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Viewpoint

Patients with early breast cancer benefit from effective axillary treatment

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Summary

We have reviewed the available clinical data on the benefit of axillary treatment in patients with early breast cancer. The results of these studies suggest that perhaps 5–10% of patients are cured by effective axillary treatment. We conclude that effective axillary treatment should still be considered an essential aspect of primary treatment.

Treatment of the axilla in patients with early breast cancer, once considered an essential part of primary therapy, has been recently questioned. In this article we present a brief summary of theories of breast cancer spread, and review data from studies which evaluate the importance of axillary treatment in patients with early breast cancer. We present the view that there is currently insufficient data to justify abandoning effective treatment of the axilla in these patients.

Any discussion of the value of axillary treatment must be related to an understanding of the spread of breast cancer. Axillary treatment can only be of survival value if the cancer spreads sequentially from the breast to axillary nodes and finally to distant sites, at least in some patients. If there is a subset of patients with cancer confined to the breast and axillary nodes, then axillary treatment will be of value. Theories on the spread of breast cancer have changed markedly since the early part of this century when Samson Handley and, later, William Halsted espoused the concept that breast cancer spreads by direct extension of the primary (1). According to this view, metastasis to the axillary lymph nodes, bones, and liver all occur sequentially by direct permeation of breast cancer cells. This concept of spread by permeation was used to provide a rationale for the radical mastectomy, an en-bloc resection of the breast with both the major and minor pectoral muscles and the axillary lymph nodes.

By the 1930's, however, the prevailing view that breast cancer spreads by direct permeation of tumor cells had been abandoned and replaced by the concept of noncontiguous spread by embolization. Initial pathological studies on breast cancer spread had used specimens from patients with locally advanced and terminal breast cancer and revealed continuous involvement (or permeation) of the lymphatics. Later studies using specimens from patients with early breast cancer rarely disclosed such lymphatic permeation. More commonly, emboli of cancer cells were seen in the lymphatic channels or in the draining lymph nodes. Studies of this kind

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led to the conclusion that breast cancer spreads to draining lymph nodes by embolization rather than permeation. Nevertheless, the theory that breast cancer spreads sequentially remained.

In the last two decades, the concept of sequential spread has been questioned. One major argument against the concept of sequential spread is the clinical observation that approximately 25% of patients with histologically negative axillary nodes develop distant metastases. In these patients, the cancer apparently has spread directly from the primary to distant sites without involvement of the axillary nodes. It has been suggested that in these patients, the cancer may have drained to the internal mammary nodes, an alternative site of regional lymph node involvement. Multiple studies, however, have revealed that treating the internal mammary nodes by surgery or radiation therapy did not eliminate these distant metastases. Another attempt was made to bolster the sequential theory by suggesting that, in patients with distant relapse, some lymph nodes which were considered negative by routine pathological examination in fact contained small amounts of breast cancer when subjected to more careful scrutiny. Those studies, however, failed to show that such small nodal deposits of breast cancer predicted for distant relapse (3, 4, 5). It now seems well-documented that, in some patients, breast cancer does not spread sequentially through the axillary lymph nodes to distant sites, but directly from the primary by way of the blood stream or by traversing the lymph nodes without implantation. This observation, however, does not eliminate the possibility that breast cancer does spread sequentially in some patients.

The results of the National Surgical Adjuvant Breast Project (NSABP) Study B-04 have been used to provide the strongest evidence against the sequential theory of breast cancer spread. In this study, breast cancer patients without clinically-suspicious axillary lymph nodes were randomized to one of three treatment arms: 1) radical mastectomy, 2) total mastectomy and postoperative radiation to the chest wall and draining lymph node areas, and 3) total mastectomy alone. This study tested the value of axillary treatment, since arms 1 and 2 provided treatment to the axilla and arm 3 did not. The first report was published in 1977 and provided two lines of evidence that axillary treatment was not valuable (6). It was observed in this study that 38.6% of the patients randomized to radical mastectomy had histologically positive nodes. Since patients were randomly allocated to treatment, it is assumed that a similar percentage of patients randomized to total mastectomy alone had occult axillary metastases. It was noted, however, that only 15% of patients treated by total mastectomy alone subsequently developed axillary nodes requiring dissection during the observation period. These data were interpreted as indicating that occult breast cancer in axillary lymph nodes does not always progress. The other line of evidence was the observation that failure to provide effective treatment to the axilla was not associated with an increased risk of distant relapse or death due to breast cancer. The outcome for patients treated with total mastectomy alone was comparable to that for patients treated by radical mastectomy or total mastectomy and radiation.

The results of this NSABP trial have had such a major impact on the philosophy of treatment of the axilla that we will examine this trial in greater detail. The original report published in 1977 acknowledged that 35% of the patients assigned to total mastectomy, in fact, had a limited axillary dissection. A second report, published in 1981 (7), indicated that the proportion of patients assigned to total mastectomy alone who subsequently required an axillary dissection was related to the extent of the initial axillary dissection. Twenty-one percent of the patients who had no nodes recovered subsequently required axillary dissections compared to 12% for patients who had 1–5 nodes recovered, and 0% for patients who had six or more nodes recovered. These results indicate that 21%, rather than 16%, of patients actually treated by total mastectomy alone subsequently required an axillary dissection.

In analyzing the results of the NSABP B-04 trial, we believe that it is important to distinguish between the questions, 'How often do occult axillary metastases progress?' and 'How often do occult axillary metastases progress to require treatment?' The NSABP trial addressed the latter question

only. To answer the first question, it is necessary to consider patients who develop suspicious axillary lymphadenopathy simultaneously with or subsequent to the appearance of distant metastases. Such patients obviously do not require an axillary dissection, but do have progression of occult axillary metastases. The NSABP reports do not provide the proportion of patients who developed suspicious axillary lymph nodes simultaneously with or subsequent to distant relapse. It is assumed that patients who develop axillary lymphadenopathy as the first sign of relapse following total mastectomy undergo a metastatic workup prior to axillary dissection. If distant relapse is noted on this workup, an axillary dissection probably would not be required. Based on our own experience, we would estimate that an additional 3–5% of patients present with simultaneous axillary and distant relapse. Estimating the frequency that patients develop axillary lymphadenopathy after distant relapse is difficult since record keeping with regard to asymptomatic findings is often inadequate in patients with distant metastases. An estimate of another 3–5% is probably a conservative one. Using these estimates, of the presumed 38% who had occult axillary metastases and did not have any initial axillary dissection, we calculate that 21% + 4% + 4% = 29% progress to develop axillary lymphadenopathy. This represents 76% of the total presumed to have axillary involvement. This percentage would be further increased by using an actuarial calculation which adjusts for patients who die too quickly to manifest axillary lymphadenopathy. In summary, we conclude that, in the large majority of patients treated by total mastectomy alone, occult axillary breast cancer progresses.

The second major finding of the NSABP B-04 trial which we will examine in greater detail is that axillary treatment, either surgical or radiotherapeutic, did not result in any advantage in freedom from distant relapse or survival. Before accepting this conclusion, it is important to ask whether or not enough patients were included in the study. Approximately 360 patients were assigned to each treatment arm. It is clear that the value of axillary treatment is restricted to patients who have positive nodes. Patients with negative axillary nodes cannot benefit from axillary treatment. As a result, the critical population is, therefore, restricted to the 137 patients (38.6% of 360) who are presumed to have positive axillary nodes. It is also clear that axillary treatment is not of value in patients who have occult distant disease at the time of presentation. It is well known that only one-quarter of patients with positive axillary nodes are free of occult distant disease (8, 9). Therefore, the critical population is further restricted to one-quarter of 137, or 34 patients who have positive nodes and no occult distant spread and could therefore benefit from axillary treatment. In addition, one must consider the salvage potential of delayed axillary treatment. If one estimates that one-quarter of patients initially treated by total mastectomy alone who subsequently develop axillary adenopathy are curable, then delayed axillary dissection cures an additional 8 patients. This leaves 26 patients who could possibly have benefited from initial axillary treatment, or 7% of the total group. It is important to note that in order to have a 90% chance of detecting a 7% difference between 2 treatment arms of a clinical trial at a statistically significant level of $p = 0.05$, 2000 patients are required (10). We conclude from this analysis that the negative result obtained in the B-04 study does not prove that axillary treatment is of no value, but rather, that the number of patients who might benefit is small.

There are other studies that can be quoted relative to the survival benefit associated with effective axillary treatment, but they are limited by either small numbers of patients or short follow-up time. In the second series of the trial performed at Guy's Hospital between 1971 and 1975 (11), 253 patients with Stage I (clinically negative axillary lymph nodes) breast cancer were randomized to either radical mastectomy (RM) or wide local excision (WLE). Patients treated by WLE did not undergo an axillary dissection. Both groups received postoperative radiation therapy with a dose and technique which are now considered inadequate. As a result, there was an excess of axillary recurrences in the WLE group compared to the RM group. At eight years, there was a highly statistically significant difference in both distant recur-

rence and survival in favor of patients treated by radical mastectomy. In the Southeast Scotland Trial (12), 275 Stage I patients with localized breast cancer were randomly assigned to either radical mastectomy (RM) or total mastectomy and radiation (TM + XRT). Axillary treatment by radiation appeared to be relatively ineffective since recurrence in the axilla was noted in 14% of patients treated by TM + XRT, compared to 1% for RM patients. As in the Guy's Hospital trial, the incidence of chest wall recurrence was not significantly different between the two arms. The 10 year survival rates show a statistically significant advantage for patients treated by RM compared to those treated by TM + XRT. The results from these 2 smaller studies suggest that effective axillary treatment is important for survival. In the study conducted by the Cancer Research Campaign (CRC) 2,243 evaluable patients with stage I and II breast cancer were randomized to total mastectomy and postoperative radiation therapy (TM + XRT) or TM alone (13). The five year results indicated that there is a significant improvement in local-regional control for the TM + XRT treatment group (89% versus 70%) but not a significant improvement in survival (73% versus 70%). These preliminary results suggest that axillary treatment does not have survival benefit, but further follow-up is required. It is of interest in this regard that in the Southeast Scotland trial, the five year survival rates were not different. It was only at 10 years that a difference emerged.

In considering the value of axillary treatment, we would like to stress the observation that patients with documented axillary metastases apparently have been cured following axillary treatment. As noted above, approximately one quarter of node-positive patients treated by effective therapy remain free of recurrence for long periods of time and can be considered cured. We believe this observation provides the strongest prima facie evidence that breast cancer spreads sequentially in some patients. Until proven otherwise, it must be assumed that ineffective treatment to the axilla would result in residual cancer, and that in most cases this cancer would progress to be fatal. The analysis presented here indicates that the percentage of patients who might benefit from effective axillary treatment is small, since in the large majority of patients, axillary treatment is either not needed, to no avail, or could have been used equally well at a later time. It is also likely that the effect on survival may not become apparent for many years. Nevertheless, we conclude that effective axillary treatment is likely to result in a survival benefit to a small percentage of patients (approximately 5–10%) with early breast cancer.

Finally, it is worthwhile to consider what constitutes effective axillary treatment. It is now generally accepted that resection of the pectoral muscles is not required for effective surgical treatment. A thorough dissection with preservation of the pectoral muscle does have the potential of leaving nodal tissue behind in the upper-most portion of the axilla and between the pectoral muscles. Haagensen, however, was the first to show that when the upper-most portion of the axilla (the subclavicular region or Level III) is involved, survival following radical mastectomy is essentially zero (14). Auchincloss amplified that observation to show that too few people benefited from radical mastectomy to justify the sacrifice of the pectoral muscles (15). The data from Haagensen also indicates that only 3 of 182 patients (2%) had isolated involvement of interpectoral nodes and survived free of disease for 10 years or greater (14). Axillary failure following a thorough dissection with preservation of the pectoral muscles is rare.

Comparative studies, including the NSABP B-04 trial, have shown that axillary dissection and properly-delivered radiation therapy to the axilla (4500–5000 rad in 5 weeks) provide comparable levels of tumor control. The major advantage of axillary dissection is the opportunity to determine the histological status of those nodes for purposes of estimating prognosis and determining the need for adjuvant systemic therapy.

The analysis presented here suggests that axillary treatment is of survival benefit to a small group of patients with early breast cancer. A thorough axillary dissection without pectoral muscle resection is a well-tolerated procedure with little morbidity and insures an optimum level of cure for patients with early breast cancer. Effective axillary

treatment should still be considered an essential aspect of the primary treatment of early breast cancer.

References

1. Halsted WS: The results of radical operations for the cure of cancer of the breast. Ann Surg 46: 1–19, 1907
2. Haagensen CD, Stout AD: Carcinoma of the breast: criteria of operability. Ann Surg 118: 859–870, 1932
3. Huvos AG, Hutter RVP, Berg JW: Significance of axillary macrometastases and micrometastases in mammary cancer. Ann Surg 173: 44–46, 1971
4. Pickren JW: Significance of occult metastases: a study of breast cancer. Cancer 14: 1266–1271, 1961
5. Rosen PP, Saigo PE, Braun DW, Weathers E, Fracchia AA, Kinne DW: Axillary micro- and macro-metastases in breast cancer. Ann Surg 194: 585–591, 1981
6. Fisher B, Montague E: Comparison of radical mastectomy with alternative treatments for primary breast cancer. Cancer 39: 2829–2839, 1977
7. Fisher B, Wolmark N, Bauer M, Redmond C, Gebhardt M: The accuracy of clinical nodal staging and of limited axillary dissection as a determinant of histologic nodal status in carcinoma of the breast. Surg Gynec Obstet 152: 765–772, 1981
8. Fisher B, Slack N, Katrych D, Wolmark N: Ten year follow-up results of patients with carcinoma of the breast in a co-operative clinical trial evaluating surgical adjuvant chemotherapy. Surg Gynec Obstet 140: 528–534, 1975
9. Valagussa P, Bonadonna G, Veronesi U: Patterns of relapse and survival following radical mastectomy. Cancer 41: 1170–1178, 1978
10. Boag JW, Haybittle JL, Fowler JF, Emery EW: The number of patients required in a clinical trial. Brit J Radiol 44: 122–125, 1971
11. Hayward J: The surgeon's role in primary breast cancer. Breast Cancer Res Treat 1: 27–32, 1981
12. Langlands AO, Prescott RJ, Hamilton T: A clinical trial in the management of operable breast cancer. Brit J Surg 67: 170–174, 1980
13. Cancer Research Campaign Working Party: Cancer Research Campaign trial for early breast cancer. Lancet II (8185): 55–60, 1980
14. Haagensen CD: Diseases of the Breast. Revised 2nd Ed. WB Saunders, Philadelphia, 1971
15. Auchincloss H: Significance of location and number of axillary metastases in carcinoma of the breast. Ann Surg 158: 37–46, 1963