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Recurrence patterns in esophagel cancer

The impact of histology on recurrence patterns in esophageal cancer treated with definitive chemoradiotherapy

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ABSTRACT

Background: To assess the impact of histology on recurrence patterns and survival outcomes in patients with esophageal cancer (EC) treated with definitive chemoradiotherapy (CRT).
Methods: We analyzed 590 consecutive EC patients who received definitive CRT from 1998 to 2014, including 182 patients (30.8%) with squamous cell carcinoma (SCC) and 408 (69.2%) with adenocarcinoma. Recurrence pattern and timing, survival, and potential prognostic factors were compared.
Results: After a median follow-up time of 58.0 months, the SCC group demonstrated a comparable locoregional recurrence rate (42.9% vs. 38.0%, $P = 0.264$) but a significantly lower distant failure rate (27.5% vs. 48.0%, $P < 0.001$) than adenocarcinoma group. No significant difference was found in overall survival or locoregional failure-free survival between groups, whereas the SCC group was associated with significantly more favorable recurrence-free survival ($P = 0.009$) and distant metastasis-free survival ($P < 0.001$). The adenocarcinoma group had higher hematogenous metastasis rates of bone, brain, and liver, whereas the SCC group had a marginally higher regional recurrence rate. Among patients who received salvage surgery after locoregional recurrence, no significant difference in survival was found between groups ($P = 0.12$).
Conclusions: The patterns and sites of recurrence, survival outcomes, and prognostic factors were significantly different between esophageal SCC and adenocarcinoma.
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Esophageal cancer (EC) is the 7th most common cause of cancer-related death for male population in the United States [1]. EC has two major histological types: squamous cell carcinoma (SCC) and adenocarcinoma. There has been a general consensus that SCC and adenocarcinoma are two different entities with different etiology, epidemiology, tumor biology, and clinical characteristics [2]. However, most studies still regard these two histology groups as a homogenous cohort in terms of treatment strategies, survival, recurrence pattern, and surveillance [3–7].

For patients undergoing surgery alone, SCC is associated with a worse long-term survival and a higher risk of locoregional recurrence (LRR) than adenocarcinoma [8,9]. Nevertheless, since SCC seems to be more chemoradiosensitive than adenocarcinoma, the results are much more conflicting after neoadjuvant chemoradiotherapy (CRT) followed by surgery in the literature [9–12]. The CROSS trial demonstrated similar LRR rates between the two histology groups in patients who received neoadjuvant CRT, and the FFCD 9901 trial indicated that SCC had similar LRR rates but significantly lower risk of distant recurrences compared with adenocarcinoma [9,10]. In contrast, Koshy et al. reported that SCC had an evidently higher rate of distant failure than adenocarcinoma after trimodality therapy [11]. Therefore, the impact of histology on recurrence patterns and prognosis will vary depending on therapeutic strategies in EC.

Although definitive CRT is the standard care for EC with unresectable disease and an alternative option to surgery [5–7,13], the importance of histology on clinical outcomes has never been well addressed in this setting. Understanding these data is very helpful for defining the optimal treatment strategy and designing future clinical trials. The purpose of this study was to assess the impact of histology on recurrence pattern and timing, survival, and potential prognostic factors for EC patients treated with definitive CRT.

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Patients and methods

Patients and pretreatment evaluation

Consecutive EC patients who underwent definitive CRT with curative intent from the prospectively maintained database at The University of Texas MD Anderson Cancer Center between January 1998 and April 2014 were retrospectively analyzed. All patients successfully completed CRT and had histologically confirmed thoracic esophageal SCC or adenocarcinoma. Patients with prior or concomitant malignancy, M1 disease, those who received esophagectomy within 6 months after CRT, and those with incomplete records were excluded. The institutional review board approved this study and waived the requirement for written informed consent.

All patients had pretreatment evaluation that included standard laboratory tests, physical examination, esophagogastroduodenoscopy (EGD) with endoscopic ultrasound (EUS) and biopsies, chest/abdominal computed tomography (CT), and/or positron emission tomography (PET). Staging was classified according to the 7th TNM staging system of the American Joint Committee on Cancer [14]. Before initiation of treatment, each patient was evaluated by a multidisciplinary team according to institutional practice guidelines.

Treatment

All patients underwent concurrent platinum- or taxane-based chemotherapy during radiotherapy, and a fraction of patients received 2–4 cycles of induction chemotherapy before CRT. Radiation was delivered by using three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), or proton beam therapy (PBT). Gross tumor volume (GTV) was defined as the primary tumor and positive lymph nodes on CT or PET/CT and EUS. Clinical target volume (CTV) was defined as the primary tumor plus 3-cm (for SCC) or 4-cm (for adenocarcinoma) proximal and distal margins and a radial margin of 1.0 cm. The nodal CTV was defined as the nodal GTV plus a 0.5- to 1.0-cm expansion. Supraclavicular lymph nodes were included electively for upper EC based on the discretion of radiation oncologists. Planning target volume was determined by adding a 0.5–1.0 cm margin to the CTV. The typical prescribed dose was 50.4 Gy in 28 fractions, 5 days per week.

Follow-up and recurrences

After completion of CRT, patients were followed every 3 months during the first year, then every 6 months for the next 2 years, and then yearly until 5 years. During follow-up, clinical examinations included blood tests, periodic EGDs with biopsies, thoracoabdominal CT, and PET/CT when available. For patients with PET response evaluation after CRT, PET complete response (CR) was defined as no distant metastasis and the maximum standardized uptake value (SUV_{max}) in the primary region at a physiologic level or distributed in the esophagitis pattern. Recurrences were established on histologic, cytologic, or explicit radiologic proof. LRRs included persistence or recurrence within esophagus or regional lymph nodes, whereas distant recurrences included distant organ metastases, non-regional lymph node metastases (supraclavicular and paraaortic nodes), and peritoneal carcinomatosis. Only the pattern of first recurrence was analyzed and used to classify LRR or distant recurrence. The data were last updated in August 2016.

Statistical analysis

Continuous variables were compared with the Mann–Whitney U test and categorical variables were compared using the Chi-square test or Fisher's exact test. Age, primary tumor length, baseline PET SUV_{max}, and radiation dose were grouped by the median value as a cut-off.

Survival times were defined from the date of diagnosis. Timing of recurrence was calculated from completion of CRT to the first event. Kaplan–Meier method was used to analyze overall survival (OS), recurrence-free survival (RFS), locoregional failure-free survival (LRFFS), and distant metastasis-free survival (DMFS). Log-rank test was used to examine intergroup differences, and Cox proportional hazards regression model was used in multivariate analysis (backward stepwise). Univariate Cox regression model was also used to analyze the intergroup difference for separate site of recurrence. Statistical analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago, IL). $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

We analyzed 590 eligible patients with EC in the study: 182 with SCC (30.8%) and 408 with adenocarcinoma (69.2%). The median age of the whole group was 67 years (range, 20–92 years) and the median length of the primary tumor was 5.0 cm (range, 1.0–20.0 cm). At baseline staging, 517 patients (87.6%) were PET-staged. A total of 191 patients (32.4%) received induction chemotherapy prior to concurrent CRT. IMRT use increased from a rate of 25.1% in 1998–2006 to 61.5% in 2007–2014, and PBT use increased from a rate of 1.2% to 38.5% in the same periods. The median radiation dose was 50.4 Gy (range, 41.4–66.0 Gy) for photon therapy and 50.4 Gy (range, 45.0–63.0 Gy) for PBT, respectively.

Comparisons of the two histology groups are summarized in Table 1. Analysis of patient characteristics revealed no significant intergroup differences in age, performance status, weight loss, or clinical TNM stage. As expected, there were more female patients and more proportion of upper/middle tumors in the SCC group than adenocarcinoma group. Additionally, SCC was more likely to receive higher radiation dose (>50.4 Gy) delivered by 3DCRT, whereas adenocarcinoma was more often to receive induction chemotherapy and lower dose ($\leq$50.4 Gy) delivered by IMRT.

Recurrence pattern

After a median follow-up of 57.7 months for SCC and 58.0 months for adenocarcinoma in patients who remain alive, 103 patients (56.6%) with SCC had recurrences versus 285 patients (69.9%) with adenocarcinoma ($P = 0.002$). A total of 53 patients (29.1%) experienced LRR only, 25 (13.7%) experienced distant failure only, and 25 (13.7%) experienced concurrent LRR and distant recurrences in patients with SCC. In the adenocarcinoma group, 21.8% (89) of patients had LRR only, 31.9% (130) had distant failure only, and 16.2% (66) had concurrent LRR and distant failure. The SCC group demonstrated a comparable LRR rate (42.9% vs. 38.0%, $P = 0.264$) and a significantly lower distant failure rate (27.5% vs. 48.0%, $P < 0.001$) compared with the adenocarcinoma group.

No significant differences were found between the two histology groups in OS ($P = 0.535$; Fig. 1A) or LRFFS ($P = 0.391$; Fig. 1B). However, the SCC group had significantly more favorable RFS ($P = 0.009$; Fig. 1C) and DMFS ($P < 0.001$; Fig. 1D) than did the adenocarcinoma group.

Recurrence timing

For patients who experienced recurrences, the median time to the first recurrence was 5.3 months (interquartile range [IQR],