

Gastric cancer : the french survey

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Abstract

Presentation of a multicentric retrospective french study concerning 4 655 cases of gastric cancer operated between 1980 and 1996. The mean age was 67,4 years old with a male predominance of 63,1%. Pains was the predominant presenting symptom (60%) followed by alteration of the general condition (44%) and anaemia (20%). 35,5% of tumors were of distal, 18,8% of middle and 18,6% of proximal localisation. As regard cancer stages, 40% were of stage I-II and 60% of stages III-IV. Subtotal gastrectomy was realised in 44%, total radical gastrectomy in 42,1% and other surgical procedures in 14% of cases (proximal gastric resection or atypical resection). D1 lymphadenectomy was associated in 58,4% and D2 in 41,6%. Morbidity was of 23% and mortality of 11,9% which passed from 19% during the first (1980,-85) to 8% in the last interval of time (1990,-96). The 5 years survival was 41% in case of gastric resection. In univariate analysis the 5 years relative survival was better in female patients (44% at 5 years), in patients younger than 50 years old (46%), when pain was the only clinical symptom (52,7%), in middle and distal third localisation (47%), in case of subtotal distal resection (47%) and in less advanced stages (79% at 5 years for stage I cancer). In multivariate analysis the 5 years survival was essentially correlated to the stage of the tumor and no real prognosis improvement was shown during the period of the study. (Acta gastroenterol. belg., 2002, 65, 161-165).

In western Europe, the incidence of gastric cancer have shown a great decline over the last two decades (1), however even with the development of recent therapeutic modalities as intra-operative radiotherapy, chemotherapy, or extensive lymphadenectomy, no real improvement in the prognosis of gastric cancer was seen (2). Analysis of great series allow to clarify several aspects of this disease ; in this aim we report the results of a large French multicentric study concerning operated gastric cancer excluding cancer of the cardia.

Patients and methods

Our series represent a retrospective multicentric study concerning 4 665 cases of gastric cancer operated in 67 french centers : universities, regionals and privates establishments, between 1980 and 1996. This study was supported by the French Association of Surgery (A.F.C.). Three interval of times were distinguished over the whole period of the study : 1980-85, 1986-1989 and 1990-1996

Statistical Analysis

Comparisons of distributions in frequency tables were assessed with the chisquare test. Multivariate

analysis of categorical data was performed with a polychotomous stepwise logistic regression so as for categorical variables with two values, stepwise logistic regression was performed. The value of (p) used to control entry and removal of items in the model was 0,10. Variables selectionned for the multivariate analysis should have a $p < 0,20$ in the univariate model. The program used was BMDP (BMDP Statistical software, Inc. Cork). Recurrence rates were calculated by Kaplan-Meier's method for analysis of censored observations, and comparison of curves was realised using Logrank test. Uni- and multivariate analysis of the relative survival was done using a proportional hazard model. Multivariate analysis was performed with an ascendant stepwise approach. When the net mortality rates were not proportional, a separate analysis was made. Results are given with a 95% confidence interval.

Results

A total of 4 655 patients were included in the study : 2 937 male (63,1%) and 1 718 female (36,9%) the sex ratio was of 1,71. The mean age was 67 years old (69,4 in female versus 66,2 in male), the median age was 72 years.

Clinical presentation

Pain was the most common symptom (59,8%) ; in 21,8% of cases pain was associated with alteration of the general condition and in 10,2 % with other symptoms (haemorrhage or anaemia). Alteration of the general condition and anaemia came in 2nd and 3rd position with a prevalence of 43,9% and 20,3% respectively.

Localisation

Distal third cancer was observed in 1 615 cases (35,5%), middle third in 857 (18,8%) and proximal third in 848 cases (18,6%). Distal third cancer was more frequent in females (44%), the prevalence of the two other localisation being less than 20%. In males 30,4% of gastric cancer were of distal third and 23,2% if proximal third localisation. Middle third cancers were more frequent in patients of less than 50 years old. The rate of

Table 1. — Cancer stage in correlation with time

Stage	1980-1985	1986-1990	1991-1996	Total
I A	9,8	13	11,6	11,6
I B	13,8	10,4	11,1	11,5
II	17,2	17,2	17,4	17,3
III A	26	21,5	23,9	23,6
III B	12,7	15,1	16,3	15,1
IV	20,6	22,8	19,7	20,9

localisation have not evolved with time. Cancer of the gastric stump was noted in 262 cases (6,4%); it was more frequent in males (8,5% versus 2,8% in female) and those patients after 50 years old (6,8%).

Staging

59,8% of cases were diagnosed in advanced stages (III,-IV) versus 40,2% in stages I,-II; there was no sex difference in cancer stage distribution. Stages Ia and Ib were more frequently seen associated with distal localisation (29,8% versus 16,9% in proximal ones). Secondary lymph nodes metastasis were observed in 58,9% of cases. The analysis of cancer stage in correlation with time have not shown any difference for a given stage (table I). Well differentiated gastric cancers were observed in 45,6%, with no significant sex difference. It was more frequent in elderly patients: 47,1% beyond 70 versus 34,5% beneath 50 years old.

Particular forms

Superficial gastric cancer represents 11,5% of cases; it was more frequent beneath 50 (16,4%) than from 50,-70 (12,5%) and beyond 70 years old (9,5%). Signet ring cell cancer was seen in 15,5%; it was more frequent in female patients (17,7% versus 14,1% in males) and affected most frequently patients of less than 50 years old (27,1%) versus 16,2%, from 50 to 70 and 12,4% beyond 70.

Surgical treatment

Subtotal gastrectomy was the most common intervention (44%) followed by total gastrectomy (42,1%) and then other surgical procedure: proximal gastrectomy (3,3%), atypical gastric resection (6,3%), isolated gastro-entero-anastomosis (0,8%), and exploratory laparotomy without gastric resection in 3,6% of cases. If we consider the stage of gastric cancer at the time of intervention we found that for stages Ia and Ib, subtotal gastrectomy was realised in 30,8% of cases and total gastrectomy in 19,1%. However for stages III or IV total gastrectomy came first followed by subtotal gastrectomy (63,3% versus 49,4%). An increasing percentage of total gastrectomy have been shown throughout the period of study: it passed from 36,4% in 1980 to 54,8% in 1996 when exploratory laparotomy showed a considerable decline passing from 8,4% to 2,2% over the same period of time. No changes in the percentage of subtotal gastrectomy have been observed.

Associated surgery

It was observed in 598 cases (14,9%): splenectomy was the most frequently associated intervention (49,5%), particularly in proximal (65,3%) rather than distal third gastric cancer (36,2%).

Type of surgery

Surgery was of curative purpose in 63% of cases and was associated with a so called "extensive" lymphadenectomy in 1 763 cases (43,8%); this last kind of lymphadenectomy was more frequently realised during the last period of the study (fig. 1). As regard the extent of lymphadenectomy, 1 941 (58,4%) was of D1 type (non extensive) and 1 383 (41,6%) of D2-D3 types (extensive); the later have shown a steady increase throughout the period of study with a frequency around 30% at 1979,-81 versus more than 60% of all realised lymphadenectomy at 1991,-96 (fig. 2). A marked discordance was observed between the number of removed lymph nodes and the type of realised lymphadenectomy. In fact if we consider that a D1 lymphadenectomy should include at least 15 lymph nodes, 41,7% of them were revealed to be much more extensive, whereas 62,2% of presumed D2,-D3 contained less than the minimum of 25 lymph nodes provided for such type of lymphadenectomy. The quality of lymphadenectomy was not really improved throughout the period of the study: the percentage of lymphadenectomy including more than 25 lymph nodes was of 39,4% between 1980 and 1985 and 34,8% between 1991 and 1996. The mean number of removed lymph nodes was 12,5.

Morbidity

It was 23%: 26,8% for total gastrectomy versus 19,7% for subtotal gastrectomy. As regard the type of lymphadenectomy, 24,6% and 21,3% of the morbidity were associated with D1 and D2- D3 respectively. Splenectomy was shown to increase the rate of post-operative complications from 20% to 27,5% (without splenectomy).

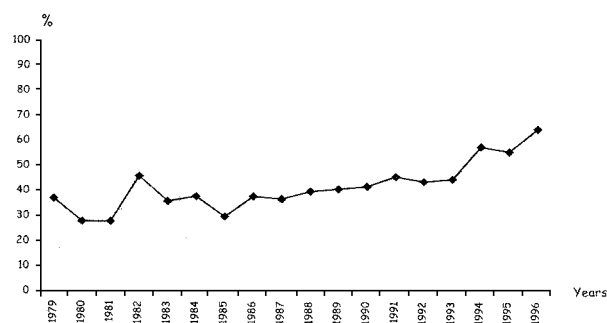


Fig. 1. — Rate of "extensive" lymphadenectomy during the study.

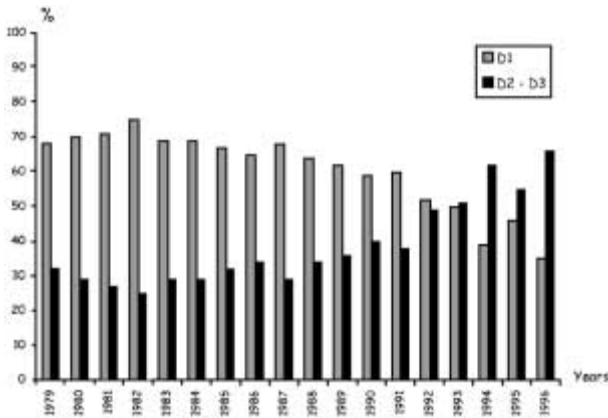


Fig. 2. — Distribution of the type of lymphadenectomy during time.

Mean hospitalisation period

It was longer with, than without post-operative complications : 27,1 and 17,5 days respectively with a mean of 19,6 days.

Mortality

Surgical related mortality was noted 11,9% (471 cases over 3 970 operated patients). It was higher in male (12,9% versus 10% in female) and increased significantly with age : 4,8% in patients less than 50 ; 9% between 50 and 70, and 15,6% in patients of more than 70 years old. Mortality rate have shown a steady decline over the period of study and it passed from 19,2% in 1980 to 8,3% in 1996.

Survival

* Univariate Analysis

- The one and five years survival rates after curative gastric resection was of 67% and 41% respectively, with a higher mortality in the first two years following the intervention.
- Five years survival rate, regardless of the type of operation, was of 34%, 39% and 33% respectively between 1980, -85, 1986, -90 and 1991-96.
- It was higher in female (44% versus 33%) and in younger patients : 46% in patients of less than 50, 38% between 50 and 70, and 33% in those beyond 70 years old ($p = 10^5$). When pain was the only presenting symptom, survival was of 52,7% versus 37% in presence of associated symptoms and 24% with altered general condition ($p = 10^5$).
- Middle and distal third localisations had 47% 5 years survival, whereas upper third 30%, and total gastric involvement 6% ($p = 10^5$).
- After distal subtotal resection, the survival rate was of 47% versus 36% for total gastrectomy ; it was of 54% in curative and 10% in palliative surgery ($p = 0,02$).
- Lymphadenectomy of whatever extent, was associated with a 5 years survival of about 46% versus 30,4%

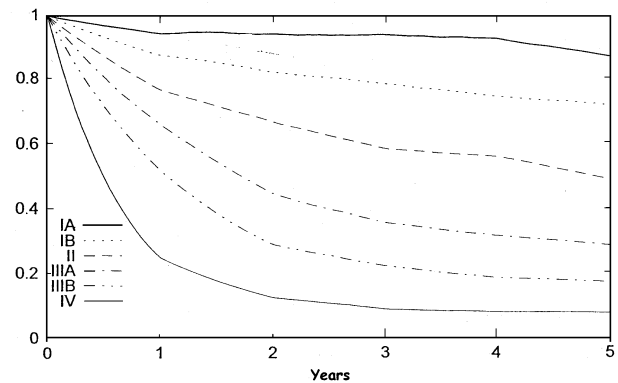


Fig. 3. — Five years survival correlated with the stage

in it's absence ($p = 10^5$) ; the survival was of 39% in case of D1 and 47% in D2,-D3 lymphadenectomy ($p = 0,4$).

- For cancer grades, the 5 years survival was of 48% for well and 32% for poor differentiated cancers ($p = 10^5$) ; it was of 15% in cases of signet ring cell cancer versus 42% for the other types ($p = 10^5$).
- Five years survival was shown to be closely correlated to cancer stage : thus it was of 79% in stages I versus 7% in stage IV gastric cancer ($p = 10^5$) (fig. 3).

* Multivariate Analysis

- For each of the three main localisations : proximal third, distal third the survival was influenced by the age of the patients : it was better between 50 and 70 years old.
- The rate of survival have shown a slight deterioration during the last interval of time of the study after an initial improvement during the second in comparison with the first interval of time.
- The stage of cancer was found to modify the survival rate in all localisations.

Discussion

Gastric cancer localisations as well as stages of the cancer have not shown modifications throughout the three periods of the study. Proximal third cancer was not seen to increase in frequency with an incidence which was quiet similar to that found in other series (3,-4). Advanced stages (III,-IV) constitute 59,8% of our series and stage I was more frequent in distal than in proximal localisation (29,8% and 16,9% respectively). Superficial cancer was observed in 11,5% of our cases essentially in those less than 50 years of age (16,4%) : probably this would be due to the better access to health care in those relatively younger patients.

Subtotal and total gastrectomy were the most common realised interventions (44% and 42,1% respectively). The later was more frequently realised in male than in female (47% and 33,6% respectively) : this could be explained by the higher incidence of proximal third gastric cancer in men (23,2% versus 10,9% in women). The

former however was more common in women (54,2% versus 37,9% in men) and this is due to the preferential distal localisation of gastric cancer in women (44% versus 30,4% in men). The rate of total gastrectomy raised with time 32,4% in 1980 and 53,7% in 1996. Extensive lymphadenectomy was realised in 43,8% of cases and its practice have shown an appraisal with time : it was realised in more than 60% of operated gastric cancer between 1995 and 1996. As regard the type of lymphadenectomy, serious discordance was observed concerning the definition of each type. If we consider that D1 lymphadenectomy should contain at least 15 lymph nodes, 41,7% of them were revealed to be much more extensive (more than 25 lymph nodes) in contrary to D2,-D3 lymphadenectomy where 62,2% contained less than 25 lymph nodes. In fact no real improvement in the quality of lymphadenectomy was seen over the three periods of time.

The post-operative mortality was of 11,9% : it have shown an improvement over the three period of times of the study : 19,2% in 1980 versus 8,3% in 1996. Before 1990, corresponding in Europe to the diffusion of the technique of extensive lymphadenectomy, post-operative mortality after surgery for gastric cancer was around 10% ; it varied in large series between 3% and 8% with a morbidity ranging between 25% and 30% (5, 6, 7, 8) and this irrespective to the age. On this basis, the results of gastric resection with D2,-D3 lymphadenectomy have shown in a multicentric prospective non randomised study a 5% mortality rate versus 5,2% with D1 (9). A similar conclusion was obtained from a retrospective american study concerning less number of cases, where the morbidity consisted essentially of anastomotic leakage (9% versus 4%) and intra-abdominal abscesses (17% versus 8%) (10). However two other prospectives randomised trials have concluded to the higher morbidity and mortality rates in association with D2 lymphadenectomy. The former (11) over 331 cases of gastric resection with D2 lymphadenectomy, have shown a mortality and morbidity rates of 10% and 42% respectively (30% of distal splenopancreatectomy) versus 4% and 25% respectively over 380 cases associated with D1 lymphadenectomy (30% of splenectomy). For the later (12), over 200 cases of D2 lymphadenectomy mortality and morbidity were of 13% and 46% respectively versus 6,5% and 28% in case of D1 lymphadenectomy (200 cases). The higher rate of complications in the D2 lymphadenectomy group was also correlated to the more frequently associated distal splenopancreatectomy (113/200 cases versus 8/200 in the D1 group).

In our study, the morbidity rates associated with D1 and D2 lymphadenectomy (who did not include distal splenopancreatectomy) was quiet similar, 24,6% and 21,3%. On the opposite side, Japanese series shows a relatively low mortality rates oscillating between 2% and 5% and a morbidity around 25%, with less lethal consequences than in european series (13,14,15,16). In the western part of Europe, it seems that extensive

lymphadenectomy (D2,-D3) necessitating distal splenopancreatectomy predispose to a higher post-operative morbidity rate, which consist essentially of anastomotic leakage and intra-abdominal abscesses (11). However in absence of splenectomy, D2 and D1 lymphadenectomy were associated with a similar post-operative morbidity (17).

In the present study, on the basis of multivariate analysis, the 5 years survival was closely correlated to the stage of the tumor and this irrespective to the localisation. In the literature, the 5 years survival rate after curative surgery of cancer stomach was essentially related to the stage despite of the great divergence concerning the rate of survival encountered when we compare western (european and north american) to eastern series (Japan, Taiwan) (18,19,20,6,7,21,22) for the same stages. Reasons for such variations are not well known, however after many debates they are thought to be probably in relation with : the presence of "biological" differences between gastric cancer in western countries and in Asia, a less precise staging and in western a limited surgical experience in term of lymphadenectomy. Attempts to avoid such bias could be achieved by standardisation of the minimal number of lymph nodes to be removed in each type of lymphadenectomy together with the quality of the anatomopathological study (28,17,21,9). Finally, we should mention that no significant improvement in the 5 years survival rate in relation to extensive lymphadenectomy was seen in a randomised study comparing survival rate after D1 and D2 lymphadenectomy (23); this was also noted in our study.

In a survey of 99 785 cases of gastric cancer operated between 1970 and 1990, it was noted a survival rate after curative surgery of 60,5% in Japanese series versus 39,4% in others (24). The main prognostic factors were the degree of tumor invasion, the persistence of residual lesions after surgical excision, and the degree of lymph nodes involvement. Among all prognostic elements the most significant seems to be the percentage of involved lymph nodes with a survival rate around 60% when it was less than 20% to 25% and 30% when it was between 25% and 50% respectively (25,21,16). The number of involved lymph nodes will influence as well the survival, the limit being fixed at 3 metastatic lymph nodes and this irrespective to their localisation.

The rate of survival according to the stage of the tumor have been appreciated through three retrospective studies, a north american one (22) and 2 other eastern series, the first concern a japanese one (26) and the second a more limited series from Taiwan (20) where the survival varied between 56,3% and 47,5% versus 19% for the former. In a french study concerning 1 164 cases of treated gastric cancer between 1984 and 1989, surgical treatment was realised in 57% of cases. The overall survival rate was of 20% : 45% after curative and 15% after palliative surgery (20). The favorable prognostic elements were : age (less than 75 years), a longer

interval before diagnosis (more than 3 months), the macroscopic aspect of the tumor (vegetating rather than infiltrating tumors), a limited tumoral extension with no lymph node involvement and a complete surgical excision.

Conclusion

This retrospective multicentric study shows that the diagnosis of gastric cancer is done in more than 50% of cases at an advanced stage, and that there is equal repartition in the practice of total and partial gastrectomy. It shows as well a considerable decline in the operative mortality over the period of study, a 5 years survival of 41% after gastric resection, this mainly related to the stage of the tumor, and finally the absence of improvement of survival over the same period of time.

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