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Impact of super-extended lymphadenectomy on relapse in advanced gastric cancer☆

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Abstract

Background: In gastric cancer the incidence of loco-regional recurrences decreases when lymphadenectomy is expanded from D1 to D2. The present study aimed at evaluating whether the pattern of recurrence in advanced gastric cancer (AGC) is further modified when lymphadenectomy is expanded from D2 to D3.

Methods: 568 patients undergoing curative gastrectomy for AGC (274 D2 and 294 D3) were considered; none of them received preoperative chemotherapy. MantelHaenszel test of homogeneity was used to verify whether the relation between extension of lymphadenectomy and recurrence varied as a function of each risk factor considered. The impact of D2 and D3 on relapse was further investigated by multivariable logistic regression model.

Results: Cumulative incidence of recurrence did not significantly differ after D2 and after D3 in the whole series (45.3% vs 46.3%; $p = 0.866$). However, the association between recurrence and extension of lymphadenectomy was significantly affected by histology (Mantel–Haenszel test of homogeneity: $p = 0.007$). The risk of recurrence was higher after D3 than after D2 (45.1% vs 35.3%) in the intestinal histotype while the pattern was reversed in the mixed/diffuse histotype (48.3% vs 61.5%). This pattern was confirmed in multivariable logistic regression: the interaction between histology and extension of lymphadenectomy was highly significant ($p = 0.004$). In particular, cumulative incidence of locoregional recurrences was higher in the diffuse histotype after D2, while being higher in the intestinal histotype after D3.

Conclusions: D3 reverses the negative impact of diffuse histotype on relapses, especially on locoregional recurrences. Therefore D3 could be considered a valid therapeutic option in histotype-oriented tailored treatment of AGC.

Keywords: Gastric cancer; Super-extended (D3) lymphadenectomy; Lauren's diffuse; Loco-regional recurrences

Introduction

Despite the declining incidence, gastric cancer is still the third cause of cancer related death worldwide.[1] Radical surgery is the only chance of cure for gastric cancer patients, however the rate of relapse even after a curative resection remains high.[2–4]

Western authors have debated for a long time whether the extension of lymphadenectomy could affect the incidence of recurrences and survival in gastric cancer patients. Interestingly, the Dutch trial, after a median follow-up of 15 years, showed that D2 lymphadenectomy was associated with an improved disease-related survival and a lower locoregional recurrence rate as compared to D1.[5] Hence it

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could be speculated that extending lymphadenectomy beyond D2 dissection could further improve local control of advanced gastric tumours.

The Japanese JCOG 9501 trial concluded that routinely adding para-aortic dissection to D2 lymphadenectomy does not affect the rate and the pattern of recurrences in advanced gastric cancer.[6] Of note, in the Japanese trial D2 lymphadenectomy, for tumours located in the lower third of the stomach, included also dissection of retro-pancreatic nodes (No. 13) and nodes along the superior mesenteric vein (No. 14v),[7] which are currently not comprised in the standard D2 dissection.[8]

According to the results of the JCOG 9501 trial, we believe that lymphadenectomy should not be routinely extended beyond D2 in patients with advanced gastric cancer. Nevertheless we hypothesized that D3 dissection could be useful in subgroups of patients[9,10] regardless of clinical positivity of para-aortic nodes, as also suggested by the rather high 5-year survival (18.2%) reported in the Japanese trial[8] in patients with pathologically positive para-aortic nodes after a prophylactic PAN dissection. Hence further investigations are necessary before definitely abandoning D3 lymphadenectomy. Moreover, it has been clearly shown that in high volumes Western centres, D3 lymphadenectomy can be performed without increasing postoperative morbidity and mortality.[9,11–14]

The present study aimed at evaluating the impact of super-extended D3 lymphadenectomy on overall and specific recurrences in a series of advanced gastric cancer patients. For this purpose, the GIRCG (Italian Research Group for Gastric Cancer) database was retrospectively reviewed. As the pattern of recurrence is affected by histotype, with peritoneal relapse being more common in diffuse tumours,[15] both the whole series and subgroups of patients were examined, to evaluate whether D3 dissection could be useful in specific subsets when compared with D2.

Patients and methods

D3 lymphadenectomy has been routinely performed in two GIRCG centres, Verona and Siena, since the early Nineties. The series from Verona was operated on from January 1992 to May 2011, the series from Siena from January 1994 to June 2011, and the two series comprised 791 subjects altogether.

Nineteen subjects with Bormann IV tumour were excluded as well as 2 subjects with neuroendocrine tumours and 75 subjects with early gastric cancer. Among the remaining 695 patients, 127 had non-curative resection: the proportion of R1 resection was similar in the D2 (39/350 = 11.1%) and D3 groups (36/345 = 10.4%), while the proportion of R2 resection was remarkably higher in the D2 group (37/350 = 10.6% vs 15/345 = 4.3%) ($p = 0.007$). After excluding non-curative resections, 568 subjects (312 from Verona, 256 from Siena) were left for the analysis. Of these 274 underwent D2 lymphadenectomy and 294 D3 lymphadenectomy.

Postoperative deaths, defined as deaths occurred during the hospital stay, were included in our analysis.

D2 and D3 lymphadenectomies were performed according to the Japanese Classification of Gastric Carcinoma – 2nd English Edition.[16] Tumour invasion (pT) and lymph node status (pN) followed the UICC pathological tumour node metastasis (pTNM) criteria, 7th edition,[17] while histological type was classified as intestinal or mixed/diffuse according to Lauren's classification.[18] Nearly all patients (539/565 = 95.4%) could be adequately staged, as they had at least 15 lymph nodes retrieved. None of the patients received preoperative chemotherapy.

Patients were generally followed-up regularly after hospital discharge. Blood tests including CEA and CA19-9 levels and chest/abdomen CT-scan were evaluated every six months for the first 5 years after the operation then once a year for the following 5 years. Upper GI endoscopy was performed once a year for 10 years after the operation. In this series patients were followed-up till December 2011. Median follow-up in surviving patients was 89 months (range 7–240).

The pattern of recurrence was classified as locoregional, peritoneal or distant based on the findings of examinations or reoperation. When multiple recurrences had occurred, each of them was separately considered. Recurrences diagnosed in other hospitals, referred by other physicians or by the patient but lacking documentation or description, were defined as unknown.

Statistical analysis

Significance of differences in the proportion of relapses between different lymphadenectomy and different clinical and pathological groups was evaluated by Fisher's exact test. Mantel–Haenszel test of homogeneity was used to verify whether the relation between extension of lymphadenectomy and relapse varied as a function of each risk factor considered. The impact of D2 and D3 on relapse was further investigated by multivariable logistic regression model, controlling for centre, sex, age, site, histology, T and N status. Results were synthesized through the odds ratios, and p values were computed by the LR test. The interaction between extension of lymphadenectomy and each potential confounder was also tested. The statistical analysis was performed using STATA software, release 12 (StataCorp, College Station, TX, USA).

Results

Main demographic and clinico-pathological characteristics of the present series are shown in Table 1. Sixty-two percent of patients were male, and mean age ±SD was 66.4 ± 11.7 years, ranging from 24 to 92 years. D2 was the procedure of choice among patients aged 75 years and over and in cancer arising from the antrum, while D3