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Postoperative complications do not impact on recurrence and survival after curative resection of gastric cancer☆

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Abstract

Background: We assessed the impact of complications on recurrence and survival after curative gastric cancer resection.
Methods: Patients undergoing R0 resections between 1990 and 2009 were identified in a prospectively maintained database and were categorized by presence of any complication Clavien-Dindo (CD) ≥ II, sepsis or intra-abdominal sepsis. Cox regression analyses to relate complications and clinico-pathological variables to time to recurrence (TTR) and overall survival (OS) were performed.
Results: A total of 271 patients were included with a median follow-up of 149.9 months (range 140.1–159.9). Complications CD ≥ II occurred in 162 (59.8%) patients, sepsis in 66 (22.5%), and intra-abdominal sepsis in 37 (13.6%). Recurrence developed in 88 (32.4%) patients. Independent predictors of short TTR were pTNM stage (IIIB-IIIC vs. IA-IIA) (hazard ratio [HR] = 37.55, 95% confidence interval [CI] 17.57–80.24; $p < 0.001$), D1 lymphadenectomy (HR = 3.14, 95% CI 1.94–5.07; $p < 0.001$), and male gender (HR = 1.65, 95% CI 1.06–2.57; $p = 0.026$). pTNM stage (IIIB–IIIC vs. IA–IIA, HR = 10.28, 95% CI 6.51–16.23; $p < 0.001$), male gender (HR = 1.64, 95% CI 1.17–2.31; $p = 0.005$), age (HR = 1.03, 95% CI 1.02–1.05; $p < 0.001$), and adjuvant therapy (HR = 0.55, 95% CI 0.37–0.83; $p = 0.004$) were identified as independent predictors of OS..
Conclusions: Evidence provided by this study does not support a negative impact of postoperative complications CD ≥ II, sepsis, and intra-abdominal sepsis on the oncologic outcome after curative gastric cancer resection.

Keywords: Gastric cancer; Postoperative complications; Recurrence; Survival

Introduction

Gastrointestinal cancer surgery is associated with high rates of postoperative complications. It has been suggested that these complications may promote tumor recurrence and decrease long-term survival, particularly in colorectal cancer surgery.[1–3] This relationship appears to be stronger for infectious complications.[4] Conflicting results have been reported regarding the association between postoperative complications and poor survival after resection of oesophageal cancer.[5–7] A more consistent relationship, however, has recently been described for gastric cancer resection, mainly in series from Eastern Asia, although differences in classifying or grading complications make these results still unclear.[8–12] It appears plausible that these results can be extrapolated to Western series where the incidence of

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overall and infectious postoperative complications, as well as the percentage of cases with advanced stages (II–III) are higher as compared with Eastern Asia series.[13]

Clinical and experimental data suggest that persistent systemic inflammatory response by infectious complications may promote tumor recurrence and progression after cancer surgery.[14,15] It is worthwhile to assess the impact of septic events (sepsis and intraabdominal sepsis) uniformly classified on the oncologic outcome of patients undergoing curative gastric cancer resection.

The purpose of the present study was to examine the effects of postoperative complications especially those associated with a systemic inflammatory response, on recurrence and long-term survival after curative surgery for gastric cancer.

Methods

Study population

Between January 1990 and December 2009, 315 consecutive patients with gastric adenocarcinoma underwent R0 resection at the Gastrointestinal Surgical Units of Hospital Universitario del Mar and Hospital Clínic, in Barcelona, Spain. A specialized team following similar perioperative protocols over the time frame of the study performed gastric resection with associated lymphadenectomy. Given the time span of patients included in the study, the extent of lymphadenectomy varied but D2 dissection without splenectomy was commonly performed. The Institutional Review and Boards of both participating hospitals approved data collection and analysis.

Clinicopathological data and follow-up status for all operated patients were collected from a prospectively maintained database, which was common to both institutions. Two experienced pathologists (M.I., M.C) re-reviewed all diffuse and mixed type adenocarcinomas to identify signet ring cell (SRC) types, defined according to World Health Organization criteria.[16] Tumors were re-classified according to the seventh UICC/TNM classification system.[17]

In the context of clinical trials carried out during the study period,[18,19] patients with pathological stage (pStage) II/III disease were treated with adjuvant chemotherapy, which consisted of mitomycin C (MMC), 10–20 mg/m^2 i.v. bolus 4 courses (period 1990–1994) or MMC plus Tegafur 500 mg/m^2 p.o daily for 6 months (since 1995 to 2004). After 2004, adjuvant chemoradiation therapy was also indicated in patients with a high number of affected nodes.

Definition of postoperative complications

Complications were categorized into five grades according to the modified Clavien–Dindo (CD) classification.[20] If multiple complications occurred, the higher grade was used. For the purpose of this study, patients with CD $\geq$ II were considered as the "complication group". Additionally, the Comprehensive Complication Index (CCI) was calculated as the sum of all complications that are weighted for their severity.[21] The final formula yields a continuous scale to rank the severity of any combination of complications from 0 to 100 in a single patient.

Perioperative blood transfusion (PBT) was defined as transfusion of allogenic red blood cells from 30 days before surgery until hospital discharge.[22] Indication of blood transfusion was left to the discretion of the treating physician. Sepsis was defined as an infection that had evoked a systemic inflammatory response syndrome (SIRS).[23] Respiratory septic complications included pneumonia (defined as new or progressive infiltrate on chest X-ray, accompanied by fever/leukocytosis or leukopenia and purulent sputum, for which antibiotic treatment was started) and pleural empyema. Wound infection was defined as purulent drainage from the deep or superficial incision. Intraabdominal sepsis origins included anastomotic leakage (defined as full thickness gastrointestinal [GI] defect involving the anastomosis), duodenal stump fistula (bile or purulent drainage from a drain placed close to the duodenal stump), intraabdominal abscess (fluid collection diagnosed by ultrasound [US] or computed tomography [CT] with positive culture), pancreatic fistula (drain output with amylase content), and cholecystitis. Catheter-related bloodstream infection was defined as bacteraemia/fungemia in a patient with an intravascular catheter with at least one positive blood culture obtained from a peripheral vein and no other apparent source for the bloodstream infection except the catheter. Finally, catheter-related urinary tract infection (patient had an indwelling urinary catheter and positive urine culture) was also considered.

Follow-up

All patients were seen at the outpatient clinic by a medical oncologist and a surgeon at 3 months intervals during the first 2 years after operation, and every 6 months thereafter for 3 years. After 5 years, patients were followed every year. At follow-up patients underwent clinical examination, biochemistry with serum tumor markers (CEA and CA 19.9) and abdominal CT alternating with ultrasound examination every 6 months. More specific examinations (upper gastrointestinal endoscopy, laparoscopy, magnetic resonance imaging [MRI], or bone scintigraphy) were performed according to the patient's clinical condition. Histological confirmation of tumor recurrence was sought in all instances. Follow-up was extended to December 2012 ensuring a minimal potential follow-up of 36 months.

Statistical analysis

Data are shown as frequencies and percentages for categorical variables or as median (interquartile range, percentile 25th–75th) for quantitative variables.