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Prognostic Value of Histological Grading in Ductal Adenocarcinoma of the Pancreas

Klöppel vs TNM Grading

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Summary

A new histological grading system with prognostic correlation for pancreatic cancer was proposed by Klöppel et al. in 1985. Histological sections from 60 ductal adenocarcinomas operated on between January 1980 and December 1990 were retrospectively reviewed in order to compare Klöppel's grading with standard TNM's grading and assess their prognostic value. Klöppel grading was determined through the following histologic and cytologic factors: number duct-like structures, mucus production, neoplastic epithelium, arrangement and pleomorphism of nuclei, and mitotic activity. A score from 0 (well differentiated) to 2 (poorly differentiated) was given to each factor. The mean value obtained dividing the sum of the different values by the number of parameters was used to construct a malignancy scale and therefore allocate each patient to his Klöppel grading. The concordance index K between the two grading systems was relevant ($K = 0.85$ $p < 0.001$). There was no relation either between gradings (Klöppel or TNM) and preoperative duration of symptoms or between gradings and UICC stages. TNM's G2 grades of malignancy, N status, and tumor stage were significantly related to survival time ($p < 0.05$). Klöppel's grading does not show any advantage over the classical and simpler TNM's grading, even though it can be considered more objective and therefore more easily reproducible. This characteristic further should be enhanced by the introduction of a malignancy scale such as the "mean value."

Key Words: Exocrine pancreas; ductal adenocarcinoma; histopathological factors; neoplasm staging; prognosis; tumor grading.

Introduction

Carcinoma of the exocrine pancreas currently ranks fourth as the leading cause of death from malignant disease in men and the sixth in women *(1)*. There has been actually only a marginal improvement in the outcome of pancreatic cancer since the beginning of the century *(2)*. Mean survival time after resection varies from 10–20 mo, with a 5-yr survival of approx 2% regardless of therapy *(3)*.

Despite the existence of several histopathologic classification for ductal adenocarcinoma *(4–7)*, the surgeon is still without any reliable prognostic factor that assists him in identifying and separating that population who may benefit from a radical operation

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with selective adjuvant therapy from patients deserving only palliative procedures. Long-term survival in histologically confirmed pancreatic carcinoma is a rare unpredictable event *(8)*. An improvement in pancreatic cancer therapy depends on a better understanding of the biology of the disease.

A relationship between clinical behavior and histological grading was proposed by Klöppel et al. in 1985 *(4)*. Through the examination of six histocytological parameters (glandular structure, intensity of mucus production, arrangement, size and pleomorphism of nuclei, and mitotic activity), Klöppel's grading distinguished three levels of malignancy (G1, G2, G3), with a good correlation to the preoperative duration of symptoms, the tumor stage, and the survival time.

The aim of this work is to investigate the relationship between histological grades of malignancy and biological cancer behavior in a group of patients who had a radical (R0) resection of the head of the pancreas for proven ductal adenocarcinoma and to compare Klöppel's grading with TNM's grading *(5)*.

Materials and Methods

Clinical data from 70 consecutive patients who underwent a radical pancreatoduodenectomy according to Manabe's criteria *(9)* for histologically proven ductal adenocarcinoma of the head of the pancreas between January 1980 and December 1990 were evaluated.

All hospital records were collected and reviewed in order to examine patients' baseline characteristics and determine the time from the occurrence of the first symptoms to histologically or cytologically proven diagnosis. The T status, the N status, and the tumor stage were assessed following the 1989 UICC recommendations *(5)*.

Patients included in the study underwent two types of radical pancreatoduodenectomy: 46 had a pylorus preserving pancreatoduodenectomy and 17 a classical Whipple operation. Whipple operations were performed in most of the cases ($n = 14$) in the first two years. From January 1982 the preservation of the stomach was considered the first therapeutical option and Whipples were only performed when technical reasons, such as insufficient blood supply to the duodenal stump ($n = 1$) or a previous gastric resection ($n = 2$) hindered the sparing of the pylorus. The minimum follow-up period was 12 mo.

Postoperative survival was defined as the time from radical surgery to death from neoplastic recurrence. Operative death was defined as any resection related exitus, including those who died after the thirtieth day from the operation *(10)*. All these cases (3/70, 4.2%) were excluded from survival figures. No patient was treated with antiblastic therapies (i.e., chemotherapy or radiation therapy) either before or after surgery.

Klöppel's and TNM's Evaluation

Surgical specimens were collected from files of the Pathology Department of Pisa University Hospital. Histological sections were reviewed by two pathologists (G. F. and J. B.) not involved in the original evaluation, in order to confirm the previous diagnosis of ductal adenocarcinoma and assess each case both with Klöppel's and TNM's grading. The grading was carried out blindly, that is without knowing the original grade of malignancy, the clinical data and the survival status of the patients. The analysis was separately carried out by the two examiners (i.e., the two pathologists examined the slides on their own, in different days, and without any exchange of information). Those cases that were differently graded by the two reviewers received their final grade after collegial discussion.

Specimens were taken from different parts of the tumor, fixed in 10% formalin, embedded in paraffin, and stained with hematossilin and eosin. Whenever grades of malignancy changed from area to area, pathologist judgment was only based on findings detected in those fields in which the differentiation appeared the poorest (represented for at least 5% of the total tumor). Because of poor quality and or insufficient number of slides, seven cases were excluded from the analysis. In each of the remaining 63 cases at least five well-preserved sections were available.

Klöppel's grading was assessed following six histocytological parameters: glandular structure (i.e., number of duct-like structures), intensity of mucus production (i.e., extracellular mucus), neoplastic epithelium, arrangement and pleomorphism of nuclei, and mitotic activity. Furthermore, in order to obtain the maximum degree of objectivity, a score from

Table 1
Histocytological Klöppel's Parameters

Parameter	Description	Observation	Score[a]
Duct-like structures, 10 F × 125	Numerous	>30 Duct-like structures	0
	Few	5–30 Duct-like structures	1
	Scanty	<5 Duct-like structures	2
Mucus production, 10 F × 125	Abundant	>30%[b]	0
	Scanty	<30%[b]	1
	Absent	0%[b]	2
Neoplastic epithelium, × 500	Regular	Single cell layer	0
	Irregular	Pluristratified cell layers	1
	Very irregular	Solid cell nests	2
Arrangement of nuclei, × 500	Normal	All in basal position	0
	Abnormal	In basal and irregular position	1
	Very abnormal	All in irregular position	2
Pleomorphism of nuclei, × 500	Normal	[c]	0
	Anisonucleosis	[c]	1
	High grade of anisonucleosis	[c]	2
Mitotic activity, 10 HPF × 500	Low	<5 mitosis	0
	Intermediate	5–10 mitosis	1
	High	>10 mitosis	2

[a]0, Well differentiated; 1, moderately differentiated; 2, poorly differentiated.
[b]Mucus production expressed in percentage of the number of duct-like structures with mucus respect to the total umber of duct-like structures.
[c]Normal: nuclei of normal size and shape with homogeneous chromatin; Anisonucleosis: large and irregular nuclei with clumped chromatin; High grade of anisonucleosis: completely aberrant nuclei.

0 (well-differentiated) to 2 (poorly differentiated) was given to each parameter (Table 1). The mean value obtained dividing the sum of the different values by the number of parameters was used to construct a malignancy scale and therefore allocate each patient to his Klöppel grading (G1: 0–0.66; G2: 0.67–1.32; G3: 1.33–2).

TNM's grading was evaluated using criteria commonly utilized in the assessment of the histological grade of malignancy: G1 well differentiated, G2 moderately differentiated, G3 poorly differentiated, G4 undifferentiated *(5)*.

Statistics

Differences in baseline characteristics between the two groups (Whipple vs Longmire) were assessed using the *t*-test, Fisher's Exact test (two-tailed), and the chi-square test. As shown in Table 2, the two groups were homogeneous in all baseline characteristics but Klöppel grading. A 3-yr period was considered in the survival analysis and patients alive with a follow-up less than 3 yr were therefore considered censored. Survival times were estimated for both pylorus preserving and Whipple procedures by Kaplan-Meier method and thereafter compared each other by Breslow and Mantel-Cox tests. The Cox Proportional Regress Hazard Model was also used and three different tests were applied to assess treatment effects while adjusting for patients baseline characteristics: L-ratio test, Wald test, and score function test. In order to compare the two grading systems (three grades of malignancy for Klöppel and four for TNM), TNM grades four and three were considered together. Concordance was then evaluated using the Concordance index K and the Student's *t*-test.

Table 2
Baseline Characteristics

		PPPD, $n = 43$	Whipple, $n = 17$
Sex	m	26 (60.4%)	11 (64.7%)
	f	17 (39.5%)	6 (35.2%)
Mean age		64.5 ± 10	62.7 ± 7
T status[a]	T_1	4 (9.3%)	
	T_2	33 (76.7%)	15 (88.2%)
	T_3	6 (13.9%)	2 (11.7%)
N status[a]	N_0	27 (62.7%)	10 (58.8%)
	N_1	16 (37.2%)	7 (41.1%)
Tumor stage[a]	I	22 (51.1%)	9 (52.9%)
	II	5 (11.6%)	1 (5.8%)
	III	16 (37.2%)	7 (41.1%)
TNM grading[a]	G_1	6 (13.9%)	2 (11.7%)
	G_2	12 (27.9%)	7 (41.1%)
	G_3	15 (34.8%)	6 (35.2%)
	G_4	10 (23.2%)	2 (11.7%)
Klöppel grading[b]	G_1	6 (13.9%)	2 (11.7 %)
	G_2	13 (30.2%)	11 (64.7%)
	G_3	24 (55.8%)	4 (23.5%)

[a]The T and N status, the tumor stage and the TNM grading were assessed following the 1989 UICC.
[b]Statistical significant difference between PPPD and Whipple ($p < 0.05$) was found.

Statistical correlation between grading systems and preoperative duration of symptoms, tumor stage and survival time were determined by using the Kruskal-Wallis test, Fisher's Exact test, and Breslow and Mantel-Cox test, respectively. Finally, Breslow and Mantel-Cox tests were used to investigate relationships between single histocytological parameters and survival time.

Furthermore, in order to verify whether a grade of malignancy or a histocytological feature (i.e., a single histocytological parameter or a combination of them) could be related to a particular neoplastic behavior or not, we compared the grading systems with the recurrence pattern using chi-square and Fisher's Exact tests. To do so we divided the neoplastic recurrence in three types: Loco-regional recurrence (i.e., retroperitoneal), liver metastasis, and diffuse metastatic disease (i.e., massive peritoneal carcinosis and/or one or both the previous modalities) *(11)*. Finally, relationships between classical TNM grading (four grades of malignancy) and survival time were evaluated.

In conclusion, in order to complete the analysis of all those specimen related parameters that might influence survival *(6,8,10–14)* we evaluated relationships between Tumor stage and survival time. All the statistical analysis were handled by the BMDP programs *(15)*.

Results

The reevaluation of the specimens showed that in three out of 63 cases (4.76%) the original diagnosis changed from ductal adenocarcinoma to other malig-

Table 3
Correlation Grading Systems/Tumor Stage (UICC)

	Stage		
	I	II	III
TNM			
G_1	4 (50%)	1 (12.5%)	3 (37.5%)
G_2	9 (47.3%)	13 (15.7%)	7 (36.8%)
G_3	18 (54.5%)	2 (6%)	13 (39.3%)
Klöppel			
G_1	4 (50%)	1 (12.5%)	3 (37.5%)
G_2	11 (45.8%)	3 (12.5%)	10 (41.6%)
G_3	16 (57.1%)	2 (7.1%)	10 (35.7%)

Table 4
Concordance Klöppel/TNM Grading

	TNM			
	G_1	G_2	G_3	
Klöppel				
G_1	8			8 (13.3%)
G_2		19	5	24 (40%)
G_3			28	28 (46.6%)
	8 (13.3%)	19 (31.6%)	33 (55%)	

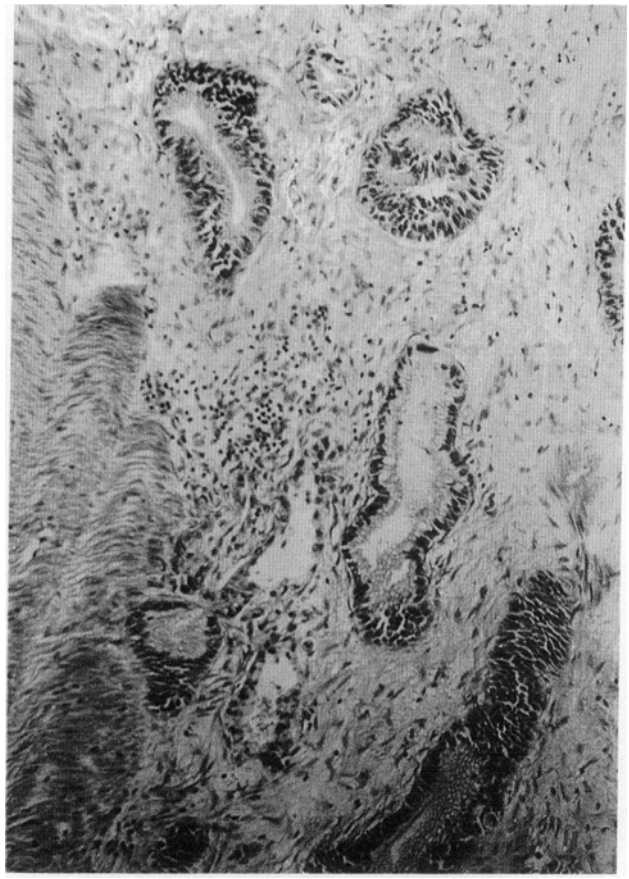


Fig. 1. Well-differentiated tumor (G1): score 3, mean value 0.50. Numerous duct-like structures (0), mucus absent (2), regular neoplastic epithelium (0), normal arrangement of nuclei (0), anisonucleosis (1), low mitotic rate (0).

nancies (one squamous carcinoma and two carcinomas of the papilla of Vater).

The results of the analysis of the histocytological parameters are shown in detail in Table 3. Illustrative representations of the different grades of malignancy are provided in Figs. 1, 2, and 3. In most cases the histocytological appearance of pancreatic carcinoma consists of poorly or quite poorly differentiated aspects. So, although it seems that in the majority of instances pancreatic cancer has a high number of duct-like structures ($n = 40$, 66.6%) (i.e., a well-differentiated neoplastic glandular structure), it usually shows a scanty or absent extracellular mucus production ($n = 51$, 84.9%), an irregular or very irregular neoplastic epithelium ($n = 55$, 91.6%), an abnormal arrangement of nuclei ($n = 53$, 88.3%), a high grade of anisonucleosis ($n = 58$, 96.6%), and a homogeneous pattern of mitotic activity. According to these results, pancreatic carcinoma is more likely to be found as a little or poorly differentiated cancer rather than as a well-differentiated one.

By our modification of the TNM grading, the two systems overlapped almost perfectly with a relevant concordance index K ($K = 0.85$) and a high significant p value ($p < 0.001$). As shown in Table 4, the two grading systems differ only in five cases, which were allocated to G2 in Klöppel's and to G3 in TNM's grading.

No relation was found between grading systems (Klöppel or TNM) and preoperative duration of symptoms or tumor stage. One patient, who had had an incidental diagnosis of pancreatic mass during a routine checkup, was excluded from the analysis of the preoperative duration of symptoms. No patient was lost at follow-up (range 12–107 mo). Two patients died of cardiovascular disease, without

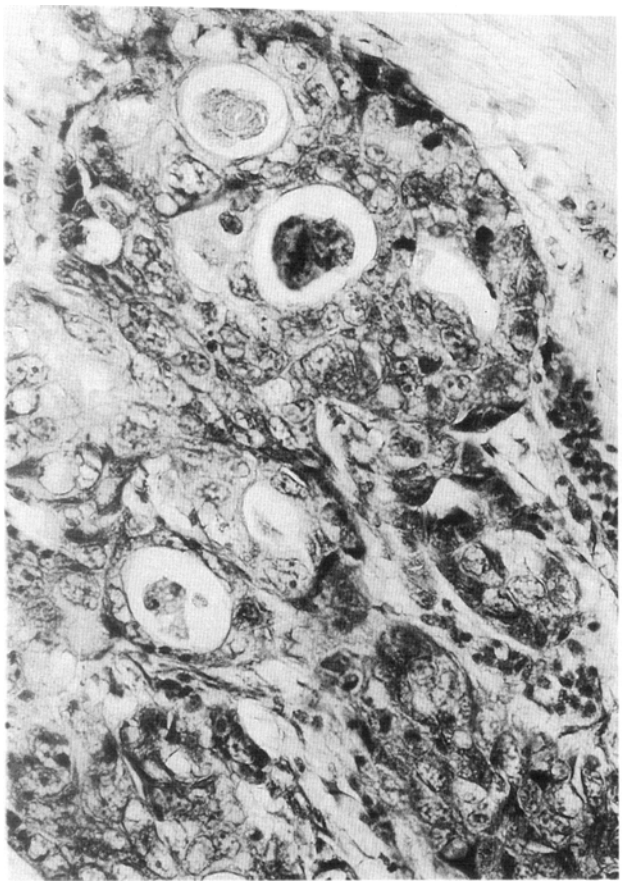


Fig. 2. Moderately differentiated tumor (G2): score 7, mean value 1.16. Few duct-like structures (1), mucus absent (2), irregular neoplastic epithelium (1), abnormal arrangement of nuclei (1), anisonucleosis (1), intermediate mitotic activity (1).

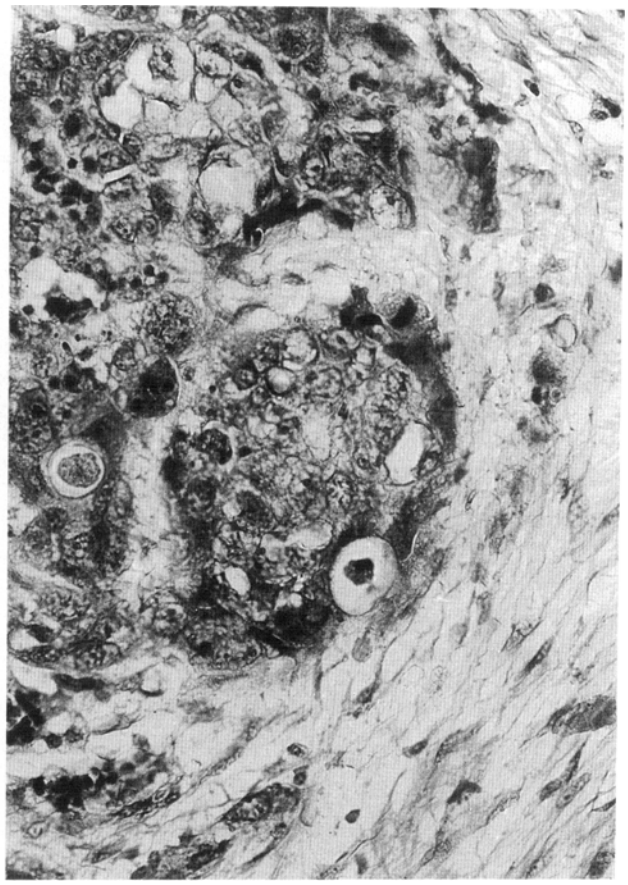


Fig. 3. Poorly differentiated tumor (G3): score 11, mean value 1.83. Scanty duct-like structures (2), mucus absent (2), very irregular neoplastic epithelium (2), very abnormal arrangement of nuclei (2), high grade of anisonucleosis (2), intermediate mitotic activity (1).

Table 5
Recurrence Pattern

	L.R.,[a] n = 11/48 22.9%	L.M.,[b] n = 14/48 29.1%	D.M.D.,[c] n = 23/48 47.9%
TNM			
G_1	1 (14.3%)	1 (14.3%)	5 (71.4%)
G_2	6 (40%)	5 (33.3%)	4 (26.7%)
G_3	4 (15.4%)	8 (30.8%)	14 (53.8%)
Klöppel			
G_1	1 (14.3%)	1 (14.3%)	5 (71.4%)
G_2	6 (31.6%)	7 (36.8%)	6 (31.6%)
G_3	4 (18.2%)	6 (27.3%)	12 (54.5%)

[a]L.R: Local recurrence.
[b]L.M: Liver metastasis.
[c]D.M.D: Diffuse metastatic disease.

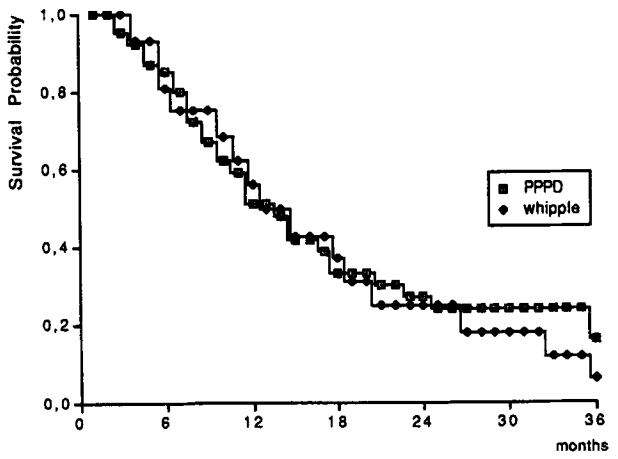
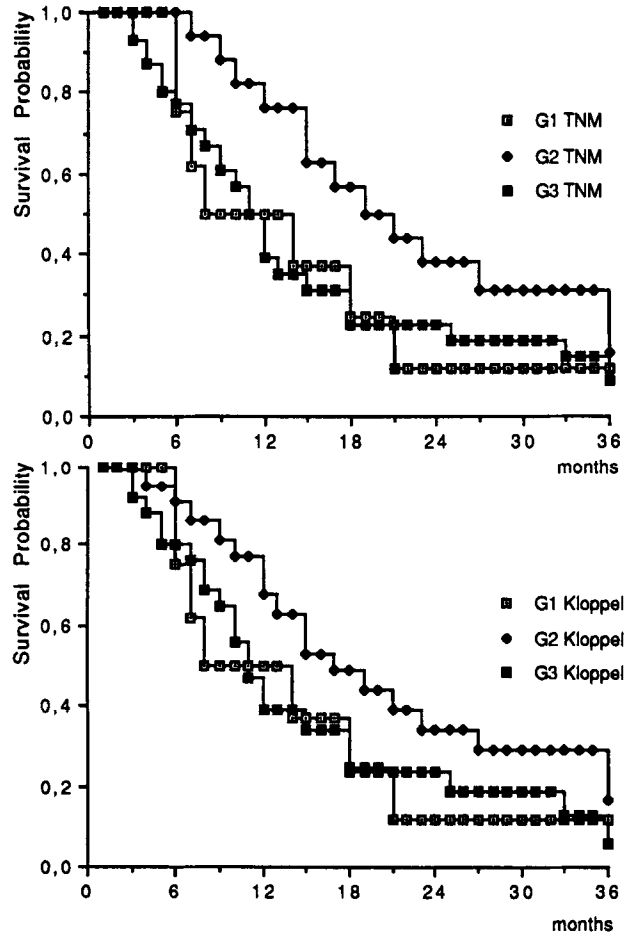


Fig. 4. In this figure, survival curves for PPPD (pylorus preserving pancreatoduodenectomy) and Whipple operations are reported. These curves were designed using the Kaplan-Meier method and thereafter compared each-other by Breslow and Mantel-Cox tests. The two curves overlapped almost perfectly. Median survival times were of 14 ± 1.9 and of 13 ± 3.0 mo for PPPD and Whipple operations, respectively. No difference was discovered.



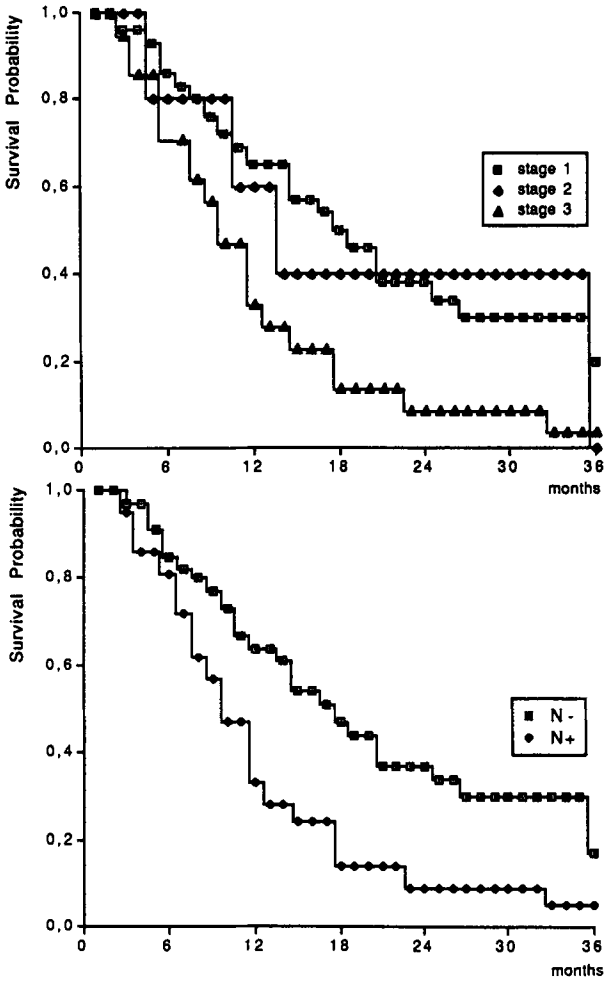


Fig. 6. In this figure, survival curves, according with N status and tumor stage (UICC), are reported. These curves were designed using the Kaplan-Meier method and differences among them assessed using Breslow and Mantel-Cox tests. Significant differences were discovered for both N status and tumor stage. In particular, patients with negative lymph nodes had a median survival of 18 ± 2.6 m vs 10.0 ± 1.4 mo for those with lymph node metastases ($p = 0.012$). Patients in stage I had a median survival time of 19.0 ± 3.0 mo vs 14.0 ± 3.3 and 10.0 ± 1.4 mo for those in stage II and III ($p = 0.038$).

Fig. 5. In this figure, survival curves, according with both TNM's and Klöppel's grades of malignancy, are reported. These curves were designed using the Kaplan-Meier method. Statistical correlation between grades of malignancy and survival time was evaluated using Breslow and Mantel-Cox tests. In both grading systems, G2 carcinomas had the best prognosis and in the TNM system a significant difference ($p < 0.05$) was found between G1 and G2 carcinomas.

neoplastic recurrence, 5 and 11 mo after surgery, respectively.

Survival curves for patients operated on with PPPD or Whipple procedures are reported in Fig. 4 (on previous page) (3-yr survival was 25%). Well differentiated neoplasms (G1) seem to have a lower survival expectancy than moderately (G2) or poorly (G3) differentiated cancers (Fig. 2). In particular, with both systems the survival time appears to be widely different between G1 (8 ± 4.9 mo) and G2 carcinomas (21 ± 3.9 and ± 3.3 mo with TNM's and Klöppel's grading, respectively). A significant p value ($p < 0.05$) was found between G1 and G2 TNM grades of malignancy (Fig. 5 on previous page). No single Klöppel's parameter or combination of parameters seems to represent a valid prognostic factor. The recurrence pattern is shown in detail in Table 5 (on p. 284). No relation was found between type of recurrence and histological grade of malignancy or a single Klöppel's parameter or a combination of them.

The classical TNM grading (four grades of malignancy) did not add any further information. Lymphonodal involvement and tumor stage showed a significant relation with the survival time ($p < 0.05$) (Fig. 6 on previous page). N positive patients ($n = 23$) had a 3-yr survival of 5% (median 10 ± 1.4 mo), whereas negative lymphnodes ($n = 37$) reached 27% (median 18 ± 2.6 mo).

Discussion

During the 1980s, despite improvements in diagnosis and treatment of pancreatic cancer, especially in terms of decreased postoperative morbidity and mortality rates *(16–21)*, the outlook of patients undergoing pancreatic resection has remained at a discouraging level *(3,8,11,22–25)*.

The introduction of newer complex adjuvant therapies may lead to an improvement of results. It should be very important to get available some prognostic, simple, easily assessable histocytological parameters of malignancy useful for planning the appropriate individual therapy. Unfortunately, as regards pancreatic cancer, we have not even a reliable scale of postsurgical staging *(26)*.

The classical UICC staging system is not far from criticism, lymphonodal metastasis, which are the central clue of this staging system, are not always strictly related to prognosis in all experiences. Connolly *(8)*, in a wide report from the Chicago University, did not find a prognostic impact of nodal involvement. The same results are reported by other authors *(6,11,27)*. The majority of authors, however, agree to the importance of nodal spread in determining survival *(10–14,28)*. In our experience the lymphonodal involvement significantly shortened life expectancy (Fig. 3).

Japanese surgeons emphasize the relevance of other histological parameters, such as capsular invasion, retroperitoneal and vascular infiltration, and perineural spread *(14,29,30)*. In this confusing field, Klöppel's observation of a significant correlation between his new grading system and survival gave rise to much interest *(4)*.

In this case, the neoplastic grading could become as important as staging for planning therapeutical strategies like in other neoplasms, such as sarcomas *(31)*, prostatic *(32,33)*, endometrial *(34)*, and vesical *(35)* cancers.

Klöppel's study included 75 pancreatoduodenectomies in which the histological grading was statistically related to:

1. The time from the occurrence of first symptoms to cytological or histological proven diagnosis;
2. Tumor stage (Pollard, 1981); and
3. Total postoperative survival.

Klöppel found that G2 and G3 carcinomas were generally in a more advanced stage than G1 and that statistically significant differences were present between the single groups (G1, G2, G3) with regard to the median duration of preoperative symptoms and the median postoperative survival time. Klöppel concluded his paper saying that his combined histocytological grading system is a simple low power microscopic method that may help to estimate the intrinsic malignancy of these neoplasms more accurately. Unfortunately, our experiences do not confirm Klöppel's results.

Our histological review, according to the typical aggressive behavior of ductal adenocarcinoma and to results reported by other authors *(7,28)*, showed a wider prevalence of moderately and poorly differentiated cancers than the Klöppel study did (G1 [$n = 8/60$ 13.3%] G2 [$n = 24/60$ 40%] G3 [$n = 28/60$ 46.6%] vs G1 [$n = 34/75$ 45.3%] G2 [33/75 44%] G3 [$n = 8/$

75 10.6%]). No correlation at all was demonstrable between duration of symptoms, *N* status, survival time, and grading.

Moreover, when Klöppel's grading was compared with the classical TNM's grading, no statistical difference was found. It would therefore appear that Klöppel's grading, though more complex, does not own any significant advantage over the more simple but subjective TNM's grading. An interesting point is the longer life expectancy expressed by G2 cancer than G1.

This could mean that grading systems for pancreatic ductal adenocarcinoma are currently of no prognostic relevance, at least in our series. Which single biological parameter inside G2 group contributes maximally to give rise to such a result is not clear. This result was apparent with both grading systems, but with the TNM the difference was so large to lead to statistical significance.

This finding, that seems to be confirmed by other authors *(28,36,37)*, does not fit with the malignancy scale based on current grading systems. Weger, in a series of 71 cases *(36)*, and Eskelinen, in a series of 111 cases *(7)*, found similar survival curves. Tannapfel, using Klöppel's parameters, obtained analogous results: "The median survival time for G1 tumors was 10 mo; for G2, 11 mo; and for G3 carcinomas, 10.5 mo" *(28)*. The author concluded that "the prognostic irrelevance of the tumor's grade of differentiation contradicts Klöppel's premise," but agrees with results reported by others. Moreover, according to our results, he underlined the lack of correlation between histological grade of malignancy and tumor stage, suggested by Klöppel: "In our study there was a similar proportion of G1, G2, and G3 carcinomas in all tumor stages." Matsuno and Sato, analyzing prognostic factors after pancreatic resection, failed to demonstrate any correlation between grade of malignancy and survival time *(38)*. In the end, Lack, in a recent overview of pancreatic cancer pathology, concludes that "in most cases the ultimate prognosis" of ductal adenocarcinomas of the pancreas "is not significantly influenced by the histologic grade of the primary tumor and" that "even well-differentiated tumors usually pursue a high-grade biologic course with fatal outcome" *(39)*.

Nuclear morphology with morphometric measurements seems to be one of the most important single parameters to evaluate *(4,7)*, but it is not easily determined using a low power microscopic method. Much more reliable becomes its computation by electronic microscope *(4)*. Some other parameters, which are not usually considered in the classical grading systems, could be of relevant importance for pancreatic cancer: DNA content by image cytometry (IMC) or flow cytometry (FCM) *(37,40)*, S cellular fraction (TLI) *(41)*, receptorial expression by immunohistochemistry.

A cautionary note at last resulted from this study: In 3 out of 63 cases, the original diagnosis of ductal adenocarcinoma changed to less ominous malignancies.

Van Heerden *(19)* and Connolly *(8)* described similar findings in their series. We therefore agree with Carter's suggestion of seeking for misdiagnosis in all the long-term survivors after resection for ductal adenocarcinoma *(25)*.

In the end, according to others, it is our belief that histocytological grade of malignancy, in its present method of assessment (either TNM's or Klöppel's method), seems to be unreliable in predicting either the prognosis or the biological behavior of pancreatic cancer and that new histocytological parameters need to be investigated. Klöppel's analysis with its meticulous definition of each single histocytologic parameter could be of some help in collecting large series of statistical relevance. In our experience several parameters, especially those referring to the nucleus, have shown a trend toward statistical significance. It is possible that increasing the sample's size correlation with prognosis may become evident. The implementation of a multicentric international study with analysis of a large number of cases could verify the prognostic relevance of current as well as new histocytological parameters. From this point of view, the use of a malignancy scale, such as our "mean value," could simplify the exchange of information among centers and further facilitate the investigation of new histocytologic parameters becoming the framework of a new grading system.

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