Perineural Invasion Independent Prognostic Factors in Patients with Gastric Cancer Undergoing Curative Resection

Fatih Selçukbiricik*, Deniz Tural, Evin Büyükünal, Süheyla Serdengeçti

Abstract

Objective: The prognostic significance of perineural invasion (PNI) in gastric cancer has been previously investigated but not clearly clarified. The objective of our study was to investigate the role of PNI as prognostic factor in patients undergoing curative surgical resection and without distant metastasis in comparison with other clinicopathological factors. Methods: Between 2001 and 2010, 287 cases of gastric adenocarcinoma underwent radical gastrectomy recorded in hospital based registries. PNI was assessed as positive when cancer cells were seen in the perinerium or neural fascicles intramurally. Categorical and continuous variables were summarized using descriptive statistics and compared using chi-square and Mann-Whitney U tests, respectively. Cancer related survival rates were estimated by the Kaplan-Meier method. Results: PNI was positive in 211 of 287 cancers (73%), with a positive relation to lymph node metastases and advanced stage (p=0.0001, p=0.0001, respectively), mural invasion, and lymphatic and blood vessel invasion (p=0.0001, p=0.0001, respectively). The median survival of the PNI positive patients was significantly shorter than that of their PNI negative counterparts (24.1 versus 38.2 months, p=0.008). In the multivariate analysis, we detected PNI was an independent prognostic factor (p=0.025, HR=1.21, 95% CI 1.08-2.3) along with classical clinicopathological variables such as lymph node involvement (p=0.001), pT stage (p=0.03), and LVI (p=0.017), but not age, gender, tumour localization, stage, histologic type, and surgery procedure. Conclusions: PNI positivity in gastric cancers was related mural invasion, lymph node involvement, advanced stage and lymphatic and venous blood vessels. The presence of PNI appeared as an independent prognostic factor on survival on multivariate analysis, not influenced by tumor stage, lymph node metastases and other classical factors.

Keywords: Perineural invasion - gastric cancer - prognostic factors

Asian Pacific J Cancer Prev, 13, 3149-3152

Introduction

Currently, gastric cancer is the second leading cause of cancer related death in both men and women (Ferlay et al., 2010; Ferlay, 2010). Incidence rates for gastric cancer have declined worldwide (Parkin, 1993; 2004; Bertuccio et al., 2009; Jemal et al., 2009). However, gastric cancer is the fourth most commonly diagnosed cancer (Ferlay et al., 2010). Gastric cancer prognosis has not improved much, and the five-year survival rates of all patients with gastric cancer have changed only slight over the past decades but remain under 20 percent (Starzyńska, 2007).

Total and subtotal gastrectomy with lymph node dissection is the cornerstone treatment of gastric cancer (Yokota et al., 2003). However, after curative resection if determined high risk for poor prognosis, these patients get benefits from additional adjuvant treatment (Macdonald et al., 2001).

Perineural invasion (PNI) is the infiltration of perineurium or neural fascicles around a tumor by cancer cells. It also has been called neurotropic carcinomatous spread and perineural spread. PNI is a distinct pathologic entity that can be observed in the absence of lymphatic or vascular invasion. PNI is often seen in carcinomas head and neck, prostate, pancreas and biliary tract but is relatively rare is rectal carcinomas and it is reported to be crucial route for the local spread of tumour associated with poor prognosis in head and neck, prostate, pancreas and biliary tract cancers (Carter et al., 1983; Ueno, 2001). However, the prognostic importance of PNI in gastric cancer has been evaluated in a few studies. Prior some trials, PNI have not been provided any additional information to the classical prognostic factors (Tanaka et al., 1994; Duraker, 2003). But recently two studies, Bilici et al. and Tianhang et al. demonstrated that incidence of PNI in gastric cancer was high and PNI independent prognostic factor worse effect on survival (Tianhang et al., 2008; Bilici et al., 2010).

The objective of our study was to investigate the role of PNI as prognostic factor in patients who underwent curative surgical resection and without distant metastasis at gastric cancer and determined association of PNI with the other clinicopathological factors. A better understanding of PNI in gastric cancer may lend insight at tumor recurrence and metastasis and may be improved staging strategies and new treatment modality.
Materials and Methods

Patients

Gastric cancer patients treated at Istanbul University Cerrahpasa Medical School between 2001-2010 were retrospectively evaluated. Cancer was coded according to the International Classification of Disease for Oncology, 3rd edition (ICD-O-3) (A. Fritz et al., 2000). We included only gastric adenocarcinoma in this study. Patients were included when adenocarcinoma of stomach underwent either partial gastrectomy or total gastrectomy with regional lymph node dissection as curative intent and survival data were available. Chemotherapy concurrent with postoperative radiotherapy (RT) was protracted 5-fluouracil (5FU) infusion. Five cycles of adjuvant bolus 5FU (425 mg/m²/day) and leucovorin (20 mg/m²/ day) as Mayo regimen on days 1-5 every 28 days were administered after surgery, as indicated. Bolus 5FU and leucovorin was employed on days 1-4 every 28 days concurrent with postoperative RT in the 2nd and 3rd cycles of planned 5 cycles of adjuvant chemotherapy (Macdonald et al., 2001). Patients were not included in the study if they had metastatic disease, positive surgical margins, poor performance status (Eastern Cooperative Oncology Group (ECOG) >2), inadequate renal and hepatic function, other second primary cancers. Those not undergoing surgery for various reasons were also excluded.

Clinic information about age, gender, operation type, tumor location, histopathology, tumor stage, lymph node involvement, mural invasion, perineural invasion, lymphatic and blood vessel invasion, resection margin, treatment and outcome were obtain from patients chart. Gastric adenocarcinoma stage was determined according to seventh edition of the International Union Against Cancer guidelines (Wittekind, 2010). We divided cases two sub group based of anatomic localization of stomach. Group 1; proximal stomach (cardia) and group 2: noncardia (gastric antrum, pylorus, lesser curvature and greater curvature of stomach) (Devesa, 1998).

Histopathological evaluation

Surgical specimens were fixed in 10% formalin and embedded in paraffin. Paraffin-embedded blocks were cut into 5-µm-thick sections, and stained with haematoxylin and eosin. PNI was assessed as positive when cancer cells were seen in the perineurin or neural fascicles intramurally. Cases were divided based on histopathological subtype into: group 1, intestinal gastric cancer; group 2, diffuse gastric cancer; and group 3; mixed adenocarcinoma (Laurén, 1965).

Follow-up

Patients were followed every 3 months for 2 years and every 6 months between 2-5 years and annually thereafter. Evaluation included clinical examination, complete blood count, serum chemistries, thorax and abdomen CT and endoscopy as indicated. Recurrence was diagnosed on the basis of imaging findings. Pathologic confirmation was obtained in selected cases. Follow-up data of patients were collected by telephoning the patients and their relatives or outpatients service.

Results

Between 2001 and 2010, there were 287 cases of gastric adenocarcinoma that had undergone radical gastrectomy recorded in hospital based registries. The median age at diagnosis was 59 years (range=23-89) and 75(26%) female, 212(74%) male; lymph node metastases (68%), pT3 (52%) and stage III (58%).

Patients PNI was positive in 211 of 287 patients (73%). There was no association between PNI positivity and gender, age, stomach localization, histologic type and surgery procedure type. Tumors with PNI positive had more lymph node metastases and advanced stage (p=0.0001, p=0.0001, respectively). The positivity of PNI was also significantly increased in mural invasion, lymphatic and blood vessel invasion (p=0.0001, p=0.0001, respectively). The details of between PNI and clinicopathological factors are shown in Table 1.

Overall survival analyses were performed in 287 patients. The median survival of the PNI positive patients was significantly shorter than that of the PNI negative patients (24.1 versus 38.2 months, p=0.008, Figure 1). The positivity of PNI was closely associated with worse OS of patients who underwent curative resection in gastric adenocarcinoma in the univariate analysis (long-rank, p=0.008). Therefore, we performed multivariate analysis with Cox proportional hazard model in order to further evaluate the prognostic significance of PNI and other clinicopathological factors.
In the multivariate analysis, we detected PNI was an independent prognostic factor (p=0.025 HR=1.21, 95% CI 1.08-2.3) as were classical clinicopathological variable such as lymph node involvement (p=0.001), pT stage (p=0.03), LVI (p=0.017). Other hand, age, gender, tumour localization, stage, histologic type, surgery procedure, analyses we was not determined effect on survival in multivariate analysis.

Discussion

PNI was demonstrated as a crucial route of spread for pancreatic and biliary tract and colorectal cancer. PNI has been recognized in many series as prevalent pathologic features of colorectal biliary and is reported in up to 33% of these tumors at the time resection (Knudsen et al., 1983; Ueno, 2001). In otherwise PNI rate were much higher in pancreatic cancer (70-100%) and 75-85% in biliary tract cancer (Nagakawa et al., 1993; Seki et al., 1993). It is reported to be crucial route for the local spread of tumour associated with poor prognosis in head and neck, prostate, pancreas and biliary tract cancers (Carter et al., 1983; Ueno, 2001).

In our studies, we investigated the effect of PNI on survival in patients with gastric carcinoma who underwent curative resection. In this study, we stained specimen with haematoxylin and eosin to determine the positivity of PNI in patients with gastric adenocarcinoma and we found that 211 of the 287 patients (73%) were PNI. We found that there was a statistical different with respect to Overall survival between PNI positive and negative patients. The median OS for patients with PNI positive and negative patients was 24.1 and 38.2 months (p=0.008, log-rank) respectively. At multivariate analysis, the presence of PNI appeared as an independent prognostic factor on survival. It can be an independent prognostic factor which is not influenced by tumor stage, lymph node metastases and other classical factors.

Prior studies detected PNI related with the rate of large tumours and lymph node metastases, advanced stage, lymph and blood vessel invasion (22-26). In current study, PNI positivity, we found 15%, 60%, 80%, and 81% in pT1, pT2, pT3, pT4 respectively. It is increased when mural invasion increased (p=0.0001). In addition, we found as...
same priors studies, lymph node involvement, advanced stage, lymph and vessel blood invasion were significant higher in the PNI positive than negative patients.

The pathogenesis of PNI has not yet been sufficiently clarified. Nagakawa et al reported that the high incidence of PNI in pancreas and biliary tract cancer was related to rich autonomic innervation of these organs. They think that cancer cell infiltrated the perineural space directly through the perineurum from the cancer nest. It is thought that cancer cells could invade into the perineurum and infiltrate the perineural space and interstitium with little resistance but they also indicated that the pathogenesis of entry of cancer cells into the nerves remains unelucidated (Nagakawa et al., 1993). Seki et al found that PNI which is frequently determined in bile duct cancer. It was not dependent only anatomical specificity, but also special ability of the cancer cell to recognize neural tissue easily by secreting the neural cell adhesion molecule (NCAM). They also demonstrated a significant correlation between PNI and lymphatic and venous blood vessels in bile duct cancer and they suggested that PNI of cancer cells occurred not only as result of direct infiltration, but also by invading the lymphatic vessels and veins around the nerves (Seki et al., 1993). However, the perineural space is now usually accepted as an independent route of cancer spread because it is anatomical different the lymphatic canals (Takahashi et al., 1997). In current study, we indicated that the PNI positivity was closely related to lymphatic and vessel bloods invasion. But, PNI positivity independent variable which is not influenced lymphatic and venous bloods vessels effect on survival.

In conclusion, our study demonstrated PNI positivity high percent with patients gastric cancer who underwent curative resection. PNI positivity was related mural invasion, lymph nodal involvement, advanced stage and lymphatic and venous blood vessels. The presence of PNI appeared as an independent prognostic factor on survival at multivariate analysis. It can be an independent prognostic factor which is not influenced by tumor stage, lymph node metastases and other classical factors. A better understanding of PNI in gastric cancer may lend insight at tumor recurrence and metastasis and may be improved staging strategies and new treatment modality.

References


