TREATMENT OF EARLY BREAST CANCER WITH PRIMARY RADIATION THERAPY: RATIONALE, RESULTS, AND TECHNIQUES

JOSEPH B. WEISSBERG, M.D., AND LEONARD R. PROSNITZ, M.D.
Department of Therapeutic Radiology
Yale University School of Medicine
New Haven, Connecticut

Halsted introduced radical mastectomy to treat breast cancer at the turn of this century.[1] Although initially designed for the treatment of locally advanced disease, radical mastectomy became the standard treatment in the United States for operable breast cancer of all stages. Particularly now that the disease more often presents in its early stages, it is important that we examine other less devastating forms of local treatment. Since McWhirter introduced simple mastectomy and postoperative radiation therapy during the mid-1940s,[2,3] interest in local treatment of breast cancer by less extensive surgery than the Halsted mastectomy has heightened. Primary radiation therapy following local excision of the breast tumor with or without axillary dissection is now an important treatment option.

Breast cancer is a heterogenous disorder, and many factors are known to influence prognosis. Among these are clinical stage, pathologic status of the axilla, histologic appearance of the tumor, and estrogen-binding characteristics of the tumor. Most reports of breast cancer treatment have separated patients only by clinical or pathological staging and have analyzed results according to stage. The TNM classification[4] is the most widely used system and the one we have employed as well. T1 lesions measure less than 2 cm., T2 lesions 2 to 5 cm., and T3 lesions are greater than 5 cm.; T4 signifies extension to the chest wall or skin. Axillary nodes may be absent (N0), present and movable (N1), or fixed (N2); N3 signifies the presence of supraclavicular nodes. Stage I lesions are T1N0, stage II lesions T1N1 or T2N0-1, and stage III lesions T3N0-3 or T1-3N2,3; stage IV lesions are metastatic (M1). Many older papers in the literature classified operable breast cancer

Address for reprint requests: Department of Therapeutic Radiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510

patients without regard to the size of the primary lesion as pathological stage I or II based on whether axillary nodes histologically contained metastatic tumor.

RATIONALE

Many studies over the years, some randomized and some not, have demonstrated equivalent results in breast cancer patients treated by radical surgery (with or without radiotherapy) or by a less extensive surgical procedure plus radiotherapy. Brinkley and Haybittle observed equivalent survival in pathologic stage II patients treated by either radical or simple mastectomy, both followed by radiotherapy.[5] A Hammersmith Trial also demonstrated equivalence of radical and simple mastectomy when followed by radiotherapy.[6] An Edinburgh Trial showed that patients with stages I, II, and early stage III disease have identical survival rates whether treated by radical mastectomy or by simple mastectomy plus radiation.[7] Kaae and Johansen from Copenhagen compared the results of extended radical mastectomy with simple mastectomy plus radiation therapy and also showed identical survival rates at follow-up periods as long as 15 years.[8] The Cardiff breast trial showed that radical and simple mastectomy were equivalent when both were followed by radiotherapy.[9] The National Surgical Adjuvant Breast Project compared radical mastectomy with simple mastectomy (with and without radiation) and found no difference in survival rates.[10] Finally, in the Manchester trial no difference was observed between radical mastectomy and simple mastectomy with or without radiation.[11]

All of these studies in essence compared radical mastectomy to a less extensive procedure combined with radiation. Both survival and local control were the same in the groups being compared. Thus, it appears that the type of local-regional treatment of breast cancer makes for the most part very little difference in outcome. Two explanations are probable. Radiotherapy effectively kills small numbers of breast cancer cells (i.e., microscopic disease) that might remain after a less extensive surgical procedure. Breast cancer is generally a systemic disease, and its prognosis is largely determined by the biological propensity for distant metastases, which is not much affected by any type of local treatment.[12]

In recognition of the lack of superiority of radical mastectomy, modified radical mastectomy has been declared the standard surgical approach in the United States to which other alternatives are to be compared.[13]

Radiation therapy, like surgery, is a local form of therapy designed to kill

cancer cells within the treatment area. It is unlikely to result in improved survival when compared with mastectomy because both are local treatments. However, radiation has a great advantage over surgery in preserving the breast and producing superior functional and cosmetic results. It is well recognized as effective therapy for many gynecologic, head and neck, and other malignancies where, in many instances, it has replaced surgery as primary treatment. If primary breast irradiation can provide local tumor control while simultaneously preserving the breast with satisfactory cosmetic results, it requires careful consideration as an alternative to mastectomy. All available radiobiological data indicate that radiation will kill breast cancer cells as readily as cells from other malignancies.

While postoperative radiation therapy in the treatment of breast cancer following mastectomy remains highly controversial, extensive experience with the technique and complications of this treatment has been accrued. Dose-response data indicate that 4,500 to 5,000 rads in four or five weeks are required to control subclinical axillary and supreclavicular lymph node metastases with greater than 90% probability, while 6,000 rads or more are required to control clinically apparent (2 or 3 cm.) masses.[14] Unfortunately, many older breast cancer trials did not carefully consider these data and used inadequate doses, inadequate fields, or both. More recent studies of primary radiation therapy have been better designed and have achieved results comparing favorably to the standard surgical procedures.

RESULTS

Radiation therapy as primary treatment for locally advanced breast cancer is well established. Radical surgery is viewed as inadequate treatment for advanced disease not only because of distant metastases but because of the frequency of local recurrence. The criteria of operability proposed by Haagensen and Stout[15] have been widely accepted. Protracted radiation techniques without mastectomy as developed by Baclesse[16] have been employed by Fletcher [17,18] with approximately 65% control of inoperable stage III breast cancers.

Primary radiation therapy without mastectomy to treat operable breast cancer has actually been used for several decades. The earliest reports are from European treatment centers, and virtually all show local control and survival rates equivalent to those obtained by radical surgery. Probably the first report is that of Mustakallio from Helsinki who, in 1954, described an 84% five-year survival in 127 patients with early stage breast cancer treated

by simple excision of the primary lesion followed by orthovoltage irradiation.[19] Doses of radiation less than 3,000 rads, however, now known to be inadequate for achieving local control, were employed, and long-term follow-up did in fact reveal a relatively high local recurrence rate of 25%.[20] Nonetheless, an observed 10-year survival of 61% was comparable to that obtained by radical mastectomy in the same institution.

Peters from Toronto in 1967 described a series of stage I and II patients treated by local resection and radiotherapy in doses of 4,500 to 5,500 rads from 1939 to 1959.[21] The local recurrence rate was approximately 5%, and five and 10-year survivals were equivalent to those obtained by radical mastectomy and postoperative irradiation. In 1971 Wise, Mason, and Ackerman[22] employed local tumor excision and radiation in doses of approximately 6,000 rads over nine weeks. They observed a local recurrence rate of 10% and five-year survivals of 95% and 71% for stage I and II patients respectively.

In the United States primary radiation therapy has been slower to gain acceptance. Among the first reports was one from Yale in 1975 of 30 patients with stages I and II breast cancer treated by primary radiation between 1960 and 1973.[23] Lumpectomy was carried out in 25 women; in the other five the diagnosis was established by needle biopsy. External beam irradiation was given by conventional fractionation in total doses of 4,500 to 5,000 rads to the entire breast and regional nodes, following which a boost dose of an additional 1,500 to 2,000 rads was administered. Boost treatment was delivered initially by interstitial implantation but more recently by electron beam therapy. This series was expanded to 83 patients in 1980.[24] Actuarial survival at five and 10 years was 91% for stage I and 86% for stage II patients. The overall local control rate was 90%. Radiation complications were few and largely reversible. These included mild pneumonitis in five patients, limitation of motion of the ipsilateral arm in three patients, rib fractures in two patients, and mild brachial plexus injury in one patient. Cosmetic results were highly satisfactory in all but two patients.

Because of the difficulty in accruing patients in any single institution, and because treatment techniques and philosophies at Yale and Harvard were similar, these two institutions undertook a cooperative venture to investigate primary radiation therapy for breast cancer. Hahnemann and Jefferson Medical Colleges in Philadelphia subsequently joined. Results from these four institutions have been published[25] but are here brought up to date.

Two hundred and ninety-three patients with stages I and II breast cancers were treated by primary radiation therapy without mastectomy. Five-year survival rates were 91% for stage I and 77% for stage II. Five-year relapse-free survival rates were 87% for stage I and 63% for stage II. Ten-year survival rates were 81% for stage I and 54% for stage II, and 10-year relapse-free survival rates were 71% for stage I and 40% for stage II.

The overall local recurrence rate, defined as tumor appearing within either the treated breast, or lymph nodes, or both, was 8%. Nineteen of 23 relapsing patients had tumor confined to the breast, two had tumor in the breast and nodes, and two in axillary lymph nodes alone. In contrast to patients who have had mastectomy, where local recurrence virtually always signifies the presence of disseminated cancer, 10 of these 23 patients have had prolonged disease-free survival following mastectomy or axillary dissection or both. Similar data concerning the more benign nature of local recurrence in patients who have had radiotherapy as primary treatment compared to those who have had mastectomy have been reported by Spitalier.[26]

There were 45 complications in 40 patients, the great majority of which were not serious. Rib fracture was most common and occurred in 11 patients. Other complications were radiation pneumonitis (seven patients), limitation of motion of the ipsilateral arm (five patients), brachial plexus injury (four patients), and excessive soft tissue fibrosis (eight patients). Brachial plexus injury was sensory only, radiation pneumonitis was reversible without residual effect in six of the seven patients, and the rib fractures healed. No fatalities were attributed to treatment.

Many other studies have been published with essentially the same results. Calle and coworkers[27] at the Foundation Curie have continued treatment of breast cancer by primary radiation therapy as initiated by Baclesse.[16] 514 patients with stages I, II, and early III breast cancers were treated from 1960 to 1970. Patients with tumors 3 cm. or less and without axillary adenopathy underwent local tumor excision followed by radiotherapy to total doses as high as 6,500 rads over six weeks. Patients with larger tumors or palpable nodes had radiotherapy without lumpectomy to doses as high as 8,500 rads over eight or nine weeks. More than half of the patients in the latter group subsequently underwent operation. Five and 10-year survivals were 85% and 75% respectively in the lumpectomy group and 68% and 43% respectively in the group undergoing radiotherapy alone. These results suggest that lumpectomy is advantageous when radiation therapy without mastectomy is undertaken.

Pierquin and coworkers[28] similarly employed primary radiation therapy following lumpectomy for stage I and early (less than 3 cm.) stage II lesions and radiotherapy alone for later stage II and early stage III tumors. They employed conventionally fractionated external beam radiation to doses of approximately 4,500 rads, following which boost irradiation was delivered by interstitial iridium[192] to total tumor doses as high as 9,500 rads. Five-year survival rates were 84% for T1, 79% for T2, and 56% for T3 tumors. Radiation complications were few and cosmetic results highly satisfactory.

At the M.D. Anderson Hospital, 162 patients with early stage breast cancer have been treated by either lumpectomy or segmental mastectomy with or without axillary dissection followed by radiation therapy.[29] The local and regional control rate was 96%. Chu and associates reported 85 patients with stage I and II breast cancer treated by primary radiation therapy without mastectomy at the Massachusetts General Hospital between 1956 and 1974.[30] The five-year survival rates were 83% and 76% for stages I and II respectively, and did not differ significantly from the results of a radical mastectomy series at the same institution. These authors emphasized the importance of technique in the avoidance of even minor complications.

All the above studies have been nonrandom collections of patients. Taken together, however, they seem to indicate high local control rates, good to excellent cosmetic results, few complications, and survival equivalent to that of patients treated with mastectomy. It should be remembered that modified radical mastectomy, the procedure recommended by the National Cancer Institute consensus committee, has *never* been compared to the radical mastectomy in a randomized trial.

An early randomized trial of primary radiation therapy versus mastectomy at Guy's Hospital[31] showed equivalent survival of stage I patients but decreased survival in stage II patients undergoing radiation when compared to mastectomy. The trial has been criticized, however, on the basis of inadequate doses of radiation (2,500 to 3,000 rads orthovoltage radiation in three weeks). Three randomized trials are currently in progress (National Cancer Institute, Milan, National Surgical Adjuvant Breast Project, and National Cancer Institute, Bethesda). The largest of these, the Milan trial, has accrued approximately 700 patients and at five years shows no difference between radiated patients and those treated primarily with mastectomy.[32]

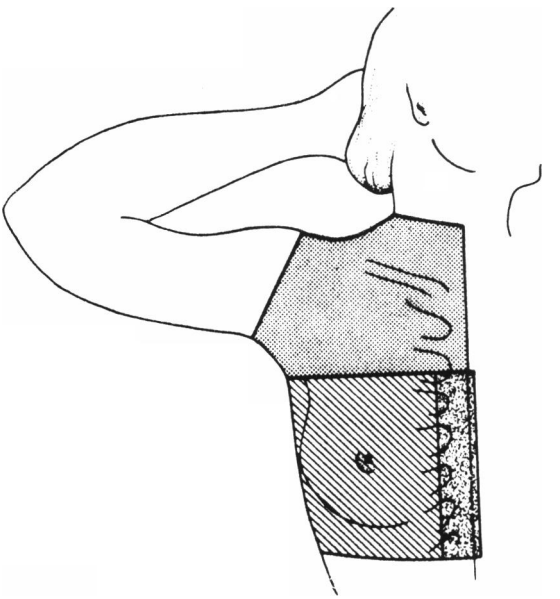
TECHNIQUE AND CURRENT APPROACHES

Primary radiation therapy is offered to patients with operable breast can-

cer (stages I, II, and early III) as an alternative to conventional mastectomy. Excisional biopsy is an integral part of this procedure and is necessary to produce the highest degree of local control with the best cosmetic result. It is not necessary to remove a large amount of normal breast tissue with the tumor, because radiation stands a high probability of killing any cells left behind. Only the tumor with a very small margin of normal tissue need be removed. If the tumor size relative to the breast size, however, is such that removal of the tumor will produce a significant distortion in the breast that remains, primary radiation is probably not worthwhile but mastectomy should be performed. Mastectomy is also recommended for women with large and pendulous breasts because these patients have a more severe radiation reaction, both acute and chronic, and will often have a long-term cosmetic result not nearly as satisfactory as thinner patients.

If information about the histological status of the axillary lymph nodes is desired, axillary dissection or axillary sampling may be carried out at the same time as the excisional biopsy or as a separate procedure. It is not necessary, of course, to do a mastectomy to do an axillary dissection. A decision regarding adjuvant chemotherapy can then be made on the basis of information obtained from the axillary dissection, as well as from other relevant prognostic factors. The axilla should always be dissected if clinically suspicious nodes are palpated and appear to be resectable, because otherwise there is a high risk of axillary injury with doses of radiation necessary to control palpable disease (i.e., 6,000 rads or more).

Patients undergoing primary radiotherapy receive a dose of 4,500 to 5,000 rads over five weeks time, five fractions weekly, administered to the entire breast. This is the dose of radiation necessary to control microscopic disease, so-called sublinical disease. If there has been no axillary sampling or dissection, then axillary, supraclavicular, and internal mammary nodes are also treated. If axillary dissection has been carried out, the axilla is subsequently excluded from the radiation field, regardless of the findings at the time of operation because the risk of arm edema is considerably enhanced if the axilla is irradiated after surgery. In a few cases, for example, if gross residual tumor has been left behind, the axilla is irradiated. If the axillary nodes contain metastases, supraclavicular and internal mammary nodes are irradiated. If axillary nodes histologically contain no metastases and if the primary lesion is located in the lateral half of the breast, none of the nodes are treated. If the primary lesion is in the medial half of the breast, supraclavicular and internal mammary nodes are irradiated despite histologically negative axillary nodes.



Schematic representation of the treatment fields for primary breast radiation therapy

The treatment fields are shown diagramatically in the figure. It can readily be seen from the figure and from the above discussion that the treatment volume in most patients is quite extensive, in fact, the radiotherapeutic equivalent of an extended radical mastectomy. The wisdom of treating such extensive fields is another complex subject, for which we do not have sufficient space. There are many fine points of technique, also beyond the scope of this paper, to which attention must be paid if the cosmetic result is to be optimal and the long-term complications minimal. Careful treatment planning is necessary to deliver a homogenous dose throughout the treatment volume. Ideally, treatment of these patients should be carried out in a center with some experience in this technique.

Following completion of the large field external beam therapy, a boost dose is administered to the area where the primary tumor was originally located. The volume of the boost dose should be no more than one quarter to one third of the breast itself. This should more than adequately cover the great majority of the tumors that we consider suitable for primary radiation in the first place. The boost may be carried out either by electron beam treatment with a direct en face field or by a two plane interstitial iridium implant. The purpose of administering the boost dose by either of these

modalities is to minimize the volume being treated and to avoid completely any damage to the underlying tissues. According to radiobiologic theory, the boost dose is probably not necessary because the external beam dose of 4,500 to 5,000 rads should be sufficient for control of microscopic disease. However, it carries very little morbidity and it is our policy to administer a boost dose in almost all cases.

Delivering the boost by external beam is generally a very simple outpatient procedure. The patient is usually given an additional 1,600 to 2,000 rads in fractions of 200 rads each. In contrast, the iridium implant is usually performed under general anesthesia and requires hospitalization for two to four days. Both appear to produce satisfactory end results as far as tumor control and treatment complications are concerned.

CONCLUSIONS

Many studies have confirmed the equivalence of the traditional Halsted radical mastectomy and less extensive surgical procedures in the treatment of operable breast cancer. Primary radiation therapy without mastectomy has been carried out for many years but is only recently gaining acceptance in this country. Results of many series to date suggest that cure rates with primary irradiation following local tumor excision are equivalent to those obtained by mastectomy. The cosmetic and functional results are clearly superior. Randomized clinical trials are currently in progress to assess the role of radiation in the treatment of early breast cancer. It is hoped that the increased application of radiation therapy in the treatment of breast cancer will provide incentive for earlier diagnosis and hence increased cure rates among women for whom the fear of mastectomy has been lessened.

REFERENCES

1. Halsted, W.: The treatment of wounds with especial reference to the value of blood clot in the management of dead space. IV. Operations for carcinoma of the breast. *Johns Hopkins Hosp. Ref. 2:* 255-75, 1891.
2. McWhirter, R.: Cancer of the breast. *Amer. J. Roentgenol. 62:* 335-40, 1949.
3. McWhirter, R.: Simple mastectomy and radiotherapy in the treatment of breast cancer. *Br. J. Radiol. 28:* 128-39, 1955.
4. Union Internationale Contre le Cancer (UICC): *TNM Classification of Malignant Tumors,* 2nd ed., Geneva, UICC, 1974.
5. Brinkley, D. and Haybittle, J.L.: Treatment of stage II carcinoma of the female breast. *Lancet 2:* 1086-87, 1971.
6. Burn, J.I.: Early breast cancer: The Hammersmith trial, an interim report. *Br. J. Surg. 61:* 762-65, 1974.
7. Hamilton, T., Laughlands, A.O., and

Prescott, R.J.: The treatment of operable cancer of the breast: a clinical trial in the southeast region of Scotland. *Br. J. Surg. 61:* 758-61, 1974.
8. Kaae, S. and Johansen, H.: Does simple mastectomy followed by irradiation offer survival comparable to radical procedures? *Int. J. Rad. Oncol. Biol. Phys. 2:* 1163-66, 1977.
9. Forrest, A.P.M., Roberts, M.M., Cant, E.L.M., et al.: Simple mastectomy and pectoral node biopsy: the Cardiff-St. Mary's trial. *World J. Surg. 1:* 320-23, 1977.
10. Fisher, B., Montague, E., Redmond, C., et al.: Comparison of radical mastectomy with alternative treatments for primary breast cancer. A first report of results from a prospective randomized clinical trial. *Cancer 39:* 2827-39, 1977.
11. Lythgoe, J.P., Leck, I., and Swindell, R.: Manchester Regional Breast Study: preliminary results. *Lancet 1:* 744-47, 1978.
12. Fisher, B.: Breast cancer management. Alternatives to radical mastectomy. *N. Engl. J. Med. 301:*326-28, 1979.
13. Treatment of primary breast cancer (special report). *N. Engl. J. Med. 301:* 340, 1979.
14. Fletcher, G.H.: Clinical dose-response curves of human malignant epithelial tumors. *Br. J. Radiol. 46:* 1-12, 1973.
15. Haagensen, C.D. and Stout, A.P.: Carcinoma of the breast. II. Criteria of operability. *Ann. Surg. 118:* 859-70, 1943.
16. Baclesse, F.: Roentgen therapy as the sole method of treatment of cancer of the breast. *Am. J. Roentgen. 62:* 311-19, 1949.
17. Fletcher, G.H.: Local results of irradiation in the primary management of localized breast cancer. *Cancer 29:* 545-51, 1972.
18. Fletcher, G. H. and Montague, E. D.: Radical irradiation of advanced breast cancer. *Am. J. Roentgen. 93:* 573-84, 1973.
19. Mustakallio, S.: Treatment of breast cancer by tumor extirpation and roentgen therapy instead of radical operation. *J. Fac. Radiol. 6:* 23-26, 1954.
20. Mustakallio, S.: Conservative treatment of breast cancer. Review of 25 years following. *Clin. Radiol. 23:* 110-16, 1972.
21. Peters, M.V.: Wedge resection and irradiation — an effective treatment in early breast cancer. *J.A.M.A. 200:* 18-21, 1967.
22. Wise, L., Mason, A.Y., and Ackerman, L.V.: Local excision and irradiation: an alternative method for the treatment of early mammary cancer. *Ann. Surg. 174:* 392-401, 1971.
23. Prosnitz, L. R. and Goldenberg, I. S.: Radiation therapy as primary treatment for early stage carcinoma of the breast. *Cancer 35:* 1587-96, 1975.
24. Goldenberg, I.S., Prosnitz, L.R., and Peters, L.: Local excision and radiation therapy for early stage breast cancer. *Surg. Clin. N.A. 60:* 1179-86, 1980.
25. Prosnitz, L.R., Goldenberg, I.S., Harris, J., et al.: Primary radiotherapy for stage I and II breast cancer: following report from four east coast university hospitals. *Int. J. Rad. Oncol. Biol. Phys. 6:* 1339-40, 1980.
26. Spitalier, J., Brandone, H., Ayme, Y., et al.: Cesium therapy of breast cancer. A five year report on 400 consecutive patients. *Int. J. Rad. Oncol. Biol. Phys. 5:*231-35, 1977.
27. Calle, R., Pilleron, J.P., Schlienger, P., and Vilcoq, Jr.: Conservative management of operable breast cancer: ten year experience at the Foundation Curie. *Cancer 42:* 2045-53, 1978.
28. Pierquin, B., Owen, R., Maylin, C., et al.: Radical radiation therapy of breast cancer. *Int. J. Rad. Oncol. Biol. Phys. 6:* 17-24, 1980.
29. Montague, E.D., Gutierrez, A.E., Barker, J.L., et al.: Conservation surgery and irradiation for the treatment of favorable breast cancer. *Cancer 43:* 1058-61, 1979.
30. Chu, A.M., Cope, O., Russo, R., et al.: Treatment of early stage breast cancer by limited surgery and radical irradiation. *Int. J. Rad. Oncol. Biol. Phys. 6:* 25-30, 1980.
31. Atkins, H., Hayward, J.L., Klugman,

D.J., and Wayte, A.B.: Treatment of early breast cancer: a report after 10 years of a clinical trial. *Brit. Med. J. 2:* 423-29, 1972.

32. Veronesi, U., Saccozzi, R., Del Vecchio, M., et al.: Comparing radical mastectomy with quandrandectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N. Engl. J. Med. 305:* 6-11, 1981.

ERRATA

The following corrections apply to the articles in the December 1981 issue:

p. 911. Table III. In the column indicating virus quantities in secretions, the last figure should be: >1,000.

p. 979. Table I. The fifth compound in the last column should be: 1,2 Dichloroethane.

p. 981. The fifth sentence of the paragraph on aromatic hydrocarbons should read: It is in paints, varnishes, glues, enamels, and lacquers.

p. 1030. The equation describing indoor concentration of contaminants should read:

$$C_s = \frac{V_o C_o + N_p}{\frac{V_r E}{100} + V_e + N_s}$$

p. 1045. The removal constant and ventilation constant are incorrectly represented in the text by T_r and T_v, respectively. They should be: τ_r and τ_v, as in Figure 6.