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Predictors for local recurrence and distant metastasis of mucinous colorectal adenocarcinoma

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ABSTRACT

Background. Mucinous adenocarcinoma (MA) is a unique subtype of colorectal carcinoma. Although some investigators considered MA a predictor for poor prognosis, predictors for poor clinical outcome of MA were not elucidated. The present study aimed to investigate the predictors for local recurrence and distant metastasis of MA.

Methods. This was a retrospective review of patients with MA who underwent operation with curative intent. Variables included patient and tumor characteristics, TNM stage, investigations, details of surgery, and postoperative outcomes, including local recurrence and distant metastasis. Univariate and multivariate regression analyses were performed to determine the risk factors for local and systemic disease recurrence.

Results. A total of 106 patients (83 male) of a mean age of 51.5 years were included; 62% of patients had colonic tumors, and 38% had rectal tumors; 77% and 58% of colonic and rectal cancers, respectively, were T3–T4 tumors. There were no lymph node metastases in 61% of colonic tumors and 55% of rectal tumors. Local recurrence occurred in 15 patients (14%) and distant metastasis in 9 (9%). Predictors for local recurrence were age (odds ratio [OR]: 1.04; $P = .04$), female sex (OR: 4.5; $P = .01$), rectal tumors (OR: 3.73; $P = .02$), and T4 tumors (OR: 10.9; $P = 0.03$). Predictors for distant metastasis were age (OR: 1.1; $P = .016$), local recurrence (OR: 24.28; $P < .0001$), and T4 tumors (OR: 19.3; $P = .049$).

Conclusion. Patients' age, female sex, and T4 tumors were significant predictors for local recurrence and distant metastasis. Rectal tumors had a greater likelihood for regional recurrence than colonic tumors. Local recurrence was an independent risk factor for distant metastasis.

Introduction

Colorectal cancer (CRC) is one of the most common gastrointestinal cancers, representing the second most common cancer in women and the third most common in men (9% and 10% of all cancers in each sex, respectively).[1] CRC tends to affect men and women equally with a median age at diagnosis of 68 years.[2]

CRC has various pathologic subtypes, the most common of which are adenocarcinomas, particularly adenocarcinoma not otherwise specified (NOS). Mucinous adenocarcinoma is a unique pathologic entity that was first described by Parham in 1923.[3] Mucinous adenocarcinoma constitutes less than 15% of all primary CRCs. The main distinguishing feature of mucinous adenocarcinoma is its mucinous pattern, which involves more than half of the tumor mass on pathologic examination, with abundant extracellular mucin, unlike signet ring carcinoma, which lacks the presence of such features.[4,5]

Mucinous adenocarcinoma has been recognized as a separate entity from adenocarcinoma NOS with clear differences in clinical, pathologic, and molecular characteristics.[6] In contrast to the usual presentation of adenocarcinoma NOS, mucinous tumors usually afflict younger patients, with a predilection to occur in the proximal colon.[7] Mucinous adenocarcinoma also tends to present clinically in a more advanced manner with a poorer prognosis than adenocarcinoma NOS. Furthermore, mucinous adenocarcinoma exhibits greater rates of molecular aberrations, such as microsatellite instability and 12K-ras mutations, and less p53 expression compared with typical colorectal adenocarcinoma.[8]

Mucinous adenocarcinoma was postulated to have a more aggressive behavior than adenocarcinoma NOS. Green et al[9] reported that mucinous rectal carcinomas present at an advanced stage more than nonmucinous carcinomas with substantially worse 5-year survival rates. Similarly, Secco et al[10] studied 39 patients with primary mucinous adenocarcinoma, which accounted for 11% of all

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adenocarcinomas included in their study. The authors noted mucinous tumors to be located commonly in the rectum and sigmoid colon, with 41% of patients having Duke stage C disease. Approximately half of the patients with mucinous pathologic subtypes had tumor recurrence, with a median overall 5-year survival of only 28 months compared with 45 months for adenocarcinomas NOS.

Because of the aggressive behavior of mucinous adenocarcinoma, some investigators[11] recommended extensive lymph node (LN) dissection with more radical excision of the surrounding tissues to avoid the risk of local recurrence that is anticipated to be particularly high with such entity. Others[12,13] attributed the high failure rate in the treatment of advanced-stage mucinous adenocarcinoma to its high affinity to infiltrate more aggressively than nonmucinous adenocarcinoma; hence, in addition to radical surgery and radiotherapy, further therapy addressing the genetic and molecular characteristics of mucinous adenocarcinoma may help improve the prognosis.

Although previous reports emphasized the distinctive clinicopathologic features of mucinous adenocarcinoma and their implication on the therapeutic strategy and prognosis, no designated analysis of the predictors for poor outcome of mucinous tumors was conducted. The present study aimed to elucidate the incidence and clinical and pathologic characteristics of mucinous adenocarcinoma in a subset of Egyptian patients and to investigate the risk factors for local and systemic recurrence of the disease after a curative operative.

Patients and Methods

Study design and setting

This is a retrospective review of a prospective database of patients with mucinous adenocarcinoma who were treated in the general surgery department of Mansoura University Hospitals and Oncology Center of Mansoura University. Patients admitted and treated for mucinous adenocarcinoma between January 2012 and November 2016 were included in the analysis.

Eligibility criteria

The study included adult patients of both sexes who underwent resection with curative intent for mucinous adenocarcinoma. Diagnosis of mucinous adenocarcinoma was based on review of the histopathologic reports of the patients. Mucinous tumors were identified by the presence of intracellular mucin in more than 50% of the tumor specimen with associated extracellular mucin[4] as confirmed by 2 independent pathologists in each report.

We excluded patients with systemic metastases (TNM stage IV) and patients with other pathologic types such as adenocarcinoma, signet ring carcinoma, gastrointestinal stromal tumors, lymphoma, neuroendocrine tumors, and carcinoid tumors. Patients with missing vital data in the records were also excluded.

Diagnosis

Patients were diagnosed by colonoscopy and confirmed via biopsy. To assess the regional extent of the disease and to exclude the presence of liver metastasis, preoperative pelviabdominal computed tomography (CT) with oral and intravenous contrast was performed for patients with colon cancer and pelviabdominal magnetic resonance imaging (MRI) was performed for rectal cancer. Metastatic workups were performed preoperatively on a routine basis to exclude distant metastasis. The seventh pathologic TNM staging system of the American Joint Committee on Cancer was used for preoperative staging of the patients.

Protocol for postoperative follow-up

Patients were followed in the outpatient clinic at 1 and 2 weeks after colectomy surgery, then every month in the first 6 months postoperatively, then every 6 months for 5 years. During follow-up visits, patients were interviewed regarding any complaints or symptoms related to their procedure or any general complaints; in addition, a physical examination was done during each visit. Serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were measured at 3 and 6 months and 1 year postoperatively, and then every 6 months for 4 years. Abdominopelvic CT scanning was done at 6 months and 1 year postoperatively, then on a yearly basis for 4 years. Colonoscopy was performed every year to detect recurrence or new lesions.

Data collection

Three investigators extracted the following information from the electronic records of patients:

- Patients' characteristics as age, sex, and comorbidities'
- Tumor characteristics, including anatomic location, gross appearance, number of harvested LNs, number of metastatic LNs, TNM stage, safety margins, and completeness of total mesorectal excision for rectal cancer;
- Results of investigations performed, including preoperative CEA and CA 19-9 levels, pelviabdominal CT and MRI, bone scans, and metastatic workups;
- Data about receiving and response to neoadjuvant chemoradiotherapy, type of operative procedure performed for each patient, operation time, and perioperative complications; and
- Postoperative outcomes, including local recurrence and distant metastasis, the timing of their occurrence, overall survival, and disease-free survival.

Outcome definitions

The objectives of this report were to learn about the incidence and clinical and pathologic features of mucinous adenocarcinoma in our locality. In addition, we aimed to investigate the predictors for local recurrence and distant metastasis of mucinous adenocarcinoma after resection with curative intent.

Local or regional recurrence of mucinous tumors was defined as "recurrence of the tumor after resection with curative intent either in the anastomosis, tumor bed, mesentery, draining lymphatics, surgical scar, or port sites."[14] Local tumor recurrence was diagnosed by clinical examination, imaging modalities including CT or MRI of the abdomen and pelvis, and biopsies either directly from any malignant nodules at the surgical scar or port sites or CT-guided biopsies of suspicious abdominal or pelvic masses.

Distant metastasis was defined as "the spread of the disease outside the local surgical field to distant organs such as the liver, lungs, bones, or brain."[14] Distant metastasis was detected by the routine metastatic workup (ie, bone scan, abdominal ultrasonography or CT, or chest radiograph/CT) performed postoperatively.

Statistical analysis

Data were analyzed using SPSS Version 21 (IBM Corp, Bristol, UK). Continuous variables were expressed as mean ± standard deviation (SD) or median and normal range and were analyzed by Student *t* test. Categorical variables were expressed as number and percent and were processed by Fisher exact test or χ^2 test.

Analysis of the predictive factors for local tumor recurrence and distant spread was undertaken by a univariate analysis, and then

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