A B S T R A C T  Cancer is still the chief cause of death by disease in children, ages one to 14. As improved survival rates have been reported for pediatric cancer patients who are treated on controlled clinical trials, it is important to understand the national utilization of such protocols.

In 1993, a survey of childhood cancer was conducted by the Commission on Cancer of the American College of Surgeons. Data regarding type of disease, protocol participation, age, sex, race, insurance, and geographical region were voluntarily submitted by more than 200 hospital cancer registries. Included in this study were 2,208 children and adolescents 21 years of age or younger who were diagnosed in 1987, and 2,293 who were diagnosed in 1992. Pediatric centers (i.e., members of the Pediatric Oncology Group or Children’s Cancer Group) submitted 55.1% of the cases and other institutions, 44.9%.

It was found that more patients treated at pediatric centers were on protocols (53.8%) than were those treated at other institutions (25.1%). In general, the younger the patient (five years of age or younger), the greater the chance of being on protocol (pediatric centers, 63.7%; others, 42.0%), with very poor adolescent protocol participation (pediatric centers, 34.8%; others, 12.1%). Nevertheless, overall protocol participation was still lower than expected, even in children younger than five years of age, and adolescent participation in controlled clinical trials was low and similar to adult figures. The percentage of childhood cancer cases seen at pediatric centers was smaller than in other series. It was concluded that pediatric cancer centers need to continue to encourage patient participation in controlled clinical trials, with special emphasis on adolescents. (CA Cancer J Clin 2001;51:119-130.)
cancer is still the chief cause of death by disease in children between the ages of one and 14.¹

In 1993, the Commission on Cancer (COC) of the American College of Surgeons undertook a survey of patterns of care in childhood cancers for several purposes; due to the complex nature of childhood cancers, this article focuses on one main area of concern that cuts across most of these diseases: Participation in clinical trials.

It is generally recognized³ that childhood cancer patients should be treated according to specific protocols, as improved survival has been associated with factors such as referral to a tertiary care pediatric cancer center where large numbers of cancer patients are treated, and enrollment in controlled clinical trials.⁴⁻⁶ To better understand the utilization of such protocols on a national level, we compared two time periods—1987 and 1992—and examined protocol participation according to various factors, such as patient demographics, insurance coverage, geographic region, and type of cancer.

**METHODS AND MATERIALS**

The methodology of the American College of Surgeons COC patterns of care studies has been described in earlier reports.⁷ In the current study, we collected data on patient demographics, diagnostic methods, stage at diagnosis and staging system used, type of surgery, other treatment, and insurance coverage for the two study years of 1987 and 1992.

For purpose of analysis, insurance categories were limited to private, health maintenance organization (HMO), Medicaid, and “other.” (Note: Other included Champus, Medicare, military, not insured, self-pay, Veterans Administration, other, and unknown.) Hospitals that participated in either the Pediatric Oncology Group (POG) or the Children’s Cancer Group (CCG) were designated as pediatric centers while other hospitals were designated as general treatment facilities.

Approximately 2,000 hospitals were invited to submit data on up to 25 consecutive patients (for each study year) with newly diagnosed cancers whose ages at diagnosis ranged from birth to 21 years. Of the 2,000 participating hospitals, 1,350 hospitals had a COC-approved cancer program and approximately 650 hospitals had a registrar in place. Data were received by January 1995 from 191 hospitals (9.5% of those invited) on 2,208 pediatric patients diagnosed in 1987 and from 226 hospitals (11.3% of those invited) on 2,293 patients diagnosed in 1992. The percentage of responding hospitals was small, as expected, because the majority of hospitals refer patients with childhood cancers to pediatric centers. Based on American Cancer Society estimates, the reported data represent 33.5% of the 6,600 predicted cases for 1987⁸ and 29.4% of the 7,800 predicted cases for 1992.⁹

Of the 251 hospitals submitting data for 1987 and/or 1992, 32 hospitals were members of POG and 35 were members of CCG. Both groups combined (29% of the reporting hospitals) saw a total of 2,830 patients, or 55% of all cases. In 1987, 57 of the 191 hospitals submitting data were pediatric centers, while in 1992, 65 of the 226 hospitals submitting data were pediatric centers.

In the 1987 data, 66.8% (1,474) of patients were treated at the hospital where they were diagnosed. In 1992, this increased to 70.3% (2,063). To determine whether a child participated in a research protocol, the survey asked if the patient was treated on an in-house, cooperative intergroup protocol, a cooperative group protocol, or none. For simplified analysis, all protocol groups were combined.

Geographical regions were defined by the
patient's zip code at time of diagnosis. The geographical distribution for each study year was similar, with the combined distributions being: Midwest 29.8%, Northeast 16.1%, Pacific 22.4%, Southeast 17.3%, South 10.1%, and Mountain 4.3%.

The International Classification of Childhood Cancer was used to group the patients into 12 major categories and 40 subgroups. For specificity, two other major groups were added (peripheral neuro-ectodermal and benign tumors with uncertain behavior) and three subgroups (acute myeloid leukemia, rhabdoid sarcoma, and clear cell, which was included under renal cell). Thus, a total of 14 major groups and 43 subgroups were defined for this study.

Race/ethnicity was based on information derived from the patient’s chart. However, it is not known whether each hospital used self-report or visual observation by staff to determine this information.

Because this Patient Care Evaluation study was intended as a descriptive national survey of trends rather than a definitive evaluation of hypotheses, statistical significance tests were not performed. The data that emerged from this survey are best evaluated from the perspective of existing clinical, biologic, and epidemiologic literature rather than by statistical tests.

RESULTS

Diagnostic Groups

The most frequent diagnoses in this study were:
Acute lymphocytic leukemia (921); Hodgkin’s disease (420); astrocytoma (406); neuroblastoma and ganglioneuroblastoma (238); non–Hodgkin’s lymphoma (226); medulloblastoma (194); Wilms’ tumor (193); gonadal germ-cell and trophoblastic neoplasms (189); acute non-lymphocytic leukemia (181); rhabdomyosarcoma, embryonal sarcoma, and soft-tissue Ewing’s tumor (153); and osteosarcoma (153).

In general, the distribution of diseases remained the same from 1987 to 1992. However, the percentage of leukemia cases decreased from 25.8% of all diseases in 1987 to 22.9% in 1992. Lymphomas also decreased from 16.3% to 14.6%. The percentage of cases classified as carcinoma and other malignant epithelial neoplasms increased from 8.1% in 1987 to 13.5% in 1992.

Data Representativeness

The data were then compared with those published by the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, which collects data on cancer incidence and patient survival from nine population-based registries.

Table 1 indicates that there is little difference between the two groups in case distribution by major diagnostic groups, race, and sex for patients younger than 15 years old. However, these comparisons are only of diagnostic groups, or subgroups, for which the SEER data listed 100 cases, by gender.

Patient Age, Gender, Race

Data were submitted on 2,208 patients diagnosed in 1987 and on 2,933 diagnosed in 1992, from birth to 21 years. Age and racial/ethnic distributions were similar for both study years (Table 2). White, non–Hispanic patients comprised 75.6% of the cases; African-Americans, 11.2%; Hispanics, 9.0%; and other racial/ethnic groups, 4.2%.

Age distribution analysis showed that 32.5% of the patients were younger than six years; 15.5%, were six to 10; 13.7% were 11 to 14; and 38.0% were 15 to 21.

In 1987, 53% of the patients were male and
### TABLE 1

Comparison Between SEER Data, 1973-1982* and Commission on Cancer Childhood Cancer Study Data, 1987 and 1992

| Diagnostic Group** | SEER | COC | SEER | COC | SEER | COC | SEER | COC |
|--------------------|------|-----|------|-----|------|-----|------|-----|
|                    | %*** | %   | %    |     | %    |     | %    |     |
| All Leukemias      | 32.1 | 31.1| 29.6 | 28.2| 21.9 | 28.6| 24.3 | 27.6|
| Acute Lymphocytic  | 23.9 | 25.9| 22.0 | 21.8| 13.1 | 22.2| 13.8 | 17.1|
| Acute Non-Lymphocytic | 4.1 | 3.0 | 5.1  | 4.0 | 4.2  | 2.5 | 5.9  | 6.1 |
| All Lymphomas      | 15.7 | 14.8| 10.4 | 9.2 | 14.4 | 11.3| 5.9  | 7.2 |
| Hodgkin’s Disease  | 5.4  | 5.2 | 5.9  | 4.5 | 7.8  | 4.9 | 2.0  | 2.8 |
| Non-Hodgkin’s Lymphoma | 5.3 | 5.2 | 2.3  | 2.6 | 3.9  | 3.0 | 1.3  | 2.8 |
| All Brain and Spinal | 18.9 | 21.9| 19.0 | 21.1| 20.3 | 22.2| 21.4 | 28.7|
| Astrocytoma        | 9.0  | 10.1| 10.3 | 9.5 | 9.2  | 11.8| 8.2  | 12.7|
| Medulloblastoma     | 4.9  | 5.0 | 3.4  | 5.1 | 4.9  | 3.4 | 4.3  | 4.4 |
| All Sympathetic NS | 7.7  | 6.9 | 8.6  | 8.9 | 8.2  | 9.9 | 8.9  | 6.1 |
| Neuroblastoma*     | 7.6  | 6.4 | 8.4  | 8.7 | 7.8  | 8.9 | 8.9  | 6.1 |
| All Kidney         | 5.0  | 5.2 | 7.1  | 7.6 | 9.8  | 10.8| 11.8 | 12.2|
| Wilms’ Tumor       | 4.9  | 4.5 | 7.0  | 6.3 | 8.5  | 10.3| 10.5 | 12.2|
| All Bone           | 4.5  | 4.5 | 5.3  | 4.3 | 4.6  | 4.4 | 4.9  | 1.7 |
| All Soft Tissue Sarcoma | 6.5 | 7.4 | 6.7  | 6.8 | 9.2  | 5.4 | 7.2  | 5.0 |
| All Epithelial Neoplasms | 2.7 | 2.3 | 5.5  | 4.1 | 4.2  | 4.4 | 3.9  | 4.4 |

NS= Nervous System

*Source for SEER data: World Health Organization International Incidence of Childhood Cancer, IARC Scientific Publication No. 87. World Health Organization, International Agency for Research on Cancer, Lyon, France, 1988, pp. 101-107.

** Diagnostic groups were included if the SEER data listed 100 cases for either males or females.

*** Percents are of that column’s total number of diagnosed cancers for all diagnostic groups that include more than those shown in the table. Thus, each column does not total 100%.
47% female; in 1992, the percentage of male patients decreased to 48.6% and female patients increased to 51.3%.

Insurance Coverage

The majority of patients had private health insurance (49.5%), Medicaid (19.1%), or were members of an HMO (13.4%). Although type of insurance coverage was similar for both years, there were some changes in the intervening period: The percentage of patients with private insurance decreased from 53.8% in 1987 to 46.2% in 1992, while membership in an HMO increased from 9.7% to 16.2%. The percentage of patients with Medicaid coverage also increased from 15.5% to 21.9% (Table 2).
Figure 1 shows the distribution of protocol participation by type of treatment facility and age. Twice as many patients (53.8%) who were treated at pediatric centers were enrolled in trials as were patients treated at other facilities (25.1%). Although protocol participation declined with increasing age, at pediatric centers, participation ranged from 63.7% of children ages five and younger to 34.8% for those 15 to 21. Other treatment facilities reported similar patterns, with participation ranging from 42.0% for the youngest group to 12.1% for the oldest. If analysis was limited to patients younger than 15 years of age, however, these figures increased to 52.7% overall on protocol and 61.6% of those managed at pediatric centers on protocol.

Patients in diagnostic groups for which clinical trials exist were analyzed by protocol participation, treatment center, and age (Table 3). Selected cancer diagnostic groups without known US protocols were excluded from analysis. Overall, we found that across all ages, and for each diagnostic group shown in Table 3, a greater percentage of patients treated at pediatric centers were on protocols compared with patients at other facilities.

In general, although younger children were more likely to be on protocol than older children (Fig. 1, Table 3), protocol participation for osteosarcoma patients at pediatric centers increased with age, from 33.3% for children under six years of age to...
### TABLE 3

Percentage of Patients with Childhood Cancer on Protocol by Selected Diagnostic Groups, Type of Treatment Center, Age, and Study Year

| Age in Years | 0-5 | 6-10 | 11-14 | 15-21 |
|--------------|-----|------|-------|-------|
| Study Year   | 1987 | 1992 | 1987 | 1992 |
| Acute Lymphocytic Leukemia |       |       |       |       |
| Pediatric Center** | 81.1% | 89.1% | 86.4% | 82.6% |
| Other | 59.1% | 70.5% | 39.1% | 65.7% |
| Acute Non-Lymphocytic Leukemia |       |       |       |       |
| Pediatric Center | 78.6% | 90.9% | 100.0% | 75.0% |
| Other | 59.5% | 100.0% | 80.0% | 83.3% |
| Lymphomas |       |       |       |       |
| Pediatric Center | 42.6% | 66.7% | 61.8% | 61.4% |
| Other | 44.4% | 28.6% | 53.3% | 18.2% |
| Neuroblastoma |       |       |       |       |
| Pediatric Center | 55.2% | 69.1% | 75.0% | 80.0% |
| Other | 48.5% | 55.9% | 100.0% | 25.0% |
| Wilms’ Tumor |       |       |       |       |
| Pediatric Center | 76.5% | 71.7% | 77.8% | 100.0% |
| Other | 57.9% | 67.7% | 66.7% | 71.4% |
| Hepatoblastoma |       |       |       |       |
| Pediatric Center | 66.7% | 90.0% | — | — |
| Other | 0.0% | 33.3% | — | — |
| Osteosarcoma |       |       |       |       |
| Pediatric Center | 50.0% | 0.0% | 20.0% | 57.1% |
| Other | 0.0% | 0.0% | 66.7% | 0.0% |
| Rhabdomyosarcoma |       |       |       |       |
| Pediatric Center | 71.4% | 81.3% | 90.0% | 100.0% |
| Other | 64.7% | 63.6% | 66.7% | 50.0% |
| Germ-Cell, Gonadal |       |       |       |       |
| Pediatric Center | 66.7% | 25.0% | 33.3% | 83.3% |
| Other | 12.0% | 14.3% | 0.0% | 40.0% |
| Central Nervous System |       |       |       |       |
| Pediatric Center | 37.3% | 43.1% | 35.8% | 36.9% |
| Other | 17.5% | 28.3% | 16.7% | 25.9% |
| All Diagnostic Groups*** |       |       |       |       |
| Pediatric Center | 61.7% | 65.2% | 61.8% | 59.2% |
| Other | 41.2% | 42.6% | 34.9% | 38.7% |

* Percents are based on number of patients in an age group diagnosed with that disease and treated at the specific type of facility.
** Member of the Pediatric Oncology Group or Childhood Cancer Group.
*** “All” refers just to those groups listed above.
— Indicates no patients were in that age group treated at that type of facility.
59.6% for those 15 to 21.

Patients were more likely to be on a protocol if they had the following diseases: Acute lymphocytic leukemia (84.7% of those at a pediatric center; 58.1%, other); acute non-lymphocytic leukemia (77.3%; 64.2%); Wilms’ tumor (76.0%; 62.5%); hepatoblastoma (78.9%; 27.3%); and rhabdomyosarcoma (80.7%; 50.8%).

**Protocol Participation, Treatment Center, Insurance, and Race**

Table 4 presents results of an analysis of protocol participation by treatment center, type of insurance, and race/ethnicity. In general, white, non-Hispanic patients had a slightly lower participation rate than other patients for most insurance categories, independent of where they were treated. For example, 51.4% of white, non-Hispanic patients enrolled in an HMO and treated at a pediatric center were on a protocol compared with 61.4% of other patients. Similarly, 25.4% of white, non-Hispanic patients who had private insurance and were treated at another type of facility were on a protocol compared with 39.1% of other patients.

Across all insurance groups, a marked difference between the two racial/ethnic groups was noted for patients treated at facilities other than pediatric centers: 23.3% of white, non-Hispanic patients were on protocol compared with 30.8% of “other” patients.

**TABLE 4**

| Race/Ethnicity | White Non-Hispanic | Other | Total |
|---------------|--------------------|-------|-------|
|               | %                  | %     | %     |

### Pediatric Center*

| Type          | White Non-Hispanic | Other | Total |
|---------------|--------------------|-------|-------|
| Private       | 55.6               | 58.9  | 56.1  |
| HMO           | 51.4               | 61.4  | 53.8  |
| Medicaid      | 56.8               | 56.3  | 56.6  |
| Other/None    | 42.2               | 45.7  | 43.5  |

### Other

| Type          | White Non-Hispanic | Other | Total |
|---------------|--------------------|-------|-------|
| Private       | 25.4               | 39.2  | 27.0  |
| HMO           | 21.6               | 30.1  | 23.6  |
| Medicaid      | 26.1               | 25.8  | 25.9  |
| Other/None    | 16.8               | 31.0  | 20.5  |

### All Insurance Groups

| Type          | White Non-Hispanic | Other | Total |
|---------------|--------------------|-------|-------|
| Pediatric Center | 53.4               | 54.8  | 53.7  |
| Other         | 23.3               | 30.8  | 25.0  |

* Member of the Pediatric Oncology Group or Childhood Cancer Group.
Geographic patterns of participation in clinical trials for children younger than 15 years of age are shown in Figure 2. For five of the regions, protocol participation was fairly consistent (i.e., between 51% to 58%). In the Mountain region, however, only 20.9% of the children were on protocol. Similarly, the smallest percentage of patients treated at pediatric centers (14.2%) was also in the Mountain region (Fig. 2).

**Protocol Participation and Place of Diagnosis/Treatment**

In this study, 63.1% (2,003) of patients younger than 15 were reported by pediatric centers where the patients were either diagnosed and/or treated. An additional 1,173
patients younger than 15 were reported by non-pediatric centers. Of these patients, 8.4% (98) were diagnosed at the reporting hospital, but were treated at another facility, and of these, 36 had been referred to a pediatric center. Another 25.6% (300) were diagnosed at a different facility and treated at the reporting hospital. Of these, 88 had been referred from a pediatric center. If these 36 referred to a pediatric center and 88 referred from a pediatric center are added to the 2,003 patients reported by pediatric centers, then 2,127 (67.0%) of the 3,176 patients younger than 15 were seen at pediatric centers.

Of these 2,127 patients reported by pediatric centers, 1,282 (60.3%) were described as being on a protocol. Those on protocol included 1,234 who were reported by a pediatric center and 48 who were reported by a non-pediatric center but were referred to or from a pediatric center.

Of the remaining 1,049 patients younger than 15 years who were reported by non-pediatric centers but were not referred to or from pediatric centers, there were 393 patients who were also on protocols. Thus, a total of 1,675 patients (52.7%) younger than 15 were reported as being enrolled in a clinical trial.

CONCLUSION

The focus of this article has been to describe patterns of protocol participation for children diagnosed with cancer in 1987 and 1992. Hammond et al. have stated, “Progress in the cure of cancers of children can be optimized if children with cancer are entered into the NCI-supported cooperative group trials of the Children’s Cancer Group and the Pediatric Oncology Group.” Specifically, children and adolescents with acute lymphocytic leukemia, Wilms’ Tumor, medulloblastoma, rhabdomyosarcoma, and non-Hodgkin’s lymphoma have significantly improved survival when treated according to protocol in a pediatric cancer center.

Our goal was to better understand how protocols are being utilized in the treatment of childhood cancer. We recognize, however, that the data in this study are based on a convenience sample. Up to 25 cases for each study year were voluntarily submitted by hospitals across the US and as such may not be representative of the nation’s childhood cancer population as a whole. Only 33.5% of the 6,600 predicted cases for 1987 and 29.4% of the 7,800 predicted cases for 1992 are included in this database. However, the percentage distribution of disease groups analyzed here is very similar to that obtained by the SEER program from population-based cancer registries.

As previously mentioned, selected cancers were omitted from analysis because of known lack of active protocols. However, this analysis is based on actual protocol participation and does not control in detail for which protocols may have been available at specific locations and during specific time periods. It also does not account for ineligibility of patients for specific protocols.

Although we must be cautious about extrapolating from this study, some observations can be made about the status of clinical trial participation at the more than 200 hospitals that submitted data.

As would be expected, more than twice as many patients who were treated at pediatric centers (members of POG or CCG) were on protocols as patients who were treated at other facilities (53.8% versus 25.1%). Likewise, protocol participation at both types of institutions decreased with age, except for those patients with osteosarcoma who were treated at pediatric centers. Participation by children with osteosarcoma increased from 33.3% for children younger than six years of age to 59.6% for those between 15 and 21.

In general, type of insurance coverage did
not seem to affect protocol participation. However, patients who had no insurance or who were covered under an insurance type not included in the study seemed to have lower rates of participation than those who had private, HMO, or Medicaid coverage. White, non-Hispanic patients tended to have lower participation rates than did other patients for all insurance and type of institution comparisons. This finding confirms those by Ross et al., namely that non-whites have a higher protocol participation in POG and CCG institutions than do whites.

Overall, only 40.9% of the patients were enrolled in a clinical trial. For this study, protocol participation included patients who were on an in-house, cooperative intergroup, or cooperative group protocol. Participation was higher at pediatric centers, which reported 53.8% enrolled in some sort of trial. When analysis was limited to patients under 15 years of age, 52.7% were on protocols overall, with 61.6% of those reported by pediatric centers on protocol. If patients younger than 15, who were reported by non-pediatric centers but referred from or to pediatric centers, are included with those reported by a pediatric center, 60.3% of that combined group were enrolled in a trial.

While total protocol participation remains disappointing, the number of pediatric patients enrolled in trials is far superior to the 2% of adult US cancer patients said to participate in clinical trials, according to the National Cancer Data Base. Although the low level of protocol participation among children in this study was unexpected, several encouraging findings should be noted. The number of protocol participants in pediatric centers is markedly better than in non-pediatric institutions and there has been an important increase in protocol participation between 1987 and 1992 among children younger than five years of age with leukemia, hepatoblastoma, rhabdomyosarcoma, and neuroblastoma. In addition, the number of patients with gonadal germ cell tumors who were on protocols increased among the six-to-14-year-old age group in 1992, possibly because of an intergroup germ cell protocol initiated by POG and CCG. Nevertheless, the number of youngsters with central nervous system tumors being placed on protocol remains discouraging, especially in light of the improved survival rates reported by Foreman et al. in patients with such tumors treated at a major regional center in the United Kingdom.

Across all ages and for each diagnostic group, a greater percentage of patients treated at pediatric centers were on protocols compared with patients at other facilities.

In this study, there were 2,003 patients younger than 15 years of age reported by pediatric centers and another 124 who were reported by non-pediatric centers but who had been referred from or to pediatric centers. Thus, 67.0% (2,124) of the 3,176 who were younger than 15 were seen at a pediatric center. In contrast, Ross et al. found that 94% of childhood cancer patients younger than 15 years are seen at either a POG or CCG hospital. The discrepancy is probably attributable to the fact that Ross et al. extrapolated percentages from the observed number of cases diagnosed at pediatric centers from 1989 through 1991 and compared those with estimates from the SEER Program. Our data, on the other hand, were based on a convenience sample of patients diagnosed in 1987 and 1992, with 55.1% of the cases submitted by pediatric centers and 44.9% by other types of institutions. Of interest in the Ross et al. study is the notable under-representation of patients between 15 and 19 years of age within POG and CCG—a finding.
compatible with our observation of decreased participation in protocols in this age group.

While an increasing number of children in the five and younger age group are being enrolled in controlled clinical trials and are cared for by institutions belonging to either POG or CCG, the adolescent age group continues to be problematic. As 38% of the patients in this study fell into this age category, greater attention must be focused on this group of patients so that increased enrollment in controlled clinical trials is encouraged by the pediatric cooperative groups. Fortunately, the second largest group of patients were those younger than six years of age (32.5%) and the diseases represented in this age group, such as acute lymphocytic leukemia, Wilms’ tumor, hepatoblastoma, and rhabdomyosarcoma, have excellent protocol participation.

It is our hope that as efforts are made to ensure that an increasing number of pediatric cancer patients are enrolled in controlled clinical trials or managed by member institutions of POG and CCG, we will continue to see improving survival statistics for all childhood malignancies.

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