Over-D1 dissection may question the value of radiotherapy as a part of an adjuvant programme in high-risk radically resected gastric cancer patients

The aim of our analysis was to assess retrospectively the effect on local relapse, overall survival (OS) and disease-free survival (DFS) of a limited or an extended lymphadenectomy in radically resected gastric cancer patients. This study was performed in order to identify a subgroup of patients possibly not benefiting from a therapeutic approach such as chemoradiation therapy. We divided our patients into two groups according to lymphadenectomy type: group A for limited (<25 resected lymph nodes) and group B for extended (>25 resected lymph nodes) lymph nodes resection. A total of 418 patients were analysed: tumour stage at diagnosis was pT2–3 pN1–3 M0 in 339 patients and pT3 N0 M0 in 79 patients. Median age at diagnosis was 68 years (range 30–92 years). A total of 306 patients (73.2%) were in group A and 112 (26.8%) in group B. The median survival time (OS) for patients in groups A and B was 58.8 and 84.8 months, respectively (P = 0.0371); median DFS was 28.8 months in group A and 59.9 months in group B (P = 0.0027). At multivariate analysis, extension within the gastric wall, nodal involvement and the number of resected lymph nodes appeared to affect both OS and DFS. An inadequate lymph nodes resection can affect survival and result in a higher incidence of local relapse, making the latter group of patients optimal candidates for adjuvant chemoradiation.

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Although in the last few years the overall incidence of gastric cancer has gradually decreased worldwide, it remains second only to that of lung cancer, with an estimated 755,000 new cases diagnosed annually around the world (Jemal et al., 2002). Although many advances have been made in the diagnosis and treatment of gastric cancer, the global outcome for patients diagnosed with this disease is still disappointing with a 5-year survival rate not exceeding 30% of all cases in Western Countries (Bouvier et al., 2002; Nitti et al., 2003).

In operable gastric cancer, both the extent of surgery and the value of adjuvant treatment remain matter of scientific debate, with surgery still representing the cornerstone of any curative procedure (van de Velde and Peeters, 2003; Hohenberger and Gretschel, 2003). Nevertheless, controversy still exists about the adequate extent of lymphadenectomy, which may be limited to perigastric lymph nodes (D1 dissection) or may include removal of the lymphatic chains along the celiac axis, the common hepatic and splenic artery and the hilus of the spleen (D2 dissection) (Kim and Karpeh, 2002; Alberts et al., 2003; Nitti et al., 2003).

Although a D2 dissection is the generally accepted surgical procedure in Japan, the debate about the benefits of D1 vs D2 lymph nodes dissection is still ongoing (Bonenkamp et al., 1999; Cuschieri et al., 1999; Davis and Sano, 2001; Lewis et al., 2002; Reis et al., 2002; Sierra et al., 2003).

More recently, a general agreement has been achieved about a so-called over-D1 lymphadenectomy (D1 dissection and retrieval of at least 25 nodes) on the basis of the finding that the probability of accurate assessment of lymph node status increases with the number of nodes resected, with a plateau reached at 20–25 nodes (Marubini et al., 2002).

Although this recommendation addresses to the principle that lymph nodes are regarded as indicators rather than governors of disease, several clinical data also indicated that a lymph nodes resection including more than 25 lymph nodes could have a major impact on the global outcome of patients who underwent apparent radical surgery for gastric cancer (Siewert et al., 1998; Marubini et al., 2002). It has been suggested that this improvement could be mainly due to a reduction in local recurrences (Kim and Karpeh, 2002).

Furthermore, it has been recently reported that a chemoradiotherapy adjuvant approach may improve the outcome of
radically resected gastric cancer by lowering the incidence of local relapse (Macdonald et al., 2001).

The aim of our analysis was to assess retrospectively the possible effects on local relapse, and consequently on overall survival (OS) and disease-free survival (DFS), of limited or extended lymphadenectomy in a homogeneous group of radically resected gastric cancer patients. This analysis was performed in order to identify a subgroup of patients not likely to benefit from a toxic therapeutic approach such as chemoradiation therapy.

**PATIENTS AND METHODS**

**Patients selection**

The study population was selected from a central database that includes 765 patients with gastric cancer operated in four different institutions.

At the end of each surgical resection, all nodes were dissected from the specimen by a member of the surgical team. Classification of the N-factor was made according to the numeric system introduced by the fifth TNM (N1: metastases in 1–6 regional lymph nodes; N2: metastases in 7–15 regional lymph nodes; N3: metastases in more than 15 regional lymph nodes) (Sobin and Wittekind, 1997).

A total of 418 patients were eligible for our analysis: 339 patients with pT2–3 pN1–3 M0 (tumour invading muscularis or serosa (T2–3), lymph node metastasis in one to more than 15 regional lymph nodes (N1–3), no distant metastasis (M0)) and 79 patients with pT3 N0 M0.

Our analysis was limited to pT3N0, pT2–3N + tumours since they either represent the largest group of patients candidates to radical surgery and those in which an adjuvant therapy may have a role in improving prognosis.

A dissection of <25 or more than 25 lymph nodes was, respectively, classified as limited or extended lymphadenectomy. A cutoff of 25 resected lymph nodes has been arbitrarily chosen according to data reported by Marubini et al. (2002), Siewert et al. (1998) and Wagner et al. (1991). Therefore, we divided our patients into two groups: group A for limited and group B for extended lymph nodes resection. All surgical centres involved presented comparable characteristics for the number of gastric cancer patients seen and the number of surgical procedures performed per year. All surgeons involved had the same scientific background and training.

Follow-up of both groups occurred at 3 months intervals for 2 years, then at 6 months intervals for 3 years and yearly thereafter. Follow-up consisted of physical examination, a complete blood count, chest radiography and CT scanning as clinically indicated. The site and date of first relapse and the date of death were recorded.

**Data management and statistical analysis**

Statistical analysis was performed with SAS software version 8.2 for Windows (SAS Institute Inc., Cary, NC, USA).

The association between categorical variables was estimated by \( \chi^2 \) test.

Survival distribution was estimated by the Kaplan–Meier method (Kaplan and Meier, 1958). Significant differences in probability of relapsing between the strata were evaluated by log-rank test.

Cox multiple regression analysis was used to assess the role of lymphadenectomy as prognostic factor adjusted for those variables significant at univariate analysis (Cox, 1972).

Hazard ratios and 95% confidence intervals were estimated from regression coefficients. A significant level of 0.05 was chosen to assess the statistical significance.

For statistical analysis, OS and DFS were defined, respectively, as the interval between radical surgery and death or last follow-up visit and as the interval between radical surgery and clinical progression or death or last follow-up visit if not progressed.

**RESULTS**

A total of 418 patients were eligible for our analysis: 339 patients with pT2–3 pN1–3 M0 and 79 patients with pT3 N0 M0. A total of 249 patients were males (59.6%) and 169 females (40.4%), and median age at diagnosis was 68 years (range 30–92). A total gastrectomy was performed in 249 patients (59.6%), whereas the remaining patients underwent a subtotal resection of the stomach.

A total of 306 patients (73.2%) received a limited and 112 (26.8%) an extended lymph nodes dissection. In all, 210 patients (50.2%) were classified as N1, 98 (23.5%) as N2, 31 (7.4%) as N3 and 79 (18.9%) as N0. In the whole group, a median of 18 (range 0–68) lymph nodes were resected. A total of 66 patients (15.8%) had a pT2 and 352 (84.2%) had a pT3 gastric cancer (Table 1).

With a median follow-up of 25 months (range 1–130 months), we recorded information on the site of the first relapse and these sites were categorised as local or distant (Table 2). Local recurrence occurred in 23% of cases with <25 lymph nodes resected and in 4.7% of those with >25 lymph nodes resected (\( P = 0.0001 \)); however, 37% of those with <25 lymph nodes resected and 24.8% of those with >25 lymph nodes resected had distant relapses (\( P = 0.12 \)).

The median DFS for patients in groups A and B was, respectively, 28.8 and 59.9 months (\( P = 0.0027 \)) (Figure 1). At multivariate analysis, extended lymph node dissection appeared an independent prognostic factor for DFS (HR = 0.52, CI 0.36–0.74, \( P = 0.0003 \)), which was also influenced by extension within the gastric wall (pT2 vs pT3; HR = 0.41, CI 0.26–0.63, \( P = 0.0001 \)) and nodal involvement (N0 vs N+; HR = 0.33, CI 0.21–0.52, \( P = 0.0001 \)).

The extension of lymphadenectomy also resulted determinant in median survival time (OS) with an OS of 58.8 months for patients

**Table 1** Patients characteristics

|       | Whole group | Group A (%) | Group B (%) |
|-------|-------------|-------------|-------------|
| Number | 418         | 306 (73.2)  | 112 (26.7)  |
| Age (range) | 68 (30–92) | 68 (30–92) | 67 (33–87) |
| Sex     | Male        | 249 (60.6)  | 189 (58.2)  | 60 (53.6) |
|         | Female      | 169 (39.4)  | 117 (41.8)  | 52 (46.4) |
| Gastrectomy | Total     | 249 (59.7)  | 155 (49.3)  | 94 (84)  |
|         | Subtotal    | 168         | 151 (49.3)  | 18 (16)  |
| pT stage | pT2        | 66 (16.0)   | 53 (17.3)   | 13 (11.6) |
|         | pT3        | 352         | 253 (82.7)  | 99 (88.4) |
| pN stage | pN0        | 79 (18.9)   | 59 (19.3)   | 20 (17.9) |
|         | pN1        | 210         | 165 (53.9)  | 45 (40.2) |
|         | pN2        | 98          | 73 (23.9)   | 25 (22.3) |
|         | pN3        | 31          | 9 (2.9)     | 22 (19.6) |

**Table 2** Local and distant relapse

| Resected lymph nodes | Patients | Local relapse (%) | Distant relapse (%) |
|----------------------|---------|-------------------|---------------------|
| <25                  | 306     | 71 (23%)          | 115 (37%)           |
| >25                  | 112     | 5 (4.7%)          | 28 (24.8%)          |
| P-value              | 0.0001  |                   | 0.12                |
in group A and 84.8 months for patients in group B \( (P = 0.0371) \) (Figure 2).

At multivariate analysis, three variables seemed to influence OS: extension within the gastric wall (pT2 vs pT3; HR = 0.47, CI 0.29 – 0.76, \( P = 0.002 \)), nodal involvement (N0 vs N+; HR = 0.46, CI 0.29 – 0.74, \( P = 0.0015 \)) and the number of resected lymph nodes (\( > 25 \) vs \( < 25 \); HR = 0.59, CI 0.39 – 0.89, \( P = 0.012 \)).

These results were confirmed in subgroups analysis, separately considering N-positive and N-negative patients. In fact, among N-positive patients, OS was 51.3 months for those who received limited lymphadenectomy and 84.8 months for those who received extended lymphadenectomy \( (P = 0.0316) \).

Also, DFS appeared to be influenced by the extension of lymphadenectomy in this latter group of patients, as it was 22.4 months for patients who underwent limited lymphadenectomy and 56.6 months for patients who underwent extended lymphadenectomy \( (P = 0.0036) \).

In N-negative patients, DFS was progressively affected by a progressively more extended lymph nodes dissection: at a follow-up of 25 months (range 1 – 130 months), the DFS of patients with 0 – 6 and 7 – 15 resected lymph nodes was, respectively, 23 and 30 months, while it was not reached for patients with 16 – 22 resected lymph nodes. The difference between the four survival curves was statistically significant \( (P = 0.0067) \) (Figure 3). Similar results were observed for OS: for patients with 0 – 6 and 7 – 15 resected lymph nodes, OS was, respectively, 24 and 76 months, while OS was not reached for patients with 16 – 22 and with more than 22 resected lymph nodes \( (P = 0.0032) \) (Figure 4).

**DISCUSSION**

One of the main reasons for disease progression in apparently radically resected gastric cancer patients is represented by the frequent occurrence of locoregional relapse (Macdonald et al, 2001; Gunderson, 2002; Park et al, 2003). This high incidence of local relapse provided the rationale for the INT-0116 trial (Macdonald et al, 2001). In fact, this trial showed that a chemoradiotherapy adjuvant approach was able to improve prognosis mainly by lowering the incidence of local relapse (from...
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