Virchows Arch [Pathol Anat] (1985) 406:213–221

Virchows Archiv A

Advanced gastric cancer and prognosis

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Summary. The morphological features of 158 gastric carcinomas were analyzed in an attempt to identify patterns best correlated with prognosis. To this end, the depth of infiltration, vascular invasion, intra- and perineoplastic lymphocytic infiltrate, lymph node metastases and number of metastatic lymph nodes were evaluated according to the several classifications for advanced gastric cancer. A good correlation between prognosis and histological features of malignancy were observed, as well as different five-year survival rates for Mulligan, Lauren and Ming histotypes. However, when the influence of each single morphological criteria of malignancy was examined, these differences disappeared for Mulligan and Lauren histotypes. On the other hand, the better prognosis for Ming expanding type carcinomas appeared unrelated to any individual feature of malignancy.

Key words: Gastric cancer – Prognosis – Morphological features

Introduction

The prognosis in advanced gastric cancer is still very poor (Wei and Hsu 1980) and despite early diagnosis with modern endoscopic technique, the five-year survival rates for advanced disease are low and data reported in the last ten years indicate that they are not related to the type of radical surgery employed (Bizer 1983).

These findings, however, refer to cases of gastric carcinoma in general, regardless of patient sex and age, tumour site, histotype or morphological pattern. In fact, while prognosis is not influenced by the patient's sex (Eisemberg et al. 1967; Lempinen 1971), it is related to age, since cancers arising in very young or old individuals show a very rapid course (Ederer et al.

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1960). In addition, localization at the cardia and in the corpus is associated with a poorer prognosis than antrum sitings (Schmitz-Moormann et al. 1979). Histologic findings, such as histotype, depth of infiltration, vascular invasion, lymph node metastases, and peri- and intra tumour lymphocytic infiltrate also seem to be very important (Black et al. 1971; Gupta et al. 1981; Hawley et al. 1970; Wei and Hsu 1980).

That the histotype influences the prognosis in many neoplasias, including gastric carcinoma, is well known (Correa et al. 1970; Lauren 1965; Ming 1977; Muñoz and Matko 1972; Ribeiro et al. 1981; Stemmermann and Brown 1974). In their classifications, Lauren (1965) and Ming (1977) attempted to differentiate histotypes not only according to morphological pattern, but also in terms of biological behavior. In fact, Lauren diffuse type and Ming infiltrative type carcinomas have a poorer prognosis than Lauren intestinal type and Ming expanding type carcinomas, respectively (Correa et al. 1970; Lauren 1965; Ming 1977; Muñoz and Matko 1972; Ribeiro et al. 1981; Stemmermann and Brown 1974). Both are often associated with other indicies of malignancy, such as deep gastric wall infiltration, vascular invasion, lymph node metastases, etc. (Arslan Pagnini and Rugge 1982; Arslan Pagnini and Rugge in press).

Other classifications for advanced gastric cancer have been proposed by the WHO (1977) and by Mulligan (1954, 1972); the former is purely descriptive, but the latter, which has mostly histogenetic objectives (Arslan Pagnini and Rugge 1983), also has a prognostic significance.

In this study, we analyzed the morphological aspects of gastric carcinoma in an attempt to identify patterns, most influencing prognosis, in reference to the classifications most pertinent to the biology of advanced stomach cancer. To this end, cases of early gastric cancer were excluded because of consistently good prognosis (Elster et al. 1979; Murakami 1979; Ohman et al. 1980; Yamada et al. 1980). Cases with extra lymph node metastases were also excluded, because morphological characteristics in disseminated neoplasia lose their importance in determining the prognosis.

Materials and methods

In the period January 1, 1968 to December 31, 1977, 246 cases of gastric carcinoma were diagnosed at this Institute. From these, we collected cases which were in stage 2 or 3 according to A.J.C. criteria (A.J.C. 1977) (Stage 2 = T2, T3, N0; Stage 3 = T1, T2, T3, T4, N1, N2, N3), and in which 5 year follow-up was available. Cases dying before one-month post surgery were excluded. This series thus refers to 158 cases of gastric carcinoma, consisting of 106 men and 52 women, ranging in age from 23 to 86 years. In each case, routine histological sections (H & E, and PAS) of the primary tumor, as well as the adjacent gastric wall and perigastric lymph node were reviewed in a double-blind crossover study. Each case was then classified according to Mulligan, Lauren and Ming. The reproducibility of each classification been previously stressed (Arslan Pagnini and Rugge 1982). In case of disagreement, the slides were studied together in order to reach consensus. In addition, the depth of infiltration, according to the TNM system (UICC 1974), as well as vascular invasion and intra- and perineoplastic lymphocytic infiltrate, according to Hawley et al. (1970); presence of lymph node metastases and number of metastatic lymph nodes were also noted.

The data were then analyzed according to Peto et al. (1977), using a H.P. 1000 calculator.

Table 1. Age and sex distribution according to histotypes
Mulligan histotypes: I.C. = intestinal cell ca.; P.C. = pylorocardiac gland cell ca.; M.C. = mucous cell ca. *Lauren histotypes:* Int. = intestinal type ca.; Diff. = diffuse type ca.; Uncl = unclassifiable. *Ming histotypes:* Exp. = expanding type ca.; Inf. = infiltrative type ca.

	Age < 39		40–49		50–59		60–69		> 70	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
	9	(5.7)	22	(13.9)	33	(20.9)	67	(42.4)	27	(17.1)
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
	4 (3.7)	5 (9.6)	12 (11.3)	10 (19.2)	24 (22.6)	9 (17.3)	50 (47.2)	17 (32.7)	16 (15.1)	11 (21.2)
Mulligan Histotypes										
IC 38 (26.0)	2 (100)	–	1 (33.3)	2 (66.7)	7 (77.8)	2 (22.2)	14 (73.7)	5 (26.3)	3 (60)	2 (40)
PC 45 (30.8)	1 (100)	–	6 (100)	–	8 (72.7)	3 (27.3)	12 (63.2)	7 (36.8)	4 (50)	4 (50)
MC 63 (43.2)	1 (16.7)	15 (83.3)	4 (33.3)	8 (66.7)	8 (72.7)	3 (27.3)	19 (82.6)	4 (17.4)	7 (63.6)	4 (36.4)
(*12 unclass.)										
Lauren Histotypes										
Int. 71 (44.9)	3 (100)	–	6 (75.0)	2 (25.0)	10 (83.3)	2 (16.7)	27 (75.0)	9 (25.0)	6 (50.0)	6 (50.0)
Diff. 72 (45.6)	1 (16.7)	5 (83.3)	6 (42.9)	8 (57.1)	11 (64.7)	6 (35.3)	19 (79.2)	5 (20.8)	6 (54.5)	5 (45.5)
Uncl. 15 (9.5)	–	–	–	–	3 (75.0)	1 (25.0)	4 (57.1)	3 (42.9)	4 (100)	–
Ming Histotypes										
Exp. 51 (32.7)	1 (100)	–	1 (50.0)	1 (50.0)	11 (68.8)	5 (31.3)	13 (56.5)	10 (43.5)	4 (44.4)	5 (55.6)
Infil. 105 (67.3)	3 (37.5)	5 (62.5)	11 (55.0)	9 (45.0)	12 (75.0)	4 (25.0)	37 (86.0)	6 (14.0)	12 (66.7)	6 (33.3)
(*1 unclass.)										

Table 2. Comparison of Ming and Lauren classifications by number of cases

	Total		Lauren Classification					
			Intestinal		Diffuse		Unclass	
	n	%	*n*	%	*n*	%	*n*	%
Ming Classification								
Expanding	52	33.1	36	69.2	10	19.2	6	11.6
Infiltrative	105	66.9	35	33.3	62	59.1	8	7.6
Total			71	45.2	72	45.9	14	8.9

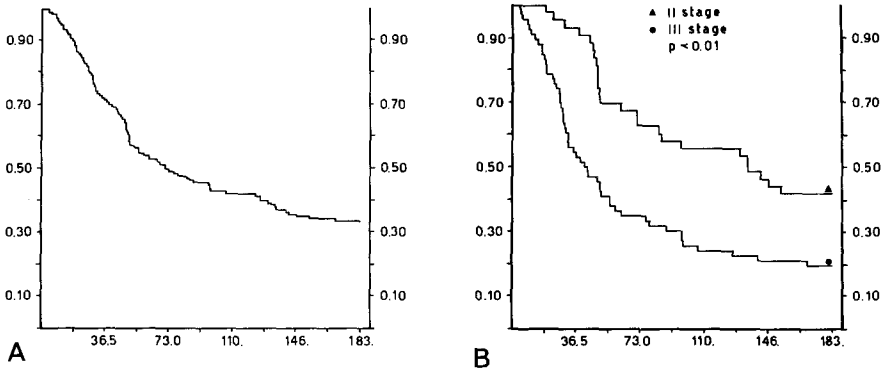

Fig. 1. Overall and A.J.C.-stage five-year survival rates

Results

38,8% of the patients were in stage II, and 61,2% were in stage III. Table 1 reports patient distribution according to age, sex, and Mulligan, Lauren and Ming classifications. Table 2 shows the correspondence we observed between Ming and Lauren histotypes.

Overall and A.J.C.-stage real five-year survival rates are shown in Fig. 1.

Patient sex and age were not significantly correlated with survival, but the morphological features of malignancy were well correlated with prognosis. As shown in Fig. 2, in fact, cases with deeper gastric wall infiltration, vascular invasion, lymph node metastases and with more than three metastatic lymph nodes, have a poorer prognosis than cases without these morphological features of malignancy. No statistical correlation between intra- and perineoplastic lymphocytic infiltrate and the prognosis emerged.

In addition, Mulligan intestinal cell carcinoma showed a better prognosis than pyloro-cardiac gland cell and mucous cell carcinomas, and a better five-year survival rate was observed with Lauren intestinal-type and Ming expanding-type carcinomas (Fig. 3).

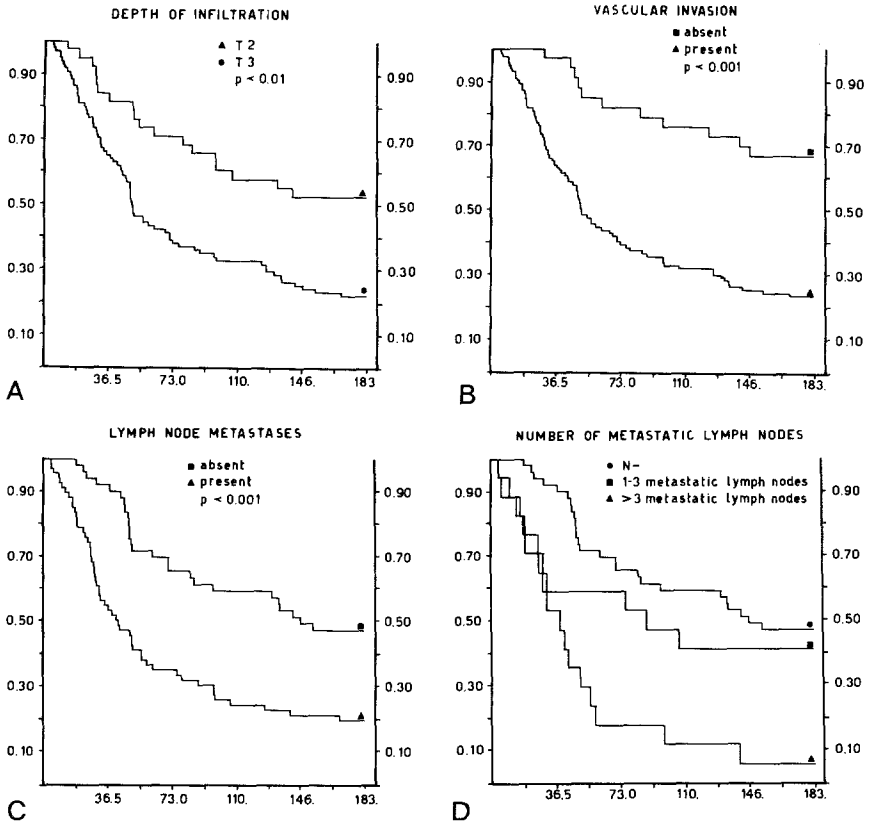

Fig. 2. Five-year survival rates according to histological features of malignancy

However, when the influence of each single variable (gastric wall penetration, vascular invasion, lymph node metastases and number of metastatic lymph nodes) was examined, the prognostic differences previously noted for the Mulligan and Lauren histotypes no longer emerged; in contrast, the good prognosis observed in Ming expanding-type carcinoma persisted, and appeared independent of the criteria for malignancy (Table 3).

Discussion

Although the distribution of the patients in this series according to sex, age and histotype agrees with reports in the literature (Correa et al. 1970; Correa et al. 1973; Lauren 1965; Muñoz and Matko 1972; Schmitz-Moormann et al. 1979), we observed a relatively higher frequency of Lauren diffuse-type and Ming infiltrative-type carcinomas. On the other hand, Northeast Italy is not a high risk area for gastric carcinoma, and this may explain the low number of Ming expanding-type and Lauren intestinal-type carcinomas in this series (Correa et al. 1976; Correa et al. 1973; Muñoz

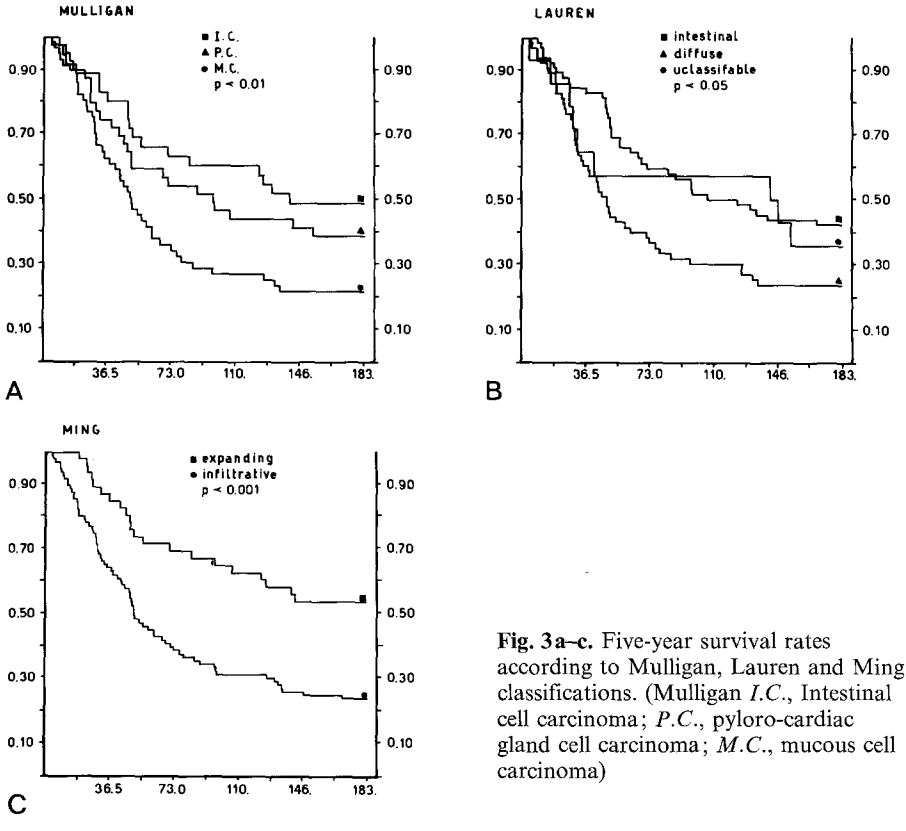

Fig. 3a–c. Five-year survival rates according to Mulligan, Lauren and Ming classifications. (Mulligan *I.C.*, Intestinal cell carcinoma; *P.C.*, pyloro-cardiac gland cell carcinoma; *M.C.*, mucous cell carcinoma)

et al. 1968; Ribeiro et al. 1981). The results of this study confirm the poor prognosis in gastric carcinoma (Fig. 1). However, as observed in other neoplasm, morphological features of malignancy appear to influence the survival rates (Fig. 2). We observed a high frequency of lymph nodes metastases and vascular invasion, but five-year survival rates are related to the number of metastatic lymph nodes, and as in other neoplasms (Fisher et al. 1983) if less than three lymph nodes are involved, the prognosis is almost the same as in cases with no lymph node metastases (Fig. 2). In the TNM system (1974), the definition of T is also based on the depth of infiltration, since this variable influences prognosis highly, as further confirmed by our findings.

In formulating distinctive criteria for histotype subdivision, Mulligan's objective was mostly histogenetic, and thus we may presume that a different histogenesis leads to a different biological behaviour, and consequently to a different prognosis. In fact, according to this criterion, intestinal cell carcinoma shows a better prognosis than pyloro-cardiac gland cell carcinoma, which in turn is more favourable than mucous cell carcinoma (Fig. 3). Most likely, the different prognosis is related to other morphological variables as well (Table 3). In reference to the Lauren and Ming classifications, our

Table 3. Statistical analysis of the prognostic value of each classification when influence of each pathologic parameter is controlled

	Mulligan classification				Lauren classification			Ming classification		
	E_1/O_1	E_2/O_2	E_3/O_3	p	E_1/O_1	E_2/O_2	p	E_1/O_1	E_2/O_2	$p <$
Depth of infiltration	0.72	0.92	1.24	n.s.	0.82	1.18	n.s.	0.65	1.18	0.05
Vascular invasion	0.73	0.88	1.27	n.s.	0.82	1.19	n.s.	0.61	1.22	0.01
Lymph node metastasis	0.77	0.96	1.17	n.s.	0.74	1.33	n.s.	0.60	1.24	0.01
N° of lymph node metastasis	0.64	0.98	1.30	n.s.	0.72	1.33	n.s.	0.59	1.26	0.05
	E = expected O = observed 1 = I.C. (intestinal cell ca.) 2 = P.C. (pylorocardiac gland cell ca.) 3 = M.C. (mucous cell ca.)				E = expected O = observed 1 = intestinal 2 = diffuse			E = expected O = observed 1 = expanding 2 = infiltrative		

findings confirm the poor prognosis for Lauren diffuse-type carcinoma and seem to substantiate the prognostic significance of this scheme (Fig. 3). Nevertheless, when the influence of each single morphological variable of malignancy was examined, the difference in five-year survival rate for intestinal and diffuse type carcinomas disappears (Table 3), and consequently the unfavourable prognosis for diffuse-type carcinoma appears highly conditioned by its different "spread". In contrast, the difference in five-year survival rates for Ming expanding and infiltrative-type carcinomas seems related to the "pathobiological" characteristics of the two histotypes. If the influence of the single histological variable considered is controlled, a better prognosis for expanding type carcinoma is substantiated (Table 3). Therefore, despite partial similarity between the two classifications (Table 2), the prognostic significance of Lauren's scheme appears to be highly influenced by the different extension of the neoplasm (depth of infiltration, vascular invasion, lymph node metastases and number of metastatic lymph nodes). In Ming classification, instead each histological feature of malignancy apparently does not influence the more unfavourable prognosis in infiltrative type carcinoma. In our opinion, therefore, routine use of the Ming classification can provide meaningful prognostic information regarding gastric carcinoma.

Acknowledgments. We wish to thank Mrs Patricia Segato for reviewing the English manuscript, Ing. Enore Grattoni of Centro Ricerche Biomediche of Pordenone for performing the data analysis, and Mr Agostino Leorin for technical assistance.

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Accepted February 1, 1985