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Appendiceal goblet cell carcinomatosis treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Background: Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) is a treatment commonly applied to peritoneal surface disease from low-grade mucinous tumors of the appendix. Some centers have extended this therapy to carcinomatosis from more aggressive malignancies. Therefore, we reviewed our experience with CRS/HIPEC for patients with goblet cell carcinomatosis.

Methods: Patients with carcinomatosis from appendiceal primaries with goblet cell features were identified in a prospectively maintained database of 1198 CRS/HIPEC procedures performed between 1991 and 2014. Patient demographics, disease characteristics, morbidity, mortality, and survival were reviewed.

Results: A total of 31 patients with carcinomatosis originating from appendiceal goblet cell tumors underwent CRS/HIPEC during the study period. Patients were generally young (mean age, 53 y) and otherwise healthy (84% without comorbidities) with good performance status (94% Eastern Cooperative Oncology Group 0 or 1). The mean number of visceral resections was 3.5, and complete cytoreduction of macroscopic disease was accomplished in 36%. Major 90-d morbidity and mortality rates were 38.7% and 9.7%, respectively. Median overall survival (OS) for all patients was 18.4 mo. Patients with negative nodes had better survival than those with positive nodes (median OS, 29.2 *versus* 10.2 mo), respectively ($P = 0.002$). Although complete cytoreduction was associated with longer median OS after CRS/HIPEC (R0/R1 28.6 *versus* R2 17.2 mo, $P = 0.47$), the observed difference did not reach statistical significance.

Conclusions: CRS/HIPEC may improve survival in patients with node negative goblet cell carcinomatosis when a complete cytoreduction is achieved. Patients with disease not amenable to complete cytoreduction should not be offered CRS/HIPEC.

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1. Introduction

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) is a viable oncologic treatment option for well-selected patients suffering from carcinomatosis. Although high volume centers have extended this therapy to a variety of primary sites including the ovaries, stomach, colon, and rectum as well as to peritoneal mesothelioma, it is most commonly applied to the peritoneal dissemination of appendiceal tumors [1–5]. Within the subset of appendiceal tumors, however, a spectrum of histologies exist.

Goblet cell carcinomas are rare malignancies that may arise at any location along the gastrointestinal tract, although frequently occur at the appendix. Neuroendocrine tumors of the gastrointestinal tract have been associated with a variety of biologic behaviors, and goblet cell appendiceal carcinomas typically share features of both adenocarcinoma and carcinoids. Because appendiceal goblet cell carcinomas possess a relatively aggressive nature and are capable of early peritoneal seeding, a close examination of the peritoneum has been suggested when these tumors are encountered [6]. Unfortunately, the peritoneal dissemination of appendiceal goblet cell carcinomas is usually a rapidly fatal process with very few long-term survivors listed in the literature.

To better define the impact of CRS/HIPEC as a treatment strategy for appendiceal goblet cell carcinomatosis, we decided to review our experience with patients suffering from this disease. Specifically, we aimed to identify the effects of tumor biology as manifested by nodal involvement and the impact of completion of CRS in patients with goblet cell carcinomatosis undergoing CRS/HIPEC.

2. Methods

2.1. Patients

Using a prospectively maintained database of 1198 CRS/HIPEC procedures performed between 1991 and 2014, we identified patients with carcinomatosis and a final pathologic diagnosis of appendiceal cancer with goblet cell features. We limited our search to tumors originating from the appendix. Neuroendocrine tumors without goblet cell features were not included. In general, patients were highly selected based on their ability to tolerate an aggressive surgical procedure and on the feasibility of obtaining a complete cytoreduction. More specifically, retroperitoneal disease, extraperitoneal disease, unresectable primary, or volume or distribution of disease not amenable to cytoreduction functioned as exclusion criteria. Patients with low volume disease presumably amenable to a complete cytoreduction were taken to surgery upfront if they were referred before receiving systemic chemotherapy. Patients with a larger volume of disease or aggressive features on pathology (i.e., signet ring cells) were referred for chemotherapy first and taken to CRS/HIPEC if their disease seemed resectable at completion. There were no cut offs based on peritoneal carcinomatosis index (PCI).

2.2. Procedures

CRS/HIPEC was performed as has been previously described by our institution [7]. Patients deemed appropriate for the procedure were explored through a generous midline incision. When complete cytoreduction was considered feasible, all involved visceral organs and peritoneal surfaces were resected. The omentum was routinely removed when present. This was followed with HIPEC using the closed-abdominal technique [8]. HIPEC agents included mitomycin C or oxaliplatin. Resections were considered complete, R0/R1, if all gross disease were removed before HIPEC. Incomplete resections (R2) were subdivided based on the diameter of the largest lesions remaining (R2a $\leq$ 5 mm, R2b $>$ 5 mm and $\leq$2 cm, and R2c $>$ 2 cm). R2a resections were not included in the complete cytoreduction group. Morbidity and mortality were graded according to the Clavien-Dindo classification system [9].

2.3. Statistical analyses

Descriptive statistics included frequency and percent for categorical variables and mean and range for continuous variables. Recurrence was only evaluated in patients after an R0 or R1 resection. Survival was estimated with the Kaplan-Meier method and compared using the log-rank test. Overall survival (OS) was measured from the date of CRS/HIPEC (not the date of diagnosis) to the date of death or of last recorded follow-up. Univariate and multivariate analyses were performed using Cox proportional hazard models. Multivariate analysis included all variables from univariate analysis with P values <0.1. Analyses were performed with SAS 9.3 (SAS, Cary, NC) and statistical significance was defined as a P value <0.05.

3. Results

3.1. Patient characteristics

A total of 31 patients with appendiceal goblet cell carcinomatosis underwent CRS/HIPEC during the study period. No patient had more than one CRS/HIPEC procedure. The number of procedures performed increased in each quartile of the study period with 61.3% occurring in the last quartile and 96.8% occurring in the latter half. Patients were relatively young (mean age, 53 y) and generally healthy (84% without comorbidities). Eastern Cooperative Oncology Group performance status was also good with 94% of patients scored 0–1 (Table 1). Lymph node data were available for 28 patients and 60.7% of these had lymph node metastases. Most patients received chemotherapy before HIPEC (21 of 31 or 67.7%), and the most common regimen was folinic acid, 5-fluorouracil, and Oxaliplatin (FOLFOX) with or without Avastin (18 of 21 or 85.7%). The mean length of preoperative chemotherapy was 4.6 mo (range, 1.5–9.5 mo). The agent used at HIPEC was mitomycin C in 26 (83.9%) and oxaliplatin in five patients (16.1%). Only eight patients (25.8%) received systemic chemotherapy after CRS/HIPEC. No patients were lost to follow-up and median follow-up time was 9.9 mo.