the study included only subjects who were already 10-year survivors.) The cumulative 20-year incidence of developing a second neoplasm was 0.95% among nonirradiated survivors. Among those who had received craniospinal irradiation, the incidence was 20.9% (13.3% after excluding basal cell carcinomas). The most common second malignancies were tumors of the brain, thyroid, oral cavity and pharynx, and liver, and myeloid leukemia. Most second neoplasms occurred within or adjacent to the irradiated area.

The indicators of socioeconomic status reflected the known impact of cranial irradiation on physical and neurocognitive development. Women seemed particularly susceptible to these problems. Unemployment rates among female ALL survivors, and particularly those who had been irradiated, were higher than the national average. Relative to the national average, only those men who had been irradiated were more likely to be unemployed. Compared with national averages, the percentage of survivors currently married was lower among women who had received radiation therapy, but was not significantly different among non-irradiated women, or among men, regardless of their treatment. Rates of private health insurance coverage were not influenced by treatment in either men or women.

A few decades ago, the outlook for children with ALL was bleak, recalled Joseph V. Simone, MD, in an editorial accompanying the study. Treatment improvements since that time “are surely among the most dramatic in the history of cancer,” wrote Simone, a pediatric oncologist and Chairperson of the National Cancer Policy Board. Indeed, a graph in Simone’s editorial illustrates that long-term survival rates have increased from only a few percent in 1950 to their current level in excess of 80%.

Simone also recounted how addition of irradiation to chemotherapy made long-term survival a reality for children with ALL, and how craniospinal irradiation has been largely replaced by intrathecal chemotherapy once the late effects of the former were recognized.

However, the current practices and systems for follow-up care of childhood cancer survivors are inconsistent. With this in mind, the National Cancer Policy Board and Institute of Medicine reviewed current evidence and developed a report, Childhood Cancer Survivorship: Improving Care and Quality of Life. The report, which includes recommendations on services, professional education, and research, is available on the National Academies website, http://books.nap.edu/books/0,3090,88984/html/index.html.

“Cancer in children has largely become a chronic illness rather than an acute illness..., which is what it used to be. [The] cancer may be eliminated, but the effects of cancer and its treatment may not be. We need to maintain responsibility for that child and eventual adult to try to mitigate the effects of disease and treatment,” said Simone.

RESULTS NEVER REPORTED FOR MANY LARGE CANCER TRIALS

Many large Phase III clinical trials whose results were presented as abstracts at meetings of the American Society of Clinical Oncology (ASCO) were not published in the medical literature by as many as five years later, according to a new study. Aside from the ethical concerns this raises regarding relationships among study subjects, investigators, and funding organizations, failure to promptly publish results may affect which studies will be done in the future, and even how patients are treated, according to the study authors.

Writing in JAMA (2003;290:495–501), Monica Krzyzanowska, MD, MPH, of the Dana-Farber Cancer Institute, and colleagues from the University of Toronto found that more than one fourth of these Phase III trials remained unpublished after five years—their results unknown to researchers, clinicians, and patients.
Of 510 large (≥ 200 patients) Phase III trials presented at ASCO meetings between 1989 and 1998, 26% remained unpublished five years after their initial presentations. This incomplete reporting becomes especially problematic when the likelihood of publication is influenced by the study outcome—a phenomenon known as publication bias.

Whether the abstracts reported a statistically significant difference between outcomes of standard and experimental arms of the trials played a role in whether the study was published: 81% of studies with significant results were published within five years, as opposed to only 68% of studies with nonsignificant results. Studies with positive results (more favorable outcomes in the experimental therapy group) were more likely to be published than those with negative findings (81% and 70%, respectively for positive and negative studies).

In multivariate analyses, several factors were predictive of shorter time to publication:

- Results that were statistically significant,
- Studies selected for oral or plenary presentation (as opposed to those abstracts printed in the proceedings but not presented at the meeting), and
- Studies with pharmaceutical industry sponsorship.

Although one might suspect this bias might reflect preference of journals for studies with positive and significant results, the reasons for nonpublication cited most often by investigators were lack of time, funds, and other resources.

Although it might seem reasonable that studies finding a better therapy are considered more important (and therefore more publishable), in reality the results of all studies are equally important, as they add to our knowledge base. Knowing that a new treatment does not work better is just as important as knowing that it does.

This publication bias creates a problem with systematic reviews and meta-analyses; if only the positive results have been published, it may seem that a treatment is more effective than it really is, and both clinicians and patients may choose among treatment options based on this flawed information.

Another problem with the lack of publishing, according to the authors, is that in a broader sense it can be seen as a breach of trust between the researchers and the patients who consented to participate in the trial, as well as the funding sources that supported the study. Government agencies and private foundations support trials and many subjects enter clinical trials expecting that future patients will benefit from the knowledge gained by their support and participation, but this may not happen when the study results are not published.

How can such a problem be remedied? One solution, according to a separate article in the same journal (JAMA 2003;290:516–523), would be to require that all new clinical trials be registered in a single database—something that does not happen now. Although a single clinical trials registry has been recommended by various groups and individuals for many years, the idea has run into some resistance, according to authors Kay Dickersin, PhD, MA, of Brown University and Drummond Rennie, MD, a deputy editor of JAMA.

Some pharmaceutical companies have been reluctant to register their clinical trials, usually citing concerns about protecting their intellectual property, the authors say. But whether providing limited information to a registry would compromise this protection is debatable, they add. Concerns have also been raised about who would pay for such a registry, and who would enforce registration.

The FDA Modernization Act, passed in 1997, required that study sponsors register all cancer clinical trials at www.ClinicalTrials.gov, a large government registry that is accessible online. But the law did not provide for funding or any mechanism of enforcement.
According to Dickersin and Rennie, a single comprehensive clinical trials registry would increase researchers’ knowledge of studies that have been completed or are in progress. This would reduce the duplication of studies and could encourage more researchers to publish their findings. It would also alert those searching the medical literature that unpublished studies have been done or are in progress. The researcher then could investigate what happened with the study (even if it were not published) and factor this in to any recommendations being made about treatment, which would help reduce publication bias.

Krzyzanowska and colleagues also discuss trial registries as a solution, as well as initiatives by medical journals to publish brief reports of negative and/or nonsignificant studies, or even establishing entire journals dedicated to publication of such studies.