COMMUNICATION

The American College of Surgeons Commission on Cancer and the American Cancer Society

The National Cancer Data Base Report on Cutaneous and Noncutaneous Melanoma

A Summary of 84,836 Cases from the Past Decade

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BACKGROUND. This study reviews the case-mix characteristics, management, and outcomes of melanoma cases occuring in the U. S. within the last decade.
METHODS. Analyses of the National Cancer Data Base (NCDB) were performed on cases diagnosed between 1985 through 1994. A total of 84,836 cases comprised of cutaneous and noncutaneous melanomas were evaluated.
RESULTS. The percentages of melanomas that were cutaneous, ocular, mucosal, and unknown primaries were 91.2%, 5.2%, 1.3%, and 2.2%, respectively. For cutaneous melanomas, the proportion of patients presenting with American Joint Committee on Cancer Stages 0, I, II, III, and IV were 14.9%, 47.7%, 23.1%, 8.9%, and 5.3%, respectively. Factors associated with decreased survival included more advanced stage at diagnosis, nodular or acral lentiginous histology, increased age, male gender, nonwhite race, and lower income. Multivariate analysis identified stage, histology, gender, age, and income as independent prognostic factors. For ocular melanomas, 85.0% were uveal, 4.8% were conjunctival, and 10.2% occurred at other sites. During the study period, there was a large increase in the proportion of ocular melanoma patients treated with radiation therapy alone. For mucosal melanomas, the distribution of head and neck, female genital tract, anal/rectal, and urinary tract sites was 55.4%, 18.0%, 23.8%, and 2.8%, respectively. Patients with lymph node involvement had a poor prognosis. For unknown primary melanomas, the distribution of metastases as localized to a region or multiple sites at presentation was 43.0% and 57.0%, respectively. Surgical treatment of patients with unknown primary site of the melanoma resulted in better survival compared with no treatment.
CONCLUSIONS. Treatment of early stage cutaneous melanoma resulted in excellent patient outcomes. In addition to conventional prognostic factors, socioeconomic factors were found to be associated with survival. ***Cancer* 1998;83:1664–78.**

KEYWORDS: melanoma, cutaneous melanoma, outcomes, National Cancer Data Base (NCDB).

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The common feature of all melanomas is the cell of origin, the melanocyte. Melanocytes are pigmented dendritic-like cells located in various anatomic sites. These sites include the base of the

epidermis, the eye, and in epithelia of the nasal cavity, oropharynx, anus, vagina, and urinary tract. Cutaneous melanomas are much more prevalent than noncutaneous melanomas, which are comprised of ocular and mucosal sites.

The incidence of cutaneous melanoma is increasing at a greater rate than any other human cancer in the U. S., and the increase in mortality is second only to lung cancer.[1] Since 1973, the incidence rate has been rising 4% to 6% each year. In 1998, it is estimated that approximately 41,600 new cases will be diagnosed in the U. S.[2] It is estimated that there will be 7200 deaths due to melanoma in the U. S., or 1 death every hour and 13 minutes. Lifetime analysis reveals that approximately 1 in 75 persons born in the year 2000 will develop a cutaneous melanoma during his or her lifetime.[3] One of the major factors associated with this rise in the incidence of cutaneous melanomas is the increased exposure of individuals to ultraviolet radiation. Unlike cutaneous melanomas, the incidence of both ocular and mucosal melanomas is believed to have remained stable.[4,5]

The purpose of this article was to review the case-mix characteristics, management, and outcomes of melanoma in the U. S. for the last decade. This report includes patients diagnosed with cutaneous, mucous membrane, and ocular melanomas as well as melanomas of unknown primary sites. To depict these patterns of treatment and survival, analyses were performed on the National Cancer Data Base (NCDB), a database of cancer registry information created by the American College of Surgeons' Commission on Cancer (COC) and the American Cancer Society in 1987.[6,7] All acute care hospitals are invited to submit their cancer registry data on an annual basis. For the most current NCDB call for data, 1227 hospitals contributed 689,714 records, representing an estimated 57% of all newly diagnosed cancer patients in 1994. Unlike single-institution studies, the NCDB registry data are able to provide treatment and survival information on a very large number of patients from a broad range of community-based and academic hospitals. These cancer registry data are a direct reflection of the actual information that is being compiled on these patients; for this reason, the database at times contains a large percentage of cases with unknown variables (such as stage and grade) with no capacity to audit the information.

Although cancer registries are planning to collect records directly from physicians' offices in the year 2000, the data in this article were not collected using this protocol. Because certain early stage melanomas can be diagnosed and treated in physicians' offices, it is possible that the counts in this article represent an undersampling of these types of patients.

METHODS

Hospital-based cancer registries provide their data to the NCDB through a computerized format.[6] To ensure standardization, the data are coded at the hospital level according to the *Data Acquisition Manual,*[8] the third and fourth editions of the American Joint Committee on Cancer (AJCC) *Manual for Staging of Cancer,*[9,10] and the second edition of the World Health Organization's *International Classification of Disease for Oncology* (ICD-O 2).[11]

Cases to be included in this study were extracted from the data base according to histology (ICD-O 2 melanoma codes M872–M879), year of diagnosis (1985–1994), the patient's having been diagnosed and/or treated at the reporting hospital, and the patients' having presented with a primary tumor (vs. recurrent disease). An algorithm based on selected patient and disease characteristics was employed to identify and eliminate duplicate cases in which more than one hospital submitted a record on the same patient (e.g., a patient who received surgery at one facility and radiation therapy at another).

AJCC staging, used to describe the extent of disease, was applied to melanomas of the skin. This staging system employs Breslow's depth of penetration and Clark's level of invasion, regional lymph node status, and the presence or absence of metastatic disease. (Breslow's depth and Clark's level were not available for separate analysis.) For selected analyses, stage was grouped into early (Stages 0–II) and advanced (Stages III–IV). Melanomas involving the eyelid were grouped with cutaneous melanomas. Although melanoma of the eyelid has a separate staging system, it is equivalent to the staging system for cutaneous melanomas. Histologies were classified as per ICD-O 2 codes. The four main histologic groupings, representing cutaneous melanomas, were: nodular (M8721), lentigo maligna (M8742), superficial spreading (M8743), and acral lentiginous (M8744) melanomas. The remaining histologies were categorized as "other" (e.g., melanoma, not otherwise specified [NOS], amelanotic, desmoplastic, or spindle cell). Ocular melanomas were lesions involving the conjunctiva and uvea. Uveal melanomas involved tumors arising in the iris, ciliary body, and choroid. AJCC staging was recorded for uveal melanomas. However, AJCC stage groupings for conjunctival melanomas currently are not recommended. Mucosal melanomas are mucous membrane lesions arising in the head and neck, female genital tract, anal/rectal, and urinary tract. There is no staging system for mucosal melanomas, but

lymph node status was a data element collected by cancer registries and analyzed in this report. Melanomas presenting as isolated metastatic lesions from unknown primary sites (i.e., no documentation of arising from cutaneous, ocular, or mucosal primary melanomas) were coded as "unknown primary melanomas" (according to ICD-O 2).[11] The presentation of these unknown primary melanomas as regional (i.e., lymph node) or distant metastasis (i.e., nonlymph node) was determined from the General Summary Stage (according to the *Data Acquisition Manual*)[8] and the presence of lymph node disease.

In addition to tumor site, histology, and staging, data regarding patient characteristics including age, gender, race/ethnicity, and income also were collected. Patient income was based on the average family income of the patient's zip code of residence as per the U. S. Census. Income was grouped into low ($<$ \$20,000, which was approximately the lowest 10% of all NCDB cancer cases), high ($\geq$ \$47,000, which was approximately the highest 10% of all NCDB cancer cases), and a middle-income group ranging from \$20,000–46,999.[6]

In this report, treatment represents the first course of cancer-directed therapy for the index disease. More detailed surgical information (e.g., margin width) and subsequent management of persistent or recurrent disease are not available.

All analyses were performed using SPSS software.[12] To determine changes across time, patient and disease characteristics and treatment were broken down by diagnostic year groupings (with 1985–1989 representing the earlier time period and 1990–1994 the later time period). Case-mix and treatment variables were broken down further by patient and disease stratifications of interest, with chi-square statistics performed on selected cross-tabulations.

Outcome information was calculated on patients diagnosed in the earlier time period only to allow for sufficient follow-up. Annual survival rates, illustrated through 5 years using the life tables method, represent disease specific rates from the date of diagnosis to the endpoint (defined as death with cancer). Pairwise comparisons using the Wilcoxon statistic were performed on selected survival analyses to determine whether the stratifications had significantly different survival rates. For cutaneous melanoma, those variables with significantly different ($P < 0.05$) survival rates in the univariate analyses were entered into a Cox proportional hazards model of regression analysis to determine their independent influence on survival.

RESULTS

Disease Characteristics

The anatomic site of melanomas changed little across these two year groups (Table 1A). The vast majority of melanomas originated in the skin (91.2% for all years), with the next highest percentage being ocular (5.3% for all years). Other melanoma sites included unknown primary melanomas and mucous membrane melanomas comprising 2.2% and 1.3% of all reported melanomas, respectively. Among the unknown primary melanomas, 43.0% presented with regional (i.e., lymph node) metastasis and 57.0% presented with distant metastasis. Among mucosal melanomas, the incidence of head and neck, female genital, anal/rectal, and urinary tract melanomas was 55.4%, 18.0%, 23.8%, and 2.8%, respectively.

The histologic and stage distributions for cutaneous melanomas are illustrated in Table 1B. A large variety of histologic classifications were recorded. Among these classifications, four represented the more traditional "phenotypic" characteristics that commonly are referred to in clinical practice, which include lentigo maligna, superficial spreading, nodular, and acral lentiginous melanomas. There was no difference in the incidence of these phenotypic categories between the two year groups. Among these four categories for all years (excluding histologies classified as "other"), the percentages of lentigo maligna, superficial spreading, nodular, and acral lentiginous melanomas were 21.4%, 57.6%, 18.9%, and 2.1%, respectively. Histologies included in the group labeled "other" comprised 53.4% of all the cutaneous melanoma cases. Of these "other" histologies, 92.5% were "melanoma, NOS" cases, with the remaining representing unique, descriptive histologic features.

A large percentage of cutaneous melanomas were diagnosed at a localized stage, with 85.7% being Stage 0–II for all years (Table 1B). Although this percentage changed little between 1985–1989 and 1990–1994, the proportion of early stage melanomas that were reported as noninvasive (Stage 0) increased from 11.4% in the earlier time period to 16.4% in the later time period. For all years, the percentage of patients presenting with localized invasive melanomas (Stage I and II) was 70.8%. Patients who presented with regional lymph node disease (Stage III) or metastatic disease (Stage IV) at the time of their diagnosis was 8.9% and 5.3%, respectively, for all years. There was an impressive decrease in the proportion of patients who were not staged, dropping from 42.0% in 1985–1989 to 17.6% in 1990–1994.

The stages at presentation for the different histologies of cutaneous melanoma (all years combined) are

TABLE 1A
Disease Sites by Diagnostic Year for Melanoma

	1985–1989		1990–1994		Total: all years	
	Count	Percent	Count	Percent	Count	Percent
Site						
Cutaneous	29883	91.7	47464	90.9	77347	91.2
Mucous membrane	393	1.2	681	1.3	1074	1.3
Ocular	1647	5.1	2875	5.5	4522	5.3
Unknown primary site	675	2.0	1218	2.3	1893	2.2
Total	32598	100	52238	100	84836	100
Mucous membrane site						
Head and neck	212	53.9	383	56.3	595	55.4
Female genital	75	19.1	118	17.3	193	18.0
Anal/rectal	93	23.7	163	23.9	256	23.8
Urinary	13	3.3	17	2.5	30	2.8
Total mucous membrane	393	100	681	100	1074	100
Ocular site						
Uveal	1365	82.9	2481	86.3	3846	85.0
Conjunctival	86	5.2	130	4.5	216	4.8
Other site	196	11.9	264	9.2	460	10.2
Total ocular	1647	100	2875	100	4522	100
Unknown primary site at presentation						
Regional metastasis	287	42.5	527	43.3	814	43.0
Distant metastasis	388	57.5	691	56.7	1079	57.0
Total unknown primary site at presentation	675	100	1218	100	1893	100

summarized in Table 1C. Lentigo maligna lesions were predominantly Stage 0 or I lesions, which comprised 88.6%. For superficial spreading melanomas, the most prevalent stage was Stage I (68.1%) followed by Stage II lesions (19.7%). Nodular and acral lentiginous lesions were more aggressive according to their stage at presentation. For both nodular and acral lentiginous histologies, the most common presentation was Stage II, representing 51.1% and 37.0% of these histologies, respectively. In addition, both nodular and acral lentiginous lesions presented with higher percentages of Stage III and IV disease compared with the other histologies.

Among the 4522 ocular melanomas for all years, 3846 patients (85.0%) had uveal melanomas (Table 1A). Among these uveal melanomas, AJCC staging was recorded in 2286 patients; the percentage of patients with AJCC Stages I, II, III, and IV were 31.3%, 28.9%, 31.9%, and 7.4%, respectively. There were 216 patients with conjunctival melanomas. The remaining 460 patients with ocular melanomas were classified as "other" and comprised cornea, NOS; retina; lacrimal gland; orbit, NOS; overlapping lesion of the eye; and eye, NOS.

There is no recommended AJCC stage groupings for conjunctival melanomas, and no staging classification for mucosal melanomas. However, when information could be retrieved from the medical records, the lymph node status of mucosal melanomas was recorded. Among the 1074 mucosal melanomas for all years, lymph node status was recorded in 28.4% of cases (Table 2). This represented 305 cases, 40.3% of which had positive lymph nodes and 59.7% of which had negative lymph nodes. A breakdown of lymph node status by site revealed that the incidence of positive lymph nodes for head and neck, female genital tract, anal/rectal, and urinary tract melanomas was 26.6%, 23.0%, 61.0%, and 11.1%, respectively. The presence of positive lymph nodes in mucosal melanomas had a significant adverse effect on survival.

Patient Characteristics

Patient characteristics were broken down for all years with respect to cutaneous, mucosal, ocular, and unknown primary melanoma classifications in Table 3A. Compared with other histologic groups, there was a definite trend toward a skewing of older patients diagnosed with mucosal melanomas with 49.0% of patients being age $\geq$70 years. As one would expect, there was a higher percentage of females (63.5%) than males diagnosed with mucosal melanomas due to lesions arising in the female genital tract. By contrast, there

TABLE 1B
Histologic Classifications and AJCC "Combined" Staging by Diagnostic Year for Cutaneous Melanoma

	1985–1989		1990–1994		Total: all years	
	Count	Percent	Count	Percent	Count	Percent
Histology						
Lentigo maligna	2779	9.3	4933	10.4	7712	10.0
Superficial spreading	8430	28.2	12318	26.0	20748	26.8
Nodular	2850	9.5	3969	8.4	6819	8.8
Acral lentiginous	177	0.6	592	1.2	769	1.0
Other	15647	52.4	25652	54.0	41299	53.4
Total	29883	100	47464	100	77347	100
"Combined" stage[a]						
Stage 0	1970	11.4	6420	16.4	8390	14.9
Stage I	8742	50.4	18113	46.3	26855	47.6
Stage II	4026	23.2	9041	23.1	13067	23.2
Stage III	1635	9.4	3461	8.9	5096	9.0
Stage IV	956	5.5	2062	5.3	3018	5.3
Subtotal known stage	17329	100	39097	100	56426	100
Unknown stage	12554	42.0[b]	8367	17.6[b]	20921	27.0[b]
Total	29883		47464		77347	

AJCC: American Joint Committee on Cancer.
[a] "Combined" stage represents pathologic stage, augmented by clinical stage in cases in which the pathologic stage was not available.
[b] Percentage was based on total cases.

TABLE 1C
"Combined" Stage by Histology by Site for Cutaneous Melanoma, All Years

	Stage						
	0	1	2	3	4	Total	Cases
Cutaneous	14.9	47.6	23.2	9.0	5.3	100	56426
Lentigo maligna	51.9	36.7	8.2	2.5	0.7	100	5569
Superficial spreading	6.7	68.1	19.7	4.3	1.2	100	15572
Nodular	0.5	20.4	51.1	22.8	5.2	100	5106
Acral lentiginous	9.3	34.0	37.0	14.9	4.8	100	579
Other	14.8	43.8	22.7	10.3	8.4	100	29600

was a higher percentage of males (65.8%) than females diagnosed with unknown primary melanoma. With respect to race/ethnicity, there was a larger percentage of African-American and Hispanic individuals diagnosed with mucosal melanomas compared with the percentage of African-American and Hispanic patients diagnosed with cutaneous, ocular, or unknown primary melanomas. Approximately 8.8% of patients with mucosal melanomas were of African-American or Hispanic race/ethnicity compared with a substantially lower percentage of melanomas (<3%) of the other sites. Levels of income (i.e., low, middle, and high) between the various sites of melanoma were not substantially different. Levels of income were different for early versus advanced stage within cutaneous melanoma, with 21.2% of low income patients presenting with Stage III or IV disease compared with 14.6% of high income patients.

An analysis of patient characteristics by histology for cutaneous melanomas for all years is summarized in Table 3B. There were large differences between histologies with respect to age and race/ethnicity. A larger percentage of older patients presented with lentigo maligna lesions compared with the other histologies; 76.7% of the patients diagnosed with lentigo maligna were age ≥60 years compared with 33.5%, 46.5%, and 61.8% for superficial spreading, nodular, and acral lentiginous histologies, respectively. With regard to race/ethnicity, African Americans and Hispanics comprised 15.9% of all patients diagnosed with acral lentiginous melanomas whereas individuals of these racial/ethnic backgrounds comprised only 1.3%,

TABLE 2
Lymph Node Status by Diagnostic Year for Mucous Membrane Melanoma in which Lymph Nodes Were Examined

	1985–1989		1990–1994		Total: all years	
	Count	Percent	Count	Percent	Count	Percent
All cases						
No positive lymph nodes	85	65.9	97	55.1	182	59.7
Positive lymph nodes	44	34.1	79	44.9	123	40.3
Total	129	100	176	100	305	100
Head and Neck						
No positive lymph nodes	36	69.2	44	60.3	80	73.4
Positive lymph nodes	16	30.8	29	39.7	29	26.6
Total	52	100	73	100	109	100
Female genital tract						
No positive lymph nodes	24	85.7	31	72.1	55	77.0
Positive lymph nodes	4	14.3	12	27.9	16	23.0
Total	28	100	43	100	71	100
Anal/rectal						
No positive lymph nodes	19	44.2	20	35.1	39	39.0
Positive lymph nodes	24	55.8	37	64.9	61	61.0
Total	43	100	57	100	100	100
Urinary tract						
No positive lymph nodes	6	100	2	66.7	8	88.9
Positive lymph nodes	0	0	1	33.3	1	11.1
Total	6	100	3	100	9	100

1.2%, and 1.9% of patients diagnosed with lentigo maligna, superficial spreading, or nodular melanomas, respectively. Levels of income were not substantially different between these histologic classifications.

Treatment

The vast majority (91.5%) of cutaneous melanomas were treated with surgery alone (Table 4). Surgery alone also was the primary modality, but to a lesser extent, for managing mucous membrane melanomas (56.4%) and ocular melanomas (57.0%). A higher percentage of these noncutaneous melanoma patients also received radiation therapy, either alone (25.7% of ocular melanomas) or in combination with surgery (19.3% of mucous membrane melanomas). Approximately 58% of patients with unknown primary melanomas were treated surgically with or without radiation therapy and/or chemotherapy for management of the metastasis. However, a substantial percentage (17.7%) received no treatment in the form of surgery, radiation therapy, or chemotherapy. Although not shown in Table 4, there were few changes across the years in treatment for the various sites. However, surgery with radiation therapy has been used with increasing frequency for treating mucous membrane melanomas (from 11.3% in 1985–1989 to 15.3% in 1990–1994). The treatment of ocular melanomas also demonstrated a large rise across these years in the percentage treated with radiation therapy alone (from 17.4% to 30.4%). There was a concomitant drop in the percentage of ocular melanomas treated with surgery alone (from 60.6% to 55.2%). Information regarding the use of biologic response modifier therapy was recorded for 16,987 of these patients with melanoma. Within this group, 498 patients (2.9%) received a biologic response modifier as part of their treatment.

Survival

Disease specific survival analyses, performed on patients diagnosed between 1985–1989, indicated that 78.8% were alive 5 years after diagnosis (Table 5A). When stratified by anatomic site, cutaneous melanomas had the highest 5-year survival rate (80.8%), followed by ocular melanomas (74.6%). The proportion of patients with mucous membrane melanoma who survived 5 years was much lower (25.0%). Patients with unknown primary site of the melanoma also had a low survival rate, with only 29.1% alive at 5 years.

Mucosal melanomas were analyzed with respect to site and lymph node status. Patients with head and neck, female genital tract, and anal/rectal mucosal melanomas had 5-year survival rates of 31.7%, 11.4%,

TABLE 3A
Patient Characteristics by Anatomic Site for Melanoma, All Years

	Cutaneous		Mucosal		Ocular		Unknown primary site	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Age (yrs)								
< 30	5398	7.0	10	0.9	149	3.3	104	5.5
30–39	11036	14.3	35	3.3	322	7.1	253	13.3
40–49	13500	17.4	108	10.1	619	13.7	316	16.7
50–59	13202	17.1	149	13.9	839	18.5	368	19.4
60–69	15778	20.4	244	22.7	1210	26.8	416	22.0
70–79	12574	16.2	306	28.5	980	21.7	299	15.8
80+	5795	7.5	220	20.5	400	8.8	136	7.2
Unknown	64	0.1	2	0.2	3	0.1	1	0.1
Total	77347	100	1074	100	4522	100	1893	100
Mean age (yrs)	55.3		67.0		60.4		56.0	
Gender								
Male	42013	54.3	391	36.4	2352	52.0	1245	65.8
Female	35132	45.4	682	63.5	2158	47.7	646	34.1
Other/unknown	202	0.3	1	0.1	12	0.3	2	0.1
Total	77347	100	1074	100	4522	100	1893	100
Race/ethnicity								
White non-Hispanic	72500	93.7	918	85.5	4168	92.2	1794	94.8
African-American, non-Hispanic	590	0.8	72	6.7	37	0.8	34	1.8
Hispanic (any race)	911	1.2	42	3.9	86	1.9	19	1.0
Other/unknown	3346	4.3	42	3.9	231	5.1	46	2.4
Total	77347	100	1074	100	4522	100	1893	100
Income[a]								
Low (< $20,000)	5634	7.3	137	12.8	526	11.6	192	10.2
Middle ($20,000–46,999)	56922	73.6	768	71.5	3350	74.1	1365	72.1
High (≥$47,000)	10852	14.0	118	11.0	359	7.9	194	10.2
Unknown	3939	5.1	51	4.7	287	6.4	142	7.5
Total	77347	100	1074	100	4522	100	1893	100

[a] Income groupings based on the lowest (< $20,000) and highest (≥$47,000) 10% of all cancer patients on the National Cancer Data Base data set.

and 19.8%, respectively. There were too few cases of urinary tract melanomas for survival analyses. The survival rate for head and neck mucosal melanoma was significantly better ($P < 0.05$) than female genital tract or anal/rectal mucosal melanomas. Combining all sites, 96 patients were identified with known lymph node status in cases diagnosed between 1985–1989. Patients with positive lymph nodes had a poorer outcome, demonstrated by a 5-year survival rate of 16.4% compared with 38.7% for all patients with negative lymph nodes. There were too few cases within the positive lymph node group to perform statistical analyses.

Patients with ocular melanomas had survival broken down between uveal and conjunctival sites. The overall, 5-year survival for uveal and conjunctival melanomas was 83.5% and 75.7%, respectively, which was not significantly different. The majority of ocular melanomas were of uveal origin. Among uveal melanomas, patients with AJCC Stages I, II, III, and IV had survival rates of 83.9%, 84.9%, 64.4%, and 59.3%, respectively (Fig. 1). All stage subgroups were significantly different from each other.

Cutaneous melanoma survival rates were disaggregated by "combined" stage when staging information was available in 13,547 patients (Fig. 2). For Stage 0 melanomas (also known as melanomas in situ), the 5-year survival rate was 96.0%. For localized, invasive melanomas (representing Stages I and II), the survival rates were 92.5% and 74.8%, respectively. Lymph node positive Stage III patients had a survival rate of 49.0%, whereas Stage IV patients with metastatic disease had a survival rate of only 17.9% (Fig. 2). All stage subgroups were significantly different from each other.

A breakdown of cutaneous melanoma survival according to histologic subtype is summarized in Table 5B. The 5-year survival rates for lentigo maligna, superficial spreading, nodular, and acral lentiginous

TABLE 3B
Patient Characteristics by Histology for Cutaneous Melanoma, All Years

	Lentigo maligna		Superficial spreading		Nodular		Acral lentiginous	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Age (yrs)								
< 30	44	0.6	1790	8.6	443	6.5	31	4.0
30–39	195	2.5	3885	18.7	908	13.3	56	7.3
40–49	550	7.1	4419	21.3	1114	16.3	91	11.8
50–59	1001	13.0	3687	17.8	1176	17.3	116	15.1
60–69	2163	28.0	3759	18.1	1398	20.5	196	25.5
70–79	2468	32.0	2340	11.3	1113	16.3	193	25.1
80+	1286	16.7	860	4.1	659	9.7	86	11.2
Unknown	5	0.1	8	0.1	8	0.1	0	—
Total	7712	100	20748	100	6819	100	769	100
Mean age (yrs)	67.5		51.3		56.4		61.6	
Gender								
Male	4613	59.8	10451	50.4	4005	58.7	346	45.0
Female	3091	40.1	10231	49.3	2792	41.0	422	54.9
Other/unknown	8	0.1	66	0.3	22	0.3	1	0.1
Total	7712	100	20748	100	6819	100	769	100
Race/ethnicity								
White non-Hispanic	7185	93.1	19586	94.4	6477	95.0	617	80.2
African-American, non-Hispanic	35	0.5	49	0.2	55	0.8	89	11.6
Hispanic (any race)	63	0.8	206	1.0	78	1.1	33	4.3
Other/unknown	429	5.6	907	4.4	209	3.1	30	3.9
Total	7712	100	20748	100	6819	100	769	100
Income[a]								
Low (< $20,000)	573	7.4	1361	6.5	577	8.5	101	13.2
Middle ($20,000–46,999)	5642	73.2	15378	74.1	5151	75.5	543	70.6
High (≥$47,000)	1063	13.8	2876	13.9	776	11.4	84	10.9
Unknown	434	5.6	1133	5.5	315	4.6	41	5.3
Total	7712	100	20748	100	6819	100	769	100

[a] Income groupings based on the lowest (< $20,000) and highest (≥$47,000) 10% of all cancer patients on the National Cancer Data Base data set.

TABLE 4
Treatment by Anatomic Site for Melanoma (All Years)

	Surg only	RT only	CH only	Surg+ RT	Surg+ CH	RT+ CH	All three	None	Unknown	Total	Cases
Site											
Cutaneous	91.5	0.7	0.5	1.4	1.5	0.3	0.4	3.0	0.7	100	77347
Mucous membrane	56.4	8.5	1.6	19.3	2.0	2.0	2.8	6.1	1.3	100	1074
Ocular	57.0	25.7	0.3	8.8	1.5	0.2	0.2	4.6	1.7	100	4522
Unknown primary	39.4	8.2	8.4	11.0	5.5	4.5	2.6	17.7	2.7	100	1893

Surg: surgery; RT: radiation therapy; CH: chemotherapy.

melanoma were 93.2%, 91.6%, 64.6%, and 66.4%, respectively. All histologic subgroups were significantly different from each other except the nodular and acral lentiginous subgroups. One potential factor contributing to differences in survival between certain histologic subtypes most likely is due to the distribution of stages within each group. As indicated in Table 1C, both the nodular and acral lentiginous melanoma subtypes were comprised of a higher percentage of Stage II, III, and IV cases compared with the lentigo maligna and superficial spreading histologic subtypes. When accounting for stage, patients with nodular melanomas still fared significantly worse than individuals with superficial spreading melanomas for all stages of invasive disease (Table 5B). There were no significant differences in survival for patients with superficial

TABLE 5A
Five-Year, Disease Specific Survival for 1985–1989 Melanoma

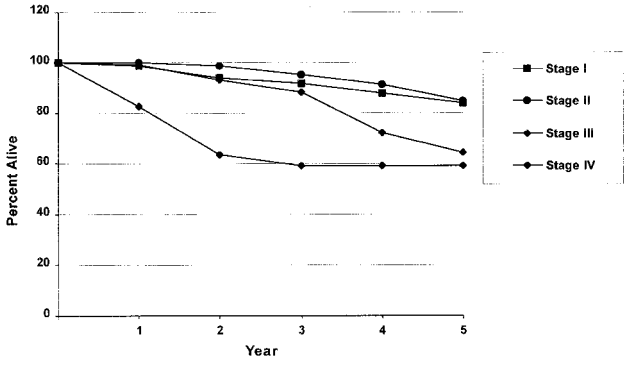
	Years after diagnosis						
	1	2	3	4	5	Cases	*P* value
All cases	93.1%	87.8%	84.2%	81.1%	78.8%	25795	
Site							
Cutaneous	94.1	89.3	85.9	83.0	80.8	23696	
Mucous membrane	74.5	49.3	38.4	30.2	25.0	306	
Ocular	96.4	89.2	84.6	79.2	74.6	1275	
Unknown primary	51.7	41.1	34.9	31.6	29.1	518	
Mucous membrane site[a]							
Head and neck	82.0	54.4	46.5	37.4	31.7	163	0.0034[b]
Female genital tract	68.1	40.1	26.3	21.1	11.4	59	
Anal/rectum	61.6	44.0	27.4	19.8	19.8	74	
Known lymph node status for mucous membrane							
Positive	61.9	33.6	25.7	16.4	16.4	33	
Negative	84.9	55.6	44.0	38.7	38.7	63	
Ocular site							
Conjunctival	100	94.6	86.4	86.4	83.5	64	<0.0001[c]
Uveal	97.3	90.5	86.6	80.6	75.7	1062	
Other ocular	88.8	78.8	70.3	66.5	63.2	149	

A pairwise comparison of "combined" Stages I–IV showed that each stage is significantly different from all other three stages, using the Wilcoxon (Gehan) statistic.

[a] There were too few cases for the urinary tract for survival analyses.

[b] At the $P < 0.05$ level, all site subgroups were significantly different from each other except female genital tract and anal/rectum.

[c] At the $P < 0.05$ level, all site subgroups were significantly different from each other except conjunctival and uveal.

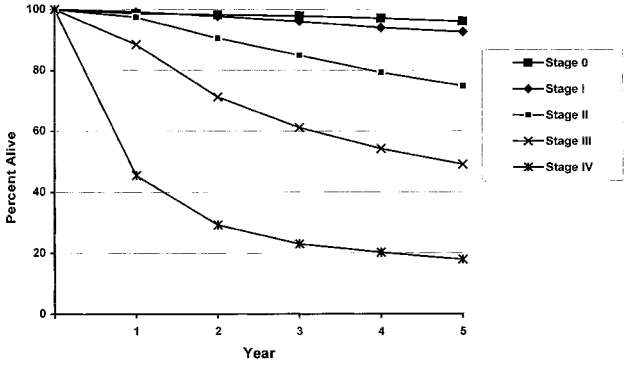


STAGE	1	2	3	4	5	CASES
Stage I	98.5	93.8	91.6	87.8	83.9	156
Stage II	100	98.8	95.2	91.2	84.9	114
Stage III	99.0	93.0	88.1	72.3	64.4	106
Stage IV	82.4	63.4	59.3	59.3	59.3	54

FIGURE 1. Five-year, disease specific survival by "combined" stage for 1985–1989 uveal melanoma. (Note:"combined" stage represents pathologic stage, augmented by clinical stage in cases in which the pathologic stage was not available)

spreading or lentigo maligna melanomas within Stages I or II. There were too few patients with acral lentiginous melanoma to analyze for survival differences.

Survival analyses by stage were performed with respect to age, gender, race/ethnicity, and income for cutaneous melanoma patients (Table 5C). Patients were classified as presenting with "early" (Stages I and II) or "advanced" (Stages III and IV) disease. Patients age ≥60 years did significantly worse than patients age <60 years, with 5-year survival rates of 81.4% and 90.1%, respectively, for patients with early stage disease. For patients with advanced stage disease, the 5-year survival rate of patients age ≥60 years (32.0%) was significantly less than the rate of patients age <60 years (40.5%). Males fared significantly worse than females, with the two genders having 5-year survival rates of 83.5% versus 90.5% for early stage and 32.7% versus 43.7% for advanced stage disease, respectively. In regard to race/ethnicity, white individuals had significantly better survival compared with nonwhite individuals for early stage melanoma (86.8% and 74.0%, respectively). For advanced melanoma, nonwhite patients fared worse than white patients, with a 5-year survival rate of 33.9% compared with 36.6%, respectively, although the difference was not statistically significant. In regard to income, there was a significant trend toward improved survival in patients with early melanomas as income increased. In early melanomas, the 5-year survival rates for patients with low income versus high income were 83.2% and 90.9%, respectively. For patients with advanced stage melanomas,



STAGE	1	2	3	4	5	CASES
Stage 0	98.6	98.2	97.8	97.0	96.0	1470
Stage I	99.2	97.7	96.0	93.9	92.5	6838
Stage II	97.4	90.5	84.9	79.2	74.8	3165
Stage III	88.4	71.2	61.1	54.2	49.0	1251
Stage IV	45.4	29.2	23.0	20.2	17.9	823

FIGURE 2. Five-year, disease specific survival by "combined" stage for 1985–1989 cutaneous melanoma. (Note: "combined" stage represents pathologic stage, augmented by clinical stage in cases in which the pathologic stage was not available)

the 5-year survival rates for patients with low income versus high income were 30.0% and 45.4%, respectively, but the difference was not statistically significant.

For cutaneous melanoma, age, gender, race, income, stage, and histology indicated significantly different survival rates within their stratifications. These six variables were entered into a Cox regression analysis as dichotomous variables (Table 5D). Age was <60 or ≥ 60 years, gender was male or female, race was white or minority individuals, income was individuals in the lower 50% or the upper 50%, stage was early or advanced, and histology was nodular and acral lentiginous (with low 5-year survival rates of 64.6% and 66.4%, respectively) or lentigo maligna and superficial spreading (with high 5-year survival rates of 93.2% and 91.6%, respectively). Race was the only variable that was not significantly associated with survival. The strongest predictors were stage (with advanced disease having a 2.08 relative risk value) and histology (with the classifications demonstrating lower survival rates [nodular and acral lentiginous] having a 1.78 relative risk value). The relative risk values for the remaining variables were 1.33 for males, 1.20 for patients age ≥ 60 years, and 1.12 for patients in the lower 50% income bracket.

The survival of patients determined to have metastases from unknown primary sites were evaluated with respect to regional versus distant disease at presentation. Patients with regional disease (i.e., lymph node) had a 5-year survival rate of 46.3% compared with a rate of only 15.8% for patients who presented with distant (i.e., nonlymph node) sites of disease, a statistically significant difference ($P < 0.0001$) (Table 5E). The survival of individuals with unknown primary melanomas was analyzed further with respect to treatment. Treatment was grouped into surgical resection (with or without adjuvant treatment) or no treatment. For all patients with unknown primary melanomas, the 5-year survival rate for those patients undergoing surgical resection (38.8%) was significantly better than that for patients who received no treatment (19.6%). This was broken down further into individuals with regional (i.e., lymph node) or distant disease at presentation. For regional presentation, the 5-year survival rates for patients with surgical treatment versus those with no treatment were 54.5% and 26.5%, respectively (with the number of patients receiving no treatment being too small for statistical comparisons). For distant presentation, 5-year survival rates associated with surgical treatment versus no treatment were 20.3% and 15.9%, respectively, which represented a statistically significant difference.

DISCUSSION

Based on hospital registry data during a 10-year period, this report documents the relative percentages of cutaneous and noncutaneous melanomas diagnosed in >86,000 patients. To our knowledge, this represents one of the largest databases comprising patient characteristics, histology, staging, therapy, and survival for melanomas. The last NCDB study of melanoma, reported in 1994, reviewed 20,165 cases of cutaneous melanoma.[13] Prior to that, the American College of Surgeons performed a *Patient Care Evaluation* study of cutaneous and noncutaneous melanoma comprising 11,904 patients that was reported in 1992.[14] In the current study, cutaneous melanomas comprised 91.2% of the cases, followed by ocular (5.3%), unknown primary (2.2%), and mucosal (1.3%) melanomas. The peak age at diagnosis for cutaneous, ocular, and unknown primary site of melanomas was between ages 60–69 years. By contrast, for mucosal melanomas, the peak age of incidence was between ages 70–79 years. There was a predominance of white individuals diagnosed with cutaneous, ocular, and unknown primary site of melanomas, with African-American or Hispanic individuals comprising only 5.4% and 3.4% of cases, respectively.

In discussing the results by anatomic site of origin, cutaneous melanoma patients represented the majority of individuals in the data base, totaling 77,347 cases. Among the patients diagnosed between 1985–

TABLE 5B
Five-Year, Disease Specific Survival of Histology by "Combined" Stage for 1985–1989 Cutaneous Melanoma

	Years after diagnosis						
	1	2	3	4	5	Cases	*P* value
Histology for cutaneous cases							
Lentigo maligna	99.1	97.4	96.2	94.8	93.2	2157	< 0.0001[a]
Superficial spreading	99.0	97.1	95.2	93.0	91.6	6761	
Nodular	91.5	81.7	74.4	68.7	64.6	2267	
Acral lentiginous	96.1	88.4	80.0	73.8	66.4	138	
"Combined" stage by histology for cutaneous cases[b]							
Stage 0[c]							
Lentigo maligna	99.4	99.1	98.9	97.7	97.7	511	0.9355
Superficial spreading	100	100	100	98.8	96.0	229	
Stage I[d]							
Lentigo maligna	99.4	98.7	97.4	95.2	93.6	513	< 0.0001[e]
Superficial spreading	99.7	99.0	98.2	96.6	95.7	2772	
Nodular	97.0	91.4	87.8	82.4	79.8	351	
Stage II[d]							
Lentigo maligna	100	98.1	95.0	90.4	85.1	122	< 0.0001[e]
Superficial spreading	99.2	95.0	90.8	85.1	81.3	753	
Nodular	96.9	86.7	78.9	73.6	68.0	663	
Stage III[f]							
Superficial spreading	97.9	80.9	73.4	63.5	58.4	204	0.0040
Nodular	86.5	71.4	61.8	54.0	48.5	299	
Stage IV[f]							
Superficial spreading	63.3	58.5	47.6	44.7	44.7	60	0.0263
Nodular	52.1	33.6	22.2	17.2	13.6	87	

[a] At the $P < 0.05$ level, all histologic subgroups were significantly different from each other except nodular and acral lentiginous.
[b] "Combined" stage represents pathologic stage, augmented by clinical stage in cases in which the pathologic stage not available.
[c] There were too few cases of Stage 0 nodular and acral lentiginous to be reported.
[d] There were too few cases of Stage I or Stage II acral lentiginous to be reported.
[e] At the $P < 0.05$ level, all histologic subgroups were significantly different from each other except lentigo maligna and superficial spreading.
[f] There were too few cases of Stage III or Stage IV lentigo maligna and acral lentiginous to be reported.

1989, the overall 5-year survival was 80.8%. As expected, survival was associated with stage. Stage 0 (in situ melanoma) and Stage I disease were highly curable, with 5-year survival rates of 96.0% and 92.5%, respectively. Fortunately, 62.6% of patients diagnosed with melanoma fell into these stage groups. Surgical excision was the major therapeutic modality, employed in 94.8% of patients alone or in concert with other modalities. Of the patients in this database who had information regarding the administration of biologic response modifier therapy, only 2.9% were treated with this modality. Because of the recent findings that interferon-α is an effective adjuvant therapy after surgery for patients with Stage III disease, it is anticipated that there will be an increase in the use of this biologic response modifier in the future.[15] Moreover, vaccine therapies have seen a resurgence of interest in the management of patients with melanoma.[16,17]

Of interest was the association between histologic subtype (i.e., lentigo maligna, superficial spreading, nodular, and acral lentiginous) and survival. Both the lentigo maligna and superficial spreading subgroups presented with a higher percentage of earlier stage disease (Stages 0 through II). By contrast, the nodular and acral lentiginous subgroups presented with a higher proportion of advanced disease (Stages III and IV), underscoring the aggressive biology of these histologic subtypes. Even when accounting for stage, the nodular histologic subtype behaved more aggressively than the lentigo maligna and superficial spreading subgroups. These observations validate the continued use of these histologic descriptions in the reporting of pathologic diagnoses of melanomas. There have been other histologic features that may account for the observed differences in this report, including ulceration, vertical growth phase, angiolymphatic invasion, mitotic activity, presence of infiltrating lymphoid cells, and evidence of regression.[18–20] However, these features were not recorded within the hospital cancer registries from which the NCDB is drawn, and therefore could not be analyzed.

TABLE 5C
Five-Year, Disease Specific Survival by Patient Characteristics by Early versus Advanced "Combined" Stage for 1985–1989 Cutaneous Melanoma

	Years after diagnosis						
	1	2	3	4	5	Cases	*P* value
Age (yrs)							
Early stage							
<60	99.2	96.8	94.6	92.1	90.1	6230	< 0.0001
≥60	97.9	93.0	89.0	84.4	81.4	3760	
Advanced stage							
<60	75.3	59.2	49.8	44.7	40.5	1131	< 0.0001
≥60	66.6	49.1	41.5	36.0	32.0	941	
Gender							
Early stage							
Male	98.4	94.2	90.4	86.5	83.5	5194	< 0.0001
Female	99.0	96.7	94.6	92.2	90.5	4799	
Advanced stage							
Male	69.9	52.8	42.8	36.6	32.7	1306	0.0010
Female	73.8	57.6	51.7	47.9	43.7	767	
Race/ethnicity							
Early stage							
White	98.7	95.4	92.5	89.2	86.8	9420	0.0001
Nonwhite	97.3	89.4	81.4	75.2	74.0	158	
Advanced stage							
White	71.7	54.7	46.0	40.8	36.6	1945	0.3202
Nonwhite	63.0	48.8	45.4	35.9	33.9	77	
Income							
Early stage							
Low	98.5	93.7	90.1	85.5	83.2	631	< 0.0001[a]
Middle	98.6	95.3	92.2	89.0	86.5	7335	
High	98.8	96.7	9.6	92.5	90.9	1578	
Advanced stage							
Low	66.7	45.7	37.5	33.6	30.0	202	0.0914
Middle	71.7	54.8	45.9	40.1	35.9	1491	
High	71.1	58.2	50.8	47.8	45.4	283	

"Early" stage represents "combined" Stages I and II, and "advanced" stage represents "combined" Stages III and IV.
[a] At the $P < 0.05$ level, all income subgroups were significantly different from each other.

Because of the NCDB's large database of cutaneous melanoma patients, the effects of different patient characteristics on survival could be evaluated. Age ≥60 years was found to be an adverse prognostic factor for both early stage and advanced stage disease. Analysis of age by increasing decades also demonstrated the same trend of decreased survival (data not shown). Deaths due to causes unrelated to melanoma were censored and only disease specific survival data were calculated. Hence, comorbid conditions associated with increasing age were unlikely to be reasons for decreased survival from cutaneous melanoma.

Gender was found to be a significant prognostic factor, with males having worse survival than females. This was true for both early stage and advanced stage patient groups. It is known that the distribution of the anatomic origin of cutaneous melanomas differs between males and females; women have a higher percentage of extremity melanomas, whereas males have a higher percentage of truncal melanomas.[21] The axial location of melanoma has been reported to be associated with a worse prognosis.[22] In the NCDB the percentage of males and females with axial melanomas (i.e., head and neck or truncal sites) was 64.8% and 39.1%, respectively. The proportion of males with cutaneous melanomas of the extremities (i.e., arm/shoulder and leg/hip) was 39.2% compared with 55.4% for females. The gender differences identified in this database also may be related to hormonal influences on the prognosis of melanoma. With respect to race/ethnicity, whites fared better than nonwhites (i.e., African Americans and Hispanics) for early stages of melanoma. There was a trend toward poorer survival in nonwhite patients who presented with advanced melanoma compared with whites; however, the numbers were too small to reach sta-

TABLE 5D
Patient and Disease Characteristics Influencing Disease Specific Survival for 1985–1989 Cutaneous Melanoma

Variables entered into model	*P* value	Relative risk	Confidence intervals	
			Lower	Upper
Stage (0–II vs. III–IV)	< 0.0001	2.08	1.93	2.24
Histology (low vs. high survival rate)[a]	< 0.0001	1.78	1.65	1.92
Age (yrs) (< 60 vs. 60+)	< 0.0001	1.20	1.12	1.28
Income (lower vs. upper 50%)	0.0011	1.12	1.05	1.20
Gender (male vs. female)	< 0.0001	1.33	1.24	1.43
Race (white vs. African American)	0.9971	—[b]	—[b]	—[b]

These results were obtained using Cox regression analysis.
[a] The cutaneous histologies with higher 5-year survival (lentigo maligna and superficial spreading, with 93.2% and 91.6% rates, respectively) were grouped together and compared with the histologies with lower 5-year survival (nodular and acral lentiginous, with 64.6% and 66.4% rates, respectively).
[b] Not applicable because race was not significant.

tistical significance. Also interesting was the differences in survival related to income levels. There was a direct relationship between increasing income level and improved survival in patients with early stages of cutaneous melanoma. This trend also was observed for advanced stage melanoma; however, the numbers again were too small to reach statistical significance.

A multifactorial analysis was performed to determine which case-mix variables (AJCC stage, histologic subtype, age, gender, race, and income) were predictive of survival for cutaneous melanoma. The factors that proved to be independent predictive factors for survival, in decreasing order, were: stage, histology, gender, age, and income. We are not aware of any report documenting income as a prognostic factor for cutaneous melanoma. In cross-tabulations, higher income levels (i.e., low, middle, and high) were associated with lower stages of disease at presentation (data not shown). Nevertheless, the multivariate analysis demonstrated income to be an independent prognostic factor in addition to stage, which indicates that the effects of income on survival are due to influences besides stage. These effects of income on melanoma survival are unknown and should be investigated further because it is a factor that potentially can be altered.

For all years, there was a total of 4522 ocular melanomas, 85.0% of which were uveal and 4.8% of which were conjunctival lesions. Surgery has been the mainstay of treatment over all years; however, there was a significant increase in the use of primary radiation therapy as the sole treatment between 1985–1989 and 1990–1994 (from 17.0% to 30.4%).

A total of 1074 mucosal melanomas was recorded in the database. The overall, 5-year survival rate of those patients diagnosed between 1985–1989 was only 25.0%. The most prevalent site of mucosal melanomas was the head and neck region (55.4%), followed by anal/rectal melanomas (23.8%). Surgery was the main component of treatment in 80.5% of cases. The combined approach of utilizing surgery plus radiation therapy for mucosal melanomas involved 19.3% of patients compared with 1.4% for cutaneous melanomas. Approximately one-third of patients with mucosal melanomas had positive lymph nodes when lymph node status was known. The presence of positive lymph nodes was associated with a 5-year survival of 16.4% compared with 38.7% for patients with negative lymph nodes. These findings document the important prognostic effect of lymph node status in mucosal melanomas, which should be incorporated in any formal staging system established for this disease entity.

Patients with unknown primary melanomas fared poorly. The database contained information that permitted identification of whether the patients presented with regional or distant metastases. If one assumes that the predominant source of these unknown primary melanomas arose from a cutaneous site that spontaneously regressed, it is interesting to note that the 5-year survival rate of patients with regional metastasis (46.3%) was similar to the rate of survival for patients with Stage III cutaneous melanoma (49.0%). In addition, patients with distant metastases from unknown primary sites had a 5-year survival rate (15.8%) that was similar to the survival of Stage IV cutaneous melanoma (17.7%). Despite the poor prognosis of this category of patients, surgical treatment did result in a significant 5-year benefit in this subgroup of patients compared with the subgroup of patients given no treatment. Although there most likely is a selection bias in favor of patients who received surgical therapy versus those who received no treatment, several reports have observed that the surgical management of patients with lymph node disease from unknown primary melanomas fared as well as patients with known cutaneous primary sites.[23] The data in this current report appear to substantiate the potential benefit of surgical resection of patients with isolated lymph node or visceral disease from unknown primary melanomas.

In summary, patients with cutaneous melanomas fared much better than patients with noncutaneous

TABLE 5E
Five-Year, Disease Specific Survival by Presentation and by Treatment (for All Cases, Regional Presentation, and Distant Presentation) for 1985–1989 Unknown Primary Melanoma

	Years after diagnosis						
	1	2	3	4	5	Cases	*P* value
Presentation status							
Regional metastasis	72.8	62.4	54.9	50.1	46.3	225	< 0.0001
Distant metastasis	35.4	24.5	19.4	17.2	15.8	293	
Treatment							
All cases							
Surgery[a]	64.9	54.4	46.2	41.8	38.6	306	< 0.0001
No treatment	36.9	28.0	24.2	20.9	19.6	125	
Regional presentation							
Surgery[a]	80.4	71.3	63.1	58.0	54.5	160	—[b]
No treatment	57.9	49.0	39.2	31.4	26.5	40	
Distant presentation							
Surgery[a]	47.5	35.0	26.8	23.2	20.3	146	0.0001
No treatment	27.4	18.7	17.4	15.9	15.9	85	

[a] Surgery with or without adjuvant radiation therapy.

[b] The number of patients in the group receiving no treatment was too small for statistical comparisons.

melanomas after treatment. Fortunately, the majority of individuals with cutaneous melanomas present at an early stage when therapy is highly successful in achieving 5-year cure rates. The mainstay of therapy for patients with melanomas of all sites has been surgical excision, except for patients with ocular melanomas, in whom a significant trend toward primary radiation therapy has been observed. Surgical resection of isolated disease due to unknown primary site of the melanomas should be instituted when medically feasible because a subgroup of those patients fare well. Hopefully, with a better understanding of the biologic and socioeconomic factors influencing melanoma treatment, the survival of patients with melanoma will improve. In this regard, adjuvant strategies utilizing biologic response modifiers after surgical resection appear promising.

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