NWTS LATE Effects Study Grows

We have wonderful news to share. The NWTS Late Effects Study (LATE) recently has been renewed for another five years. National Cancer Institute renewals are achieved through a competitive process and are not guaranteed. Fortunately, because you and so many others contributed to our research, the reviewers concluded that this is an important study that deserves to continue. Thank you for making this possible.

This is the launch of “LATE Breaking News” the NWTS participant newsletter. We wish to share information on what we have learned during the thirty-two years of multi-site clinical trials conducted through the NWTS and to introduce you to some of the staff who have made this research possible. We depend on your feedback and welcome your comments and suggestions for future articles.

Best Wishes for the New Year,

Norman Breslow, PhD
University of Washington Professor and NWTS Statistician

What is the Late Effects Study?
The Late Effects Study is being conducted to serve as a resource for treated Wilms tumor patients and their families. Although most enjoy good health, some may be at risk for certain health conditions. We are collecting information from as many participants as possible to determine whether there are risks, and if so, what they might be. If there is more than one case of Wilms tumor in a given family, we work with geneticists to estimate heritability and recurrence risks and to identify the specific gene(s) responsible. We would like to answer your questions about possible long term effects of treatment for Wilms tumor. This is why we are collecting information on health issues and pregnancies.

What is the National Wilms Tumor Study?
The National Wilms Tumor Study (NWTS) is a federally funded, multi-institutional study of the treatment of patients with Wilms tumor. The study involves the collaboration of a large number of pediatric surgeons, oncologists, radiation oncologists, urologists, pathologists and allied health professionals with the goals of developing more effective treatments for children with Wilms tumor, as well as studying the special cells that grow to form this cancer.

What is the Data and Statistical Center?
The Data and Statistical Center (DSC), located in Seattle, is the site to which treatment and follow-up records for all patients entered on the National Wilms Tumor Study are sent. Statistical analyses of patient data are conducted at the DSC.

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How many people will take part in this study?
Over 4,000 people have chosen to participate. By 2006, we expect that over 1,600 more will enroll.
FAQs Continued

How long will you follow me/my child?
We plan to follow you/your child once a year throughout your lifetime through correspondence directly with you/your child or your physician or the institution where you/your child was treated.

What about confidentiality?
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality, but only those involved in the science of the study will be granted access to your medical records or any other personal information. Your personal identity will not be revealed in any publication or report.

What does the LATE study involve?
Participation involves completing a brief Annual Status Report form every year that asks about significant health events and confirms that we have your most recent address on file. Every five years we send a more detailed Medical History Form for you to fill out and a Physical Exam Form for your physician to complete and return. Reports of conditions of particular interests are followed up with requests for consent to obtain confirming medical records. Currently conditions of interest include pregnancy in participant or partner; heart, kidney, or lung conditions; the development of other cancers; and the diagnosis of Wilms tumor in a family member.

What are the risks of participation in the study?
We respect that each person has a different comfort level with sharing certain aspects of his or her medical history, and this discomfort is the primary risk of participation. However, we ask that you let us know if there is a particular part of the study for which you would rather not provide

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For more answers to FAQs see http://www.nwtsg.org.

Cure Rates Over Time

When discussing this topic once before a lay audience, I emphasized how far we had come in such a short time.

A member of the audience then said “I don’t think that is so good; it has taken you 70 years.”

That is correct, but we need to see this in another context. The time frame becomes clearer if we take all of human history and put it on a 24-hour clock. Having done so, we see it is now one minute after midnight, and all children with Wilms tumor will die. It is 3 AM and none survive. It is 6 PM, 9:00, 10:00, 11:00, and all children with Wilms tumor die. It is 11:15, 11:30, 11:44, all succumb.

It is 60 seconds later, and 5% live. It is 11:47 and 15% survive. Four minutes more, and 45% are alive. Another four minutes and 80% are cured. It is 11:59. Ninety percent of the children will live, most to become healthy adults: and the clock is still ticking for us—and for them.

Giulio D’Angio, MD,
Founding Chairman of the NWTS

Know Your Diagnosis and Treatment

In this excerpt, “Cure Is Not Enough”, interviewer Bonnie Allen talks with Wendy Hobbie and Kathy Ruccione, coauthors with Nancy Keene of Childhood Cancer Survivors: A Practical Guide to Your Future (copyright 2000 by O’Reilly & Associates, Inc.) about important survivor issues such as the importance of knowing your/your child’s diagnosis and treatment.

Hobbie is coordinator of the FU Program at the Children’s Hospital of Pennsylvania (CHOP), and Ruccione at Children’s Hospital Los Angeles (CHLA), where she established the CHLA LIFE Program for survivors.

Ruccione: One of the things Wendy and I hope to accomplish with this book is for survivors to understand that potential late effects vary according to their disease and the specific treatment they received. Long-term survivors sometimes get hold of information about the range of possible late effects and assume it applies to them. In fact, it’s a very individual matter. This underscores how important it is for parents and survivors to keep records of their illness and treatment.

Allen: What are some specific steps you’d advise a parent or survivor to take after treatment ends?

Ruccione: Number one, know what their diagnosis and treatment were, and learn what needs to be monitored in the future. They may want to schedule an appointment to talk with their treating physician, outside of the usual appointments for tests and physical exams. Sometimes it’s called an “exit interview,” but it’s not a real exit—we don’t really want them to disappear from our lives! We want to help them monitor their health into the future—to be knowledgeable about their own history so that they have that knowledge at hand if they go to another health care provider who may not know very much about childhood cancer.

Allen: In the back of your book is a tear-out health history pamphlet with space for survivors to record treatment information. Did you include that with the exit interview in mind?

Hobbie: Yes. All patients should have an exit interview. However, many institutions do not have exit interviews and families have found it difficult to get all the necessary information about treatment and potential late effects once treatment has ended.

The pamphlet can act as a guide to what information is important to gather. In a situation where an exit interview isn’t
**Who was Max Wilms? And Why Was a Cancer Named After Him?**

Initially, German surgeon Max Wilms, born in Hünshoven, Germany, studied law as did his father and his oldest brother. After only one semester, however, he decided to switch to medicine. This fateful choice led him to discoveries to which he dedicated the rest of his years.

At the start of his medical career, Wilms examined children’s kidney tumors, added seven cases to a thorough review of the literature, and produced what was the definitive work on the subject in 1899. Throughout his life he studied ulcers, burns, tuberculosis, and the uses of radiation, and co-edited a book on surgery. He may be best remembered for his thorough work with childhood cancer.

Max Wilms would probably be surprised to learn that his name is now linked with this childhood disease. But Dr. Wilms would be even more surprised—and delighted—no doubt—to learn how many children can now be cured of Wilms tumor.

In light of recent events it is important to note that Dr. Wilms died saving the life of an enemy prisoner of war. In May 1918, during World War I, Wilms died of diphtheria. He was infected by one of his patients, a French officer, on whom he had operated. This utterly dedicated physician never lived to know that his last patient would fully recover.

**Study of the Late Effects of Treatment for Wilms Tumor**

By Giulio D’Angio, MD

All treatments, even taking aspirin, can lead to complications. It was learned early in the 1900’s that radiation therapy given to developing tissues can cause disturbances in normal growth. It also was found that adding radiation therapy to children after surgery for Wilms tumor appeared to increase their chances for survival. One way of avoiding treatment effects is not to treat at all, of course. This is not an option when radiation therapy is known to be beneficial. The same holds for chemotherapy.

The NWTS has therefore focused on defining low and high risk groups of patients according to how advanced the disease is at the time of diagnosis, and what the tumor cells look like under the microscope. By doing this, it has been possible to use the least amount of treatment for patients at low risk, reserving the more aggressive treatments such as radiation therapy and certain toxic drugs only for those children in whom relapse and death are real threats.

The successive clinical trials run by the NWTS have been successful in these endeavors with extremely gratifying results. However, “success” when treating children with cancer requires a very demanding definition. Not only a cure, but also normal subsequent development through the adolescent years, and—eventually—a productive adulthood. The NWTS has therefore included the monitoring of treatment-related complications from its inception in 1969. It was the first childhood cancer study group to do so. As a result, we know that treating patients in the low risk category with only two drugs is not associated with late complications, especially now that the length of treatment has been reduced from 1-1/4 years to only three months. Radiation therapy and a drug that can cause heart problems in long-term survivors are used only in patients who clearly need these forms of therapy.

The NWTS can take great pride in the fact that from the beginning, a firm eye was kept on the adage “Cure is not enough.”

**FACTS ABOUT WILMS TUMOR**

- About 500 children and teens develop Wilms tumor in the U.S. each year.
- The highest incidence is in the first four years of life.
- In 7% of children with Wilms tumor, both kidneys are involved at diagnosis.
- In only 1% of the children who have a kidney removed due to Wilms tumor, does the cancer re-appear later in the other kidney.
- Possible causative factors in the environment of parents or their child that might lead to Wilms tumor have not been determined.
- There is a family history of the disease in only 1% of cases.

To view this entire interview, visit the website at www.patientcenters.com or for book information, call (800) 998-9938.

Please see insert for a helpful questionnaire regarding your treatment.
The True Heroes – Our Inspirational Participants

To Whom It May Concern:

I filled out your survey. I just wanted to thank you all for being concerned. Not everyone understands the feelings of people with cancer. I know someday there will be a cure.

Whenever I had cancer the doctors did so much. I thank them from the bottom of my heart. Thanks to them I have so many memories from my family. I have 5 wonderful nieces, 5 great nephews, and a great nephew on the way. I can’t have children of my own due to all of my surgeries but I have lots of “kids” with my family and I visit all the hospitals around and visit with these kids. My goal is to get up to Tennessee to visit with the great kids at St. Jude. Those are the true heroes of the world.

So guys, just keep up the good work. I just wanted to thank you all.

Thanks again,
Kimberly Gower

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PREGNANCY AND HEALTH OF OFFSPRING

“Can I have children?”

“Will treatment I had when I was a child have any impact on the health of my kids?”

You can help answer these questions by choosing to participate in the Late Effects Study. When we receive a report of pregnancy we ask the mother to fill out a one page questionnaire about the pregnancy. If the pregnancy lasted more than twenty weeks we will ask her permission to obtain the medical records on this pregnancy. As our study continues, and if we have received your permission to do so, we will request annual updates on the health of your children.

Researchers are working to see if there is any relationship between treatment and pregnancy outcomes. Please stay in contact with us so that we can share any future publications with you.

If you want to report a pregnancy, or request that we keep you informed when manuscripts are published, please call us any time at (800) 553-4878.

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FAQs

Information. When we ask for the annual updates you may decline to provide answers or permission to review your medical records if you are uncomfortable with sharing this information. Please let us know whenever we have touched on a sensitive area.

What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to take part and you may leave the study at any time.

Will I/my child be able to have children?

Most patients who have been treated for Wilms tumor will be able to become mothers and fathers. There are some exceptions to this generalization. Females who receive total abdominal radiation therapy may be sterilized by this treatment. If you do not know what your treatment was, please contact the institution where you were treated. If you have lost the address or phone number, we would be happy to provide it to you. In addition, patients, especially males, who received cyclophosphamide may become sterile.

What tests can be done to find out whether I/my child is infertile?

A laboratory test called a semen analysis can be performed in sexually mature males. However, even a semen analysis that shows total absence of sperm is not definitive. Men have sired pregnancies within 6-12 months of having a semen analysis that suggested that they were sterile. Men can receive evaluation from a specialist called a urologist. Most large metropolitan areas have one or more urologists who specialize in male infertility evaluation. Women can undergo a variety of endocrinological tests suggested by their gynecologists. These tests can determine whether the ovaries are functioning normally.

INFERTILITY RESOLVE

Infertility Resolve is a nonprofit organization founded in 1974 to provide timely, compassionate support and information to those who cannot have children or are having fertility problems; and to increase awareness of infertility issues through public education and advocacy.

RESOLVE Contact Info

Telephone: 617-623-0744
Website: www.resolve.org

Monday - Friday:
9-noon, 1-4 (EST)
Monday Evening:
5-9 pm
**Treatment of Wilms Tumor**

When a child is diagnosed with Wilms tumor the first treatment in North America is almost always surgery. Usually this procedure is the removal of the kidney and the tumor, called a nephrectomy, although occasionally a biopsy of the tumor is performed. The surgeon’s goal is to remove the kidney completely without rupturing the tumor capsule. The other kidney is inspected. (7% of patients have Wilms tumor in both kidneys) as well as regional lymph nodes.

The surgeon makes a preliminary determination of the tumor stage and sends tissue samples to the pathologist who examines the tumor under a microscope. The pathologist’s findings are very important in determining treatment. If some of the cancer cells are irregular or larger than normal, the tumor type (histology) is called anaplastic. Treatment must be more aggressive when these unusual cells are abundant within the tissue.

Fortunately, 95% of Wilms tumor histologies are determined to be favorable. Oncologists, the doctors who administer chemotherapy, use the findings of stage and histology to determine appropriate treatment. Most children receive two drugs, dactinomycin and vincristine. If their stage is local and histology is favorable, that is all the treatment they will receive. Doxorubicin, cyclophosphamide, etoposide, and carboplatin are drugs that may be added if the stage is more advanced or if much anaplasia has been found. Many children with tumor in both kidneys (bilateral Wilms tumor) have surgical biopsies followed by chemotherapy before any more surgery is done. The goal for patients with bilateral Wilms tumor is to cure while preserving as much normal kidney as possible.

Before 1970 almost all children were also treated with radiation. Please see NWTS founder Dr. Giulio D’Angio’s article on page 3 to learn more about the long-term risks following radiation therapy. His article describes the NWTS efforts over the past 32 years to decrease the number of children who receive this treatment and to reduce the dose of radiation given.

Today we know the optimal treatment for most children diagnosed with Wilms tumor. Work continues on trying to identify effective treatment for children with unfavorable histologies. The NWTS also continues to follow participants after treatment has stopped to make sure that we know how different types of treatment may or may not be related to health problems in later years. Today we know the optimal treatment for most children diagnosed with Wilms tumor. Work continues on trying to identify effective treatment for children with unfavorable histologies. The NWTS also continues to follow participants after treatment has stopped to make sure that we know how different types of treatment may or may not be related to health problems in later years.

We recognize that some participants may not have health insurance. While completion of the Physical Exam form is not a requirement for participation, we encourage all childhood cancer survivors to schedule annual physicals. Even if you are long overdue for a physical exam, it’s never too late to have one. You can obtain a physical exam from any physician. He or she does not have to be an oncologist.
Wilms’ tumor affects one or both kidneys and generally occurs in children age three to four. With an overall cure rate of more than 80 percent, Wilms’ tumor has afforded investigators a chance to follow their cured patients for long lengths of time to evaluate the late effects of treatment.

It is now known that women who were treated as children for Wilms’ tumor with hemi-abdominal radiation are at increased risk for having lower birthweight babies and delivering them prior to 36 weeks’ gestation. Those have been the major findings of the National Wilms’ Tumor Study Group’s (NWTSG’s) Long-Term Follow-Up Study reported at the American Society of Clinical Oncology’s 1999 and 2001 Annual Meetings.

In a recent interview, NWTSG Chair Daniel M. Green, MD, a pediatric oncologist at Roswell Park Cancer Institute and Professor of Pediatrics at the School of Medicine and Biomedical Sciences at State University of New York at Buffalo, noted that the manuscript regarding follow-up study results of pregnancy outcomes is currently undergoing the journal review process.

Tracing Results

The main difference between the manuscript submitted for publication and the initial abstract in 1999, explained Dr. Green, was that the group first reported on results from 301 pregnancies. The ASCO 2001 abstract reported on data the group had gathered regarding 594 pregnancies.

Another difference, noted Dr. Green, who was the first author, is that the final paper did not include women who had undergone full-abdominal radiation. A few of those women had been included in the original study results, even though most who receive full-abdomen radiation are sterilized after treatment.

Those patients were excluded from the final analysis, on the advice of the team’s radiation oncologists, Dr. Green said. The radiation oncologists pointed out to study authors that doses for full and hemi-abdominal radiation are different, and might confound efforts to make effective comparisons between pregnancy occurring in former Wilms’ tumor patients.

What Was Analyzed

Women’s pregnancy outcomes comprise just one group of the factors tracked long-term by NWTSG. Other late effects such as risk for congestive heart failure after doxorubicin are also being followed and reported. (Green et al: Congestive heart failure after treatment for Wilms’ Tumor Study Group, J Clin Oncol 2001;19:1926-1934).

When patients are enrolled in the late-effects study, all their data are processed and analyzed through the study group’s Data Service Center located at the University of Washington in Seattle. Many of the NWTSG member institutions, however, take responsibility for patient contacts, said Dr. Green.

The Long-Term Follow-Up Study of the NWTSG entered women into their study from 1969 to 1994. Investigators analyzed a number of pregnancy outcomes and complications. In the 2001 abstract, they reported there were 80 miscarriages (prior to 20 weeks) in a total of 594 pregnancies. Forty-three women had elective abortions, and there were six stillbirths (after 20 weeks’ gestation). Women in the study delivered a total of 465 liveborn infants.

Further analysis of the liveborn births revealed that 17.5 percent of the infants were delivered prematurely (prior to 36 weeks’ gestation). Low birthweight (less than 2,500 grams) was also common, occurring in 19.5 percent of 304 infants.

Several other complications were analyzed, including pregnancy-related hypertension, early or threatened labor, malposition of the fetus (such as breech presentation), obstructed labor and umbilical cord complications. In both the 1999 and 2001 analyses, malposition of the fetus occurred approximately 10 percent of the time, and early or threatened labor was also more frequent.

The take-home message, he said, is that fetal malposition, low birthweight and prematurity are much more frequent among the irradiated women. In light of the long-term findings, the NWTSG Web site for patients advises women who have been treated with radiation for Wilms’ tumor to see their obstetricians early in their pregnancies. Patients can be referred to the Web site—www.nwtsg.org—where they can find helpful information. Links to member institutions and other sites are also available.

Reporting Intervals Vary

During the interview, Dr. Green also commented on the process for reporting results from such a long-term project. Journal reports from the long-term study group occur at different intervals than do those from the NWTSG’s therapeutic studies, he explained. “Long term results are dependent on our having enough data to report. We publish articles as studies are completed. The therapeutic studies usually require four or five years of patient accrual, and we try to publish the results as soon as we have completed the accrual and have a minimum of two years of follow-up on essentially all the patients in the study.”

*Dr. Norman Breslow is the biostatistician in charge. He maintains an office at the University of Washington and at the Data and Statistical Center at the Fred Hutchinson Cancer Research Center. Both are in Seattle.
Thank You

We would like to recognize and thank all of the families, businesses and civic groups that have helped us financially over the years. We have received donations from corporations, individual families, even a Girl Scout troop, and every contribution is gratefully received. Like most projects primarily supported by federal grants we have faced some lean times, and the extra money received from private donations has helped see us through those times.

Bibliography of the NWTS is Available On-line

Recent publications include:


* To view a listing of articles published by committee members please visit:

2. bibliography

We are restricted from publishing articles for which journals hold the copyright. However, we will try to contact the paper’s author to obtain a reprint if you specify one or two specific articles that interest you.

FAQs

Will I/my partner/my child have problems with pregnancy and delivery?

Women who have received radiation therapy to their abdomen are at substantially greater risk of having a baby born either early or of small size. These women should notify their obstetricians at the onset of pregnancy regarding their past medical history. If you have access to a medical library, you may consult the article by Li et al. listed in the bibliography*; if not, we will be happy to send you a copy.

What are the chances that my child/grandchild will develop Wilms tumor?

Based on the data presently available, the risk of occurrence of Wilms tumor in the child of a patient treated for a Wilms tumor of one kidney appears to be less than 0.5%. If Wilms tumor has been diagnosed in a brother, sister, parent, aunt, uncle or first cousin, the risk may be increased. The specific risk can only be estimated with detailed evaluation of the family history in consultation with a medical geneticist.

Are You Moving?

Have you moved in the last two years?

Please call the study line at 1 (800) 553-4878 or email us at nwtsg@fhcrc.org to keep us updated or to request information at any time.
Please Stay In Touch!

Has it been two or more years since we have heard from you?

Perhaps you have not replied to any of our mailings for a while. We would still very much like to hear back from you.

Please help us continue this important research by getting back in touch with us. We are happy to answer any questions you may have. It is never too late to respond. Please call 1-800-553-4878 or write to us. You may also email us at: nwtsg@fhcrc.org.

When leaving a message please speak slowly, spell your full name, and let us know the best time to return your call.

The DSC is very proud of its dedicated staff of eleven who work on several projects: the current clinical trial protocol (NWTS-5), an epidemiology study associated with the University of North Carolina, and the Late Effects Study. Ian Hamilton and Blythe Takashima Hart devote their complete attention to the Late Effects Study. Many of you have already met them on the telephone.

Ian has worked and volunteered at nonprofits since middle school. He says, “I have found those experiences to be the most rewarding and fulfilling in my life.” The favorite aspect of his job is “reaching a family who has lost contact with the study or the doctors who treated the participant, being able to answer their questions, and letting them know what resources the study can provide.” Before coming to the DSC Ian coordinated volunteer resources at the Whitman-Walker Clinic in Washington D.C., the third largest HIV/AIDS Clinic in the country. He has been at the Hutch for two years. He is an avid fan of both the University of Washington Husky football team and the Seattle Mariners. In addition to Native American art he collects comic books. (There are three comic book shops in Seattle’s Roosevelt District where he’s been known to place special orders). The main reason he moved to the Seattle area is “because it’s near the mountains for biking and hiking and you’re still close enough to the city.”

Blythe joined the DSC staff a year ago. She and Ian coordinate all the LATE correspondence and contact participants to conduct phone interviews and answer their study questions. After graduating from the University of Washington, where she studied English Literature, she moved to Japan and taught English for five years. Blythe joined the Fred Hutchinson Cancer Research Center two years ago, first conducting telephone interviews for various cancer prevention studies with Collaborative Data Services. “Here at the DSC the interviews are brief, which often leaves more time to really talk with participants and their families—that’s the most enjoyable part,” “Most are happy to do all they can to advance research and help others. This is very inspiring.” Blythe’s hobbies include cooking, walking, and working with black and white photography. She is not only interested in graphic arts, she designed the layout for this newsletter! If you speak with Blythe on the phone you may want to congratulate her on her recent marriage.

Meet the Late Effects Study Staff

Blythe Takashima Hart and Ian Hamilton
Data Coordinators at the DSC

The NWTS has centers located at several sites around the country. Our chairman, Dr. Daniel Green, is located at the Roswell Park Cancer Institute in Buffalo, NY. He is supported there by his secretary of 11 years, Diane Piacente. The NWTS Pathology Center, headed by Dr. Elizabeth Perlman, is at Johns Hopkins Hospital in Baltimore, MD. Dr. Norman Breslow, the NWTS statistician and principal investigator of the Late Effects Study, has his primary office at the University of Washington in Seattle, WA, but also has an office in the Data and Statistical Center (DSC) located at the Fred Hutchinson Cancer Research Center.