Combination Radiation Therapy and Chemotherapy: A Logical Basis for Their Clinical Use

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THE CLINICAL PROBLEM

Since the first site of relapse often determines the therapeutic strategy, a logical basis for integrating radiation, chemical and surgical treatments requires recognition of the failure patterns of each specific cancer. Most patients with cancer fail for three reasons: inability to control the primary tumor (T failure); nodal involvement (N failure); dissemination to distant visceral sites (M failure). Thus, failure may occur from one of these categories or from a combination of factors, as shown in the Venn diagram. (Fig. 1.) The result is seven failure pathways.

Seven Failure Pathways

Primary (T) Failures

Inability to control primary tumors, particularly in locally advanced stages when invasion of contiguous structures and viscera has occurred, remains a significant obstacle to cancer cure. Suit has estimated the failure rate of advanced cancers at specific sites that are not readily eradicable: cancers of the oral cavity, oropharynx and nasopharynx (T3, T4, N2, N3); gynecologic cancers of the cervix (Stages III, IV), ovary (Stage IIIB) and vulva; large advanced genitourinary cancers of the bladder (Stage T2C) and prostate (Stage C). (Table 1.) Gastrointestinal tumors frequently begin insidiously and can reach advanced stages in the stomach, colon and inaccessible sites, such as the pancreas. Soft tissue sarcomas are often locally recurrent and invasive prior to metastasizing. Malignant brain tumors, for example, glioblastoma multiforme, medulloblastoma and mixed gliomas, which are locally invasive and rarely disseminate outside the central nervous system, illustrate the problem clearly.

Nodal (N) Failures

Nodal failures can occur at major node-bearing regions that drain the sites of invasive cancers. Metastatic lymph nodes, which can be difficult to control, include: cervical nodes in head and neck cancer, axillary and supraclavicular nodes in breast cancer, mediastinal nodes in esophageal and lung cancers, paraaortic and pelvic nodes in gynecologic and genitourinary cancers, and mesenteric nodes in gastrointestinal cancers. As primary tumors are con-
trolled, the N category is frequently seen as a major failure pathway; this failure has necessitated extended field radiation at many sites. The introduction of total nodal irradiation techniques for Hodgkin's and non-Hodgkin's lymphomas has focused on the control of nodal extensions due to reseed mechanisms, whether the failure patterns are random or non-random.

Metastatic (M) Failures
The majority of cancer patients fail as a result of disseminated disease. The most common cancers, the breast and lung, are aggressive and metastasize in the early stages of growth, often before clinical detection. Undifferentiated and anaplastic cancers are generally aggressively metastasizing; melanomas, sarcomas of the bone and soft tissue, chro-
mosarcomas and ovarian cancers can also be widespread at the time of diagnosis. Although metastases affect more than one organ system, the documentation of the first metastatic site may suggest elective treatment to specific organs.

Combinations of T, N, M
Four additional failure pathways (TN, NM, TM, TNM) represent combinations of the T, N, M compartments. In many advanced cancers of the breast, lung, head and neck, gynecologic sites (T3, T4, N2, N3 groupings in Stages III and IV), both primary and nodal involvement are difficult to completely resect or eradicate by irradiation. For example, local control of the primary may occur in testicular and ovarian tumors, but nodal and metastatic spread are the
main failure pathways. Oat cell cancer, as well as other types of lung cancer, advanced gastric and rectal cancers and pancreatic cancer can and often do fail in all three compartments. Although the T and N categories may be the overt areas of failure, better local control is certain to unmask occult metastases.

**Seven Treatment Strategies**

By identifying the failure pathways, it is possible to choose specific therapeutic strategies designed to manage each pattern. Failure can be due to persistent disease that has not responded favorably to conventional surgery or irradiation, or to recurrent disease that reappears after eradication, perhaps in a new compartment. This article assumes that reliance has been placed on complete resection when possible, other modalities being used if the disease is unresectable or if it recurs in a given compartment. These treatment strategies, briefly tabulated according to failure patterns (Table 2.), emphasize the potential use of combined radiation therapy and chemotherapy.

For primary (T) and/or regional (N) failures, tumor persistence due to unresectability is generally managed by irradiation preoperatively or postoperatively. The concept of postirradiation conservation surgery is relatively new and has been recommended for metastatic neck nodes. Chemotherapy’s ability to augment irradiation is widely appreciated for advanced head and neck cancers, brain tumors and gynecologic...
and genitourinary cancers, to mention only a few sites. Although radiation therapy is used widely to treat microscopic residuum in the surgical bed, chemotherapy may prove to be as effective in selected sites, such as the breast. High-risk and relapse demand the immediate integration of modalities, since

### Table 2. Therapeutic Strategy According to Failure Pattern

| Failure Pattern | Therapeutic Strategy: |
|-----------------|-----------------------|
|                 | T | N | M |
| T Persistence*  | X + C | X or C |
| Recurrence**    |     |    |    |
| N Persistence   | X + C |     |
| Recurrence      | X    |    |
| M Persistence   | C + X |     |
| Recurrence      | C    |    |
| TN Persistence  | X + C | X  |
| Recurrence      | X ± C | X  |
| TM Persistence  | C + X |     |
| Recurrence      | C    |    |
| NM Persistence  | X + C | X  |
| Recurrence      | X ± C | X  |
| TNM Persistence | X + C | X  |
| Recurrence      | X ± C | X  |

Key: X = Radiation therapy preferred. C = Chemotherapy preferred. X + C = Combination usually used. X or C = Either is used.

*X Persistence = Tumor persistence due to the inability to remove the tumor surgically or ablate it with conventional irradiation.*

**Recurrence = Relapse in a given compartment after complete excision; reliance on other treatment modes when failure occurs.*
control of overt nodal recurrence is very difficult. The ability of irradiation to control suspected microscopic lymph node deposits with moderate doses (4500-5000 rads) is widely accepted. Oncologists are challenged to produce an effective combined treatment without increasing the undesirable reaction in normal structures.

Overt metastases (M failures) are the most difficult to control with current treatment methods. High-risk patients should be treated electively, since the majority of those who eventually die of metastases are apparently free of metastatic disease when the primary cancer is detected. The most successful strategy has been to treat suspected micrometastases with chemotherapy, as has been done in pediatric patients with Wilms' tumor, embryonal rhabdomyosarcoma, and Ewing's sarcoma. It is assumed that most cancer patients have micrometastases at the time of presentation, but these occult deposits are undetectable with present methods of diagnosis. In order to make use of irradiation's ability to sterilize small tumor deposits in specific organs, careful documentation of the first metastatic site is required. Using Herring's calculations, based on Lionel Cohen's formula...
COMBINATIONS OF RADIATION THERAPY AND CHEMOTHERAPY

**Fig. 3.** Venn diagram showing the seven possible combinations of chemotherapy with radiation therapy before (B), during (D), and/or after (A) radiation therapy.

...combinations, doses in the range of 2000-3000 rads are used to eradicate cell deposits numbering from $10^2$ to $10^3$. (Fig. 2.) It is possible to irradiate an entire organ, such as the lung or the brain, electively. Because of the cerebral blood-brain barrier and the inability of chemical agents to reach cells in the central nervous system, irradiation of brain sanctuary sites has been advocated for other highly metastatic tumors; this technique has been used successfully in treating acute lymphatic leukemia.

New therapeutic strategies for cancer control should be based on the failure patterns of a given cancer at each stage of presentation. In addition, all modalities should be optimally combined to achieve the necessary control in the three categories of T, N and M. Combined irradiation and chemotherapy will augment each other to control advanced disease in the primary (T) or nodal (N) compartments; in a supplementary or complementary manner, combined treatments should be used to control suspected occult micrometastases. Patients with a high risk of recurrence are the optimal target group for clinical trials and protocols investigating the elective addition of treatments.

**THERAPEUTIC SEQUENCE AND COMBINATION**

Empiricism, rather than scientific evidence, has dominated the selection of chemotherapeutic agents used in combination with irradiation; success to date...
has been promising, but limited. At first, selection of combined treatments was based on attempts to understand the mechanisms of drug and radiation actions. However, such choices failed to provide the necessary differential effects in tumors and normal tissues. Often, the special interests of an investigator, group or institution in a particular drug(s) have been the basis for drug choice and radiation dose schedules. The lack of a coordinated clinical approach to the combined use of radiation and chemotherapy is revealed in the conflicting statements and the variety of formulations proliferating in the literature.

Choice of Sequence
There are three basic combinations of chemotherapy and radiation therapy. (Fig. 3.) When one adds to this the variety of drugs available and the multitude of dose schedules for radiation therapy and chemotherapy, the possible permutations rapidly approach infinity. The applications and sequencing of chemotherapy and radiation therapy have varied from anatomic site to organ site, with chemotherapy used before, during and after irradiation; it is apparent that there is little or no consistency in approach. The guide to treatment has involved considerations of toxicity and the limits of patient tolerance, rather than a consideration of tumor control. A summary of the common combinations of radiation therapy and chemotherapy according to drug sequence (Table 3.) and anatomic site (Table 4.) is presented.

For locally advanced or regional nodal disease, chemotherapy used before irradiation is expected to cause maximal tumor regression, thereby allowing for a more effective full dose of radiation, or a reduction in the effective dose or treatment volume. It is also hoped that chemotherapy will affect micrometastases and will reduce the possibility of greater metastatic spread while the T and N compartments are being treated with conventional surgery or radiation. Occasionally, a chemical agent acts as a radiosensitizer to “prime” the tumor for radiation. The concept of

| Common Combinations of Radiation Therapy and Chemotherapy, by Drug Sequence |
|---|
| Before Radiation | During Radiation | After Radiation |
| Cytoxan | 5-Fluorouracil | Cytoxan |
| Adriamycin + Vincristine | Methotrexate | Phenytoin Mustard |
| Phenytoin Mustard | Actinomycin D | Cytoxan-Vincristine-Actinomycin D-Adriamycin |
| Thiopeta | Bromodeoxyuridine | Nitrogen Mustard-Vincristine-Prednisone-Procarbazine |
| Hydroxyurea | Bleomycin | Cytoxan-Oncovine-Prednisone |
| Methotrexate ± Leucovorin | Chlorambucil | Bleomycin-Adriamycin-Cytoxan-Oncovine-Prednisone |
| Bleomycin | Hydroxyurea | BCNU |
| Nitrogen Mustard-Vincristine-Prednisone-Procarbazine | BCNU | MeCCNU |
| Cytoxan-Oncovine-Prednisone | BCNU + DTC | |
| Vincristine-Prednisone | | |
chemotherapeutic induction eliminating circulating cancer cells and radiation ablation of the remaining cells in a sanctuary site is exemplified by experiences in the treatment of acute lymphatic leukemia.\textsuperscript{11} This sequence may be widely accepted as an adjuvant form of treatment for different cancers depending on the stage of disease and the effectiveness of chemotherapeutic agents.

Chemotherapy employed during radiation therapy is designed to have a separate, additive or interactive effect, but these are difficult effects to measure or assess. (Fig. 4.) Normal tissue toxicity is the main guide.\textsuperscript{12} Ideally, radiation and chemotherapy should have different target organ toxicity; however, this is unfortunately not always the case. Few major improvements have been noted with this approach. Although there is some measurable gain in survival in weeks (brain cancer, glioblastoma multiforme) and in months (stomach cancer),\textsuperscript{13} the simultaneous use and sequencing of these modalities need further exploration to determine optimal dose and time interval selection.

The greatest advance has been the use of chemotherapy after irradiation and/or surgery. As stated above, chemotherapy can eradicate micrometastases and eliminate subclinical deposits in vital viscera.

Choice of Combination

The integration of effective chemotherapy with the local modalities of surgery and radiation therapy has greatly improved the cure rates of solid tumors. The philosophical basis for this combined modality approach recognizes that surgery and radiotherapy are local modalities that kill tumor cells only where they are applied; they fail to cure many patients, even when all tumor visible to the naked eye or on diagnostic X-ray film is removed. This failure appears to be due to the presence of disseminated microscopic disease foci when the primary tumor, surrounding tissue and some of the regional lymph nodes are excised.

Chemotherapy, when used optimally, has the potential to eradicate metastatic foci of early disease. Those drug regimens that show the highest degree of efficacy in advanced disease have been the major candidates for use in the combined modalities approach. The degree of cell-kill necessary to shrink a bulky solid tumor mass by more than 50 per-

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**Table 4.**

| Chemotherapy Before Radiation | Chemotherapy During Radiation | Chemotherapy After Radiation |
|-----------------------------|-----------------------------|-----------------------------|
| Lung, Oat Cell Cancer       | Lung, All Types             | Lung, Oat Cell Cancer,      |
| Breast Cancer               | Breast Cancer               | Epidermoid Cancer, Adenocarcinoma |
| Ovarian Cancer              | Ovarian Cancer              | Ovarian Cancer              |
| Head and Neck Cancer        | Cervical Cancer             | Hodgkin's Disease          |
| Hodgkin's Disease           | Head and Neck Cancer        | Non-Hodgkin's Disease      |
| Non-Hodgkin's Lymphoma      | Brain Cancer                | Lymphoma                   |
| Leukemia (ALL)              | Esophageal Cancer           |                             |
|                             | Stomach Cancer              |                             |
|                             | Pancreatic Cancer           |                             |
|                             | Colo-Rectal Cancer          |                             |

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Fig. 4. The various effects of chemotherapy as it is combined with radiation therapy.

cent, usually the minimum definition of objective regression, is quite large. If this level of cell-kill could be directed against the relatively small tumor burden remaining after surgery and/or radiation therapy, perhaps eradication of these neoplastic cells could be achieved.

Experimentally, it is well established that the best chance of eradicating a tumor mass with chemotherapeutic agents is when the tumor cell population is small, a situation occurring immediately after resection of the primary tumor. The ability of chemotherapy to produce a cure is greater when all visible tumor is excised, than after subtotal resection. The inverse relationship between tumor cell population and chemotherapeutic cure has been clearly expressed in quantitative terms in mice bearing L1210 transplanted leukemia. Similar conclusions have been reached in experimental solid tumor systems.

The major success of chemotherapy has been in the hematologic cancers, especially lymphocytic leukemia and advanced Hodgkin's disease. However, these triumphs of cure and long-term disease-free survival have not been translated to the common solid tumors, which are the primary causes of cancer mortality throughout the world. The obvious reasons for this disparity in results are the differences in cell kinetics and the relative accessibility to effective drug concentration exhibited by cells in fast- and slow-growing tumors. One additional factor, which is often neglected, is the point in the treatment strategy when chemotherapy is introduced.
As a general rule, the major potential for cure of any tumor lies in the initial therapeutic approach. In leukemia, a disseminated disease, chemotherapy is the treatment of choice for all stages of disease. The optimum drug regimens are used in primary therapy and new drugs or regimens are tried in recurrent or advanced disease, with the successful ones being integrated into the primary therapeutic approach.

On the other hand, the primary treatment for disseminated solid tumors is surgery and/or radiotherapy. Chemotherapy is relegated to secondary or tertiary use after local modalities fail and the disease is advanced and disseminated. Since this therapy is rarely curative, it is understandable that chemotherapy has not been tried in the initial treatment of solid tumors, although chemotherapy used in this manner has produced tumor regression, palliative benefit and some gain in survival. Any comparison of the results of chemotherapy in solid tumors and in hematologic cancers should consider the differences in the treatment flow, as well as other dissimilarities between the two tumor types.

Table 5 is a broad outline cross-reference chart, based on the published and unpublished results on file in the Cancer Therapy Evaluation Program (CTEP), showing the clinical evaluation of 30 drugs against 17 solid tumors. Each of the 30 drugs has shown definite evidence of activity against at least one tumor type from among the hematologic cancers or solid tumors. Investigational drugs that have not been adequately evaluated or that have shown no evidence of activity in any tumor, as well as hormonal agents, have been excluded from this review.

Choice of Combined Modes, by Tumor Site and Type

The window through which to view the progress of the combined modality approach is the development of clinical trials in national cooperative oncology groups. Single agent chemotherapy has been supplanted by multiple agents. The Cancer Therapy Evaluation Program (CTEP) of the Division of Cancer Treatment is responsible for drug development and for monitoring the clinical trials of new anti-cancer agents, and more recently of combined modality approaches. The following analysis uses their tabular evaluation of chemotherapeutic agents, lists of on-going clinical trials and a concise summary of the response to date. An outline of some of the current combined modality trials is shown in Table 6. Twenty-five different chemotherapeutic regimens are being evaluated, as are nine immunotherapy plus chemotherapy regimens. Also, there are 15 regimens employing chemotherapy and radiation therapy. Although this list is not intended to be encyclopedic, it does show the wide range of studies being done in attempts to improve survival rates for solid tumors with combined modality approaches. As data accumulate and are analyzed, we will begin to learn where treatment successes and failures have occurred, so that we can plan more intelligently for future investigations.

Head and Neck Cancer

All stages and sites have been selected for study, with the oropharynx, oral cavity, hypopharynx and supraglottic larynx most often used as target areas, particularly the T3, T4, N1-N3 categories. Since the TNM system has been undergoing modification and conflict exists between the classification systems of the American Joint Committee for Cancer Staging and End Results Reporting and the International Union Against Cancer, careful analysis will be required to compare the results. The predominate failure pattern is tumor persistence and/or recurrence in the primary site and/or nodal compartments. Once advanced cancers are controlled, more evi-
## Table 5.
### Chemotherapy for Solid Tumors

| Tumor types | Totals of tumor activity |
|-------------|--------------------------|
| Drugs       | NE | + | ++ |
| Arelating agents | | | |
| CYC | NE | NE | ++ | ++ | NE | NE | ++ | NE | ++ | NE | NE | NE | NE | NE | 8 | 1 | 3 | 5 |
| HN2 | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 9 | 3 | 2 |
| CHL | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 9 | 2 | 5 | 1 |
| MPL | NE | NE | ++ | NE | NE | NE | NE | NE | NE | NE | 10 | 3 | 2 | 2 |
| BUS | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 15 | 2 | 0 | 0 |
| Antimetabolites | | | |
| 6-FU | ++ | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 5 | 3 | 6 |
| MTX | NE | NE | ++ | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 9 | 1 | 4 | 3 |
| 6-MP | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 12 | 4 | 1 | 0 |
| 6-FG | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 16 | 1 | 0 | 0 |
| AIC | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 13 | 4 | 0 | 0 |
| Antigenic antibodies | | | |
| VCR | NE | ++ | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 9 | 3 | 2 | 2 |
| VBL | NE | ++ | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 10 | 3 | 2 | 2 |
| Antitumor | | | |
| Actinomycin | | | |
| ACT | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 12 | 2 | 1 | 2 |
| MTX | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 10 | 6 | 1 | 1 |
| DNR | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 17 | 6 | 0 | 0 |
| ADR | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 5 | 3 | 4 | 5 |
| BLM | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 9 | 3 | 3 | 2 |
| MTC | + | NE | ++ | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 9 | 1 | 4 | 3 |
| Random systems and miscellaneous | | | |
| BCNU | NE | ++ | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 10 | 1 | 5 | 1 |
| CCNU | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 8 | 5 | 2 | 2 |
| MBCNU | NE | ++ | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 6 | 5 | 4 | 2 |
| STZ | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 15 | 2 | 0 | 0 |
| DTIC | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 10 | 5 | 1 | 1 |
| HKM | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 8 | 3 | 4 | 2 |
| DDD | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 11 | 3 | 0 | 0 |
| HYD | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 17 | 0 | 0 | 0 |
| POB | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | NE | 16 | 2 | 0 | 0 |
| Totals of drug activity | | | |
| NE | 27 | 22 | 6 | 20 | 5 | 29 | 14 | 22 | 8 | 7 | 27 | 21 | 14 | 19 | 19 | 22 | 24 | 30 |
| + | 0 | 1 | 11 | 10 | 6 | 0 | 4 | 0 | 8 | 17 | 12 | 2 | 3 | 2 | 3 | 0 | 9 |
| ++ | 2 | 4 | 5 | 8 | 4 | 1 | 10 | 2 | 8 | 5 | 1 | 3 | 7 | 4 | 4 | 2 | 9 |

| NE | Not Evaluated |
| + | Positive Response |
| ++ | Negative Response |
idence of distant metastases is likely to appear. Radiation and chemotherapy have been used serially, since they have similar toxicities and can induce severe mucositis when used simultaneously.

The active agents and their response rates include: methotrexate (47 percent) and bleomycin (15 percent), with good response rates noted for hydroxyurea (39 percent) and vinblastine (29 percent). The agent most actively used is methotrexate. A recently completed national study of methotrexate indicated a gain in survival for patients with tumors in certain sites, such as the oral cavity and hypopharynx, but not in others, for example, the supraglottic larynx and oropharynx. Two recent reviews of the combined use of chemotherapy and radiation therapy failed to find a significant improvement in survival. Part of the problem is poor reporting, in which different types of head and neck cancers are grouped at different stages of disease, muddling the apparent survival gains at specific sites. High-dose methotrexate and Leucovorine rescue have achieved good regression rates, but have not led to long-term control. In a study employing correlative research techniques, Friedman and Nervi failed to show significant improvement with combined methotrexate and irradiation; they suggested that failure was due to the development of resistant subcultures of tumor cells.

Lung Cancer
Since the majority of cancers are unresectable with mediastinal or scalene nodes (T3, T4, N2, N3), the problem of controlling the primary and regional node (T, N) compartments is equal to that of controlling metastases. Lung cancer is normally quite advanced at the time of diagnosis, indicating the presence of distant visceral metastases. More thorough investigations and radioisotopic scans of liver, brain and bone, along with bone marrow aspiration, have uncovered occult metastases. The failure pattern is predominantly metastatic, but often all three compartments have extensive uncontrolled cancer.

The list of agents used and the availability of patients for study have provided extensive experience but, unfortunately, there is little or no evidence of a gain in survival or in tumor control for squamous and adenocarcinomas of the lung. Active agents and their response rates are cyclophosphamide (20-21 percent), nitrogen mustard (21-29 percent), methotrexate (25-32 percent), Adriamycin (15-23 percent), bleomycin (13 percent) and nitrosurea (17 percent). According to many investigators, reductive treatment of the T and N compartments with radiation and surgery is essential before metastases can be successfully contained and eradicated with chemotherapy and/or immunotherapy. All three (or four) modalities must be used.

Many agents have been used in combination with irradiation, both as radiosensitizers and as active chemotherapeutic drugs. Preoperative radiation therapy sterilizes 30 percent of the tumors. In lung cancer, postirradiation chemotherapy has been the main testing area for new agents. In practical terms, the effectiveness of alkylating agents, particularly Cytoxan as used in the treatment of undifferentiated small cell carcinoma (oat cell variety), has been sporadic.

Chemotherapy is used before, during and after irradiation in many protocols. There is continued interest in the combination of radiation therapy and chemotherapy to control the TNM compartments. Oat cell carcinomas are the most responsive, and three or four drug combinations are being actively explored. A large number of cooperative groups are studying a variety of treatment schedules using as many as 10 to 12 agents in different sequences. Immunostimulation and chemotherapy are advocated by Israel. The measurement of relapse-
free survival in patients with early cancer may serve as a better index of chemotherapy's effectiveness. Elective CNS and/or liver irradiation is being studied for the eradication of micrometastases.

Sequences of chemotherapy and radiation therapy have had little success. A major problem is the lack of a radiological method to accurately assess tumor response.

Alimentary Tract Cancers

All of the major sites in the alimentary tract are a challenge to the oncologist and have been the focus of much protocol development in combined modalities. Cancers of the esophagus, stomach and pancreas are generally advanced at the time of diagnosis and it is often difficult to control any of these tumors. At the time of death, primary and nodal involvement are frequently uncontrolled and metastases are present. Only colorectal cancers have been diagnosed in localized stages to affect overall results, but most patients have sufficiently advanced cancers (Duke's Stages B, C) so that local recurrence, nodal metastases and eventually distant metastases appear. Again, the pattern is that of TNM failures.

In esophageal cancer, one agent, bleomycin, has documented activity, with an unimpressive response rate of 17 percent. Studies of combined radiation therapy and chemotherapy are limited and have produced poor results and no interesting leads. The dismal record of radiation therapy, except in the treatment of high thoracic and cervical esophageal cancer (T1, NO, MO), in which 15-20 percent of the five-year survivals are recorded, is a mandate for the investigation of combined modalities. Adequate use of megavoltage therapy to deliver doses of 6000-7000 rads has not achieved primary tumor control in a significant percentage of patients. Doses as high as 8000-10,000 rads have failed to control the primary cancer in the 25 MeV range. Augmentation of standard radiation therapy with chemotherapy is essential to control the T and N compartments. Bleomycin used in combination with radiation therapy to achieve greater local tumor control is still being explored in protocol studies. When the tumor is extensive, as in Stages II and III, combinations of agents before, during and after irradiation should be considered.

The active agents for stomach cancer are 5-Fluorouracil (5FU) and Mitomycin, with poor response rates of 20 percent or less. Moertel has been a leader in combining chemotherapy and radiation therapy to control advanced disease. Five-FU is given on the first three days of irradiation and is used again after the completion of radiation treatment. The combination of 5FU and 4000 rads of radiation administered over four weeks was superior to either modality alone. More recently, the combination of 5FU, MCCNU and radiation therapy, which has a response rate of 25-30 percent, has been favored in protocol design. Adriamycin is the third agent being investigated, but its use should be cautiously studied.

There is a longer list of active chemothepapeutic agents in colo-rectal cancer than in other GI sites. These agents and their response rates are: 5FU (21 percent), MTC (16 percent), MCCNU (12 percent), CYC (21 percent), MTX (21 percent), BCNU (13 percent) and HXM (12 percent). However, there has been no evidence to support the routine use of combined radiation therapy and chemotherapy at these sites. Rather, protocol design has focused on resectable versus non-resectable lesions in advanced stages (Duke's Stages B, C). The use of preoperative irradiation has been studied for more than a decade and despite the recent evidence of controlled studies indicating the value of preoperative irradiation in localized resectable
### Table 6.
Combined Modality Trials Currently in Progress

| Regimens* | Tumor Type | Overall Trials | Surgery + Chemotherapy | Surgery + Immunotherapy | Chemotherapy + Immunotherapy | Radiation Therapy + Chemotherapy |
|-----------|------------|----------------|------------------------|-------------------------|-------------------------------|----------------------------------|
| Colon     | 4          | • 5FU          | • CCNU + 5FU           | • MER BCG               | • MeCCNU + 5FU + VCR         | • 4000RT + 5FU                   |
|           |            | • MeCCNU + 5FU |                        | • BCG                   |                               | • 6000RT + 5FU                   |
| Pancreas  | 4          | • 5FU          | • CCNU + 5FU           | • MER BCG               | • MeCCNU + 5FU + VCR         | • 4000RT + 5FU                   |
|           |            | • CCNU + 5FU   |                        | • BCG                   |                               | • 6000RT + 5FU                   |
| Stomach   | 3          | • 5FU          | • MeCCNU + 5FU (2)     | • "CMF" + MER          | • "CMF" + BCG (2)            | • 5000RT + 5FU                   |
|           |            | • CCNU + 5FU   |                        | • BCG                   | • "CMF" + BCG + all cells    | • 5FU + MeCCNU                   |
| Breast    | 8          | • L-PAM (5)    | • "CMF" (2)            | • BCG                   | • "CMF" + BCG (2)            | • "RT + "CMF"                    |
|           |            | • "CMF" + BCG  | • "CMF" + V          | • BCG                   | • "CMF" + BCG + all cells    | • "RT + "CMF"                    |
|           |            | • "CMF" + tamoxifen | • "CMF" + tamoxifen | • BCG                   | • "CMF" + BCG + all cells    | • "RT + "CMF"                    |
|           |            | • "CMF" + V   | • "CMF" + tamoxifen   | • BCG                   | • "CMF" + BCG + all cells    | • "RT + "CMF"                    |
| Lung (epidermoid) | 4          | • CCNU        | • CCNU + hydroxyurea (2) | • BCG               | • RT + CCNU + hydroxyurea    | • RT + hydroxyurea               |
| Lung (small cell) | 4          | • CCNU + hydroxyurea | • CCNU + CTX + MTX | • BCG               | • RT + CCNU + hydroxyurea    | • RT + hydroxyurea               |
| Melanoma  | 11         | • DTIC (4)     | • MeCCNU               | • BCG (6)               | • DTIC + BCG (2)             | • RT + CCNU (3)                  |
|           |            | • MeCCNU       |                       | • BCG + allogenic cells | • DTIC + BCG + allogenic cells | • RT + MeCCNU                  |
|           |            | • CCNU         |                       | • BCG + "normal" cells | • DTIC + BCG + allogenic cells | • RT + MeCCNU                  |
|           |            | • CCNU         |                       | • BCG + "normal" plasma| • DTIC + BCG + allogenic cells | • RT + MeCCNU                  |
|           |            | • CCNU         |                       | • BCG + "unblocking" plasma| • DTIC + BCG + allogenic cells | • RT + MeCCNU                  |
| Ovary     | 2          | • L-PAM (2)    |                       | • BCG                   | • RT + L-PAM                  | • RT + hydroxyurea               |
| Cervix    | 1          |                |                       | • BCG                   |                               | • RT + CCNU                     |
| Brain (glioma) | 3          | • BCNU          | • MeCCNU               | • BCG                   | • RT + BCNU (3)               | • RT + MeCCNU                    |
| Testicular | 2          | • Actinomycin D | • MeCCNU               | • BCG                   | • RT + Actinomycin D + Chlorambucil | • RT + BCNU (3)               |
|           |            | • VLB + Bleomyacin | • MeCCNU               | • BCG                   | • RT + Actinomycin D + Chlorambucil | • RT + BCNU (3)               |
| Esophagus | 2          | • VLB + Bleomyacin | • MeCCNU               | • BCG                   | • RT + Actinomycin D + Chlorambucil | • RT + BCNU (3)               |
| Total     | 48         | 25             | 9                      | 7                      | 15                            |                                  |

*Numbers in parentheses refer to cases of two or more trials in progress with the same regimen.
disease,\textsuperscript{29} it has not gained the favor of the general surgical community. In fact, a recent Radiation Therapy Oncology Group protocol exploring preoperative irradiation in these sites has been discontinued. Gunderson has presented evidence to show that lymph nodes represent a major failure pathway and may precede distant metastases.\textsuperscript{30} For this reason, postoperative irradiation versus chemotherapy (5FU and MCCNU) is being evaluated for unresectable stages of colo-rectal cancer.

Advanced unresectable colo-rectal lesions are the target for combined treatment. Protocols are available to study full-dose irradiation followed by the best combination of agents (5FU and MCCNU). Irradiation and 5FU are still used, but there is no evidence that tumor regression or complete clearance rates have been improved. Interest in the addition of vincristine and in the use of immunostimulation (MER) is apparent in some protocols.

The combined modality approach for pancreatic cancer has begun, as in other sites, with sequential irradiation and chemotherapy. The active agents and their response rates are again limited to 5FU (28 percent) and MTC (27 percent).\textsuperscript{16}

The results are poor (less than five percent five-year survival), but an isolated report of 20-25 percent survival with a split-course irradiation schedule of 2000 rads/two weeks repeated three times with two-week rest intervals (6000 rads/10 weeks, total) had indicated an effective, well-tolerated radiation schema to be used with chemotherapy.\textsuperscript{31} Such split-course schedules allow for pulsing chemotherapy in the intervals between radiation therapy, reducing toxicity as compared with continuous schedules.

Genitourinary Cancers

The predominate failure pattern for genitourinary cancers is metastatic disease, but there is now increased awareness of regional lymph node involvement. By using surgery and/or radiation therapy to control primary tumors and microscopic nodal involvement, the setting is optimal for chemotherapeutic treatment of occult metastases. The successful management of childhood Wilms' tumor with the addition of Actinomycin D and vincristine is a good clinical model.\textsuperscript{4} The primary tumor is resected by surgery; Actinomycin D is administered to augment the effects of moderate-dose irradiation in the tumor bed for residual disease. Actinomycin D is then employed in maintenance cycles for two years.

Unfortunately, there are few agents of value in renal, bladder or prostatic cancers.\textsuperscript{16} The most promising results appear to be occurring in some of the non-seminomatous testicular cancers.\textsuperscript{32}

In renal cancer, no truly active agent exists. The two chemotherapeutic agents of DBD (21 percent) and HYD (28 percent) require further study;\textsuperscript{16} no protocols are planned for their combination with irradiation. For bladder cancer, there are a few active agents with good response rates (ADR, 21 percent; 5FU, 35 percent; MTC, 25 percent), but many of the available drugs have not been adequately tested.\textsuperscript{16} Only 5FU and irradiation have been intensively studied.\textsuperscript{33} Reports indicate that 5FU augments the effect of radiation on bladder tumors, causing an increase in sterilization rates, compared to the use of radiation therapy alone. A re-examination of this lead would be worth considering. The major problem in bladder cancer, local recurrence, is not limited to the originally treated primary site; new primaries form if the bladder has been preserved intact.\textsuperscript{34} The age of the patients and the high frequency of associated medical diseases make vigorous chemotherapeutic maintenance often untenable.

The treatment of prostatic cancer de-
serves more study, since local control in even advanced Stage C tumors is a reality with high-dose supervoltage irradiation (7000 rads). The high frequency of metastases to bone demands an attack on this problem during the occult stages of disease. The palliative effect of estrogen has been a deterrent to the exploration of more aggressive chemotherapy. Active agents include 5FU (29 percent), CYC (14 percent) and HN2 (39 percent).46 No combinations with irradiation have been attempted.

Chemotherapeutic agents for the treatment of testicular tumors, particularly the highly metastasizing nonseminomatosus cancers, are being intensively investigated.32 Very active agents of proven usefulness exist, including VBL (52 percent), ACTD (52 percent), MTH (36 percent), BLM (42 percent), MPL (57 percent) and ADR (20 percent).16 Patients with positive nodal disease have the greatest risk of metastases; accordingly, protocols have been developed for retroperitoneal nodal dissection and/or irradiation with and without chemotherapy. The high rates of complete regression reported by Samuels and the suppression of bone marrow with irradiation have led to the competitive use of these modes.33 For overt pulmonary metastases, particularly in seminoma, Cytoxan and irradiation have been used together with some success.31

Breast Cancer

While surgery and irradiation control local disease in the primary (T) and nodal (N) compartments, metastases appear to be the most common failure pathway in breast cancer. Patients with extensive primary tumors, particularly the inflammatory variety that is rapidly growing and disseminating, may fail in all three TNM categories. The number of active agents exceeds that of any other solid tumor, resulting in a major attack on these clinical problems. The response and clearance rates of single3 and multiple agents16 have been impressive, leading to an increase in remission intervals, which ultimately may be translated into increased survival rates. The increased elective use of chemotherapy with other modalities has become a model for management of other cancers.

As seen in a national study,3 L-PAM, an agent with only a fair response rate of 23 percent, effectively increases the remission interval in premenopausal patients with early breast cancer. This has been followed by the use of multiple agent chemotherapy-CMF, bringing a further gain in remission intervals to high-risk patients (those with three or more axillary nodes).35 These experiences reinforce the concept that moderately active chemotherapeutic agents are very effective against micrometastases in overt disease. Patients with a high risk of metastases will become a key target group for the investigation of drug effectiveness.

Combined chemotherapy and irradiation will be used to control advanced local and regional masses. Many protocols have been proposed using chemotherapy before, during and after irradiation. The high regression rate obtained by Bonadonna with Adriamycin and vinblastine needs confirmation.35 Currently, three drugs—CMF, MMF and CAF—are being considered for use in a number of preliminary trials in combination with irradiation.

Gynecologic Cancers

The gynecologic cancers can be divided into favorable and unfavorable varieties. Cancers of the uterine cervix and fundus are generally well treated with conventional radiation and/or surgery. Most cancers are usually detected in Stages I and II and are limited to the uterus, with a low incidence of regional nodal disease. For advanced cancer of the cervix, local control of the primary and regional nodes, including both pelvic and paraaortic nodes, is the challenge; the addition
of chemotherapy to radiation therapy is becoming accepted in protocol study. There are numerous active agents of fair response rates, which include: CYC (19 percent), 5FU (23 percent), CHL (25 percent), MBL (21 percent), VCR (29 percent), ADR (32 percent), BLEO (10 percent), MCCNU (17 percent) and HXM (28 percent). Few of these agents have been studied in combination with irradiation. The Gynecologic Oncology Group's cooperative study of combined hydroxyurea with irradiation showed some improvement in results. Further investigation is required in view of the number of active agents available.

Advanced and often widely metastatic ovarian cancer is the most problematic of the female genital tumors. Recent attention to lymphatic invasion of the diaphragmatic lacteals and paraaortic lymph nodes has reoriented the approach to radiation therapy, extending the emphasis of the field arrangements from the pelvis to the abdomen. The major limitation to irradiation is the vital viscera in these extended fields. Active agents and their response rates include: CYC (44 percent), CHL (51 percent), MPL (47 percent), 5FU (32 percent), ADR (38 percent), HXM (39 percent), HN2 (31 percent), CCNU (32 percent) and MTX (25 percent). Despite this impressive list, single agent chemotherapy used sequentially with irradiation remains comparable to multiple drugs. The sequencing of chemotherapy, limited to before or after irradiation due to bone marrow irradiated in the pelvic and abdominal fields, has resulted in competition over which modalities should initiate treatment. Results to date are unimpressive despite the good responses recorded, and further trials are in progress to modify the radiation dose and field arrangements, allowing for more aggressive chemotherapy.

Hematologic Cancers
The patterns of failure of leukemia and Hodgkin's disease were important leads in the development of corrective strategies in their treatment. In acute lymphatic leukemia (ALL), the frequency of CNS relapse with bone marrow remission suggests that chemotherapeutic agents are unable to penetrate the blood-brain barrier. Elective irradiation of cerebral sanctuary sites following chemotherapeutic induction illustrates the effectiveness of the combined approach. This model has been adopted in the treatment of other cancers in which central nervous system spread is a problem, such as Ewing's sarcoma and oat cell cancer.

In Hodgkin's disease, full doses of both modalities have resulted in definite gains in the control of advanced Stages III and IV disease. The increase in toxicity requires the modification of treatment, particularly to bone marrow when total nodal irradiation techniques are combined with multiple drug schedules, (for example, MOPP). The recent report of Prosnitz and Farber in which chemotherapeutic induction was followed by low-dose (2000 rads) segmental fields encompassing the large nodal masses is another demonstration of a corrective strategy based on failure patterns. Overt nodal involvement is the common site of recurrence or relapse in Stages III and IV Hodgkin's disease. When added to effective chemotherapy, irradiation of these sites has made possible the control of tumors and long-term survival. The lower radiation dose causes less toxicity, indicating effectiveness without the use of full doses. The experience of Prosnitz and Farber serves as a model for new studies in non-Hodgkin's lymphoma and, perhaps in oat cell cancer as well.

Brain
Glioblastoma multiforme is the most malignant tumor of the brain. Inability to control the primary tumor, the main cause of death, is best illustrated in the
treatment of this disease. Extremely high doses of irradiation (7000-8000 rads) have been unable to control this tumor because of its radiosresistance and volume at the time of detection. Larger doses of irradiation will certainly exceed brain tolerance and, therefore, new modes of treatment are required. Unfortunately, preliminary reports of high LET neutron treatment are unfavorable and survival curves are unchanged.

The combined use of irradiation and chemotherapy has been actively explored by the Brain Tumor Study Group (BTSG) with limited success. The combination of BCNU and 6000 rads has increased the median survival rate by six weeks over that of radiation therapy alone. Current studies use MCCNU, but the results fail to show any improvement in survival. A larger number of active agents are being identified. These include BCNU (47 percent), CCNU (41 percent), MCCNU (33 percent), MTX (54 percent), VCR (57 percent), VBL (44 percent), PLB (52 percent) and MTH (52 percent). Some of these agents are now being studied in a medulloblastoma protocol. The optimal sequencing of agents as well as multiple agents in combination with irradiation must be explored. The absence of the blood-brain barrier in glioblastomas as compared to the normal brain may favorably distribute agents differentially.

Sarcomas and Pediatric Tumors

The most successful combination of modalities involves the very malignant soft tissue and bone sarcomas. The failure pattern has been local tumor recurrence or persistence, coupled with widespread metastases. Active agents of moderate response include CYC (52 percent), VCR (47 percent), ACT (24 percent) and ADR (25 percent). Following the lead of Wilms' tumor, surgical excision, postoperative irradiation and chemotherapy (using the four agents listed above) were successfully employed to treat embryonal rhabdomyosarcoma. This approach has also been used to treat Ewing's tumor, in which irradiation of the primary is combined with CYC, VCR and ACT, yielding a high rate of freedom from metastases. Even more recently, the addition of high-dose MTX-Leucovorin rescue to CYC, VCR and ADR has controlled osteogenic sarcoma for the first time in most patients. In all of these circumstances, chemotherapy is applied electively before the manifestation of metastases. Indeed, it is the successful eradication of micrometastases by chemical agents that has significantly altered the course and outcome of patients with these fatal tumors.

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