire contents of the axilla are removed together with the pectoralis muscle, leaving only the intercostal muscles and the ribs after mastectomy.

After five years the National Surgical Adjuvant Breast Protocol Groups have shown no difference in survival among almost 1,000 patients who underwent different types of mastectomy. This would affirm that the reason for failure of breast carcinoma treatment is due to distant metastases which are not visible at the time of surgery. This concept has had an enormous impact on the area of breast cancer because it has led to trials of adjuvant chemotherapy which have, in fact, greatly improved survival where surgery could not.

In Hodgkin disease we have a similar situation but with one additional complicating factor. First, we do know that in Hodgkin disease the total body burden of the disease does bear a close relationship to prognosis. Early in the treatment of Hodgkin disease, many of the observers at Stanford and other institutions concluded that most Hodgkin disease spread by contiguity and that the disease essentially could be cured if radiotherapy could be applied to all the involved fields plus an additional margin of safety around the field. Thus, Stage I could be treated by radiotherapy to the axilla and the mediastinum.

An additional important prognostic factor in Hodgkin disease is the histologic type of the disease. Four current histologic classifications are recognized: lymphocytic predominance, nodular sclerosis, mixed cellularity, and lymphoid depletion. In this progression the last type has the most Reed-Sternberg cells, the least lymphocytes, and the worst prognosis, no matter what the stage. Each of these histologic pre-

sentations is closely associated with a specific stage of the disease; for example, lymphoid depletion is extremely rare in Stage I and is most found in Stage III or IV. On the other hand, lymphocytic predominance is usually found as Stage I or Stage II. Although there is some overlap between histologic patterns of the disease, in the main the histologic patterns tend to persist for long periods of time.

It is beginning to appear that Hodgkin disease may consist of at least four separate clinical entities, each of which pursues a different course and for which different management strategies are indicated. For Hodgkin sarcoma, which tends to disseminate rapidly and probably does not spread by contiguity, localized radiotherapy would be useless and systemic chemotherapy would be the more effective agent. Similarly, for lymphocytic predominance, chemotherapy would probably represent too much treatment. An important corollary has been that the presence of systemic symptoms indicates that the disease is aggressive and probably will also require systemic treatment. Thus, even if the disease is Stage II during intensive investigation but systemic symptoms are present, the recurrence rate after radiotherapy only is high so that chemotherapy should be considered even at that early stage.

There are other examples of tumors of different biologic aggressiveness. It is easy to recall the difference in aggressiveness, growth rate and prognosis in patients with estrogen-receptor positive and estrogen-receptor negative breast cancer. In malignant melanoma as well, it has become apparent that certain types of melanoma, particularly the lentigo maligna or the superficial spreading melanoma, are much less virulent than the nodular melanoma. This undoubtedly will be important at a later time in treatment, but as yet no effective treatment regimen has been designed for any of these stages.

Another important topic for which great interest has been generated during the past decade is that of the possibility of immunotherapy, that is to say, that of immunizing the patient against his own tumor. Unfortunately, this treatment will also have to await the future because there is no firm evidence that immunizing patients with their own tumor in any way has altered survival or produced regression of the disease on its own. When used in combination with chemotherapy, most controlled studies have not

indicated that there is any additional benefit of adding immunotherapy, although the work is not yet completed. One of the important dividends of immunotherapeutic research has been the notion that there are certain antigens on the surfaces of tumor cells which may be important in diagnosis and detection.

The carcinoembryonic antigen (CEA) is a specific antigen which is represented on the surface of colonic tumors and also on the surface of the fetal colon as well. The tumor sheds CEA into the serum, and this can be detected by radioimmunoassay. Whereas CEA levels have not been found to be particularly useful in the detection and screening of colonic carcinoma, they have been valuable for following the course of the patient after surgery. Typically, normal patients do not have CEA levels above five nanograms per ml; colon cancer patients may have much higher levels. If resection is

successful and complete, the levels fall rapidly after operation. In 30–40% of cases, the CEA rises several months before recurrence is clinically detectable.

In acute myeloblastic leukemia we have been carrying out similar experiments at this institution in conjunction with the University of Toronto, and we have been performing tests on bone marrow of leukemia patients in remission to determine whether we might predict relapse at an earlier time. Some of our data on 43 patients will soon be published in the *New England Journal of Medicine*.

This suggests that tests can be devised which will pick up impending relapse in patients with myeloblastic leukemia approximately four to five months before the tumor appears in the bone marrow. We hope to exploit this fact by applying reinduction chemotherapy at an earlier stage.