2008

Vanderbilt-Ingram Cancer Center

Cancer Registry and Cancer Committee Report

From the Cancer Committee Chair

We are pleased to present this report of the Vanderbilt-Ingram Cancer Center's Cancer Committee, featuring Cancer Registry Data from 2006. In this report, you'll find case reports and selected survival data from our Cancer Registry, as well as a selected site summary on lymphomas, by Dr. John Greer, professor of Medicine and Pediatrics.

This has been an exciting year for the Vanderbilt-Ingram Cancer Center, with the appointment of Jennifer Pietenpol, Ph.D., as center director and B.F. Byrd Jr. Professor of Oncology.

Other recent developments and accomplishments include:

- Ranking among the top 10 centers in competitive research funding from the National Cancer Institute, with more than $67 million in NCI support in 2007.
- Successful renewal of Specialized Programs of Research Excellence in gastrointestinal and lung cancers, and anticipated renewal of a SPORE in breast cancer later this year.
- Launch of a significant expansion of our Henry-Joyce Cancer Clinic and Chemotherapy Infusion Center, which will double our capacity to serve patients and families when completed in 2009.
- Renovation of space at Nashville's 100 Oaks Mall for the Vanderbilt Breast Center as part of an exciting and innovative outpatient center called Vanderbilt Health: One Hundred Oaks.
- Enrollment of more than 70,000 participants, toward a goal of 90,000, in the Southern Community Cohort Study, a historic population-based study aimed at understanding why those who live in the Southeast, and African Americans in particular, face a disproportionate burden from cancer.
- Inclusion of Vanderbilt Medical Center on *U.S. News & World Report's* Honor Roll of Best Hospitals and ranking of Vanderbilt in the top 15 hospitals for cancer treatment.
- Designation as a Blue Distinction Center for complex and rare cancers by Blue Cross Blue Shield Association, in collaboration with BlueCross BlueShield of Tennessee.

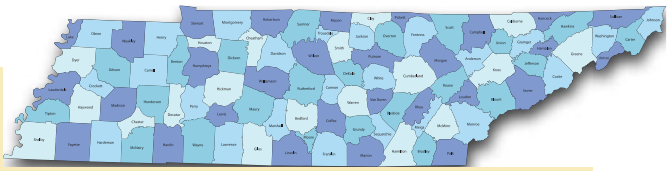
Great gains continue to be made against cancer. Nationwide, death rates continue to decline. Still, Tennesseans continue to face death rates that are among the highest in the country. Our mission is to change that through collaboration with local, regional and national partners, including academic peers and community-based colleagues.

I encourage you to learn more about our work online at www.vicc.org.

Sincerely,

Mark Kelley, M.D.
Chair, Cancer Committee
Chief, Surgical Oncology

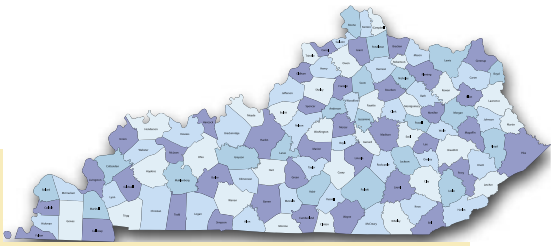
BY GEOGRAPHY



Tennessee County of Residence at Diagnosis
2006 All Cases

Anderson	14	Giles	16	Macon	10	Sumner	83
Bedford	52	Grainger	3	Madison	37	Tipton	3
Benton	13	Greene	11	Marion	4	Trousdale	4
Bledsoe	5	Grundy	12	Marshall	28	Unicoi	1
Blount	16	Hamblen	9	Maury	84	Union	3
Bradley	15	Hamilton	90	Meigs	2	Van Buren	1
Campbell	5	Hardeman	7	Monroe	3	Warren	33
Cannon	7	Hardin	17	Montgomery	163	Washington	17
Carroll	14	Hawkins	14	Moore	2	Wayne	9
Carter	9	Haywood	5	Morgan	4	Weakley	29
Cheatham	21	Henderson	13	Obion	26	White	33
Chester	10	Henry	25	Overton	12	Williamson	204
Claiborne	6	Hickman	16	Perry	4	Wilson	88
Clay	6	Houston	10	Pickett	8		
Cocke	5	Humphreys	22	Polk	2		
Coffee	72	Jackson	7	Putnam	47		
Crockett	3	Jefferson	5	Rhea	7		
Cumberland	49	Johnson	2	Roane	16		
Davidson	629	Knox	58	Robertson	53		
Decatur	6	Lake	2	Rutherford	188		
DeKalb	8	Lauderdale	2	Scott	5		
Dickson	37	Lawrence	18	Sequatchie	3		
Dyer	8	Lewis	14	Sevier	10		
Fayette	1	Lincoln	37	Shelby	36		
Fentress	6	Loudon	11	Smith	13		
Franklin	32	McMinn	4	Stewart	20		
Gibson	24	McNairy	6	Sullivan	44	**Total Cases:**	**2848**

BY GEOGRAPHY, CONTINUED



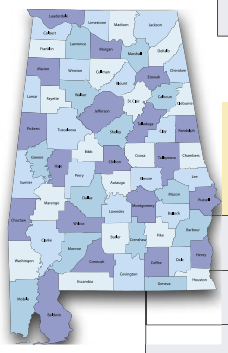
Kentucky County of Residence at Diagnosis
2006 All Cases

Adair	2	Daviess	37	Knox	1	Ohio	7
Allen	13	Edmonson	6	Laurel	3	Pike	1
Ballard	5	Fayette	10	Letcher	1	Powell	1
Barren	9	Frankllin	4	Lewis	1	Pulaski	23
Boyd	2	Fulton	5	Lincoln	2	Rowan	1
Boyle	1	Graves	19	Logan	23	Russell	3
Breathitt	1	Grayson	2	Lyon	16	Scott	3
Breckinridge	1	Green	1	Madison	2	Shelby	1
Bullitt	1	Greenup	1	Marion	1	Simpson	14
Butler	7	Hancock	4	Marshall	21	Taylor	2
Caldwell	12	Hardin	5	Mason	3	Todd	12
Calloway	23	Harrison	2	McCracken	39	Trigg	16
Carlisle	7	Hart	2	McCreary	3	Union	3
Casey	1	Henderson	11	McLean	3	Warren	72
Christian	53	Hickman	2	Mercer	2	Wayne	3
Clark	1	Hopkins	17	Metcalfe	3	Webster	3
Clinton	4	Jefferson	11	Monroe	5	Whitley	2
Crittenden	3	Jessamine	2	Muhlenberg	17	Woodford	1
Cumberland	3	Johnson	1	Nelson	3	**Total Cases:**	**608**

BY GEOGRAPHY, CONTINUED

State of Residence at Diagnosis
2006 All Cases

Alabama	106	Louisiana	8	Oklahoma	5
Arkansas	12	Massachusetts	1	Pennsylvania	2
Arizona	1	Michigan	1	South Carolina	10
California	1	Minnesota	2	South Dakota	1
Colorado	3	Missouri	3	Tennessee	2934
Connecticut	2	Mississippi	46	Texas	10
Florida	19	Montana	3	Virginia	42
Georgia	61	North Carolina	9	Wisconsin	1
Iowa	1	Nebraska	2	West Virginia	2
Illinois	22	New Jersey	1	Outside No. America	3
Indiana	17	Nevada	1		
Kansas	2	New York	1		
Kentucky	621	Ohio	1	**Total Cases:**	**3957**



Alabama County of Residence at Diagnosis
2006 All Cases

Baldwin	1	Lawrence	3
Calhoun	3	Limestone	10
Colbert	6	Madison	17
Dale	1	Marion	1
Dallas	1	Morgan	1
DeKalb	1	Mobile	1
Franklin	3	Monroe	1
Greene	2	Montgomery	3
Henry	1	Morgan	17
Jackson	7	Tuscaloosa	2
Jefferson	2		
Lauderdale	12	**Total Cases:**	**96**

BY CASE COUNT

Comparison of All Case Counts by Year: 2000 - 2006

Cancer Site	2000	2001	2002	2003	2004	2005	2006
Lip	2	4	6	3	3	7	10
Tongue	40	47	40	50	62	52	54
Salivary glands	12	14	19	10	10	14	9
Gum & hard palate	14	21	18	10	20	18	20
Floor of mouth	9	12	6	6	16	9	21
Buccal mucosa	9	9	9	12	8	10	15
Oropharynx	29	26	38	36	31	45	51
Nasopharynx	6	10	6	12	12	7	8
Hypopharynx	7	15	5	11	9	9	7
Other oral cavity	6	2	2	4	1	4	4
Esophagus	37	31	30	31	39	39	34
Stomach	18	25	24	14	20	34	38
Small Intestine	9	13	15	13	10	15	10
Colon	115	122	146	111	95	131	115
Rectum/Anus	50	53	78	62	80	98	88
Liver	48	54	49	54	72	71	64
Gallbladder	14	17	11	24	14	20	20
Pancreas	57	74	76	87	60	71	68
Other digestive tract	8	22	12	13	17	17	21
Nasal cavities, sinuses, ear	6	12	21	13	14	16	18
Larynx	51	60	51	44	74	73	71
Trachea, bronchus, lung-small	39	29	27	44	36	41	46
Trachea, bronchus, lung-NSC	236	259	255	223	260	265	254
Other respiratory	6	20	12	5	5	8	8
Bone	40	26	34	44	45	55	35
Connective & soft tissue	83	69	63	77	84	89	77
Malignant melanoma	120	153	143	174	206	215	264
Other skin	24	24	21	10	13	7	14
Breast, female & male	280	285	248	264	258	299	328
Cervix	80	85	107	46	32	40	40
Endometrium (corpus uteri)	79	76	67	56	72	70	85
Ovary	49	40	54	43	43	49	48
Other female genital organs	49	45	52	42	41	35	49
Prostate	288	341	388	397	451	592	683
Testis	27	40	25	27	36	20	26
Other male genital organs	5	9	9	12	4	7	9
Bladder	124	124	146	143	165	165	183

BY CASE COUNT, CONTINUED

Comparison of All Case Counts by Year: 2000 - 2006

Cancer Site	2000	2001	2002	2003	2004	2005	2006
Kidney	97	117	138	167	184	216	165
Other urinary organs	20	20	16	9	24	28	22
Eye	1	6	2	6	2	2	2
Brain	67	80	73	65	73	91	92
Other CNS	4	4	4	4	6	11	5
Thyroid	57	74	94	80	103	138	138
Other endocrine	12	9	4	8	11	15	14
Hodgkin's	32	21	35	38	29	33	27
Non-Hodgkin's Lymphomas	141	171	143	138	142	167	152
Plasma cell tumors	29	39	44	55	60	67	77
Lymphocytic leukemias	44	38	51	52	62	56	63
Myeloid leukemias	49	77	67	70	89	73	62
Other leukemias	14	15	11	9	7	8	8
Myeloprolif. & myelodysplas.	0	24	19	32	50	27	27
Other hematopoietic diseases	8	14	20	16	21	22	23
Other & ill-defined sites	1	0	1	2	0	2	2
Unknown primary	32	53	43	45	39	38	39
Benign/borderline brain, CNS	0	0	0	0	122	153	144
Total Cases:	**2684**	**3030**	**3078**	**3023**	**3442**	**3864**	**3957**

Comparison Case Counts Primary System

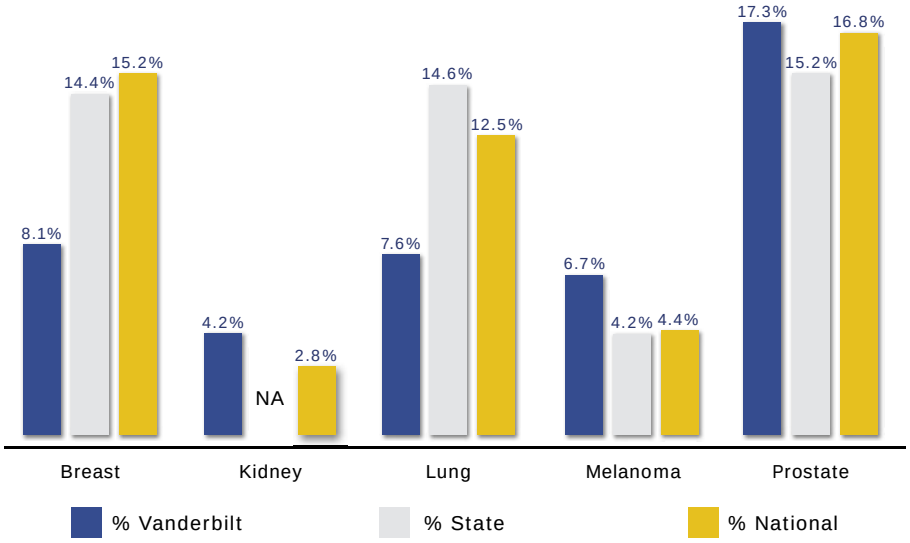
All Class of Case 2000 - 2006

PRIMARY SYSTEM	2000	2001	2002	2003	2004	2005	2006
Head and Neck	134	160	149	154	172	175	199
Digestive System	356	411	441	409	407	496	458
Respiratory System	338	380	366	329	389	403	397
Bone, Skin/Soft Tissue	267	272	261	305	348	366	390
Breast, female & male	280	285	248	264	258	299	328
Reproductive Orgams	257	246	280	187	188	194	222
Male Sites	320	390	422	436	491	619	718
Urinary System	241	261	300	319	373	409	370
Central Nervous System	72	90	79	75	81	104	99
Endocrine System	69	83	98	88	114	153	152
Lymphatic System	173	192	178	176	171	200	179
Hematopoietic	144	207	212	234	289	253	260
Other & ill-defined sites	1	0	1	2	0	2	2
Unknown primary	32	53	43	45	39	38	39
Benign/borderline brain, CNS	N/A	N/A	N/A	N/A	122	153	144
Total Cases:	**2684**	**3030**	**3078**	**3023**	**3442**	**3864**	**3957**

INCIDENTS & SURVIVAL, SELECTED SITES

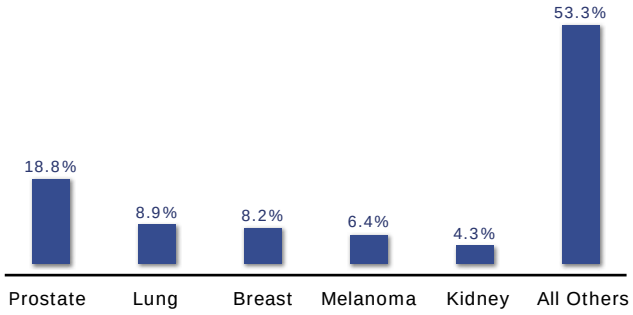
COMPARISON INCIDENCE SELECTED PRIMARY SITES AT VANDERBILT

ALL CASES 2006 WITH ESTIMATED NEW CASES
FOR SELECTED SITES BY STATE, U.S., 2006

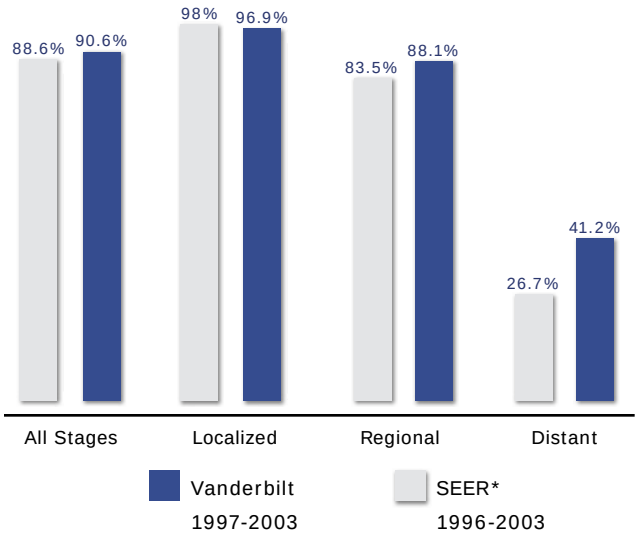


PERCENT TOP FIVE PRIMARY SITES AT VANDERBILT

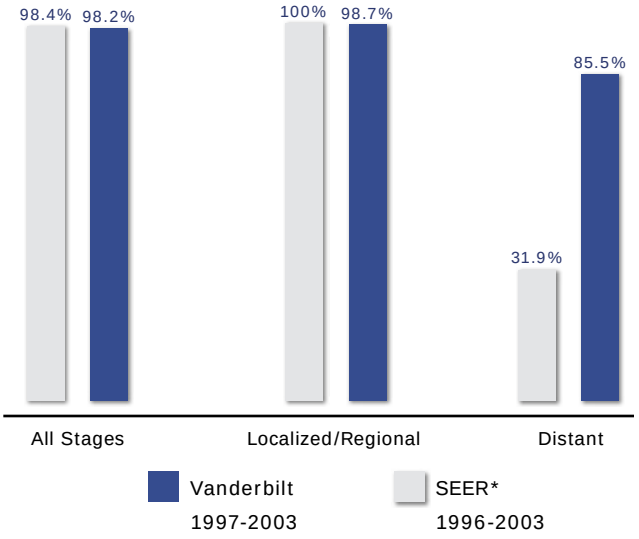
2006 ANALYTIC CASES



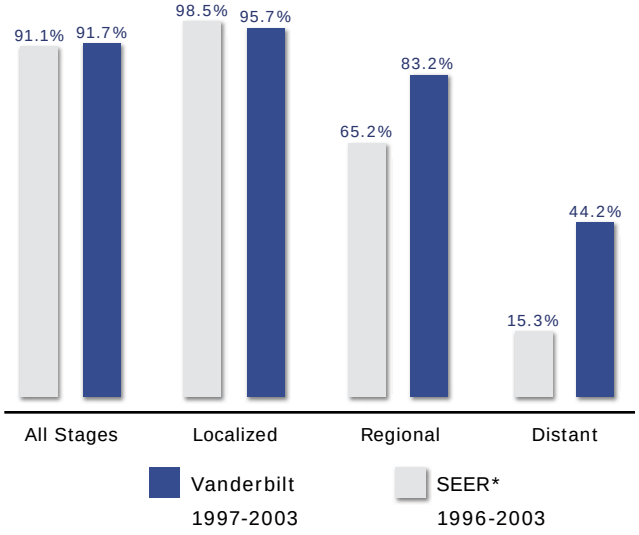
Overall Comparison 5-Yr Survival Rate
Breast Cancer



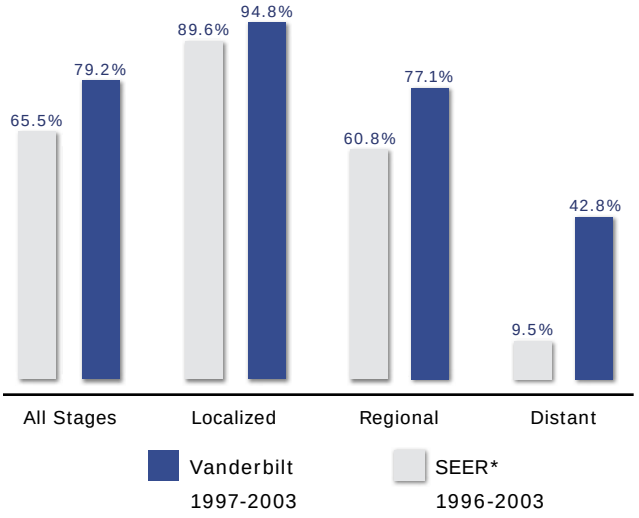
Overall Comparison 5-Yr Survival Rate
Prostate Cancer



Overall Comparison 5-Yr Survival Rate
Melanoma of the Skin

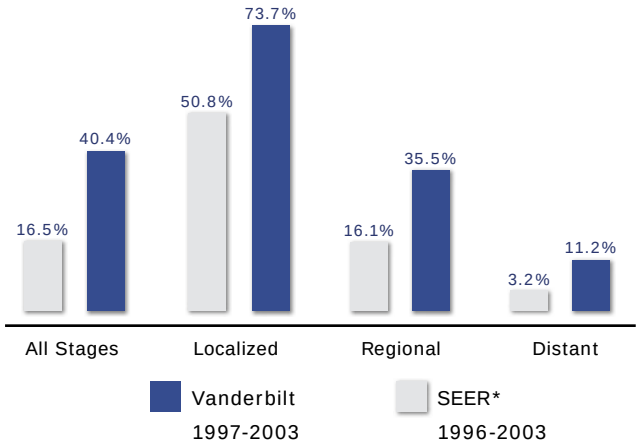


Overall Comparison 5-Yr Survival Rate
Kidney and Renal Pelvis

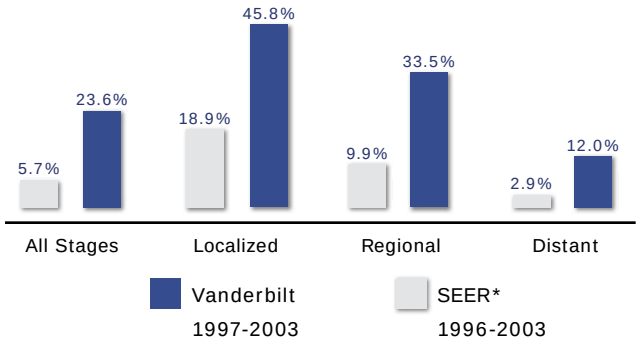


* SEER is the surveillance epidemiology and end results database, National Cancer Institute

Overall Comparison 5-Yr Survival Rate
Non-Small Cell and Bronchus Cancer



Overall Comparison 5-Yr Survival Rate
Small Cell Lung and Bronchus Cancer



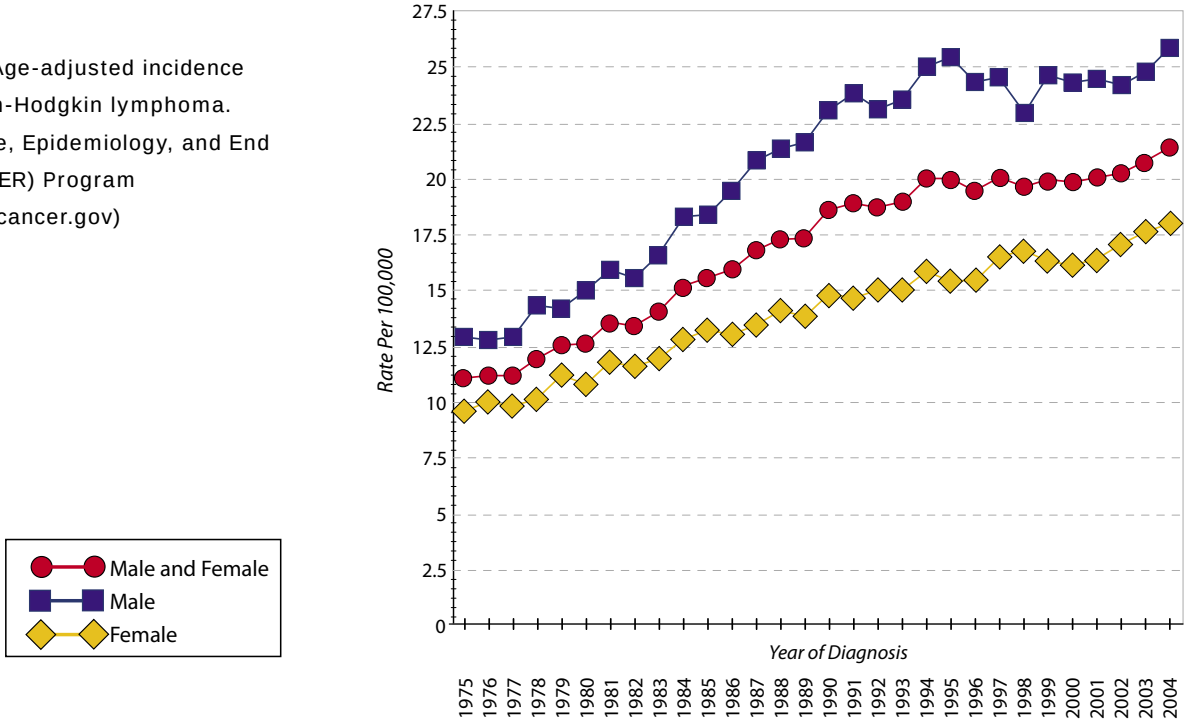
Selected Site Summary: Lymphomas

By John P. Greer, M.D., Professor of Medicine and Pediatrics

Epidemiology

A worldwide epidemic of non-Hodgkin lymphoma (NHL) varies according to gender, race and location. Incidence has been rising faster than all other malignancies except melanoma, prostate cancer, and lung cancer among women. Age-adjusted incidence in the United States increased from 11.1 per 100,000 people in 1975 to 19.3 in 2002 (figure 1). More than 60,000 new cases per year will be diagnosed in the United States this decade.

Figure 1. Age-adjusted incidence rate for non-Hodgkin lymphoma. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov)



In addition, lymphomas:

- Represent about 10% of all childhood cancers in developed countries (third in relative frequency behind acute leukemias and brain tumors).
- Are more common in adults than children.
- Have a steady increase in incidence from childhood through age 80.
- Are the fifth most common cancer in the United States, representing 4% of all cancers.
- Have a median age at diagnosis of 67 (from 2000-2004).

Incidence of NHL is 40% higher for males (23.2 per 100,000) than females (16.3 per 100,000), with an age-adjusted death rate of 7.6 per 100,000 men and women per year. From 2000-2004, the highest age-adjusted mortality was among white males (9.9 per 100,000); the lowest mortality has been in Asian/ Pacific Islander females (3.90 per 100,000).

Classification

The immunologic origin of NHL has led to a better understanding and to development of more effective therapy over the past 35 years. In 1974, Karl Lennert in Germany, and Robert Lukes (University of Southern California) and Robert Collins (Vanderbilt University) in the United States, classified NHL on the basis of the cell of origin within the immune system and sub-divided them into B- and T-cell neoplasms. In the 1980s, the lymphoid origin of NHL was confirmed at the molecular level, with the identification of specific immunoglobin gene and T-cell receptor gene rearrangements in B- and T-cell lymphomas, respectively. In 1982, a Working Formulation (WF) of NHL separated diseases according to histologic grade and made correlations with survival; however, the WF was based on morphology and clinical features and did not utilize the immunologic concepts developed by Lukes and Collins.

Physicians: (left to right, back row) Drs. Wichai Chinratanalab, David Morgan, Madan Jagasia, Friedrich Schuening, Richard Stein, John Greer, Bipin Savani; (front row) Nishitha Reddy, Anne Neff and Stacey Goodman.

Drs. Adetola Kassim, and Brian Engelhardt

Table 1.

Malignancies of the Lymphoid System

B-Cell Lineage	T-Cell Lineage
Indolent Lymphomas/ Leukemia (untreated survival measured in years)	
Chronic lymphocytic leukemia and small lymphocytic lymphoma	Large granular lymphocytic leukemia, T-cell and natural killer-cell types
Lymphoplasmacytic lymphoma, immunocytoma, Waldenström macroglobulinemia	Mycosis fungoides and Sézary syndrome
Hairy cell leukemia	Primary cutaneous anaplastic large cell
Splenic marginal zone lymphoma	Smoldering and chronic adult T-cell leukemia/lymphoma (human T-cell lymphotropic virus type I positive)
Marginal zone B-cell lymphoma Extranodal (mucosa-associated lymphoid tissue B-cell lymphoma) Nodal (monocytoid)	
Follicular lymphoma (grade I and II)	
Aggressive lymphomas (untreated survival measured in months)	
Plasmacytoma, multiple myeloma	Prolymphocytic leukemia
Mantle cell lymphoma	Peripheral T-cell lymphoma, unspecified
Follicle center lymphoma, follicular (large cell) - grade III	Angioimmunoblastic lymphoma
Diffuse large B-cell lymphoma	Extranodal NK/T-cell lymphoma, nasal type
Primary mediastinal (thymic) large B-cell lymphoma	Intestinal T-cell lymphoma (enteropathy-type)
	Systemic anaplastic large cell lymphoma (T-cell and null-cell type), ALK+ and ALK-
	Hepatosplenic T-cell lymphoma
	Cutaneous gamma delta lymphoma Subcutaneous panniculitis-like T-cell lymphoma (alpha beta)
Highly aggressive lymphomas and acute leukemias (untreated survival measured in weeks)	
Precursor B-lymphoblastic lymphoma/leukemia	Precursor T-lymphoblastic lymphoma/leukemia
High-grade B-cell lymphoma, Burkitt-like	Adult T-cell lymphoma/ leukemia (human T-cell lymphotropic virus type I positive)
Burkitt lymphoma and B-cell acute leukemia	
Plasma cell leukemia	Aggressive NK cell leukemia
Hodgkin Lymphoma **Nodular lymphocyte predominant Hodgkin lymphoma**	
Classic Hodgkin lymphoma	
Nodular sclerosis Hodgkin lymphoma	
Mixed cellularity Hodgkin lymphoma	
Lymphocyte-rich classic Hodgkin lymphoma	
Lymphocyte depleted Hodgkin lymphoma	

In 1994, a revised European American lymphoma (REAL) classification was purposed to identify specific types of lymphomas of B- and T-cell origin. The REAL classification dropped the grading scheme of the WF and developed a diagnosis by identifying clinical features, morphology, immonophenotype, and genetic data when available. The World Health Organization (WHO) has adopted the diagnostic principles first proposed by Lukes and Collins and utilized by the REAL classification (Table 1).

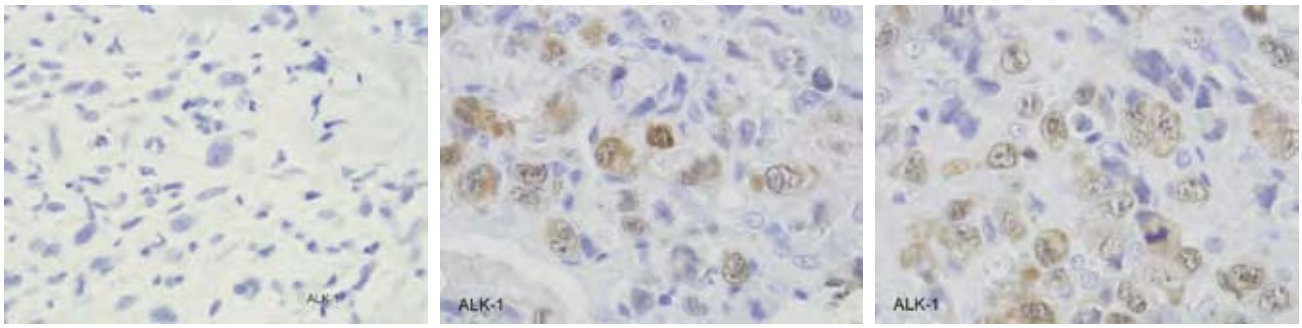
Nurse Practitioners: (left to right) Jennifer Mitchell, Anne Galloway, Leigh Ann Vaughn, Kelly Smith

Hematopathology

Numerous clinicopathologic projects have been reported from Vanderbilt-Ingram Cancer Center through a close collaboration between clinicians and the Division of Hematopathology, led by Dr. Mary Zutter and including Drs. David Head, Thomas McCurley, Mary Ann Thompson, and Claudio Mosse. In 2007, they reviewed more than 4,500 cases, including 206 new cases of acute leukemias and 181 new "in-house" lymphomas. Projects have included series of follicular lymphoma (1), large cell lymphoma (2), peripheral T-cell lymphoma (3), anaplastic large cell lymphoma (4), T-cell rich B-cell lymphoma (5), splenic marginal zone lymphoma (6), natural killer-like T-cell lymphoma (7), and hepatosplenic alphabeta T-cell lymphoma (8). Investigators at Vanderbilt were among the first to recognize that most peripheral T-cell lymphomas had an adverse prognosis when compared to the large B-cell counterpart (3, 9).

A sub-type of peripheral T-cell lymphoma, anaplastic large cell lymphoma (ALCL) associated with a specific translocation, t(2;5), has a prognosis similar to diffuse large B-cell lymphoma. Since the original description of ALCL in 1985, the clinical, morphologic, immunophenotypic and genetic spectrum of ALCL has been defined (4, 10). One of the genes involved in the t(2;5) is the anaplastic lymphoma kinase (ALK) gene, which can be identified through immunostaining (figure 2).

Figure 2. Negative immunostaining for anaplastic lymphoma kinase (far left) and positive (right) in dysplastic lymphocytes with prominent nucleoli in a patient with ALCL.



ALK-positive ALCL represents a common lymphoma (2% - 8% of NHL) with:

- a wide morphologic spectrum
- young median age (15 - 30 years)
- peripheral adenopathy with relative sparing of the mediastinum
- frequent extranodal disease (skin, soft tissue and bone as the most common extranodal sites)
- and a good prognosis.

ALK expression subdivides ALCL into at least three clinical subtypes:

- ALK-positive systemic ACL
- ALK-negative systemic ALCL
- and a more indolent disease, primary cutaneous ALCL (also ALK-negative).

A better response to chemotherapy has resulted in two-fold or higher increase in survival for ALK-positive ALCL (71% - 93% at five years) compared to systemic ALK-negative ALCL (15 - 46%) in retrospective series (10).

Nursing Staff: (left to right, back row) Fran England, Carey Clifton, Meera Kumar, Katie Kaye, Howard Thomason, Carol Sanders, Christina Salajanu, Rhonda Neblett, Andrea Murray, Marsha Burns, Karen Proctor, Carol Kelso, Gwendolyn Morrison (front row) Melissa Anderson, Krista Kuhnert, Melissa Logue, Donna Dunn, Leslie Wyttenbach, Sharon Sims, Laura Winslow

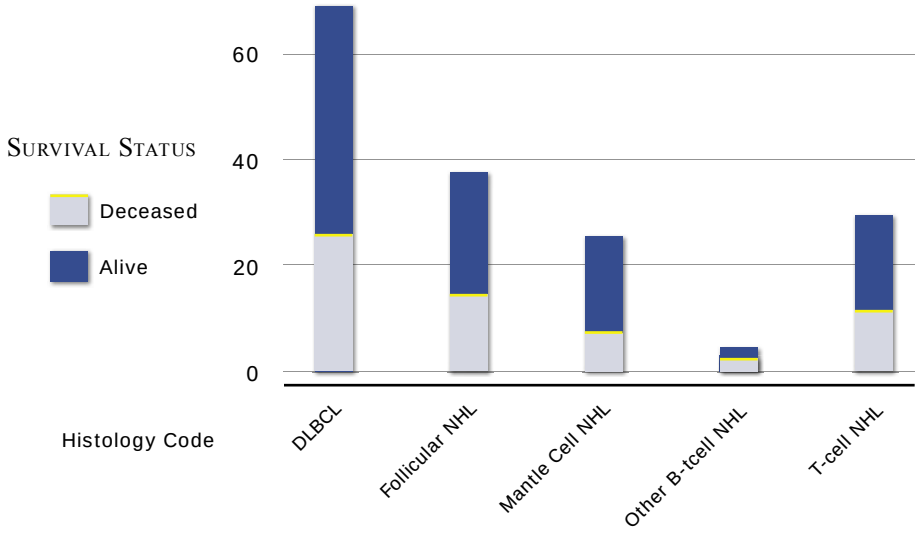
Data Management: (left to right) Cristina Nicolescu, Mihaela Constantin, Oana Marciuc, Carole Hunt, Joe D'Souza, Veronica Buhas, Felicia Cristoloveanu, Dana Stoiclescu, Natalie McCarver, Steve Curtis

Non-Hodgkin Lymphoma Analytic Cases

NHL analytic cases from 1997 - 2003 are reviewed by histologic type in table 2. Of these 591 cases:

- 59.7% were male.
- 40.3% were female.
- Mean age was 54.3 years.
- 91.8% were white.
- 6.3% were African-American.
- 1.9% was of other racial origin.

Figure 3A. Five-year survival, NHL.



The five-year survival for NHL, according to histology, is depicted in Figure 3A and compared to the SEER survival in Figure 3B.

Figure 3B.

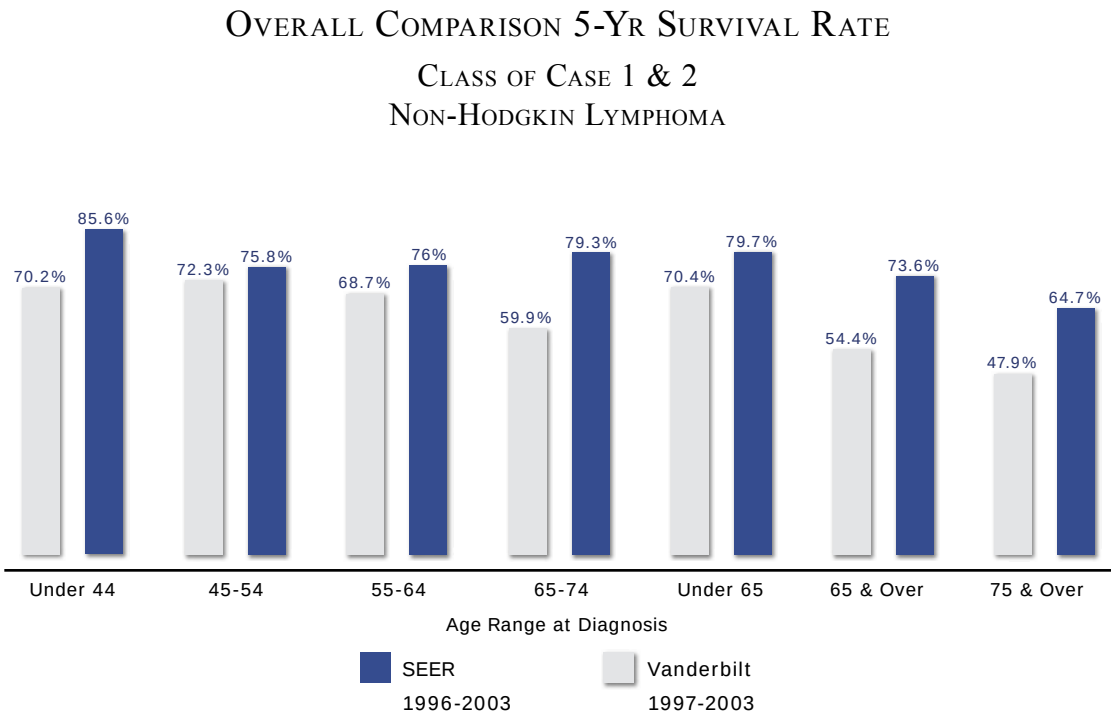


Table 2

Study of Histology		
Num Pts.	Histo Code	Histology Code Description
33	9590	Malignant Lymphoma, NOS
16	9591	Malignant Lymphoma, non-Hodgkin, NOS
1	9596	Composite Hodgkin and non-Hodgkin lymphoma
37	9670	Malignant lymphoma, small B lymphocytic, NOS
3	9671	Malignant lymphoma, lymphoplasmacytic
22	9673	Mantle cell lymphoma
6	9675	Malignant lymphoma, mixed small and large cell, diffuse (obs)
181	9680	Malignant lymphoma, large B-cell, difuse, NOS
9	9684	Malignant lymphoma, large B-cell, diffuse, immunoblastic, NOS
32	9687	Burkitt lymphoma, NOS
1	9689	Splenic marginal zone B-cell lymphoma (C42.2)
23	9690	Follicular lymphoma, NOS
13	9691	Follicular lymphoma, grade 2
49	9695	Follicular lymphoma, grade 1
14	9698	Follicular lymphoma, grade 3
20	9699	Marginal zone B-cell lymphoma, NOS
13	9702	Mature T-cell lymphoma, NOS
4	9705	Angioimmunoblastic T-cell lymphoma
4	9708	Subcutaneous panniculitis-like T-cell lymphoma
45	9709	Cutaneous T-cell lymphoma, NOS
19	9714	Anaplastic large cell lymphoma, T cell and Null cell type
1	9716	Hepatosplenic ψo (gamma-delta) cell lymphoma
14	9718	Primary cutaneous CD30+ T-cell lymphoproliferative disorder(C44.)
4	9719	NK/T-cell lymphoma, nasal and nasal-type
20	9727	Precursor cell lymphoblastic lymphoma, NOS
2	9728	Precursor B-cell lymphoblastic lymphoma
4	9729	Precursor T-cell lymphoblastic lymphoma
1	9827	Adult T-cell leukemia/lymphoma (HTLV-1 positive)
591	**Total Cases**	

Non-Hodgkin Lymphoma Analytic Cases continued...

Table 3

Study of Age at Diagnosis
Mean = 54.316 Std Dev = 19.968
Number = 591 Sum = 32101.000
Min = 2 Max = 105

Study of Gender

Sex	Num Pts	% Cases
Male	352	59.7%
Female	238	40.3%
Total Cases:	**590**	**100.0%**

Study of Race

Race	Num Pts	% Cases
White	542	91.8%
Black	37	6.3%
Japanese	1	0.2%
Asian Indian, Pakistani	1	0.2%
Vietnamese	2	0.3%
Laotian	1	0.2%
Other	3	0.5%
Unknown	3	0.5%
Total Cases:	**590**	**100.0%**

Study of Case Accession Year

Year Entered	# Cases	% Cases
1997	73	12.4%
1998	61	10.3%
1999	84	14.2%
2000	93	15.7%
2001	105	17.7%
2002	89	15.1%
2003	86	14.6%
Total Cases:	**591**	**100.0%**

Analytic Cases of Hodgkin Lymphoma

Table 4

Study of Age at Diagnosis
Mean = 29.479 Std Dev = 17.364
Number = 121 Sum = 3567.000
Min = 4 Max = 76

Study of Gender

Sex	Num Pts	% Cases
Male	70	57.9%
Female	51	42.1%
Total Cases:	**121**	**100.0%**

Study of Race

Race	Num Pts	% Cases
White	105	86.7%
Black	14	11.6%
Asian Indian, Pakistani	2	1.7%
Total Cases:	**121**	**100.0%**

Study of Case Accession Year

Year Entered	Num Cases	% Cases
1997	14	11.6%
1998	15	12.3%
1999	21	17.4%
2000	16	13.2%
2001	11	9.1%
2002	19	15.7%
2003	25	20.7%
Total Cases:	**121**	**100.0%**

Analytic Cases of Hodgkin Lymphoma

Of 121 cases of Hodgkin lymphoma (HL) in 1997-2003:

- Mean age was 29.5.
- Male-female ratio was 57.9%:42.1%.
- Race distribution was 86.7% white, 11.6% African American and 1.7% other.

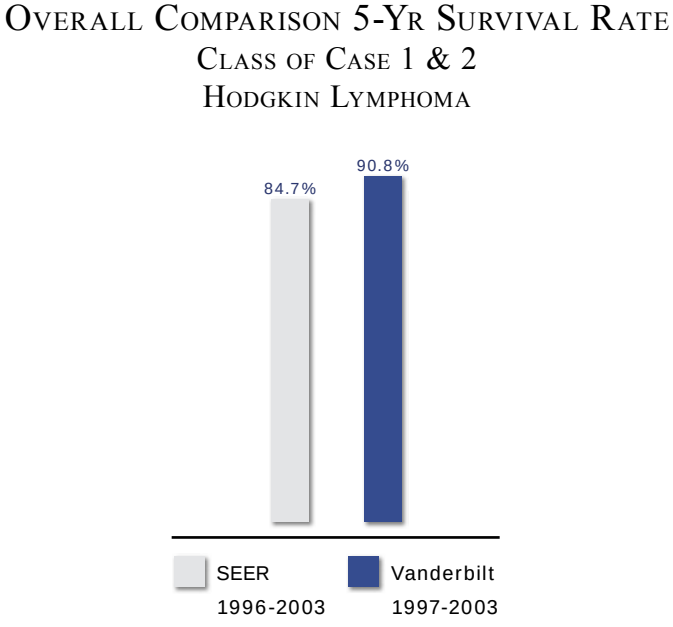
Tables 4 and 5 indicate the number of HL cases per year and the distribution by histology, respectively. The 5-year survival rate at VUMC was 90.8%, compared to 84.7% through the SEER program (figure 4).

Table 5

Study of Histology	
Histology Type	Num Pts
Hodg Lymph, Lymphocyte Depletion, NOS	2
Hodg Lymph Nodular Lymphocyte Predominance	3
Hodg Lymph Nodular Sclerosis, Grade 2	5
Hodg Lymph Nodular Sclerosis, NOS	81
Hodg Lymph Mxd Cellularity, NOS	9
Hodg Lymph, Lymphocyte-rich	4
Hodg Lymph Nodular Sclerosis, Cellular Phase	1
Hodgkin Lymph, NOS	16
Total Cases:	**121**

Addditional Data:	
Age Range at Diagnosis	Num Pts
Under 44	98
45-54	11
55-64	3
65-74	8
75+	1
Under 65	112
65 & Over	9

Figure 4.



Clinical Trials

Clinicians at Vanderbilt-Ingram have used investigator-initiated regimens, cooperative group trials, and transplantation in the therapy of lymphoma. Dose-intensive regimens, known as mega therapy, were developed in the 1980s for patients with lymphoma and multiple adverse prognostic factors. (11).

In the last five years, investigators at Vanderbilt-Ingram have offered patients with lymphoma entry into a number of clinical trials sponsored by national cooperative groups, including the Children's and the Eastern Cooperative Oncology Groups, and by the pharmaceutical industry. In addition to offering access to novel approaches, the results of several of these trials have played a pivotal role in altering standard or optimal therapy. Dr. David Morgan has led efforts to place patients with lymphoma on clinical trials.

Diffuse large B-cell lymphoma (DLBCL) is a curable disease with cyclophosphamide, doxorubicin, vincristine and prednisone therapy (CHOP), which was introduced in the 1970s. Although new regimens were reported as superior to CHOP, an intergroup trial reported in 1993 indicated that none were better than CHOP (12). With approval of the anti-CD20 monoclonal antibody rituximab as a single agent for low-grade lymphoma in 1997, a randomized phase III trial addressed CHOP in the treatment of DLBCL (13). Patients over age 60 were randomized to receive standard CHOP or CHOP plus rituximab. Those who responded were randomized again to receive rituximab alone as maintenance therapy, four doses every six months for two years. With a median follow-up time of 3.5 years, the three-year failure-free survival rate was 53% in the R-CHOP vs 46% for CHOP alone (p=.04); there was no further improvement in outcome with the addition of maintenance rituximab. This and similar studies established R-CHOP as the standard treatment for DLBCL.

The role of rituximab maintenance in follicular and other low-grade non-Hodgkin lymphomas was investigated in ECOG 1496, another Phase III randomized controlled clinical trial that accrued patients at Vanderbilt-Ingram. The initial study design randomized patients to one of two induction chemotherapy regimens: cyclophosphamide, vincristine and prednisone (CVP), or cyclophosphamide and fludarabine (CF) (14). Responders were then randomized to maintenance rituximab or observation. The CF induction arm was closed early in the course of the trial due to increased infections, and ECOG 1496 became a trial of the role of maintenance rituximab versus observation after CVP induction therapy. Median progression-free survival (PFS) from the time of randomization was 15 vs 61 months, comparing observation to maintenance rituximab, respectively. The PFS at four years from randomization was 34% vs 58%. Despite these positive results, it is not yet known whether a strategy of

Patients with advanced and/or bulky disease have a somewhat more guarded prognosis, but the majority will be cured with modern therapy.

Administrative Staff: Ginny Felts, Willa Bean, Michelle Keesee, Pamela Johnson, Aundra Brown, Deborah Brandle, Trisha Williams, Janice Tracy, Sharon Smith, Sheavon Robinson

maintenance rituximab is superior for all patients and whether it is superior to rituximab at the time of relapse. A common current treatment strategy is induction chemotherapy with rituximab. It is not known whether there is a benefit to maintenance rituximab.

Treatment of HL is one of the major success stories of oncology. More than 75% of patients with HL can be cured with current therapies, primarily based on the doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen. In patients with nonbulky clinical stage I to IIA HL, an ECOG randomized trial comparing ABVD alone to combined modality indicated inferior progression-free survival (88% vs 95%, p=.004) but no differences in event-free (85% vs 88%) or overall survival (95% vs 92%) (15).

Patients with advanced and/or bulky disease have a somewhat more guarded prognosis, but the majority will be cured with modern therapy. Long-term toxicity of the curative regimens remains an area of great concern and active investigation, as many patients with HL are young. The long-term toxicities of standard combined modality therapy for HL include cardiac toxicity, pulmonary fibrosis, neuropathy, and second malignancies.

ECOG 2496 is a randomized controlled Phase III clinical trial comparing the efficacy and toxicity of standard ABVD therapy versus a multi-drug chemoradiotherapy treatment, known as Stanford V, for patients with advanced disease. The putative advantages of Stanford V include its brevity (weekly doses for three months versus biweekly doses for 6-8 months in standard ABVD) and the markedly lower cumulative doses of doxorubicin and bleomycin compared to ABVD. The hypothesis is that the lower doses of known toxic drugs will reduce the rate of long-term complications as compared to ABVD, while the compressed schedule will maintain dose intensity and thus high efficacy rates. Vanderbilt-Ingram investigators were active in accruing patients to this trial, which is under analysis.

Mantle Cell Lymphoma (MCL) is an uncommon and difficult form of NHL, accounting for about 8% of all diagnoses. Most patients respond well to initial chemotherapy; however, relapses are common and the disease tends to be resistant to chemotherapy at relapse, with average survival of only one to two years. Vanderbilt-Ingram investigators participated in a multi-center, Phase II study of bortezomib in patients with relapsed or refractory MCL (16). The response rate in assessable patients

was 33%, with 8% complete responses. While this was a Phase II trial with no control group, the results are considered significant and have contributed to the approval of bortezomib for relapsed MCL and to the design of several further trials for treatment of newly diagnosed and relapsed patients with MCL.

Drs. John Zic and John Greer conduct a cutaneous lymphoma clinic where patients are evaluated and treated for a variety of lymphomas involving the skin, with the most common type being mycosis fungoides (MF). Zic has one of the largest reported experiences utilizing photopheresis as therapy for MF (17) and has evaluated new therapies, including denileukin difitox (ONTAK) and a Phase II trial for a human monoclonal anti-CD4 antibody.

SEVERAL TRIALS IN NHL ARE ACCRUING PATIENTS AT VANDERBILT-INGRAM:

- a phase II trial ECOG trial (l405) of adding bortezomib to the highly active hyperCVAD regiment or untreated MCL
- a randomized trial of rituximab versus bortezomib and rituximab for patients with relapsed follicular lymphoma
- ECOG 2404, a trial of bevacizumab added to CHOP for peripheral T cell and natural killer (NK)-cell lymphoma
- an open-label, long-term safety and tolerability study of VEGF trap administered intravenously in patients with advanced solid tumors or lymphoma.
- An open label, dose escalation study of the safety of SNX-5422 mesylate in patients with refractory hematological malignancies.

For info about clinical trials at Vanderbilt-Ingram: (800) 811-8480

PHASE I AND PHASE II PROGRAMS

Dr. Nishitha Reddy has joined the SCT/hematology program with an interest in Phase I and II trials. The Phase I program focuses on investigating new agents that target molecular pathways based on the preclinical data in various hematological malignancies. For example, in NHL we are investigating the role of SNX-5422 mesylate, a prodrug of a selective, small molecule inhibitor of the chaperone heat shock protein that is over-expressed in cancer cells and targets the transcriptional pathways. Phase I investigation of this orally administered drug in solid tumors is near completion. In the United States, Vanderbilt-Ingram has the largest number of patients enrolled on this study. Other

strategies under investigation:

- agents that target the apoptotic ubiquitin pathway
- immunotherapeutic agents which may provide lower toxicity than chemotherapy
- monoclonal antibodies, either alone or with other agents.

Dr. Reddy has studied the combination of lenalidomide (an immunomodulatory agent) and rituximab in preclinical mouse models (18,19) . These promising results are now being evaluated in patients with lymphoma.

The goal of our Phase II program in lymphoma is to identify novel combinations of new agent(s) and/or chemotherapeutic drugs that would offer the greatest, sustained anti-tumor effects with minimal long-term side effects. Monoclonal antibody therapy, either alone or in combination with other agents, is under investigation. In this exciting era of novel targeted agents, we are offering patients the unique opportunity to participate in various trials in NHL.

Transplantation

The Vanderbilt-Ingram Cancer Center Blood and Bone Marrow Transplant Program is the most experienced and comprehensive in the region. Its leadership includes:

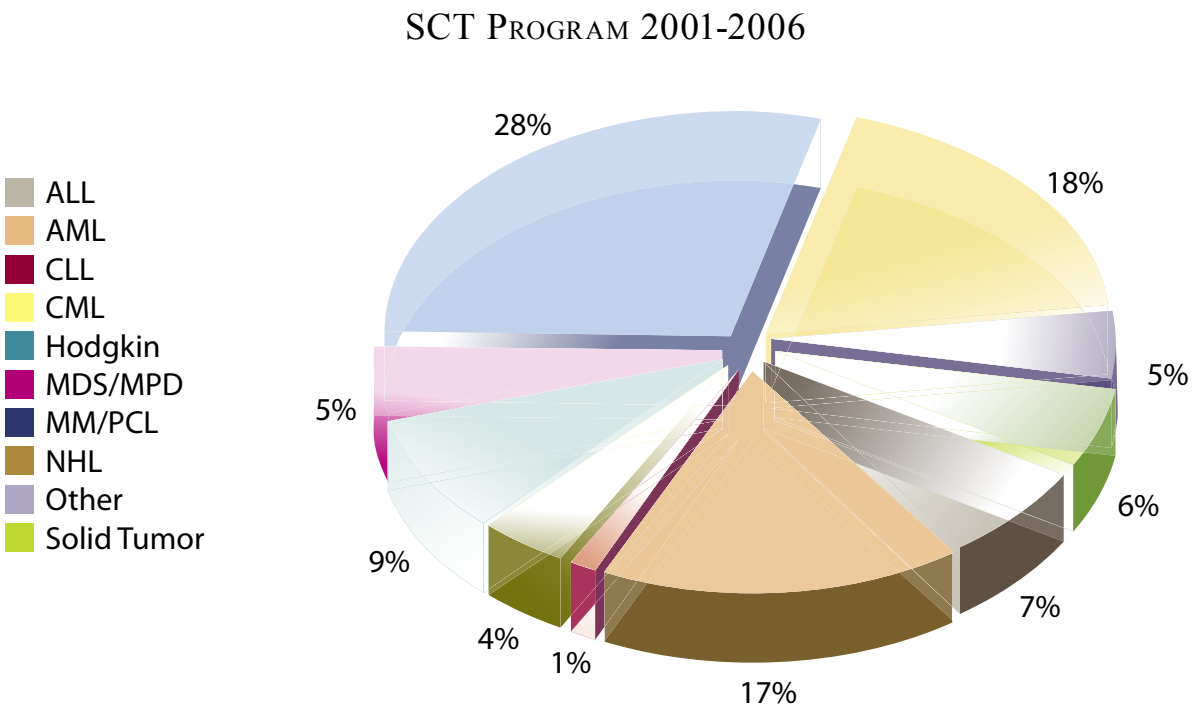
- Dr. Friedrich Scheuning, who directs the Stem Cell Transplantation program, begun in 1981 by Dr. Steven Wolff
- Dr. Stacey Goodman, who directs the Veterans Administration SCT component, begun in 1995, and oversees data management with Carole Hunt
- Dr. Haydar Frangoul, who leads the pediatric SCT program
- Dr. Steve Brandt, who directs the Stem Cell Processing laboratory led by Karen Prater
- Dr. Madan Jagasia, who directs the outpatient of SCT clinic

Dr. Jagasia has validated new criteria for graft versus host disease (GVHD) (20). He also reported the impact of pathology on outcome of relapsed PTCL patients undergoing SCT and noted that ALK-positive ALCL had a better survival with SCT than other subtypes of PTCL (21). Dr. Brian Engelhardt is investigating the role of T regulatory cells in GVHD.

Transplantation for NHL and HL in 2001-2006 represents 27% of the transplants performed at Vanderbilt (figure 5). The most common NHL subtype to undergo SCT was diffuse large B-cell lymphoma (41.7%). For NHL, 77.3% of the transplants were autologous; 22.7% were allogeneic. Overall survival is 56.5% (±9.6%) at five years; there have been no statistical differences in survival between autologous and allogeneic transplantation. Engelhardt et al. reported the long-term follow up of patients undergoing transplantation for relapsed or refractory HL between January 1990 and April 2001 (22). There were 115 patients who underwent high dose chemotherapy followed by autologous

stem cell transplant for HL and the 5-year progression free survival and overall survival were 46% and 58%, respectively.

Figure 5. Distribution of diseases undergoing SCT, ALL= acute lymphoblastic leukemia, AML = acute myeloid leukemia, CLL = chronic lymphocytic leukemia, CML = chronic myeloid leukemia, MDS/MPD = myelodysplasia/ myeloproliferative disease, MM/PCL = multiple myeloma/ plasma cell leukemia, NHL = non-Hodgkin lymphoma.



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