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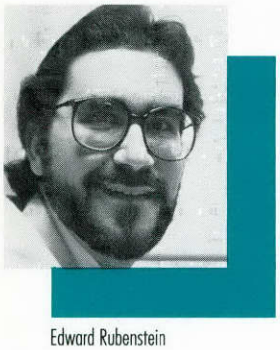
For Cancer Patients, Home May Be Their Hospital

Physicians at M. D. Anderson Cancer Center like John Kavanagh, M.D., are referring patients to home health care agencies for many treatments that used to be administered on an inpatient basis. "Life—particularly for cancer patients—is very valuable, so hospital days are wasted days. If you can reduce their stay, that's a service to them," said Kavanagh, chief of the Section of Gynecologic Medical Oncology.

Kavanagh said he became interested in home health care when he noticed that many of the patients he saw on rounds did not require intensive nursing care. Knowing that patient education had become so specialized that nurses could evaluate patients and provide them with safe home-care standards, Kavanagh began to realize that "some patients were wasting their time in the hospital."

Currently, providing hospice care and administering chemotherapy, pain control therapy, parenteral nutrition, and intravenous antibiotic therapy to patients at home is a $3 billion/year industry that may reach $10 billion/year by the year 2010, according to Edward Rubenstein, M.D.



Edward Rubenstein

Rubenstein, chief of General Internal Medicine for the Department of Medical Specialties, is director of the Ambulatory Treatment Center, where outpatient chemotherapy is administered and patients with medical emergencies are treated. He, like Kavanagh, believes that more patients can be referred to home health care agencies. "Patients recuperate best when they're at home, not in the hospital, Rubenstein said. For some, home care means a combination of home and hospital therapy. For example, one patient admitted for a liver chemoembolization required hospitalization. "But after she was discharged," Rubenstein said, "some of her blood cultures came back positive. She was called into the outpatient area; because she looked well, she was treated at home with intravenous antibiotics administered via infusion pumps. She subsequently was readmitted to the hospital for drainage of a liver abscess and then was discharged for more home care," Rubenstein summarized.

Patients recuperate best when they're at home.

"What happens now is that some patients are routed directly to home care without being admitted. Other patients are discharged from the hospital early to finish up treatment at home or referred for nutritional support at home. Patients on 14 days of antibiotics may be admitted for the first 7 days to make sure they're stable and finish up the last half of their therapy at home. Chemotherapy also can easily be given at home."

Deciding where patients are treated "depends upon what the patients' resources are, how comfortable they are, and what kind of support systems they have in the home environment," Rubenstein said. In fact, selecting patients who will do well in home care is critical to making home

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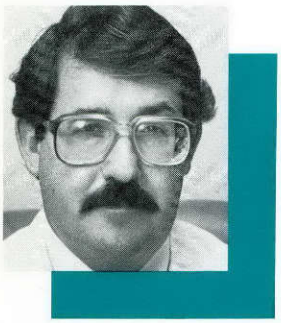
care work. "The key to choosing patients is what happens in the clinic, in the outpatient arena," Rubenstein said. "If you make the wrong decision in the outpatient area, the patient who should be admitted is discharged only to return, and the patient who is admitted to the hospital but doesn't need to be does not get the benefits of the home care system. People in health care must understand that the model for home care really begins in the outpatient area, in selective utilization of diagnostic evaluations and patient assessment."


John Kavanagh

Home Care Reduces Patient Anxiety

Home care is usually less expensive, but more important it also has the potential to reduce patient anxiety. "Patients who have cancer have a very delicate emotional homeostasis," Kavanagh said. "They are upset very easily; they are constantly coping with the disease while trying to maintain some degree of contentment and satisfaction in their lives. Many patients do not want to be treated in an outpatient area or be admitted to the hospital. While M. D. Anderson segregates patients according to disease and general strength, outpatient areas still provoke anxiety in most patients. Typically, there are both very ill and relatively well patients in these areas, with a wide range of pain and discomfort."

Also, some patients do not feel they can afford the time away from work that even outpatient visits require. "Many patients would like to protect their employment status and are, in a sense, healthy enough to have active lives. They would like a minimum of infringement on their normal lives," Kavanagh said.

Cost Containment the Impetus for Home Care

Kavanagh and Rubenstein agree that the national push for cost containment, largely driven by Medicare and private insurance companies, has doubtless powered the movement toward home care. In 1986, Kavanagh and co-investigators found, for example, that a cisplatin regimen administered at home for women with gynecologic cancers was just as effective as and somewhat less expensive than cisplatin therapy in the hospital.

Other studies have shown a 50 to 70% cost savings for home parenteral nutrition, cost savings and comparable efficiency for home antibiotic infusion, and hospice care quality comparable to that of hospital care. Medicare will cover more home care services beginning in 1990 under its new catastrophic coverage rules.

An accompanying technology boom has given home care agencies the ability to compete on more than a price basis. Particularly in the past five years, advances in pump, data facsimile, and paging technology, along with a larger array of antibiotics and devices such as portable x-ray machines, have "made it seem very reasonable that much of what you do in the hospital could be done at home—with the same or greater efficiency," according to Kavanagh. Candidates for home chemotherapy must be ambulatory and free of disease symptoms, such as nausea, that would intensify therapy side effects, Kavanagh said. Usually, patients also need someone (generally a relative or friend) to assist in their care. "In most home care situations, except for the extremely ambulatory patients, somebody has to assist in the care, which involves a multitude of tasks."

Patients Referred to Approved Agencies

Patients or their insurance companies contract with home care agencies, and M. D. Anderson physicians and discharge-planning nurses work from a list of approved agencies in referring patients to home care. "The physician should have a major role in the choice because he or she is ultimately responsible for the care of that patient. Furthermore, the physician has to have a regular, reliable line of communication with agency personnel. Because the home environment is not problem free, medical and nursing decisions have to be made on a continuous basis," Kavanagh said.

Some inpatient treatments can be done at home "with the same or greater efficiency."

Money is not necessarily an obstacle to home care, as a number of agencies take a proportion of indigent patients. Rubenstein added that the 1990 expansion of Medicare/Medicaid home care coverage will allow many more indigent patients to receive therapy at home.

How often physicians at M. D. Anderson see their home care patients in the clinic depends on the therapy the patients are receiving and how ill they are. For instance, a

patient on a routine antibiotic who is discharged feeling well may be seen every two or three days. These patients learn to hang the antibiotic bags on their IV poles and to heparin flush their lines, or they may be on an ambulatory pump that delivers the antibiotics on a preprogrammed schedule. Sicker patients or those in pain may be seen daily at first, whereas others may be seen once a week or once a month. If possible, patients are discharged to their community physicians.

More Home Care Research Is Necessary

Kavanagh encourages his colleagues not only to refer more patients to home nursing care but also to conduct home care research. His 1986 home chemotherapy study was unique because it used cisplatin. "At the time, people said it couldn't be used safely at home, so we were very cautious about it. It turned out we needn't have." Other innovative home chemotherapy studies are under way, and more studies using available pump technology to deliver medications for resistant pain are needed, he said. "My patient population (women with cervical or recurrent pelvic cancers, for the most part) has very difficult pain problems. Since some are unable to take medications orally, pump technology is very exciting." M. D. Anderson's outpatients currently use the Baxter Travenol Infusor balloon pump, the portable large-volume Pancreatec pump, the Baxter Auto-Syringe, and the Medfusion Infumed-300 pump for home therapy. About 400 patients a month now receive home chemotherapy.

Liability May Impede Advances

Although innovation and caution necessarily go hand-in-hand, Kavanagh worries that potential liability issues could unduly impede technologic advancement. For instance, questions about potential liability have been raised about home blood transfusions, although no problems have occurred yet. Kavanagh wants to see a reasonable partnership between law and medicine in new areas of medicine and health care delivery, with the emphasis on developing innovative home care techniques.

Some therapies are not given in patients' homes because the therapies are too new. Experimental chemotherapy for example, is only given in the hospital because "the drugs we're using are more unusual and the side effects are more difficult to discern and deal with, particularly for the biologic compounds," Kavanagh said. Rubenstein added that a definitive diagnosis is essential before home care is considered. Surgery candidates and patients who have chest pain, are severely short of breath, require intensive inpatient monitoring, or are otherwise unstable are not home care candidates, Rubenstein said.

Terminally ill patients, even those with intractable pain, might still be eligible for home care. For these patients, "the hospice contribution is immense; it is the exception rather than the rule that we have to keep people in the hospital for the final phases of their illnesses," Kavanagh said. "I always give them a choice. If they are comfortable and the communication with the family is good, patients, almost without exception, will want to be at home." Unless they have a medically uncontrollable problem, they can go home. "And as time goes on, we're able to treat more of the previously uncontrollable problems at home, including pain, vomiting, agitated states, and seizure disorders."

The model for home care really begins in the outpatient area.

Intermediate-care Units Should Be Developed

For those who cannot be placed under hospice care because they do not have someone to assist in their care, Kavanagh would like to see intermediate-care units developed. "There are people who have no spouse, no family. Their friendships are limited, their religious ties are weak. And so they have no one. One thing that has not really been developed is the concept of intermediate-care units for predominantly self-reliant patients who nevertheless require very limited nursing care. Inpatient hospice units are generally places of intense supportive care," he said.

Kavanagh cautioned against too heavy a reliance on traditional methods of treatment. "We shouldn't automatically dismiss the idea that something can be done at home just because it never has been. It should be subjected to clinical research. As any technology develops in medicine, we should consider whether it has any home-care applications. We should view home care from the perspective of how we can make life more efficient and easier for the patient." ■

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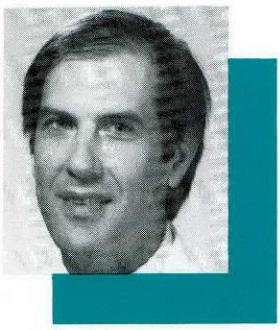
Newer Methods of Delivery To Enhance GI Cancer Treatment



Tyvin Rich

When the medical breakthrough does not happen, the only alternative is painstaking research—progress in steps, not leaps. It is a reality that Tyvin Rich, M.D., Department of Clinical Radiotherapy, well understands. Rich and his colleagues at the M. D. Anderson Cancer Center have been studying new ways of administering conventional chemoradiation treatments for advanced local gastrointestinal (GI) cancer. These treatments consist of various combinations of low-dose continuous-infusion 5-fluorouracil (5-FU) and cisplatin, external and intraoperative radiotherapy, and surgery. In terms of patient survival rates, Rich acknowledged that "we have yet to hit the home run, but in any research home runs are few and far between."

Nevertheless, progress is being made. Because of reports suggesting that these combined-modality approaches improve tumor response and have acceptable levels of toxicity, Rich believes that research "has come a step forward in the treatment of advanced GI diseases."

Continuous Infusion of 5-FU Allows Higher Cumulative Doses

For the past five years, the M. D. Anderson Cancer Center has been studying low-dose continuous-infusion 5-FU combined with conventionally fractionated external radiotherapy. The improvement in tumor response, local control, and survival rates as yet can only be compared with those for historic controls; consequently, Rich said that "we will need to verify these results with appropriate randomized studies." What is certain, he added, is that the side effects associated with a 5-FU dose given in bolus schedules (15 mg/kg/day for three days) are different, more easily managed, and sometimes less severe (hematopoietic) when the drug is given continuously (300 mg/m^2/day for 30 to 40 days). All patients can be treated as outpatients, he added, since safe, practical, low-cost infusion pumps are now available.

"Our goal is for the patient to maintain a normal dietary intake and GI bowel habit and to still be active. But the toxicities of the fractionated radiotherapy and low-dose chemotherapy are cumulative, so usually by the fourth or fifth week, a maximum tolerated dose is achieved. If we can't control the complications with medications, we will stop the chemotherapy first, and frequently the toxic effects reverse enough so that the patient can maintain his or her course of radiotherapy," Rich said.

Traditionally, 5-FU has been the chemotherapeutic agent of choice for advanced adenocarcinoma of the GI tract, achieving objective response rates of 8 to 20% when administered in bolus-dose schedules. One obstacle to improving these rates was the maximum tolerated dose. Bolus-dose 5-FU must be limited to 15 mg/day administered for no more than three days. Higher bolus doses result in unacceptable degrees of leukopenia and stomatitis and sometimes death. With the advent of new portable infusion pump technology, continuous infusion of 5-FU began to be explored. Since 1981, various reports have indicated that the cumulative dose of continuous-infusion 5-FU can be three to four times higher than 5-FU administered in bolus-dose schedules.

Phase-specific agents are "almost exclusively effective" in dividing cells.

The rationale for continuously infusing low doses of 5-FU rests not only in the lower toxicity. Continuous infusion also increases the drug's ability to induce tumor responses. In vitro studies show "that tumor cell kill increases as time of exposure to this chemotherapeutic agent increases. Furthermore, if one looks at tumor cell kill when 5-FU is combined with radiotherapy, one can, again, further maximize tumor cell kill by giving the drug over time periods that are at least equal to the cell cycle (10 to 30 hours)," Rich said.

Cancer Cells Are Vulnerable Only in Certain Phases of Cycle

Most antimetabolites like 5-FU are phase-specific agents that "almost exclusively kill" cells that are dividing, Rich

said. "These drugs have a very short half-life. This, combined with the fact that in any given tumor only a very small proportion of the cells may be in a susceptible phase of the cell cycle, means that short bolus doses may be less effective. Bathing the tumor in a low-dose continuous-infusion drug will ensure that, when the cell goes into cycle, the drug will be there to affect it."

Rich said that this effect may be enhanced when radiation is administered with chemotherapy, since the radiation, in addition to killing cells, may also induce dormant cells to proliferate, thus making them more vulnerable to 5-FU. "Notice that I said 'enhance,' not 'radiosensitize.' We're not certain exactly how this interaction is occurring, so to use 'radiosensitize' would presume the drug exclusively affects the tumor's response to radiation. From a mechanistic point of view, the radiation may just as well be altering the cell's metabolism, making the cell more susceptible to the drug," he said.

Other chemoradiation research includes a multi-institution study directed by the Radiotherapy Treatment Group, headquartered in Philadelphia. "This study focuses on patients with rectal cancer who need adjuvant treatment. We're trying to determine whether bolus-dose 5-FU or continuous-dose 5-FU combined with pelvic radiotherapy reduces the risk of pelvic disease recurrence. Two hundred patients are entered in the study, and we hope to have a total of 400 early in 1990."

Rich and his colleagues also plan to extend their 5-FU and external-beam radiation studies by adding cisplatin to the protocol. "We've completed a phase I study in patients with advanced primary or recurrent rectal cancer, our objective being to determine the maximum tolerated dose of low-dose continuous-infusion cisplatin with preoperative radiotherapy. We're particularly interested in cisplatin because it interacts, we believe, differently with radiotherapy than do the antimetabolites, and it also may have an enhanced effect when combined with 5-FU."

Intraoperative Radiotherapy Minimizes Normal Tissue Complications

One objective of the continuous-infusion studies has been to mitigate the toxic effects of chemotherapy. On another front, Rich and his colleagues are examining how radiotherapy administered during surgery can reduce toxicity. "When using external-beam radiotherapy, there comes a point at which the risk of severe toxic effects to normal tissue is too great," Rich said. "Rather than ask the patient to undergo that risk, we sometimes use intraoperative radiotherapy. We can consequently improve the therapeutic ratio by literally removing normal tissue from the beam's path and precisely focusing the radiation on the tumor itself during surgery."

Rich again stressed that intraoperative radiotherapy is but one facet of the combined-modality approach that includes resection of the tumor (when possible), as well as chemotherapy and conventional radiotherapy. "Since we appear to be achieving a greater amount of tumor shrinkage with the combination of chemotherapy and radiotherapy, it was logical to bring the surgeon into the equation to maximize the chance for local cure."

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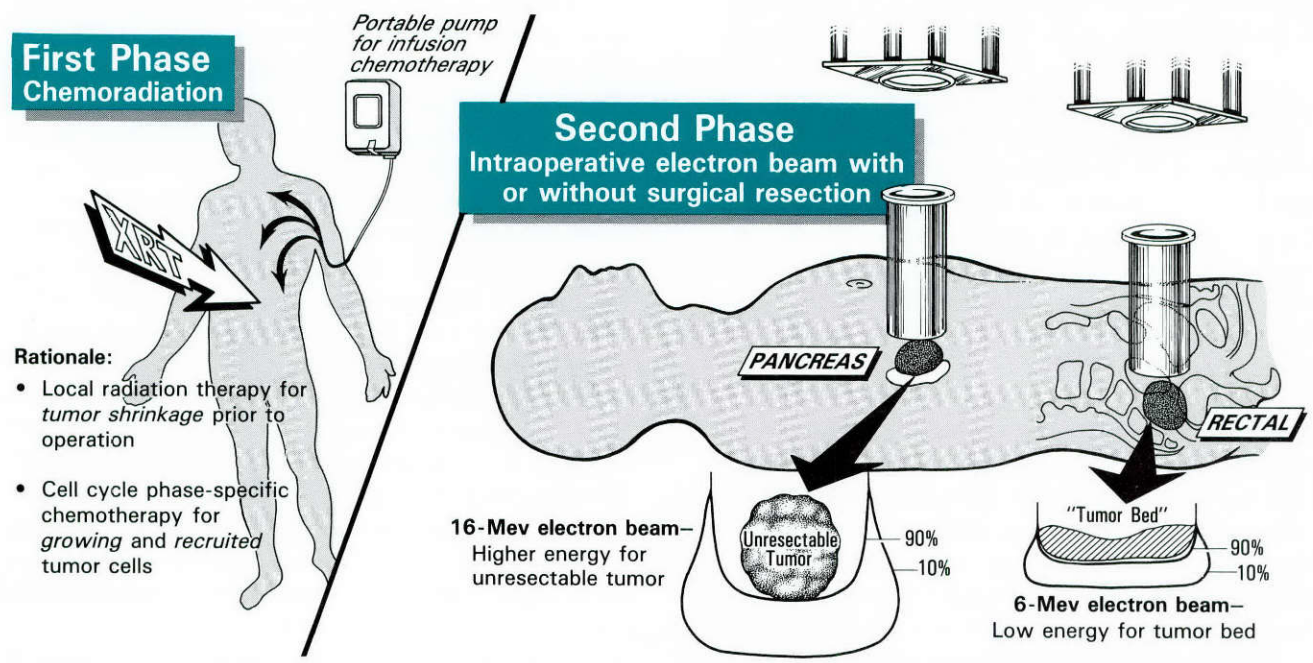

Schematic representation of combined-modality therapy for gastrointestinal cancer. Treatment consists of two phases. First phase, external radiotherapy (XRT) plus chemotherapy. Second phase, intraoperative XRT. Figure shows treatment of patient with either pancreatic (unresectable) or rectal (resectable) tumor. "90%" and "10%" indicate isodose lines.

Neoadjuvant continued from page 8

reduced to between 20 and 30%. However, the major problem with patients with stage III breast cancer is distant metastases, which inevitably cause organ dysfunction and death.

By the early 1970s, it became clear that chemotherapy had to play a role in treatment if metastases were to be controlled, and consequently several centers initiated combined-modality programs. Investigators at the National Cancer Institute of Italy in Milan gave four cycles of combined neoadjuvant chemotherapy consisting of doxorubicin and vincristine to patients with locally advanced breast cancer. ("Neoadjuvant chemotherapy" is the name given to chemotherapy administered before primary therapy, be it surgery or radiotherapy.) All patients received radiation therapy, which was the only local treatment, and were then randomly assigned to a control group or a group that received adjuvant chemotherapy. Eighty-three percent of 110 patients in the control group were rendered disease free, with a three-year survival rate of 50%, and the patients who received adjuvant chemotherapy had an even better survival rate.

Micrometastases can be abrogated by neoadjuvant chemotherapy.

In a subsequent study, the same investigators demonstrated that, after neoadjuvant chemotherapy, either radiation therapy alone or surgery alone produced equivalent local control rates. The overall experience of the Milan group has shown, however, that combined-modality therapy, including neoadjuvant chemotherapy followed by surgical resection and adjuvant chemotherapy, produced the best long-term local control and overall survival rates.

In 1973 our group at The University of Texas M. D. Anderson Cancer Center initiated a combined-modality program with FAC chemotherapy (5-fluorouracil, adriamycin (doxorubicin), cyclophosphamide) administered for three cycles before local treatment. Most patients were then treated with a total mastectomy followed by radiation therapy and adjuvant chemotherapy; a few others had achieved a marked reduction in tumor volume after neoadjuvant chemotherapy and consequently received radiation therapy as the only local modality, followed, in turn, by adjuvant chemotherapy. Ninety-six percent of 174 patients were rendered disease free by this combined-modality therapy, and their median survival was 66 months. The five-year overall survival rate of this group was 55%, and at 10 years 30% was disease free.

Combined-modality Therapy Improves Remission and Survival

Many other clinical trials of combined-modality treatment have been initiated over the last 15 years. Most of them have a shorter follow-up than the studies mentioned above. However, all of them have confirmed that neoadjuvant chemotherapy, followed by local treatment and adjuvant chemotherapy, produces a high complete remission rate and substantially improved three- and five-year survival rates compared with those historically achieved with local therapies only. The Milan experience and our own also demonstrate that many of these patients remain disease free without maintenance therapy longer than 10 years and that recurrences beyond five years are exceptional. This information suggests that some patients with locally advanced breast cancer derive a major, long-term benefit from combined-modality therapy.

Patients with Inflammatory Breast Cancer Demonstrate Most Improvement

The most dramatic benefit from combined-modality therapy occurred in those patients who had inflammatory breast carcinoma. Ninety-five percent of these patients develop local recurrence, distant metastases, or both within one year of local treatment, and almost all of them die within two years of diagnosis. Since the introduction of combined-modality therapies including neoadjuvant chemotherapy, the prognosis of patients with inflammatory breast carcinoma—the majority of whom can be rendered disease free—has improved dramatically. Many recent publications report three-year survival rates of 25 to 80%. Our own experience shows five-year survival rates of 34% for our first combined-modality protocol (FAC-radiotherapy-FAC) and 55% for our second (FAC-surgery-FAC-radiotherapy). The largest report published by investigators from the Institut Gustave-Roussy in Paris included 170 patients treated with combined-modality therapy. A five-year survival rate of 66% was reported by this group, a clear departure from historical experience.

Preoperative, or neoadjuvant, chemotherapy was developed simultaneously with standard postoperative adjuvant chemotherapy. Both have theoretical advantages and disadvantages. Because standard postoperative chemotherapy is administered after surgical resection has reduced the tumor burden to a minimum, the physician

has the benefit of an accurate surgical pathological staging for evaluation of prognosis. The disadvantages of postoperative adjuvant chemotherapy consist of delayed initiation, since local therapies have to be completed first, and the fact that, in the absence of any disease, adjuvant chemotherapy is administered blindly, without any practical way of monitoring results.

Ineffective Therapy Can Be Discontinued Early

Neoadjuvant chemotherapy, on the other hand, can be started early, upon confirmation of the diagnosis of malignant disease, and the primary tumor itself (or the enlarged regional lymph nodes) serves as a signal lesion for monitoring the effects of therapy. Thus, ineffective therapy can be discontinued early, avoiding unnecessary toxicity. In addition, patients who achieve a marked reduction in tumor volume by neoadjuvant chemotherapy may benefit from breast conservation therapy, as opposed to radical local treatments. Finally, preclinical experiments have suggested that shortly after surgical resection of the primary tumor, there is a substantial growth spurt of micrometastases, which is difficult to treat with postoperative chemotherapy. However, micrometastases possibly can be abrogated by the administration of neoadjuvant chemotherapy. Extensive experience with these combined-modality therapies has already taught us that neither surgical nor radiotherapy-related complications are increased. However, neoadjuvant chemotherapy, like all treatment modalities, is less effective against a large tumor burden; large tumors usually harbor many tumor cells with inherent resistance to chemotherapy.

Many questions remain in relation to the proper place of adjuvant versus neoadjuvant chemotherapy for primary breast cancer. However, for patients with inoperable, locally advanced breast cancer, it appears that neoadjuvant chemotherapy is the treatment of choice, and that combined-modality treatments that include neoadjuvant chemotherapy are not only palliative but also provide long-term, disease-free survival for a substantial fraction of these patients. For patients with operable stage III breast cancer, it is uncertain if neoadjuvant chemotherapy is superior to postoperative adjuvant therapy. However, the one advantage of neoadjuvant chemotherapy is that it may offer (by producing substantial reductions in tumor burden) the possibility of breast conservation therapy for 50 to 70% of patients. The study of these two combined-modality therapies will allow us to develop better treatment strategies for our patients within the next decade. ■

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Currently, patients with advanced colorectal disease are being treated using all modalities. Preoperative therapy consists of 5-FU and cisplatin infusion plus external radiotherapy. Therapy ceases for several weeks to allow maximum tumor regression. The tumor is then resected, and an intraoperative radiation boost is given.

"We're very excited about the preliminary results," Rich said. "Patients get through the preoperative treatment well, and at surgery we're finding that the tumor has been reduced. But we're still in a pilot phase."

For patients with advanced GI cancer, the home run has yet to be hit; the bottom line in any cancer research is patient survival. Rich acknowledged the task is difficult. The therapeutic ratio for these patients needs improvement, survival averaging less than 50% at five years.

Rich hopes that improved tumor response due to newer methods of drug and radiotherapy delivery will translate into improved patient survival, but a definitive conclusion awaits the results of prospective, randomized studies. ■

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Neoadjuvant Chemotherapy for Patients with Stage III Breast Cancer

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Gabriel Hortobagyi

Many physicians once considered stage III breast cancer essentially incurable. Consequently, curative attempts were seldom initiated, and patients with locally advanced breast cancer were included in palliative treatment programs. However, beginning two decades ago, it soon became apparent that the objective response rate to combination chemotherapy was quite high, and many patients previously considered inoperable had substantial reduction in the extent of tumor, which often converted the primary tumor from inoperable to operable.

These responses were an improvement over previous therapies that consisted only of local therapy—surgery, radiation, or both. Patients who underwent these therapies achieved five-year survival rates ranging from 30 to 40% for operable stage III breast cancer and 10 to 20% for inoperable disease. Because of high, early mortality, few data on 10-year survival rates exist, but the accepted estimates are approximately 20 to 25% for patients with operable disease and less than 10% for those with inoperable disease, although an occasional report shows slightly better results. When only one local therapy was given, local control rates were poor, and depending on the exact selection of patients, the lifetime local recurrence rate varied from 30% to as high as 87%.

Primary Obstacle Is Distant Metastases

Combined surgery and radiation therapy improved local control rates, and local or regional recurrence rates were

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