CHAPTER 9

CANCER REPORT

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The patterns of cancer which develop in immunosuppressed renal transplant recipients are now clearly established. The conclusion that the incidences of almost all cancers are increased compared to those in the age-matched general population, over and above the long-recognised increases in the so-called "transplant-specific" cancers, appears solid.

The patients surveyed here are those reported from Australia and New Zealand until 30 September 2000. In this report all patients who received primary renal grafts and survived with functioning grafts for at least three months following transplantation are included. Patients whose cause of renal failure was related to malignancy (renal, renal tract or paraproteinaemia [including multiple myeloma]) were excluded.

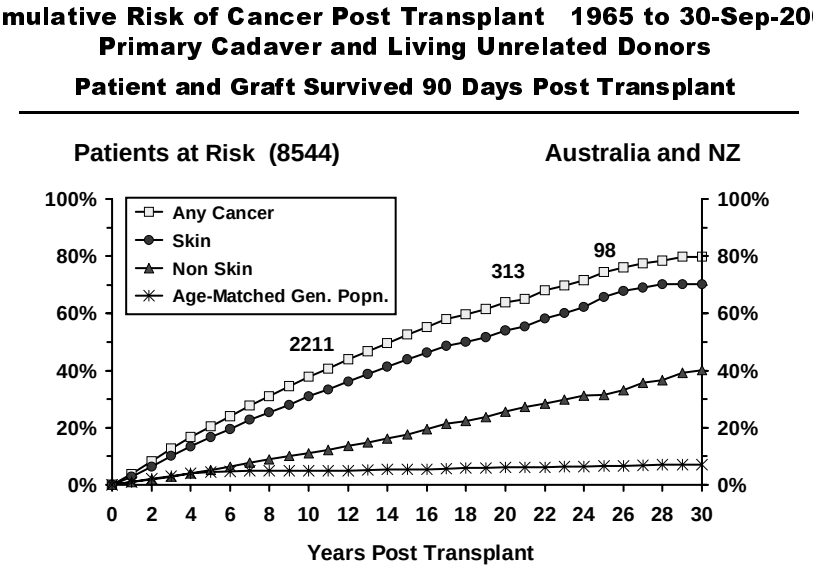
Ten thousand one hundred and fifteen patients received grafts of whom 8,554 (84.5%) received cadaveric/living unrelated donor renal transplant (CD/LUDRT) and 1561 (15.5%) received living related donor grafts (LRDRT). Mean follow-up for the groups is 8.7 years and 7.4 years respectively. With the exclusion of non-melanotic skin cancers, 1060 malignancies occurred in 943 CD/LUDRT patients (11% of total) and 106 occurred in 97 LRDRT patients (6.2%).

Cadaveric and Living Unrelated Donor Renal Recipients

The risk of cancer following primary CD/LUDRT and primary living unrelated donor transplantation is shown graphically in Figure 9.1. Here, the numbers of patients surviving beyond 10, 20, 25 and 30 years, are 2211, 313, 98 and 22 respectively. It can be seen that the risks of developing both skin cancer and non-skin cancer increase logarithmically with time. By 30 years post-transplantation, 80% of patients can expect to have had some form of cancer, with 70% having had skin cancer and 40% non-skin cancer. Thus many patients have both skin cancer and non-skin cancer.

The risk of cancer in different sites throughout the body following CD/LUDRT is shown in Figure 9.2. The cancers observed in the transplant recipients are compared with those expected in the age-matched general population (SA Cancer Registry). For the great majority of malignancies the frequency of occurrence is increased compared to that in the age-matched general population. The 95% confidence figures shown in Figure 9.2 reveal that, in most cases, the increases are statistically significant.

Figure 9.1



The cancers with the greatest increased risk have in common an established or suspected viral component to the aetiology. These include lymphomas (RR 9.5), Kaposi sarcoma (RR 77.9), liver (RR 7.3), oesophagus (RR 5.2), cervix in situ and invasive (RR 16.7, 3.1), vulva and vagina (RR 36.9), penis (RR 20.6), and leukemia (RR 3.0). Renal and renal tract malignancies also occur frequently (bladder RR 6.9, kidney RR 6.2, ureter RR 280). Other cancers with increased frequency are those of the endocrine glands (RR 5.0), especially the thyroid gland, and malignant melanoma (RR 3.5). Despite suggestions from Europe that both breast and rectal cancer might occur less frequently in transplant recipients, the rate of breast cancer in female Australian transplant recipients remains equal to that of the age-matched general population, while rectal and anal cancers are somewhat increased (RR 1.5). The only two cancers which occur less frequently in the Australian / New Zealand population of transplant recipients are ovarian cancer and prostate cancer (both RR 0.7). It was suggested in one of our earlier reports that this might reflect a decreased hormonal drive in these patients.

Figure 9.2

Risk of Cancer * Following Primary Cadaveric and Living Unrelated Donor Renal Transplantation (n=8554) 1965 to 30 September 2000

Site of Cancer	Observed Cancer	Expected Cancer	Risk Ratio	95% Confidence Intervals	
ALIMENTARY TRACT	194	85.07	2.3	1.97	2.63
Buccal Cavity	33	13.34	2.5	1.70	3.47
Pharynx	7	2.50	2.8	1.13	5.77
Oesophagus	18	3.47	5.2	3.07	8.20
Stomach	12	8.08	1.5	0.77	2.59
Small Intestine	1	0.76	1.3	0.03	7.33
Colon	65	27.35	2.4	1.83	3.03
Rectum & Anus	28	18.91	1.5	0.98	2.14
Liver	13	1.77	7.3	3.91	12.60
Gall Bladder & Extra Hepatic Bile Ducts	4	2.36	1.7	0.46	4.34
Pancreas	13	5.93	2.2	1.17	3.75
RESPIRATORY	88	40.21	2.2	1.76	2.70
Larynx	6	3.07	2.0	0.72	4.25
Trachea, Bronchus & Lung	77	35.59	2.2	1.71	2.70
Pleura	5	1.55	3.2	1.05	7.53
BONE	3	0.68	4.4	0.91	12.90
CONNECTIVE TISSUE	1	3.07	0.3	0.01	1.81
BREAST	52	50.83	1.0	0.76	1.34
Breast - female	51	50.45	1.0	0.75	1.33
Breast - male	1	0.38	2.6	0.07	14.70
GENITO-URINARY	313	86.97	3.6	3.21	4.02
Cervix - In situ	65	3.89	16.7	12.90	21.30
Cervix - Invasive	14	4.51	3.1	1.70	5.21
Uterus	11	7.99	1.4	0.69	2.46
Ovary	4	5.39	0.7	0.20	1.90
Vulva & Vagina	41	1.11	36.9	26.50	50.10
Prostate	29	41.85	0.7	0.46	1.00
Testis	4	2.93	1.4	0.37	3.50
Penis	7	0.34	20.6	8.28	42.40
Bladder	65	9.42	6.9	5.33	8.79
Kidney	59	9.50	6.2	4.73	8.01
Ureter	14	0.05	280.0	153.00	470.00
CENTRAL NERVOUS SYSTEM [excluding lymphoma]	9	7.62	1.2	0.54	2.24
ENDOCRINE GLANDS	18	3.58	5.0	2.98	7.95
Thyroid	16	3.56	4.5	2.57	7.30
Parathyroid	1	0.01	100.0	2.53	557.00
Other Endocrine	1	0.01	100.0	2.53	557.00
LYMPHOMA	142	15.00	9.5	7.97	11.20
Lymphoproliferative	13	0.01	>1000	692.00	>1000
CNS	16	0.01	>1000	915.00	>1000
Non-Hodgkins Disease	110	13.24	8.3	6.83	10.00
Hodgkins Disease	3	1.76	1.7	0.35	4.98
MULTIPLE MYELOMA	9	3.86	2.3	1.07	4.43
LEUKAEMIA	27	9.09	3.0	1.96	4.32
KAPOSI SARCOMA	17	0.23	73.9	43.10	118.00
MALIGNANT MELANOMA	114	32.79	3.5	2.87	4.18
MISCELLAENOUS	73	12.80	5.7	4.47	7.17
TOTAL	**1060** (11%)**	**351.58**	**3.0**	**2.84**	**3.20**

* Non-Melanotic skin cancers are not included
** The 1060 cancers occurred in 943 (11%) patients

Figure 9.3

Risk of Cancer * Following Primary Living Related Donor Renal Transplantation (n=1561) 1965 to 30 September 2000

Site of Cancer	Observed Cancer	Expected Cancer	Risk Ratio	95% Confidence Intervals	
ALIMENTARY TRACT	11	4.69	2.3	1.17	4.20
Buccal Cavity	2	1.00	2.0	0.24	7.22
Pharynx	0	0.14	0.0	0.00	26.30
Oesophagus	2	0.16	12.5	1.51	45.20
Stomach	2	0.39	5.1	0.62	18.50
Small Intestine	0	0.04	0.0	0.00	92.20
Colon	3	1.43	2.1	0.43	6.13
Rectum & Anus	1	0.96	1.0	0.03	5.80
Liver	1	0.08	12.5	0.32	69.60
Gall Bladder & Extra Hepatic Bile Ducts	0	0.12	0.0	0.00	30.70
Pancreas	0	0.29	0.0	0.00	12.70
RESPIRATORY	5	1.84	2.7	0.88	6.34
Larynx	0	0.14	0.0	0.00	26.30
Trachea, Bronchus & Lung	5	1.62	3.1	1.00	7.20
Pleura	0	0.07	0.0	0.00	52.70
BONE	0	0.09	0.0	0.00	41.00
CONNECTIVE TISSUE	2	0.29	6.9	0.84	24.90
BREAST	8	3.55	2.3	0.97	4.44
Breast - female	8	3.53	2.3	0.97	4.47
Breast - male	0	0.02	0.0	0.00	184.45
GENITO-URINARY	41	5.02	8.2	5.86	11.10
Cervix - In situ	17	0.72	23.6	13.80	37.80
Cervix - Invasive	3	0.46	6.5	1.34	19.10
Uterus	3	0.46	6.5	1.34	19.10
Ovary	0	0.34	0.0	0.00	10.80
Vulva & Vagina	9	0.07	128.6	58.80	244.00
Prostate	0	1.39	0.0	0.00	2.65
Testis	1	0.55	1.8	0.05	10.10
Penis	1	0.02	50.0	1.27	278.60
Bladder	2	0.46	4.3	0.53	15.70
Kidney	4	0.54	7.4	2.02	19.00
Ureter	1	0.01	100.0	2.53	557.00
CENTRAL NERVOUS SYSTEM	2	0.64	3.1	0.38	11.30
Other than lymphoma	2	0.64	3.1	0.38	11.30
ENDOCRINE GLANDS	2	0.42	4.8	0.57	17.20
Thyroid	2	0.41	4.9	0.59	17.60
Parathyroid	0	0.00	0.0	0.00	0.00
Other Endocrine	0	0.00	0.0	0.00	0.00
LYMPHOMA	17	1.25	13.6	7.92	21.80
Lymphoproliferative	5	0.01	500.0	162.00	>1000
CNS	0	0.00	0.0	0.00	0.00
Non-Hodgkins Disease	11	0.96	11.5	5.72	20.50
Hodgkins Disease	1	0.29	3.4	0.09	19.20
MULTIPLE MYELOMA	1	0.21	4.8	0.12	26.50
LEUKAEMIA	1	0.61	1.6	0.04	9.13
KAPOSI SARCOMA	3	0.03	100.0	20.60	292.00
MALIGNANT MELANOMA	10	3.19	3.1	1.50	5.76
MISCELLAENOUS	3	0.54	5.6	1.15	16.20
TOTAL	**106 ** (6.2%)**	**22.49**	**4.7**	**3.86**	**5.70**

* Non-Melanotic skin cancers are not included
** The 106 cancers occurred in 97 (6.2%) patients

Living Related Donor Renal Recipients

The risk of cancer following LRDRT is shown in Figure 9.3. It should be noted that these patients are younger (mean age 37 years) than CD/LURDT recipients (mean age 46 years) and follow-up is shorter (7.4 years vs 8.7 years). The mean age at which patients developed cancer following LRDRT was 40 years and that following CD/LUDRT 53 years. While the sites of cancers following LRDRT are closely similar to those following CD/LUDRT the overall risk ratio is significantly more following LRDRT (RR 4.7 vs 3.0 $p<0.05$). While the mean time to diagnosis of cancer following transplantation is approximately the same (99 months for LRDRT vs 104 months for CD/LUDRT) as is the occurrence of metastases (37% vs 42%), patients who have died of cancer are considerably less following LRDRT (27%) than following CD (47%). Overall, while 68% of patients remain alive following cancer diagnosed in LRDRT, 33% remain alive following cancer diagnosis in CD/LUDRT.

Immunosuppressive Drug Use and Cancer

The analyses of the cancers which have occurred in patients following treatment with azathioprine (but never cyclosporin [CSA]), with CSA (but never Az), with combination of Az plus CYA and with other or unknown agents continues and is shown in Figures 9.4-6. In patients in these groups who received the drugs continuously up to five years post-transplant there was a significantly increased number of cancers occurring in one group only. This was the Az plus CYA group compared with the Az group (P=.002). Virtually all the difference was due to an increased rate of skin cancer in the Az plus CYA group vs the Az group (P=.01). There was no significant difference between any of the groups for non-skin cancers.

Figures 9.7 and 9.8 document the risk of non-skin cancers with different treatment modes.

Figures 9.9 and 9.10 document clinical features of cancer.

Figure 9.4

Risk of Cancer Post Transplant 1981 to 30-Sep-2000
Primary Cadaver and Living Unrelated Donors
Patient and Graft Survived 90 Days Post Transplant

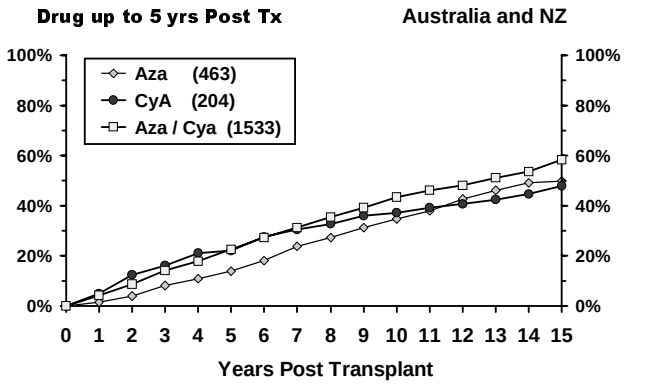


Figure 9.5

Risk of Skin Cancer Post Transplant 1981 to 30-Sep-2000
Primary Cadaver and Living Unrelated Donors
Patient and Graft Survived 90 Days Post Transplant

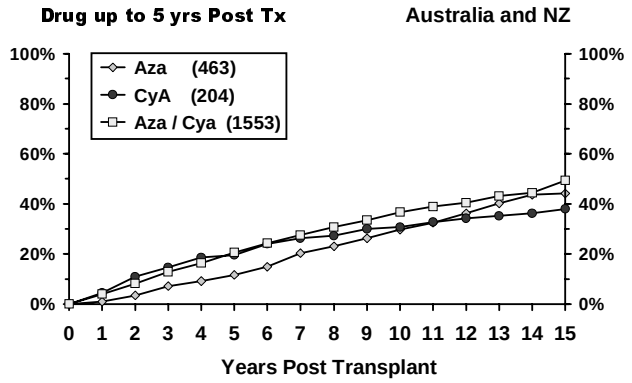


Figure 9.6

Risk of Non Skin Cancer Post Transplant 1981 to 30-Sep-2000
Primary Cadaver and Living Unrelated Donors
Patient and Graft Survived 90 Days Post Transplant

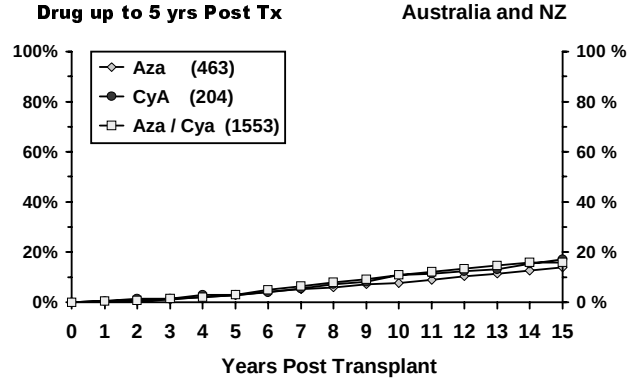


Figure 9.7

Renal Failure Patients
Sites of Cancer * Diagnosed
During Different Treatment Periods
1965 to 30 September 2000

Site of Cancer	Prior to Dialysis	On Dialysis	Living Related Donor	Cadaver /Living Unrelated Donor
ALIMENTARY TRACT	258	172	11 (10%)	194 (18%)
Buccal Cavity	21	19	2	33
Pharynx	4	5	0	7
Oesophagus	4	12	2	18
Stomach	20	20	2	12
Small Intestine	6	4	0	1
Colon	150	62	3	65
Rectum & Anus	47	23	1	28
Liver	2	12	1	13
Gall Bladder & Extra Hepatic Bile Ducts	1	4	0	4
Pancreas	3	11	0	13
RESPIRATORY	29	130	5 (5%)	88 (8%)
Larynx	5	7	0	6
Trachea, Bronchus & Lung	24	121	5	77
Pleura	0	2	0	5
BONE	6	2	0	3 (0.3%)
CONNECTIVE TISSUE	1	0	2 (2%)	1 (0.1%)
BREAST	166	75	8 (8%)	52 (5%)
Breast - female	164	74	8	51
Breast - male	2	1	0	1
GENITO-URINARY	986	285	41 (39%)	313 (30%)
Cervix - In situ	47	21	17	65
Cervix - Invasive	26	8	3	14
Cervix - Unknown	3	0	0	0
Uterus	41	10	3	11
Ovary	21	8	0	4
Vulva & Vagina	7	2	9	41
Prostate	143	46	0	29
Testis	37	1	1	4
Penis	2	0	1	7
Bladder	181	94	2	65
Kidney	448	80	4	59
Ureter	30	15	1	14
CENTRAL NERVOUS SYSTEM	4	15	2 (2%)	9 (0.8%)
Other than lymphoma	4	15	2	9
ENDOCRINE GLANDS	25	24	2 (2%)	18 (2%)
Thyroid	17	20	2	16
Parathyroid	4	3	0	1
Other Endocrine	4	1	0	1
LYMPHOMA	59	24	17 (16%)	142 (13%)
Lymphoproliferative	1	0	5	13
CNS	1	2	0	16
Non-Hodgkins Disease	45	18	11	110
Hodgkins Disease	12	4	1	3
MULTIPLE MYELOMA	214	21	1 (0.9%)	9 (0.8%)
LEUKAEMIA	37	10	1 (0.9%)	27 (3%)
KAPOSI SARCOMA	2	3	3 (3%)	17 (2%)
MALIGNANT MELANOMA	107	54	10 (9%)	114 (11%)
MISCELLAENOUS	31	60	3 (3%)	73 (7%)
TOTAL	**1,925**	**875**	**106**	**1,060**
Total Patients with Cancer	**1,726**	**818**	**97 (6.2%)**	**943 (11%)**
Patients at Risk	**30,686**	**27,588**	**1,561**	**8,554**

* Non-Melanotic skin cancers are not included

Figure 9.8

Risk of Cancer Other than Skin-related to Treatment Period 30 September 2000

Period of Cancer Development		Males				Females				Both Sexes				
		Patients at Risk	Obs Ca *	Exp Ca **	Risk Ratio ***	Patients at Risk	Obs Ca *	Exp Ca **	Risk Ratio ***	Patients at Risk	Patient Years at Risk	Obs Ca *	Exp Ca **	Risk Ratio ***
Prior to Dialysis		17,338	1,051	1,837	0.6	13,348	874	1,301	0.7	30,686	1,545,151	1,925	3,138	0.6
On Dialysis		15,542	484	404	1.2	12,046	391	211	1.9	27,588	64,772	875	615	1.4
Post Transplant	LRD	922	41	11.19	3.7	639	65	11.30	5.8	1,561	11,501	106	22	4.7
	CD	5,019	505	199	2.5	3,535	555	153	3.6	8,554	74,380	1,060	352	3.0

* Obs Ca = Observed Cancers
** Exp Ca = Expected Cancers
*** Risk Ratio = Observed Ca / Expected Ca

Figure 9.9

The Clinical Features of all Cancers* Other than Skin Diagnosed Following Cadaver and Living Unrelated Donor Renal Transplantation (n=8554) 1965 to 30 September 2000

	No of Cancers	Age of Pts (Years)		Sex		Time of Diagnosis After Transplant (Months)		Occurrence of Metastases	Death		Patients Alive
		Range	Mean	M	F	Range	Mean		Of this Cancer	Other Cause	
ALIMENTARY TRACT	194	23-78	56	110	84	4-353	131	101	119	29	46
Stomach	12	48-67	59	7	5	11-168	73	5	10	0	2
Colon	65	35-77	59	30	35	11-353	136	40	36	15	14
Rectum	28	30-68	53	9	19	35-337	150	14	13	5	10
Other	89	23-78	55	64	25	4-334	129	42	60	9	20
RESPIRATORY	88	31-77	60	53	35	3-277	105	54	73	9	6
Trachea & Lung	77	31-77	61	46	31	3-277	108	49	65	7	5
Other	11	47-63	59	7	4	6-214	84	5	8	2	1
BONE	3	51-58	54	1	2	70-90	82	0	2	0	1
CONNECTIVE TISSUE	1	60-60	60	0	1	33-33	33	0	0	1	0
BREAST	52	31-72	53	1	51	3-278	110	22	15	7	30
GENITO-URINARY	313	23-77	51	94	219	3-360	102	45	77	101	135
Cervix - In situ	65	23-65	39	0	65	3-236	83	0	0	21	44
Cervix - Invasive	14	26-69	45	0	14	21-249	98	7	8	3	3
Uterus	11	40-77	57	0	11	15-296	124	3	4	2	5
Vulva & Vagina	41	25-60	44	0	41	21-284	146	5	6	16	19
Prostate	29	51-72	64	29	0	16-360	120	6	4	11	14
Bladder	65	27-70	54	26	39	4-315	99	10	24	22	19
Kidney & Ureter	73	29-75	56	29	44	3-307	89	8	26	24	23
Other	15	23-69	50	11	4	16-231	97	6	5	2	8
CENTRAL NERVOUS SYSTEM											
Other than lymphoma	9	35-71	51	8	1	26-250	118	1	6	0	3
ENDOCRINE GLANDS	18	23-66	47	9	9	6-249	75	8	3	4	11
LYMPHOMA	142	13-77	50	82	60	3-342	81	49	82	17	43
Lymphoproliferative	13	13-48	35	9	4	8-189	71	5	7	0	6
CNS	16	27-72	48	9	7	4-106	29	0	10	6	0
Non-Hodgkins Disease	110	17-77	52	61	49	3-342	90	41	64	10	36
Hodgkins Disease	3	53-67	60	3	0	48-78	65	3	1	1	1
MULTIPLE MYELOMA	9	44-77	62	6	3	10-315	121	0	6	2	1
LEUKAEMIA	27	32-67	52	16	11	11-225	104	8	26	0	1
KAPOSI SARCOMA	17	30-65	51	9	8	4-216	60	9	8	2	7
MALIGNANT MELANOMA	114	21-74	53	69	45	7-338	93	38	28	31	55
MISCELLAENOUS	22	31-70	55	17	5	7-244	115	13	14	4	4
UNKNOWN	51	41-78	61	30	21	5-363	104	49	45	1	5
TOTAL	**1060 ** (11%)**	**13-78**	**53**	**505**	**555**	**3-363**	**104**	**397**	**504**	**208**	**348**

* Non-Melanotic skin cancers are not included
** The 1060 cancers occurred in 943 (11%) patients

Figure 9.10

The Clinical Features of all Cancers* Other than Skin Diagnosed Following Living Related Donor Renal Transplantation (n=1561) 1965 to 30 September 2000

	No of Cancers	Age of Patients (Years)		Sex		Time of Diagnosis After Transplant (Months)		Occurrence of Metastases	Death		Patients Alive
		Range	Mean	M	F	Range	Mean		Of this Cancer	Other Cause	
ALIMENTARY TRACT	11	31-69	45	6	5	16-235	116	7	5	1	5
Stomach	2	37-43	41	1	1	16-103	60	2	1	0	1
Colon	3	36-46	42	2	1	52-197	118	3	2	0	1
Rectum	1	40-40	40	1	0	198-198	198	0	0	0	1
Other	5	31-69	49	2	3	71-235	120	2	2	1	2
RESPIRATORY											
Trachea & Lung	5	45-69	55	2	3	12-234	110	4	3	1	1
CONNECTIVE TISSUE	2	39-46	43	1	1	45-70	58	0	0	0	2
BREAST	8	31-67	49	0	8	32-290	168	5	4	0	4
GENITO-URINARY	41	2-56	34	7	34	5-313	95	5	5	7	29
Cervix - In situ	17	22-42	29	0	17	9-159	69	1	0	3	14
Cervix - Invasive	3	34-48	41	0	3	106-126	118	2	2	0	1
Uterus	3	43-50	47	0	3	23-259	155	2	1	1	1
Vulva & Vagina	9	24-52	33	0	9	18-280	105	0	0	3	6
Bladder	2	41-43	43	2	0	102-313	208	0	0	0	2
Kidney & Ureter	5	2-56	34	3	2	5-123	50	0	2	0	3
Other	2	35-46	41	2	0	79-216	148	0	0	0	2
CENTRAL NERVOUS SYSTEM											
Other than lymphoma	2	42-55	49	2	0	11-92	52	1	1	0	1
ENDOCRINE GLANDS	2	30-39	35	1	1	67-184	126	1	0	1	1
LYMPHOMA	17	2-72	38	9	8	3-182	75	7	4	1	12
Lymphoproliferative	5	2-72	37	3	2	5-140	52	2	3	0	2
Non-Hodgkins Disease	11	23-63	39	6	5	3-182	83	5	1	1	9
Hodgkins Disease	1	24-24	24	0	1	104-104	104	0	0	0	1
MULTIPLE MYELOMA	1	58-58	58	1	0	59-59	59	0	0	1	0
LEUKAEMIA	1	19-19	19	1	0	59-59	59	1	1	0	0
KAPOSI SARCOMA	3	11-43	31	2	1	9-146	70	0	0	0	3
MALIGNANT MELANOMA	10	28-64	45	8	2	20-222	97	2	1	1	8
UNKNOWN	3	43-60	51	1	2	50-213	130	3	2	1	0
TOTAL	**106 ** (6.2%)**	**2-72**	**40**	**41**	**65**	**3-313**	**99**	**36**	**26**	**14**	**66**

* Non-Melanotic skin cancers are not included
** The 106 cancers occurred in 97 patients