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Brief Correspondence

Predictors of Cancer-specific Mortality After Disease Recurrence in Patients with Squamous Cell Carcinoma of the Penis

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Abstract

Disease recurrence occurs frequently after surgical treatment for squamous cell carcinoma of the penis (SCCp). We sought to determine prognostic factors that influence cancer-specific mortality (CSM) after disease recurrence in patients with SCCp. We performed a retrospective analysis of 314 patients who experienced disease recurrence after surgical treatment for SCCp between 1949 and 2012. Competing risk regression analysis addressed factors associated with CSM after SCCp recurrence. Median time from surgery to disease recurrence was 10.5 mo (interquartile range [IQR]: 5.9–21.3). Of the recurrences, 165 (53%), 118 (38%), and 31 (9.9%) were local, regional, or distant, respectively. Within a median follow-up of 4.5 yr (IQR: 2.0–6.5), 108 patients died of SCCp and 41 patients died of causes other than SCCp. Shorter time to disease recurrence was found to be significantly associated with a higher risk of CSM ($p = 0.0006$). Lymph node metastasis at the time of initial treatment (subdistribution hazard ratio [SHR]: 1.96; 95% confidence interval [CI] 1.23– 3.11; $p = 0.005$) and regional recurrence (SHR: 4.14; 95% CI, 2.16–7.93; $p < 0.0001$) or distant recurrence (SHR: 5.75; 95% CI, 2.59–12.73; $p < 0.0001$) were associated with increased risk of CSM after disease recurrence. Inclusion of time to recurrence into risk stratification may help patient counseling and treatment planning.

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Squamous cell carcinoma of the penis (SCCp) is a relatively rare disease with low incidence rates of approximately 0.5–1.0 per 100 000 person-years in Europe and the United States [1]. Treatment of SCCp is stage dependent and includes, for nondistant metastatic SCCp, surgery of the primary lesion as well as regional (inguinal/pelvic) lymph node dissection when indicated [2]. A recent analysis of cancer registries shows that survival for SCCp patients has not improved in Europe or the United States in the last 20 yr [3]. Approximately 30% of all SCCp patients experience disease recurrence, with >90% of these recurrences occurring within 5 yr after primary treatment [4]. In the present

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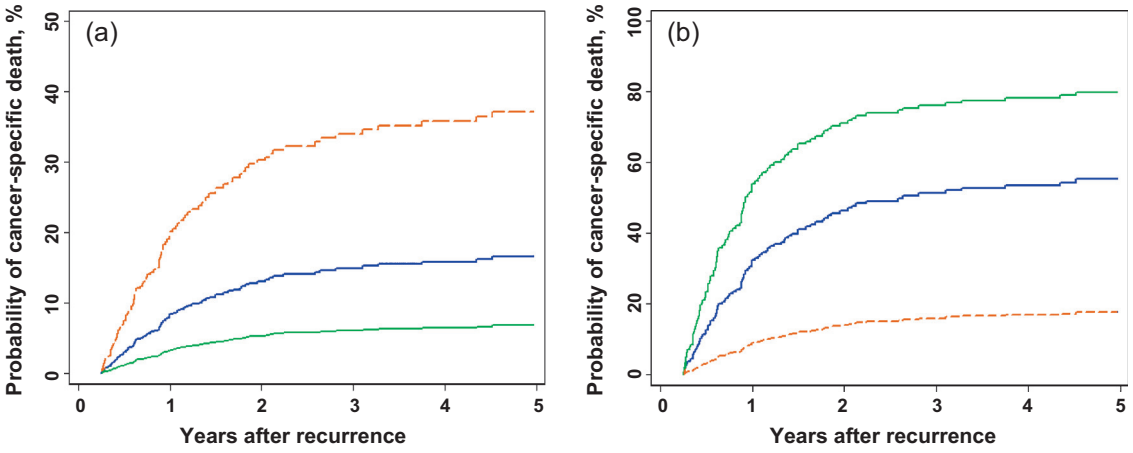

Fig. 1 – (a) Cumulative incidence of cancer-specific death by time of recurrence. All other covariates are set to the mean. Orange: 1 yr; blue: 3 yr; green: 5 yr. (b) Cumulative incidence of cancer-specific death by recurrence site. All other covariates are set to the mean. Orange: local; blue: regional; green: distant.

study, we describe the natural history of patients who experience disease recurrence after primary treatment for SCCp with curative intent and identify risk factors of cancer-specific mortality (CSM) after disease recurrence. We hypothesized that, as is the case with most other malignancies, a shorter time from surgery to recurrence would be associated with a shorter time from recurrence to death.

Full study methods are described in Supplement 1. Data from 314 patients from two high-volume tertiary care referral centers treated between 1949 and 2012 were included. All patients had pathologic documentation of SCCp and pathologic, clinical, or radiographic documentation of recurrence of SCCp. No patient had any evidence of distant metastasis at the time of primary treatment. Local recurrence was defined as recurrence of SCCp at the penis after a disease-free interval. Regional recurrence was defined as spread to the inguinal or pelvic lymph nodes; distant recurrence was defined as metastatic spread of SCCp to any site other than the inguinal or pelvic lymph nodes, respectively. The competing risk regression model included time from surgery to disease recurrence, age, pathologic stage, lymph node status, surgery type, and recurrence site. Time to disease recurrence was entered using restricted cubic splines with knots at its tertiles to account for a nonlinear association with the outcome. All statistical analyses were performed using Stata v.12.0 (StataCorp, College Station, TX, USA).

Supplemental Table 1 summarizes the clinicopathologic characteristics of the 314 patients. Median time from surgery to disease recurrence was 10.5 mo (interquartile range [IQR]: 5.9–21.3). Of the recurrences, 165 (53%), 118 (38%), and 31 (9.9%) were local, regional, or distant, respectively. Local disease recurrence occurred predominantly after local excision of SCCp; regional or distant disease recurrences were mostly detected in patients who had undergone partial or total amputation for tumors pT2 or higher ($p < 0.001$; Supplemental Table 2). Within a median follow-up of 4.5 yr (IQR: 2.0–6.5) for survivors, 108 patients died of SCCp and 41 patients died of causes other than SCCp. The 1-yr risk of death from cancer was 20%, 8%, and 3% for patients who recurred at 1, 3, or 5 yr, respectively (Fig. 1a). In competing risk regression analysis, time to disease recurrence was found to be significantly associated with shorter survival ($p = 0.0006$; Table 1). The association between time to recurrence and survival was not different by recurrence site ($p = 0.8$). Lymph node metastasis at the time of initial treatment ($p = 0.005$) and regional recurrence ($p < 0.0001$) or distant recurrence ($p < 0.0001$) were associated with increased risk of CSM after disease recurrence (Table 1 and Fig. 1b). In contrast, initial pathologic tumor stage ($p = 0.7$) and initial surgery type ($p = 0.2$) were not associated with CSM after disease recurrence (Table 1).

Our principal finding is that the time from surgery to disease recurrence is an independent predictor of CSM in patients with SCCp recurrence. The probability of cancer-specific death was significantly higher in patients recurring at the first year after surgery compared with patients recurring at 3 and 5 yr. The early occurrence of distant recurrences, which are associated with a poor prognosis [4], cannot explain our results because the competing risk regression model accounted for recurrence site. Although not reported in SCCp previously, shorter time to disease recurrence was found to reduce significantly the chance of survival in other malignancies [5]. However, it remains unclear whether a tumor that recurs early harbors a more aggressive biologic or clinical potential than a late recurrence.

We also found that CSM after disease recurrence is associated with site of disease recurrence. This is in accordance with a study on 700 patients with SCCp reporting a 5-yr cancer-specific survival after local, regional, and distant recurrence of 92%, 33%, and 0%, respectively [4]. In our study, local disease recurrence mainly occurred after penile-preserving treatment, whereas distant disease recurrence primarily affected patients who underwent partial or total amputation and had tumor stage pT2 or higher.