Eur J Cancer Clin Oncol, Vol. 21, No. 2, pp. 149–154, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

Perspectives and Commentaries

Organization of Clinical Oncology in the U.S.A.: Role of Cancer Centers, Cooperative Groups and Community Hospitals*†

PAUL P. CARBONE

Department of Human Oncology, Wisconsin Clinical Cancer Center, University of Wisconsin, 600, Highland Avenue, Madison, WI, 53792, U.S.A.

IN 1982 in the U.S.A. 785,000 patients were diagnosed with serious cancers, defined as excluding skin cancers and carcinoma in situ of the cervix. According to a recent report of the Director of the NCI, 350,000 or 45% are now curable [1]. Approximately 27% (214,000) are curable by surgery alone. Another 12% (90,000) are effectively treated with surgery and radiation therapy and 6% (46,000) by combining surgery, radiotherapy and/or drugs. Thus any discussion of the organization of cancer treatment in the U.S.A. must include definition of roles for the specific specialists as well as the institutions, cancer centers, cooperative clinical trials groups and community hospitals.

CANCER PERSONNEL

In the U.S.A. surgical oncology has only recently received formal recognition as a distinct speciality. The elements of training are still only defined broadly as an additional year of surgery residency dedicated primarily to cancer care. No certification is available as yet, but programs are reviewed by the Society of Surgical Oncology [2].

Since 1971 there has been a dramatic increase in the numbers of trained physicians in medical oncology and radiation oncology. According to estimates by the NCI, there were 1880 certified medical oncologists in 1980, with the numbers increasing annually by about 300. The number of certified radiation oncologists in 1980 were 1400. Both of these figures for 1971 were less than 100. The training for medical oncologists requires 3 yrs of general medicine and 2 yrs of subspeciality experience, with very often a third year added for research. A specific written examination is required for certification [3]. The programs are now being reviewed for quality and content by a committee of the American Society of Clinical Oncology and the Residency Review Committee of the American Medical Association (AMA).

Radiation oncology requires 4 yr of training after medical school, with written examinations and a formal program review. The first year of training is a mixed medical-surgical experience.

As more and more individuals are trained in the cancer specialities, they are becoming widely distributed throughout the country. According to the NCI, 80% of cancer patients are treated in community hospitals, defined as primary care, non-university-operated facilities. Cancer patients may receive all of their primary care in community hospitals and may not be referred to any cancer center or participate in research protocols. Referrals to centers are now being done for second opinions, rare tumors and pediatric cancers. More and more patients are sent to centers after they fail primary treatment.

CANCER CENTERS

In 1971 the National Cancer Act stimulated the funding and development of regional comprehensive cancer centers with broad missions in cancer research, education and control. At the time there were only three categorical cancer centers in the U.S.A. After extensive planning and review, 20 comprehensive cancer centers were

Accepted 26 July 1984.
*Supported by Core grant No. P30CA14520 and ECOG grant No. U10CA-21115.
†Presented at Dr. Daniel den Hoed Symposium, Rotterdam, The Netherlands.

recognized (Table 1). The purposes of the cancer centers were to extend knowledge and understanding of the causes, mechanisms, detection, diagnosis and tretment of multiple forms of cancer through multidisciplinary programs in basic and clinical research. The concept was to provide conducive environments for interdisciplinary collaboration.

The comprehensive cancer centers are located at major medical institutions, usually universities, and were intended to be regionally responsible for cancer activities. The original plan called for cancer centers within 100 miles of each patient. The centers received federal funding for construction, administration and research. Most have organized research programs with NIH grant support independently reviewed and funded. The minimum needed for core grant eligibility was $750,000 of approved grants.

In 1982, 62 Centers had active core grants from the NCI. Of these, only 20 have the designation comprehensive. Laboratory research centers are located at 16 universities and 26 are designated as clinical research centers. Recognition as a center involves funding a core grant. The core grants are used to support salaries for the director(s) key scientific and administrative personnel, shared equipment, developmental research grants and facilities remodelling. The specific research projects are not supported by the core grant and neither are educational or control projects. Control efforts are defined as community outreach efforts that may or may not contain research elements.

Table 1. Comprehensive cancer centers

University of Alabama in Birmingham
Los Angeles—University of Southern California
UCLA—Jonsson Comprehensive Cancer Center
Comprehensive Cancer Center for Connecticut at Yale
Georgetown University—Howard University Comprehensive Cancer Center
Comprehensive Cancer Center for the State of Florida
Illlinois Cancer Council
The Johns Hopkins Comprehensive Cancer Center
Metropolitan Detroit Cancer Center, Detroit, MI
Dana-Farber Cancer Institute
Mayo Comprehensive Cancer Center
Columbia University, New York City
Memorial Sloan-Kettering Cancer Center
Roswell Park Memorial Institute
Duke University Comprehensive Cancer Center
The Ohio State University Comprehensive Cancer Center
Fox Chase Cancer Center—University of Pennsylvania
The University of Texas System Cancer Center
Fred Hutchinson Cancer Research Center
University of Wisconsin Clinical Cancer Center

WISCONSIN CLINICAL CANCER CENTER

As an example of a comprehensive cancer center, I would like to briefly decribe the origins and development of our center, located at the University of Wisconsin Medical School, a major American university. The university is located in a town (Madison, WI) of 180,000 people and in a state of 4.5 million people. We are geographically 150 miles from Chicago and 200 miles from Rochester, MN and 250 miles from Minneapolis. MN. At each of these cities major medical facilities exist.

In 1973 the University was awarded a grant to develop the Wisconsin Clinical Cancer Center (WCCC), combining two major efforts in radiation oncology (then part of Radiology) and clinical oncology (part of Surgery) to form the Department of Human Oncology. Thus the Cancer Center started as a multidisciplinary program, although medical oncology was not directly involved. I became the Director of Clinical Oncology and increased the medical involvement greatly, so that we now have ten medical oncologists, eight radiation therapists and four surgical oncologists. In addition, we have over 20 Ph.D.s with specific laboratory projects. In 1979 we moved into a new, seven-story tower attached to the University Hospital with over 70,000 square feet of space and near the 50 inpatient beds located in the main hospital. The tower contains over 40,000 square feet of research space, 10,000 square feet for an outpatient clinic, 10,000 square feet of animal housing and 10,000 square feet of radiation therapy facility. The structure of the Department of Human Oncology is shown in Fig. 1. The members of the Department have professorial rank and, as Chairman, my rank is equivalent to the Professors of Surgery, Medicine and Pediatrics. The faculty can teach courses in the University and we have recently received permission to teach and grant a Ph.D. degree. This is usually reserved for non-clinical, basic research departments.

The Cancer Center has an overlapping, but distinct, entity from the Department. Its objectives are shown in Table 2 and its structure in Fig. 2.

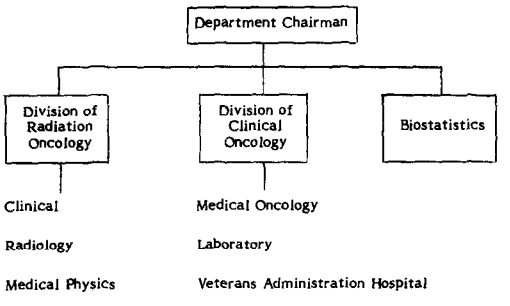

Fig. 1. Department of Human Oncology.

Table 2. Objectives of Wisconsin Clinical Cancer Center

1. To undertake innovative laboratory, preclinical and clinical research
2. To encourage and facilitate multidisciplinary research between laboratory scientists and clinical investigators
3. To improve clinical cancer care through multidisciplinary research and clinical trials
4. To be a focal point for cancer education throughout Wisconsin and the surrounding region
5. To provide the best setting for training health personnel

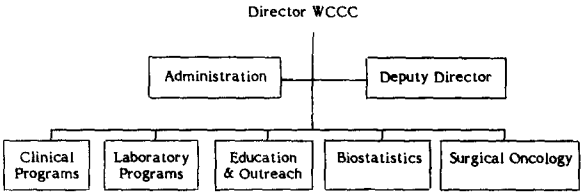

Fig. 2. Wisconsin Clinical Cancer Center.

The Center is interdepartmental and attempts to coordinate some, but not all, cancer activities throughout the medical school. Its responsibility includes cancer education for medical students, residents, fellows and post-graduate medical personnel, and clinical protocol review. The Center provides space and support for research in terms of administration and shared resources (Table 3). Membership in the Cancer Center is voluntary and carries no academic rank. The 80 Center Associate Members are elected by the Center leadership group on the basis of cancer-related research, educational training or service. Altogether the Center has 120 members.

The budget of the Cancer Center is shown in Table 4. About 70% of the effort is supported by grants from the NCI. Other resources are supplied from the state budget, practice income and voluntary contributions. The core grant provides for about 20% of our support and usually takes care of partial salary support for research investigators, salaries for administrators, and for developmental project support to support new initiatives. We also receive support from voluntary organizations such as the American Cancer Center, Leukemia Society, etc.

Table 3. Wisconsin Clinical Cancer Center

Shared Resources	Supporting Services
Glassware washing	fiscal management
Radiation—experimental	personnel
Scintillation counting	purchasing
Safety	
Histology laboratory	
Analytical laboratory	
Data management	

Table 4. Budget 1981/1982 of Wisconsin Clinical Cancer Center

	Direct costs	Share (%)
Federal Government	$4,341,984	69.8
U.W. Medical School	696,537	11.2
Other U.W.	60,592	1.0
Corporate/private	466,489	7.5
Clinical fees	394,934	6.3
Reimbursed services	260,722	4.2
Total	$6,221,258	100

CLINICAL RESEARCH AT THE WCCC

Laboratory research is traditionally investigator-initiated and oriented. The individual researcher may or may not seek collaboration with others. Clinical research is usually interdisciplinary and involves laboratory-clinical interactions or intermedical discipline collaborations. At the WCCC we have organized research groups concentrating on specific research topics (Table 5). These groups oversee specific research areas and initiate protocols based on clinical or laboratory findings.

As an example, a recent idea arose over applying laboratory concepts to clinical studies of cancer prevention. Drs Boutwell and Verma, from the laboratory, had worked out the principles of initiation and promotion in mouse skin. They had shown a direct relationship between induction of skin cancer in the mouse and the induction of ornithine decarboxylase after initiation and promotion with phorbol esters [4]. A small group was formed to take human skin and work out the assay system *in vitro* using specimens of skin obtained from surgical amputations. A young clinical resident became involved and the work proved successful, showing that ODC activity could be induced in human skin by TPA application *in vitro*. A series of experiments are planned to form the basis of future trials in cancer prevention.

Table 5. Wisconsin Clinical Cancer Center Research Programs, 1984

Breast	phase I
Urologic cancer	prevention
Gynecologic cancer	bone marrow transplantation
Immunobiology	colon cancer
Pharmacology	medical physics
Hyperthermia	brain tumors

CLINICAL TRIALS AND THE EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG)

Our efforts in the Cancer Center are usually designed to test new and innovative possibilities in small plot projects. Even though at the University of Wisconsin we see over 2000 cancers a year, we would not be able to mount large-scale clinical trials strictly in-house. The results of these pilot projects, if positive, require large-scale testing. Our outlets for these studies are two, the ECOG and the Wisconsin Oncology Group (WOG). The latter organization is small and limited as yet. Major efforts involve the ECOG.

The ECOG was organized in 1954 to test the cancer drugs developed by the NCI. The Group has now grown to include 28 members, scattered throughout the U.S.A., and involves over 236 hospitals and 1287 physicians. The administrative structure is shown in Fig. 3.

The major components are the Statistical Center, the Operations Office and the institutional members. The responsibilities of each are outlined in Tables 6-8. The Statistical Center, under Professor Zelen, is located in Boston, MA at Harvard University. The Statistical Center has responsibility for data management, quality control, statistical considerations of protocols and data analyses. The Operations Office provides administrative support for the Group, develops and distributes protocols, initiates randomizations and distributes data to investigators and the Statistical Center for analyses. The office also maintains manuscript files and arranges for audits. The Principal Investigators at each of the institutions provide leadership and organization to conduct research.

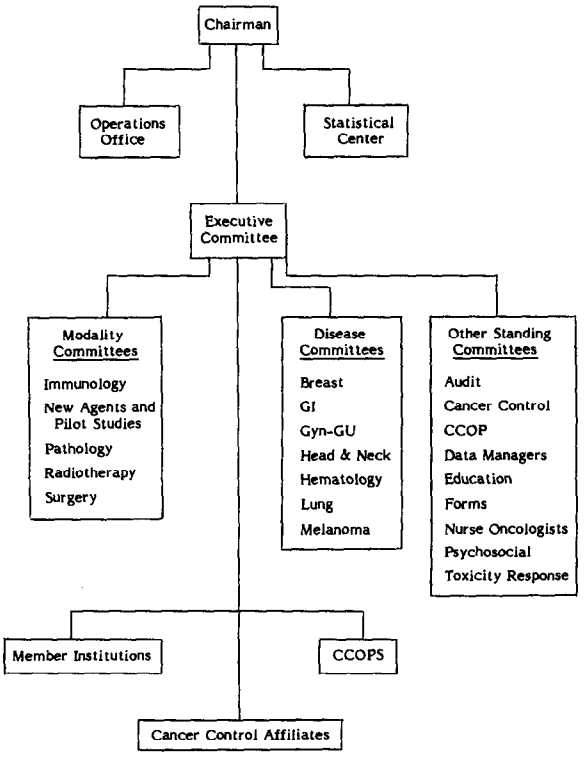

Fig. 3. ECOG structure.

Table 6. ECOG Statistical Office responsibilities (Director, Professor Marvin Zelen: Harvard University)

Statistical design
Data management
Quality control
Data analysis
Study reports

Table 7. ECOG Operations Office (Director, Dr. Paul P. Carbone: University of Wisconsin—Madison; Executive Director, Dr. Thomas E. Davis)

Administrative support
Develop and distribute protocols
Initiates randomization
Distributes forms
Arranges on-site audits
Maintains manuscript files

Table 8. ECOG principal investigators

Provide leadership
Arranges for data management
Conducts research program
Training of fellows

The two other important aspects of the group are the Disease/Modality Committees and the Executive Committee. The Disease/Modality Committees consist of interested individuals who develop and coordinate research protocols in specific disease or modalities. The Executive Committee is the main policy group for ECOG, recommending members and setting procedures. The Chairman of ECOG serves for a 3-yr term. The elected members of the Executive Committee serve for 2 yr. The Committee Chairman are selected by the Group Chairman and serve for 2 yr.

Funding for the Group comes primarily from the NCI through grants on a 3- to 5-yr basis. Separate grants are given to the Operations Office, the Statistical Center and individuals. The overall allocation is $3.5 million/yr. Even this large amount does not pay for all research costs and additional monies for salaries come from other sources. Special projects may come from drug companies and receive separate funding. Membership and participation in ECOG is not tied into funding from the NCI.

COMMUNITY CANCER PROGRAMS

Since 1970 an increasing proportion of our patients in ECOG have come from our com-

munity affiliates. With increasingly larger numbers of cancer specialists located at community hospitals, the ECOG adopted a policy of encouraging participation from community groups. Besides providing patients for clinical trials, particularly early disease stages, the cancer outreach program hoped to improve cancer care by making available up-to-date research protocols to community physcians. These protocols provide not only treatment regimens, but also staging requirements and safe dose modification schema designed to provide optimal care. The results of the first 5 yr of this progrm have been published recently [5].

Over the 5-year period patient accrual went from 568 patients per annum to 1339 patients entering on-study from the 112 affiliates. The percentage of patients on ECOG studies from affiliates went from 16 to over 42% in 1981. While initially there was concern that protocol errors and violations would be very high and would complicate our study analysis, the data from the comparisons clearly indicated no disproportionate error rates [5]. Analyses of response rates, survivals and toxicities from the member and community affiliates were quite similar. This project clearly indicated that involvement of community hospitals in cancer clinical trials could be done. Adequate patient accrual could be maintained with high-quality data.

The program not only provided protocols, but also educational and training sessions for the community physicians, nurses and data managers. This effort could be likened to a 'university without walls' in that each member helped to educate large numbers of others. Community involvement in ECOG now includes broad-scale participation and membership in the Executive Committee, Disease and Modality Committees and protocol development. The data obtained on participation in studies clearly was helpful to NCI to spawn the second-generation community participation.

The new initiative in community outreach is called the Community Clinical Oncology Program (CCOP). The NCI reviewed and approved 52 hospitals, mostly larger community facilities, that can provide 50 or more patients for protocol studies. The older outreach program participants were the primary recipients of the funds in this new program. Not only is more money provided, but the money goes directly to them. Support is usually for nurse oncologists or data management and not for investigator salaries. About 22 of the 52 programs are affiliated with ECOG, with the additional expected accrual of 1400 patients/yr.

SUMMARY AND DISCUSSION

The cancer specialists in the U.S.A. have increased by a factor of 10–20 over the past 10 yr. They have become distributed widely throughout the U.S.A. and into community hospitals. Sixty-two centers are supported by the NCI for cancer research in the laboratory and/ or clinic. The Wisconsin Clinical Cancer Center is a major center located at a university that has a broad research program in human cancer-related problems. The multidisciplinary representation both in the laboratory and the clinic forms the basis of several research programs. The initial trials in cancer patients are taken to larger clinical trials through ECOG.

The ECOG is a multidisciplinary clinical trials mechanism involving over 235 hospitals and 1250 physicians contributing 3000 new patients for protocol studies annually. The research efforts have been extended to include community physicials through an outreach program. The current version involves smaller hospitals directly affiliated through member institutions and larger, independently funded hospitals through the CCOP program. This outreach effort has resulted in a continued flow of patients for protocol studies since fewer patients are primarily referred to the centers for initial treatment. The analyses of the data from these community hospitals clearly indicate that they supply good data and that the results are comparable for toxicity, response and survival.

The flow of patients and research organizations seems to be adequate in the U.S.A. for clinical trials. There is much duplication of effort and initiatives considering the relative slow input of new research data. The cost of maintaining these resources active is high and increasing yearly. The NIH budget is not increasing proportionately and priorities change rapidly from one initiative to another. Disagreements exist as to how much should be spent on laboratory vs clinical research. Within clinical research objectives competition for resources exist between treatment and prevention trials. The balancing of the various factions requires Solomon-like judgement and juggling.

New initiatives in cancer therapy, such as biological response modifiers, monoclonal antibodies and growth factors, require close collaboration between the laboratory and the clinical investigator. Private industry is also becoming more interested in supporting clinical trials. This relatively large amorphous research program is making progress. Unfortunately, the efforts are not always well coordinated. The leadership provided by cancer centers, cooperative

groups and the NCI hopefully will assure progress by mass action, if not by fine movements.

However, I see two problems that need more attention. First, new research leads must be generated to provide truly innovative ideas for clinical trials. This requires better support of highly integrated laboratory and clinical projects defining new frontiers of clinical research. Unfortunately, NCI funding is not increasing in this area. Hopefully the private companies see opportunities for financial profit by fostering good clinical research.

Another problem in cancer organization and clinical trials is that of cancer prevention trials. The usual hospital, cancer center and group is highly organized to treat cancer patients. Prevention is directed at the non-sick relative or patient who ordinarily does not come to the hospital. We must provide for an alternative organization to provide the flow of patients to do these clinical trials. While medical insurance will pay for cancer treatment, as yet no good mechanism exists for inclusion of non-ill patient into clinical trials for prevention. This challenge must be met by our country as well as yours.

REFERENCES

1. National Cancer Program 1982. *Directors Report and Annual Plan.* FY 1984-1988, May 1983.
2. Schweitzer RJ, Edwards MH, Lawrence W, Mozden PJ, Scanlon EF, Lefall L. Training guidelines for surgical oncology. *Cancer* 1981, **48,** 2336-2340.
3. Kennedy BJ, Calabresi P, Carbone PP *et al.* Training program in medical oncology. *Ann Intern Med* 1973, **78,** 127-130.
4. Verma AK. Inhibitors of skin tumor promotion. In: Crispen RG, ed. *Cancer: Eitiology and Prevention.* Amsterdam, Elsevier, 1983, 241-260.
5. Begg CB, Carbone PP, Elson PJ, Zelen M. Participation of community hospitals in clinical trials. Analysis of five years of experience in the Eastern Cooperative Oncology Group. *N Engl J Med* 1982, **306,** 1076-1080.