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AN INTERNIST'S VIEW OF BREAST CANCER MANAGEMENT

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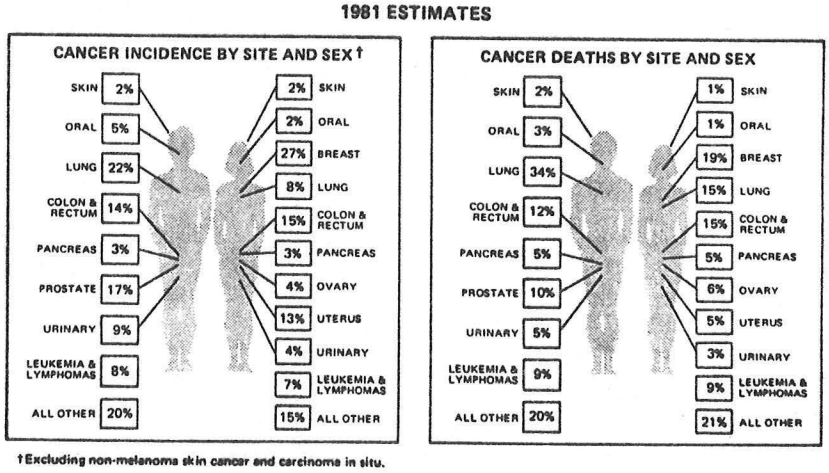
Breast cancer was last reviewed in this forum in 1976 by Drs. Frenkel (1) and Smith (2). Since that time, many of the concepts discussed have evolved so that approaches and treatment plans in the mid '70s are either not applicable or no longer considered to be dogmatically accepted. The purpose of my discussion today is to consider issues and problems in breast cancer management that the physician may come upon in his day-to-day exposure. In discussing these issues, I hope to impart a general philosophy which is applicable to the treatment of other malignancies.

I. RISK FACTORS IN BREAST CANCER



The incidence of breast cancer is approximately 1/1,000 women. This represents 27% of all cancer in women and 19% of female cancer deaths per year (3). In the Dallas-Fort Worth Metroplex there will be approximately 1,250 new cases of breast cancer. At least one out of eleven women will develop breast cancer during their lifetime. The most recent cancer statistics, which were compiled in 1980 and have not as yet been published, suggest that the incidence may be as high as one in ten women.

TABLE 1

RISK FACTORS IN BREAST CANCER

Factor	Favorable	Unfavorable
Benign breast disease	absent	present
Family history	absent	present
Hormonal status:		
Age at menarche	later	earlier
Pregnancy		
1. Parity	> 2	0
2. Age at first pregnancy	< 20	> 35
Age at menopause		
Natural	< 45	> 55
Surgical	< 35	---

A. Benign Disease

Benign disease is ubiquitous; it is fair to say that every woman will have a palpable mass in her breast at some time during her life. Thus, the importance of distinguishing benign breast lesions is one which clinicians are continually facing. It is critical for us to predict those that are at higher risk in order to extensively screen those with a more significant chance of developing breast cancer.

TABLE 2

BREAST CANCER RISK ASSOCIATION WITH BENIGN DISEASE

Diagnosis	Incidence per 1,000
Fibrocystic Disease	2.8
Fibroadenoma	3.1
Adenosis	6.4
Metaplasia	3.2
Papillomatosis	7.5
All	3.2

The diagnosis of benign disease has been associated with increased risk; the exact evaluation of the risk is difficult to determine. Table 2 shows data from Kaiser-Permanente Hospital in Oakland, California (4). When the same pathologic material is scored by the Black-Chabon method (5), which classified breast disease by duct atypia, there is an even stronger correlation with the more atypic breast diseases (Table 3). Similar results have been obtained from Black et al. (5), Donnelly et al. (6), and Monson et al. (7). However, one cannot say that the diagnosis of benign disease per se places a patient at higher risk because the incidence of breast cancer is higher in the population which would undergo a biopsy for benign disease than the expected 1 per 1,000 per year. This relates to the fact that breast cancer incidence increases with age. Thus, one can only say with assurity that breast cancer is associated with hyperplastic benign disease.

TABLE 3

BREAST CANCER RISK ASSOCIATION WITH BENIGN DISEASE

Black-Chabon Score	Incidence per 1,000
1 or 2	2.5
3	3.6
4	9.9
5	21.1

Another factor which is difficult to assess is the variation in the pathologic diagnosis of the benign diseases. All these studies represent efforts by extremely good surgical pathologists to give standardized diagnoses for highly variable diseases for purposes of compiling pathologic data. No such impetus exists in the absence of a study where the major concern of the pathologist is to distinguish benign from malignant disease. The relative proportions of duct atypia and hyperplasia are rarely consistently considered, and even in these studies it is difficult to determine how much epithelial hyperplasia is required to achieve a higher score.

TABLE 4

Estimated Increase in Lifetime Risk of Female Relatives of Women with Breast Cancer

Disease in patient	Relative risk: Breast cancer relatives / Control relatives		Calculated increase in lifetime risk
Premenopausal	3.1	× 6%	18.6%
Postmenopausal	1.5	× 6%	9.0%
Bilateral	5.4	× 6%	32.4%
Premenopausal, bilateral	8.8	× 6%	52.8%
Postmenopausal, bilateral	4.0	× 6%	24.0%

Note: Data obtained by multiplying familial relative risk times average lifetime risk.

B. Family History

Family history of breast cancer has been established as an important risk factor (9). Table 4 demonstrates that the age of the family member at the time of diagnosis is very important in determining the relative risk to an individual woman. The risk is even higher when the relative tumor was either multicentric or bilateral. When one considers the relative risk on the basis of family members involved, the risks become less obvious. Table 5 is data assimilated from a large Swedish study (10); it appears that mothers and maternal grandmothers do not affect risk whereas sisters and aunts do. As the incidence of breast cancer in the general population increases, the relevance of a single family member having breast cancer decreases. Thus, a general rule for a significant familial history of breast cancer is the presence of two or more maternal relatives and particularly if one of those relatives was premenopausal or had bilateral disease. Then the risk rises significantly and may approach 50 times that of the general population (11). It should be emphasized that only 10-15% of patients with breast cancer have a family history of a primary or secondary relative with breast cancer. Thus, its importance as a risk factor in the general population may be minimal.

TABLE 5

FAMILY HISTORY: RISK OF BREAST CANCER

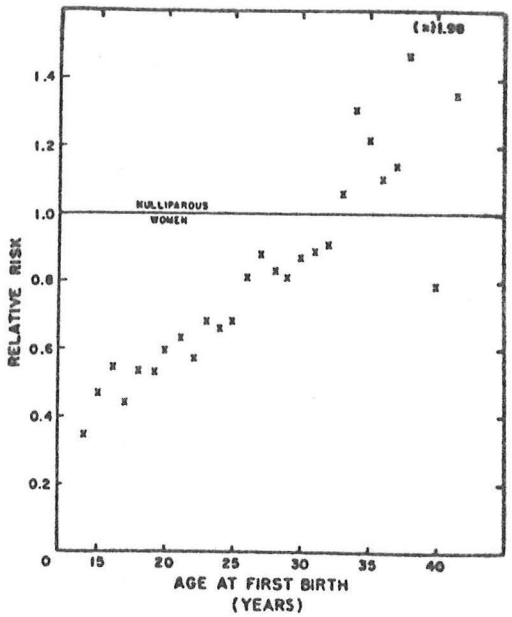
Relationship	Risk	P
Primary Relatives	1.7	< 0.01
Mother	1.4	NS
Sister	2.0	< 0.01
Secondary Relatives	1.5	< 0.05
Maternal Aunts	1.8	< 0.01
Grandmother	1.3	NS

After Adami et al. 1980

C. Hormonal Status

Much has been written as to the influence of the exposure to endogenous sex steroid hormones and the development of breast cancer. The major theory that has developed is that of the "estrogen window" (12). Briefly, this hypothesis suggests that a major etiologic factor in the development of breast cancer is the exposure to estrogens and that secretion of progesterone diminishes the effect of estrogens. The theory implies that estrogen, although not a classic chemical promoter, is capable of affecting environmental carcinogens. Secondly, progestational agents decrease estrogenic effects and are, thus, protective. The evidence for this theory is scanty and speculative. The total duration of estrogen exposure in women should be of major importance. No study to date has demonstrated this. Studies have shown that the age of menarche and the age of menopause affect risk (13). There is some difficulty in interpreting these data. The age of menarche which was most significant was greater than 16 (14), and that is relatively unusual in this country. Secondly, the age at menopause has been shown to be a beneficial risk factor if early and a significant risk factor if late. Again, the women at higher risk undergo menopause after 55 and surgical menopause is only a beneficial risk factor when it occurs prior to 35. Thus, these events which affect the duration of estrogen exposure are so rare one wonders of the statistical significance as well as the clinical relevance. Thirdly, no study examines the time from menarche to menopause in patients who develop breast cancers to demonstrate that it is prolonged.

FIGURE 2



The other major events in a woman's life affecting estrogen and progesterone are parity. It is always stated that this is an important risk factor, and that women who are less than 20 at the time of their first pregnancy are favorably affected and women older than 35 are unfavorably affected (13,15). However, if one examines the data in Figure 2, one sees that risk only increases after age 35 when compared to the nulliparous women. And that when one examines the numbers of patients in each group, the statistical significance of the later points is questionable (16). The risk with age of parity becomes even less significant when one divides the patients into fixed age groups and the beneficial risks vanish (14,15). At best, there is a trend toward greater risk or less benefit with increasing age at first pregnancy. The influence of the number of pregnancies is equally as perplex. There is little doubt that women who have been pregnant more than twice have a reduced risk of breast cancer (13,15,17). But successive pregnancies impart no further benefit (15,17). Thus, it is presumed that the lack of a pregnancy is most important. But it must be emphasized that statistically one cannot distinguish a different risk in women who have either none, one, or two full-term deliveries. It is argued that the time of first pregnancy and the number of successive pregnancies should be important factors with regard to the "estrogen window" hypothesis because of the estrogen and progesterone exposure. The lack of a decreased risk with less than two pregnancies or greater than three is not consistent with that hypothesis. This suggests that if the hypothesis is true, then there must be other potentially more important factors which have not been taken into account.

One would expect exogenous hormones to increase the risk of breast cancer; there is little data to support this. Birth control pills have no effect (18). Estrogens taken during pregnancy do not affect the incidence of breast cancer in either the mother or the fetus. However, one should emphasize that it may be too soon to detect an increased incidence with these associations. Similarly, there is no marked effect of perimenopausal and postmenopausal estrogens on breast cancer incidence. This is associated with an increase in chronic mastopathy in this age group, and there are data indicating that prolonged estrogen administration (greater than five years) has an increased risk of breast cancer with a latency of 10-15 years (18).

II. DIAGNOSIS OF BREAST CANCER

It is obvious that the diagnosis of breast cancer must be made by pathologic examination of tissue. The issues at hand are two: What type of screening is required, and when does one biopsy a breast mass.

A. Screening

Approximately 90% of breast masses are detected by the patient's deliberate or accidental self-examination. The latest NCI statistics indicate that no more than 20% of women are doing regular breast self-examination and that this percentage is decreasing each year since 1975 (19). The remaining 10% of breast cancers are detected by physician and mass screening techniques such as mammography. Since earlier clinical breast cancers have a better prognosis, a major emphasis needs to be placed on screening women for breast cancer (20). The HIP study, a screening evaluation of 62,000 women, demonstrated a dramatic increase in detection of early lesions and a better survival (20). This study, although encouraging, is laden with bias. There is a lead-time bias -- early detection may increase the time that the physician is aware of the tumor but not affect eventual survival; therefore, comparable breast cancers detected by screening will have a longer disease-free interval. There may also be a bias related to the growth rate of the tumor. Slower growing tumors are more likely to be detected by an interval examination, more rapidly growing tumor will be detected by the patient. Those diagnosed by screening examination would tend to be more benign and selected as to having a better prognosis. To determine if periodic screening is of value in breast cancer, studies must be evaluated over longer periods to determine actual differences in mortality. It is obvious that early diagnosis cannot adversely affect the patient with breast cancer.

Probably, the major role that we as physicians can have on detection of breast cancer is to encourage self-examination; there is no associated morbidity. It is important to question patients, provide literature on self-examination which is readily available from the National Cancer Institute, the American Cancer Society and our Cancer Center (phone 688-2182), and instruct them as to how to examine themselves. The second approach is to identify patients who are at higher risk to develop breast cancer so that we can be more selective with aggressive diagnostic studies. Recently, the NCI-ACS has developed guidelines for the use of mammography in women (21). The concensus suggests that mammography be used yearly for screening purposes in women accordingly:

TABLE 6

GUIDELINES FOR MAMMOGRAPHY

A. Significant suspicion of cancer (regardless of age)

B. Baseline mammogram at 35-40.

C. Yearly exam at 40-49 in high risk patients

D. Annual mammography for all women $\geq$ 50.

This recommendation takes into account what is felt to be negligible risk from low dosage mammography (0.1-0.5 rad/examination), the chance of detecting minimal breast cancer, and the cost of the procedure. Some of these suggestions are highly controversial. Many investigators feel that the increased costs greatly outweigh the benefits. There is no disagreement in following patients with high risks. The difficulty is in the suggestion of yearly mammography for women over 50. This is based on information which indicates that there is no risk to this age group from radiation induced breast cancer as to mammography, but does not consider the increment in the cost of medical care. Sadowsky et al. (22) and Cheek (23) have listed the following indications for mammography:

TABLE 7

Indications for Mammography
1. Suspected cancer in one breast
2. Survey of remaining breast
3. Large breasts
4. Screening (after age 45 to 50)
5. Suspicions aroused on BSE
6. High-risk women
(a) family history
(b) gross fibrocystic disease
(c) hyperplastic changes on biopsy
(d) intraductal papillomatosis
7. Evidence of metastatic disease without known primary

Studies underway will determine whether annual screening is appropriate in postmenopausal women and whether there is utility in a baseline examination. The remainder of the suggestions outlined in Tables 6 and 7 are not controversial.

Once a mammogram has been obtained, the following are indications for biopsy:

TABLE 8

Mammographic Indications for Biopsy
1. Calcifications
(a) focal collection
(b) diffuse
(c) linear or tubular (branching)
2. Masses
(a) stellate
(b) discrete or semidiscrete
3. Localized fibrotic area (asymmetry)
4. Altered subareolar duct pattern
5. Unrecognized skin edema
6. Unrecognized nipple retraction
7. Increased vascularity

B. Criteria for Biopsy

Frequently, patients will present to their physician with a mass which feels cystic. The cyst will be aspirated either by the surgeon or the gynecologist. Once the cyst has been aspirated, the following is indication for either biopsying or doing nothing (24).

TABLE 9

TREATMENT OF BREAST CYSTS

No further therapy

1. Serous fluid obtained
2. Mass completely disappears
3. Mass has not recurred at follow-up

Biopsy

1. No fluid obtained
2. Bloody fluid
3. Mass does not disappear completely
4. Mass rapidly recurs

Most investigators agree that cytologic evaluation of cyst fluid is not helpful because it is difficult to report consistently, particularly in institutions where it is done infrequently. This results in false positive and negative, and most investigations would rely on the above criteria for persuing other studies and/or biopsies (25,26).

TABLE 10

INDICATIONS FOR BIOPSY

1. Dominant mass
2. Cyst -- dry aspirate
   blood aspirate
   residual mass
3. Spontaneous nipple discharge or bleeding
4. Eczema of the nipple.
5. Suspicious mammograms
6. Presence of a breast cancer which is associated with multicentric disease

The above guidelines are reasonable indications for doing a breast biopsy.

III. PRIMARY THERAPY

The intent of primary therapy is, where possible, to erradicate all tumor. The therapy which will be appropriate is dependent on the tumor burden at diagnosis and

the predictions as to prognosis which can be made on the basis of a given presentation. These predictions are based on staging data which is presented in Table 11 (27).

TABLE 11

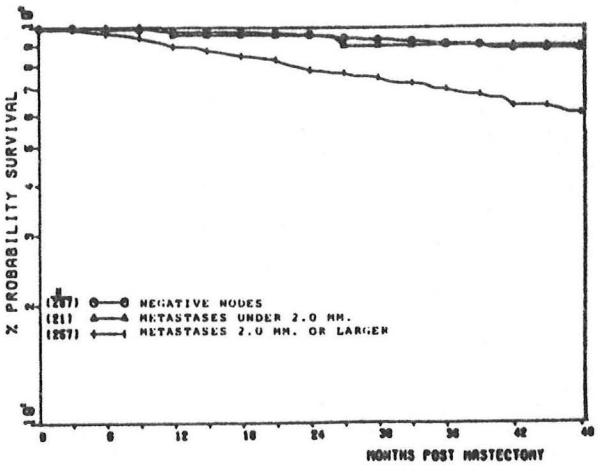
PROGNOSIS ACCORDING TO PATHOLOGIC STAGE

Stage	Tumor	Nodes	Ten Year Survival
I	< 2 cm	0	85%
II	< 5 cm	1-3 > 4	35
III	> 5 cm; grave signs	+	rare
IV	metastatic disease	+	rare

Most staging classifications are based on clinical data as opposed to the final histologic data. Palpable axillary nodes are not involved with tumor in approximately 20% of patients and non-palpable axillary lymph nodes are involved in at least one-third of patients (28,29). Thus, presurgical staging is only a guideline and predictions as to prognisis should be modified when the additional data of an axillary node dissection becomes available.

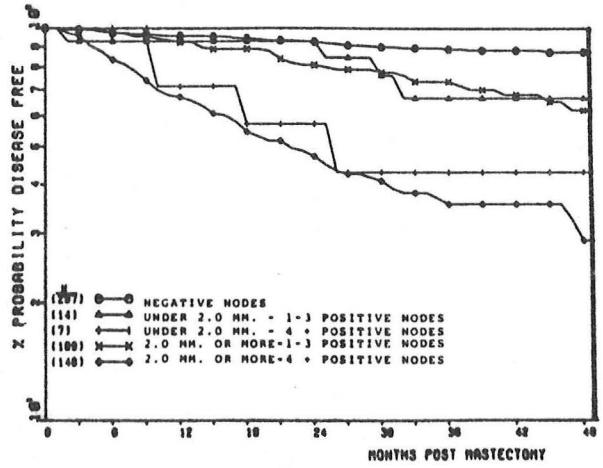
It is clear that the size of the tumor and the presence of axillary lymph nodes are the two most important prognostic factors. Recent studies have suggested that micrometastasis (< 2mm) to lymph nodes and breast cancer found only on additional pathologic section of lymph nodes does not affect prognosis similarly to macroscopic metastatis (30,31). Fisher et al's data does not support these conclusions (31). One can see that at four years survival is identical to patients without nodes, but those disease-free are identical to those presenting with axillary nodes. It can be presumed that this difference relates to the tumor burden and the growth rate of the tumor and that the ultimate survival will be similar to those patients with positive axillary nodes. Whether this is similarly applicable to breast cancer which is found only in lymph nodes by more extensive examination is not known since there are very few patients at risk (30). Based on tumor doubling times, one would estimate that it could take ten years to distinguish differences if they existed and the patients at risk have not been followed for that long.

FIGURE 3



Life table probability of survival after mastectomy in patients with negative axillary nodal metastases and those measuring <2 mm or ≥2 mm.

FIGURE 4



Life table probability of survival without disease by months after mastectomy in patients with micro- and macrometastases according to number of involved nodes.

It is important to note that most breast cancer staging results are often given as a 5-year survival; this does not indicate that patients are disease-free. Most investigators think in terms of 10-year disease-free survival as a point which indicates relative curability. Even after 10 years, there is a small proportion of patients that continue to relapse (32,33). As a generalization of staging data, Table 11 summarizes prognosis. Suffice it to say that stage I is highly curable with local-regional therapy alone and with stage II disease there is a very highly likelihood that the patient will go on to develop metastatic disease. Stages III and IV represent systemic disease at presentation. Treatment should be designed to reflect these prognoses.

A. Limited Disease

Since stage I disease has such a good prognosis, investigators have been trying to determine if radical surgery is necessary. The classic Halsted radical mastectomy was designed for local control -- i.e., to eradicate disease on the

chest wall. This approach has best been expressed by Haagensen and his results have become the "gold standard" against which all other therapies must be compared (34). The initial studies compared radical surgery to simple mastectomy plus radiation therapy -- these were essentially equivalent as to survival (35,36). Other studies have compared radical surgery with and without radiation therapy (37) and radical surgery with simple mastectomy with and without radiation therapy in patients without clinically evident nodes (38). Although published follow-up in many of these studies is only five years old, there is no evidence to suggest that radical surgery alone is any different from simple mastectomy plus radiotherapy in clinical stage I and II breast cancer. The modern "gold standard" is now the modified radical. The simple mastectomy has few proponents because it does not include an axillary node dissection which is critical to the pathologic staging.

Since radiation had been shown to be effective in controlling local and regional disease when used in conjunction with a simple mastectomy, many groups have treated selected stage I patients with primary excision of the mass (this is called tylectomy, lumpectomy, segmental mastectomy, or wedge resection) and radiation therapy (39-42). The approach with radiation therapy has been approximately 5,000 rads to the breast and axillary lymph nodes and an additional boost of 2,000 rads to the tumor-bearing area by either tangential radiation or iridium (^{192}Ir) implants. Dr. Hellman presented his impressive data last year. Clearly, at five years in small numbers of selected patients, there is no difference between patients treated with modified radical and those treated with minimal surgery plus radiation therapy. And certainly the cosmetic result is spectacular when minimal surgery is done. Veronisi et al. have recently reported a randomized study using a more extensive surgical procedure, the quadrenectomy, showing no difference in local recurrence (Table 12), or sites of metastatic disease (Table 13) (42). There is no difference in disease-free interval or survival (Figures 5 and 6).

TABLE 12

Local or Regional Recurrences, Second Primary Breast Cancers, and Distant Metastases.

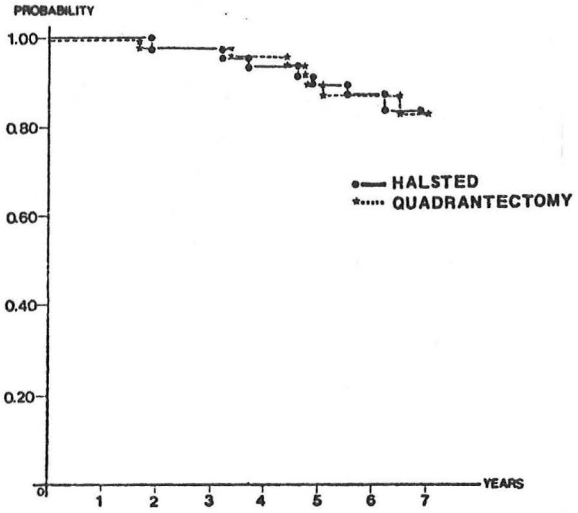
VARIABLE	TREATMENT	
	HALSTED	QUADRANTECTOMY
	number of patients	
Local recurrences	3	1
Second primary tumors		
Ipsilateral breast	0	4
Contralateral breast	5	9
Distant metastases	30	22

TABLE 13

Distribution of Distant Metastases by Site.

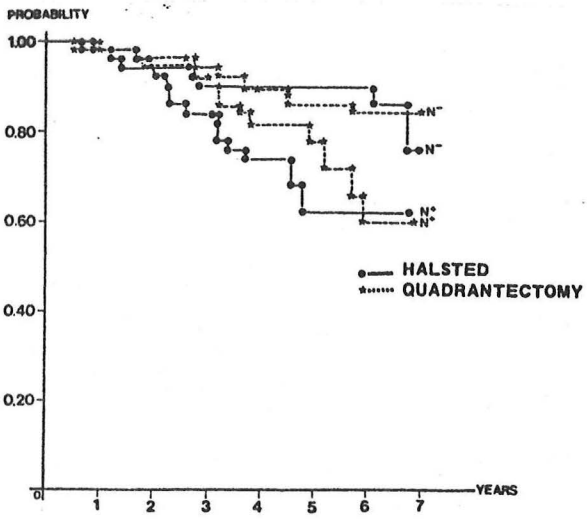
SITE OF METASTASIS	TREATMENT	
	HALSTED	QUADRANTECTOMY
	number of metastases	
Lung or pleura	9	11
Bone	16	10
Liver	5	3
Lymph nodes or skin	9	5
Central nervous system	1	1
Other sites	2	2

FIGURE 5



Actuarial Overall Survival in Patients Treated with Halsted Mastectomy or with Quadrantectomy, Axillary Dissection, and Radiotherapy (Log-Rank Test: Overall Chi-square, 0.02 with 1 Degree of Freedom; P = 0.88).

FIGURE 6



Actuarial Disease-Free Survival According to Presence (N+) or Absence (N−) of Axillary-Node Metastases (Log-Rank Test, Adjusted Value: Overall Chi-square, 0.75 with 1 Degree of Freedom; P = 0.38).

One of the major controversies with Dr. Hellman's work is that his patients are selected. For this reason, the NCI and the NSABP have undertaken randomized trials to overcome this bias. A second issue has been whether the combined radiation and limited surgery radiates patients unnecessarily; this is being addressed by a limited surgery with no radiation therapy arm in the

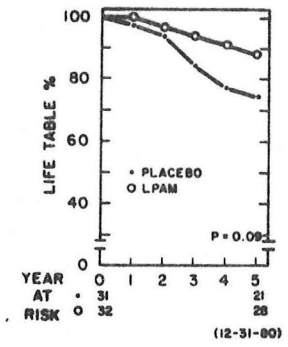
NSABP protocol. Since most of the patients treated with limited surgery and radiation did not have axillary node dissection, it is impossible to predict their pathological stage and how well they would have done with standard treatment regimens. Hellman's group presently is doing and recommending "limited" (i.e., approximately 10 lower axillary nodes) axillary dissections. Approximately 10% of all breast cancer is multicentric and probably a similar proportion is associated with co-existant minimal cancer (59). It is not obvious that radiation will be adequate therapy for these situations. Another important question is whether patients who have axillary node involvement treated with limited surgery plus radiation therapy will tolerate and respond as well to adjuvant chemotherapy. This is particularly important if Bonadonna is correct as to the importance of the percentage of the total chemotherapeutic dose required to obtain a response to chemotherapy (43). It may also be important if the delay in administration of adjuvant chemotherapy necessitated by the radiation therapy is critical as Holland et al. have suggested (44).

I am optimistic that most of these questions will be answered in a preliminary fashion within the next five years. However, with the numbers of patients involved and the small differences which may be detected, it is conceivable that definitive answers in a comparison of truly minimal surgery plus radiation therapy with the modified radical will not be obtained for 10-15 years, if ever. It is fair to say that as of 1982 in patients with pathological stage I breast cancer that limited surgery plus radiation therapy appears to be as effective as surgery.

B. Adjuvant Chemotherapy

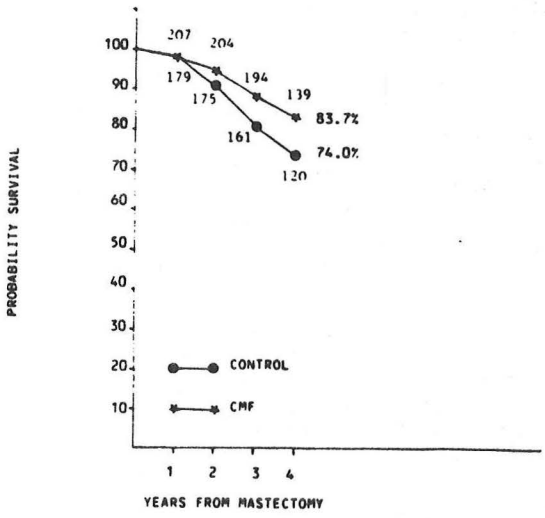
Adjuvant chemotherapy of breast cancer has been a generally accepted form of therapy in premenopausal patients with disease involving the axillary nodes (pathological stage II). In this group of patients ineffective regimens, like melphelan for one year (Figure 7) (45), and more effective regimens, like CMF (Figure 8) (46), have prolonged survival (Figures 7 and 8).

FIGURE 7



Survival
Comparison of L-PAM with Placebo
-Pts. 49 Yrs; 1-3 Pos. Nodes-

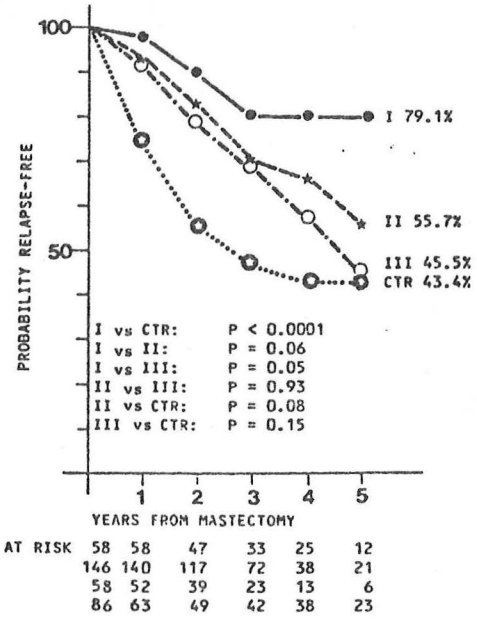
FIGURE 8



CMF program: overall survival

The effect of adjuvant chemotherapy on postmenopausal patients is less clear. In my previous grand rounds, I discussed the changes that were observed by Bonadonna as the CMF data matured from two to five years (47). In a recent paper, he has reviewed the dosage of medication which postmenopausal patients received and tolerated (Figures 9 and 10) (43). This retrospective analysis demonstrated the importance of the total medication dosage received with only those patients receiving 85% of predicted dose doing significantly better than controls at five years. I, frankly, do not know how to interpret this data. It is a retrospective study, biased by the investigator's conception that CMF is effective in postmenopausal disease. The numbers of patients that received less than optimal therapy are skewed towards those that did not do well with chemotherapy. Other adjuvant studies which are less mature are demonstrating a significant effect on postmenopausal women (45,48,49). These studies, however, have the potential to become less significant with time.

FIGURE 9

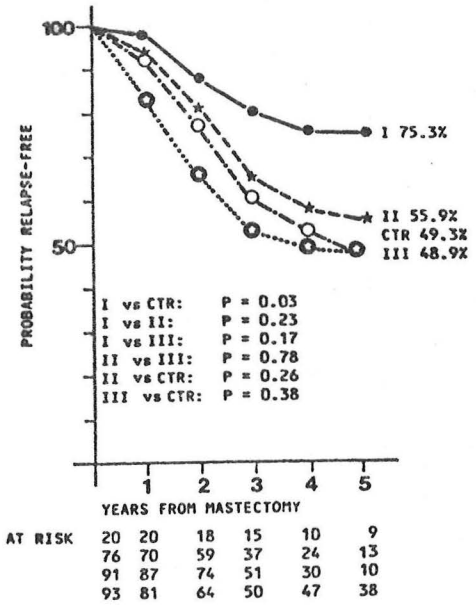


Relation of Relapse-Free Survival to Dose Level in 348 Premenopausal Patients.

The dose levels are indicated by I (>85 per cent of the optimal calculated dose), II (65 to 84 per cent), and III (<65 per cent); CTR denotes controls. The percentages beside the dose levels show the proportion of patients who did not have relapses during the five years.

The numbers at the bottom of the figure denote the number of patients at risk.

FIGURE 10



Relation of Relapse-Free Survival to Dose Level in 280 Postmenopausal Patients.

The second major question to be asked of adjuvant therapy is: Does adjuvant therapy cure patients with breast cancer? The concern is that adjuvant therapy may be just delaying the time to relapse, that is prolonging the disease-free interval (DFI). There is some recent data to suggest that with adjuvant therapy the time to relapse is prolonged as well as survival (45,46). The original NSABP melphelan study (50) demonstrated an affect on the DFI in premenopausal patients with four or more nodes, but no effect on survival.

Now their study no longer shows a difference in the percentage of patients that are disease-free, but there has been an increase in survival (51). This suggests that there will be an eventual prolongation of survival without benefiting overall survival. In Bonadonna's CMF study, the percentage of patients disease-free with 1-3 positive nodes remains greater than the controls, but it is no longer greater in those with more than three nodes (Table 14) (52). This suggests that both ineffective regimens and greater tumor burden adversely affect adjuvant chemotherapy.

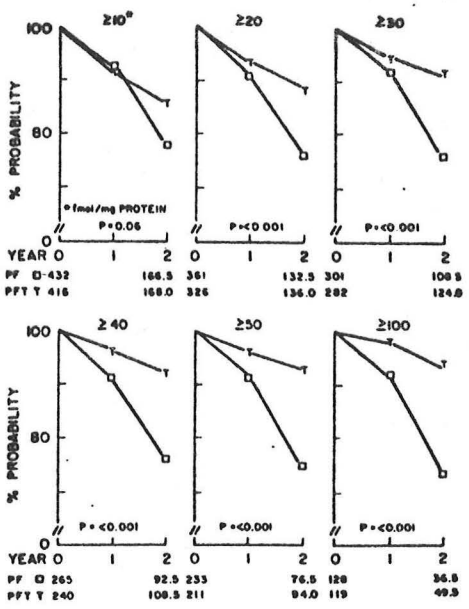
TABLE 14

CMF vs Control: 6-year Results
Data are in percent

	Control (179)	CMF 12 (207)	P Value
RFS, total	43.8	55.7	0.001
Nodes 1-3	45.6	65.1	< 0.001
Nodes > 3	31.8	35.7	0.27
Premenopause	42.7	59.8	< 0.001
Postmenopause	44.9	50.5	0.35
Survival, total	64.5	73.9	0.12

Another approach to adjuvant therapy currently under investigation is the combination of hormone therapy with chemotherapy. Fisher, et al. have shown that tamoxifen, a drug with antiestrogen and estrogenic effects, in combination with fluorouracil and melphelan significantly increases the percentage of patients disease-free when stratified on the basis of the tumor estrogen receptor value (Figure 11) regardless of menopausal status (49). Approximatley 50% of the patients with ER receptor values greater than 10 fmole/mg protein would be expected to respond to tamoxifen. It is possible that the difference in DFI relates not to a synergistic effect of hormones and chemotherapy, but to the separate action of these modalities. Unfortunately, no tamoxifen alone, control arm, was included in the initial study. The study does not necessarily indicate a survival advantage for the hormone therapy could be implemented at a later time when patients recur without deliterious effects. The NSABP made the assumption that tamoxifen would have no deliterious effects on the population of patients who would not respond to hormones. However, they have found that the addition of tamoxifen to melphelan and fluorouracil in premenopausal women who have low levels of ER and/or PR significantly effects the response to chemotherapy (51). As a result, they are no longer treating these patients (ER < 20 fmole/mg protein) with hormones and therapy. Thus, the combination of hormone and chemotherapy may have adverse effects on selected patients. It is only with controlled studies and continued observations of this trial that we can determine if it is appropriate to treat patients with hormones and chemotherapy.

FIGURE 11



Disease-Free Survival of All Patients Compared with Estrogen-Receptor Positivity.
The numbers of patients at risk are shown along the x axis. P values were derived through the life-table method.

Our Approach to Adjuvant Therapy

CMF remains the standard adjuvant therapeutic regimen. Studies suggest that fluorouracil plus melphelan, CMFVP, and cytoxan-adriamycin are equally effective. We use CMF because 1) the drugs have not been associated with a major increased risk of leukemia (melphelan), 2) there is no cumulative toxicity (adriamycin cardiac toxicity), and 3) it is much simpler than CMFVP. We treat for twelve months, although there is preliminary data suggesting that six months may be adequate (52). Our approach has been to treat all patients with stage II disease (lesions > 2 cm and/or positive nodes) regardless of menopausal status and estrogen receptor values. Premenopausal patients whose tumors contain no estrogen receptor have a poor prognosis (49). There are ongoing studies where these patients with stage I disease are receiving chemotherapy but there is no data to justify this approach outside a clinical trial. We are not combining tamoxifen with chemotherapy. Although this is an attractive concept, the data presented to date does not justify this approach outside a clinical trial.

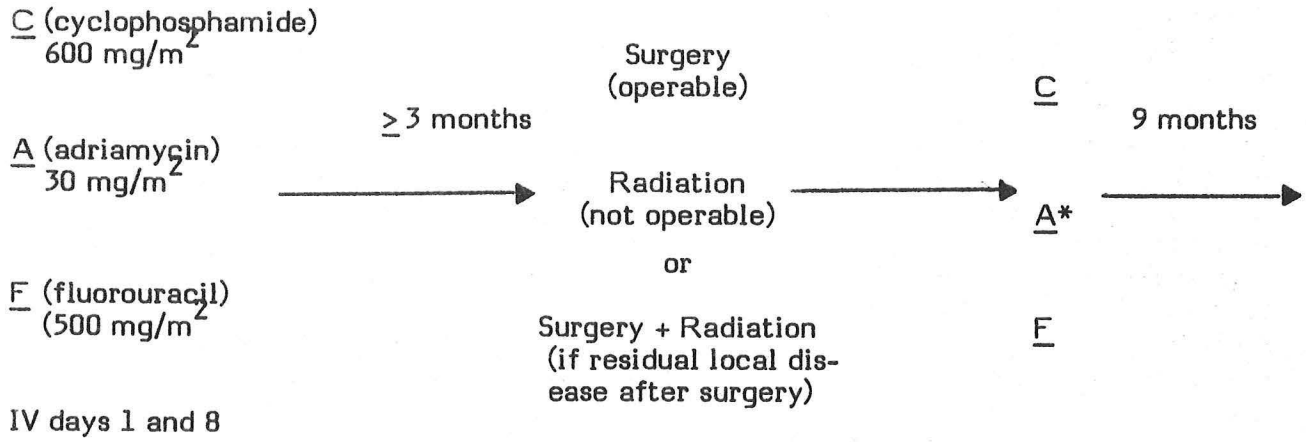
We do not use radiation therapy in our patients who receive adjuvant chemotherapy. Bonadonna has demonstrated that adjuvant chemotherapy effectively reduces the risk of local recurrence to that of patients treated with surgery and radiation therapy (53). Secondly, we have concern as to our abilities to give adequate doses of chemotherapy in patients who have received radiation therapy. Thirdly, radiation therapy if given in the immediate post-operative period delays adjuvant chemotherapy approximatley two months, which is probably inappropriate. The last point is that radiation therapy does not affect survival.

C. Advanced Disease

It is obvious to any individual who has cared for patients with extensive disease at presentation that neither surgery nor radiation therapy or the combination of the two modalities have been little more than paliative procedures. Recurrence is rapid, patients have both local recurrence and metastatic disease, and survival is rare. The addition of chemotherapy as an "adjuvant" has not significantly affected survival. The reason for this failure of chemotherapy is due to the tumor burden and the resistance of breast cancer to the chemotherapeutic agents and regimens which are now available. To put it simply: We cannot cure metastatic breast cancer. For this reason, we have developed a somewhat different approach to patients who present with advanced disease (Table 15). Since these patients die of metastatic disease, it is our assumption that the appropriate approach is to treat the metastatic or potentially metastatic disease first and, secondarily, treat the extensive local disease. Patients are treated initially with chemotherapy for at least three courses unless there is obvious progression. We have selected CAF as the combination chemotherapy; it probably works the best in metastatic breast cancer with approximatley an 80% remission rate (54). This is followed by surgery if the tumor has become "operable" and by radiation therapy if there is residual disease following surgery. If the tumor is not "operable" after three cycles of chemotherapy, then radiation therapy alone is utilized. We have treated twelve patients with this protocol over the past year and our results, although preliminary, do suggest that we can obtain both local control and probably delay the time to the development of metastatic disease in most patients. We do not think that we will be able to cure patients using this present regimen because the chemotherapy has such a transient effect on metastatic disease, the mean duration of remissions being between 8 and 14 months (54). Since our approach is logical, based on the natural history of extensive breast cancer, we will probably demonstrate its efficacy. However, without better drugs or drug regimens, we will probably not have any long-term survivors.

TABLE 15

PRIMARY TREATMENT OF EXTENSIVE BREAST CANCER



*methotrexate (40 mg/m^2 substituted for adriamycin after total dose of 450 mg/m^2

D. Pre-malignant and minimal breast cancer

The management of patients with breast disease which has a high likelihood of becoming invasive has modified somewhat over the past few years. As we discussed in an earlier section, there is a group of patients who are at high risk to develop a breast malignancy. When the clinical situation suggests that the risk is real, then the patient should be considered for prophylactic bilateral total glandular mastectomies (55,56). This procedure differs from a subcutaneous mastectomy in that the nipple is removed but the areolar complex remains. An example of a patient to be treated would be a woman who has a strong family history -- one primary and one secondary relative -- who has proliferative fibrocystic disease. Another type of patient might have fibrocystic disease who has multiple biopsies in the past with proliferative mastopathy and can no longer be evaluated by physical examination or mammography. A patient with proven malignancy in one breast with mastopathy which suggests that a tumor may develop in the other breast is a candidate for a single glandular mastectomy.

The surgical procedure requires removal of the nipple and greater than 95% of breast tissue (56). It is usually done with an immediate reconstruction and the implants are placed submuscularly (57). Five to ten percent of these patients will have invasive cancer detected at surgery (58). When this occurs, patients should undergo a more extensive surgical procedure including axillary node dissection. The arguments against a total glandular mastectomy are that careful observation decreases the risk of developing invasive cancer so that the procedure is unnecessary and, secondly, the remaining 5% of breast tissue may still become cancerous.

Minimal breast cancer or non-infiltrating breast cancers are either lobular, papillary, or intraductal in cell type. Haagensen has reported that 30% of cases become invasive cancer with a delay in development of as long as 25 years (59). When the tumors become invasive, they are associated with multicentric and bilateral disease. Haagensen has defined it as having the following criteria:

TABLE 16

CHARACTERISTICS OF MINIMAL BREAST CANCER

1. Premenopausal women
2. Multifocal
3. Does not form palpable tumor
4. Does not metastasize
5. Does predispose to invasive carcinoma
6. Carcinomas occur equally in contralateral and ipsilateral breast

Various authors make the case for either surgery or observation. Only an occasional plastic surgeon would consider a subcutaneous or glandular mastectomy, and this is inappropriate because of the breast tissue which

remains (60). Given the length of time between diagnosis of the minimal cancer and the progression to invasive disease, it is difficult to demonstrate that immediate extensive surgery is effectively curing a subset of patients who would go on to die of invasive disease.

Patients with minimal cancer have not been treated with segmental mastectomy followed by radiation therapy. This would not be expected to be effective since the growth rate and the growth factor of these tumors should be very low and, therefore, not responsive to radiation therapy.

It must be emphasized that it is often quite difficult to distinguish non-invasive disease from invasive breast cancer. Multiple sections from these tissues should be carefully reviewed by pathologists who are experts in breast cancer. It is obvious that the prognosis is very different when there is tumor invasion.

III. THERAPY OF METASTATIC DISEASE

It is estimated that about one-third to one-half of patients with breast cancer will go on to develop metastatic disease. Few, if any, patients have been cured of metastatic disease. Therapy does prolong survival and relieve symptoms in up to 80% of patients. The predictors listed in Table 17 are associated with a prolonged survival with metastatic disease. In breast cancer, three therapeutic approaches are available for palliative purposes: radiation therapy, hormone therapy, and chemotherapy. In a patient with metastatic disease, they will all be brought into play to achieve maximal survival and alleviation of symptoms.

TABLE 17

PREDICTORS OF PROLONGED SURVIVAL WITH METASTATIC DISEASE

DFI > 2 years

Postmenopause

ER positive

Soft tissue or osseous metastasis only

A. Radiation therapy

Radiation therapy has four roles in the treatment of metastatic disease. It is the only effective treatment for CNS metastases; this includes brain, spinal, and retro-orbital disease. It is the most effective means to alleviate a painful bone lesion, particularly one that no longer responds to another therapeutic modalities. Thirdly, radiation should be used to prevent fractures in lesions affecting weight-bearing bones. And in patients with local recurrence, it is felt to be the only means whereby local control can be achieved (61).

B. Chemotherapy

More than 15 drugs have been demonstrated to induce tumor regression in more than 20% of patients (62). The major drugs used today are cyclophosphamide, adriamycin, methotrexate, and fluorouracil. These are usually given in combinations which can achieve up to an 80% response rate (54). The philosophy that we use is to attempt to achieve a response with a regimen that does not contain adriamycin. Adriamycin is then used at a point later on in the disease when the patient has failed the initial therapy. This avoids the cardiac toxicity and the generalized malaise, myopathy, diarrhea, alopecia, etc., that is associated with adriamycin. This approach allows us to use adriamycin to salvage those who have failed the initial regimen. This gives us an agent with a 50% response rate for salvage therapy (62). Our approach would include adriamycin in the primary regimen if the disease were life-threatening like with liver metastases or lymphangitic involvement of the lung.

In patients who do not have life-threatening disease, chemotherapy is typically reserved for those patients who have either failed hormone manipulations (see the following section) or whose tumors have no significant levels of estrogen receptor. Since chemotherapy acts more rapidly than hormonal therapy, patients with life-threatening visceral disease will be treated initially with chemotherapy regardless of their potential to respond to a hormone manipulation.

C. Hormone therapy

TABLE 18

Rates of Objective Response to Newer Forms of Endocrine Therapy.

Therapy	No. of Patients	Response Rate (%)	Range of Responses (%)
Antiestrogens*			
Tamoxifen†	504	35	22–49
Nafoxidine‡	283	31	28–38
Clomiphene‡	167	28	16–39
Medical adrenalectomy§			
Aminoglutethimide‡	280	31	25–50

TABLE 19

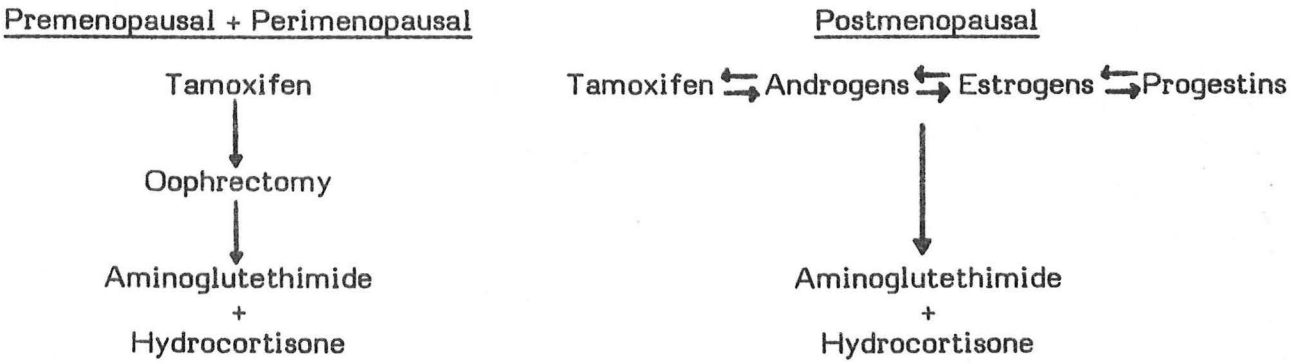
Objective Response Rates to Conventional Forms of Endocrine Therapy.

Therapy*	No. of Patients	Response Rates(%)	Range of Responses
Hormones[120,133-151]			
Estrogens†	1683	26	15–38
Androgens‡	2250	21	10–38
Progestins	508	25	9–43
Corticosteroids	589	23	0–43
Ablation[152-177]			
Oophorectomy§	1674	33	21–41
Adrenalectomy	3739	32	23–46
Hypophysectomy	1174	36	22–58

Hormone therapy is either ablative or the exogenous administration of steroid hormones or antagonists. It is effective in about 50% of patients whose tumors contain estrogen receptor and about 70% of those patients whose tumors have either high values of ER or both ER and PR (63). Since the data for each approach has been accumulated over a period of 30 years, it is difficult to compare relative responses unless the data has been accumulated in a large trial comparing specific agents. It is particularly difficult to compare the new agents like tamoxifen with estrogens and androgens (Tables 18 and 19). Studies are presently underway to do this. There are many statements in the

literature, indicating that 1) hormones do not work in visceral disease, 2) estrogens work only on postmenopausal patients with visceral metastasis, 3) androgens work best in postmenopausal patients with osseous lesions. These are largely unsupported by data. Combinations of hormones or hormones plus ablations have not been shown to be more effective than a single manipulation -- this is in contrast to chemotherapy where mulit-agents are necessary for optimal benefit. To date, there is little evidence to suggest a logical approach to hormone therapy. Most investigators would agree with the following plan:

TABLE 20



In premenopausal patients, tamoxifen is the first choice because it has been shown that premenopausal patients responding to tamoxifen can respond to oophrectomy at a later time but patients responding to oophrectomy will not respond to tamoxifen (64). For those who have responded to oophrectomy, aminoglutethimide is the next agent rather than ablative surgery. Aminoglutethimide blocks steroidogenesis and estrogen synthesis as effectively as hypophysectomy or adrenalectomy without requiring surgery, it does not suppress the pituitary except for ACTH synthesis, and the antagonistic effects are completely reversible (65). The situation is a little more confused in the treatment of postmenopausal patients. All agents probably are equally effective as a primary approach. Most investigators agree that failure to respond to one agent does not preclude a response to a second agent. However, most would not persue further intervention following two failures. Tamoxifen is the most widely used drug in this group; the data to support its use are highly selected. Ongoing studies are comparing it to other agents and the preliminary data suggests that the differences are small, if any. Once primary endocrine therapy fails, approximately 50% of patients who have responded will respond to an ablation of steroidogenesis.

Patients to be treated with hormone therapy should be selected by the presence of ER in the primary tumor or, if possible, in the metastatic lesion. The response to an endocrine therapy correlates best with the level of the ER or the presence of ER and PR. Hormone therapy is usually used empirically in postmenopausal patients where ER was not obtained. It is generally reserved for patients that do not have liver or lymphangitic lung metastases. However, in a smaller percentage of patients, probably less than 20%, it will be effective in these disorders.

In treating metastatic disease with chemotherapy, the oncologist attempts to obtain a remission. If this is not obtained, the therapy is stopped and other therapies begun. In hormone therapy, one tries to attain a remission. However, since the hormones are not toxic, an oncologist will continue to treat a patient with hormones as long as there is no evidence of disease progression.

IV. CONCLUDING REMARKS

This overview has presented a number of important issues in the approach to a patient with a breast mass and breast cancer. My comments obviously have been prejudiced by my experience and my interpretation of the available data. The bias is that of a medical oncologist, an internist, and a breast cancer researcher. The purpose of this review has been to impart a philosophy of patient care that is based on the clinical data available and oriented towards the future. It is presumed that the suppositions and generalizations made will be supported by studies that are ongoing and anticipated.

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