A Reappraisal of Oophorectomy in Carcinoma of the Breast

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Bilateral oophorectomy was used to treat 601 patients with disseminated breast carcinoma from 1974–1984. The total response rate was 31.2%. Complete regression occurred in 10.5% of patients and partial regression occurred in 20.8%, whereas 28.3% of patients showed no change and the disease progressed in 36.9% of patients. The patients who had a total regression had good survival rates (60.8% at 5 years and 47.3% at 7 years). No significant differences were found in the various age groups or with different types of dissemination. Patients with syncronous primary carcinoma and distant metastases had a high rate of regression as did patients with slow-growing carcinomas that metastasized many years after primary treatment. Estrogen receptor (ER) rates were good indicators of response only when determined on metastatic tissue at the time of oophorectomy. The value of ER determined on the primary tumor was of limited predictivity of response. A total of 220 patients received chemotherapy before oophorectomy. In this group the response rate was 22.3%, lower than that observed in patients who did not receive chemotherapy (36.6%). No important differences in total response rates were found among patients with amenorrhea and without amenorrhea although total regressions were more frequent in the latter patients than in the former patients.

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BILATERAL OOPHORECTOMY is the endocrine manipulation most likely to produce a regression of breast cancer in premenopausal women. Although this therapy has been practiced for nearly a century since its first description by Beatson,[1] a number of problems are still open. The most important questions are: (1) is there any indication for oophorectomy as adjuvant therapy immediately after the treatment of primary carcinoma? (2) What is the efficacy of oophorectomy in relation to the status of endocrine receptors? (3) When must oophorectomy be a treatment of first choice in disseminated disease? (4) What are the indications for oophorectomy in patients with disseminated disease who had previous chemotherapy?

Although all these items are of great relevance in common oncologic practice, surprisingly only a few studies have been devoted in recent years to the evaluation of ovarian suppression in breast carcinoma.

Previously we reported the results of bilateral oophorectomy in 639 patients with breast carcinomas from 1960–1962.[2,3] In our current study we report the results of 601 patients with advanced breast carcinoma treated with bilateral oophorectomy from 1974–1984, in order to clarify the aspects of oophorectomy that are still controversial.

Patients and Methods

From 1974–1984, 601 patients with advanced carcinoma of the breast had bilateral oophorectomy at the Milan Institute. Eighty-seven patients had locally advanced, inoperable breast carcinoma, or synchronous distant metastases, and the rest had recurrent disseminated cancer. Most of the patients (572) were premenopausal (less than 1 year after the last menstrual period), whereas 28 patients were postmenopausal (less than 5 years after the last menstrual period). 101 patients were less than 35 years old, 322 were between 35 and 44 and 178 were over 45.

Estrogen receptors (ER) were tested in 239 patients on the mammary carcinoma at the time of the previous primary treatment and in 134 patients on metastatic tissue at the time of the recurrence. The ER evaluation was made according to the European Organization on Research and

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Treatment of Cancer method by using the dextran–charcoal technique. Tumors with ER concentrations above 10 fmol/mg cytosol protein were considered positive.

Two-hundred-twenty patients had had previous chemotherapy, either adjuvant (183 patients) or as a first treatment of advanced disease (37 patients).

All patients were accurately staged before treatment and at 2 and 4 months after oophorectomy. The early restaging after two months was done to detect disease progression early so that other treatments could be initiated. The evaluation of the efficacy of oophorectomy was made 4 months after operation.

The evaluation of response to the oophorectomy was made as follows: (1) total regression: complete disappearance of metastatic localizations (and/or of the primary carcinoma) with recalcification of osteolithic lesions, (2) partial regression: reduction of more than 50% of all measurable lesions and partial recalcification of osteolithic metastases, (3) stable disease: reduction of less than 50% of all measurable lesions, or no change, without progression, for at least 4 months and (4) progression: increase in diameter of one or more measurable lesions and/or appearance of new metastases. Mixed responses (progression of some lesions and stabilization or regression of others) were considered in this group. For simplicity, the sum of total and partial regressions was expressed as "response rate."

Follow-up was at regular quarterly intervals for the duration of the patient's life, and actuarial survival curves were established up to 10 years. Twenty-one patients (4%) were lost to follow-up.

Statistical analysis of contingency tables was done by the chi-square test, and survival rate was calculated by the Kaplan–Maier method.

Results

Overall Response Rates

An objective response was found in 188 patients (31.2%), whereas in 170 patients the disease remained stable (28.3%) and in 222 patients the disease progressed (36.9%). Complete regression of all lesions occurred in 63 of 601 patients (10.5%). In 21 patients the response to oophorectomy was not evaluable.

The type of response was significantly related to the survival rate: the 5-year survival rate of 60.8% observed in the 63 patients who had complete response fell to 3.4% in the 222 patients who had progression of the disease, with intermediate values (31.1% and 16.0%, respectively) in patients with partial response and stable disease (Fig. 1).

The response rate (partial plus total regression) according to age and site of the lesions observed in the various

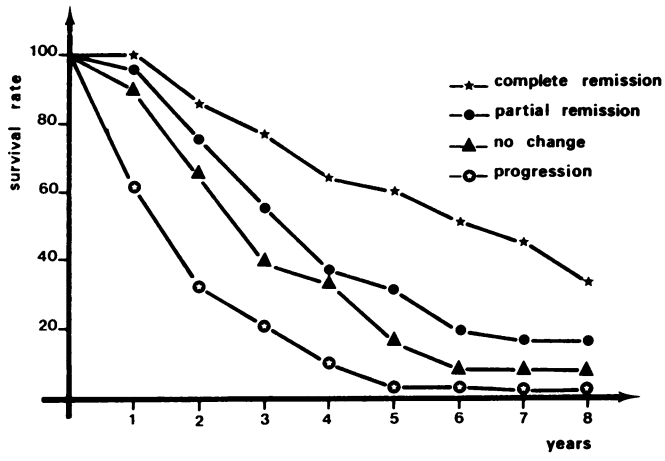

FIG. 1. Survival of 580 patients according to type of response to oophorectomy.

age groups (Table 1) is higher with increasing age: response rate was 23.5% in patients less than 30 years old and 38.4% in patients more than 50 years old. However, the statistical analysis did not show significant values ($p = 0.40$). As shown in Table 2, 428 patients had distant metastases at multiple sites, and of these patients 125 (29.2%) showed objective response; in 173 patients recurrent disease was present in a single organ and the frequency of response ranged from 32.6% in patients with bone metastases to 40.4% in patients with a locoregional disease. The observed differences were not statistically significant.

Disease-free Interval

In the 514 patients who had metastases after mastectomy, the response rates were evaluated according to the time elapsed between surgery for primary carcinoma and the first recurrence (Table 3). The patients with a disease-free interval longer than 4 years had the greater chance of response. High response rates were, however, also observed in patients with synchronous metastases and with a short disease-free interval of less than 1 year.

TABLE 1. *Frequency of Objective Response to Oophorectomy According to Age**

Age	No. of Patients	No. of Responses	%
<29	17	4	23.5
30–39	229	65	28.4
40–49	303	99	32.7
>50	52	20	38.4

* $X^2 = 2.88$, $p = 0.40$, DF = 3.

TABLE 2. *Frequency of Responses to Oophorectomy According to Site of Metastases**

Site of Metastases	No. of Patients	No. of Responses	%
Locoregional only	42	17	40.4
Lungs only	36	15	41.6
Bone only	95	31	32.6
Multiple sites	428	125	29.2

* $X^2 = 4.39$, $p = 0.22$, DF = 3.

ER Values

In 239 patients ER values were evaluable on primary carcinoma of the breast at the time of radical surgery. ER values were positive for 183 patients and negative for 56 patients. The response rate was 36.6% in the 183 patients with positive ER values, whereas the response rate was 21.4% in the 56 patients with negative ER values. This difference has a borderline significance ($p = 0.051$). In 134 patients ER was evaluated on a recurrent lesion at the time of oophorectomy: 94 patients had positive ER values and 40 patients had negative ER values. The response rate was 47.8% for the 94 patients with positive ER values (with 16.8% of complete regression), whereas the response rate was 22.2% for the 40 patients with negative ER values. This difference is statistically significant ($p = 0.001$). The impact of ER values on survival was also evaluated: patients with positive ER values had a higher survival rate after oophorectomy.

Previous Chemotherapy

Two hundred and twenty patients (36.8%) received chemotherapy before oophorectomy. Most patients (183) had adjuvant cyclophosphamide, methotrexate, fluorouracil (CMF) (for 1 year or for 6 months) at the time of the primary surgery, 1–9 years before the oophorectomy, and 37 patients had chemotherapy (mainly CMF) as a curative attempt at the first diagnosis of advanced disease. In these 220 patients we observed a total response rate of 22.3%, considerably lower than that of 371 patients who did not have previous chemotherapy (36.6%). This difference is statistically significant ($p = 3 \times 10^{-4}$). Of 180 patients in whom the information on the presence or absence of menses at the time of oophorectomy was available and clearly definable, 68 patients had full amenhorrea and 112 were still menstruating. Of the 68 women with amenorrhea, 27 (24.1%) responded to oophorectomy. However, only three patients with amenorrhea had a total regression (4.4%), whereas 13 patients without amenorrhea had total regression (11.6%) (Table 4).

TABLE 3. *Frequency of Objective Responses According to Disease-free Period*

	No. of Patients	No. of Responses	%
Synchronous	87	35	40.2
<1 year	130	41	31.5
1–2 years	156	33	23.1
2–3 years	83	26	21.3
3–5 years	87	30	34.5
>5 years	58	26	44.8

* $X^2 = 15.8$, $p = 7 \times 10^{-3}$, DF = 5.

Discussion

The most important result of this study is that the objective response to oophorectomy is strongly associated with an improved prognosis. In the current study, a complete regression after oophorectomy was associated with high survival rates: 60.9% survival rate at 5 years after oophorectomy. The chances of survival were less impressive but still considerable (five-year survival rate of 31.1%) in patients who had partial regression. Patients who had no change or progression of the disease after oophorectomy had a much less chance of surviving five years (18% and 3.4%, respectively). The length of the survival after oophorectomy was therefore proportional to the degree of the response, underlining the great impact of the modification of the endocrine environment on the biology of the hormone-conditioned cancer cells. The degree of the response denotes the dimension of the fraction of hormone-dependent cells.

A crucial problem is the timing of oophorectomy, as there are indications that support the hypothesis that this procedure at the time of mastectomy may achieve better results. Paterson and Russel,[4] Cole,[5] Meakin et al.,[6] and Nissen-Meyer[7] reported some advantages in long-term survival of patients with breast cancer if ovarian suppression (with or without prednisone) was performed immediately after treatment of the primary carcinoma. However, two other studies reported no advantage in performing an immediate postoperative oophorectomy, compared with the oophorectomy done at the appearance of overt metastases.[8,9] We have no hard data to answer the question. On the one hand our results showed that the response rate was not significantly different in patients with locoregional recurrences and with visceral, lung, and bone metastases. As the tumor burden is heavier in patients with extensive visceral metastases and lighter in patients with limited locoregional recurrence, the extent of the disease is not an important factor in determining the response, a fact that contraindicates early oophorectomy. On the other hand, recent data showed that endocrine receptor rates decrease in breast cancer cells with the progression of the disease, therefore implying that an early ovarian suppression should be more successful than a late one. In our study the oophorectomy performed in patients with primary carcinoma and syncronous distant metastases, who may be defined as patients with aggressive, fast-

TABLE 4. *Response to Oophorectomy in Patients who had Previous Chemotherapy According to Amenorrhea*

	No. of Patients	Complete Response (%)	Partial Response (%)	No change (%)	Disease Progression (%)	Not Evaluable (%)
Amenorrhea absent	112	13 (11.6)	14 (12.5)	38 (33.9)	40 (35.7)	7 (6.2)
Amenorrhea present	68	3 (4.4)	12 (17.6)	25 (36.8)	27 (39.7)	1 (1.4)
Amenorrhea not defined	40	1 (2.5)	7 (17.5)	12 (30.0)	17 (42.5)	3 (7.5)
Total	220	17 (7.7)	33 (15.0)	75 (34.1)	84 (38.2)	11 (5.0)

growing disease, had a high response rate (40.2%). Equally high response rates were also observed in patients with metastases that appeared more than 4 years after the mastectomy, who may be considered patients with slow-growing disease. Patients who had metastases at intermediate periods from mastectomy (2–4 years) had the lowest response rate.

It is believed that patients with extensive visceral metastases should not be candidates for oophorectomy, but they should be treated first with aggressive chemotherapy.[10] In our study, however, patients with visceral secondaries had a response rate (23.8%) to oophorectomy that was not much lower than that of patients with other types of metastases.

ER values were an important factor in predicting the response to oophorectomy only if the determination was done on the metastatic tissue at the time of oophorectomy. In these conditions when ER values were positive the response rate was 47.8%. On the contrary the ER evaluation made on the breast carcinoma at the time of the primary treatment was of much less value in predicting the response to oophorectomy done at the appearance of distant metastases. In these conditions when ER values were positive, the response rate was 36.6%. The loss of the predicting value of ER values that were evaluated earlier on the primary tumor may be due to the biologic fluctuation of the cancer cells during the growth process, the selection of different cell clones that alter the biologic properties of the original tumor.

Patients who had previous chemotherapy, both as an adjuvant or as a curative measure, responded to oophorectomy at a lower rate (22.3%) compared with the patients who had not been treated with chemotherapy (36.6%). This reduction might be due to the fact that chemotherapy may partially act as an inhibitor of the ovarian function, therefore reducing the chances of the efficacy of a subsequent oophorectomy. Patients with or without amenorrhea after chemotherapy did not have significant differences in their response rates to oophorectomy. However, total regression was rare in patients with amenorrhea (4.4%) whereas it was not uncommon in patients without amenorrhea (11.6%). Although our data showed a reduced efficacy of oophorectomy in women who had previous chemotherapy, no clear indications as to the extent of the indirect endocrine effect of chemotherapy in premenopausal women were shown.

Conclusions

From our study we found that there are no elements in favor, or against, the indication of oophorectomy as an adjuvant treatment at the time of primary therapy. Appropriate studies are therefore needed.

Our data show that ER values as predicting factors of efficacy of oophorectomy are significant only when determined on secondary deposits at the time of oophorectomy. The ER value on the breast tumor determined at the time of the primary treatment is of limited relevance. Moreover, oophorectomy should be the treatment of first choice in all premenopausal patients with disseminated disease and with positive ER values or unknown ER values, including patients with visceral metastases. Finally, our results show that patients who had previous chemotherapy may remain candidates for oophorectomy (although with reduced expected rates of response), especially if menstrual periods were not suppressed.

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