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SURGICAL ONCOLOGY IN THE 1990s

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The field of surgical oncology has matured enormously over the past decade. It is now a frequent focus of postgraduate study for general surgeons in both clinical and research fellowships. Many new clinical research projects and controlled trials have been reported which have altered clinical care in surgical oncology in a number of different areas.

Conservative Surgery

Major clinical advances in the past 10 years have largely concerned the conservation of tissue or function with equivalent or even better survival through multidisciplinary management. For example, limb preservation in soft part sarcoma with the use of adjuvant radiotherapy, and preservation of continence and normal bowel function in anal carcinoma with the use of chemotherapy, radiation therapy, and relatively minor surgery, point the way toward future cancer management. Of course, the preservation of the breast with limited surgery and adjuvant radiotherapy is another classic example. Another area where multidisciplinary management and conservation of function with limited surgery is being studied includes small rectal carcinomas treated with local excision and radiation therapy. Moreover, conservative excision margins in melanoma produce survival rates that are identical to those achieved by more traditional, radical local resection margins. A current, multi-institutional trial is addressing this issue, as well as that of prophylactic node dissection.

However, the debate between ultraradical and conservative surgery continues, as evidenced by current articles from Japan concerning wide lymphatic resections for gastric adenocarcinoma. Data from these series resemble data for colon cancer, breast cancer, and melanoma in the 1950s and 1960s in this country, in that survival rates from routine, ultraradical surgery pro-

duce higher mortality and morbidity rates without improving survival. Recent analyses of data from the Japanese gastric cancer experience confirm the same results with an ultraradical approach to gastric cancer. "Improved" results by ultraradical surgery are achieved only when compared to previous decades when disease presentation was much more advanced. However, not only does the data fail to demonstrate improvement stage for stage, but morbidity and mortality rates are higher.

Prognostic Markers

Surgical oncology will increasingly depend on prognostic markers in the selection of appropriate operations. The discovery of oncogenes that relate to recurrence rates, the usefulness of DNA flow cytometry data in predicting outcome, and cathepsin D analysis and oncogene overexpression, are all areas being intensively studied in breast cancer. Unfortunately, these prognostic markers relate only by statistical probability to outcome. Markers that predict outcome for an individual have yet to be discovered. However, new genetic information in cases of familial breast cancer may yet help identify members of high-risk families who are destined to develop carcinoma. Similar data on genetic markers in colon cancer and familial polyposis cases may also help predict which patients should have preventive surgery and which will be free of risk from these genetically linked cancers.

Adjuvant Therapy

Adjuvant treatment with chemotherapy and/or radiation therapy has become more widely applied in breast and colon cancer. Recent information suggests that Tamoxifen in postmenopausal breast cancer patients, particularly patients who are estrogen receptor positive, and multidrug chemotherapy in premenopausal patients,

may improve outcome. Recurrent disease rates may decrease by 33 percent in premenopausal patients who receive chemotherapy and by 20 percent in postmenopausal patients who are treated with Tamoxifen. Whether this improved outlook will translate into improved survival, rather than just disease-free survival, has yet to be confirmed. Nevertheless, many patients with node negative breast cancers who have a significant risk of morbidity due to the large size of the tumor or poor histologic features are now being treated. Hopefully, such patients are being treated within the context of a clinical trial, because present results are not clear cut. In fact, critics of the wide application of adjuvant therapy indicate that expensive, toxic, and complex adjuvant therapy holds little room for improvement and will not significantly benefit patients who are at very low risk of dying of breast cancer.

Several clinical trials report an increase in disease-free survival when a combination of fluorouracil and levamisole is administered as adjuvant therapy in colon carcinoma. Significant reductions in mortality in patients with Dukes' B and C colon cancers have been reported. A recent consensus conference at the NCI addressed the issue of adjuvant therapy in colon and rectal carcinoma and concluded that these are reasonable drug treatments that can be more widely applied. Further adjuvant trials to confirm and solidify these assumptions are required.

Trials by the Gastrointestinal Tumor Study Group (GITSG) indicate a decreased local recurrence rate, as well as improved survival, in rectal carcinomas treated with a combination of chemotherapy and radiation therapy. The original GITSG study included the combination of fluorouracil and methyl CCNU, but the latter drug has been eliminated because of its long-term toxicity. The radiation dose used with fluorouracil is modest (about 4500cGy) and again indi-

cates the likelihood that fluorouracil acts as a radiation sensitizer when used in combination with radiotherapy.

Recent reports from Germany outlining the use of Adriamycin, Platinum, and Etoposide (APE) as adjuvant therapy for advanced gastric cancer and neoadjuvant therapy for unresectable gastric cancer are suggestive of dramatic response rates and the ability to resect previously inoperable lesions. The results of several trials utilizing this chemotherapy combination are awaited with interest, because of the particularly poor response from surgery alone.

Neoadjuvant multidrug chemotherapy in head and neck squamous cell carcinoma has been used for many years, but recent data indicate that while high rates of complete and partial response can be achieved prior to radiation or surgery, overall survival results may not improve. Thus, neoadjuvant chemotherapy agents may be more valuable as selection devices for defining cases that are likely to do well (complete responders), because the therapeutic results with patients who do not respond completely are extremely poor. These studies indicate that merely responding to multidrug chemotherapy does not necessarily translate into improved survival, reinforcing the need for control groups in randomized trials and caution in interpreting early results.

New Therapies

Newer therapies which may have a future role in detecting obscure recurrences for resection and/or the treatment of small lesions include radioactive iodine labeled antibodies to carcino-embryonic antigen. However, the basic biology of colon cancer indicates that few patients will be salvaged despite earlier detection of metastatic disease. Careful analysis of data from hepatic resections for colorectal carcinoma metastases indicate that these successes are the result of biological phenomena, not temporal phenomena. Therefore, earlier detection will not necessarily translate into improved survival. Thus, large metastases are as successfully resected as small metastases, and large resections are no more successful than small resections, in the treatment of hepatic metastases, as long as an adequate surgical margin is achieved. Despite early detection and early resection, only rarely will patients with colorectal carcinoma metastatic to sites other than the lung and the liver have long-term, disease-free survival.

Cryotherapy of hepatic lesions as a method of destroying a metastasis seems to be as successful as hepatic resection, and may be utilized in select cases. However, the fact that patients survive only when a few metastatic nodules are present indicates the basic biological control of survival after treatment for hepatic metastases. Therefore, cryotherapy would not dramatically improve results even if multiple lesions could be frozen, but it may enable more conservative treatment of appropriate biological situations, particularly when there are bilobar metastases. Between 10 and 20 percent of patients undergoing hepatic resection for metastatic colon carcinoma are candidates for resection if only a few, small lesions reappear. A number of reports indicate substantial long-term survival in such cases (30 to 40 percent).

Chemoembolization of diffuse liver cancer, particularly metastases from endocrine cancers or primary hepatocellular carcinomas, has been reported with substantial disease control, but longer-term analyses need to be performed to establish its overall role in the handling of primary or metastatic cancer of the liver.

Transplantation for hepatic cancer has been established as a successful treatment. Patients undergoing transplantation for cirrhosis who are discovered incidentally to have small hepatocellular carcinomas do extremely well. However, patients who have clinically manifest hepatocellular carcinomas do rather poorly. Thus, the principle of transplantation as treatment for primary liver cancer is established, but the exact parameters of when it is applicable have yet to be determined. It would seem that lesions resected early enough so that micro-metastases have not occurred might be transplanted, but occult, extrahepatic metastases probably are more rapidly lethal if there is immunosuppression.

The Impact of Screening

The increasingly widespread use of mammography has led to early detection of many carcinomas, both invasive and non-invasive, and has substantially improved the stage presentation of breast cancer. Whether earlier detection will translate into overall improvement in survival rates in breast cancer has yet to be completely established, but early reports of mammographic trials suggest that this is true. It has

been demonstrated that many duct carcinoma in-situ (DCIS) cases can be handled by local excision if they are detected by mammography, small in size, marked by calcification, and carefully and meticulously managed. The recurrence rate when a DCIS of less than 2.5 cm. in diameter is resected without radiation therapy may be as low as 10 percent, and probably does not exceed 20 percent. Half of such recurrences will be DCIS and half will be tiny invasive carcinomas, but survival after retreatment is 100 percent in early reports.

Studies to date indicate that patients who benefit the most from mammographic screening are between the ages of 50 and 65. The cost effectiveness of widespread screening of women in their 40s or over the age of 65 (because of competing risks from other illness) is less clear. Thus, the exact parameters of frequency, age, and technique (one view vs. two views) in mammography screening have not been resolved, but will be analyzed in extensive trials over the next few years.

Stool guaiac screening for rectal and colon carcinoma continues to be investigated, but clear results are not yet apparent. The cost effectiveness of such screening remains in doubt, because of the high false positive rates and the significant costs of diagnostic workup in such patients. However, the cancers that are discovered in such screening programs are of much earlier stage with far better expectations of cure.

Public and professional education campaigns for the recognition of melanoma and its precursor lesions have already yielded marked increases in very early clinical presentation and survival. Thus, the effect of dramatic increases in melanoma incidence throughout the world are somewhat ameliorated by the striking improvement in overall survival. Deaths from melanoma have increased only 50 percent in three decades, despite the quadrupling in number of cases in the United States.

Summary

The field of clinical surgical oncology is expanding in a variety of areas. It is expected that major in-roads will be made in the two most common solid tumors, colon and breast cancer, over the years ahead. Until more effective progress in smoking and tobacco use cessation occurs, however, the most lethal human cancer will continue its inexorable rise in deaths and disabilities. ■