Pre-operative predictive factors of early recurrence after resection of adenocarcinoma of the esophagus and cardia

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SUMMARY

Objectives — To determine pre-operative predictive factors of early recurrence in patients with esophageal and cardial adenocarcinoma.

Patients and methods — We retrospectively analyzed consecutive patients who underwent resection for esophageal and cardial adenocarcinoma in our institution between October 1992 and October 2001. Patient files were studied and classified according to the occurrence of early recurrence (within one year) (group A) and patients without recurrence (group B). Pre-operative clinical, biological and radiological parameters were recorded. Both groups were compared in univariate and multivariate analysis.

Results — One hundred patients underwent surgical resection. Tumor was located in lower esophagus in 71 cases and at the cardia in 29 cases. R0 resection was feasible in 95 cases. Hospital mortality was 2%. Survival rate at 3 years was 56%. Recurrence before 1 year occurred in 28 patients (group A) and not in 72 (group B). In univariate analysis, younger age (P = 0.01), dysphagia (P = 0.04) and percentage of weight loss (P < 0.0004) were significantly different between both groups. Weight loss more than 10% was observed in 2 patients of group B, and in 9 patients of group A. In multivariate analysis, weight loss more than 10% was the only pre-operative factor associated with early recurrence (P = 0.018).

Conclusion — Important weight loss could be a pre-operative predictive factor of early recurrence after resection of esophageal and cardial adenocarcinoma and surgery as first line treatment could be avoided in these patients.

RÉSUMÉ

Facteurs prédictifs préopératoires de récidive précoce après résection des adénocarcinomes de l’œsophage et du cardia

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Objectifs — Déterminer les facteurs prédictifs de récidive postopératoire précoce chez les malades ayant un adénocarcinome de l’œsophage ou du cardia.

Malades et méthodes — Une analyse rétrospective des malades consécutifs opérés dans une seule institution, de Octobre 1992 à Octobre 2001, a été réalisée. Les malades ont été classés selon la survenue d’une récidive précoce (avant un an) (groupe A) ou non (groupe B). Les données préopératoires cliniques, biologiques et radiologiques ont été analysées et comparées dans les 2 groupes en analyse uni et multivariée.

Résultats — Cent malades ont eu une résection chirurgicale. La tumeur était localisée au niveau inférieur de l’œsophage dans 71 cas et au cardia dans 29. Une résection R0 a été réalisée chez 95. La mortalité hospitalière a été de 2%. Le taux de survie à 3 ans était de 56%. Une récidive avant un an survenait chez 28 malades (groupe A) et 72 étaient exempts de récidive à 1 an (groupe B). En analyse univariée, l’âge (P = 0,01), la présence ou non d’une dysphagie (P = 0,04) et le pourcentage de perte de poids corporel (P < 0,0004) étaient statistiquement différents entre les 2 groupes. Une perte de poids de plus de 10% était observée chez 2 malades du groupe B et chez 9 malades du groupe A. En analyse multivariée, une perte de poids de plus de 10% était le seul facteur préopératoire associé une récidive précoce (P = 0,018).

Conclusion — Une perte de poids importante pourrait être un facteur préopératoire prédictif de récidive précoce chez les malades opérés d’un adénocarcinome de l’œsophage ou du cardia et conduire à éviter une résection chirurgicale d’emblée chez ces malades.

Introduction

Adenocarcinoma of the esophagus or the gastric cardia carries a poor prognosis and half of patients have metastatic disease at initial evaluation [1]. In patients referred to surgery, the 5-year survival rate is about 20% [1-3]. Improved survival could be achieved by radical oesophagectomy in selected patients [4-7]. However, this surgical procedure carries a hospital mortality rate of about 3-10% in specialized centers and a rate of perioperative complications (mainly pulmonary complications and anastomatic leaks) of 30 to 40% [5, 8]. Neither neoadjuvant nor adjuvant therapies have to date substantially modified long term prognosis [8-10]. Analysis of survival and disease-free curves clearly shows that above 30% of operated patients (R0 resection) developed recurrence within a year [5, 8]. Some prognostic factors after surgical resection are well known, such as tumor length, pathological stage and percentage of involved lymph nodes [4, 11, 12]. However, predictive factors of early recurrence are lacking, especially those available before surgical procedure. Their identification could select patients prone to early recurrence and, in these cases, other therapeutic modalities may be considered. The aim of this study was to identify pre-operative predictive factors of early recurrence in a cohort of 100 patients with adenocarcinoma of the esophagus or the gastric cardia referred to our surgical unit.

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Patients and methods

Patient population

All consecutive patients operated between October 1992 and October 2001 in our surgical unit for an adenocarcinoma of the esophagus or the gastric cardia, were evaluated. In all cases, liver or lung metastasis were ruled out by tomography. Endoscopy with biopsy and the site of recurrence (regional or distant) was noted. Depending on their status one year after treatment, patients were assigned to 2 groups: group of patients with recurrence (group A), and group of patients without recurrence (group B). Several parameters recorded at the initial pre-operative assessment were compared between both groups: age, gender, percentage of body weight loss (difference between body weight at a steady state before the first symptoms and body weight at consultation in our unit), presence of body weight loss more than 10%, dysphagia, anorexia, duration of symptoms, history of reflux disease, smoking, serum hemoglobin (g/dL), serum albumin (g/L) and CEA (ui/ml), presence of Barrett’s esophagus, length and diameter of the tumor measured in cm on the CT-scan, presence of lymphatic mass on the CT-scan, T and N staging by endosonography, histological tumor differentiation on biopsy and neoadjuvant therapy.

Several other parameters were also evaluated: histological stage, differentiation, number of resected lymph nodes and percentage of involved lymph nodes at pathological examination, type of surgical procedure and its approach, need of peri-operative blood transfusion and adjuvant or neoadjuvant therapy.

Statistics

Categorical data were summarized in both groups using frequencies and percentages. Continuous data were summarized using mean values and standard deviation. Ordinal variables were compared using the Student’s t-test, and proportions using the chi-square test. Research of prognostic factors of early recurrence after resection was performed by the logistic regression model. The step-wise regression technique was used to identify the most significant variables. The significance levels for a variable to be entered into a model were set to 0.05. The statistical analysis was performed using the SAS V8 software. All statistical tests were two-sided with a significance level of 5%.

Results

One hundred patients were included in the study. The abdominal approach was laparoscopic in 60 cases and a thoracotomy was performed in 74 patients. Patients’ characteristics are summarized in tables I and II. The tumor was located at the gastric cardia in 29 cases and in the lower part of the esophagus in 71. Radical (R0) resection was feasible in 95 patients. Five patients had R1 resection. The mean number of resected lymph nodes was 22 ± 11. The hospital mortality rate was 2%: pulmonary thromboembolism occurred in one patient and very early recurrence in another with occult diffuse metastases. Neoadjuvant therapy was given in 11 patients and adjuvant therapy in 8 patients. Table II indicates the pTNM characteristics in both groups. Median follow-up was 23 months. The survival rate at 3 years in the whole cohort was 56%.

Caractéristiques des malades. Analyse univariée (groupe A : récurrence à 1 an; groupe B : absence de récurrence à 1 an).
Disease recurrence occurred within one year in 28 patients (group A). Recurrence was local, peri-anastomotic in 8 and metastatic in 20. Conversely, 72 patients were disease-free at one year (group B). Kaplan-Meier disease-free survival curve is displayed in figure 1. Median delay of recurrence was 38 months. Some parameters available before surgery were not significantly different between both groups: sex, past history of reflux disease, presence of Barrett’s esophagus, duration of symptoms, smoking habits, anorexia, differentiation at biopsy (P = 0.43), concentration of hemoglobin (P = 0.2) and albumin (P = 0.63). Early recurrence was not linked to the location of the tumor (esophageal versus cardial) (P = 0.92). On the other hand, younger age and dysphagia were significantly more frequent in group A patients (table I). In the same way, the percentage of weight loss was higher in patients of group A (P < 0.0004). Weight loss more than 10% was observed in only 2 patients of group B (specificity: 97.2%) and in 9 patients of group A (sensitivity: 32%) (table I).

Elevated CEA serum concentration was significantly more frequent in group A (P = 0.005). Length of the tumor, its diameter, and the presence of lymph nodes enlargement on CT-scan were significantly more frequent in group A (table II). At endosonography, T-stage greater than T2 and N positive status were significantly more frequent in group A (table II). Discrepancy between uT and pT occurred in 32 cases, and between uN and pN in 17.

Both groups were not significantly different with regard to the type of surgical approach (with or without thoracotomy), the abdominal approach (laparoscopy or laparotomy), peri-operative blood transfusion (19 patients) or involved lymph nodes on pathologic examination (P = 0.20). However, more than 30% of lymph nodes involvement was strongly associated with early recurrence (table III). Multivariate analysis of pre-operative factors disclosed a link only between weight loss of more than 10% and early recurrence after surgery (P = 0.018). If post operative factors were also included in the analysis, a ratio of involved lymph nodes greater than 30% was the only independent predictive factor of early recurrence (P = 0.03).

Discussion

This is the first study analyzing pre-operative predictive factors of early recurrence after surgery for adenocarcinoma of the esophagus and the gastric cardia. Our results demonstrate a 28% rate of post-operative recurrence one year after an extended resection of the adenocarcinoma in a cohort of highly selected patients with 95% of R0 resection and a 3-year survival rate of 56%. Among pre-operative parameters, dysphagia, weight loss more than 10%, length of the tumor, lymphatic mass at TDM, T-stage > T2 and N positive at endosonography were associated with early recurrence in univariate analysis. In multivariate analysis of pre-operative parameters, weight loss more than 10% was the only feature predictive of early recurrence, with a good specificity but a poor sensitivity. Thus, pre-operative predictive factors of early recurrence independent of body weight loss are lacking. Regarding postoperative parameters, involvement of lymph nodes itself was not associated with early recurrence. However, if there were up to 30% positive lymph nodes, this feature was highly predictive of early recurrence.

The incidence of esophageal adenocarcinoma is increasing in Western countries. Radical surgery alone can yield a 5-year survival rate up to 48% after R0 resection [4, 7], despite up to 30% of recurrence at one year [5]. These fairly good results are obtained in centers with low mortality rate and strict selection of patients. Results of neoadjuvant chemotherapy in the Western world are conflicting in 2 studies that included several hundreds of patients, irrespective of the histological type of the esophageal carcinoma, with respectively a postoperative mortality of 6 and 10% [8, 10]. In both studies, R0 resection rate was only 60%. In another study, neoadjuvant chemoradiotherapy was superior to surgery alone in the treatment of esophageal adenocarcinoma [9]. In this series with an acceptable hospital mortality of 6%, long term results of surgery alone were extremely low with a 6% survival rate at 3 years, which totally differs with usual surgical series. Moreover, the number of resected and analyzed nodes was not known in this series. Thus, indications for neoadjuvant therapy are not yet clearly defined. However, this strategy is often proposed for patients with locally advanced carcinoma and presumed high risk of relapse after surgery alone [13]. Some predictive factors of long term prognosis are well known, but most of them are only available after surgical resection, such as pTNM, number or percentage of involved lymph nodes, urokinase plasminogen activator expression. More than 30% of involved lymph nodes are associated with no survival rate at 5 years [11]. Urokinase plasminogen activator, which could reflect the aggressiveness of the tumor, has been studied on pathology specimens [14]. Its prognostic value was independent of involved lymph nodes. However, this factor cannot be currently measured pre-operatively on biopsy samples.

Table III – pTNM stratification in both groups. Group A: recurrence at one year; group B: disease free at one year.

<table>
<thead>
<tr>
<th>Stade pTNM dans chaque groupe.</th>
<th>Group A N = 28</th>
<th>Group B N = 72</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-2 NO</td>
<td>0</td>
<td>27</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>T3-4 NO</td>
<td>3</td>
<td>3</td>
<td>0.21</td>
</tr>
<tr>
<td>Any T N+ (%)</td>
<td>19 (68)</td>
<td>37 (51)</td>
<td>0.2058</td>
</tr>
<tr>
<td>More than 30 % involved lymph nodes (%)</td>
<td>13 (46)</td>
<td>14 (22)</td>
<td>0.001</td>
</tr>
<tr>
<td>R0 post RC</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>R1 post RC</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>R2 post RC</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

R0 post RC: lack of tumoral tissue at histological examination after neoadjuvant radio and/or chemotherapy ; R1: microscopic residue ; R2: macroscopic residue.
Among pre-operative parameters, body weight loss less than 10% was associated with better survival in a Scandinavian study of esophageal carcinoma [15]. Elevated C-reactive protein was also associated with a poor prognosis [16]. Tumor length and esophageal deformation have also been studied in esophageal carcinoma and tumor length was predictive of survival [12,17]. Esophageal deformation combined to response to neoadjuvant radio-chemotherapy was predictive of R0 resection and survival [18]. Ultrasonographic findings were recently related to survival and R0 resection [19]. In a recent study, C-reactive protein level, body weight loss and clinical TNM staging (using CT-scan, endosonography and endoscopy) were correlated with the prognosis in a multivariate analysis and a predictive index of esophageal cancer was proposed [20]. Pattern of recurrence after complete resection were recently studied in esophageal carcinoma, irrespective of histological type [21]. Recurrence occurred in 52%, and before one year in 46% of them. In multivariate analysis, only histological tumor depth invasion was predictive of recurrence, but no factors were predictive of early recurrence. Finally, it is not fully surprising that some parameters associated with early recurrence in our study would be also those associated with long term prognosis of other studies. Interestingly, the presence of nodal involvement in our study was predictive of recurrence, but no factors were predictive of early recurrence. In summary, our results suggest that important weight loss could be predictive of early recurrence after resection of esophageal or cardial adenocarcinoma, even if this result should be confirmed in a prospective study. We failed to find any other independent pre-operative predictive parameter. These results suggest that surgery could be avoided as first line treatment in some patients and help to clarify the indications for neoadjuvant chemotherapy.

REFERENCES