Endocrine Ablative Therapy of Metastatic Breast Cancer

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It is estimated that 60 percent of the patients treated for breast cancer will eventually develop disseminated disease. While radiation therapy may provide palliation of local metastases for these patients, it has no beneficial systemic effect. Chemotherapy, especially with multiple drug regimens, is frequently effective for systemic therapy. However, it carries with it significant toxicity and does not prolong survival as effectively as endocrine manipulation. Hormonal additive therapy may also be quite useful but response rates and duration of response are not as good as with endocrine ablation. The major difficulty involved in electing endocrine ablation lies in choosing patients likely to respond to a major surgical operation. This review of the literature on endocrine ablative therapy is intended to provide the clinician with guidelines for selecting those patients who should be offered endocrine ablation as palliative treatment of their metastatic cancer. Although subjective improvement usually accompanies objective regression, only those reports are included which accept as evidence of objective response a period of six months or longer, during which time there is a decrease in the size of measurable lesions, healing of cutaneous ulcerations, radiographic evidence of calcification of osteolytic metastases, or decrease in the size or number of pulmonary nodules, without the appearance of new lesions.

In general:

- Soft tissue metastases have a better chance of response to endocrine ablation than does osseous involvement;
- Visceral metastases, especially to liver or brain, respond most poorly;
- Discrete nodular pulmonary lesions respond moderately well;
- Lymphangitic spread to the lungs responds poorly;
- Indolently progressing disease responds better than does rapidly progressive cancer;
- Patients with fulminant progression respond so poorly as to interdict endocrine ablation.

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The free interval (the time between mastectomy and the development of disseminated disease) is an index of the relative aggressiveness of the neoplasm and of the prognosis for response. Patients with a prolonged free interval not only have a better probability of response to endocrine ablation, but they are also likely to have a longer duration of remission if they do respond.

**Oophorectomy**

Premenopausal women with locally advanced ("primary inoperable"), recurrent, or metastatic disease will respond to oophorectomy in approximately one-third of the cases, the palliative effect lasting an average of 10 to 14 months. Oophorectomy, however, is rarely of benefit to women postmenopausal longer than one year. It also rarely benefits women more than 51 years of age who have had a hysterectomy. In the Memorial Hospital series, patients with regular menses had a 34.5 percent objective response rate while patients with irregular menses had a response rate of 27.2 percent. Postmenopausal women had a 7.1 percent response rate if they were within one year from the time of naturally occurring menopause. There was virtually no response if they were postmenopausal for more than one year. The overall response rate in premenopausal women was 32 percent, and the probability of response was best in perimenopausal patients. Age alone was shown to be of prognostic significance: 22 percent of women less than 35 years of age responded while 37 percent of those 46 to 50 years old responded. Similar results were observed in the Joint Committee investigation, in which Taylor reported a response rate of 16 percent in women younger than age 35, as opposed to 32 percent in older women. Only rarely did women more than one year postmenopausal respond. Women who did respond to oophorectomy lived an average of 31.2 months, while those who did not lived only 8.8 months.

The longer the free interval, the higher the response rate. In premenopausal women with a free interval of less than one year, there is a 28 percent probability of response; at two to four years, the probability reaches 34 percent and after five years or more it climbs to 55 percent. The probability of response according to the anatomic site of metastasis, in descending order, is as follows: opposite breast or chest wall recurrence, osteoblastic metastases, lymph nodes, osteolytic lesions, primary inoperable breast cancer, soft tissues and skin, and ovaries. Nodular lung metastases have a low probability of response, but have a better rate than that for lymphangitic spread to the lungs, metastasis to liver, or metastasis to brain. In fact, central nervous system metastasis, massive involvement of the liver with jaundice or ascites, pulmonary lymphangitic spread with respiratory insufficiency, pleural effusions, skeletal metastases with hypercalcemia, and myelophthisic anemia respond so infrequently and have such a high operative mortality rate that oophorectomy is generally not recommended for such disease.

The histologic type or grade of the primary breast cancer has no demonstrable effect on the probability of response to oophorectomy. The presence of mature follicles and corpora lutea in removed ovaries improves the chance of response.

Prophylactic oophorectomy performed at the time of initial mastectomy (without demonstrable metastasis) delays recurrence but does not improve overall survival. When effective, therapeutic oophorectomy prolongs the
survival time from the discovery of metastasis until death. Total survival time from initial breast cancer therapy until death, is not significantly greater in patients having prophylactic oophorectomy than in patients who are castrated only for recurrent or metastatic disease. Prophylactic oophorectomy does not benefit the patients (40 percent) who do not experience recurrent cancer. Since the response to therapeutic oophorectomy is one of the best determinants of probability of response to subsequent endocrine ablative therapy, it is suggested that prophylactic oophorectomy not be performed. If castration is delayed until appearance of recurrent cancer, only those women who are actually in need will undergo surgery. Survival rates are equal whether the operation is performed prophylactically or therapeutically. In addition, results can be used to evaluate patients for further endocrine ablation.

In premenopausal women, the rate of response to simultaneous oophorectomy and adrenalectomy, as the initial endocrine ablative therapy, is the same, or at most five to 10 percent higher than for oophorectomy alone. However, the duration of response is not increased over oophorectomy alone. The sequential employment of oophorectomy followed by adrenalectomy in responders who relapse produces an overall improvement in survival. Therefore, sequential rather than simultaneous oophorectomy and adrenalectomy is pre-
ferred for premenopausal patients.

Radiotherapeutically induced ablation of ovarian function produces the same response rate as oophorectomy but takes longer to achieve its effect.

Adrenalectomy

The response rate to adrenalectomy is reported in various series at between 30 to 50 percent. Patients who sustain an objective response live significantly longer (mean, 22 months) than non-responders (6 months). In most series, the operative mortality has been about four percent.

Older patients have a higher probability of response; the longer the time since naturally occurring menopause, the better the response rate. In the series from Roswell Park Memorial Institute, 25 percent of patients less than age 50 responded, while 38 percent of patients over 50 years of age responded. In the Ellis Fischel Cancer Hospital series, the response rate in women under age 40 was so low as to suggest that adrenalectomy not be performed on these patients unless they had responded objectively to previous oophorectomy.

With a free interval of less than one year, about 28 percent of patients will respond to adrenalectomy. At one to two years this increases slightly to 30 percent, but climbs to 44 percent with a free interval of more than two years. This indicates that the longer the free interval, the more likely the patient is to respond. In the Memorial Hospital
series (in which one-third of the patients sustained objective remission after adrenalectomy), opposite breast, soft tissue, skin, and osseous metastases were associated with a response rate of approximately 33 percent, while pleural metastasis or effusion and nodular pulmonary metastases were less affected (about 25 percent). Primary inoperable breast cancer had a 46 percent response rate, and inflammatory carcinoma a rate of 35 percent. Liver metastasis, myelophthisic anemia, and bone metastases with hypercalcemia responded poorly (about 10 percent); brain metastases did not respond at all. Thus, the anatomic site of metastatic disease served as an index of probability of response. In many series, central nervous system metastases, recurrent or persistent bloody pleural effusions, markedly restrictive pulmonary or pleural disease, liver metastases with jaundice and ascites, hypercalcemia, myelophthisic anemia, and fulminantly progressive disease responded so poorly to adrenalectomy as to prohibit the operation in such patients.

In patients who are premenopausal at the time their disseminated disease becomes manifest, the response to therapeutic oophorectomy serves as a good index of probability of response to subsequent adrenalectomy. In the Memorial Hospital series, patients who had previously responded to oophorectomy sustained a 40 percent remission rate after adrenalectomy, whereas patients who had not responded to oophorectomy sustained only a 17 percent rate of remission. In other series, premenopausal patients who had proven unresponsive to oophorectomy had only a five percent probability of response to adrenalectomy, an extremely low response rate, suggesting that adrenalectomy for patients unresponsive to oophorectomy is contraindicated.

Although some investigators have reported a positive correlation between response to androgens, estrogens, or corticosteroids, most have failed to demonstrate the prognostic value of prior response to additive hormonal manipulation. Furthermore, if endocrine additive therapy is used initially, with the intention of performing adrenalectomy as a secondary maneuver in hormonally responsive patients, there is a significant loss in the number of patients who will be constitutionally able to withstand the stress from adrenalectomy at that later time. A substantial proportion of patients will become greatly debilitated by their metastatic disease while under additive therapy, rendering them prohibitive operative risks. As a result, most surgical oncologists recommend adrenalectomy as the primary therapy in postmenopausal or oophorectomy-responsive premenopausal women while their general condition will allow them to tolerate the operation. Similarly, with regard to primary chemotherapy, some investigators have reported an inverse relationship between response to chemotherapeutic agents and subsequent response to adrenalectomy. Once again, during the time the patient is receiving chemotherapy, she may become too poor a risk for adrenalectomy. Consequently, adrenalectomy should be the initial rather than delayed therapy.

Recently, determination of estrogen-binding receptor protein in the primary breast cancer or its metastases has proven to be a promising prognosticator of response to endocrine ablative therapy (and, perhaps paradoxically, to endocrine additive therapy). Patients whose cancer contains the estrogen-binding receptor have a 50 to 65 percent
probability of response to adrenalectomy, while those lacking the receptor protein have less than a five percent response rate. Determination of estrogen-binding receptor protein can be useful in the selection of patients for endocrine ablative therapy and, perhaps more significantly, can eliminate such surgery for patients with a low probability of response. Similarly, the response of elimination of bone pain by the administration of L-DOPA can serve as a positive prognostic index of response to endocrine ablation.\(^6\),\(^7\)

**Hypophysectomy**\(^8\)-\(^20\)

The objective response rate to hypophysectomy in postmenopausal or oophorectomy-responsive premenopausal women ranges from 25 to 50 percent, a rate essentially the same as that for adrenalectomy. The operative mortality rate has been equal, approximately four percent. Responders live significantly longer than non-responders; mean survival in responders is comparable for adrenalectomy and hypophysectomy. Patients likely to respond to adrenalectomy are also likely to respond to hypophysectomy, although hypophysectomy appears to be somewhat more effective for visceral metastases. However, when the transsphenoidal route is used, hypophysectomy may frequently be employed in patients too debilitated to withstand adrenalectomy. In most respects, the benefits of hypophysectomy and adrenalectomy are equivalent. Only rarely will a patient who has responded to adrenalectomy sustain further objective regression after hypophysectomy.

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