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Primary cutaneous adenoid cystic carcinoma in the United States: incidence, survival, and associated cancers, 1976-2005

Graça M. Dores, MD, MPH^{1,2,*}, Mark M. Huycke, MD^{1,3}, Susan S. Devesa, PhD², and Carlos A. Garcia, MD⁴

¹Medical Service, Department of Veterans Affairs Medical Center, Oklahoma City, OK

²Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD

³Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK

⁴Department of Dermatology, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Abstract

Background—Primary cutaneous adenoid cystic carcinoma (PCACC) is a rare appendageal tumor of uncertain origin. Details on epidemiologic features of PCACC are sparse and largely based on clinical reports.

Objective—To develop an understanding of PCACC incidence, survival, and associated cancers using population-based data.

Methods—We utilized the Surveillance, Epidemiology and End Results program to calculate age-adjusted incidence rates (IRs), IR ratios, 95% confidence intervals, standardized incidence ratios (SIRs), and 5-year relative survival rates of PCACC diagnosed during 1976-2005.

Results—In a population of 723,174,580 person-years, the overall PCACC IR was 0.23 per one million person-years (n=152), with similar IRs among males and females (IR=0.24). Most cases of PCACC presented at a localized stage and arose on the face/head/neck. Among 122 two-month survivors of PCACC and more than 2.4 million two-month cancer survivors, risk of associated cancers overall was not significantly increased (SIR=1.17 (n=24) and SIR=1.43 (n=16), respectively). However, PCACC was associated with significantly increased risks of subsequent lymphohematopoietic (n=6; SIR=3.70) and thyroid (n=2; SIR=15.25) cancers, whereas the converse associations were not observed. Five-year relative survival was excellent (96.1%; n=122) with more favorable survival noted for PCACC involving the face/head/neck than the trunk.

Limitations—A pathologic review of reported cases was not undertaken.

Conclusion—PCACC is a rare appendageal tumor that affects males and females equally, primarily presents at localized stage, predominates in the face/head/neck, and is associated with favorable survival. Immunosuppression does not appear to contribute to the development of PCACC, and the observed associated cancer patterns will need to be confirmed in larger studies.

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*Corresponding author: Graça M. Dores, MD, MPH, Department of Veterans Affairs Medical Center, Medical Service (111), 921 N.E. 13th Street, Oklahoma City, OK 73104, doresg@mail.nih.gov.

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Keywords

adenoid cystic carcinoma; skin cancer; epidemiology; incidence; survival; second primary cancers

The World Health Organization classifies primary cutaneous adenoid cystic carcinoma (PCACC) within the broader category of appendageal or adnexal skin tumors.¹ The formal description of PCACC is often attributed to Boggio, who described the entity in 1975;² however, reports of PCACC are thought to have been included in the literature previously.³⁻⁸ Despite its clinical recognition for well over 30 years, the origin of PCACC remains uncertain,¹ and the etiology of this neoplasm is undefined. Adenoid cystic carcinoma can occur at other sites, including salivary gland, breast, lung, and external auditory canal, and therefore the diagnosis of PCACC must exclude metastatic disease to skin from another primary site.

PCACC commonly presents as a variably symptomatic, slowly expanding, firm, skin-colored nodule.¹ Typical histopathologic features include a poorly circumscribed tumor “composed of basaloid cells with a glandular, cystic, cribriform and tubular arrangement embedded in a loose fibrous and sometimes mucinous stroma.”¹ PCACC is characterized by an indolent but progressive course, frequent involvement of the scalp, perineural infiltration, a tendency to recur locally, and rare nodal or metastatic spread.^{1, 9} Treatment generally includes surgical resection,⁹⁻²⁴ with some patients also receiving adjuvant or therapeutic radiation therapy;^{7, 25-30} however, use of chemotherapy is uncommon.^{31, 32} In a recent review including 50 cases of PCACC, the largest series reported in the English literature, mean age at diagnosis was 59 years, with a slight female predominance.⁹ Although information on race is not uniformly specified in clinical series, reports of PCACC have originated from institutions in North America, South America, Europe, and Asia.^{12-14, 16, 17, 19, 25, 28, 33-35}

Population-based studies can provide insights into epidemiologic and clinical characteristics of disease, thereby complementing information gathered through clinical reports. In addition, studies of multiple primary cancers can provide etiologic clues through risk patterns that may suggest a role for shared risk factors, hereditary predisposition, immunosuppression, and/or treatment effects.³⁶ To the best of our knowledge, population-based studies of PCACC have not been previously reported, and studies have not evaluated multiple primary cancers occurring in association with PCACC. Therefore, we used data from the U.S. Surveillance, Epidemiology, and End Results (SEER) program to develop a better understanding of PCACC incidence, survival, and associated cancers.

Methods

Using data from nine population-based cancer registries of the SEER program (SEER-9), we considered all cases of PCACC diagnosed during the 30-year period 1976-2005.³⁷ SEER-9 represents approximately 10% of the U.S. population and includes the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah as well as the areas of Detroit, Michigan; San Francisco, California; Atlanta, Georgia; and Seattle (Puget Sound), Washington. We utilized SEER-9 to maximize the number of cases available for study. In 1992 the SEER Program increased its coverage of minority populations through the addition of Los Angeles County and the San Jose-Monterey area, both in California, and expanded information on race (e.g., Asian/Pacific Islanders (APIs)) also became publicly available. SEER-11 includes the SEER-9 areas and the registry areas in Los Angeles and San Jose-Monterey. Therefore, to assess the incidence of PCACC among APIs, we included data from SEER-11 (1992-2005) for select race analyses to maximize the number of APIs available for study.

The SEER program classifies histology and topography information according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3).³⁸ We included all cases of cutaneous (C440-449) adenoid cystic carcinoma (M-8200) with malignant behavior (/3) that were microscopically confirmed. We assessed incidence and survival rates overall and according to gender (male, female), race (SEER-9: White, Black, other and unspecified; SEER-11: White, Black, API), age (<50 years, 50+ years), stage (localized, regional, distant, unstaged), calendar period (1976-85, 1986-95, 1996-2005), and site (lip (C440), eyelid (C441), external ear (C442), other and unspecified face (C443), scalp and neck (C444), trunk (C445), upper limb and shoulder (C446), lower limb and hip (C447), overlapping sites (C448), and unspecified (C449)). We included C440-444 in a category entitled “face/head/neck.”

Incidence

Age-specific and age-adjusted incidence rates (IRs), incidence rate ratios (IRRs), and 95% confidence intervals (CI) for PCACC diagnosed during 1976-2005 were calculated using SEER*Stat (version 6.4.4). All incidence rates were adjusted to the 2000 U.S. population and expressed per one million person-years (PY). Following the convention of the SEER program, IRs were not presented for fewer than 16 cases.³⁹ Age-specific incidence rates were calculated in seven age groups (<25, 25-34, 35-44, 45-54, 55-64, 65-74, and 75+ years) and depicted on a log-linear scale as previously described.⁴⁰ As a basis for comparison, given the paucity of population-based data available on PCACC, we also assessed age-specific incidence rates of other rare skin cancers (C440-449), including sebaceous carcinoma (M-8410), another appendageal tumor, and Merkel cell carcinoma (M-8247). Because the histology code for Merkel cell carcinoma was introduced into the SEER program in 1986, cases of Merkel cell carcinoma were limited to those diagnosed from 1986-2005.

Multiple Primary Cancers

Using SEER*Stat (version 6.4.4), we assessed the risk of subsequent cancer among 2-month survivors of microscopically confirmed PCACC and more than 2.4 million 2-month survivors of all cancers diagnosed between January 1, 1976 and December 31, 2005. Standardized incidence ratios (SIRs), or observed (Obs.)-to-expected number of subsequent cancers, and exact 95% CI were calculated by compiling PY of observation according to age, gender, race, and calendar period beginning two months after the diagnosis of cancer to the study end date, date of death, or date of last known follow-up, whichever occurred first. The expected number of subsequent cancers was estimated by calculating cancer IRs according to gender, race, 5-year age groups, and 5-year calendar intervals and multiplied by the PY at-risk. We considered risk of non-melanoma skin cancers separately from other cancer sites. Basal cell, squamous cell, and papillary cell carcinomas of the skin are not reportable to the SEER program and therefore not included in these analyses.

Survival

Using the actuarial survival method in the SEER*Stat Survival Session (version 6.4.4), we estimated 5-year relative survival and 95% CI among individuals diagnosed with PCACC. Our analyses included all cases of microscopically confirmed PCACC with malignant behavior among individuals with known age who were diagnosed in SEER-9 during 1976-2004 and actively followed for vital status through 2005. We excluded cases diagnosed among individuals with second or later primary cancers (n=23), diagnosed by death certificate or autopsy (n=0), with invalid vital status or dates (n=0), or with unknown survival time (n=1).

Results

Over the 30-year period of study, 152 cases (IR 0.23 per one million PY) of PCACC were diagnosed among 723,174,580 resident PY in SEER-9, with similar IRs among males (IR 0.24)

and females (IR 0.24) (Table I). Median age at diagnosis of PCACC was 64 years (mean 63 years, range 23-94 years). The majority of cases were observed among Whites, with an insufficient number of cases among Blacks to calculate IRs. In SEER-11, the number of cases of PCACC occurring among Blacks (n=6) and APIs (n=5) were also too few to calculate IRs; the IR among Whites was 0.25 (n=98).

Incidence rates did not change significantly over the three time periods of study. Incidence of PCACC was 89% lower among individuals <50 years compared to those 50 years of age or older (IRR 0.11). Among cases with specified stage, 70% presented with localized stage, and 5% had metastatic disease at diagnosis. Incidence was highest for PCACC occurring on the face/head/neck (IR 0.16), with IRs for trunk (IR 0.04) and extremities (IR 0.02) being considerably lower. Among PCACC occurring on the face/head/neck, most cases occurred on the scalp and neck (n=35), followed by external ear (n=31), face (n=24), eyelid (n=9), and lip (n=5).

Age-specific incidence of PCACC rose exponentially until plateauing at the oldest ages (Figure 1). This pattern contrasts with that of sebaceous carcinoma and Merkel cell carcinoma of the skin, which were characterized by IRs that continued to rise rapidly at older ages. Although age-specific sebaceous carcinoma IRs were recently shown to differ according to sex and skin site,⁴¹ the small number of cases of PCACC did not permit subset analyses of age-specific patterns.

Among 122 two-month survivors of first primary PCACC that were followed for a mean of 9.94 years (1,212 PY) during 1976-2005, 24 second or higher order cancers (excluding non-melanoma skin cancers) were diagnosed among 21 individuals (SIR 1.17, 95% CI 0.75-1.74) (Table II). In contrast to the risk of all subsequent solid cancers which did not occur above expectation (Obs.=17; SIR 0.93, 95% CI 0.54-1.48), the SIR of all lymphohematopoietic malignancies following PCACC was increased nearly 4-fold (Obs.=6; SIR=3.70, 95% CI 1.36-8.06). Based on small numbers of cases, SIRs were greater than 3 for malignant melanoma, thyroid cancer (papillary carcinoma, n=2), multiple myeloma, and chronic myeloid leukemia following PCACC, although not all ratios reached statistical significance.

Among more than 2.4 million two-month survivors of all first primary cancers followed for an average of 6.1 years, the risk of subsequent PCACC was 43% higher than expected in the general population (Table III). An increased risk of PCACC was limited to survivors of solid cancers, with no cases of PCACC observed following lymphohematopoietic cancers. Based on few cases, SIRs of 2 or more were observed following cancers of the oral cavity and pharynx, colon, and urinary bladder.

The overall 5-year relative survival for patients diagnosed with PCACC was excellent (96.1%) (Table IV). Survival appeared slightly better among males than females and among those diagnosed prior to age 50 years than those diagnosed at older ages, although these findings are based on small numbers. There was a suggestion of improved survival over the three calendar-year periods studied, increasing from 91.4% (1976-1985) to 94.5% (1986-1995) to 97.5% (1996-2004). Patients diagnosed with PCACC of the face/head/neck generally fared better than those with PCACC involving the trunk, with 5-year relative survival of 99.1% and 75.6%, respectively.

Discussion

With 152 cases of PCACC diagnosed in SEER-9 over a 30-year period, we triple the number of cases previously reported within a single series and describe new population-based information on PCACC incidence, survival, and associated cancers. We found that PCACC affects males and females equally, occurs largely among Whites, predominates in the face/

head/neck region, and rarely presents with metastatic disease. Incidence increases with age, but the rise in incidence appears to slow at older ages. There is a significantly increased risk of lymphohematopoietic cancers following PCACC, but the converse association was not observed. Survival is generally excellent, with a suggestion that patients with PCACC of the trunk may have an inferior survival to those with PCACC of the face/head/neck region.

Most epidemiologic information on PCACC has been derived from case reports, with a recent review noting fewer than 50 cases in the English literature,⁹ although additional cases continue to be documented.^{10, 42} Based on frequencies, a slight female predominance has been reported,⁹ however, we found similar overall IRs for men and women. This finding contrasts with the male predominance of other skin cancers reported in SEER, including sebaceous, basal cell, squamous cell, and Merkel cell carcinomas.^{41, 43-45} Nevertheless, heterogeneity in sex-specific incidence of cutaneous malignancies according to anatomic site has been described with sebaceous carcinoma of the eyelid, for example, affecting men and women equally, whereas non-eyelid tumors predominate among males.⁴¹ In addition, cutaneous melanoma of the trunk among non-Hispanic Whites predominates among women prior to approximately age 40, but not at older ages.⁴⁶ Unfortunately the limited number of PCACC cases did not permit evaluation of incidence patterns by gender and anatomic site, and the few cases of PCACC among Blacks and APIs precluded assessment of IR patterns according to race.

PCACC has been reported following treatment for childhood acute lymphoblastic leukemia,⁴⁷ rheumatoid arthritis,⁹ and Hashimoto's thyroiditis²⁸ with few other reports describing lymphoproliferative, immunologic, or immunocompromised conditions preceding a diagnosis of PCACC. Immunosuppression is a purported risk factor for both Merkel cell carcinoma⁴⁸⁻⁵⁰ and sebaceous carcinoma.^{41, 50} In support of this, significantly increased risks of Merkel cell carcinoma and sebaceous carcinoma have been reported following lymphohematopoietic cancers and infection with human immunodeficiency virus.^{41, 48-50} In contrast, we report a notable absence of PCACC occurring after lymphohematopoietic malignancies, suggesting that immunosuppression may not have a major role in the development of PCACC. This finding may, in part, contribute to the less prominent rise in incidence of PCACC at older ages, in contrast to the IR patterns of Merkel cell carcinoma and sebaceous carcinoma. Differences in incidence patterns may also reflect distinct risk factors, varying disease biology, and/or less aggressive diagnostic evaluation of PCACC at older ages, particularly given its favorable prognosis.

Cancer following or occurring concurrently with PCACC has been rarely reported.³⁴ Although based on small numbers, we found a significantly increased risk of lymphohematopoietic cancers following PCACC. Interestingly, lymphohematopoietic cancers as a group have not been found to occur significantly above expectation following Merkel cell carcinoma⁴⁹ or sebaceous carcinoma,⁴¹ but a significantly increased risk of non-Hodgkin lymphoma following Merkel cell carcinoma has been reported.⁴⁹

Increased risks of malignant melanoma (although not significant) and thyroid cancer were also observed following PCACC. These findings may suggest shared risk factors, reflect detection bias resulting from increased surveillance for PCACC, or represent chance observations. Radiation is a well-established risk factor for thyroid cancer,⁵¹ and it is plausible that radiotherapy administered for PCACC may contribute to thyroid cancer risk. Larger studies are needed to further evaluate the cancer patterns observed in our study.

Case reports suggest that PCACC generally follows an indolent course, although with frequent recurrences within months to more than 20 years after initial diagnosis.⁹ We found that overall 5-year relative survival was favorable for localized and regional disease, and based on small numbers, our data raise the possibility of improved survival in more recent time periods. In

addition, a survival advantage was suggested for PCACC occurring in the face/head/neck region in contrast to PCACC occurring on the trunk. The prognosis of PCACC has been described to differ according to histologic subtype (tubular, solid, cribriform),⁹ but this information is not included in the ICD-O-3 classification scheme and therefore not available in SEER. Additional follow-up and a larger number of cases of PCACC are necessary to elucidate whether survival differences exist according to site and stage at presentation, which may have implications for therapeutic approaches.

Strengths of our study include its relatively large size and population-based nature which allowed us to describe incidence and survival patterns of PCACC and associated cancer risks without biases inherent to case reports. However, our results may underestimate the true incidence of PCACC because, as has been suggested for melanoma,⁵² underreporting of skin neoplasms to cancer registries is a likely occurrence due to the increasing diagnosis and treatment in the outpatient setting. Other limitations include that we did not undertake a pathology review and cannot exclude the possibility that there may be diagnostic misclassification, although we included only microscopically confirmed cases of PCACC. It is also possible that cases of metastatic adenoid cystic carcinoma to the skin from other primary sites were included, particularly from the more commonly occurring adenoid cystic carcinoma of the salivary gland. However, it is reassuring that salivary gland cancer was not found to occur in association with PCACC. Furthermore, the SEER program has high reliability, and more than 90% of multiple cancers have microscopic confirmation.³⁶ Finally, despite the large size of our study, many observations are based on small numbers, and the possibility of chance associations cannot be excluded.

In summary, PCACC is a rare tumor that affects men and women equally, generally presents with localized disease, and largely occurs in the face/head/neck region. Incidence increases with advancing age but rates plateau at older ages, unlike several other cutaneous neoplasms. The notable absence of PCACC occurring subsequent to lymphohematopoietic malignancies suggests that immunosuppression may not have a major role in the development of PCACC. However, PCACC may be associated with subsequent development of lymphohematopoietic and thyroid cancers and malignant melanoma. To provide further insight into the etiology and biology of PCACC, larger studies are needed to explore gender, race, age, and site-specific incidence and survival patterns as well as possible cancer associations.

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Abbreviation and Acronym list

APIs	Asian/Pacific Islanders
CI	Confidence interval
ICD-O-3	International Classification of Diseases for Oncology, 3 rd edition
IR	Incidence rate
IRR	Incidence rate ratio
Obs.	Observed
PCACC	Primary cutaneous adenoid cystic carcinoma
PY	Person-years
SEER	Surveillance, Epidemiology and End Results
SEER-9	Nine population-based cancer registries of the SEER program
SEER-11	Eleven population-based cancer registries of the SEER program
SIR	Standardized incidence ratio

Figure 1. Age-specific incidence rates of primary cutaneous adenoid cystic carcinoma (1976-2005), sebaceous carcinoma of the skin (1976-2005), and Merkel cell carcinoma of the skin (1986-2005) diagnosed in SEER-9

Age groups with fewer than 16 cases of PCACC are omitted from the figure.

Table I

Age-adjusted primary cutaneous adenoid cystic carcinoma incidence rates and incidence rate ratios, overall and according to gender, race, age, stage, calendar period, and skin site, SEER-9, 1976-2005*

Characteristic	Total			
	No.	IR	IRR	(95% CI)
Total	152	0.23	NA	
Gender				
Females	86	0.24	1.00	(referent)
Males	66	0.24	1.01	(0.71-1.41)
Race				
Whites	133	0.24	1.00	(referent)
Blacks	11	~	~	
Other/unspecified	8	~	~	
Calendar period				
1976-1985	36	0.19	1.00	(referent)
1986-1995	61	0.28	1.50	(0.97-2.35)
1996-2005	55	0.21	1.12	(0.72-1.77)
Age (years)				
50+	118	0.65	1.00	(referent)
<50	34	0.07	0.11	(0.07-0.16)
Stage				
Localized	91	0.14	1.00	(referent)
Regional	33	0.05	0.36	(0.23-0.54)
Distant	6	~	~	
Unstaged	22	0.03	0.23	(0.14-0.38)
Site[†]				
Face, head, neck (C440-444)	104	0.16	1.00	(referent)
Trunk (C445)	29	0.04	0.28	(0.18-0.42)
Upper and lower extremities (C446-447)	16	0.02	0.15	(0.08-0.26)
Not specified (C449)	3	~	~	

Abbreviations: SEER-9, nine cancer registry areas of the Surveillance, Epidemiology and End Results program; No., number of cases; IR, incidence rate; IRR, IR ratio; CI, confidence interval; NA, not applicable; ~IRs and IRRs not calculated for fewer than 16 cases.

* Incidence rates are age-adjusted to the 2000 U.S. standard population and expressed per one million person-years. Incidence rate ratios are based on unrounded rates.

[†] International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) topography codes are defined in the text.

Table II

Standardized incidence ratios of subsequent cancer among two-month survivors of first primary cutaneous adenoid cystic carcinoma diagnosed in SEER-9, 1976-2005

Subsequent cancer*	Obs.	SIR	95% CI
All, excluding non-melanoma skin	24	1.17	(0.75-1.74)
All solid	17	0.93	(0.54-1.48)
Colon and rectum	2	0.74	(0.09-2.68)
Lung and bronchus	4	1.26	(0.34-3.23)
Malignant melanoma, skin	2	3.73	(0.45-13.46)
Thyroid	2	15.25	(1.85-55.10)
All lymphohematopoietic	6	3.70	(1.36-8.06)
Multiple myeloma	2	7.37	(0.89-26.64)
Chronic myeloid leukemia	2	27.46	(3.33-99.20)

Abbreviations: SEER-9, nine cancer registry areas of the Surveillance, Epidemiology and End Results program; Obs., observed number of subsequent cancers; SIR, standardized incidence ratio; CI, confidence interval.

* Limited to cancers with >1 case diagnosed among 122 two-month survivors (1,212 person-years) of primary cutaneous adenoid cystic carcinoma.

Standardized incidence ratios of subsequent primary cutaneous adenoid cystic carcinoma among two-month survivors of other first primary cancers diagnosed in SEER-9, 1976-2005*

Table III

First primary cancer			Subsequent PCACC		
Site	No.	Mean PY	Obs.	SIR	95% CI
All, excluding non-melanoma skin	2,463,191	6.1	16	1.43	(0.82-2.32)
All solid	2,215,503	6.2	15	1.43	(0.80-2.36)
Oral cavity and pharynx	68,102	6.0	2	6.77	(0.82-24.47)
Colon	209,208	6.1	4	3.45	(0.94-8.84)
Female breast	396,555	8.4	2	0.91	(0.11-3.29)
Prostate	378,698	6.3	2	0.76	(0.09-2.74)
Urinary bladder	112,770	7.3	2	2.53	(0.31-9.15)
All lymphohematopoietic	207,062	5.5	0	~	~

Abbreviations: SEER-9, nine cancer registry areas of the Surveillance, Epidemiology and End Results program; PCACC, primary cutaneous adenoid cystic carcinoma; No., number of first primary cancers; PY, person-years at-risk; Obs., observed number of subsequent PCACC; SIR, standardized incidence ratio; CI, confidence interval; ~, not applicable.

* Except for the general category of "All lymphohematopoietic," the table is limited to cancers with >1 case of subsequent PCACC. One case of subsequent PCACC developed following a "miscellaneous cancer" and SEER does not include this primary site in the "all solid" or "all lymphohematopoietic" site categories.

Table IV

Five-year relative survival among patients diagnosed with primary cutaneous adenoid cystic carcinoma according to gender, age, stage, calendar period, and skin site, SEER-9, 1976-2004^{*}

Characteristic	5-year relative survival		
	No.	(%)	(95% CI)
Total	122	96.1	(87.9-100.0)
Gender			
Females	68	88.6	(77.4-99.8)
Males	54	98.5	(86.9-100.0)
Calendar period			
1976-1985	31	91.4	(73.6-100.0)
1986-1995	53	94.5	(82.0-100.0)
1996-2004	38	97.5	(86.5-100.0)
Age (years)			
50+	94	94.2	(83.4-100.0)
<50	28	100.0	
Stage			
Localized	70	97.5	(87.9-100.0)
Regional	29	94.5	(76.5-100.0)
Distant	4	~	
Unstaged	19	90.4	(71.0-100.0)
Site[†]			
Face, head, neck (C440-444)	86	99.1	(90.9-100.0)
Trunk (C445)	23	75.6	(52.9-98.3)
Upper and lower extremities (C446-447)	11	~	
Not specified (C449)	2	~	

Abbreviations: SEER-9, nine cancer registry areas of the Surveillance, Epidemiology and End Results program; No., number of cases; CI, confidence interval; ~, relative survival not calculated for fewer than 16 cases.

^{*} Relative survival is based on cases diagnosed during 1976-2004 and followed through 2005.

[†] International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) topography codes are defined in the text.