APRIL 5, 1986

THE NSABP EXPERIENCE WITH CCOPs

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I am pleased to represent the National Surgical Adjuvant Breast and Bowel Project (NSABP) and to discuss the impact that the Cooperative Group Outreach Programs (CGOP) and the Community Clinical Oncology Programs (CCOP) have had on the NSABP. More specifically, it is a privilege to represent the Chairman of the NSABP, Bernard Fisher, M.D., and to discuss with you some of the experiences of the approximately 2,000 physician investigators and more than 600 nurses and data managers who are integral parts of our cooperative group.

The NSABP is a specialized research base. Our interest is operable breast and bowel cancer exclusively. We have tried to answer specific biologic questions as they relate to these two diseases. Some questions studied include:

1. What is the appropriate local/regional therapy for these diseases?
2. Who is at risk for systemic spread and how do we define that risk?
3. What is the effect of systemic adjuvant therapy on micrometastases?

Our mechanism, or clinical tool, to accomplish these objectives is the large prospective, randomized, controlled clinical trial. The NSABP has conducted 13 such trials since 1970. It is my job to tell you, in a limited manner, something about these trials, specifically emphasizing our cancer control network (CGOP) and its influence in the community. Finally, I will discuss our more recent early experience with the CCOPs that are affiliated with the NSABP.

Dr. Peter Deckers, Chairman of Cancer Control for the NSABP, highlights data on results from the group.

Protocol B-04 of the NSABP, depicted in Figure 1, is a surgical protocol with which I am sure most are very familiar. This trial has demonstrated that prophylactic axillary dissection is not, in and of itself, a therapeutic event. It does help stage the axilla. It defines those women at high risk for microscopic metastatic disease. It also demonstrated quite clearly that regional radiation therapy can sterilize metastatic disease in the axilla and it set the stage for Protocol B-06, Figure 2—a segmental mastectomy study designed to understand the clinical significance, if any, of multicentric disease in the affected breast.

B-06, at least at five years of follow up, has provided data to support the longstanding belief that selected women need not have their breast amputated for Stage I and Stage II disease. Selected patients can be treated by segmentectomy and radiation therapy with the same survival and freedom from breast recurrence as that offered by the traditional modified mastectomy. Moreover, a much better cosmetic result and less psychologic insult is usually associated with the lesser operative procedure. Patients in B-04 and B-06 will continue to be followed for many years.

FIGURE 1

NSABP PROTOCOL B-04
Trial Design

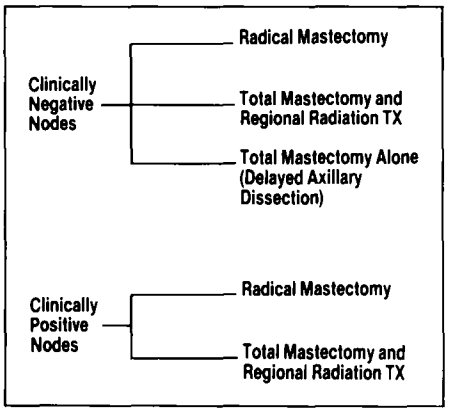

FIGURE 2

NSABP PROTOCOL B-06
Trial Design

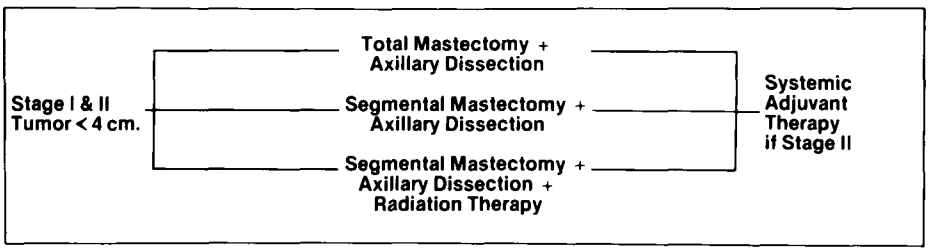

FIGURE 3

NSABP
Breast Cancer Trials—Stage II

				Accrual
B-05	P	VS	M	380
B-07	P	VS	PF	741
B-08	PF	VS	PMF	737
B-09	PF	VS	PFT	1891
B-10	PF	VS	PF-CP	252
B-11	PF	VS	PAF	689
B-12	PFT	VS	PAFT	1082

TOTAL PATIENTS = 5772

These two studies have had significant impact on clinical practice throughout the United States. Both have given considerable information regarding the impact on prognosis of positive nodes in the axilla. Most patients with positive nodes have systemic, micrometastatic disease elsewhere in their body. These systemic micrometastases will eventually grow, destroy the function of the involved organ and, ultimately, unfortunately, destroy the patient.

This new biology, that most breast cancer is a systemic disease, led to nine adjuvant trials conducted by the NSABP, seven of which are listed in Figure 3. In each trial, accrual has been completed. Note that almost 6,000 patients have been accrued to the seven trials. Additionally, when B-15 and B-16 (active Stage II trials) are completed, over 8,000 patients with Stage II breast cancer will have been studied. This very important data base should define the role of adjuvant chemotherapy against micrometastases. Is such therapy cytostatic or cytolytic? Will survival in breast cancer be improved? These studies also provide much important data about unexplored pathologic variables including hormone receptor data. As Dr. Fisher has often remarked, adjuvant chemotherapy has at least perturbed the natural biology of breast cancer in some subsets of women.

The NSABP became convinced, early in the course of its trials, that it could not depend on large medical centers alone for accrual of patients. Many patients with breast cancer were treated quite successfully by community physicians in community hospitals. This resource could not be ignored if timely answers to the biologic questions under study were to be achieved. Since 1971, the NSABP has accrued over 14,000 patients. In 1985 alone, over 2,000 patients were accrued to our adjuvant trials and more than 50% of these patients were cared for exclusively by community physicians.

In Figure 4, some very interesting and provocative data supplied to the NSABP from the National Cancer Institute regarding accrual to NSABP adjuvant trials as compared to other breast trials that are ongoing in the United States is presented. The NSABP has two trials in the Stage I disease and two trials in Stage II disease—a total of 4 of the 15 trials now active. At first glance, the NSABP can be proud of the fact that over three out of four patients accrued to Stage I trials are accrued to the NSABP studies. Overall, one out of every two patients with Stage I and Stage II disease are accrued to the NSABP activity. The sad part of this data is the fact that only 2,372 women with Stage I and II disease were studied in the United States last year. This represents, even for the most optimistic, well less than 5% of the people who were eligible for study or inclusion in active adjuvant trials. Moreover, at best only 60% of the patients with breast cancer are cured. It is hard to understand why so many physicians would advocate chemotherapy outside of a trial as standard when we are doing this poorly.

From where do the NSABP patients originate? To be sure, they come from our grant institutions which are, in general, large University institutions or large hospitals affiliated with Universities. However, an increasing number of our patients come from our network activity and from the CCOPs affiliated with the NSABP. This community involvement through our cancer control networks (CGOP) will be first explored in more detail.

The NSABP realized, as did many other cooperative groups, that optimal cancer management required not only a multidisciplinary approach, but more importantly, if patients were to be accrued in a timely fashion, a multi-institutional approach was necessary. This was to be the backbone of the NSABP CGOP activity. Many of the NSABP networks developed Regional Oncology Programs with one nucleus institution and several satellite hospitals. The purpose was the transfer of knowledge, technology and expertise normally found, and frequently only affordable, in the medical centers, to the community institutions. The satellite community hospitals were often small in bed number, i.e., between 100-200 patients. In many of them, medical oncologists and nurse oncologists did not exist; radiation therapy was not present. In fact, no cancer program was operative. Many of the patients in these institutions received surgical intervention, but then, because of the frequent long distances involved in travel to a major medical center, they did not receive the adjuvant therapy that the NSABP thought so important. Our network cancer control objectives were more encompassing than only treatment. They included:

1. Provision of support services for community physicians
2. Institution of quality control by analysis of accrual and treatment data
3. Provision of continuing medical education

FIGURE 4

ACCRUAL INTO ONGOING BREAST PROTOCOLS
(From NCI)

PATIENT POPULATION	NO. TRIALS	CURRENT ACCRUAL TOTAL	CURRENT ACCRUAL NSABP	CURRENT ACCRUAL % NSABP	ANNUAL ACCRUAL TOTAL	ANNUAL ACCRUAL NSABP	ANNUAL ACCRUAL % NSABP
STAGE I	4	2239	1924	86	661	515	78
STAGE II	11	4220	1347	32	1711	734	43
Pre-Menopause	4	1606	959	60	666	444	67
Post-Menopause	4	2024	388	19	589	290	49
Pre and Post Menopausal	3	590	—	—	456	—	—
TOTAL	15	6459	3271	51	2372	1249	53

4. The field testing and evaluation of new treatments
5. Rapid dissemination of information about effective treatments

The mechanism for accomplishing the end results of many of the Regional Oncology Programs, or the NSABP CGOP, including accrual to clinical trials, was the establishment of multidisciplinary clinics in our satellite hospitals. Education through conferences and tumor boards was equally important. The educational activities were also considerable. They involved the training of nurses in data management and in the administration of chemotherapy. They also involved training of physicians because there was considerable prejudice concerning administration of multi-agent chemotherapy in some of these satellite hospitals. There was also a prejudice concerning center institution physicians and nurses working in these facilities. A considerable concern was also voiced by the administrators of many of these hospitals regarding whether or not this type of intervention, specifically medical oncology practiced in their small hospitals, could be cost effective. Additionally, patients and their families needed education relative to the efficacy and side effects of these treatments. For those of us who have been immersed in this activity since 1978, we are also aware that there was a considerable technology transfer through the CGOP activity. There was no question that surgeons in the community were taught an appropriate approach to cosmetic segmentectomy and an appropriate approach to quantitatively and qualitatively correct axillary dissection. Pathologists were also instructed relative to appropriate axillary clearance and to the correct analysis of margins after segmentectomy. Tumor markers and receptors were required on all patients and antiquated radiotherapy activity and equipment was dismantled and replaced with new equipment in many hospitals.

FIGURE 5

NSABP NETWORK

1978 · 33 DEVELOPED
21 ACTIVE
>3000 PATIENTS · 21%

1985 · 813 PATIENTS · 41% (2009)

OVER 700 COMMUNITY PHYSICIANS ARE INVOLVED WITH NSABP AS A RESULT OF NETWORK OUTREACH ACTIVITIES

The impact of the outreach networks in the first year after funding on accrual alone was observed most clearly in Protocol B-09 of the NSABP which is a prospective randomized controlled trial in Stage II patients comparing l-Phenylalanine mustard and 5-Fluorouracil (PF) with PF plus tamoxifen (PFT). In the first year after network funding and involvement, there was a dramatic 27% increase in patient accrual to B-09 from our cancer control satellites. This, in our opinion, was not attributable directly to the positive ambience that was developing in the United States relevant to adjuvant chemotherapy. It was much in excess of that ambience.

Further analysis of data from B-09 showed that, as a result of the CGOP activity, 63% of all of the patients accrued had their surgery performed, their chemotherapy administered, and their follow up conducted completely in the community. The accrual activity of the entire NSABP network in our community hospitals was even more dramatic and is seen in Figure 5. Since 1978, we have developed 33 networks; 21 are now active. Over 3,000 patients have been accrued, a figure which represents 21% of the total NSABP accrual. More significant is the trend. In 1985, 813 patients were accrued which represents 41% of the total NSABP accrual for that year.

Evaluation of the data submitted was an important component of the network activity. We initially had no objective mechanism for evaluating these patients. We developed our own evaluation strategy and measured patient accrual, physician contacts, educational activities, support services, and quality control. Rigorous application of our evaluation strategies have failed to show any differences between our networks and grant institutions and, more recently, between either of these and the CCOPs affiliated with the NSABP.

In summary, the 21 cancer control networks of the NSABP are vitally important. There has been a 44% increase in accrual between 1984 and 1985 and, I emphasize, this represents, in 1985, 41% of the total NSABP accrual.

Accrual from the CCOPs which have existed for the past three years is also revealing. Initially, 18 CCOPs chose the NSABP as a specialized research base. In Figure 6, the accrual activity of the CCOPs in the NSABP for the past two years, 1984–85, is seen. While the total number of patients represents a relatively small percentage of the total NSABP activity, it is important to place this in perspective. When the CCOP activity and the network activity for 1985 are combined, this represents 52% of the total NSABP accrual (1,026 of 2,009 patients)—a very critical component of the NSABP activity. Our CCOP investigators were involved in all of the NSABP adjuvant trials; not only the more difficult Stage II breast adjuvant chemotherapy studies but, also, they have made a very significant contribution to the more surgically oriented colon portal vein perfusion study. In Figure 7, the NSABP affiliated CCOPs and their accrual is seen. I show this with some pride because the CCOP with which I now am affiliated, the Greater Hartford CCOP, had the highest number of CCOP patients accrued to NSABP trials in 1985. However, the tragedy of this particular slide is that even with 34 patients accrued from the Greater Hartford CCOP, I can tell you, as Chief of Surgery of the Hartford Hospital, that this represents only 14% of the patients who are eligible for accrual from that facility. Much work remains to be done.

As indicated earlier, when the CCOPs are evaluated, from any point of view, their performance is equal in all respects with that of our longstanding grant-funded institutions. We see no differences whatsoever. It is also true, as might be expected, that those CCOP physicians who had some experience with the NSABP have accrued a larger percentage of their total accrual to NSABP activity. We are, however, especially impressed with those CCOP physicians who did not have anything to do with the NSABP previously. They generated 130 patients in 1985. Though our network accrual

FIGURE 6

NSABP COMMUNITY ACCRUAL

	1984	1985	%INCREASE
NETWORK	563	813	+44
CCOP	110	213	+94

showed a dramatic increase in 1985, we are astounded by the CCOP improvement—a 94% increase in accrual in 1985 compared to 1984 (Figure 6). It appears that a mustard seed, if you will, has been planted; it's been nourished a bit; it's been cultivated. We hope that it will continue to grow as dramatically as it grew in the last year.

In addition, the CCOP physicians have a very important advisory and administrative role in the NSABP. They are on all of our major committees including the Executive Committee. There are 185 major committee appointments in the NSABP. Twenty percent (20%) of these now belong to community physicians or nurses and, if one adds the network (CGOP) principal investigators to this, 33% of these 185 committee appointments are allocated to community physicians.

In conclusion, the NSABP network, or CGOP, as we see it at least, is a highly effective and expanding activity. There has been a steady increase in protocol accrual, physician involvement and group wide, community-based, educational programs. Dr. Fisher, I am sure, would emphasize this next point very strongly: *The network is critical if NSABP clinical trials are to continue!* Patients with breast and bowel cancers are not at the Centers. They are in the community and will remain there. The network, we believe, can contribute much data to address unexplored cancer control issues. We find no inherent patient or physician differences between the community networks and major medical centers. The community physicians, as I've shown you, are now essential members of all NSABP committees. We believe that the NSABP network accrual, education, and evaluation techniques can be a model for all other outreach programs. We believe that CCOPs that are having difficulty meeting their accrual objectives could be helped by looking at our techniques in this regard.

Additionally, the CCOP patient and physician populations, do not, in our opinion, overlap with the CGOP activities. The CGOP activities relate primarily to smaller hospitals with less well developed cancer control activities than those operative in most CCOPs. The CCOP NSABP accrual and data management, to the present point, has been excellent. The network (CGOP) and CCOP programs allow access to community patients without unnecessary travel and expense. Moreover, as more and more medical oncologists were trained and set up community practices, the CGOP and CCOP activities allowed these physicians to remain academically involved through their participation in clinical research. We feel that the CGOPs and CCOPs are complimentary, not competitive, cancer control activities. Maintenance and expansion of both programs is essential if clinical trials are to have an impact on cancer control in the United States.

The NSABP feels very strongly about the viability of the CCOPs and would welcome non-NSABP CCOPs as members of our research activity. In the next RFA, we would strongly support qualified institutions who wish to become part of the NSABP through the CCOP mechanism. We feel there can be a considerable transfer of ideas and strategies for accrual and education between the CGOP and CCOP physicans, nurses, and data managers. If this cooperation occurs, an already good community-based cancer control activity will become much better and more patients will receive comprehensive, state of the science, rather than art, oncologic treatment planning and care. ■

FIGURE 7

Patients Entered and Followed by CCOPs with an NSABP Affiliation

INSTITUTION NAME	PATIENTS ENTERED 1983	1984	1985	# FOLLOWED (12/31/85)
CCOP, Allegheny-Singer Research Corp.	6	10	13	29
CCOP, Alton Ochsner Med. Fnd.		6	25	29
CCOP, Billings Inter-hospital Project	9	18	18	43
CCOP, Central New York, Syracuse	1	1	3	5
CCOP, Columbus, Ohio	1	14	12	26
CCOP, Grand Rapids, MI	0	6	4	10
CCOP, Greater Hartford		1	34	34
CCOP Green Mountain Oncol. Group, VT		2	13	15
CCOP, Marshfield Clinic, WI	13	20	28	60
CCOP, Midwest, Kansas City, MO	3	5	10	17
CCOP, Newark Beth Israel	0	8	15	23
CCOP, North Mississippi, Tupelo			1	1
CCOP, So. Nevada CA. Res. Fnd.	2	4	1	7
CCOP, West Virginia, Charleston		7	23	30
Total	35	102	200	329