Definitive Radiation Therapy
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Definitive therapy, that is, treatment for cure, has been a major aspect of radiation therapy since the earliest days of its use in cancer management. Prior to the development of supervoltage irradiation, radiation therapy was limited to the treatment of tumors at relatively accessible sites. At these locations, adequate tumor doses could be delivered without excessive irradiation of intervening normal tissues. Some of the best results were, and still are, obtained in tumors at sites where it was possible to use interstitial therapy, with radium needles placed directly into and around a tumor, as in cancer of the oral cavity, or intracavitary therapy with radium sources placed close to the tumor in natural body cavities, as in carcinoma of the cervix or corpus uteri. Excellent results were obtained in this manner in early oral and early gynecologic cancers. However, more advanced lesions, even at these sites, called for volumes and doses that were beyond the capability of orthovoltage therapy, and only extremely radio-sensitive deep-seated tumors, such as seminomas, could be cured regularly.

A major breakthrough occurred in the early 1950's when cobalt-beam therapy and supervoltage (in excess of two million volts) X-ray therapy became generally available. These radiations made it possible to deliver high doses of therapy to any depth of the body without damaging interposed normal tissues excessively, to encompass relatively large target volumes including the tumor and, because of the decrease in scattered radiation, to shape the high-dose volume to conform with the tumor and its extension, thus avoiding unnecessary irradiation to normal tissues not involved by the tumor. The development of sophisticated dosimetry assured precision in delivering high doses of radiation to the predetermined target volume.

At the same time, a better understanding of the biologic nature of cancer, its patterns of spread and the response of normal tissues and tumors to irradiation have led to new concepts in radiation therapy. These concepts have further demonstrated the value of definitive radiation therapy.

As it became apparent that cancer at many sites could be cured consistently, the quality of survival in the cured cancer patient assumed a major importance. It was no longer enough to rid the patient of his tumor. It became important to consider his functional and cosmetic integrity as well, so that the cured patient could resume his useful place in his family and in society. Where cure rates were comparable, radiation ther-
apy became clearly preferable to mutilating ablative surgery.

It is now recognized that the response of epithelial cancers to radiation therapy is a function primarily of tumor volume. The smaller the number of tumor cells, the lower the dose needed to eradicating the tumor. Conversely, a large tumor mass requires a much higher dose for control. For cancers of epithelial origin this, and the ability of the tumor bed to withstand an appropriate dose of irradiation, is the primary consideration for curative therapy, rather than the tissue of origin (i.e., squamous or glandular epithelium). Recognition of these factors has led to important advances in curative radiation therapy.

Management of Regional Subclinical Disease

Most epithelial tumors spread initially to regional lymph nodes and subsequently to distant sites via the lymphatic system and blood stream. The majority of patients with apparently localized primary tumors, already harbor subclinical collections of tumor cells in the regional lymphatic drainage. Thus, regional therapy is essential if these patients are to be cured. Such subclinical disease consists of aggregates of tumor cells in lymph nodes so small that they cannot be palpated in accessible regions, like the neck nodes, or discovered by other studies, such as lymphangiography in the pelvis or retroperitoneal lymph node chains.

It is now well established that such subclinical regional disease can be successfully treated by relatively modest doses of radiation therapy, so that normal tissue in these regions remains essentially unharmed in appearance and function. The concept of aggressive irradiation to the known primary tumor and modest irradiation to the regional, clinically as yet impalpable lymph nodes has greatly improved local and regional control of cancer in the head and neck and the pelvis, particularly carcinoma of the cervix and corpus uteri and seminoma of the testis. Regional failure under these circumstances has become a rarity. The

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same principle is now applied to other epithelial cancers, such as breast and prostate, and has already begun to show its value. Similar considerations apply to Hodgkin's disease, which is much more radiosensitive than the majority of epithelial tumors, and where the principle of "total nodal irradiation," that is, elective irradiation of the total axial lymph node system, has led to over 90 percent cure rates in patients with early disease.

Combination Surgery and Radiation Therapy

Clinical experience, as well as radiobiologic experimental evidence, has shown that judicial combinations of surgery and radiation therapy can not only lead to higher cure rates, but also to better preservation of function and cosmesis. Until recently, such combination therapy had been used largely preoperatively for relatively advanced lesions, when even extensive extirpative surgery frequently failed because of the high incidence of postoperative local and regional recurrences. The surgical dictum had been to perform the same extensive surgery after preoperative radiation therapy as would have been planned in its absence.

Once it is recognized that radiation therapy is effective in curing peripheral areas of the primary tumor and subclinically involved regional lymph nodes, much more conservative surgery remov-
ing the gross central portion of the primary tumor, can be used following preoperative irradiation. Here, even full doses of irradiation may fail because of the large number of tumor cells and the relatively large hypoxic proportion of tumor cells, which are more resistant to X-rays or similar conventional irradiation. We already have evidence that such combinations will improve local and regional control rates, and are now accumulating data on improved function and cosmesis.

Much less common, in the past, has been the use of postoperative irradiation for cure. Yet, theoretically, it has many advantages. It allows surgery in an unirradiated field, thus decreasing the risk of postoperative complications; it treats the residual disease where the surgical margin has cut through tumor; it can decrease recurrences in the surgically treated field by destroying any residual subclinical foci of tumor cells. Postoperative irradiation can also be given in higher doses than preoperative radiation therapy and can be specifically directed to any known or suspected areas of residual disease. Admittedly, wound healing has to be complete before initiation of postoperative radiation therapy, which may, therefore, have to be delayed. The Radiation Therapy Oncology Group is presently undertaking a controlled clinical trial comparing pre- and postoperative irradiation in advanced head and neck cancer. A similar trial is planned in the treatment of relatively advanced cancer of the bladder with combined cystectomy and radiation therapy either before or after surgery.

Various forms of combination surgery and irradiation have been eminently successful in the treatment of cancer of the colon and rectosigmoid and in soft tissue sarcomas. Cancer of the breast is an excellent example of the value of multimodality therapy. Traditionally, a combination of radical mastectomy, followed by regional irradiation in all but the earliest cancers, has been used. While it must be admitted that, in the past, many patients with breast cancer died of distant metastases, even when local and regional control had been obtained, there is overwhelming evidence that local recurrences in the chest wall and/or the axillary, supraclavicular and internal mammary lymph nodes can be prevented in the great majority of patients with breast cancer by postoperative radiation therapy. The recently reported success of chemotherapy, particularly the combination of several drugs, in preventing or at least postponing the appearance of distant metastases, makes the combination of surgery, postoperative radiation therapy and subsequent drug therapy most promising. Since there is also strong evidence that excellent local and regional control can be obtained in early breast cancer by irradiation of the breast and regional nodes after a lumpectomy (removal of the gross tumor in the breast only), it will now be possible to save many patients from the mutilation of a mastectomy and to offer them a higher rate of long-term survival by combination therapy.

Primary malignant intracranial neoplasms present a major challenge to the radiation oncologist. Almost all patients with intracranial tumors require surgery to confirm the diagnosis and provide decompression. Postoperative radiation therapy is almost always indicated. It should be remembered that brain tumors are the second most common form of cancer in childhood (exceeded only by...
the leukemias), and almost all forms of intracranial tumors in children respond well to aggressive radiation therapy. Even in the most highly malignant medulloblastomas, five-year survival rates of 50 percent are now well documented. For adults with malignant gliomas, which continue to defy any attempt at cure, the results of the National Brain Tumor Study Group clearly indicate that radiation therapy is the single most important factor in increasing survival. In patients with moderately malignant tumors, such as astrocytoma, Grade III, high-dose radiation therapy leads to 20 percent five-year survivals.

Future Prospects
In the future, definitive radiation therapy is likely to assume an even more important role in the cure of cancer, as systemic management by chemotherapy and ultimately immunotherapy become more effective. Both of these modalities are likely to be curative only when the total number of viable tumor cells throughout the body is quite small. Thus, it becomes of prime importance to rid the patient of his major tumor burden at the site of his primary and regional lymph node disease. Radiation therapy, with or without conservative surgery, can achieve this goal without loss of function and without deformity.

There remains then the group of patients with locally advanced cancer. Here the decision to treat for cure or for palliation may be extremely difficult and will depend on the physician's experience and clinical judgment. When used wisely, aggressive radiation therapy may still be of great value in some of these patients. Not only is an occasional cure obtained in a seemingly hopeless patient, but more often distressing local symptoms are relieved for a sufficiently long interval, allowing the patient some time to pursue a useful life and then to succumb to a more merciful death.

Conclusions
Definitive irradiation is a major factor in
curative cancer therapy; a decisive increase in the survival of cancer patients has resulted over the last 15 years. (Table.)

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In patients with early cancer of the oral cavity, oropharynx, larynx, cancer of the cervix uteri, seminoma of the testis and in many patients with cancer of the prostate, radiation therapy is the treatment of choice, since the cure rates are equal or superior to those obtained by ablative surgery (70-90 percent five-year survival). These patients also enjoy a better quality of life by retaining functional and cosmetic integrity.

Dramatic improvement in long-term survival has been obtained in Hodgkin's disease. At other sites, or in the above-mentioned sites with more advanced disease, the combination of radiation therapy and conservative surgery when possible, for cancer of the breast, soft tissue sarcoma, carcinoma of the corpus uteri, has shown excellent local and regional control (50-70 percent).

Much must still be done to establish the optimal combination of surgery and radiation therapy. When this occurs, it is likely that major improvements will result in the local and regional control of cancer. This, in turn, will create a stimulus for the control of disseminated subclinical disease by appropriate chemotherapeutic agents. Optimal multimodality therapy may well produce major increases in cancer survival within the next decade.