Adjuvant Therapy of Breast Cancer

An Overview

Seymour H. Levitt and B. J. Kennedy

From the Department of Therapeutic Radiology—Radiation Oncology (S. H. Levitt) and Department of Medicine (B. J. Kennedy), University of Minnesota, Minneapolis, Minnesota, USA

Correspondence to: Seymour H. Levitt, MD, Professor and Head, Department of Therapeutic Radiology—Radiation Oncology, Box 494, UMHC University of Minnesota, 420 Delaware Street, SE Minneapolis, Minnesota 55455-0110, USA. Fax: 612-626-7060

Acta Oncologica Vol. 37, No. 5, pp. 403–409, 1998

Adjuvant therapy in the treatment of breast cancer commonly refers to therapies that supplement primary treatment, traditionally mastectomy and, more recently, breast-conserving surgery. The present paper examines the evolution of systemic therapies and radiotherapy in their role as adjuvants to mastectomy, and offers a brief description of current treatment regimens for early and locally advanced disease.

Received 13 November 1997
Accepted 17 November 1997

Adjuvant therapy in the treatment of breast cancer commonly refers to therapies that supplement primary treatment, traditionally mastectomy and, more recently, breast-conserving surgery. Postmastectomy adjuvant therapies include systemic chemical and hormonal therapies, as well as loco-regional radiotherapy. Implicit in an examination of the role that each of these adjuvants may play in the treatment of breast cancer is an understanding of the mechanisms of the disease. The widely held belief that all breast cancer is a systemic disease coheres with the current emphasis on the importance of systemic therapies for disease control and cure. The growing recognition that some early disease is localized, however, has resurrected the importance of controlling local disease and therefore the essential role of radiotherapy.

This paper examines the evolution of systemic therapies and radiotherapy in their role as adjuvants to mastectomy. We have limited this discussion to adjuvant therapy associated with mastectomy, and do not discuss the issues pertaining to breast-conservation surgery. Despite the well-established evidence that breast-conserving surgery is a viable, and often preferred, treatment of choice for many women with early breast cancer, mastectomy is still commonly used and issues of adjuvant therapies in this setting remain important to the optimal care of these patients.

Although we use the term adjuvant as it is commonly understood, we also want to draw attention to the fact that just as treatment has evolved, so too has the term adjuvant itself. No longer is it accurate to limit our understanding of adjuvant to systemic therapies or radiotherapy, since current and investigational treatment includes regimens that, for example, use induction chemotherapy prior to surgery. Given this understanding of the changing concept of adjuvant, we attempt to provide a context in which to describe the current treatment options for breast cancer management. To that end, a brief summary of the development of systemic therapies and radiotherapy is given followed by a description of treatment options according to disease stage.

SYSTEMIC THERAPIES

Recommendations from the recent conference on adjuvant therapy of primary breast cancer held in St. Gallen, Switzerland confirmed the now essential role of adjuvant systemic therapies in the treatment of most women with breast cancer (1). This follows the publication of the 1992 worldwide overview on systemic treatment of early breast cancer, which showed decreased mortality in lymph node-negative and positive patients treated by ovarian oblation, tamoxifen, or chemotherapy after mastectomy (2). With this publication, all current randomized trials on mastectomy, as well as on conservative surgery, now include systemic therapies as an essential aspect of treatment.

 ISSN 0284-186X

Hormonal suppression

Hormonal suppression was the first systemic approach used as an adjuvant to mastectomy, initially, like chemotherapy, for the treatment of metastatic disease. Early studies of the effects of hormonal suppression by surgery (ovariectomy) indicated a benefit to patients with advanced primary, recurrent, or distant metastatic disease (3, 4). Irradiation also was shown to elicit an artificial menopause in inoperable breast cancer (5). Because of the success of ovarian ablation on metastatic disease, its use as a preventative treatment against disease recurrence was considered. In 1934, ovarian ablation was introduced as routine therapy along with radical mastectomy to inhibit metastatic disease (6). The term 'prophylactic' artificial menopause was coined, and by 1957, prophylactic ovariectomy was considered to delay the onset of recurrence and to prolong life (7). However, based on a study that showed no survival difference between prophylactic ovariectomy and ovarian ablation at the time of recurrence (8), there followed a marked cessation of the use of prophylactic ovariectomy for many years.

Another method of hormonal suppression of cancer was introduced during the 1960s with the finding that administered estrogen or androgen hormones produced regression of metastatic breast cancer. Early studies comparing the effect of estrogen and androgen hormones on metastatic disease regression revealed that androgenic hormones were not as effective as estrogenic hormones in postmenopausal women with metastatic breast cancer. Those patients with inoperable primary lesions and local spread had higher response rates than patients with osseous or visceral metastases (9). Early studies demonstrated that surgical procedures were considered of possible curative value and, certainly, of palliative benefit in isolated instances of advanced primary cancer of the breast of which hormonal therapy was initially effective. Therefore, it was thought that absolute survival rates could be improved if hormonal therapy was administered prior to mastectomy in postmenopausal women with stage II breast cancer (10).

The estrogen antagonist, tamoxifen, was introduced as an effective anti-breast cancer agent over 20 years ago and has evolved as one of the current treatment options for subgroups of breast cancer patients. Initial reports showed that tumors containing estrogen receptors and those that responded to previous hormonal manipulation were most likely to respond to tamoxifen in a range of 60–70% (11). Patients with receptor-negative tumors or with a history of failure of previous hormonal treatments did not respond to tamoxifen therapy. Women with estrogen receptor-positive tumors and with therapy duration of at least five years were found to benefit the most from tamoxifen in terms of reduced relapse and mortality rates. Comparison of diethylstilbestrol versus tamoxifen in postmenopausal women revealed that the antitumor response was similar, but tamoxifen had fewer side-effects (12). Other benefits include low cost and easy administration. In a 1995 consensus panel, tamoxifen was regarded as the adjuvant treatment of choice for all estrogen receptor-positive, node-positive, postmenopausal patients and all elderly patients. In premenopausal patients with receptor-positive tumors undergoing adjuvant chemotherapy, follow-up treatment with tamoxifen was recommended (13). Tamoxifen is now used in postmenopausal patients, receptor-positive where the lesions are greater than 1 cm (stage I). Since it reduces the risk of new contralateral cancers, tamoxifen is currently being evaluated as a preventive agent in women at high risk for breast cancer (14). The benefit from adjuvant hormonal therapy in smaller lesions is negligible.

Long-term data on the effects of ovarian ablation, whether by surgery, irradiation, or chemical suppression, from the Early Breast Cancer Trialists' Collaborative Group overview of ovarian ablation in early breast cancer indicate significant recurrence-free and overall survival among women under 50 years old treated by ovarian ablation after 15 years of follow-up. No similar significant benefits have been found in women older than 50 years (15).

Cytotoxic chemotherapy

Early studies on chemotherapy demonstrated the value of chemotherapy in the treatment of metastatic breast cancer. Similar to hormonal therapy, the success of adjuvant chemotherapy for advanced disease initiated its use for early disease. Over 20 years ago, two major reports began the era of chemotherapy following modified mastectomy or lumpectomy with radiotherapy for women with early breast cancer (16, 17). The survival advantage in premenopausal node-positive patients reported in these studies resulted in both a consensus statement by the National Cancer Institute that advocated for the standard use of chemotherapy in this subgroup of patients (18) and a change in the perception of the disease itself from one that was sometimes localized to one that was always systemic (19). Based on these changes in disease perception and treatment, past and current chemotherapy studies have looked at the benefits of chemotherapy in other subgroups of women, such as node-negative premenopausal women and postmenopausal women. Results from the 1992 overview of systemic therapies expanded the benefits of chemotherapy to include node-negative disease (2). Still questioned, however, is whether women with negative nodes and lesions of 1 cm or less benefit from adjuvant chemotherapy. Currently, the most effective drug combinations to treat premenopausal women with breast cancer are 5-fluorouracil, methotrexate, cyclophosphamide or doxorubicin (CMF or CAF).

For other subgroups of women, different combinations of treatment modalities have evolved as a further develop-

ment in the role of chemotherapy in breast cancer management. Induction chemotherapy (preoperative chemotherapy) is now used for subgroups of patients with large tumors (greater than 5 cm) based on the idea developed earlier in hormonal studies that reducing tumor size prior to surgery predicted increased survival rates. Data have verified this theory as reported in a recent study of the National Surgical Adjuvant Breast and Bowel Project B-18 in which survival was improved in women with tumors greater than 5 cm given preoperative chemotherapy followed by lumpectomy and radiation (20). For postmenopausal women, the combination of hormonal therapies and chemotherapy are being studied for their combined benefits versus either modality alone. The combination of postmastectomy radiotherapy and chemotherapy for premenopausal women, node-negative or positive, continues to be examined, as will be discussed in the following section on postmastectomy radiotherapy. Continuing development of chemotherapy combinations involving new agents (e.g., toxanes, biphosphonates, tamoxifen analogs) will add to the complexities of the best sequential use of the three major treatment modalities.

New approaches to drug therapy of breast cancer involve strategies to increase dose intensity, which include dose escalations, dose density, scheduling, and the use of cytokines (G-CSF). Other new modalities may include inhibitors of cancer cell proliferation, exploitation of growth factor receptors, monoclonal antibodies, immunology, and vaccines, among many (21). The integration of such new additions to the management of breast cancer emphasizes the potential of systemic therapies.

POSTMASTECTOMY RADIOTHERAPY

The role of postmastectomy radiotherapy has gone through several changes over the years. Up until 1954, irradiation as an adjuvant to mastectomy was considered unquestioned standard practice. Beginning with studies by Patterson in the 1950s (22) that showed no improvement in survival and possibly a decrease in survival in younger women treated with irradiation, the role of radiotherapy came under scrutiny. Various factors converged in the 1970s and 1980s to challenge the belief that adjuvant radiotherapy was an essential part of treatment. Early overview studies on postoperative irradiation by Stjernswärd in the 1970s (23) introduced the first skepticism on the role of postmastectomy irradiation. The decreased survival in the irradiated patients versus nonirradiated patients found in those studies was later confirmed in a 1987 meta-analysis by Cuzick et al. (24). Studies emerging during this period on the beneficial effects of systemic therapies and on the perception that the disease is always systemic further put into question the relevancy of local regional control and radiotherapy as an integral part of treatment (16, 17, 25).

Critiques of these early trials, however, revealed errors in trial design and interpretation that invalidated the results of these trials (26). More recent updates of these early trials have recognized that such factors as competing risks and radiation technique need to be considered to glean a better understanding of the true benefits of radiotherapy (27–30). A study using a competing risk approach to analyze the Stockholm trial of patients randomized to pre- or postmastectomy irradiation or no irradiation found a significant reduction in the cumulative incidence of local failure and overall cumulative incidence of distant metastaseses after 15 years in the irradiated patients with positive axillary nodes. A 10-year 2% and a 15-year 4% survival benefit was found for node-negative patients receiving postmastectomy irradiation. For node-positive patients, the improved survival rates were 6% and 9% at 10 and 15 years, respectively (29). The consideration of preoperative irradiation was tested in this trial and found not to confer better survival than postoperative irradiation (31).

The influence of radiation technique on previous trial results is highlighted by the 1994 updated meta-analysis by Cuzick et al., who looked at the specific causes of death in most of the trials included in the original analysis. The effect of outdated radiation technique in several of the included trials, which increased the number of cardiac deaths in the irradiated patients, was found as effecting the earlier conclusions of the detrimental effects of irradation. The previously reported significant increase in mortality in the irradiated patients was not longer evident in this update. Given the use of modern radiation technique and the decreased cardiac mortality associated with it, the authors concluded that radiotherapy may have a benefit beyond local control (28). The benefits to local and distant disease control as well as to survival with modern radiation technique was also reported in a combined analysis of Oslo and Stockholm trials. Node-positive patients treated with adjuvant postoperative megavoltage irradiation, which included the internal mammary chain, had a significant 37% relative reduction of distant metastases ($p < 0.01$) and a 22% relative reduction of deaths of borderline significance ($p = 0.06$) versus the non-irradiation patients. Adjuvant systemic therapy was not included in these trials (30).

Postmastectomy radiation continues to provide optimal loco-regional disease control in many patients. For early disease (stages I and II), nodal irradiation is used as needed, primarily in women with positive nodes and or lesions between 2 and 5 cm. For locally advanced disease (stage III), chest wall irradiation is added to nodal irradiation. A more detailed description of radiation technique is beyond the scope of this paper, but is well described in '*Levitt and Tapley's Technological Basis of Radiation Therapy*' (32). Following is a brief description of current clinical approaches to the treatment of early and locally advanced disease.

CURRENT TREATMENT REGIMENS BY DISEASE STAGE

Early breast cancer (stage I and II)

Adjuvant therapy after mastectomy is not routinely included in the treatment of premenopausal patients with node negative disease and lesions less that 1 cm (stage I disease). Adjuvant chemotherapy may be included if various prognostic factors indicate an increased risk of recurrence. For stage I patients with lesions of 1–2 cm, adjuvant chemotherapy is fairly standard.

For stage II patients with lesions of 2–5 cm and/or node positive, adjuvant chemotherapy has been shown to prolong disease-free survival, especially in premenopausal patients treated with CMF (or CAF). Adjuvant nodal irradiation is sometimes included if the nodes are positive, as well as chest wall irradiation for larger tumors or close margins. In those patients with estrogen receptor-positive tumors, the subsequent use of tamoxifen is employed for at least five years. In postmenopausal patients with stage II disease, adjuvant chemotherapy is now recommended as well, especially in those patients with aggressive, high-risk, receptor-negative tumors. In this older age group, comorbid diseases need to be considered in selecting an appropriate treatment program.

For subgroups of women at high risk of recurrence, the addition of nodal and chest wall irradiation to systemic therapy is indicated. Studies show a 10% rate of loco-regional recurrence in patients with 1–3 positive nodes treated with chemotherapy alone compared with a 20 to 30% rate in patients with four or more positive nodes and primary tumor of 5 cm or larger (33–35). For these high-risk women, combination chemotherapy and radiotherapy has shown important benefits to loco-regional control, disease-free survival, and overall survival over either adjuvant modality alone (36, 37).

Two recently published long-term studies on combined adjuvant chemotherapy and radiotherapy confirm the benefit of this combined modality regimen in high-risk premenopausal women. The Danish Breast Cancer Cooperative Group study reported a significant reduction in loco-regional recurrence alone or with distant metastases with the addition of nodal and chest wall irradiation to CMF versus CMF alone (9% vs 32%; $p < 0.001$). Disease-free survival after 10 years was 48% versus 34% ($p < 0.001$) respectively. New to these updated results was the significant benefit to overall survival with the addition of radiotherapy to CMF (54% versus 45% for CMF alone; $p < 0.001$). Most of the patients in this study had stage II disease, with about 14% stage III patients (36). Similar findings were reported in the 15-year follow-up report of the British Columbia study on node-positive premenopausal women, which included only stage I and II patients (37). The addition of radiotherapy (nodal and chest wall) to chemotherapy versus chemotherapy alone in these patients resulted in improved disease-free survival (50% vs 33%, $p < 0.007$), survival free of systemic disease (51% vs 34%, $p < 0.006$), survival free of loco-regional disease (87% vs 67%, $p < 0.003$), breast-cancer-specific survival (57% vs 47%, $p < 0.05$), and overall survival (54% vs 46%, $p < 0.07$).

The proper sequencing of radiotherapy and chemotherapy after surgery has not been explored in mastectomy trials, but useful information can be gleaned from studies on breast conservation surgery. In a randomized study by the Joint Center for Radiation Therapy, stage I and II patients considered at increased risk of systemic metastases (i.e., nearly all the patients had positive nodes) were randomized after breast-conserving surgery to receive a 12-week course of chemotherapy either before or after radiotherapy (38). With a median follow-up in surviving patients of 58 months, the authors found an increased risk of local recurrence in the group who received chemotherapy first (14% vs 5%) and an increased risk of distance recurrence in the group who received radiotherapy first (32% vs 20%). These results suggest that a 12-week course of chemotherapy before radiotherapy may provide better outcome for patients at increased risk for systemic metastases.

Although the possible detrimental effects of delaying radiation was not addressed in this study, an earlier study by the same authors found that delaying radiation for more than 16 weeks after surgery resulted in a 5-year 28% actuarial local failure rate versus 5% in patients treated within 16 weeks (39). Similarly, another study reported a significant increase in the relapse rate at 5 years for women in whom radiation was not delivered until 120 days after surgery (40). Other studies, however, report no difference in local control based on the timing of radiation delivery (41, 42). As of yet, optimal sequencing and timing of radiation and chemotherapy after surgery remains controversial.

Locally advanced disease

For locally advanced disease, the combination of radiotherapy with surgery and chemotherapy provides optimal treatment results. In an important retrospective study by Perez and his colleagues, this triple-modality approach was shown to be superior to other combined treatments. Loco-regional tumor control at 5 years for combined chemotherapy, radiotherapy, and mastectomy was 91%, 80% for irradiation and mastectomy, 54% for irradiation and chemotherapy, and 31% for irradiation alone. Corresponding actuarial 5-year disease-free survival rates were 36%, 19%, 10%, and 11% (43). The improved results when induction chemotherapy or irradiation was given prior to mastectomy confirm the important role of induction chemotherapy in the treatment of locally advanced disease. The best way to combine mastectomy and radiation after primary chemotherapy for locally advanced disease re-

mains unresolved. Many centers perform surgery first after chemotherapy, and reserve radiotherapy to the chest wall and nodal areas until the completion of chemotherapy. Results from the National Cancer Institute of Italy and MD Anderson Cancer Center suggest the inclusion of maintenance chemotherapy after this regimen improves outcome (44).

Another treatment approach for advanced disease under investigation is the combination of breast conserving therapy followed by radiation and chemotherapy for carefully selected patients. Studies from MD Anderson show less than 10% local recurrence rates in carefully selected patients who respond well to systemic chemotherapy (45). In these studies, patient selection for breast conserving therapy after neoadjuvant chemotherapy was based on tumor size (solitary primary of 4 cm or less or two primaries within a sphere of 4 cm), the absence of skin involvement or fixation to the chest wall, a tumor to breast ratio favorable for cosmetic outcomes, no palpable or small, low, mobile axillary lymph nodes, the absence of collagen vascular disease, and no extensive lymphatic involvement in the breast (45). Total excision of the gross tumor in these patients allowed for reduced radiation dose to avoid cosmetic complications. Other studies also indicate breast conserving therapy for some patients with locally advanced disease, although recommendations for standard care in these patients must await long-term results.

The combined use of radiation and autologous bone marrow transplantation after conventional or high-dose chemotherapy is another treatment under investigation for advanced disease. Early results from a pilot study by the Cancer and Leukemia Group B of stage II and III patients with 10 or more positive nodes treated by mastectomy followed by conventional dose plus high dose chemotherapy with autologous bone marrow transplantation and radiotherapy have indicated that the addition of radiation is required to lower the frequency of chest wall and regional lymph node recurrence (46, 47).

COMPLICATIONS OF ADJUVANT THERAPIES

Systemic therapies

Chemotherapy. Acute complications following chemotherapy range from lethal toxicity, which is highly uncommon, to less dangerous and bothersome side-effects such as alopecia, nausea and vomiting, weight gain, neutropenia, and fatigue (48). Major long-term complications may include cardiac dysfunction, premature menopause, and second malignancies, all of which are very uncommon. The incidence of cardiac dysfunction may vary according to the total cumulative dose received and perhaps according to the peak blood levels in patients treated with doxorubicin-based chemotherapy. A cumulative dose of 300 mg/m^2 or less seems to correlate with a low incidence of acute doxorubicin-induced cardiomyopathy. Premature menopause associated with chemotherapy-induced amenorrhea has an overall incidence of about 70% (49, 50). For high-risk patients, this may be a beneficial side-effect that reduces the risk of recurrence. In low-risk patients, however, the potential problems of increased risk of premature osteoporosis and cardiovascular disease associated with premature menopause may offset the benefit of adjuvant therapy in these patients. Second malignancies, notably increased risk of myeloproliferative disease and acute leukemia, are well-established potential complications following chemotherapy associated with cumulative dose and type of alkylating agent used. The risk of leukemia has been reduced under the current use of CMF or other cyclophosphamide-containing treatment regimens.

Tamoxifen. Most women endure tamoxifen well. The most frequent complications following tamoxifen relate to menopausal symptoms, such as hot flashes and irregular menses. Other reported complications are rare. The risk of developing endometrial cancer may increase over time (48). Adequate monitoring of the patient during tamoxifen and chemotherapy treatments can prevent or decrease many of the side-effects of treatment.

Radiotherapy

Short-term acute complications following modern radiotherapy, such as erythema, edema, and mild tiredness, become neither chronic nor life-threatening. Chronic more serious conditions, such as arm edema, decreased arm mobility, soft tissue necrosis, rib fractures, radiation pneumonitis, and brachial plexopathy are possible but occur very infrequently with appropriate radiation technique (51). Cardiac morbidity and carcinogenesis, two major complications prior to modern radiotherapy, have been minimized by improved radiation technique. Cause-specific mortality assessed in the updated Cuzick meta-analysis showed that cardiac deaths accounted for increased mortality in the older trials that used orthvoltage techniques (28). Trials that use current modern megavoltage technique do not indicate increased cardiac morbidity or mortality (30). Patients at most risk of cardiac mortality were those who received the highest volume of irradiation to the heart (52). A recent examination of these patients found that cardiac radiation dose volume can be reduced by the use of individual CT-based dose planning that allows for a direct evaluation of the heart volume included in the radiation fields (53).

A substantial decrease in the risk of radiation-induced carcinogenesis, including sarcomas, leukemia, and lung cancer, has occurred with the current technique to treat only the breast tangential fields. The excess risk of death due to a radiation-induced cardiac morality or secondary cancers is estimated to be less than 1% among breast cancer patients treated with radiation. Patients younger than 45 at diagnosis and treatment carry a higher risk of radiation-related contralateral breast cancer, whereas patients over 45 carry little, if any, risk (54, 55).

CONCLUSION

The management of primary breast cancer has evolved to include various combinations of treatment modalities. Combinations of surgery, radiotherapy, and systemic therapies have resulted in multiple alternatives to the approach to the treatment of breast cancer depending on disease stage, patient age and menopausal status, histologic definition and biologic characteristics of the tumor. All three of these major components of treatment—surgery, radiotherapy, and systemic therapies—have a significant role in the control and cure of breast cancer. Each may be the initial method of management, and each may therefore be an adjuvant to one or both of the remaining modalities. Therefore, the term 'adjuvant' is becoming less appropriate and applicable in the current management of breast cancer. More emphasis on the specific management of the defined cancer entity may allow for a more desirable therapeutic approach and result in the ultimate cure of breast cancer. To this end, the importance of adequate and appropriate therapeutic technique cannot be overemphasized. All three modalities require a great deal of clinical knowledge, and surgeons, medical oncologists, and radiation oncologists each must be highly trained in the craft of their discipline.

To achieve the best therapeutic approach, several questions still need to be answered: Should premenopausal patients with lesions less than 1 cm be treated with adjuvant chemotherapy? Is chemotherapy plus tamoxifen more effective than tamoxifen alone in postmenopausal women? Should postmastecomy radiotherapy be given to patients with three or less positive nodes or with lesions less than 1 cm? These questions indicate the direction of breast cancer research, much of which is aimed at identifying subgroups of patients at increased risk of recurrence. Identification of these patients will both enhance treatment and refine our notions of the natural history of the disease.

REFERENCES

1. Goldhirsch A, Wood WC, Senn HJ, Glick JH, Gelber RD. Meeting highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. J Natl Cancer Inst 1995; 87: 1441–5.
2. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. Lancet 1992; 339: 1–15, 71–85.
3. Schinzinger A. Ueber carcinoma mammae. Cbl Chr 1889; 16: 55.
4. Beatson GT. On the treatment of inoperative cases of carinoma of the mamma. Lancet 1896; 2: 104.
5. DeCourmelles FV. La radiotherapie indirect, ou dirigee par les correlations organiques. Arch Elect Med 1922; 32: 264.
6. Taylor GW. Evaluation of ovarian sterilization for breast cancer. Surg Gynecol Obst 1939; 68: 452.
7. Treves N. An evaluation of prophylactic castration in the treatment of mammary carcinoma. Cancer 1957; 10: 393.
8. Kennedy BJ, Wielke PW Jr, Fortuny IE. Therapeutic castration versus prophylactic castration in breast cancer. Surg Gynecol Obst 1964; 118: 524–40.
9. Kennedy BJ. Diethylstilbestrol versus testosterone propionate therapy in advanced breast cancer. Surg Gynecol Obst 1965; 120: 1246–50.
10. Kennedy BJ, Kelley RM, White G, Nathanson IT. Surgery as an adjunct to hormone therapy of breast cancer. Cancer 1957; 10: 1055–75.
11. Kiang DT, Kennedy BJ. Tamoxifen (antiestrogen) therapy in advanced breast cancer. Ann Intern Med 1977; 87: 687–90.
12. Ingle JN, Ahmann DL, Green SJ, et al. Randomized clinical trial of diethylstilbestrol versus tamoxifen in postmenopausal women with advanced breast cancer. N Eng J Med 1981; 304: 16–21.
13. Goldhirsch A, Wood WC, Senn HJ, et al. International consensus conference on primary treatment of breast cancer. Recent Results Cancer Res 1996; 140: 325–35.
14. Forbes JF. The control of breast cancer: the role of tamoxifen. Semin Oncol 1997; 24 (Suppl 1): S1–5, S1–19.
15. Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: Overview of the randomized trials. Lancet 1996; 348: 1189–96.
16. Fisher B, Carbone P, Economou SG, et al. 1-phenylalanine mustard (L-PAM) in the management of primary breast cancer. N Eng J Med 1975; 292: 117–22.
17. Bonadonna G, Brusamoline E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Eng J Med 1976; 294: 405–10.
18. NCI Monographs. Proceedings of the NIH. Consensus Development Conference on Adjuvant Chemotherapy and Endocrine Therapy for Breast Cancer. Bethesda, MD: National Institute of Health, 1986.
19. Fisher B, Redmond C, Elias EG, et al. Adjuvant chemotherapy for breast cancer: an overview of NSABP findings. Int Adv Surg Oncol 1982; 5: 65–90.
20. Fisher B, Brown A, Mamounas E, et al. Preoperative chemotherapy reduced the size of most breast tumors decreased the incidence of positive nodes. J Clin Oncol 1997; 15: 2483–93.
21. Norton L. Conceptual basis for advances in the systemic drug therapy of breast cancer. Semin Oncol 1997; 24 (Suppl 11): 2–12.
22. Paterson R. Breast cancer—a report of two clinical trials. J Royal Coll Sur Edin 1962; 7: 243–54.
23. Stjernswärd J. Can survival be decreased by postoperative irradiation. Int J Radiat Oncol Biol Phys 1977; 2: 1171–5.
24. Cuzick J, Stewart H, Peto R, et al. Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. Cancer Treat Rep 1987; 71: 15–25.
25. Holland JF, Gildewell O, Cooper RG. Adverse effect of radiotherapy on adjuvant chemotherapy for carcinoma of the breast. Gynecol Obstet 1980; 150: 817–21.
26. Levitt SH. Is there a role for post-operative adjuvant radiation in breast cancer? Beautiful hypothesis versus ugly facts: 1987 Gilbert H. Fletcher lecture. Int J Radiat Oncol Biol Phys 1988; 14: 787–96.
27. Levitt SH. The importance of locoregional control in the treatment of breast cancer and its impact on survival. Cancer 1994; 74: 1840–6.
28. Cuzick J, Stewart H, Rutqvist L. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol 1994; 12: 447–53.
29. Arriagada R, Rutqvist LE, Mattsson A, et al. Adequate locoregional treatment for early breast cancer may prevent secondary dissemination. J Clin Oncol 1995; 13: 2869–78.
30. Auquier A, Rutqvist LE, Høst H, Rotstein S, Arriagada R. Postmastectomy megavoltage radiotherapy: the Oslo and Stockholm trials. Eur J Cancer 1992; 28: 433–7.

31. Wallgren A, Arner O, Bergström J, et al. Radiation therapy in operable breast cancer: results from the Stockholm trial on adjuvant radiotherapy. Int J Radiat Oncol Biol Phys 1986; 12: 533–7.
32. McNeese MD, Fletcher GH, Levitt SH, Khan FM. Breast Cancer. In: Levitt SH, Khan FM, Potish RA, eds. Levitt and Tapley's Technological Basis of Radiation Therapy: Practical Clinical Applications, Second edition. Philadelphia: Lea & Febiger, 1992: 232–47.
33. Sykes HF, Sim DA, Wong CJ, Cassady JR, Salmon SE. Local-regional recurrence in breast cancer after mastectomy and Adriamycin-based adjuvant chemotherapy: evaluation of the role of postoperative radiotherapy. Int J Radiat Oncol Biol Phys 1989; 16: 641–7.
34. Griem KL, Henderson IC, Gelman R, et al. The 5-year results of a randomized trial of adjuvant radiation therapy after chemotherapy in breast cancer patients treated with mastectomy. J Clin Oncol 1987; 5: 1546–55.
35. Stefanik D, Goldberg R, Byrne P, et al. Local–regional failure in patients treated with adjuvant chemotherapy for breast cancer. J Clin Oncol 1985; 3: 660–5.
36. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med 1997; 337: 949–55.
37. Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 1997; 337: 956–62.
38. Recht A, Come SE, Henderson IC, et al. The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. N Engl J Med 1996; 334: 1356–61.
39. Recht A, Harris JR, Come SE. Sequencing of irradiation and chemotherapy for early-stage breast cancer. Oncol 1994; 8: 19–28.
40. Hartsell WF, Recine DC, Griem KL, Murthy AK. Delaying the initiation of intact breast irradiation for patients with lymph node positive breast cancer increases the risk of local recurrence. Cancer 1995; 76: 2497–503.
41. McCormick B, Norton L, Yao TJ, Yahalom J, Petrek JA. The impact of the sequence of radiation and chemotherapy on local control after breast-conserving surgery. Cancer Journal Scientific America 1996; 2: 39–45.
42. Wallgren A, Bernier J, Gelber RD, et al. Timing of radiotherapy and chemotherapy following breast-conserving surgery for patients with node-positive breast cancer. Int J Radiat Oncol Biol Phys 1996; 35: 649–59.
43. Perez CA, Graham ML, Taylor ME, et al. Management of locally advanced carcinoma of the breast: I. Noninflammatory. Cancer 1994; 74: 453–65.
44. Hortobagyi GN. Comprehensive management of locally advanced breast cancer. Cancer 1990; 66: 1367–91.
45. Singletary SE, McNeese MD, Hortobagyi GN. Feasibility of breast-conservation surgery after induction chemotherapy for locally advanced breast carcinoma. Cancer 1992; 69: 2849–52.
46. Marks LB, Halperin EC, Prosnitz LR, et al. Post-mastectomy radiotherapy following adjuvant chemotherapy and autologous bone marrow transplantation for breast cancer patients with ≥ 10 positive axillary lymph nodes. Int J Radiat Oncol Biol Phys 1992; 23: 1021–6.
47. Peters WP, Ross M, Vredenburgh JJ, et al. High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary cancer. J Clin Oncol 1993; 11: 1132–43.
48. Osborne CK, Clark GM, Ravdin PM. Adjuvant systemic therapy of primary breast cancer. In: Harris JR, Lippman ME, Morrow M, Hellman S, eds. Diseases of the breast. Philadelphia: Lippincott-Raven, 1996: 548–78.
49. Padmanabhan N, Wang DY, Moor JW, et al. Ovarian function and adjuvant chemotherapy for early breast cancer. Eur J Cancer Clin Oncol 1987; 23: 745.
50. Gradishar WJ, Schilsky RL. Ovarian function following radiation and chemotherapy for cancer. Semin Oncol 1989; 16: 425.
51. Harris JR, Morrow M. Local management of invasive breast cancer. In: Harris JR, Lippman ME, Morrow M, Hellman S, eds. Diseases of the breast. Philadelphia: Lippincott-Raven, 1996: 487–547.
52. Rutqvist LE, Lax I, Fornander T, Johansson H. Cardiovascular mortality in randomized trial of adjuvant radiation versus surgery alone in primary breast cancer. Int J Radiat Oncol Biol Phys 1992; 22: 887–96.
53. Gyenes G, Gagliardi G, Lax I, Fornander T, Rutqvist LE. Evaluation of irradiated heart volumes in stage I breast cancer patients treated with postoperative adjuvant radiotherapy. J Clin Oncol 1997; 15: 1348–53.
54. Boice JD Jr, Harvey EB, Blettner M, Stovall M, Flannery JT. Cancer in the contralateral breast after radiotherapy for breast cancer. N Engl J Med 1992; 326: 781–5.
55. Shapiro CL, Recht A. Late effects of adjuvant therapy for breast cancer. J Natl Cancer Inst Monogr 1994; 16: 101–12.