Prognostic indicators of successful endoscopic sclerotherapy for prevention of rebleeding from oesophageal varices in cirrhosis: a long-term cohort study

S. Madonia
G. D'Amico
M. Traina
G. Gatto
R. Virdone
N. Salamone [1]
A. Licata [1]
I. Tarantino [1]
L. Pagliaro [1]

Background. *Although band ligation is now recommended for prevention of rebleeding from oesophageal varices in cirrhosis, sclerotherapy is still widely used. Patients submitted to chronic sclerotherapy undergo several endoscopies and experience a large number of serious complications. However, long-term outcome is poorly defined.*
Aims. *To assess the clinical course and prognostic indicators of patients undergoing chronic sclerotherapy for prevention of variceal rebleeding as a basis for future evaluation of long-term band ligation outcome.*
Methods. *Prospective cohort study; prognostic analysis by the Cox proportional hazards model.*
Results. *A total of 218 consecutive cirrhotic patients (37 Child class A, 154 B, 27 C) were enrolled in the study. Varices were obliterated in 139 (64%) patients in a mean of 5 (±2.6) sessions and recurred in 58/139 (41.7 %) within one year. A total of 132 (60%) patients experienced 283 rebleeding episodes and 73 (33%) died. Bleeding from oesophageal ulcers was the most serious complication causing 14% of all rebleeding episodes. Significant prognostic indicators of sclerotherapy outcome were: Child-Pugh class for variceal obliteration; gastric varices and platelet count for recurrence of varices; failure to obliterate varices, variceal size and gastric varices for rebleeding; blood urea nitrogen and failure to obliterate varices for death. Presence of gastric varices was the only prognostic indicator for death in the 79 patients not achieving variceal obliteration. A mean of 10 endoscopies and of 6 hospital admissions were needed per each patient with an estimated cost of US$ 7154 per patient during the first two years of therapy.*
Conclusions. *Sclerotherapy is a very demanding and costly treatment, and is associated with frequent and serious side-effects. The probability of treatment failure is significantly higher in Child C patients with gastric varices. Alternative treatments should be considered for these patients.*

From:
Department of Medicine, Ospedale "V. Cervello", Palermo; [1] Clinica Medica R, Università di Palermo, Palermo, Italy.

Address for correspondence:
Dr. G. D'Amico, Dipartimento di Medicina, Ospedale "V. Cervello", via Trabucco 180, 90146 Palermo, Italy.
Fax +39-091-6885111.
E-mail: gedamico@libero.it

Submitted June 14, 2000.
Revised October 26, 2000.
Accepted November 10, 2000.

Digest Liver Dis 2000;32:782-91

Key words: liver cirrhosis; prognostic indicators; sclerotherapy of oesophageal varices; variceal bleeding

Introduction

Sclerotherapy is still widely used for the prevention of variceal rebleeding even though it is now recommended that elastic band ligation is to be preferred [1,2]. Even if sclerotherapy reduces the risk of rebleeding from oe-

sophageal varices by approximately half[3,4], it does requires a large number of endoscopies to achieve and maintain variceal obliteration during the course of the disease. It is also associated with a marked incidence of side-effects[5] which are frequently so severe as to require specific and urgent treatment. Therefore, patients treated with chronic sclerotherapy for the prevention of rebleeding, as already pointed out will undergo many endoscopies and, moreover, frequent hospital admissions to monitor the effects of therapy and to treat the complications. To optimise the efficiency of chronic sclerotherapy only those patients with the lowest probability of treatment failure should be selected, choosing alternative techniques for patients in whom failure is more likely. However, although several prospective studies have assessed the post therapeutic course of patients undergoing sclerotherapy[6,7], prognostic indicators of sclerotherapy failure are poorly defined. Furthermore, better knowledge of prognostic indicators of sclerotherapy outcome may serve for future evaluation of long-term ligation.

Therefore, the aim of the present prospective cohort study of the clinical course in patients submitted to chronic sclerotherapy of oesophageal varices for the prevention of rebleeding from oesophageal varices, was to assess the prognostic indicators of treatment failure.

Methods

Patients

All cirrhotic patients (total 218, 136 males, 82 females) with recent bleeding from oesophageal varices, consecutively submitted to sclerotherapy of oesophageal varices for the prevention of recurrent bleeding from oesophageal varices at our department from July 1985 to June 1996, were prospectively enrolled in the study (Table I). Diagnosis of cirrhosis was based on a previous liver biopsy or on compatible clinical, laboratory and imaging findings. The aetiology of cirrhosis was considered to be alcoholic when patients, or their relatives, admitted an alcohol consumption of 80 g/day for at least 5 years. Routine anti-HCV (hepatitis C virus) test was not available in our Department until 1992, and was, therefore, performed only in some of the patients studied. Variceal size was defined according to the criteria of the Italian Liver Cirrhosis Project [8]. When present, gastric varices were classified according to Korula et al. [9] as junctional when varices appeared as a continuation of oesophageal varices along the lesser curvature of the stomach and fundal when they extended to the fundus, distal to the gastro-oesophageal junction, or were confined to the fundus, without apparent continuity with the oesophageal varices.

At our Department, patients are submitted to sclerotherapy for the prevention of recurrent variceal bleeding if they had previously presented variceal bleeding under ß-blocker treatment or if they have contraindications or are intolerant to ß-blockers. These patients represent 20-25% of the whole population of cirrhotic patients presenting with upper digestive bleeding. Of the remaining, some 25% die during the hospitalization and approximately 50% are treated by β-blockers.

Sclerotherapy and endoscopic follow-up

Sclerotherapy was started at emergency endoscopy or within 48 hours of the termination of bleeding. Intravariceal injections (1-2 ml) of 1.5% sodium-tetradecyl-sulphate up to a total of 8-12 ml were performed at each session. Sclerotherapy sessions were repeated at 7-10 day intervals until variceal obliteration. Endoscopy was repeated six months after obliteration of varices and yearly thereafter. Patients remained in hospital for 24 hours after each sclerotherapy session. Variceal recurrence was treated by a further course of sclerotherapy until obliteration.

Clinical follow-up and outcomes of interest

Patients were monitored every three months or whenever required. At each check-up biochemical liver and renal function tests and blood cell count were recorded as well as the appearance or worsening of signs of liver decompensation. Continued alcohol intake was assessed by interviewing the patients and their relatives. The outcomes of interest for the prognostic assessment were defined as follows:

- variceal obliteration: disappearance of oesophageal varices or visible vessels with obliterated lumen confirmed by failure to inject sclerosant within them;
- failure to obliterate varices: variceal obliteration not achieved within six months of sclerotherapy;
- recurrence of varices: reappearance of injectable varices after eradication;
- recurrent bleeding: any episode of haematemesis or melena following inclusion in the study after the first sclerotherapy session;
- death from any cause.

Index bleeding and rebleeding episodes were treated by terlipressin (2 mg every 6 hours intravenously (iv) for 24 hours) or somatostatin (250 μg/h as a continuous 24-hour intravenous infusion after an initial bolus injection of 250 μg, which was repeated at 8-hour intervals), emergency sclerotherapy, and balloon tamponade, according to a standard protocol routinely in use at our institution. Blood transfusions were given only when the blood haemoglobin concentration was <8 g/dl.

The following side-effects of sclerotherapy were sought: thoracic pain, dysphagia, fever or pleural effusion requiring treatment, post-injection bleeding requiring prolongation of hospital stay or active treatment, bleeding from oesophageal ulcers, oesophageal perforation, mediastinitis. The search for side-effects was based on patient interview and physical examination. When asymptomatic pleural effusion was suspected at physical examination, a chest X-ray was performed. Portal hypertensive gastropathy was defined as mild when the gastric mucosa showed a "mosaic" pattern (multiple erythematous areas outlined by a white reticular network) or a "scarlatina-like" pattern (a fine pink speckling) on endoscopy, whereas severe gastropathy was defined by the presence of cherry red spots [5]. Portal vein flow was monitored by doppler ultrasound (US) every six months to identify portal vein thrombosis. All patients were followed until June 1997 or until death.

Statistical analysis

Patients characteristics at inclusion in the study were described as proportions or means, as appropriate. Differences between means were assessed by Student's t test and differences observed on contingency tables were assessed by the χ^2 test. The mean number of endoscopies per patient and per months of observation was calculated as follows: [Σ(total endoscopies/num-

Table I. Clinical characteristics of patients.

Clinical characteristics	Whole series (n=218)	Variceal obliteration Yes (n=139)	Variceal obliteration No (n=79)	Recurrence of varices Yes (n=58)	Recurrence of varices No (n=81)	Rebleeding Yes (n=132)	Rebleeding No (n=73)	Death Yes (n=145)	Death No
Male sex	136	86	50	40	43	82	54	51	85
Age (mean ± SD)	60.1±11	59.6±10	61.1±11	58.7±11	60.32±11	59.6±11	61±10	60.4±10	60±11
Alcohol >80 mg/day	30	22	8	8	14	21	9	16	14
HbsAg+	17	11	6	4	7	10	7	6	11
Anti-HCV[#]	70/88	43/55	27/33	19/24	24/31	42/53	28/35	23/29	47/59
Child-Pugh									
A	37	28	9	8	20	17	20	10	27
B	154	100	54	42	58	93	61	53	101
C	27	11	16	8	3	22	5	10	17
Ascites	99	54	45	27	27	67	32	41	58
PSE	21	12	9	4	8	13	8	12	9
HCC	18	12	6	7	5	9	9	5	11
BUN mg/dl[¶]	49.2±23	49.3±20	49.1±24	47.5±22	50.2±27	49.5±23	48.8±23	55.5±27	46±20
Platelet x 1000/ml[¶]	107±54	105±52	106±57	101±54	112±51	106±54	109±54	100±51	111±56
Haemoglobin g/dl[¶]	101±5.8	9.9±2	10.5±9	103±2	9.7±2	9.7±2	10.8±9	9.7±11	9.8±2
>1 previous bleed	140	92	48	32	60	84	56	47	93
Variceal size									
Small	6	5	1	5	0	2	4	2	4
Medium	34	26	8	11	15	14	20	4	30
Large	178	108	70	42	66	116	62	67	111
Gastric varices									
Absent	166	111	55	48	63	98	68	53	113
Junctional	22	15	7	6	9	13	9	6	16
Fundal	30	13	17	4	9	21	9	14	16
PHG	28	21	7	10	11	19	9	11	17
Portal vein thromobosis	8	4	4	3	1	5	3	2	6
β-blockers	63	45	18	20	25	43	20	19	44

PSE: portal-systemic encephalopathy; HCC: hepato-cellular carcinoma; BUN: blood urea nitrogen; [¶] mean ± standard deviation; PHG: portal hypertensive gastropathy; [#] routine anti-HCV determination was available after 1992 and was performed in 88 patients.

ber of months of follow-up)]/number of patients. Cumulative proportions of patients free of each of the outcomes of interest were computed by the Kaplan and Meier method and the observed differences were assessed by the log-rank test [10]. Prognostic indicators of each outcome were assessed by the Cox model for proportional hazards [11]. Candidate prognostic variables were selected from the clinical and endoscopic patient characteristics recorded at the inclusion in the study (Table I) for the prediction of failure to obliterate varices, rebleeding and death and, at the time of variceal obliteration, for the prediction of recurrence of varices. The number of variables to include in each of the final models was reduced by univariate analysis and by clinical judgement taking also into account previously reported significant prognostic indicators in cirrhosis [12-15], in order to include in the model approximately 1 variable per 5-10 observed events [16].

Results

Patients and follow-up

Clinical characteristics of the 218 patients included in the study are shown in Table I. Aetiology of cirrhosis was alcohol abuse in 30 patients, HBV infection in 17; it was possible to determine anti-HCV in only 88 patients and 70 (79.5%) of them resulted positive to the test. This prevalence of HCV infection corresponds to the prevalence we are currently observing in the population of cirrhotic patients admitted to our Department. It is, therefore, conceivable that the aetiology of cirrhosis in the 83 patients in whom anti-HCV was not determined, was, indeed, HCV infection, at least in the majority of them. Of the 30 patients who admitted alcohol abuse over the past 5 years, none was actively consuming alcohol at the time of inclusion in the study, and none admitted further alcohol abuse, during follow-up. Only 78 out of 218 were admitted at the time of their first variceal bleeding whereas the mean (± SD) of previous bleeding episodes was 1.9 (± 1.6) in the remaining 140 patients. Overall, 162 patients underwent the first sclerotherapy session during active variceal bleeding. A total of 63 patients, admitted after failure of β-blockers for the prevention of rebleeding, received sclerotherapy associated with a non selective β-blocker. In these patients, compliance with the β-blocker treatment was assessed, during follow-up, by checking the heart rate reduction of 25% with respect to the resting heart rate before treatment. The other 77 patients with previous bleeding who were not receiving treatment for the prevention of recurrent bleeding had not been previously observed at our department. Possibly, they were not treated on account of contraindications or intolerance to β-blockers identified in the peripheral hospitals in which they were admitted at the time of the first bleeding and where sclerotherapy was not available. The median follow-up was 14 months (range 1 to 96; mean 22.4±21.6). No patient was lost to follow-up. A total of 2,143 endoscopies were needed, and the mean number of endoscopies per patient and per month was 1.02±1.13.

Variceal obliteration

Variceal obliteration was achieved in 139/218 patients (64%) in a mean (± SD) of 5 (±2.6) sclerotherapy sessions in 2.4 (±2.0) months. The cumulative proportion of patients with obliterated varices after 6 months was 69% (Fig. 1).

The median follow-up in the 139 patients in whom variceal obliteration was achieved was markedly longer than in those in whom varices were not obliterated being: 24 (range 1 to 96; mean 28±21) and 6 months (range 1 to 96; mean 13±20), respectively. The median number of endoscopies was 8 (range 2 to 40) in patients whose varices were obliterated and 5 (range 2 to 17) in those in whom obliteration was not achieved; however, the mean number of endoscopies per month of follow-up was significantly lower in patients with successful variceal obliteration (0.68±0.67 vs 1.62±1.48, respectively; $p<0.00001$).

Eleven candidate prognostic variables of failure to obliterate varices were entered in the final Cox model: sex, age, Child-Pugh class, blood urea nitrogen (BUN), platelet count, haemoglobin, number of previous variceal bleeding episodes, variceal size, gastric varices, portal vein thrombosis on ultrasounds (US) and combination therapy with β-blockers. Only the Child-Pugh class was significantly associated with the

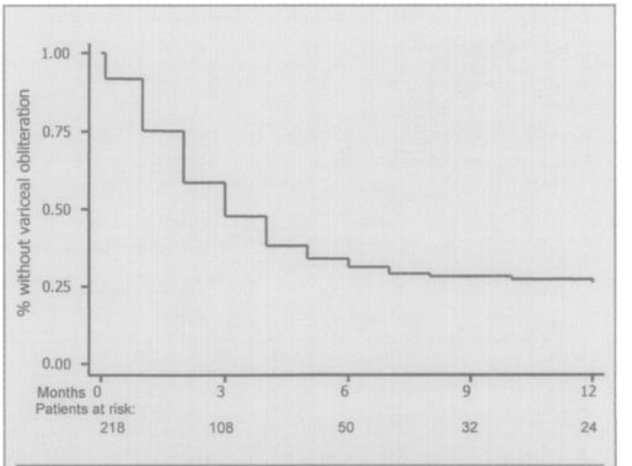

Fig. 1. Percentage of patients without variceal obliteration. Numbers below abscissa denote the number of patients in each observation period.

Table II. Prognostic indicators of sclerotherapy.

Variable and scoring	Failure to obliterate varices (n = 218) HR	p	Recurrence of varices (n = 139) HR	p	Rebleeding (n = 218) HR	p	Death (n = 218) HR	p
Child-Pugh class A = 1 B = 2 C = 3	1.55	0.006	–	NS	1.33[¶] 1.67[$]	0.028[¶] 0.04[$]	1.55[¶]	0.05[¶]
Gastric varices Absent = 0 Junctional = 1 Fundal = 2	–	NS	1.4	0.01	1.36[*] 1.5[£]	0.013[*] 0.007[£]	2.3[£]	<0.0001[£]
Platelet >80000 = 0 ≤80000 = 1	-	NS	1.5	0.03	–	NS	–	NS
Variceal size Small = 1 Medium = 2 Large = 3	–	NS	–	NS	1.9 1.77[*] 1.8[$]	0.007 0.04[*] 0.04[$]	–	NS
Variceal obliteration Yes = 0 No = 1	–	NS	–	NS	1.82	0.001	3.03	<0.0001
BUN: mg/dl	-	NS	-	NS	-	NS	1.015 1.013[¶] 1.017[$]	0.001 0.002[¶] 0.002[$]

HR: hazard ratio; BUN: blood urea nitrogen; ns: not significant; [¶] By removing from model variceal obliteration and number of sclerotherapy sessions needed to achieve variceal obliteration; [*] Before variceal obliteration; [$] After variceal obliteration; [£] Among patients not achieving variceal obliteration.

risk of failure to obliterate varices (p=0.006; Table II). The cumulative percentages of patients with obliterated varices after six months were 83% in Child-Pugh class A, 69% in B, 51% in C (p=0.01; log-rank test; Fig. 2).

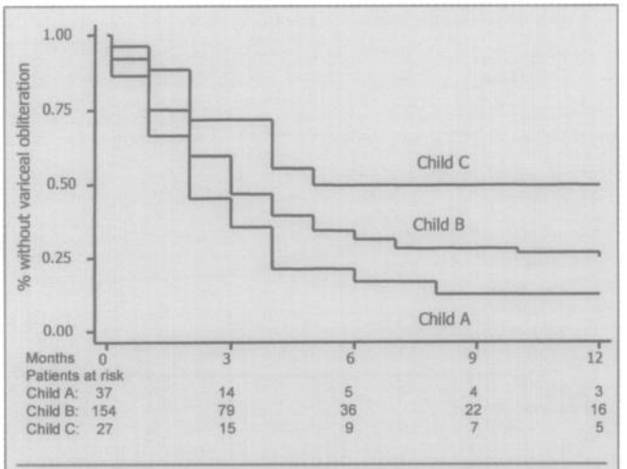

Fig. 2. Percentage of patients without variceal obliteration according to Child-Pugh class. Numbers below abscissa denote number of patients in each observation period.

Recurrence of varices

Varices recurred at least once in 58 out of 139 patients (41.7%) within 1 year of obliteration (Fig. 3). A second course of sclerotherapy led to re-obliteration of varices in 51/58 patients (87.9%). A second recurrence following re-obliteration was observed in 11 patients and more than 2 recurrences in 11.

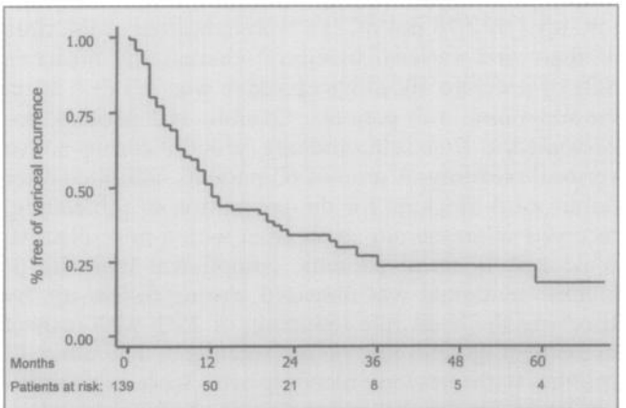

Fig. 3. Percentage of patients free of variceal recurrence in the 139 patients who achieved variceal obliteration. Numbers below abscissa denote number of patients still at risk in each observation period.

Candidate prognostic indicators of the first variceal recurrence were: sex, age, number of previous variceal bleeding episodes, Child-Pugh class, BUN, platelet count, haemoglobin, variceal size before sclerotherapy, gastric varices, portal hypertensive gastropathy, portal vein thrombosis on US, number of sclerotherapy sessions needed to achieve variceal obliteration and combination therapy with ß-blockers. Two variables were found to be significant independent predictors of variceal recurrence: gastric varices (hazard ratio 1.4, confidence interval (CI) 1.1 to 1.9, p=0.01) (Fig. 4) and platelet count ≤80000/μL (hazard ratio 1.5, CI 1.04 to 2.5, p=0.03) (Table II).

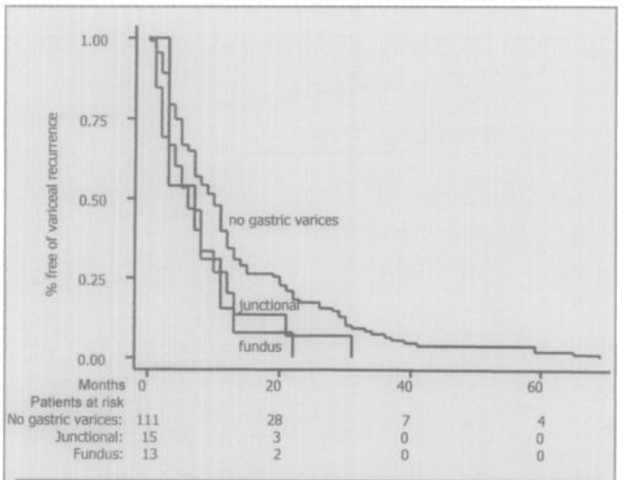

Fig. 4. Percentage of patients free of variceal recurrence according to gastric varices in the 139 patients who achieved variceal obliteration. Numbers below abscissa denote number of patients still at risk in each observation period.

Rebleeding

Overall 136 out of the 218 patients rebled during follow-up. Of these, 102 rebled before, and 34 after, variceal obliteration: causes of rebleeding are shown in Table III. Cumulative proportion of patients free of rebleeding was 42% after 1 year and 32% after 2 years. The following variables were included in the final Cox model for the analysis of the prognostic indicators of rebleeding: sex, age, Child-Pugh class, portal vein thrombosis on US, variceal size, gastric varices, portal hypertensive gastropathy, number of sclerotherapy sessions needed to obliterate varices, variceal obliteration, BUN, platelet count, number of previous variceal bleeding episodes, haemoglobin, β-blocker therapy. Independent predictors of the risk of rebleeding were: variceal size (hazard ratio 1.9; CI 1.19 to 3.04; p=0.007) and failure to obliterate varices (hazard ratio 1.82; 95% CI 1.26 to 2.63; p=0.001) (Fig. 5, Table II). When removing the number of sclerotherapy sessions

Table III. Causes of rebleeding.

	Before obliteration	After obliteration	Overall (136 patients)
Varices	72	13	85
Portal hypertensive gastropathy	6	16	22
Oesophageal ulcer	16	3	19
Fundal varices	4	–	4
Undefined	4	2	6
Total	102	34	136

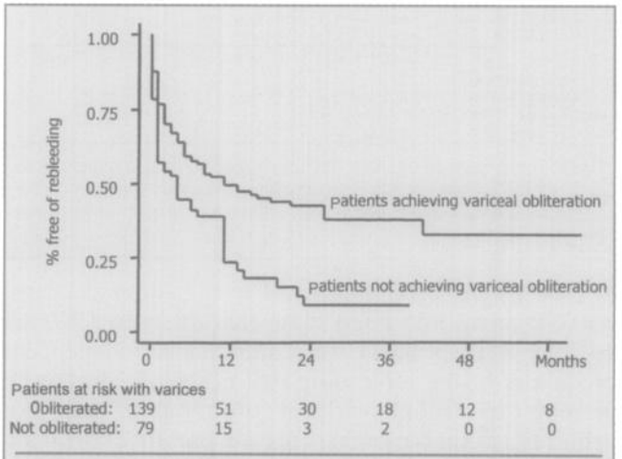

Fig. 5. Percentage of patients free of rebleeding according to variceal obliteration. Numbers below abscissa denote number of patients still at risk in each observation period.

needed to obliterate varices and variceal obliteration from the model, only the Child-Pugh class was found to be a significant indicator of the risk of rebleeding (hazard ratio 1.33; 95% CI 1.03 to 1.74; p=0.028).

During the course of sclerotherapy, before variceal obliteration, 102 patients out of the whole series of 218 bled. The proportion of patients free of bleeding before variceal obliteration (computed by censoring the observation at the time of variceal obliteration) was 26% 1 year after starting sclerotherapy. Variceal size (hazard ratio 1.77, CI 1.02 to 3.07; p=0.04) and gastric varices (hazard ratio 1.36, CI 1.07 to 1.75; p=0.013) (Fig. 6) were the only significant, independent predictors of rebleeding risk by the Cox model analysis including the same set of variables as for the overall analysis of the rebleeding risk indicators.

After variceal obliteration, 48 out of 139 (34%) rebled: one- and two-year cumulative proportions of patients free of rebleeding after variceal obliteration were 72% and 62%, respectively (Fig. 5). A separate analysis in this subgroup of patients, including the same set of variables as for the whole population, showed that variceal size (hazard ratio 1.80, CI 1.03 to 3.10;

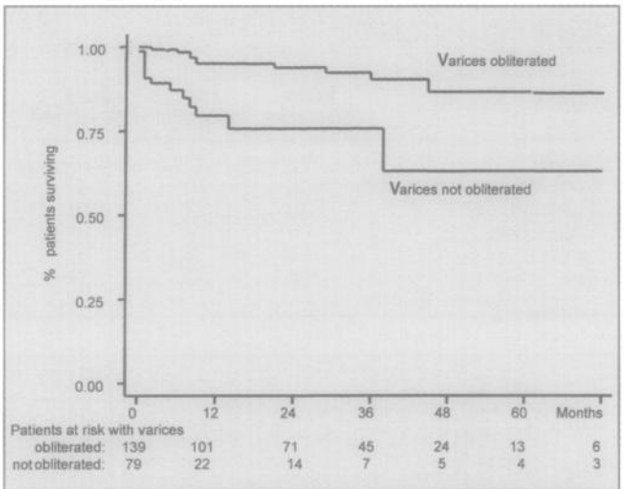

Fig. 6. Percentage of patients free of rebleeding before obliteration, according to presence and type of gastric varices. Numbers below abscissa denote number of patients still at risk in each observation period.

p=0.04) and Child-Pugh class (hazard ratio 1.67; CI 1.02 to 2.70; p=0.04) were significant, independent predictors of the rebleeding risk (Table II). In the 79 patients in whom variceal obliteration was not achieved within 6 months, only the presence of gastric varices was an independent predictor of rebleeding (hazard ratio 1.5; p=0.007).

Survival

Overall, 73 out of 218 patients (33%) died. Causes of death are reported in Table IV. Cumulative proportion of surviving patients was 78% after 1 year and 72% after 2 years. The following variables were included in the final Cox model for the analysis of prognostic indicators of death: sex, age, Child-Pugh class, portal vein thrombosis on US, variceal size, gastric varices, variceal obliteration, BUN, number of previous variceal bleeding episodes, haemoglobin, ß-blocker therapy. The analysis showed that only failure to obliterate varices (hazard ratio 3.03, CI 1.84 to 4.82; p<0.0001) (Fig. 7) and BUN (hazard ratio per each increment of 1 mg/dl of BUN: 1.015, CI 1.010 to 1.024; p=0.001) were significant death risk indicators (Table II). When removing from the model the number of sclerotherapy sessions needed to obliterate varices and variceal obliteration, the Child-Pugh class (hazard ratio 1.55; 95% CI 1.00 to 2.45; p=0.05) and BUN (hazard ratio for each increment of 1 mg/dl of BUN: 1.013, CI 1.004 to 1.021; p=0.002) were found to be a significant indicator of the risk of rebleeding.

A separate analysis, including the same set of variables, showed that BUN (p=0.002, Table II) was the only independent predictor of death risk after variceal obliteration in the 139 patients achieving this goal, and that gastric varices (p=0.001) did so among the 79 patients not achieving variceal obliteration (Table II) (Fig. 8).

Table IV. Causes of death.

Variceal bleeding	25 (34.2%)
Liver failure	27 (36.9%)
Hepatocellular carcinoma	8 (10.9%)
Sepsis	7 (9.5%)
Unrelated to liver disease	6 (8.2%)
Total	73

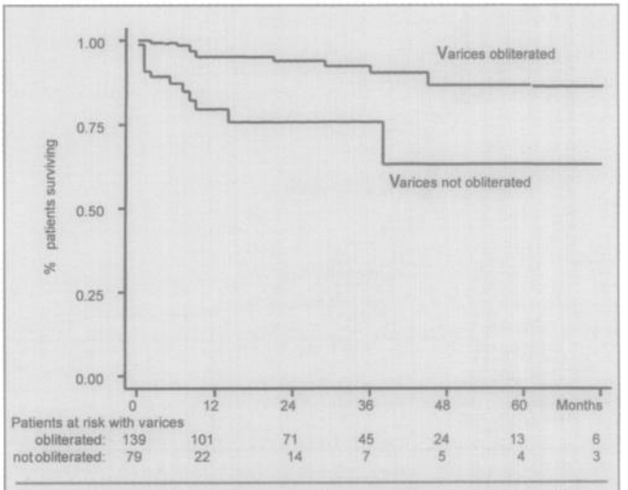

Fig. 7. Percentage of patients surviving according to variceal obliteration. Numbers below abscissa denote number of patients still at risk in each observation period.

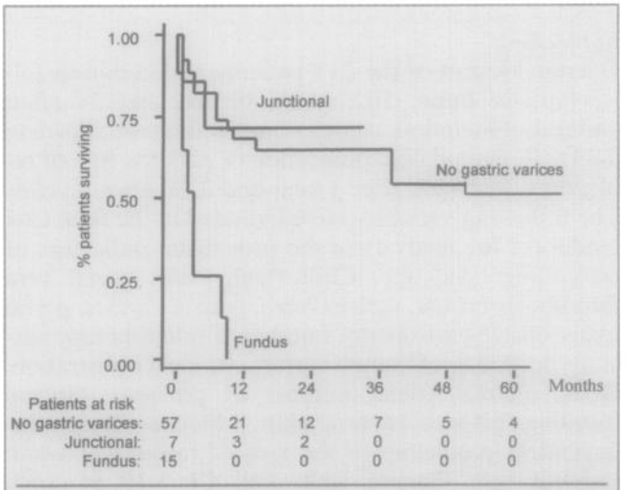

Fig. 8. Percentage of patients surviving, according to presence and type of gastric varices. Numbers below abscissa denote number of patients still at risk in each observation period.

Complications
A total of 135 patients (62%) developed at least one oesophageal ulcer. The most serious complication was bleeding from these ulcers, which was the source of 14% of the rebleeding episodes. No patient experienced symptomatic oesophageal stenosis requiring mechanical oesophageal dilatation. No other serious complications, such as mediastinitis or oesophageal perforation, occurred (Table V).

Table V. Side effects.

Thoracic pain	14 (6.4%)
Dysphagia requiring oesophageal dilatation	0
Fever or pleural effusion requiring treatment	5 (2.3%)
Bacterial peritonitis	5 (2.3%)
Post injection bleeding requiring treatment	11 (5%)
Oesophageal ulcers	135 (62%)
≥1 bleeding from variceal ulcer	15 (6.8%)
Oesophageal perforation	0
Mediastinitis	0

Other clinically relevant events
Portal hypertensive gastropathy was present in 28 patients at inclusion in the study and developed during follow-up in 58 out of 139 (42%) patients achieving variceal obliteration and in 15 out of 79 (19%) failing to reach variceal obliteration (p=0.0006). It was the source of rebleeding in 14% of the entire series of patients and in 20% of the 139 patients achieving variceal obliteration.
Gastric varices were present in 52 out of 218 patients (24%) at inclusion in the study, junctional in 22 (10%) and fundal in 30 (14%). During follow-up, gastric varices disappeared in 20 (82%) of the 22 patients with junctional varices and in 20 (66%) of the 30 with fundal varices at inclusion, whereas new varices appeared at the oesophago-gastric junction in 9 out of the 166 (7%) patients free of gastric varices when they started on sclerotherapy and in the fundus in 2/166 (1%).
Portal vein thrombosis was present in 8 patients at inclusion in the study and developed during follow-up in 9 more patients [8 of the 139 with variceal obliteration and 1 of the 79 without (p=0.10)].

Costs of sclerotherapy
Overall, the mean number of endoscopies per each patient was 9.8±6.2. The indication to endoscopy was sclerotherapy in 60% and follow-up assessment in 40% of the procedures. According to Medical charges in USA [7] the cost of one endoscopy is US$ 260, US$ 453 for one sclerotherapy session and US$ 566 for one day of hospitalization. Based on these figures, it can be estimated that the mean cost to treat a patient with sclerotherapy for the prevention of rebleeding is about US$ 7,200±3,200 in a mean follow-up time of 22.4±21.6 months.
According to the costs of these procedures at our hospital (i.e., Lit. 250,000 for one endoscopy, Lit. 750,000 for one sclerotherapy session and Lit. 600,000 for one day in hospital) the mean cost of one course of sclerotherapy is Lit. 9,100,000±5,900,000.

Discussion

This large cohort study showed that sclerotherapy of oesophageal varices for the prevention of rebleeding, is a very demanding therapy which requires a large number of endoscopies due to the need for endoscopic follow-up and repeated courses of sclerotherapy for the many patients with recurrence of varices. Moreover, complications are not rare and may require hospital admission, in some cases in an intensive care unit. Clearly, this discouraging picture may not reduce the favourable effect of sclerotherapy shown in several RCTs and meta-analyses [3,4]. However, our study explored the less well-known reality of the long-term outcome of sclerotherapy beyond the ideal situation of clinical trials, which usually do not assess the overall impact of a therapy in clinical practice.
Although the clinical impact of this study is greatly reduced by the rapid spreading of band ligation, which is now recommended, in several guidelines, as the best endoscopic therapy for the prevention of rebleeding in cirrhosis [1,2], it might be useful as a basis for future reassessment of the efficiency of band ligation when long-term outcome studies become available also for this therapeutic approach. For example, it is noteworthy, in this respect, that several recently published RCTs [17-20], comparing band ligation with sclerotherapy, reported a higher recurrence rate of varices in patients undergoing band ligation. If this observation is confirmed by other studies, it could reduce or even abolish the advantage of band ligation vs sclerotherapy, in the long term.
Outcome of treatment in this consecutive cohort of patients was rather poor: variceal obliteration was achieved in two thirds of the patients, more than half of the patients rebled during the first year and one third died. Of course, outcome depends mainly on the severity of the liver disease. However, it is also conceivable that the overall outcome is affected by sclerotherapy due to ensuing complications, although this potential harm was not apparent in the clinical trials where selected patients were enrolled.
Variceal obliteration was achieved in 64% of patients, a proportion similar to that reported in a RCT in which the same sclerosant was used as in the present study, as

well as a similar sclerotherapy technique [21]. Failure to obliterate varices was predicted only by the Child-Pugh class, with a higher risk in C-class patients, whereas variceal size, previously suggested as an important predictor of sclerotherapy failure [22], was not confirmed. On the other hand, the prognostic role of the Child-Pugh class is in keeping with the known relationship between severity of liver dysfunction and portal hypertension [23]. As expected, the recurrence rate of varices, in the first year after eradication, was almost 50%, the risk of rebleeding was very high before variceal obliteration and was almost halved after eradication of the varices.

This study shed further light on the role of gastric varices during the course of sclerotherapy of oesophageal varices. Patients with gastric varices, either junctional or fundal, had a significantly higher risk of rebleeding before achieving obliteration of oesophageal varices and those with fundal varices also had a significantly higher risk of death, in this time frame. Similar findings were previously reported by Korula et al. [9] although they did not perform a separate analysis bearing in mind the obliteration of oesophageal varices, and we failed to confirm the prognostic value of gastric varices when the whole follow-up, including also the follow-up time after variceal obliteration, is taken into account. Furthermore, gastric varices disappeared during the course of sclerotherapy in several patients, even when they were located in the fundus, and appearance of newly formed gastric varices was rare. It is also of interest that the presence of gastric varices was a significant prognostic indicator of the risk of early recurrence of oesophageal varices.

Other important prognostic indicators emerging from this study are: platelet count, variceal size, Child-Pugh class and BUN, which are well-known prognostic indicators in cirrhosis [12-14] and it is not surprising that they may also predict the outcome of patients undergoing sclerotherapy of oesophageal varices. Based on the prognostic information provided by our study, it might be suggested that Child-Pugh A and B-class patients, not presenting gastric varices, are the best candidates to sclerotherapy. Child C patients have the lowest probability of successful obliteration of varices and those with gastric varices have the highest risk not only of rebleeding and death before variceal obliteration but also of variceal recurrence. Therefore, these patients at higher risk of sclerotherapy failure should be first considered for alternative treatments. TIPS, particularly in candidates for liver transplantation, might be a perspective if β-blockers have failed and band ligation is not feasible. In those patients at high risk and not suitable for other therapies, a brief course of sclerotherapy should be attempted and when obliteration of varices is achieved, a closer endoscopic follow-up should be planned in those patients with gastric varices because of the higher risk of recurrence of oesophageal varices.

Unfortunately we were only recently able to perform endosonography and, therefore, we could not assess whether the prognostic indicators that we found are independent of the presence of large para-oesophageal varices, recently reported as predictors of both failure of sclerotherapy [24] and recurrence of oesophageal varices [25]. This relationship should be assessed in further studies as well as whether all these prognostic indicators also apply to elastic band ligation, as recently reported for the presence of large para-oesophageal varices for the risk of recurrence of varices [26].

The attempt to obliterate varices and to proceed with early treatment of recurrences, required an extremely large number of endoscopies: approximately one every three months, for successful sclerotherapy, and three every two months when sclerotherapy failed to obliterate varices. Nearly two thirds of the patients developed oesophageal ulcerations and these were the third most frequent cause of rebleeding (14%). Although it is still unclear as to whether it should be considered a complication of sclerotherapy [27], portal hypertensive gastropathy developed significantly more frequently in patients achieving variceal obliteration than in those in whom obliteration failed, and was the cause of another 14% of rebleeding episodes. Therefore, even if no other serious complications were observed in this series of patients, it might be conceived that near 28% of rebleeding episodes are a consequence of sclerotherapy itself. Portal vein thrombosis was rarely observed, probably confirming the previously reported finding that sclerotherapy is not associated with an increased risk of portal vein thrombosis [28].

The lack of other serious complications was probably due to the relatively non aggressive sclerotherapy that we used following an earlier observation that the complication rate of sclerotherapy by means of sodium tetradecyl-sulphate was related to the total amount of the drug injected in each sclerotherapy session [29].

The mean cost of the sclerotherapy programme was US$ 7,200 for a mean follow-up of less than 2 years. The comparison with the costs of other treatments would require taking into account many other variables, but this was beyond the scope of our study, and we limited the analysis of costs to endoscopy. The most important source of costs we did not account for concerns the treatment of rebleeding episodes. However, it would probably not appreciably affect a comparison with costs of ß-blockers since the rebleeding rate with these two treatment approaches is comparable [30].

In conclusion, this study shows that the outcome of patients surviving a variceal bleeding episode is general-

ly poor even after sclerotherapy. Sclerotherapy is not an easy approach for patients and implies a strict endoscopic follow-up, high rate of complications and considerable costs. The best candidates for sclerotherapy are patients with Child-Pugh class A or B disease, without gastric varices. Whether these prognostic indicators apply also to elastic band ligation should be assessed in future outcome studies in which this therapy is used.

References

[1] Grace ND. Diagnosis and treatment of gastrointestinal bleeding secondary to portal hypertension. Practice guidelines. Am J Gastroenterol 1997;92:1081-91.

[2] Grace ND, Groszmann RJ, Garcia-Tsao G, Burroughs AK, Pagliaro L, Makuch RW, et al. Portal hypertension and variceal bleeding: an AASLD single topic symposium. Hepatology 1998;28:868-80.

[3] Infante-Rivard C, Esnaola S, Villeneuve JP. Role of sclerotherapy in the long term management of variceal bleeding: a meta-analysis. Gastroenterology 1989;96:1087-92.

[4] D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. Hepatology 1995;22:332-54.

[5] Schuman BM, Berkman JW, Tedesco FJ, Griffin JW Jr, Assad RT. Complications of endoscopic injection sclerotherapy: a review. Am J Gastroenterol 1987;82:823-9.

[6] Hashizume M, Kitano S, Koyanagi N, Tanoue K, Ohta M, Wada H, et al. Endoscopic injection sclerotherapy for 1000 patients with esophageal varices. A nine year prospective study. Hepatology 1992;15:69-75.

[7] Walked I, Korula J. Analysis of long term endoscopic surveillance during follow up after variceal sclerotherapy from a 13-year experience. Am J Med 1997;102:192-9.

[8] Zoli M, Merkel C, Magalotti D, Marchesini G, Gatta A, Pisi E. Evaluation of a new endoscopic index to predict first bleeding from the upper gastrointestinal tract in patients with cirrhosis. Hepatology 1996;24:1047-52.

[9] Korula J, Chin K, Ko Y, Yamada S. Demonstration of two distinct subsets of gastric varices. Observations during a seven-year study of endoscopic sclerotherapy. Dig Dis Sci 1991;36:303-9.

[10] Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV. Design and analysis of randomized clinical trials requiring prolonged observation. II. Analysis and examples. Br J Cancer 1977;35:1-39.

[11] Cox DR. The analysis of binary data. London: Methuen; 1970.

[12] Infante-Rivard C, Villeneuve JP, Esnaola S. A framework for evaluating and conducting prognostic studies: an application to cirrhosis of the liver. J Clin Epidemiol 1989;42:791-805.

[13] Christensen E. Prognostic models in chronic liver disease: validity, usefulness and future role. J Hepatol 1997;26:1414-24.

[14] Pagliaro L, Pasta L, D'Amico G, Puleo A, Politi F, Vizzini G. Natural History of cirrhosis: predictors of death risk; overview of published studies and validation in a new test set. In: Dobrilla G, Felder M, DePretis G, editors. Advances in hepatobiliary and pancreatic disease; 1995. p. 82-93.

[15] Pagliaro L, Peri V, Linea C, Cammà C, Giunta M, Magrin S. Natural history of chronic hepatitis C. Ital J Gastroenterol Hepatol 1999;31:28-44.

[16] Harrell FE Jr, Lee KL, Matchar DB, Reichert TA. Regression models for prognostic prediction: advantages, problems and suggested solutions. Cancer Treat Rep 1985;69:1071-7.

[17] Hou MC, Lin HC, Kuo BIT, Chen CH, Lee FY, Lee SD. Comparison of endoscopic variceal injection sclerotherapy and ligation for the treatment of esophageal variceal hemorrhage: a prospective randomized trial. Hepatology 1995;21:1517-22.

[18] Shiha GE, Farag FM. Endoscopic variceal ligation versus endoscopic sclerotherapy for the management of bleeding varices: a prospective randomized trial. Hepatology 1997;4:136A.

[19] Sarin SK, Govil A, Jain AK, Guptan RC, Issar SK, Jain M, et al. Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. J Hepatol 1997;26:826-32.

[20] Baroncini D, Milandri GL, Borioni D, Piemontese A, Cennamo V, Billi P, et al. A prospective randomized trial of sclerotherapy versus ligation in the elective treatment of bleeding esophageal varices. Endoscopy 1997;29:235-40.

[21] Korula J, Balart LA, Radvan G, Zweiban BE, Larson AW, Kao HW, et al. A prospective randomized controlled trial of chronic esophageal variceal sclerotherapy. Hepatology 1985;5:584-9.

[22] Rose JDR, Crane MD, Smith PM. Factors affecting successful endoscopic sclerotherapy for esophageal varices. Gut 1983;24:946-9.

[23] Vorobioff J, Groszmann RJ, Picabea E, Gamen M, Villavicencio R, Bordato J, et al. Prognostic value of hepatic venous pressure gradient measurements in alcoholic cirrhosis: a 10-year prospective study. Gastroenterology 1996;111:701-9.

[24] Dhiman RK, Chouduri G, Sarasvat VA, Agarwal DK, Naik SR. Role of paraoesophageal collaterals and perforating veins on outcome of endoscopic sclerotherapy for oesophageal varices: an endosonographic study. Gut 1996;38:759-64.

[25] Lin CY, Lin PW, Tsai HM, Lin XZ, Chang TT, Shin JS. Influence of paraesophageal venous collaterals on efficacy of endoscopic sclerotherapy for esophageal varices. Hepatology 1994;19:602-8.

[26] Leung VKS, Sung JJY, Ahuya AT, Tumala IE, Lee TY, Lau JYW, et al. Large paraesophageal varices on endosonography predict recurrence of esophageal varices and rebleeding. Gastroenterology 1997;112:1811-6.

[27] D'Amico G, Montalbano L, Traina M, Pisa R, Menozzi M, Spanò C, et al. Natural history of congestive gastropathy in cirrhosis. Gastroenterology 1990;99:1558-64.

[28] Kawasaki S, Henderson JM, Riepe S, Brooks S, Hertzler G. Endoscopic variceal sclerosis does not increase the risk of portal venous thrombosis. Gastroenterology 1992;102:206-15.

[29] Madonia S, Traina M, Montalbano L, D'Amico G. Variceal ulceration following sclerotherapy: normal consequence or complication? Gastrointest Endosc 1990;36:76-7.

[30] Bernard B, Lebrec D, Mathurin P, Opolon P, Poynard T. Propranolol and sclerotherapy in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. J Hepatol 1997;26:312-24.