Combined Approach to the Management of Incurable Breast Cancer. Part Two: Systemic Therapy and Radiotherapy (concluded*)

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Metastases to Bone

The most common indication for radiotherapy of incurable breast cancer is painful metastases to bone. Unlike bony metastases from other tumors, breast cancer metastases usually respond to relatively low doses of irradiation and are therefore suitable for large volume radiotherapy. Regardless of the obvious need for relief of local symptoms, roentgenological survey is essential as the first step in planning effective treatment, both in terms of the immediate problem and future management.

As other symptomatic areas develop, the initial survey should be supplemented with radiographs of both symptomatic and previously suspicious areas. Initially, visible lesions tend to be isolated. The most common early metastatic sites are the eleventh dorsal vertebra, the lumbar spine and the hip joints. Occasionally, almost the entire skeleton system will be involved. Our general policy (depending somewhat on the extent of disease) is to irradiate symptomatic areas as anatomical units or subunits, leaving silent areas for evaluation of response to systemic therapy.

The volume of tissue involved, tumor dose and overall treatment time must be considered in relation to prognosis, previous chemotherapy and probable bone marrow reserve. In treating local regions for long-term relief of pain, our policy is to administer a tumor dose more or less biologically equivalent to 2,000 rads delivered in 2 weeks. Recommended doses of irradiation are for Cobalt 60 or other megavoltage units unless otherwise specified. Localization films, taken on the therapy unit or simulator are essential for accuracy and future reference (Figs. 1A and 1B and Figs. 2A and 2B) and photographs are invaluable. (Figs. 3A and 3B.)

Vertebral Column

Thoracic spine. Metastatic cancer in the lower dorsal region is treated through a single posterior field extending from T3 through T12, which prophylactically covers the mid-dorsal vertebrae (an area particularly vulnerable to compression of the spinal cord.) (Fig. 3B.) For average-sized women, a given dose of 2,500 rads delivered in 5 consecutive days is
adequate. Supportive care during radiotherapy is essential for comfort and cooperation and, although treatment can generally be administered on an outpatient basis, analgesics are required at fairly regular intervals.

Following treatment, a thoracolumbar Camp corset, worn to limit motion, may reduce minor discomfort during active hours. However, before treatment the majority of patients cannot tolerate the restriction of even a corset. A brace is contraindicated, because the rigid parts, no matter how well fitted, add to the pain.

**Lumbar spine.** The given dose for involvement of the lumbar spine is 2,500 or 3,000 rads delivered in 5 to 6 treatments. Heavy women should be treated with a tumor dose of 2,000 rads, using a pair of posterior wedge fields or through parallel opposing anterior and posterior fields (L1 through L4 or L5) over a 2 week period. Patients with involvement of the lumbar spine may require hospitalization because of incapacitating pain. Demerol® or morphine, rather than milder analgesics, may be necessary prior to radiotherapy to enable the patient to assume the treatment position.

**Cervical spine.** Because metastases to the cervical spine can be excruciatingly painful, bed rest and a cervical collar or splint may be essential to limit motion. The patient with metastases in the upper cervical spine is treated in a supine position with parallel opposing lateral fields if either the prone or lateral positions cannot be assumed because of painful spasms. If possible, however, the entire cervical spine should be treated together with the upper three dorsal vertebrae. The daily dose of irradiation depends on the severity of pain. If the pain is mild, treatment is delivered in one week as for the dorsal spine; if it is acute, therapy is protracted to avoid aggravating local symptoms.

**PELVIS**

Treatment for pain related to the hip depends on the degree of involvement. For metastatic disease limited to the hip joint, our policy is to cover the acetabulum, ischial tuberosity, the associated symphysis pubis and the upper end of the femur, with a tumor dose of 2,000 to 2,500 rads delivered in 2 weeks. Treatment for more extensive disease involving the hemipelvis depends on the status of the sacroiliac joint. If it is uninvolved, treatment may be limited to the hemipelvis. When the sacroiliac joint is involved, the best approach is to treat the entire pelvis, delivering a tumor dose of 2,000 rads in 2 weeks through parallel opposing anterior and posterior fields. (Figs. 1A and 1B and Figs. 3A and 3B.) This treatment is well tolerated, provided (1) 25 mg. Thorazine® is administered 1 hour before meals, and (2) no chemotherapy (e.g., 5-fluorouracil which is toxic to the mucosa of the small intestine) is administered immediately posttreatment. Ordinarily, excessive diarrhea does not occur unless treatment is given at a faster rate or reaches higher dose levels. A higher tumor dose level (e.g., 2,500 rads in 2 weeks or 3,000 rads in 3 weeks) can be achieved if the major portion of the small intestine is shielded anteriorly with an 8 cm. wide lead strip. (Figs. 1A and 3A.) A wider shield which excludes the brim of the true pelvis from the treatment field is unacceptable.

**LONG BONES**

Palliative radiotherapy for metastases in long bones, commonly the femora, should be administered through parallel opposing fields (Figs. 3A and 3B), with the usual tumor dose of 2,000 rads in 2 weeks. Although the upper and lower borders of the treatment fields are dependent on the extent of disease, one or both joints are commonly included.
RIBS

No treatment is given if metastases to ribs are clinically silent. Radiotherapy is indicated when acute symptomatology, caused by pathological fracture, fails to subside within a few days. A single painful rib is treated with an appositional field, with a given dose of 1,500 rads administered in 2 consecutive days. Painful pathological fractures associated with extensive involvement of ribs tend to occur bilaterally along the mid-axillary line in conjunction with involvement of the shoulder girdle. Disabling pain can be relieved by treating the shoulder girdle and the lateral aspect of the rib cage as a unit with parallel opposing anterior and posterior fields. (Figs. 2A and 2B and Figs. 3A and 3B.) To ensure adequate coverage of the scapula, the humerus should be abducted. A tumor dose of 1,500 rads delivered in 3 to 5 days is as effective as 2,000 rads tumor dose administered in 2 weeks.

EXTENSIVE GENERALIZED METASTASES TO BONE

Although patients presenting with extensive bony metastases may respond dramatically to a combination of systemic and local treatment, survival is generally a matter of months rather than years. Barring a myelophthisic anemia, recent chemotherapy or hypercalcemia, worthwhile palliation generally can be achieved by large volume radiotherapy administered to the major areas, with some compromise in the dose schedule. One feasible regimen is to initiate therapy to the pelvis concurrent with therapy to the dorsal and cervical spine. (The given dosage for the dorsal and cervical spine is 2,500 rads delivered in 1 week.) During completion of treatment to the pelvis (1,500 to 2,000 rads tumor dose administered at a rate of 1,000 rads tumor dose per week), treatment can be started to the lumbar spine through a posterior field, with a given dose of 2,500 rads in

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Figs. 1A and 1B. Model employed to demonstrate simulated anterior and posterior treatment fields for diffuse metastatic involvement of the bony pelvis. Note the area provided for a lead shield in the anterior field, the purpose being to reduce the dose to the small intestine.
Figs. 2A and 2B. Model employed to demonstrate simulated anterior and posterior treatment fields for metastatic involvement of the shoulder girdle with associated pathologic fractures of the ribs in the midaxillary line.

Figs. 3A and 3B. Model employed to illustrate treatment fields for the bony pelvis, spine, femora, shoulder girdle and associated ribs in the midaxillary line. (See Figs. 1A and 1B and Figs. 2A and 2B.)
Fig. 4A. Pathologic fracture before and after immobilization in a body cast for 65 days.

1 week. In the third week, both femora may be treated with a tumor dose of 1,500 rads in 5 days, provided the white blood cell and platelet counts have been adequately maintained. Alternatively, a painful shoulder joint may be treated with a tumor dose of 1,500 rads in 1 week.

PATHOLOGICAL FRACTURES

Prevention is the best treatment for pathological fractures. Moth-eaten or large lytic areas in long bones such as the femur are subject to fracture. As an immediate preventive measure, weight bearing should be relieved with a portable walker, and radiotherapy, frequently combined with adjuvant systemic therapy, should be instituted to promote recalcification. Although a tumor dose of 2,000 rads delivered in 2 weeks is satisfactory for pain, a more aggressive approach is indicated for impending fracture (a tumor dose of 3,000 rads delivered in 2 weeks, or 4,000 rads in 4 weeks).

When fractures occur, their treatment depends on the specific site. Compression fractures of vertebrae are managed with conservative measures and radiotherapy, unless there is a threat of compression of the spinal cord. In fractures of the humerus, excessive mobility at the fracture site is seldom a problem, probably because the tumor prevents undue motion. In these cases immobilization can be achieved with a bulky pressure dressing, light posterior splints or sling and swathe bandages, which are removed daily for irradiation therapy. Occasionally, internal fixation of a fracture of the humerus may be advantageous in nursing an otherwise incapacitated patient.

Pathological fractures of the femur are generally managed by internal fixation followed by irradiation therapy unless the fracture site was recently
weeks or 3,000 rads in 2 weeks. (Figs. 4A, 4B and 4C.)

Central Nervous System
BRAIN

If brain involvement is part of generalized carcinomatosis, patient survival is limited to a few weeks and local therapy is not indicated. On the other hand, a focus of tumor in the brain may be the first and only metastasis, or it may be preceded by a single nodule in the lung fields. Following treatment for control of intracranial tumor, one half of the patients will develop terminal disease in four treated. Occasionally, an impacted fracture of the femoral neck requires nothing more than a portable walker and irradiation therapy. Available hardware for internal fixation includes prostheses for the head and neck, plate and nail devices for intertrochanteric fractures and intramedullary nails for the shaft. Previous reports detail the orthopedic procedures and describe the results of 72 surgical procedures for pathological fractures in 60 patients admitted to the Medical Breast Service.1,2

Success of internal fixation depends on stabilization of the specific hardware by recalcification of the involved bone, induced by irradiation therapy and assisted by systemic therapy. Unless radiation therapy was administered before fracture, treatment should be instituted within a day or two of surgery. Again, our preference is to deliver a tumor dose of 4,000 rads in 4 weeks or 3,000 rads in 2 weeks. (Figs. 4A, 4B and 4C.)

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to twelve months; the other half may survive for several years. Treatment must, therefore, be concerned with patient selection as well as technique.

The clinical symptoms of breast cancer metastasis in the brain are the same as in all other intracranial neoplasms: headache, focal seizures, cranial nerve palsies, psychic changes, aberrant vomiting, aphasia or paresis of one or part of an extremity. All patients in whom an increase in the intracranial pressure is suspected are immediately placed on 80 mg. of prednisone daily and Dilantin®. The dose may subsequently be increased or decreased as symptoms indicate.

Routine diagnostic measures include neurological examination, electroencephalogram, isotopic brain scan, skull roentgenograms and occasionally angiography. Pneumoencephalography is performed only if craniotomy is to follow positive findings. Benign tumors, infection and vascular disease must be differentially considered.

Treatment. In our early experience, intracranial surgical exploration was performed in all clinically feasible situations. Seven of sixteen patients who had surgical procedures survived for less than three months. Only one of the sixteen survived for more than one year. The incidence of some neurological deficit was very high, as was dependency throughout survival.

For the last seven years, radiotherapy has been the local treatment for intracranial metastases of breast cancer. Patient selection is based on the observed natural growth rate of the tumor, the extent of generalized metastases and the prognosis if intracranial disease is controlled. All patients concomitantly receive corticosteroids and anticonvulsant drugs. Currently, treatment is given with Cobalt 60 instead of the 250 KV irradiation we originally used. Because metastases from breast cancer to the brain are frequently multiple, treatment is usually directed to the entire cranium. (Fig. 5.) Limited fields are used occasionally when symptoms are restricted to one or more anatomically associated cranial nerves. Since the use of prednisone, the fear of producing a sudden rise in intracranial pressure has been eliminated. Treatment is initiated with a daily tumor dose of 200 or 300 rads, depending on the overall plan.

Experience has shown that a tumor dose of 2,000 rads is ineffectual. A recommended tumor dose is 4,000 rads delivered in 4 weeks. When the patient’s life expectancy is limited, because of tumor involving other structures, an approximate radiobiological equivalent tumor dose of 3,000 rads delivered in 2 weeks is well tolerated. This shorter treatment time became possible as a result of the skin-sparing effect of Cobalt 60 and the support given with corticosteroids. In a few patients additional treatment directed to the major metastatic lesion has been given through reduced fields. The value of this “booster” tumor dose has not yet been established.

Results. Forty-five patients were treated for intracranial metastases at the time of this review. Forty-three of the forty-five obtained symptomatic relief. The median survival was five months. However, fifteen patients survived more than one year, and of these, three lived for more than three years. The only complications were the expected epilation and a serous otitis media.

Spinal Cord

The most common initial indication of an epidural lesion is intense pain which is accentuated when the patient lies down. Roentgenograms may show vertebral involvement, a paraspinous mass or no abnormality. A high index of suspicion is essential to an early diagnosis in this latter situation.
Fig. 5. Radiotherapy for multiple intracranial metastases. CO60—parallel opposed lateral fields. Tumor dose depends on prognosis.

| Poor prognosis | Good prognosis |
|----------------|----------------|
| R.D. 3,000 rads in 2 weeks | 4,000-5,000 rads in 4-5 weeks |

Fig. 6. Radiotherapy for retinal metastases. CO60—5 x 5 cm. field (approx.). Tumor dose 2,500 rads/2 weeks. Calculated at the estimated tumor site.

Whenever symptoms are suggestive of pressure on the spinal cord, especially in the dorsal and cervical segments, prompt investigation is mandatory since paraplegia can develop within 24 hours. A myelogram is essential to demonstrate the site of block. However, in early cases the myelogram may be negative. Until recently, we performed emergency laminectomy for any patient whose symptoms had progressed to paresthesias and paresis of the lower extremities with some loss of bladder function. Patients with less advanced disease whose only symptom was pain were treated with radiotherapy. However, our results with surgical decompression were disappointing: many patients became completely paraplegic in the immediate postoperative period. Our current approach is to start prednisone at a dose of 80 mg. daily with concurrent radiotherapy on an emergency basis to all patients with symptoms of cord compression. A tumor dose of 200 rads is delivered daily over 4 weeks to achieve a total tumor dose of 4,000 rads which is the tolerance level of the spinal cord.

**Retina**

Complaints of visual aberrations followed by loss of acuity are almost always diagnostic of choroidal or retinal metastases. In general, the extent of retinal detachment correlates roughly both with the degree of vision lost and with the possibility for its recovery. Approximately 50 percent of patients have bilateral lesions. As in cases of retinoblastoma, metastases in the symptomatic eye are more advanced. Small lesions may not be detectable with a direct ophthalmoscope, so that examination with a slit lamp is essential.

**Treatment.** Radiotherapy is the treatment for choroidal metastases. (Fig. 6.) Since progressive loss of vision develops rapidly, radiotherapy is instituted on an emergency basis. The recom
mended tumor dose is 2,000 to 2,500 rads delivered in 2 weeks. Occasionally, additional treatment may be necessary. Results of treatment are dependent on the initial extent of disease. Vision is usually salvaged in the patients who have small lesions and early visual changes but is seldom restored in patients with more advanced disease.

**Metastases to the Abdomen**

With the possible exception of hepatic involvement, abdominal manifestations of metastatic breast cancer are the result of diffuse lymphogenous spread. Barring early ascites, clinical evidence of abdominal carcinomatosis is a late manifestation of disseminated breast cancer. Symptoms are commonly related to ascites, or to functional intestinal obstruction secondary to diffuse infiltration of the mesentery. Occasionally retroperitoneal pain caused by extensive involvement of the paraaortic tissues, with associated partial ureteral obstruction, may be an additional problem.

Ascites is managed primarily by paracenteses and diuretics. In premenopausal women, ascites may respond dramatically for a year or longer to surgical or irradiation castration. In postmenopausal women, systemic alkylators may be effective.

Chemotherapy, for example, 5-fluorouracil, is currently the best treatment for both metastases to liver and diffuse lymphogenous spread. Adrenalectomy is rarely technically feasible and radiotherapy is seldom if ever indicated for abdominal carcinomatosis. If the pain associated with retroperitoneal metastases is not relieved by the usual analgesics it may be controlled by morphine administered parenterally at regular intervals. Chordotomy is indicated in patients with several months' life expectancy, whose pain is relieved by an adequate trial of chemotherapy.

**Miscellaneous Soft Tissue Metastases**

In addition to the sites previously described, soft tissue metastases may occur in orbit, scalp, nasal cavity, alveolar ridge or on the trunk. Adjacent bone may be secondarily invaded. Since these lesions are manifestations of advanced systemic disease, treatment is generally not indicated unless disfigurement or mechanical disability becomes a problem. When technically feasible, the most practical solution is local excision, supported by adjuvant hormonal therapy or chemotherapy. Radiotherapy is indicated for fixed lesions, or when bone or vital structures are involved.
Troublesome subcutaneous tumors in the scalp are treated with limited superficial therapy fields. No attempt should be made to include satellite nodules. Growth restraint may be achieved in small lesions with 1,500 rads in one treatment. Larger lesions should be treated with 3,000 to 4,000 rads in 3 to 8 days. Treatment of vital structures is protracted, because aggressive rapid therapy is not well tolerated. For the orbit, 4,000 rads tumor dose administered in 4 weeks through right-angled wedge Cobalt 60 fields is generally adequate. (Figs. 7A and 7B.) Local control of oral cavity lesions requires more intensive therapy with tumor doses up to 6,000 rads in 6 weeks.

**Radiation Castration**

If surgical castration is contraindicated, cessation of ovarian function can be achieved with 1,200 rads tumor dose applied over 3 consecutive days through parallel opposing anterior and posterior 15 x 15 cm. portals. If treatment is indicated for diffuse metastases throughout the bony pelvis, castration can be accomplished concomitantly, by omitting the anterior lead protection for the small intestine and administering a tumor dose of 2,000 rads in 2 weeks.

**Retreatment of Metastases**

The question of whether radiation therapy can be repeated for recurring symptomatology is dependent on the initial tumor dose. Bony metastases, treated to 2,000 rads in 2 weeks with either orthovoltage or megavoltage, can generally be retreated without undue risk. Results of retreatment are roughly related to the initial interim of remission. Soft tissue recurrences in the chest wall following intensive treatment should never be retreated because of the high risk of necrosis.

**Chest Wall Necroses**

Management of chest wall necroses is frequently superimposed on the problem of generalized metastatic disease. Necrosis is a calculated risk of any definitive radiotherapy program of primary breast cancer. An inexcusable common cause is repeated treatment for local recurrences on the chest wall. Although painful initially, necroses of ribs is seldom disabling. No treatment is indicated. Necrosis of soft tissue may be precipitated by a biopsy, or even by the rubbing of a tight garment. Extensive necroses seldom heal with conservative measures, although the rate of progression may be slowed. Local treatment is the same as for locally untreatable chest wall recurrences. Foul necrotic tissue is debrided and daily cleansing is accomplished with Dakin's solution. If after several months no tumor is observed, surgical repair should be considered. By combining the skills of the thoracic and plastic surgeons, the involved area can generally be resected and the deficit closed by a flap from the opposite breast.

**Comments and Conclusions**

Over the past 15 years, the Metastatic Breast Service, in cooperation with the Department of Radiotherapy, has endeavored to develop a practical program for the management of patients with incurable breast cancer. Because the available methods of treatment usually do not significantly alter survival of the incurable breast cancer patient, our principal aim has been to maintain her functional capacity in as normal a fashion as possible. Survival was prolonged in certain clinical situations when the local behavior of the tumor was altered by either systemic treatment or radiotherapy.

For maximum utilization of radiotherapy, standard techniques, suited to metastatic breast cancer, were developed and applied systematically as indicated by the progression of the metastatic process. The rationale and technical details of radiotherapy, together with data on supportive care when indicated, have
been presented for specific regions. Certain clinical manifestations of metastatic breast cancer, such as symptomatic involvement of the liver, did not respond to radiotherapy as expected. However, in recent years, chemotherapeutic agents have effected remarkable palliation for a number of previously unresponsive metastatic conditions.

Summary
The treatment policy for metastatic breast cancer at the M. D. Anderson Hospital combines local therapy, i.e., surgery and/or irradiation, with systemic therapy in three plans which emphasize the sequential use of agents. The choice of agents and the order of their use is dictated by the menopausal status of the patient, the biological behavior of the tumor and socioeconomic factors. Seventy-five percent of all cases receive some form of palliative radiotherapy.

Our policies, techniques and the results achieved with local management have been presented for the incurable primary lesion, chest wall recurrences, involvement of regional nodes and for distant metastases by systems. Treatment for metastases to the skeletal system has been described for the spine, pelvis, extremities, facial bones, ribs and for the surgical stabilization of fractures. Treatment for metastases to the central nervous system is described for the brain, cranial nerves, retina, spinal cord, and associated paraspinal tissues. Our experience in the management of other soft tissue sites is reported for intrathoracic and abdominal involvement including metastases to liver, scalp, orbit, etc. Final comments relate to radiation castration, retreatment of metastases, supportive medical management and management of necroses.

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