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The impact of location on the prognosis of squamous cell carcinomas of the anorectal region

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ARTICLE INFO

Article history:
Received 16 January 2018
Received in revised form
17 May 2018
Accepted 24 May 2018
Available online xxx

Keywords:
Rectal squamous cell carcinoma
Anal squamous cell carcinoma
Prognosis

ABSTRACT

Background: Because anal and rectal squamous cell carcinomas (R-SCCs and A-SCCs) share a common histology and an excellent response to chemoradiation, we hypothesized that R-SCC and A-SCC may represent a similar biological entity, and location would not affect clinical presentation and prognosis.

Methods: Patients diagnosed with R-SCC ($n = 2881$) and A-SCC ($n = 21,854$) were identified in the Surveillance, Epidemiology, and End Results database (1998-2013). R-SCCs were staged based on American Joint Committee on Cancer classification for A-SCC, and impact of location was analyzed accordingly.

Results: Compared to A-SCC, R-SCCs were more common in females (65% *versus* 48%, $P < 0.001$) and older patients (62 *versus* 56 yrs, $P < 0.001$). R-SCC presented with more advanced disease than A-SCC: mean size 4.2 *versus* 3.6 cm; T4 14% *versus* 5%; nodal involvement 20% *versus* 15%; and metastases 13% *versus* 6% (all $P < 0.001$). In multivariable analysis, R-SCCs and A-SCCs had similar disease-specific survival (DSS) for stages 0, I, and III; however, stage II R-SCC had significantly worse DSS than A-SCCs ($P = 0.002$). This was due to a greater proportion of T3 (>5 cm) R-SCC tumors (36% *versus* 27%, $P < 0.001$), which had a lower DSS than T2 (2-5 cm) tumors. Within T3 and T4 tumors, R-SCCs had lower DSS than A-SCCs.

Conclusions: R-SCC presented with higher stages than A-SCC, suggesting a delayed diagnosis. Larger R-SCC (T3-T4) had worse survival compared to T3-4 A-SCC, which may be due to a combination of more advanced disease within-stage as well as the use of less efficacious therapeutic regimens. Therefore, location may represent a significant prognostic factor for SCC of the anorectal region.

Introduction

Squamous cell carcinomas (SCC) of the anal canal and rectum are relatively rare malignancies. SCCs in both these locations are sensitive to chemotherapy and radiation, with chemoradiation being the accepted standard of treatment for nonmetastatic disease.[1,2] Although anal squamous cell carcinomas (A-SCCs) represent approximately 2% of all gastrointestinal malignancies, rectal squamous cell carcinomas (R-SCCs) are even more uncommon and account for

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0022-4804/$ – see front matter
https://doi.org/10.1016/j.jss.2018.05.050

only 0.01%-0.025% of all colorectal cancers.[1,3] As a result, there are few data regarding the impact of rectal compared to anal location on patient demographics, disease characteristics, and prognosis. The contemporary knowledge and current understanding regarding R-SCC is based on case series and case reports including 142 patients and two studies published from national databases.[1,2] The majority of these studies have small sample sizes or have not used consistent staging systems to analyze clinical outcomes of R-SCC, making meaningful conclusions challenging to draw.

The American Joint Committee on Cancer (AJCC) lacks a standardized staging system for R-SCC, and there is debate as to whether this neoplasm should follow the rectal adenocarcinoma or the A-SCC staging system.[1,2] For the purposes of this study, the anal cancer staging system was employed in order to allow for a uniform and equivalent comparison between A-SCC and R-SCC. Owing to the common histology and excellent response to a nonoperative management based on chemotherapy and radiation,[1,2] we hypothesized that R-SCC and A-SCC may represent a similar biological entity and that the location of the SCC in the anorectal region would not impact the clinical presentation and survival.

The aim of the present study was therefore to compare the demographic, clinical, and pathologic characteristics of R-SCC and A-SCC, as well as to evaluate their long-term prognosis.

Patients and methods

Data sources and study subjects

The Surveillance, Epidemiology, and End Results (SEER) database was used to identify patients diagnosed with R-SCC and A-SCC.[4] This database refers to the International Classification of Disease for Oncology, third edition for histology and primary site coding (squamous cell carcinoma: code 8070-8078; rectum: code C20.9, anus: code 21.0 and 21.1) and collects data from 18 different regions that collectively represent approximately 28% of the US population.[5]

Demographic information of interest included patient gender, age at diagnosis, and race. Age at diagnosis was treated as a continuous variable. Race was classified into white, black, and other. Patients younger than 18 y and diagnosed before year 1988 were excluded because of the lack of data regarding treatment.

Clinical management was classified into four categories: local excision only, radiation only, radiation with local excision, and radiation with radical resection. The nonstandard approach of abdominoperineal resection alone was not analyzed due to the limited number of cases. Chemotherapy data are not collected in the SEER database; therefore, its use and survival impact could not be analyzed.

Pathologic characteristics included tumor size, lymph node involvement, the presence of distant metastases, and AJCC stage seventh edition. Tumor size was classified in accordance with the AJCC classification system for A-SCC into three groups: ≤2.0 cm, 2.1-5.0 cm, and ≥5.1 cm; tumors >20.0 cm were excluded due to the possibility of errors in the coding process. The lymph node involvement and metastases categories were divided into negative and positive. Because the SEER database does not record data on the burden of metastatic disease or the chemotherapeutic regimens, stage IV cancers were excluded from the survival analyses. Staging codes are based on the best available clinical and pathologic information. Because the majority of the R-SCC and A-SCC were managed nonoperatively, the staging was primarily clinical. All patients were staged according to the AJCC classification of A-SCC per current standard clinical practice.[6]

Statistical analyses

Demographic, clinical, and pathologic data were analyzed using summary statistics; chi-square and Student's *t*-test were used for categorical and continuous variable comparisons, respectively. The Kaplan-Meier method was used to determine overall and disease-specific survival (DSS), and the log-rank test was used to calculate the statistical significance of comparisons of survival. The Cox proportional hazards regression was used for the multivariable models.

Data analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 23.0; SPSS Inc, Chicago, IL); all tests were two-sided, with statistical significance set at a *P*-value of <0.05. The SEER database is publicly available, and all patient information is deidentified; therefore, this study was granted an exemption from institutional review board approval.

Results

Patient characteristics

A total number of 2881 R-SCC and 21,854 A-SCC patients were identified in the SEER database between 1988 and 2013. R-SCC was more commonly diagnosed in females than A-SCC (64.8% *versus* 47.8%, $P < 0.001$) and in older individuals (mean age at diagnosis 62.1 ± 14 *versus* 57.7 ± 14 y, $P < 0.001$; Table 1).

R-SCC presented with more advanced disease than A-SCC: mean size 4.2 *versus* 3.6 cm; T4 17.8% *versus* 5.5%; nodal involvement 19.9% *versus* 14.8%; and metastases 13.0% *versus* 6.4% (all $P < 0.001$). This was reflected by the higher AJCC stages at presentation for R-SCC as compared to A-SCC patients (Table 1).

R-SCC patients were less likely than A-SCC patients (39.3% *versus* 48.4%) to undergo local excision, which was mainly for *in situ* disease. Compared to A-SCC patients, radiation-based therapy was the treatment for R-SCCs in 49.7% *versus* 45.3% of cases, radiation with local excision in 4.3% *versus* 3.0%, and radiation with radical resection in 6.7% *versus* 3.3% of cases, respectively ($P < 0.001$; Table 1).

Prognosis

In univariate analysis, R-SCC and A-SCC 5 y DSS was comparable for TisN0 (stage 0) (93% *versus* 95%, $P = 0.186$), T1N0 (stage I) (87% *versus* 89%, $P = 0.648$), T2N0 (stage II) (78% *versus* 83%, $P = 0.131$), and T1-4N+ (stage III) (42% *versus* 42%, $P = 0.181$) but