

# Challenges in Management of Squamous Cell Carcinoma of the Anus in New England and Across the United States

## *A Review of the National Cancer Data Base*

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**Background:** Management of squamous cell carcinoma of the anus (SCCA) is becoming more relevant, as its incidence continues to increase. The purpose of this study was to evaluate regional and national data to assess trends in epidemiology, access to cancer center care, and overall management strategies in SCCA.

**Study Design:** A review of available data from the American College of Surgeons Committee on Cancer National Cancer Data Base focused on incidence, sex, age, stage at diagnosis, distance traveled for care, and utilization of therapy as first course of treatment (FCT). The analysis included 40,817 patients treated for SCCA at 1513 cancer centers in the United States, of which 2347 patients were treated at 109 cancer centers in New England, between the years 2003 and 2013.

**Results:** Over the 11-year period, incidence of SCCA increased by 76% in the United States and by 83.8% in New England. Stage was unknown in 11.7% of all US cases, significantly higher than more common cancers, for example, breast (4.3%), prostate (6%), or colon (7.8%) ( $P < 0.001$ ). Patients in southern New England, compared with northern New England, traveled <10 miles more often (53.4% vs. 38.1%) ( $P < 0.001$ ), and >25 miles less often (14.3% vs. 28.7%) ( $P < 0.001$ ). Cases of early stage SCCA (0, I) were more frequent in southern New England (29.2%) than northern New England (21.7%) ( $P = 0.0025$ ), whereas more advanced stage (II to IV) cases occurred less frequently in southern New England (60.1%) than northern New England (72%) ( $P < 0.001$ ). Overall, the most common FCT was chemoradiotherapy, utilized in 49.3% of cases, followed by chemoradiotherapy plus surgery in 19.4% of cases. Stage unknown patients were treated with chemoradiotherapy in 34.6% of cases, with surgery alone in 20.2%, and with chemoradiotherapy plus surgery in 15.4% of cases.

**Conclusions:** The incidence of SCCA is steadily increasing. Its frequency of stage unknown is significantly higher than other common cancer sites. Travel distance and stage at diagnosis data may reflect regional differences in cancer center care access. Although chemoradiotherapy remains the most commonly utilized FCT, challenges in accurate staging and inconsistent use of additional prognostic variables may affect optimal treatment.

**Key Words:** anal cancer, squamous cell carcinoma of the anus, epidemiology, treatment, NCDB, NCCN guidelines

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Anal cancer is a relatively rare malignancy, but its incidence has been steadily increasing for four decades, with an estimated 8080 new cases and 1080 deaths in 2016.<sup>1,2</sup> The rising incidence of this cancer has been ascribed to an increased prevalence of anal human papilloma virus (HPV) infection in both men and women,<sup>3,4</sup> despite advances in diagnostic modalities and treatment options.<sup>5,6</sup> The American Cancer Society has been using the terms “cancer of the anus, anal canal, and anorectum” to classify this malignancy, which implies a certain breadth of range in its anatomic location, not commonly found in the classification of other solid tumors.<sup>2</sup>

Anal cancer data in the National Cancer Data Base (NCDB) include both primary and metastatic tumors, for a total of 94 different histologic types, including melanomas, neuroendocrine tumors, sarcomas, and others. Our review focused on the most common histologic type and its variants, squamous cell carcinoma of the anus (SCCA), which has been reported to account for over 90% of all cases.<sup>6</sup>

The recommendations for care of patients with SCCA are well outlined in the National Comprehensive Cancer Network (NCCN) guidelines.<sup>7</sup> Management of SCCA represents an example of multidisciplinary involvement, often including surgery, chemotherapy, and radiotherapy as the expertise required of a physicians team, to provide accurate diagnosis, appropriate treatment, and reliable survivorship plan. Such care delivery may be best accomplished within the organized structure of an American College of Surgeons Commission on Cancer (ACS CoC)-accredited Cancer Program.

In this study we obtained available data from the NCDB on variables included in the management of SCCA in the United States. In addition, we conducted a review of similar data in New England states, where our practice network is based, to detect possible regional variations in the care of this malignancy.

## METHODS

The NCDB is a joint project of the American Cancer Society and the CoC of the ACS, dedicated to the evaluation, management, and surveillance of cancer patients in the United States. The ACS has executed a Business Associate Agreement that includes a data use agreement with each of its CoC-accredited hospitals. The NCDB was established in 1989 as a nationwide, facility-based, comprehensive clinical surveillance resource oncology dataset that currently captures information on ~70% of all newly diagnosed malignancies annually in the United States. The database is populated by information entered by certified tumor registrars (CTR) from CoC-accredited cancer centers.

We accessed datasets on “cancer of the anus, anal canal and anorectum” from 2003 to 2013, but selected for analysis

only cases listed in the database with a histologic diagnosis containing the words “squamous cell carcinoma,” to ensure that our research focused on a homogenous patient population.

The NCDB web pages were exported to an excel format and subsequently converted to a comma-separated value file, which was processed through a custom script to generate results for analysis.

We obtained data on incidence variations over the 11-year study period.

Patient demographics such as sex, age, and stage at diagnosis were also collected. In addition, we analyzed distance traveled to obtain access to cancer center care in New England states. Finally, we extracted information on utilization of different therapeutic modalities, alone or in combination, as first course of treatment (FCT) for all reported stages of SCCA at initial diagnosis.

Subgroup comparisons among different patient populations were performed using statistical analysis with the 2-tailed, 2-proportion *z* test. The Holm-Bonferroni method was then used to control the family-wise error rate and generate adjusted *P*-values and confidence intervals (CI).

## RESULTS

From 2003 to 2013, a total of 52,687 cases of cancer of “anus, anal canal and anorectum” from 1513 cancer centers in the United States were available for analysis in the NCDB. Of those, 40,817 cases (77.5%) were selected as SCCA on the basis of available histopathologic data. We also conducted a subset analysis of 3024 cases of the same anatomic site treated at the 109 cancer centers in New England states (28 in Connecticut, 11 in Rhode Island, 43 in Massachusetts, 6 in Vermont, 10 in New Hampshire, 11 in Maine), and 2347 cases (77.6%) were similarly selected as SCCA.

The incidence of SCCA cases by year and by stage in the United States and in New England are reported in Tables 1 and 2, respectively. Over the 11-year study period, the incidence of SCCA cases increased by 76% in the United States as a whole and by 83.8% in New England states (Fig. 1).

Stage at diagnosis was unknown in 11.7% of all cases of SCCA in the United States, a percentage significantly higher than stage unknown reported for other common neoplasms in the NCDB during the same time period, such as breast (4.3%) ( $P < 0.001$ ; 95% CI, 0.07-0.08), prostate (6%) ( $P < 0.001$ ; 95% CI, 0.05-0.06), or colon (7.8%) ( $P < 0.001$ ; 95% CI, 0.03-0.04). After a high of 16.1% of stage unknown SCCA cases in 2007, a trend toward improvement was found from 2010 to 2013, with such occurrences falling under 10%.

Stage unknown for the New England states during the same time period was 9.6% on an average, with a low of 4.6% in New Hampshire and a high of 18.3% in Rhode Island.

There was no appreciable trend toward earlier diagnosis, that is increasing percentages of stage 0 to I cases or decreasing percentages of stage II to IV cases, over the study period (Tables 1, 2).

With respect to sex, there were 25,623 females (62.8%) and 15,194 male patients (37.2%).

With respect to age in years at diagnosis, 1956 patients (4.8%) were 39 or younger, 20,554 (50.4%) were 40 to 59, 14,945 (36.6%) were 60 to 79, and 3362 (8.2%) were 80 or older.

At the last US census during the study period in 2010,<sup>8</sup> southern New England states (Southern New England = Connecticut, Rhode Island, Massachusetts) had a combined population of 11,174,293 over an area of 17,642 mi<sup>2</sup>, with a resulting population density of 633.4/mi<sup>2</sup>. The more rural northern New England states (Northern New England = Vermont, New

TABLE 1. Incidence of SCCA by Stage in the United States From 2003 to 2013

Year Stage	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	%
0	306	297	298	331	325	365	372	343	355	322	317	3631	(8.9)
I	478	512	557	558	552	675	762	744	794	785	806	7223	(17.7)
II	948	1014	1033	993	1187	1227	1350	1370	1394	1547	1603	13,666	(33.5)
III	512	532	579	639	779	929	962	995	1143	1295	1318	9678	(23.7)
IV	104	113	113	109	167	170	199	200	212	238	233	1858	(4.5)
Unknown	312	406	418	480	579	451	497	401	387	416	414	4761	(11.7)
Total	2660	2874	2998	3105	3589	3817	4142	4053	4285	4603	4691	40,817	(100)

SCCA indicates squamous cell carcinoma of the anus.

TABLE 2. Incidence of SCCA by Stage in NE States From 2003 to 2013

Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total	%
0	23	18	12	20	23	23	14	17	20	15	17	202	(8.6)
I	29	33	34	30	36	43	40	45	50	50	51	441	(18.8)
II	71	68	73	60	73	72	84	88	95	100	112	896	(38.2)
III	23	32	22	31	40	49	52	50	59	60	83	501	(21.3)
IV	4	4	2	9	11	4	6	8	8	14	11	81	(3.5)
Unknown	10	26	19	22	36	19	21	15	21	17	20	226	(9.6)
Total	160	181	162	172	219	210	217	223	253	256	294	2347	(100)

NE indicates New England; SCCA, squamous cell carcinoma of the anus.

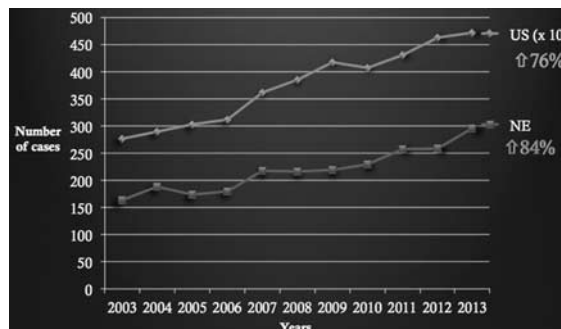


FIGURE 1. Incidence of squamous cell carcinoma of the anus in cancer centers in the United States (US) and New England (NE) States from 2003 to 2013.

Hampshire, Maine) had a combined population of 3,270,572 over an area of 54,349 mi<sup>2</sup>, with a resulting population density of 60.2/mi<sup>2</sup>. Distance traveled to access cancer center care was significantly different for SCCA patients in southern New England and northern New England. The percentage of SCCA patients who traveled under 10 miles was greater in southern New England (53.5%) than in northern New England (38.1%) ( $P < 0.001$ ; 95% CI, 0.09-0.21), and in the United States (44.3%) ( $P < 0.001$ ; 95% CI, 0.05-0.12). Also, the percentage of patients who had to travel over 25 miles to access a cancer center was lower in southern New England (14%) than in northern New England (28.7%) ( $P < 0.001$ ; 95% CI, -0.20 to -0.08), and in the United States (23.9%) ( $P < 0.001$ ; 95% CI, -0.12 to -0.07) (Table 3).

Early stage (0, I) cases of SCCA were more frequent in southern New England (29.2%) than northern New England (21.7%) ( $P = 0.0025$ , 95% CI, 0.02-0.13), whereas more advanced stage (II to IV) cases were less frequent in southern New England (60%) than northern New England (72%) ( $P < 0.001$ , 95% CI, -0.18 to -0.06) (Table 4).

The data on utilization of various treatment modalities, alone or in combination, as FCT in the United States at various stages are reported in Table 5.

For stage 0, surgery (S) was the most common FCT, utilized in 74.9% of cases. For stage 0 cases, also known as carcinoma in situ (Tis) or high-grade anal intraepithelial neoplasia, radiotherapy was used in 12.5% of cases and chemotherapy was used in 9% of cases as FCT, alone or in combination with other modalities. In stage I cases, S as FCT was used in 24.1% of cases, whereas the most common FCT modality was chemotherapy plus radiotherapy plus surgery (C+R+S), used in 31.5% of cases. C+R was used as FCT in 31.5% of cases. In stage II cases, C+R was the most common FCT in 59.4% of cases, followed by C+R+S in 22.6% of cases. C+R was also the most common FCT for stage III cases (71.9%) and for stage IV cases (53%). Stage unknown cases were most often initially managed with C+R (34.6%), followed by S (20.2%) and C+R+S (15.4%).

Overall the most common FCT modalities utilized for all cases in all stages was C+R in 49.3% of cases, C+R+S in 19.4% of cases, and S in 16.5% of cases.

With the exclusion of stage 0 and "stage unknown" cases, the 36,226 patients with invasive cancer and a known stage I through IV, C+R was used as FCT in 50.6% of cases, C+R+S in 19.5% of cases, and S alone in 8.4% of cases.

## DISCUSSION

Any single cancer program is unlikely to have a large institutional experience with SCCA. For that reason, a large

**TABLE 3.** Comparison of Distance Traveled Data for SCCA Patients in Southern NE States, in Northern NE States, and in the United States

Distance Traveled	(n [%])			P
	Southern NE (Connecticut, Rhode Island, Massachusetts) (n = 1775)	Northern NE (Vermont, New Hampshire, Maine) (n = 572)	US (n = 40,817)	
< 10 miles	949 (53.5)	218 (38.1)		<0.001
	949 (53.5)		18,093 (44.3)	<0.001
> 25 miles		218 (38.1)	18,093 (44.3)	0.015
	254 (14.3)	164 (28.7)		<0.001
	254 (14.3)		9757 (23.9)	<0.001
		164 (28.7)	9757 (23.9)	0.032

NE indicates New England; SCCA, squamous cell carcinoma of the anus; US, United States.

national database review offers the most meaningful approach for analyzing data on this malignancy. Anal squamous cell carcinoma remains a relatively rare cancer, but its incidence has now risen to about 2.6% of all new digestive system cancer cases diagnosed in the United States in 2016.<sup>9</sup>

Our study, using strict histopathology criteria, showed a lower than previously reported percentage of cases meeting inclusion in the squamous cell carcinoma only proportion of the total number of cases of malignancies of the “anus, anal canal and anorectum” (77.5% vs. over 90%<sup>6</sup>). Subclassifications of different histologic types of SCCA have recently been eliminated in the current WHO system, due to the frequency of mixed patterns within a single tumor and the lack of prognostic significance with modern therapy.

In our analysis, there was a significant increase in incidence of SCCA from 2003 to 2013 in the United States (76%), and an even greater increase in New England states (83.4%). This is in contrast to a continuing decline in the incidence of colorectal and anal adenocarcinoma, where screening and prevention initiatives are proving successful.

In addition, our study showed that there was no trend toward earlier stage at diagnosis of SCCA cases over the 11-year period.

Risk factors for invasive SCCA are similar to those of cervical cancer, with intraepithelial neoplasia as a precursor lesion. Most studies have detected high-risk HPV, predominantly HPV-16, in over 80% of cases of SCCA.<sup>10,11</sup> HPV status in SCCA specimens may also be relevant in predicting response to treatment, as it is in head and neck cancer.<sup>12</sup> It can be assessed in biopsy specimens using the surrogate

immunohistochemical marker P16, in situ hybridization, or polymerase chain reaction.

Human immunodeficiency virus (HIV) testing is recommended in all patients diagnosed with SCCA, as a concomitant HIV infection significantly affects prognosis and management decisions.<sup>13,14</sup> The NCDB collects, if available, information about HPV, but does not require data input about HIV status of SCCA patients.

Clinical presentation, histologic confirmation by biopsy, diagnostic workup, and clinical staging principles are well outlined in the most recent edition of the NCCN practice guidelines.<sup>7</sup> Determination of the exact anatomic site of SCCA is relevant, as anal margin lesions must be differentiated from anal canal lesions. In fact, a local excision with adequate margins is considered appropriate therapy for a well-differentiated anal margin SCCA staged T1N0M0, while a similarly staged lesion in the anal canal warrants chemoradiation therapy. A limitation of our study resulted from the fact that the NCDB does not collect information about location of primary tumor, that is anal margin versus anal canal.

The opportunity to review regional data in New England allowed us to compare distance traveled for cancer care access in the more densely populated southern states with the more rural northern states. It seems that a shorter distance traveled to access cancer center care was associated with an earlier stage at diagnosis. The smaller square mile territory of southern New England could also account for the shorter distance traveled. Although our study does not intend to prove a causal relationship, it does draw attention to the importance of considering sociodemographic factors in

**TABLE 4.** Comparison of Stage at Diagnosis Data for SCCA Patients in Southern NE States, in Northern NE States, and in the United States

Stage at Diagnosis	(n [%])			P
	Southern NE (Connecticut, Rhode Island, Massachusetts)	Northern NE (Vermont, New Hampshire, Maine)	US (n = 40,817)	
0-I	519 (29.2)	124 (21.7)		0.0025
	519 (29.2)		10,854 (26.6)	0.032
II-IV		124 (21.7)	10,854 (26.6)	0.032
	1066 (60.1)	412 (72)		<0.001
		1066 (60.1)	25,202 (61.7)	0.152
		412 (72)	25,202 (61.7)	<0.001

NE indicates New England; SCCA, squamous cell carcinoma of the anus; US, United States.

**TABLE 5.** Utilization of Various Treatment Modalities as FCT for SCCA in Various Stages at Diagnosis

Stage FCT	(n [%])						Total
	0	I	II	III	IV	Unknown	
S	2719 (74.9)	1739 (24.1)	1045 (7.6)	211 (2.2)	46 (2.5)	960 (20.2)	6721 (16.5)
R	53 (1.5)	179 (2.5)	498 (3.6)	349 (3.6)	113 (6.1)	234 (4.9)	1428 (3.5)
C	22 (0.6)	50 (0.7)	108 (0.8)	141 (1.5)	256 (13.8)	140 (2.9)	719 (1.8)
S + R	115 (3.2)	323 (4.5)	315 (2.3)	97 (1)	18 (1)	93 (2)	961 (2.4)
S + C	17 (0.5)	78 (1.1)	95 (0.7)	61 (0.6)	49 (2.6)	53 (1.1)	1355 (0.9)
C + R	158 (4.4)	2278 (31.5)	8113 (59.4)	6960 (71.9)	986 (53)	1646 (34.6)	20134 (49.3)
S + C + R	129 (3.6)	2303 (31.9)	3085 (22.6)	1505 (15.6)	183 (9.8)	734 (15.4)	7936 (19.4)
Oth/no	418 (4.5)	273 (3.8)	407 (3)	354 (3.7)	208 (11.2)	901 (18.9)	2563 (6.2)
Total	3631	7223	13666	9678	1858	4761	40817 (100)

C indicates chemotherapy; FCT, first course of treatment; Oth/no, other/none; R, radiotherapy; S, surgery; SCCA, squamous cell carcinoma of the anus.

evaluating availability of resources for cancer care in the United States.

A relevant finding in our study was the high incidence of “stage unknown” in 11.7% of all US cases reviewed. Although the NCDB did not offer more specific information on the possible reasons for such finding, it is likely that detailed information about size of lesions was often not available to the CTR.

Our study may serve the purpose of an audit for such variations in staging practices and may draw attention to the need for greater accuracy and consistency in coding practices by CTRs across cancer centers in the United States.

Valuable additional information such as exact tumor location (anal canal vs. anal margin), HIV status in addition to HPV variables, if consistently provided in the data entered by each cancer program, would add relevant information for staging, prognosis, and NCCN guidelines concordant care.

Although there is general consensus in the literature with respect to treatment options for SCCA,<sup>15,16</sup> a high percentage of stage unknown patients (11.7%) were treated without accurate staging. In addition, stage 0 patients, who should be best managed surgically in most cases, underwent radiotherapy in 12.5% of cases and chemotherapy in 9% of cases as FCT, alone or in combination with other modalities. Conversely, 20.2% of patients with stage unknown were treated with surgery alone. Also, 5.2% of all cases staged II, III, and IV were treated with surgery alone as FCT.

Finally, a significant challenge to be addressed to deliver GCC for SCCA patients remains the ability to perform a thorough anorectal examination, including anoscopy, as a crucial step in the early diagnosis, staging, assessment of tumor regression after therapy, and survivorship plan.

## CONCLUSIONS

This study of patients with SCCA in the NCDB found that the incidence of this cancer, unlike other gastrointestinal malignancies, continues to increase in the United States. There are challenges with respect to accurate staging of SCCA cases, with a high percentage of patients being managed with “stage unknown,” when compared with other more common solid tumors. There were variations in access to cancer center care in New England, with more densely populated states having a greater proportion of patients who could travel shorter distances. Patients with SCCA in such states were also diagnosed at an earlier stage. SCCA seems to be an increasingly common cancer that poses unique challenges in prevention, diagnosis, accurate staging, therapy, and survivorship. A renewed awareness of risk factors for this cancer, the addition of

relevant prognostic variables to the NCBD, along with renewed attention to NCCN guidelines concordant care, should provide quality improvement in the management of SCCA.

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