



## Perforated Duodenal Ulcers

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The incidence of perforation, complicating about 5% of duodenal ulcers, has not decreased proportional to the overall decline in peptic ulcer disease. To define the role of immediate definitive surgery, we conducted several prospective studies to identify risk factors that increase operative mortality as well as predictive factors associated with relapse after simple closure. Among 613 consecutive patients, major medical illnesses, pre-operative shock, and perforations exceeding 24 hours' duration were found to be determinant variables that allowed stratification of patients into different risk groups. Definitive surgery or simple closure in the absence of any risk factor had a mortality rate of less than 0.7%, whereas even closure alone incurred a mortality rate of 86.7% when all 3 risk factors were present.

The need for definitive surgery was assessed by comparing relapse rates after closure in patients who differed in respect to the chronicity, age at onset, and family history of their ulcer disease. Multivariate analysis revealed chronicity and a positive family history to be the most useful independent predictors of the likelihood of relapse after closure. The benefits of definitive surgery for perforations in chronic lesions were corroborated by a prospective controlled trial in which proximal gastric vagotomy with closure or truncal vagotomy with gastric drainage each proved as safe as closure alone but significantly more effective in reducing the frequency of relapse after operation.

Immediate nonresective definitive surgery is indicated in fit individuals who have perforations in chronic duodenal ulcers; however, closure alone is more prudent in patients who have any risk factor.

Prompt surgical intervention is generally accepted in the management of perforated peptic ulcers. Besides harboring a risk of malignancy, gastric ulcers that perforate often recur after closure alone. Consequently, most surgeons advocate immediate gastrectomy [1], an operation associated with a relapse rate of approximately 3% [2, 3].

By contrast, because perforated duodenal ulcers do not invariably recur after simple closure, immediate definitive surgery has not achieved similar acceptance. For definitive surgery to be adopted, it should be as safe as simple closure; the selected patients must bear an appreciable risk of symptomatic relapse after closure; and the curative operation must be effective yet free of serious side effects. Over the past 8 years, we have conducted several prospective studies that focus on these fundamental issues [4-8]. This article emphasizes selec-

tion of patients for definitive surgery, and extends the results of our previously published controlled trial [7].

### Material and Methods

Between November, 1978, and December, 1985, a special surgical team evaluated 613 consecutive patients with acutely perforated duodenal ulcers. The annual incidence of 86 cases per year did not fluctuate greatly (range 75-101 cases per year) over this period during which H<sub>2</sub>-antagonist drugs were widely used. An acute ulcer (defined as one with an antecedent ulcer history of less than 3 months' duration [9-11]) was present in 34.3% of patients. The profile of the patients is given in Table 1. A comparison of the characteristic features of patients with acute and chronic ulcers is also shown in Table 1.

Up until 1982, all patients were considered for inclusion in a prospective, randomized controlled trial comparing closure alone, truncal vagotomy with gastric drainage, and proximal gastric vagotomy with omental closure [7]. The selection criteria allowed only healthy patients with perforations of chronic ulcers to be included [7]. An omental patch closure was performed in the excluded patients unless they already had a past ulcer operation or a concomitant ulcer complication (bleeding or stenosis) in which case they underwent truncal vagotomy with drainage.

Since 1982, all patients have been considered for entry into a second controlled trial of definitive surgery. This differed slightly from the first trial in that fit patients with acute ulcers were also eligible for randomization. In addition, proximal gastric vagotomy with closure was the only definitive operation employed in this trial. The results of this second trial will not be detailed here as the mean length of follow-up of these patients is only 2 years.

The operative practice remained unchanged throughout the study period except that more surgeons participated during the later years. Nonoperative treatment was not employed. Perioperative prophylactic antibiotics (cephalosporins) and peritoneal lavage with saline were used routinely. No peritoneal drains were inserted unless an established abscess existed, and all wounds were closed primarily.

Discharged patients were assessed regularly in a special follow-up clinic. Some patients emigrated soon after discharge and 45 (7.3%) were lost to follow-up after 1 month. In addition

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**Table 1.** Clinical profile of patients with perforations in acute and chronic duodenal ulcers.

	All (n = 613)	Chronicity		Significance <i>p</i>
		Acute (n = 210)	Chronic (n = 403)	
Men (% of patients)	83.5	80.0	85.4	ns <sup>a</sup>
Age, mean ± SD (yr)	50.1 ± 17.6	54.8 ± 18.2	47.6 ± 16.9	0.001 <sup>b</sup>
Age at onset of ulcer disease, mean ± SD (yr)	44.6 ± 19.0	54.8 ± 18.2	39.3 ± 17.1	<0.001 <sup>b</sup>
Early onset (<30 yr) (% of patients)	29.0	14.3	36.7	<0.001 <sup>c</sup>
Family history (% of patients)	18.9	13.3	21.8	0.014 <sup>c</sup>
Chronicity				
Median (mo)	23.7	0.04	59.5	<0.001 <sup>d</sup>
>3 mo (% of patients)	65.7	—	—	
Previous ulcer operation (% of patients)	3.3	—	5.0	
Duration of perforation				
Median (hr)	11.9	12.6	11.5	ns
>24 h (% of patients)	16.5	22.4	13.4	0.006 <sup>c</sup>
>48 h (% of patients)	6.0	9.0	4.5	0.037 <sup>c</sup>
Other illness (% of patients)	10.1	18.6	5.7	<0.001 <sup>c</sup>
Shock (% of patients)	4.6	8.6	2.5	0.001 <sup>c</sup>
Gross contamination (% of patients)	6.0	11.4	3.2	<0.001 <sup>c</sup>
Risk score, median	0.14	0.23	0.10	<0.001 <sup>d</sup>
Definitive surgery (% of patients)	31.6	19.1	39.0	<0.001 <sup>c</sup>
Morbidity (% of patients)	14.5	21.0	11.2	0.002 <sup>c</sup>
Mortality (% of patients)	4.7	10.0	2.0	<0.001 <sup>c</sup>

<sup>a</sup>ns = not significant.

<sup>b</sup>Unpaired Student's *t*-test.

<sup>c</sup>Corrected chi-squared test.

<sup>d</sup>Mann-Whitney test.

**Table 2.** Hospital mortality after closure or definitive surgery in different risk groups.

Operation	Mortality with risk score of:								Total mortality	
	0		1		2		3			
	n	%	n	%	n	%	n	%	n	%
Closure	292	0.3	88	3.4	24	37.5	15	86.7	419	6.2
Vagotomy + drainage	47	0	8	12.5	1	100.0	—	—	56	3.6
Proximal gastric vagotomy + closure	138	0.7	—	—	—	—	—	—	138	0.7
Total	477	0.4	96	4.2	25	40.0	15	86.7	613	4.7

to endoscopic examinations initiated because of possible ulcer complaints, most patients had routine annual endoscopies to detect asymptomatic recurrences.

Statistical comparisons were by the corrected chi-squared test, the Fisher exact test, and the unpaired Student's *t*-test. The Mann-Whitney rank sum test was used for nonparametric data [12]. Cumulative recurrence-free rates determined by Kaplan-Meier actuarial analysis [13] were compared by the generalized Wilcoxon test [14]. The relative contribution of independent predictors of recurrence were evaluated by stepwise logistic regression analysis (Cox model) [15]. Ninety-five percent confidence limits (95% C.I.) were calculated where appropriate. Statistical significance was accepted at the 5% level.

## Results

### Mortality and Morbidity

All but 3 of the 29 (4.7%) hospital deaths followed simple closure operations. Two poor-risk patients died after vagotomy

and pyloroplasty operations that were necessitated by concurrent bleeding or pyloric stenosis. One other patient recovered initially after reoperation for lesser curvature necrosis following proximal gastric vagotomy but died later of fulminant Stevens-Johnson syndrome.

Respiratory failure, mostly related to sepsis and multiple organ dysfunction, was the primary cause of deaths [5, 8]. Of note, 2 patients who underwent closure died after reoperations for early postoperative bleeding ulcers or pyloric obstruction.

A previously validated risk scoring system [8] was used to grade the relative risks of surgery in these patients: a score of 1 was assigned for each of 3 independent risk factors—concurrent major illnesses, preoperative shock, and a longstanding perforation exceeding 24 hours—present in each patient. The mortality rates rose progressively from 0.4% in those with a risk score of 0 to 86.7% in those with a risk score of 3 (Table 2).

### Recurrence after Simple Closure

The cumulative recurrence-free rate in the 393 patients who survived simple closure is shown in Fig. 1. By the sixth

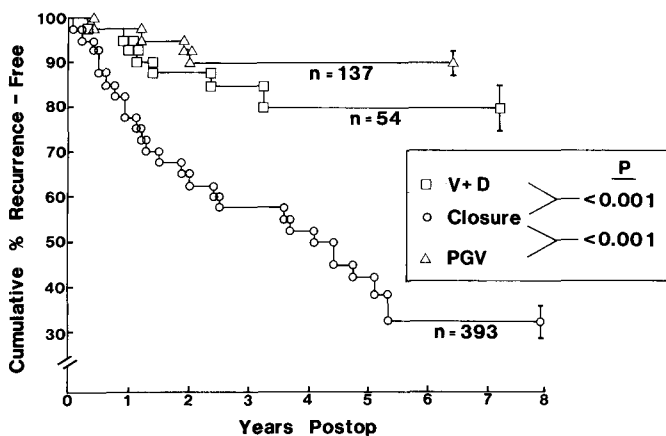


Fig. 1. Cumulative recurrence-free rates after surgical treatment of perforated duodenal ulcer in 584 surviving patients. V + D = vagotomy and drainage, PGV = proximal gastric vagotomy with closure.

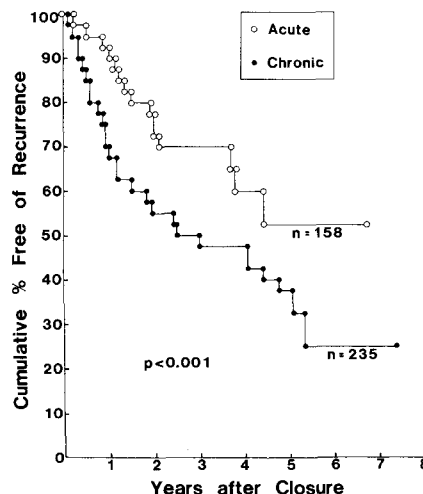


Fig. 2. Cumulative recurrence-free rates after closure alone in 393 patients with perforations in acute and chronic ulcers.

postoperative year, a cumulative 67.3% (52.5%–82.0%, 95% C.I.) of them had proven recurrences. All but 10 of these 114 patients had symptomatic recurrences. Fifty-four patients who relapsed (51.9%) had major ulcer complications: 29 (27.9%) with bleeding, 16 (15.4%) with pyloric obstruction, and 9 (8.7%) with reoperation. A total of 45 patients with recurrences (39.5%) after simple closure required a second operation.

A chronic lesion, a family history of ulcer disease, and early onset of ulcer disease (before 30 years of age) [16] were identified by univariate actuarial analysis as significant factors predisposing to relapse after closure (Figs. 2–4). The close interrelationship among these 3 variables is shown in Table 3. Chronic ulcers are especially likely in patients who develop symptoms at an early age, and in those with a family history of ulcer disease among first-order relatives. Patients with early onset of ulcer disease and a positive family history were especially likely to relapse (Fig. 5). These individual factors were further evaluated by stepwise multivariate analysis to determine their relative independent predictive value. This analysis revealed a chronic ulcer and a positive family history to be the most useful features associated with a high risk of relapse after closure (standardized coefficients of  $-0.84$  and  $+0.52$ ,  $p < 0.001$  and  $p = 0.01$ , respectively).

*Results after Definitive Surgery*

One hundred ninety-one (98.5%) of 194 patients survived immediate definitive surgery. Of these, 66 patients were part of our initial controlled trial comparing definitive surgery with closure alone in patients with perforations in chronic ulcers. On follow-up extending to 7½ years after surgery (mean 44 months), definitive surgery yielded a significantly lower recurrence rate than closure alone (Fig. 6). Two of the 3 recurrences after truncal vagotomy and drainage could be attributed to an incomplete vagotomy. One additional patient had a partially healed ulcer when endoscopy was performed 1 month after surgery but complete healing was demonstrated on subsequent examination. All relapses were symptomatic, and 2 patients required reoperation.

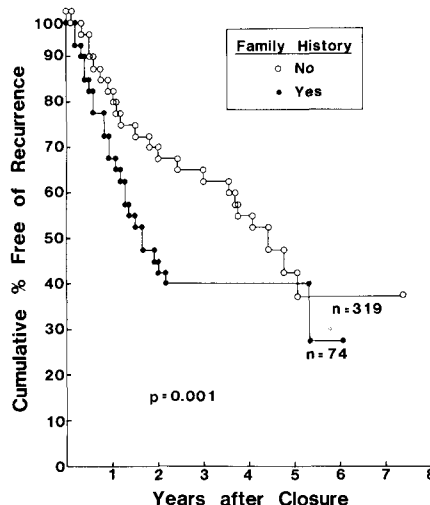


Fig. 3. Cumulative recurrence-free rates after closure alone in 393 patients with and without a family history of ulcer disease.

To date, 7 of the 137 patients who survived emergency proximal gastric vagotomy with closure have developed recurrences—a cumulative relapse rate of 9.6% (1.8%–16.2%, 95% C.I.) at 6 years' follow-up (Fig. 1). Interestingly, only 4 of them were symptomatic recurrences, and only 1 required reoperation. Two patients with an asymptomatic relapse healed medically without further recurrence but one other underwent elective surgery. Visick I and II scores were attained in 77.2% and 22.8%, respectively, of the patients who remained free of recurrence after proximal gastric vagotomy with closure.

**Discussion**

Although the recent incidence of uncomplicated ulcer disease requiring elective surgery has declined dramatically [17–20], most studies indicate the rate of perforation to be either unchanged [21] or only slightly reduced [22–24] since the introduction of H<sub>2</sub>-antagonist drugs. An exception to this trend

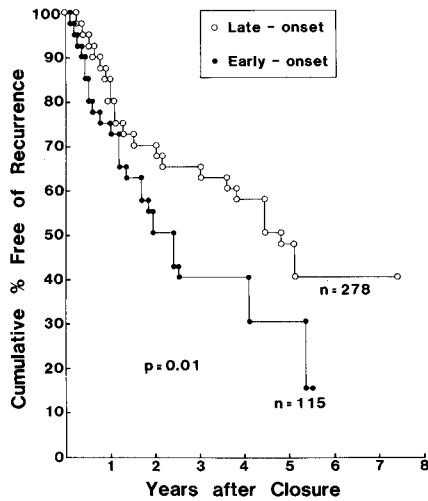


Fig. 4. Cumulative recurrence-free rates after closure alone in 393 patients with early (before 30 years of age) and late onset (after 30 years of age) of ulcer disease.

Table 3. Interrelationships between chronicity, age at onset, and family history of ulcer disease.

	Chronicity (no.)		Family history (no.)	
	Acute	Chronic	No	Yes
Early onset (before 30 yr)				
No	180	255	385	50
Yes	30	148	112	66
	<i>p</i> < 0.001		<i>p</i> < 0.001	
Positive family history				
No	182	315	—	—
Yes	28	88	—	—
	<i>p</i> = 0.01			

was noted in a retrospective survey in Hong Kong where an increase in the incidence of elective ulcer admissions as well as perforations was observed between 1970 and 1980 [25]. Our annual hospital incidence of duodenal perforations has not diminished even though H<sub>2</sub>-antagonist medications were commonly used during the study period (1978–1985).

About a third of perforations are acute ulcers occurring in patients with minimal or no antecedent ulcer history. Although only a few of our patients admitted to recent intake of steroidal or other ulcerogenic medications, Watkins et al. [23], Thompson [26], and others [27] have implicated this as an increasingly common etiological factor. This may also account for the higher proportion of acute ulcers noted in recent reports [23].

The 3 risk factors—shock, major illnesses, and longstanding perforations—that predispose to a higher mortality were determined initially from a prospective study of 213 consecutive patients [5], and subsequently validated by a second prospective survey of another 259 consecutive patients [8]. The discriminant function derived correctly predicted all 16 patients who died in the second study. The basic validity of these criteria was upheld in the most recent 141 patients of this series of 613 consecutive patients.

Patients with perforated ulcers tend to be young and other-

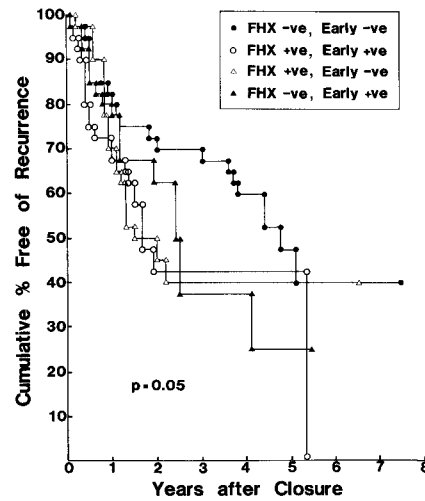


Fig. 5. The influence of family history and age at onset of ulcer disease on the cumulative recurrence-free rates after closure alone. Recurrence-free rates of patients with neither a family history nor early onset (n = 247) versus patients with both a family history and early onset (n = 43) is statistically significant (*p* = 0.01). FHX +ve = family history present, FHX -ve = no family history, EARLY +ve = onset before 30 years of age, EARLY -ve = onset after 30 years of age.

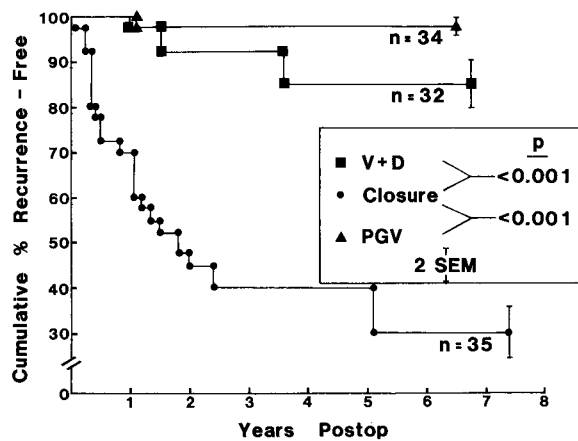


Fig. 6. Cumulative recurrence-free rates in 101 patients in the prospective randomized trial of surgical treatment of perforated duodenal ulcer. V+D= vagotomy and drainage, PGV= proximal gastric vagotomy with closure.

wise healthy. Nearly 17% of our patients developed perforations before 30 years of age. As judged by the absence of any of the 3 major risk factors, 477 of our 613 patients (77.8%) could be classified as good-risk candidates suitable for immediate definitive surgery. This is supported by the very low mortality rate of 0.4%, including only 1 death (0.5%) among the 185 patients in this group who underwent definitive surgery. This reinforces the contention that patients with perforated ulcers can be objectively selected for curative surgery. A strict comparison with matched groups would require inordinately large numbers of patients to demonstrate a lack of a statistical difference in mortality. In our relatively small, prospective, controlled trial of definitive surgery, no patient died after either closure alone or immediate definitive surgery. Extrapolating from our figures, only a minuscule difference (0.1%–0.3%, 95% C.I.) at most

might exist between closure and definitive surgery in good-risk patients selected by the criteria outlined above.

The extensive peritoneal spillage usually encountered at laparotomy does not equate with bacterial peritonitis in most perforations of less than 2 days' duration [4, 28]. Indeed, the development of an intraabdominal abscess is exceptional if it is not already extant at operation. Life-threatening sepsis is most likely in patients with longstanding perforations who present with hemodynamic instability and multiple organ failure. The presence of all 3 risk factors denotes such a critical state [8] that it is problematic whether any form of early operative intervention will be tolerated, much less beneficial. Nonoperative treatment may have its best application in such patients [29–31].

Patient selection for definitive surgery has been further clarified recently. Our prospective comparison of relapse among patients with perforations in acute and chronic ulcers [6] confirmed earlier impressions [9, 32, 33] of a higher recurrence rate in the latter group. Nevertheless, the distinction is only a relative one as not all chronic ulcers inevitably recur nor are all acute ulcers immune to relapse. An unexpectedly high 45.3% (23.2%–67.4%, 95% C.I.) of our 153 prospectively evaluated acute lesions recurred within 5 years of simple closure. Most earlier studies did not utilize actuarial analyses that adjusted for differences arising from variable lengths of follow-up. Moreover, they often failed to distinguish between single, independent, predictive factors and those bearing a close interrelationship with each other (so-called spurious variables). To refine the selection criteria, a Cox proportional hazards model was used to compare predictive factors identified by univariate analysis. This multivariate analysis performs comparisons based on actuarial recurrence-free rates while taking into account interrelationships that exist among related variables. The finding that the chronicity of a lesion is still the single most useful predictive variable reaffirms preexisting opinions. The additional knowledge that patients with a positive family ulcer history are particularly prone to relapse hints at a genetically determined physiological basis for recurrence in some individuals.

The numerous reports supporting immediate definitive surgery would seem to reduce the need for overly rigid patient selection for curative surgery. As Jordan argued [34], the safety and negligible late side effects of proximal gastric vagotomy with closure make this a most appealing operation in the hands of surgeons familiar with the technique. Our own experience with this operation in 138 patients followed for a mean length of 2 years corroborates the widespread reports of the applicability of proximal gastric vagotomy in the emergency treatment of perforated duodenal ulcers. No doubt, truncal vagotomy with drainage has its advocates as an expedient operation familiar to most surgeons. The overwhelming superiority of either type of nonresective definitive surgery over closure in terms of ulcer recurrence is not offset by deleterious side effects or an unacceptable rate of recurrence. Nevertheless, the success of proximal gastric vagotomy is surgeon-dependent: some surgeons achieve a lower recurrence rate in emergency operations than others following elective procedures [35]. Clearly, the skillful performance of any definitive operation under emergency as well as elective circumstances is indispensable to its success.

## Conclusions

Given the available information on the selection of patients for safety and risk of recurrence after closure, we would estimate the suitability of definitive surgery in our patient population as follows: about 2.5% of them will have all 3 risk factors, and present in a moribund state; another 20% will have 1–2 risk factors, and simple closure should be performed unless a coexisting ulcer complication necessitates a definitive operation. Thus, approximately three-quarters of all patients would be safe candidates for more extensive procedures.

Because definitive surgery has the most to offer in young individuals, we restrict its use to good-risk patients who are younger than 70 years of age. Among young, fit patients, 70% (representing half of all patients with perforated ulcers) will have chronic ulcers that warrant definitive surgery. Furthermore, in the remaining good-risk patients with acute ulcers, proximal gastric vagotomy with closure may be considered because of its safety and minimal side effects. Overall, at least half of all patients with perforated duodenal ulcers will benefit from immediate definitive surgery. Future studies in perforated ulcers should be directed toward the management of those who present in extremis, and the search for more reliable parameters that identify patients prone to relapse.

## Acknowledgments

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## Résumé

La fréquence de la perforation qui complique environ 5% des ulcères duodénaux n'a pas diminuée proportionnellement à la diminution globale de la maladie ulcéreuse. Pour définir la place du traitement chirurgical immédiat et définitif, les auteurs ont conduit plusieurs études prospectives de manière à identifier les facteurs de risque qui augmentent la mortalité opératoire ainsi que les facteurs associés à la récurrence après simple suture de la perforation. Parmi une série consécutive de 613 malades plusieurs faits: une affection médicale majeure, un état de choc, une perforation datant de plus de 24 heures ont constitué des variables déterminantes permettant une classification de malades en groupes différents de risques. L'exérèse gastrique aussi bien que la simple suture a entraîné un taux de mortalité inférieur à 0.7% alors que ce taux a atteint 86.7% après simple suture dès lors que les 3 facteurs de risque étaient réunis.

La nécessité d'un traitement chirurgical définitif a été évaluée en comparant les taux de récurrence après simple suture en fonction de la chronicité, de l'âge au début, et de l'histoire familiale de la maladie ulcéreuse. L'analyse de ces variables a démontré que la chronicité et que l'existence d'une diathèse ulcéreuse familiale étaient des facteurs de pronostic qui permettaient de prévoir avec vraisemblance la récurrence ulcéreuse après simple suture. Les bénéfices de la chirurgie immédiate à visée curatrice ont été corroborés par un essai contrôlé prospectif. Il a démontré que la vagotomie hautement

sélective avec suture de la perforation et la vagotomie tronculaire avec opération de drainage étaient des interventions aussi bénignes que la simple suture de la perforation alors même que les risques de récurrence étaient réduits de manière significative.

En conclusion la chirurgie immédiate à visée curatrice, à l'exclusion de la résection, est indiquée chez le sujet en bon état général alors que la simple suture doit être pratiquée dès qu'un facteur de risque est présent.

### Resumen

La incidencia de perforación, complicación que ocurre en 5% de las úlceras duodenales, no ha disminuido en forma proporcional a la declinación global que se observa en la enfermedad péptica. Con el objeto de definir el rol de la cirugía inmediata y definitiva, hemos realizado estudios prospectivos para identificar los factores de riesgo que aumentan la mortalidad operatoria así como factores de predicción asociados con la recurrencia que ocurre después del simple cierre o plicación de la úlcera perforada. En un estudio sobre 613 pacientes consecutivos, se encontró que las enfermedades graves asociadas, el shock preoperatorio, y las perforaciones de más de 24 horas fueron las variables determinantes que permitieron la categorización de los pacientes en diferentes grupos de riesgo. La cirugía definitiva o el cierre simple realizados en ausencia de alguno de los factores de riesgo tuvieron una tasa de mortalidad de menos de 0.7%, en tanto que el cierre o plicación presentó una tasa de mortalidad de 86.7% cuando los 3 factores estuvieron presentes.

La necesidad de cirugía definitiva fue evaluada mediante el análisis de las tasas de recurrencia después de cierre simple en pacientes que exhibían diferencias en cuanto a cronicidad, edad al comienzo de la enfermedad, e historia familiar. El análisis multivariable reveló que la cronicidad y una historia familiar definitiva fueron los factores de predicción independientes de posibilidad de recurrencia después del cierre simple. Los beneficios de la cirugía definitiva para casos de perforación en lesiones crónicas fue corroborado mediante un ensayo clínico prospectivo y controlado en el cual la vagotomía gástrica proximal simultánea con el cierre o la vagotomía troncular con drenaje gástrico, probaron ser tan seguras como el cierre solo, pero significativamente más efectivas en cuanto a la reducción de la frecuencia de relapso postoperatorio.

La cirugía inmediata de tipo no resectivo está indicada en pacientes en buen estado que desarrollan perforación de úlceras duodenales crónicas. Sin embargo, el cierre representa una conducta más prudente en pacientes que presentan cualquiera de los factores de riesgo.

### References

- Gall, W.J., Talbot, C.H.: Perforated gastric ulcer. *Br. J. Surg.* 51:500, 1964
- Kraus, M., Mendeloff, G., Condon, R.E.: Prognosis of gastric ulcer: Twenty-five year followup. *Ann. Surg.* 184:471, 1976
- Thomas, W.E.G., Thompson, M.H., Williamson, R.C.N.: The long-term outcome of Billroth I partial gastrectomy for benign gastric ulcer. *Ann. Surg.* 195:189, 1982
- Boey, J., Wong, J., Ong, G.B.: Bacteria and septic complications in patients with perforated duodenal ulcers. *Am. J. Surg.* 143:635, 1982
- Boey, J., Wong, J., Ong, G.B.: A prospective study of operative risk factors in perforated duodenal ulcers. *Ann. Surg.* 195:265, 1982
- Boey, J., Lee, N.W., Wong, J., Ong, G.B.: Perforations in acute duodenal ulcers. *Surg. Gynecol. Obstet.* 155:193, 1982
- Boey, J., Lee, N.W., Koo, J., Lam, P.H.M., Wong, J., Ong, G.B.: Immediate definitive surgery for perforated duodenal ulcers. A prospective controlled trial. *Ann. Surg.* 196:338, 1982
- Boey, J., Choi, S.K.Y., Poon, A., Alagaratnam, T.T.: Risk stratification in perforated duodenal ulcers: A prospective validation of predictive factors. *Ann. Surg.* 205:22, 1987
- Illingworth, C.F.W., Scott, L.D.W., Jamieson, R.A.: Progress after perforated peptic ulcer. *Br. Med. J.* 1:787, 1946
- Taylor, H.: The non-surgical treatment of perforated peptic ulcer. *Gastroenterology* 33:353, 1957
- Cassell, P.: The prognosis of the perforated acute duodenal ulcer. *Gut* 10:572, 1969
- Siegel, S.: *Nonparametric Statistics for the Behavioral Sciences*, New York, McGraw-Hill, 1956
- Kaplan, E.L., Meier, P.: Nonparametric estimation from incomplete observation. *J. Am. Stat. Assoc.* 53:457, 1958
- Benedetti, J., Yuen, K., Young, L.: Life tables and survival functions. In *BMDP Statistical Software*, W.J. Dixon, editor, Berkeley, Calif., University of California Press, 1981, pp. 557-575
- Cox, D.R.: Regression models and life tables. *J. R. Stat. Soc.* 34(B):187, 1972
- Lam, S.K., Ong, G.B.: Identification of two sub-groups of familial early-onset duodenal ulcers. *Ann. Intern. Med.* 93:540, 1980
- Smith, M.P.: Decline in duodenal ulcer surgery. *J.A.M.A.* 237:987, 1977
- Elashoff, D., Grossman, M.I.: Trends in hospital admissions and death rates for peptic ulcer in the United States from 1970 to 1978. *Gastroenterology* 78:289, 1980
- Fineberg, H.V., Pearlman, L.A.: Surgical treatment of peptic ulcer in the United States. Trends before and after the introduction of cimetidine. *Lancet* 1:1305, 1981
- Wyllie, J.H., Clark, C.G., Alexander-Williams, J., Bell, P.R.F., Kennedy, T.L., Kirk, R.M., Mackay, C.: Effect of cimetidine on surgery for duodenal ulcer. *Lancet* 1:1307, 1981
- McKay, A.J., McArdle, C.S.: Cimetidine and perforated peptic ulcer. *Br. J. Surg.* 69:319, 1982
- Dark, J.H., MacArthur, K.: Perforated peptic ulcer in south-west Scotland 1966-1980. *J. R. Coll. Surg. Edinb.* 28:19, 1983
- Watkins, R.M., Dennison, A.R., Collin, J.: What has happened to perforated peptic ulcer? *Br. J. Surg.* 71:774, 1984
- Hendry, W.S., Valerio, D., Kyle, J.: Perforated peptic ulcer in North-East Scotland 1972-1981. *J. R. Coll. Surg. Edinb.* 29:69, 1984
- Koo, J., Ngan, Y.K., Lam, S.K.: Trends in hospital admission, perforation, and mortality of peptic ulcer in Hong Kong from 1970 to 1980. *Gastroenterology* 84:1558, 1983
- Thompson, M.R.: Indomethacin and perforated duodenal ulcer. *Br. Med. J.* 280:448, 1980
- Jorgenson, G.: Drug consumption before perforation of a peptic ulcer. *Br. J. Surg.* 64:247, 1977
- Fong, I.W.: Septic complications of perforated peptic ulcer. *Can. J. Surg.* 26:370, 1983
- Kay, P.H., Moore, K.T.H., Clark, R.G.: The treatment of perforated duodenal ulcer. *Br. J. Surg.* 65:801, 1978
- Donovan, A.J., Vinson, T.L., Maulsby, G.O., Gewin, J.R.: Selective treatment of duodenal ulcer with perforation. *Ann. Surg.* 189:627, 1979
- Kristensen, E.S.: Conservative treatment of 155 cases of perforated peptic ulcer. *Acta Chir. Scand.* 146:189, 1980
- Dean, A.C.B., Clark, C.G., Sinclair-Gieben, A.H.: The late prognosis of perforated duodenal ulcers. *Gut* 3:60, 1962
- Greco, R.S., Cahow, C.E.: Alternatives in the management of acute perforated duodenal ulcer. *Am. J. Surg.* 127:109, 1974
- Jordan, P.H.: Proximal gastric vagotomy without drainage for treatment of perforated duodenal ulcer. *Gastroenterology* 83:179, 1982
- Choi, S.K.Y., Boey, J., Alagaratnam, T.T., Poon, A., Wong, J.: Proximal gastric vagotomy in emergency peptic ulcer perforation. *Surg. Gynecol. Obstet.* 163:531, 1986