

Treatment of cancer of the breast

Past, present and future

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Historical background

THERE was a great calm in the surgical world, which lasted from the turn of the century until McWhirter¹ reported the results of simple mastectomy and radiation therapy. During the period of calm there were a few stubborn renegades like Sir Geoffrey Keynes in London,² and McNealy³ in Chicago, who quietly continued to do simple operations for cancer of the breast and seemed content with their results. But such practices were generally frowned upon. In some hospitals in the United States, a surgeon had to justify the performance of a simple mastectomy or be threatened with loss of surgical privileges. During the period of relative complacency, many papers on cancer included a phrase of such as—"Just as the Halsted radical mastectomy embodies the principles of cancer surgery so. . . ." The place of radical mastectomy seemed secure.

Then, almost simultaneously the position of the conventional radical mastectomy was attacked from two sides: on one by the work of Handley,⁴ on involvement of internal mammary lymph nodes, with the result that ultraradical mastectomy was advocated, and on the other, by the clinical studies of McWhirter,⁵ which showed the value of simple mastectomy and radiation therapy. Williams, Murley, and Curwen⁶ next reported that the results of the simple operations or radium implants done by Sir Geoffrey Keynes at St. Bartholomew's Hospital were as good as those after radical mastectomy.

Under the influence of McWhirter, who had demonstrated so clearly the value of radiation in controlling metastases in axillary nodes, radiation therapy increased in popularity, and in some quarters it was administered prophylactically as routine treatment after radical mastectomy. The randomized study of Kaae and Johansen,⁷ in which no difference in survival rates was shown between those of patients treated by ultraradical mastectomy and those treated by McWhirter's technique, further strengthened the position of radiation in the treatment of breast cancer. In spite of the mounting morbidity and the high incidence of edema of the arm which followed radical or ultraradical operations combined with radiation therapy, and in spite of the failure to show higher cure rates after these combinations of therapy, the trend towards increasingly radical treatment continued.

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The first crack in the armour of conventional radical procedures was made by Paterson and Russell's⁸ randomized study of prophylactic radiation therapy after radical mastectomy. Their report showed no increased survival rate after prophylactic radiation therapy among patients in whom nodes were involved, and a lower rate of survival among the irradiated patients whose nodes were not involved. Auchincloss⁹ then reported that the local recurrence rate was not diminished by extending the amount of skin removed or by cutting the skin flaps extremely thin. Later, in 1963,¹⁰ he showed, on the basis of careful pathological studies, that modified radical mastectomies in which muscles were spared should theoretically be as successful as conventional radical mastectomies in the treatment of potentially curable patients.

Reports from the Mayo Clinic,¹¹ on the survival rate of all operable patients, showed results as good as those obtained by Urban¹² in a selected series of patients treated by ultraradical operations. Haagensen¹³ advocated a high degree of selectivity in choosing patients for radical operations, and Guttman,¹⁴ using radiation therapy only, reported a five-year survival rate of 52 percent in the patients whom Haagensen, on the basis of his "triple biopsy", had rejected for surgical treatment. Porritt¹⁵ reported as good results after simple mastectomy or simple excision of breast cancers as after radical mastectomy. Smith and Meyer,¹⁶ later confirmed by Shimkin and associates,¹⁷ showed simple mastectomy to be fully as effective as radical. The proponents of radical operations for breast cancer were beginning to lose ground on every front.

Current studies

My interest in simplifying the treatment of breast cancer arose 15 years ago, when I became convinced of the validity of McWhirter's and Keynes' reports. If radiation were as effective as it was reported to be in controlling axillary metastases, I wondered if it could not be withheld and used only if and when metastases appeared. In January 1955,¹⁸ my colleagues and I decided to compare the efficacy of simple and radical mastectomies. I, who performed approximately half of the operations for breast cancer, was to do mainly simple mastectomies, usually in clinical Stage I cases in which nodes did not seem to be involved, without addition of radiation therapy, and my colleagues were to continue to perform radical mastectomies, often using radiation therapy prophylactically as they had in the past.

The experiment lasted for only three years, because my colleagues became more and more disenchanted with radical operations and by 1958 were performing mainly simple operations. However, all the patients treated in 1955, 1956 and 1957 have been followed for a minimum of ten years, and although their treatment was not randomized, and their numbers are too few to be of great statistical significance the patients treated by simple operations, usually without irradiation, had a higher rate of survival at both five and ten years than did those treated by radical operations. The most significant feature is

that the difference in favor of simple mastectomy is greater at ten years than at five, indicating that failure to remove nodes did not predispose to late recurrences.

Our progressive simplification of treatment involved (1) more local excisions of cancer with preservation of the breast, (2) a higher proportion of simple mastectomies, and (3) complete replacement of the conventional radical mastectomy with the modified radical operation in which muscles are spared, skin flaps are cut thick and skin grafts are not employed; and in spite of the fact that there has been a progressive decrease in the use of prophylactic postoperative radiation to the point that it is rarely employed except sometimes in central or inner quadrant lesions as a strip over the internal mammary chain, the rate of survival at five years has progressively increased. In 1964 the crude survival rate of all patients in all stages of the disease, operable and inoperable, reached 65 percent and the survival of patients with operable Stage I and Stage II cancers was 80 percent. There was only one patient with intraduct cancer in the 55 patients of this group. All the others had invasive cancers. Eighty percent of them were classified as Stage I and Stage II, and as an indication that the high rate of survival was not due to selection, one should note that only one of the 11 patients classified as inoperable lived for five years.

As mentioned before, the simplification of treatment began in 1955 and by 1957 most of the surgeons at this institution had abandoned the radical operation as shown in *Table 1*. *Table 2* lists the rates of survival of the patients in various stages during this period.

Perhaps the most interesting observation on the patients in this series is that the patients whose nodes were not palpably involved at the time of simple mastectomy, and were not resected or subjected to irradiation, had as high a rate of survival at five years as did a similar group of patients whose nodes, although not palpably involved, were removed prophylactically by radical or modified radical mastectomy and the pathologist found that they contained occult cancer. In the first group, in spite of a delay between mastectomy and the resection of the involved nodes that varied from 1 to 84 months and averaged 24 months, the survival rate of the patients treated by delayed axillary dissection was nearly identical to that of those treated initially by mastectomy and axillary dissection (65 percent as compared to 62 percent). The average number of nodes found to be involved at the time of the delayed (therapeutic) dissection was likewise identical to that found in the patients who had prophylactic dissections. The number with only one node involved, in spite of the two-year delay, was actually higher (38 percent) than when the nodes were removed at the time of mastectomy (27 percent). Thus it is clear that there is little tendency for the cancer to metastasize quickly from involved nodes, and that there is no advantage to prophylactic dissection of nodes containing occult cancer. It is just as effective to defer treatment until the nodes become palpably involved.

Table 1.—Treatment of breast cancer,
1957–1964 inclusive

Type	Number of patients		Percent
Radical mastectomy	4/401	=	1
Modified radical	179/401	=	45
Simple mastectomy (or local excision)	218/401	=	54
Cobalt, postoperative	84/401	=	21

Table 2.—Breast cancer, Five-year survival, 1957–1964
inclusive (507–510 followed)

	Number of patients		Percent
All patients	300/510	=	59
Operable Stages I and II	287/401	=	72
Inoperable (from other disease)	0/8	=	0
Stages I and II			
Stages III and IV	13/101	=	13
Local recurrence	25/401	=	6

Since there is no advantage to prophylactic axillary dissection in patients who have occult cancer in nodes, it is clear that in patients without palpable nodal involvement radical mastectomy has no advantage over simple mastectomy. The next question is whether in patients whose nodes are not involved (True Stage I) radical mastectomy produces not only unnecessary mutilation but also tends to disseminate the cancer. To answer this question we have reviewed our experience in patients with True Stage I cancer in whom, if the axilla were dissected prophylactically in a radical or modified radical mastectomy, the pathologist found no involvement of nodes, or if the axilla were not dissected and only a simple mastectomy was done, there was no palpable involvement of nodes for at least five years.

Because the treatment of the patients in this series was not randomized, there is a predominance of small or noninvasive cancers in the group of patients that were treated by simple operations. For this reason, in order to obtain groups that were comparable, it was necessary to eliminate from consideration all cancers under 1.5 cm in diameter, all intraduct and special pathologic types of cancer, and to include only patients with invasive cancers 1.5 cm to 4.5 cm in diameter. This left 116 patients with True Stage I cancer who were treated by simple mastectomy without irradiation, and 60 treated by radical or modified radical mastectomy. The average diameters of the tumors in the two groups were 2.7 and 2.8 cm respectively, and the average ages of the patients 58 and 55 years. Eighty-five percent of the patients treated by simple operations without irradiation, and in whom the axillary nodes

were left intact to perform their immunologic function, survived five years as compared with only 70 percent of those whose nodes were removed.

Although the difference in the survival rates of the two groups is great enough to attain statistical significance ($p < 0.05$), it is impossible to claim that the results prove the superiority of the lesser operation. The treatment was not randomized and hence, even though the sizes and stages of the tumors and the ages of the patients were similar, it is impossible to state that factors of selection did not influence the results. I believe, that it is safe to say that analyses of the results obtained by simple operations in patients with occult cancer in nodes and with True Stage I cancer show that from the standpoint of survival there is no advantage in subjecting that patient to prophylactic nodal dissection.

One might argue that since there is no sure way of determining whether nodes are or are not involved and since removing low and central axillary nodes in a modified radical mastectomy inflicts little morbidity and saves the patient the possibility of having to undergo a second operation, it would be preferable to perform, routinely, a prophylactic axillary dissection or to irradiate the axilla. If the decision as to whether or not the axilla is to be dissected is based on preoperative clinical staging, there would be much to be said for this point of view, for it is widely recognized that in 30 percent of the cases there is involvement of nodes that cannot be palpated through the skin and subcutaneous fat. But if the mastectomy incision is transverse, ending just below the hair line of the axilla, and if the surgeon before deciding on whether or not to dissect the axilla opens the axillary space and rolls the fat pad between the thumb and finger, he is able to palpate small nodes and to evaluate their consistency. The consistency of the nodes, not their size, is the key to the diagnosis of involvement, for if they are hard or if there is beading of the lymphatics cancer is almost always present. Thus operative staging, in contradistinction to clinical staging, fails to recognize the presence of cancer in nodes in only 8 percent of the cases. Secondary operations are therefore rarely necessary.

Although in most cases irradiation causes little morbidity and if the axilla is not dissected it never causes edema of the arm, it still involves a protracted period of treatment and sometimes causes fibrosis and discomfort. Moreover, it has been shown in several randomized studies, such as that of Paterson and Russell⁸ and Bond¹⁹ that when nodes are not involved, irradiation may cause a slight but definite increase in the rate of death from systemic metastasis. This is perhaps best explained in the light of some of our observations on the role of regional nodes in maintaining systemic immunity to the dissemination of cancer.

The role of regional nodes in immunity was first reported by Mitchison,²⁰ in which he showed that immunity to an allogeneic tumor could be transferred by transplanting the regional nodes that drained it into the peritoneal cavities of mice of the same strain. Contralateral nodes and also cells from the spleen failed to transfer immunity. In our laboratory we observed the

reverse side of this coin, noting that removal of regional nodes at the same time that the tumor was removed, removed the mouse's immunity to reimplantation of the allogeneic tumor. In mice bearing isogeneic tumors, moreover, the incidence of distant metastasis was doubled when uninvolved regional nodes were removed along with the tumors.

Observations by Dr. S. D. Deodhar and myself on patients with cancer of the breast have shown that if cells from the primary tumor are grown in tissue culture with lymphocytes taken from uninvolved nodes, the lymphocytes clump around the cancer cells forming rosettes and often destroy the cancer cells. Lymphocytes taken from extensively involved nodes, however, rarely show any tendency to clump. There is therefore both laboratory and clinical evidence to support the thesis that uninvolved regional nodes play an important part in the mechanism by which the host defends itself against metastasis.

Although it seems to me that there is no justification for performing the classic radical mastectomy, and that there is much to commend simple mastectomy over modified radical in patients in whom at operation there is no palpable evidence of axillary involvement, the crucial point that has not yet been settled is the place, if any, for local excision of breast cancers.

For many years, there have been reports such as those of Mustakallio²¹ and Porritt,¹⁵ in which the rate of survival of patients treated by local excision and irradiation is comparable to or even better than that of patients with cancers in similar stages who were treated by radical mastectomy. Even Adair,²² an exponent of radical mastectomy, has reported superior results following local excision.

In the years 1955 to 1964, 57 of 465 patients with operable Stage I and Stage II breast cancer were treated at the Cleveland Clinic by local excision of the tumor.²³ Fifty-five of these have been followed for from 5 to 15 years. Seventy-three percent of the patients had clinical Stage I cancers and 27 percent had Stage II, a distribution almost identical to that of clinical Stage I and Stage II in the patients during the same period who were treated by mastectomy, 71 percent and 29 percent respectively. This is of course clinical staging, so that at least a third of the patients staged as I were really in Stage II. In pathologic grading the staging would have been nearly equally divided between I and II. The survival rates of the patients treated by local excision were almost identical to that of those treated by mastectomy, 67 percent and 68 percent respectively.

The average age of the patients treated by local excision was 57, identical to that of the patients treated by mastectomy. The average diameter of the tumors treated locally was 2.2 cm compared to 2.7 cm in the others. Most of the tumors selected for local excision were located in the periphery of the breast.

Although the Stage I tumors selected for local excision were smaller than those treated by mastectomy and hence perhaps a little more favorable, the

Stage II cancers that were treated locally tended to be more advanced than their counterparts. In several instances the reason the breast was not removed was because the axilla was considered to be inoperable. In spite of this the overall survival rates, stage for stage, were almost identical, 72.5 percent as compared to 74 percent in Stage I and 53 percent as compared to 54 percent in Stage II. It is interesting to note also that in patients with clinical Stage I cancers the incidence of local recurrence was the same in both groups (5 percent). In Stage II, due to the presence of a higher proportion of advanced cancers in the patients treated by local excision, it was 27 percent as compared with 15 percent of those treated by mastectomy. None of the local recurrences were in breast tissue, but were in skin and fat just as after mastectomy.

These observations are of the utmost significance, because if women thought that their cancers could be successfully treated by simple excision, without irradiation, and knew that after wide excision of the tumor the breast could be reconstructed they might seek treatment much earlier than they now do. At present women fear the treatment of breast cancer almost as much as they do the disease. For this reason a reward, in the form of preserving the breast, might provide incentive for earlier treatment and might result in a significantly higher rate of cure.

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