Abstract of the Workshop

Classification of Pancreatic Cancer Staging Revisited

A Meeting of the World Congress of Gastroenterology, October 5, 1994, Los Angeles, CA

UICC Classification of Pancreatic Cancer

Christian Wüttek¹ and Paul Hermanek²

¹Institute of Pathology; ²Department of Surgery,
University of Erlangen, Erlangen, Germany

Introduction. The description and classification of the anatomical extent of malignant tumors are generally designated as staging. Staging is an important factor in assessing the prognosis of patients with a given tumor, in this context of exocrine pancreatic cancer (in more than 95% ductal adenocarcinoma). However, two questions have to be answered: whether staging of a carcinoma with such an unfavorable prognosis makes any sense at all, and what the best and most adequate staging system is. A staging system in pancreatic cancer should help to select patients for specific treatments, e.g., pretherapeutically for resective surgery or following resection for additional radio- and/or chemotherapy. In recent years, there have been several attempts to create valid staging systems. The staging system of the UICC, which will be demonstrated in this article (1), has been accepted by all National TNM committees to enable international comparisons.

History of UICC Classification of Pancreatic Cancer. Pancreatic carcinoma staging was first mentioned in the UICC classification of 1987. This classification is based predominantly on the suggestions of the "AJCC Cancer of the Pancreas Task Force" of 1981. The classification of 1987 has not been changed in the revised 1992 edition (1), and was only supplemented by the inclusion of splenic and celiac lymph nodes into the regional lymph nodes. In the TNM supplement of 1993 (2), the T classification is supplied with some explanatory notes concerning T2 and T3. Furthermore, optional proposals are provided for testing new telescopic ramifications; *see below*.

The present TNM classification is not the work of some individual authors, but is indeed the result of international efforts of many groups, agreed on by all National TNM committees. By now the rules of classification and stage grouping are exactly the same in the UICC edition and in the 4th edition of the *UICC Manual for Staging of Cancer*.

The Present UICC Classification. The classification in the 1992 edition is shown in Table 1. This classification cannot be used for tumors of the endocrine pancreas.

The T classification primarily considers the limitation of a tumor to pancreas and direct extension to adjacent structures. Tumors limited to pancreas are further subdivided according to size. The N and M classifications are simple, only considering absence or presence of lymph node and distant metastases.

Comparison with Other Staging Systems. Unfortunately, the UICC definitions of the T categories are not comparable with those of the Japanese General Rules (3). Although the latter consider tumor size only, the UICC also considers serosal, retroperitoneal, and partly venous invasion.

A further drawback of the Japanese General Rules is the usage of four categories (0, no; 1, suspected; 2, definite; 3, severe) for the classification of serosal (S), retroperitoneal (Rp), and venous (V) invasion. The category "suspected" is in contradiction with the General Rules of the TNM system, which consider suspicious findings as negative. The division of positive cases into "definite" and "severe" without clear definitions leads to subjectivity and inconsistent application.

Another difference between UICC and the Japanese General Rules refers to the classification of lymph nodes. According to the UICC, the first and second node stations only are considered as regional lymph nodes, whereas involvement of other abdominal nodes is classified as distant metastases (M1 LYM) by the UICC and as N3 (juxtaregional lymph node metastasis) by the Japanese General Rules.

Residual Tumor (R) Classification. In case of treatment (not only surgical treatment!), TNM and pTNM should be supplemented by the residual tumor (R) classification (4). A chance of longer survival is given only for patients with an R₀ status (Fig. 1, according to (4)). One differentiates among R₀, no residual tumor; R₁, microscopic residual tumor; and R₂, macroscopic residual tumor. Thus, R₀ corresponds to curative (or potentially curative) treatment, and R₁ and R₂ to noncurative treatment. It must be emphasized that the R classification after tumor resection requires a careful histological examination of resection lines, especially in the retroperitoneal area with embedding of multiple blocks for histological examination.

Mechanisms for Improvement of TNM. Of course, the UICC realizes that the present TNM classification and stage grouping are not the last resort and that the continuous advances in diagnosis, treatment, and in knowledge of relations between anatomic extent and prognostic favor continuing changes. On the other side, the UICC recognizes the need for stability in the classification so that data can be accumulated in an orderly way over reasonable periods of time.

Any proposal for further improvement should be based on data, not on philosophical considerations. Such proposals should enable comparisons with the present system. Therefore, the UICC recommends the mechanism of so-called telescopic ramification. This includes as a first step the subdivision of existing

Table 1
UICC TNM Classification
of Exocrine Pancreas Carcinoma (1)

T category			
T ₁	Limited to the pancreas		
	T _{1a}	2 cm or less	
	T _{1b}	more than 2 cm	
T ₂	Extends directly to duodenum, bile duct, peripancreatic tissues		
T ₃	Extends directly to stomach, spleen, colon, adjacent large vessels		
N category			
N ₀	No regional lymph node metastasis		
N ₁	Regional lymph node metastasis		
M category			
M ₀	No distant metastases		
M ₁	Distant metastases		
Stage grouping*			
Stage I	T ₁	N ₀	M ₀
	T _{1a}	N ₀	M ₀
Stage II	T ₂	N ₀	M ₀
Stage III	T ₃	N ₁	M ₀
Stage IV	Any T	N ₁	M ₁
	Any T	Any N	M ₁

*Proposal for testing new telescopic ramification.

T, N, or M categories. By using ramification, it is possible to classify each case according to the present system, as well as according to a proposed new one. Thus, comparisons between different classifications in relation to survival are possible and may indicate which classification is superior.

The UICC recognizes that staging has to be simple enough for universal use both in highly developed and developing countries and sufficiently uncomplicated so that medical professionals are not discouraged from using the system. On the other side, for specialized institutions and for investigational purposes, a relatively simple staging system is not sufficient and runs the risk of not being used. For these specialized institutions, the TNM system may be made attractive by further subdivision of the existing categories (telescopic ramification) and by including additional descriptors. In the TNM Supplement 1993, two proposals for testing new ramifications have been published: T₃: T_{3a}, Tumor extends directly to any of the following: stomach, spleen, colon; T_{3b}, tumor extends directly to adjacent large vessels. pN₁: pN_{1a}, Metastasis in a single regional lymph node; pN_{1b}, metastases in multiple regional lymph nodes.

Improvement of Stage Grouping. Stage grouping should ensure, as far as possible, that each stage is more or less homogeneous with respect to survival. This demand is not fulfilled for the UICC stage I as can be demonstrated by unpublished data of the Japanese Joint Committee on TNM (a), as well as by data of the Erlangen Cancer Registry (b). The 5-yr survival rates after resection are the following: pT_{1a}N₀M₀: a, 67%, b, 75%; pT_{1b}N₀M₀: a, 64%, b, no patients; pT₂N₀M₀: a, 29%, b, 8%; total stage I: a, 38%, b, 19%. Therefore, the following subdivision of the present stage I should be considered: stage Ia: T₁N₀M₀, stage Ib: T₂N₀M₀.

Fig. 1. Ductal adenocarcinoma of the pancreas. Prognosis following tumor resection (any type) in relation to residual tumor (R) classification ($n = 201$). Data of the Department of Surgery, University of Erlangen (F. P. Gall). Observed overall survival calculated according to Kaplan-Meier, surgical mortality not excluded, patients treated between January 1, 1978 and December 31, 1991, closing date of the study December 31, 1992, 5-yr survival rates with 95% confidence interval. (A) Total of patients: R: 9.8 (3.2–16.4); R_{1,2}: 0%. (B) Stage I: R: 16.5 (0–33.9); R_{1,2}: 0%. (C) Stage III: R₀: 5.8 (0–12.3); R_{1,2}: 0%. From (4).

However, it should be emphasized that, whenever possible, subdivision of the patients into the individual TNM categories is preferable. Stage grouping is recommended only for institutions with limited numbers of patients.

Prognosis and Prognostic Factors. Prognosis of ductal adenocarcinoma of the pancreas is mainly determined by R classification and TNM classification. The 2- and 5-yr survival rates, as well as the median survival times depend on the type of surgical treatment (no operation, exploratory laparotomy/bypass operation/tumor resection). Additional prognostic factors have been in discussion, for example, gender, weight loss, performance status, localization, grading, invasion of lymphatic vessels, and different therapy modalities.

Outlook: Prognostic Grouping. According to the UICC program for further development of tumor classification, in coming years parameters that have an independent prognostic significance will have to be clarified, particularly taking into consideration methods of molecular biology and new attempts in therapy. These parameters can be subdivided into tumor-related (besides anatomical extent of disease, for example, biochemical markers, oncogene expression, and other molecular markers), host-related factors (age, performance status, weight loss, and so forth) and therapy-related factors. Considering that prognosis is influenced by a variety of factors and a possible multitude of associations among different prognostic factors, the fact that the influence of a particular factor on prognosis can be misleading when considered alone has to be taken into consideration. Therefore, a reliable interpretation of prognostic factors requires the use of multivariate analysis (e.g., Cox model or logistic regression analysis with simulation of nonproportional hazards).

Prognostic factors may be subdivided into three categories:

1. Factors of proven prognostic significance, including those proven to be of independent value by the use of multivariate analysis of data from at least two different institutions and where the conclusions have been in agreement;
2. Factors of probable prognostic significance, including those single multivariate studies or large body of evidence with no dissenting results; and
3. Factors of possible prognostic significance that are applied where the results of multivariate analyses are conflicting or where independent significance of a given factor has not been confirmed.

The identification of prognostic factors is an essential part of patient assessment and decision making in oncology. This holds true even for pancreatic cancer with a very poor prognosis. The collection and documentation of valid data will serve as a basis for analysis of prognostic parameters to be evaluated in the future.

References

- 1 Hermanek P, Sobin LH, eds., *UICC: TNM Classification of Malignant Tumors*. 4th ed., 2nd rev. Springer-Verlag, Berlin, 1992.
- 2 Hermanek P, Henson DE, Hutter RVP, Sobin LH, eds., *UICC: TNM Supplement 1993. A Commentary on Uniform Use*. Springer-Verlag, Berlin, 1993.
- 3 Tsunoda T, Ura K, Eto T, Matsumoto T, Tsuchiya R. UICC and Japanese stage classifications for carcinoma of the pancreas. *Int J Pancreatol* 1991; 8: 205-214.
- 4 Hermanek P, Wittekind C. Residual tumor (R) classification and prognosis. *Sem Surg Oncol* 1994; 10: 12-20.

The Prevalence of Pancreatic Cancer Lymph Node Metastasis in Japan and Pancreatic Cancer Staging Categories

Yoshifumi Kawarada, Kentaro Yamagiwa, Shuji Isaji, and Ryuji Mizumoto

First Department of Surgery, Mie University School of Medicine, Tsu City, Mie, Japan

Purpose. Whether or not lymph node metastasis is present is an important factor in the prognosis of carcinoma of the pancreas, and in Japan, we have been carefully classifying the lymph nodes adjacent to the pancreas for some time. This has served as a useful index in making prognosis. Based on the data in the National Pancreatic Cancer Registry of Japan in 1992 (chairman of the committee: Yoichi Saito), the lymph node group categories in the third edition of the *General Rules for the Study of Pancreatic Cancer* (1986) have been re-examined, and since new staging categories (1) have been drawn up, in this article, the focus of our report is the prevalence of lymph node metastasis.

Materials and Results. The materials used in this study consisted of the carcinomas of the pancreas (excluding cystadenocarcinoma and islet cell carcinoma) registered by the National Pancreatic Cancer Registry Committee of the Japanese Pancreatic Society from 334 institutions during the 10-yr period from 1981 to 1990, comprising 4725 cases (2375 resected cases) of carcinoma of the head of the pancreas, and 1145 cases (460 resected cases) of carcinoma of the body and tail of the pancreas. Also, lymph node metastasis rates, survival rates according to macroscopic stage determinants, and lymph node group classification and staging categories in relation to these cases were re-examined by the committee.

Lymph Node Metastasis Rates and Lymph Node Group Classification (Fig. 1). Among the resected cases of carcinoma of the head of the pancreas, the histological lymph node metastasis rate was highest (36.0%) in the lymph nodes of the region superior-posterior to the head of the pancreas (No. 13a in the *Japanese General Rules for the Study of Pancreatic Cancer*), followed by the lymph nodes of the region inferior-posterior to the head of the pancreas (No. 13b) with a rate of 28.1%, the lymph nodes of the superior-anterior region of the head of the pancreas (No. 17b: 19.8%), the lymph nodes along the abdominal aorta (No. 16: 18.5%), and the lymph nodes at the origin of the superior mesenteric artery (No. 14a: 15.8%). The most common site of lymph node metastasis of carcinoma of the body and tail of the pancreas was the lymph nodes along the splenic artery (No. 11: 30.0%), followed by the lymph nodes along the abdominal aorta (20%), the lymph nodes along the inferior border of the body and tail of the pancreas (No. 18: 18%), the lymph nodes of the region superior-posterior to the head of the pancreas at (18.0%), and the lymph nodes at the origin of the superior mesenteric artery (17.0%). Taking these data and lymph flow into consideration, the new classification was made below, conceiving of the lymph nodes included in routine pancreaticoduodenectomy and resection of the body and tail of the pancreas as the primary group. In carcinoma of the head of the pancreas, those lymph nodes at the origin of the superior mesenteric artery and along the abdominal aorta that were located below the celiac axis and above the root of the inferior border of the left renal vein (No. 16a₂), as

Lymph Node Group Classification		
	Carcinoma of the head of pancreas	Carcinoma of the body and tail of pancreas
Primary group	6, 8a, 8p, 12a ₂ , 12p ₂ , 12b ₂ , 13a, 13b, 14b, 14c, 14d, 14V, 17a, 17b	8a, 8p, 9, 10, 11, 18
Secondary group	9, 11, 12a ₁ , 12p ₁ , 12b ₁ , 12c, 14a, 15, 16a ₂ , 16b ₁ , 18	7, 12a ₂ , 12p ₂ , 12b ₂ , 13a, 13b, 14a, 14b, 14c, 14d, 14V, 15, 16a ₂ , 16b ₁ , 17a, 17b
Tertiary group	1, ^a 2, ^a 3, ^a 4, ^a 5, ^a 7, ^a 10, 12, 16a ₁ , 16b ₂	1, 2, 3, 4, 5, 6, ^a 12h, 12a ₁ , 12p ₁ , 12b ₁ , 12c, 16a ₁ , 16b ₂

^a1:lymph nodes of right cardiac region, 2:lymph nodes of left cardiac region, 3:lymph nodes along the lesser curvature of the stomach, 4:lymph nodes along the greater curvature of the stomach, 5:lymph nodes of the suprapyloric region, 6:lymph nodes of the infrapyloric region, and 7:lymph nodes at the origin of the left gastric artery.

Fig. 1. Lymph node group classification.

well as below the inferior border of the left renal vein and above the root of the inferior mesenteric artery (No. 16b₁) were classified as the secondary group. In carcinoma of the pancreatic body and tail, the lymph nodes at the radix mesenterii (No. 14a,b,c,d,V), and No. 16a₂ and b₁ are classified as the secondary group. In both carcinoma of the head of the pancreas and carcinoma of the body and tail, the lymph nodes around the aortic

hiatus (No. 16a₁) and the lymph nodes located below the root of the inferior mesenteric artery and above the aortic bifurcation (No. 16b₂) are designated the tertiary group. The lymph node metastases within or outside the tertiary group are referred to as distant metastases (M₁).

Staging (see Table 1). The 1–8-yr postoperative survival rates for carcinoma of the head of the pancreas was evaluated

Table 1
Stage Grouping for Carcinoma of Pancreas

Surgical stage					
	P_0, H_0, M_0				$P_{1-3}, H_{1-3}, \text{ or } M_1$
	N_0	N_1	N_2	N_3	
T_1^a ≤ 2 cm and $S_0 + RP_0 + PV_0 + A_0$	I	II	III	IVa	
T_1^b > 2 cm and $S_0 + RP_0 + PV_0 + A_0$	II	II	III		
T_2 One or more factors positive among S_1, RP_1, PV_1, A_1 with any tumor size	III	III	IVa		IVb
T_3 One or more factors positive among $S_{2,3}, RP_{2,3}, PV_{2,3}, A_{2,3}$ with any tumor size		IVa			
Conclusive stage					
	P_0, H_0, M_0				$P_{1-3}, H_{1-3}, \text{ or } M_1$
	n_0	n_1	n_2	n_3	
t_1^a ≤ 2 cm and $s_0 + rp_0 + pv_0/PV_0 + a_0/A_0 + du_0 + ch_{0,1}$	I	II	III	IVa	
t_1^b > 2 cm and $s_0 + rp_0 + pv_0/PV_0 + a_0/A_0 + du_0 + ch_{0,1}$	II	II	III		
t_2 One or more factors positive among $s_1, rp_1, pv_1/PV_1, a_1/A_1, du_{1,2,3}, ch_{2,3}$ with any tumor size	III	III	IVa		IVb
t_3 One or more factors positive among $S_{2,3}, rp_{2,3}, pv_{2,3}/PV_{2,3}, a_{2,3}/A_{2,3}$ with any tumor size		IVa			

Factors with capital letter: gross findings; factors with small letter: microscopic findings; du: invasion of the duodenal wall; ch: invasion of the intrapancreatic bile duct/; or

Subscript number is expressive of the grade of factors. Numbers 1, 2, and 3 of N, P, H, and M are excluded of the expression: 0: no evidence, 1: suspected, 2: definite, 3: severe.

N: Lymph node involvement: 1: within the primary group; 2: within the secondary group; 3: within the tertiary group. P: Peritoneal dissemination: 1: adjacent, 2: sporadic and distant; 3: multiple and distant. H: Hepatic metastasis: 1: single lobe, 2: sporadic and both lobes; 3: multiple and both lobes. M: distant metastases, 1: evidence.

according to individual macroscopic staging factors, i.e., tumor diameter, S factor (invasion of the anterior capsule of the pancreas), RP factor (retroperitoneal invasion), PV factor (invasion of the portal venous vessels), and N factor (lymph node involvement in accordance with the third edition of the general rules). Significant differences in survival rates according to tumor diameter were found from 3 yr onward between patients with lesions having a diameter of 2 cm or less and patients with lesions having a diameter of 2.1 cm or more. In the case of the S factor,

there were significant differences in survival rates between negative (S_0) and positive (S_{1-3}) from 2 yr onward. There were significant differences in survival rates between RP factor negative (RP_0) and RP factor positive (RP_{1-3}) patients from 4 yr onward. Significant differences in 1–8 yr survival rates were found with respect to the PV factor between negative (PV_0) and positive (PV_{1-3}) patients. With regard to the N factor, on the other hand, significant differences in survival rates were found for years 1–7 among the individual groups, i.e., the N_0 group (no evidence

of involvement group), the N₁ group (evidence of lymph node involvement within the primary group), the N₂ group (evidence of lymph node involvement within the secondary group), and the N₃ group (evidence of lymph node involvement within the tertiary group). Moreover, when survival rates were investigated according to a combination of the UICC TNM categories, which express overall invasion around the pancreas, and the Japanese N categories, it was obvious that it was unnecessary to classify the degree of invasion around the pancreas (S, RP, PV, A[invasion of the arterial vessels]) in group 2 and group 3. Thus, in the staging categories of the fourth edition of the *Japanese General Rules for the Study of Pancreatic Cancer* (1993), the committee has adopted the UICC T categories in the vertical column and the Japanese original lymph node group classification in the horizontal column. Also, surgical stage based on macroscopic intraoperative findings and conclusive stage based on final histological findings in surgical specimen have been drawn up, as shown in Table 1.

Discussion and Conclusion. Lymph node metastasis rates and survival rates were re-evaluated according to staging determinants in the cases in the National Pancreatic Cancer Registry, and a new lymph node group classification and staging categories devised. This new staging classification combining the original Japanese detailed lymph node group classification and T-factor is very similar to the UICC TNM classification. In the future, this classification will attract greater attention and come into more widespread use, on an international level as well, than in the past. It is expected to be useful in improving the therapeutic outcome of pancreatic cancer.

References

- 1 Mizumoto R, Isaji S. General rules for the study of pancreatic cancer, proposed by the Japan Pancreas Society—history of revision and currently revised edition. *J Bill Panc* 1993; 14: 913–920 (in Japanese).

Clinical Comparison of UICC and Japanese Staging Classification Italian Experience

Valerio Di Carlo, Alessandro Zerbi, and Gianpaolo Balzano

Department of Surgery, San Raffaele Hospital University of Milan, Italy

Introduction. A discrepancy between expected and observed survival is often noticed in patients with pancreatic carcinoma: postoperative staging classifications seldom allow early identification of long-term survivors. A number of classifications have been proposed for pancreatic carcinoma, but there is still no pathological classification accepted worldwide. The classification of the Union Internationalis Contra Cancrum (UICC) is commonly used in Western countries (1), whereas in Japan, a different staging system has been developed during the last decade by the Japanese Pancreatic Society (JPS) (2). The major difference between the two staging classifications concerns the evaluation

of the tumor local growth. The UICC classification considers local growth (T factor), lymph node involvement (N factor), and distant metastasis (M factor) as consecutive events in the cancer life history. Therefore, a tumor without nodal and distant metastasis will be assigned to the first stages (I or II) even if it involves adjacent organs or large vessels. On the other hand, in JPS classification, the tumor local growth is as important as lymph node and distant metastasis in the stage definition, since an advanced local extent can assign a patient to stage IV. The Japanese staging system includes some new parameters to assess the involvement of peripancreatic tissues, whereas the T factor describes only tumor dimensions. These parameters are: Rp factor (retroperitoneal tissues), S factor (peritoneum), and V factor (portal vein system).

Methods. We compared the prognostic value of UICC and JPS classifications in 90 patients undergoing resection for pancreatic ductal adenocarcinoma (56 males and 34 females; mean age of 57, range 20–81). Surgical procedures were: 76 pancreatoduodenectomies, 11 distal pancreatectomies, and 3 total pancreatectomies. Patients were stratified by stage according to the UICC and JPS recommendations. The resection was considered not radical when the surgeon described macroscopic cancer residual or the pathologist reported an involvement of resection margins.

In a subgroup of 29 patients, the usefulness of two further intraoperative staging maneuvers was evaluated: (1) The cytologic examination of peritoneal washings, obtained by the instillation of 100 mL of normal saline solution. The washings were performed either at the beginning of operation, immediately after laparotomy, to investigate a preoperative peritoneal spread, or at the end of operation, just before closing the abdominal wall, to investigate an intraoperative seeding. (2) The performance of random hepatic biopsies, in a negative liver at clinical staging, to investigate the presence of undetected liver metastases. Biopsies were performed by a tru-cut, one in each hepatic lobe.

Overall survival curves were calculated by the Kaplan-Meier method; the log-rank test was used to detect differences between curves. The Cox method was used for multivariate survival analysis.

Results. Patients distribution by the UICC and the JPS stages is summarized in Table 1.

Median survival times by UICC stages were as follows: 17 mo in stage I, 14 mo in stage II, 13 mo in stage III, 6 mo in stage IV. On the other hand, median survival according to JPS classification was: 43 mo in stage I, 29 mo in stage II, 15 mo in stage III, 8 mo in stage IV. The difference among postoperative survival curves calculated on UICC classification stages was significant ($p < 0.01$), but median survival and confidence intervals of stage II and stage III overlapped. The difference among survival curves of JPS stages was significant ($p < 0.001$); the median survival and confidence intervals of different stages were also quite different.

In 31 patients (34%), the operation was considered not radical. Median survival was 17 mo for patients undergoing a curative resection and 13 mo for patients with a residual cancer; the difference between the survival curves was significant ($p < 0.05$).

Two models of Cox survival analysis were performed. In the first model, UICC stages, radicality, and tumor grading were used as covariates; the radicality of operation and the tumor grading were significant indicators for survival ($p < 0.05$ and

Table 1
Distribution of Patients in Stages by UICC
and JPS Classifications

Stage	UICC	JPS
I	30 (33.3%)	3 (3.3%)
II	12 (13.3%)	15 (16.6%)
III	43 (47.7%)	41 (45.5%)
IV	5 (5.5%)	31 (34.4%)

$p < 0.01$, respectively), whereas UICC stages were not ($p = 0.14$). In the second model, the variables were JPS stages, radicality, and tumor grading; JPS stages were confirmed to be significant prognostic factors, as well as tumor grading ($p < 0.001$ and $p < 0.05$, respectively), whereas the radicality of operation was not significant in this model ($p = 0.28$).

As far as the single UICC staging factors is concerned, there was a marked difference for M-factor survival curves ($p < 0.001$) and a slight difference for T-factor and N-factor survival curves ($p < 0.05$). Among JPS staging factors, Rp-factor survival curves (for $R_p = 0$ and $R_p > 0$) showed the greatest difference ($p < 0.001$); the difference between the V-factor curves (for $V = 0$ and $V > 0$) and the T-factor curves nearly reached the significance ($p = 0.07$ and $p = 0.06$, respectively); there was no significant difference among the survival curves of the other staging factors (T-N-S).

In the peritoneal washings performed at the beginning of the operation, neoplastic cells were found in 3 of the 29 patients (10.3%). One of them survived 16 mo and another 8 mo; the third one is alive 12 mo after surgery; median survival of the other 26 patients was 16 mo. None of the 29 patients had neoplastic cells in the peritoneal washings performed at the end of operation; 10 of them underwent nonradical resection. No metastatic cells were found in liver biopsies.

Discussion. In our study, 3 patients (3%) and 30 patients (33%) belonged to JPS stage I and to UICC stage I, respectively; 31 patients (34%) and 5 patients (5%) belonged to JPS and to UICC stage IV. A stage discrepancy between the two systems was observed in 81% of our patients. Patients were generally classified in a more advanced stage in JPS than in UICC classification, because of the frequent advanced local growth at the time of surgery.

The present investigation suggests a better prognostic value of the JPS classification. Univariate analysis of overall survival curves showed a significant difference either among JPS stages ($p < 0.001$) or among UICC stages ($p < 0.01$), but UICC stage II and stage III had no difference, as shown by median survival time and by confidence intervals. Furthermore, the multivariate analysis model with JPS stages, radicality, and tumor grading confirmed the prognostic value of this classification, whereas in the model with UICC stages, only radicality and tumor grading were significantly related to survival.

Among the single factors of the two classifications, the most significant indicator for survival was the spread to retroperitoneal peri-pancreatic tissues (Rp factor JPS); none of the other JPS factors showed a significant influence on survival, even if T and V factors were close to significance. All the staging factors in UICC classification T, N, and M) showed a significant prog-

nostic value. However, the overall prognostic significance of UICC classification was lower than the Japanese staging system. A possible explanation is that the single factors of the UICC classification are not correctly grouped; it is likely that the advanced local growth is underestimated by the current stage grouping.

Peritoneal cytology and liver biopsies were not useful indicators for prognosis; malignant cells in the peritoneal washings performed at the beginning of operation were found in 3 of 29 patients, and the survival of these 3 patients was similar to that of the 26 patients with a negative cytology. Liver biopsies did not provide prognostic information, since none of the patients had malignant cells in intraoperative biopsies. Biopsies were negative even in one patient who had echographic demonstration of hepatic metastases 2 mo after surgery.

We conclude that JPS classification, though more complex, better relates to prognosis than UICC staging system; cancer invasion of the peripancreatic tissues is the most reliable prognostic factor. A modified stage grouping of UICC T and N parameters should be tested in the future to improve the prognostic reliability of this staging system.

References

- 1 Hermanek P, Sobin LH, eds., *UICC: TNM Classification of Malignant Tumors*, 4th ed., 2nd rev. Springer-Verlag, Berlin, 1992.
- 2 Japanese Pancreatic Society. *General Rules for Surgical and Pathological Studies on Cancer of the Pancreas*. Kanehara Publishing, Tokyo, 1986.

Clinical Comparison of UICC and Japanese Classifications Japanese Experience

Tsukasa Tsunoda,*¹ Toshifumi Eto,²
and Ryoichi Tsuchiya³

¹Department of Gastroenterological Surgery,
Kawasaki Medical School, Kurashiki City, Japan;

²Department of Surgery, Oshibuchi Hospital,
Satomen Mikuriya, Matsuura City, Japan;
and ³Vice-president and Director of the Hospital,
Shimane Medical University and Professor Emeritus
of Nagasaki University School of Medicine,
Izumo City, Japan

Introduction. The stage of cancer should accurately reflect the prognosis of patients suffering from the disease, as well as resectability of tumors. UICC has recommended a stage classification of pancreatic cancer based on TNM factors (UICC stage classification, UICC) (1). The Japanese Pancreatic Society has proposed a more complex stage classification plan that includes certain other factors (JPS stage classification, JPS) (2).

Unfortunately, the two staging systems are quite different, since the distant extent of tumor (lymph node and distant metastases) is thought to be the most important staging factor in

Fig. 1. Cumulative survival after resectional surgery according to UICC stage classification. No significant differences were present in the PCS rates between stages II and III. UICC stage: (□), stage I ($n = 364$); (○), stage II ($n = 183$); (■), stage III ($n = 458$); (△), stage IV ($n = 607$).

UICC, whereas the tumor local spread is considered to be the most significant prognostic factor in JPS.

The purpose of this article is to analyze the outcome of a large series of pancreatic carcinoma in view of UICC and JPS, to clarify the differences, and further to discuss the differences and usefulness of the two classification systems for staging of the disease.

Patients and Methods. Annual reports of the Japanese Pancreatic Cancer Registry from 1981 to 1990 showed 5870 cases with pancreatic ductal carcinoma excluding cystadenocarcinoma and islet cell carcinoma. Of the 5870 cases, 4725 cases were carcinoma of the head of the pancreas. There were 2750 males and 2975 females with an average age of 63.3. Resection was done on 2375 cases. The 2375 cases were analyzed according to UICC and JPS in this study. The disease is divided into four stages in both classifications. The staging factors employed in UICC are primary tumor (T factor), lymph node metastasis (N factor), and distant metastasis (M factor), whereas those in JPS include serosal invasion (S factor), retroperitoneal invasion (RP factor), and invasion to portal vein systems (PV factor). T factor refers only to tumor size in JPS. The expressions of severity and groupings of each factor differ in the two stage classifications. To avoid confusion, therefore, the UICC stage and equivalent JPS staging factors were carefully assigned and described elsewhere (3). Postoperative cumulative survival (PCS) rates by each staging factor were analyzed for which all staging factors, except tumor size and distant metastasis, had been confirmed microscopically. PCS rates were calculated by the actuarial method, and the statistical analysis was done by the Greenwood formula.

Results: The PCS Rates According to Stage. According to UICC, significant differences were observed in the 1-, 3-, and

5-yr PCS rates between stages I and II, I and III, I and IV, and III and IV, and in the 1- and 3-yr PCS rates between stages II and IV ($p < 0.01$) (Fig. 1). However, no significant differences were present in the PCS rates between stages II and III. The PCS rates of stage II were lower than those of stage III. By JPS, significant differences were observed in the 1-, 3-, and 5-yr PCS rates between stages I and II, I and III, I and IV, II and III, II and IV ($p < 0.01$), and in the 1- and 3-yr PCS rates between stages III and IV ($p < 0.05$) (Fig. 2).

The PCS Rates by Each Staging Factor: T Factor. In UICC, significant differences were observed in the 1-, 3-, and 5-yr PCS rate between T_{1a} (85.7, 66.3, 56.2% [$n = 74$]) and T_{1b} (66.9, 32.0, 20.3% [$n = 183$]), T_{1a} and T_2 (55.4, 19.6, 13.6% [$n = 661$]), T_{1a} and T_3 (33.4, 11.2, 7.8% [$n = 835$]), T_{1b} and T_2 , T_{1b} and T_3 , and T_2 and T_3 ($p < 0.01$). T factor in JPS means tumor size alone. There were significant differences in the 1-, 3-, and 5-yr PCS rates between T_1 (68.0, 39.8, 30.0% [$n = 263$]) and T_2 (50.1, 18.5, 10.7% [$n = 1122$]), T_1 and T_3 (36.0, 9.6, 6.3% [$n = 530$]), and T_2 and T_3 ($p < 0.01$), and in the 1- and 3-yr PCS rates between T_1 and T_4 (39.0, 22.0% [$n = 132$]) ($p < 0.01$) and in the 1-yr PCS rates between T_2 and T_4 ($p < 0.05$). However, the 3- and 5-yr PCS rates of T_2 and T_3 were lower than those of T_4 (22.0, 20.0% [$n = 132$]).

N Factor. According to JPS, significant differences were observed in the 1-, 3-, and 5-yr PCS rates between N_0 (63.0, 34.1, 24.3% [$n = 707$]) and N_1 (46.8, 14.9, 9.2% [$n = 924$]), N_0 and N_2 (34.0, 8.9, 5.3% [$n = 307$]), N_0 and N_3 (21.0, 2.8, 1.4% [$n = 105$]), and N_1 and N_3 ($p < 0.01$), and in the 1- and 3-yr PCS rates between N_1 and N_2 , and N_2 and N_3 ($p < 0.05$). As a matter of course, there were significant differences in the 1-, 3-, and 5-yr PCS rates between N_0 ($N[-]$) and N_1 ($N[+]$) by UICC.

Fig. 2. Cumulative survival after resectional surgery according to the Japanese stage classification. There were significant differences in the 1-, 3-, and 5-yr PCS rates between stages I and II, I and III, I and IV, II and III, and II and IV ($p < 0.01$), and in the 1- and 3-yr PCS rates between stages III and IV ($p < 0.05$). JPN stage: (□), stage I ($n = 144$); (○), stage II ($n = 623$); (■), stage III ($n = 711$); (△), stage IV ($n = 636$).

S Factor. By JPS, there were significant differences in the 1-, 3-, and 5-yr PCS rates between S_0 (60.3, 29.9, 20.7% [$n = 1017$]) and S_1 (42.2, 9.9, 4.9% [$n = 432$]), S_0 and S_2 (35.0, 8.2, 4.7% [$n = 450$]), and S_0 and S_3 (30.0, 9.7, 6.1% [$n = 172$]) ($p < 0.01$), and in the 1-yr PCS rates between S_1 and S_2 , and S_1 and S_3 ($p < 0.05$). No significant differences were observed in the 3- and 5-yr PCS rates between S_1 and S_2 , S_1 and S_3 , and S_2 and S_3 .

RP Factor. Significant differences were observed in the 1-, 3-, and 5-yr PCS rates between RP_0 (59.8, 28.0, 18.7% [$n = 973$]) and RP_1 (43.2, 15.2, 10.7% [$n = 431$]), RP_0 and RP_2 (38.0, 14.0, 9.5% [$n = 383$]), RP_0 and RP_3 (26.0, 5.2, 2.6% [$n = 149$]), RP_1 and RP_3 , and RP_2 and RP_3 ($p < 0.01$). However, there were no significant differences in the 1-, 3-, and 5-yr PCS rates between RP_1 and RP_2 .

PV Factor. There were significant differences in the 1-, 3-, and 5-yr PCS rates between PV_0 (58.5, 26.6, 18.2% [$n = 1130$]) and PV_1 (40.8, 11.0, 8.6% [$n = 339$]), PV_0 and PV_2 (38.0, 13.0, 7.1% [$n = 396$]), and PV_0 and PV_3 (29.0, 9.4, 2.7% [$n = 223$]) ($p < 0.01$) and in the 1- and 5-yr PCS rates between PV_1 and PV_3 ($p < 0.05$), and in the 1-yr PCS rates between PV_2 and PV_3 ($p < 0.05$). However, no significant differences were observed in the 1-, 3-, and 5-yr PCS between PV_1 and PV_2 .

Discussion. The present investigation using the large series of the resected pancreatic cancer cases demonstrated that the stage of JPS reflected the postoperative prognosis much better than UICC. In UICC, the PCS rates of stage II were lower than those of stage III, and there were no significant differences between them. Using the small series of the resected pancreatic cancer cases, we indicated that UICC tends to classify patients in a less advanced stage than JPS (3).

In UICC, a primary tumor without nodal and distant metastases is assigned to the stage I or II even if it involves adjacent organs or large vessels. In JPS, the patients with these conditions

(S_3 , and/or RP_3 , and/or PV_3) belong to stage IV. When severe portal vein invasion is present, for example, the tumor is usually unresectable unless the portal vein is resected. PV_3 , RP_3 , and S_3 , therefore, should be classified into the most advanced stage. The evaluation of the tumor local growth is indeed one of the major differences between the two staging classifications.

In JPS, lymph node metastasis is as important as tumor local growth in the stage classification. In UICC, positive regional lymph node metastasis is the most important factor in the definition of stage III regardless of the tumor local growth. Positive N factor in UICC is perhaps overestimated as compared to RP, PV, and S factors. Although significant differences in the 1-, 3-, and 5-yr PCS rates between N_0 ($N[-]$) and N_1 ($N[+]$) were found, there were still significant differences in those PCS rates among the four grades of JPS N factor. Japanese grading of N factor reflected the prognosis better than the all or nothing rule of UICC N factor, and it was proven to be the exact classification. In addition, the grading of lymph node involvement was also extremely important from the standpoint of surgical treatment of the disease. Even if nodal involvement was shown in the primary group (N_1) macro- and microscopically, complete clearance of both the primary (N_1) and secondary (N_2) groups has contributed greatly to the long-term survivals after surgery (4).

JPS has a disadvantage of complexities. Continuing efforts are necessary to establish a more practical, simple, and universal staging system for carcinoma of the pancreas.

Acknowledgments. The authors deeply appreciate the cordial cooperation of Y. Saitoh, Chairman of the Committee on the Pancreatic Cancer Registry, and M. Yamamoto, his colleague. This work was supported in part by Grant-in-Aid for Cancer Research from Ministry of Health and Welfare of the Japanese Government.

References

- 1 UICC, *TNM classification of Malignant Tumors*, 4th fully new ed. Springer-Verlag, Berlin Heidelberg New York, 1987.
- 2 Japan Pancreas Society, *General Rules for Surgical and Pathological Studies on Cancer of the Pancreas*, 3rd ed. Kanehara & Company LTD, Tokyo, 1987.
- 3 Tsunoda T, Ura K, Eto T, Matsumoto T, Tsuchiya R. UICC and Japanese stage classifications for carcinoma of the pancreas. *Int J Pancreatol* 1991; 8(3): 205–214.
- 4 Tsuchiya R, Harada N, Tsunoda T, Miyamoto T, Ura K. Long-term survivors after operation on carcinoma of the pancreas. *Int Pancreatol* 1988; 3: 491–496

Mode of Pancreatic Cancer Extension and Operative Curability

Osamu Ishikawa, Hiroaki Ohigashi, Shoji Nakamori, and Shingi Imaoka

Department of Surgery, The Center for Adult Diseases, Osaka, Japan

Summary. The present article is a retrospective analysis to find out the indicative factors of long-term (3-yr) survival after an extended pancreatectomy for carcinoma of the pancreatic head. As a result, 3-yr survival was obtained even in the patients whose cancers had invaded directly beyond the posterior confines of the pancreas or metastasized to the regional lymph nodes. However, in these patients, nodal involvement was limited to the pancreaticoduodenal region, and the direct invasion was slight, involving only the semicircle of the portal/superior mesenteric veins or less. On the other hand, long-term survival was scarcely expected when the nodal involvement was observed in any other regions or direct invasion was more severe. When an extended pancreatectomy is applied to the pancreatic head cancer, both the nodal involvement limited to the pancreaticoduodenal region and slight invasion into the retroperitoneal spaces should be classified into the less advanced stages than those in the previous staging.

Introduction. Some surgeons abandoned curative pancreatectomy for adenocarcinoma of the pancreas because of an extremely low curability. It was commonly accepted that patients with nodal involvement were unsuitable candidates for pancreatectomy (1). However, the following histologic studies (2) clarified that pancreatic cancer showed a variety of extensions into the surrounding tissues: nodal involvement and microscopic cancer infiltrations (MCI) into the perineural spaces, lymphatic channels, vascular vessels, and loose connective tissues. Thus, in order to eradicate these lesions, we have tried to perform both lymphatic and connective tissue clearance during pancreatectomy for this cancer (3). As a result, this procedure improved the 3-yr survival rate to 38% from 13% attained by traditional pancreatectomy alone (3). Likewise, long-term survivors were occasionally produced in the patients whose cancers metastasized in the regional lymph nodes or directly invaded the portal vein (4). The purpose of the present article is to find out more

detailed background factors that could indicate that long-term survival can be achieved by an extended pancreatectomy.

Patients and Methods. During the period between 1982 and 1990, 47 patients with ductal carcinoma of the pancreatic head received and tolerated pancreatoduodenectomy in combination with a wide range of lymphatic and connective tissue clearance at the Center for Adult Diseases, Osaka, Japan. They did not include the low-grade malignant tumors, such as cystadenocarcinoma or "mucin-producing neoplasm," and neither chemo- nor radiotherapy was done before surgery. When it was confirmed that the portal vein and/or superior mesenteric vein (PV/SMV) was involved by cancer, they were resected together with the pancreatoduodenectomy and reconstructed by end-to-end anastomosis. Excluding one patient who died of other disease within three postoperative years, 16 patients (35%) survived more than 3 yr (Group A), whereas 30 patients (65%) died of cancer recurrence within 3 postoperative yr (Group B). Their resected specimens were fixed in 20% formalin and sliced into 5-mm sections. They were stained by Hematoxylin-eosin, and observed microscopically to determine the size of the tumor and the presence or absence of nodal involvement, MCI, portal vein invasion, and direct invasion beyond the posterior confines of the pancreas. The lymph nodes were divided into seven groups as shown in Fig. 1. These factors were compared between Groups A and B. Statistical analyses performed using chi-square test and *p* values <0.05 were considered to be statistically significant.

Results. Table 1 shows the background factors in the two groups. The tumors in Group A were of a smaller size than those in Group B (*p* < 0.05). Neither retroperitoneal invasion beyond the posterior confines of the pancreas nor direct invasion into the portal vein/superior mesenteric vein (PV/SMV) differed significantly between the two groups. When the comparison was limited to the positive cases in the PV/SMV invasion, all of the seven PV/SMV invasions of Group A were hemilateral, whereas eight (53%) out of 15 PV/SMV invasions of Group B were bilateral (*p* < 0.05).

Though Group B had a higher incidence of nodal involvement than Group A, the difference was not statistically significant. Figure 1 shows the incidences of nodal involvement in association with seven nodal groups. The common sites were inferior pancreaticoduodenal area (46%), superior mesenteric area (43%), superior head/body area (39%) and para-aortic area (20%). Though neither superior head/body nor hepato-duodenal ligament areas were commonly vulnerable to cancer (17%), all of the patients with nodal involvement in one of these two areas were classified into Group B (Table 1). Likewise, most patients who had nodal involvement in the superior mesenteric, mesocolonic, or para-aortic regions were included in Group B. However, between Groups A and B, no significant difference was observed in the incidences of nodal involvement in the two pancreaticoduodenal areas.

MCI was occasionally observed even in the surrounding soft tissues, which did not include any nodal involvement at all; 56% (13/32) in the superior head/body plus hepato-biliary ligament areas (a + b); 28% (5/18) in two pancreaticoduodenal areas (d + e); 23% (6/26) in the superior mesenteric area (c); and 17% (7/41) in the inferior area (f).

Discussion. According to the UICC classification (5), the pancreatic cancers with nodal involvement are classified into

Fig. 1. The incidences of nodal involvement in association with lymph nodes groups among 46 cancers of the pancreatic head. A: superior head and body, B: hepato-duodenal ligament, C: along superior mesenteric vessels, D: superior pancreaticoduodenal, E: inferior pancreaticoduodenal, F: mesocolonic, G: para-aortic; one (11%) of nine patients who received total pancreatectomy had nodal involvement in the splenic hilum region. Group A, Incidence: 17% (8/46); Group B, Incidence: 17% (8/46); Group C, Incidence: 43% (20/46); Group D, Incidence: 39% (18/46); Group E, Incidence: 46% (21/46); Group F, Incidence: 11% (5/46); Group G, Incidence: 20% (9/46).

stage III, whereas those involving the peripancreatic tissues and adjacent vessels are classified into stage I and stage II, respectively. This classification might have been true in the era when the traditional pancreatectomy was the standard procedure, but few long-term survivors were produced. However, using an extended pancreatectomy with lymphatic and connective tissue clearance, long-term survival can be hoped for when the nodal involvement is limited to the pancreaticoduodenal area or when PV/SMV invasion is hemilateral. On the other hand, long-term survival is not expected when the nodal involvement has reached the superior mesenteric, superior head/body, or hepato-duodenal ligament areas, or when the PV/SMV invasion is bilateral. Thus, we should take this data into consideration on the staging of pancreatic cancer in the future.

With regard to the operative procedure, MCI was not rare in the region that did not include nodal involvement at all. In order to eradicate MCI, an extended dissection of neighboring connective tissues is still necessary for the region without nodal involvement.

Table 1
Background Factors Compared Between Groups A and B

Background factors	Group A, n = 16	Group B, n = 30	p value
Size of tumor			<0.05
≤2 cm	6 (38%)	3 (10%)	
2.1–4.0 cm	9 (56%)	18 (60%)	
≥4.1 cm	1 (6%)	9 (30%)	
Direct invasion beyond posterior confines of pancreas	10 (67%)	22 (73%)	NS
Portal vein invasion			NS
Negative	9 (56%)	15 (50%)	
Hemilateral	7 (44%)	7 (23%)	<0.05
Bilateral	0 (0%)	8 (27%)	
Nodal involvement			<0.05
Negative	7 (44%)	5 (17%)	
Positive	9 (56%)	25 (83%)	
Site of nodal involvement ^a			
a. Superior head/body	0 (0%)	8 (27%)	<0.05
b. Hepato-duod. lig.	0 (0%)	8 (27%)	<0.05
c. Sup. mesenteric	1 (6%)	19 (63%)	<0.01
d. Sup. pd ^b	3 (19%)	15 (50%)	NS
e. Inf. pd ^b	5 (31%)	16 (53%)	NS
f. Mesocolonic	1 (6%)	4 (13%)	NS
g. Para-aortic	1 (6%)	8 (27%)	NS

^aIllustrated in Fig. 1. ^bpd = pancreaticoduodenal.

References

- Cohen JR, et al. Pancreaticoduodenectomy: a 40-year experience. *Ann Surg* 1982; 195: 608–617.
- Nagai H, et al. Lymphatic and local spread of T1 and T2 pancreas cancer. A study of autopsy material. *Ann Surg* 1986; 204: 65–71.
- Ishikawa O, et al. Practical usefulness of lymphatic and connective tissue clearance for the carcinoma of the pancreas head. *Ann Surg* 1988; 208: 215–220.
- Ishikawa, O, et al. Preoperative indications for extended pancreatectomy for locally advanced pancreas cancer involving the portal vein. *Ann Surg* 1992; 215: 231–236.
- UICC. TNM Atlas. *Illustrated Guide to the TNM/p TNM Classification of Malignant Tumours*, 3rd. ed. Spiessl B, Beahro OH, Hermanek P, Hutter RVP, Scheibe O, Sobin LH, Wagner G. eds. Springer-Verlag, Berlin, 1989.

The Method of Preoperative Clinical Staging European Experience

H. G. Beger, M. H. Schoenberg, and D. Birk
University of Ulm, Department of General Surgery,
Ulm, Germany

Introduction. Pancreatic carcinoma remains, despite the advances in imaging methods and surgical management, a dis-

ease with an extremely poor prognosis, and presently accounts for 9–10 deaths/100,000 persons (1). Currently, pancreatic carcinoma represents the sixth most frequent cause of death resulting from a malignant disease. Despite ongoing efforts to improve early diagnosis and treatment, 90% of patients will die within 1 yr of diagnosis, and survival beyond 5 yr remains truly exceptional (2). This means that surgical resection only offers a prospect of cure to selected patients. Therefore, it is absolutely mandatory that each patient undergoes a thorough preoperative clinical staging of the disease in order to assess whether or not this patient is feasible for surgical treatment. All other therapeutic options that have been proposed in the last 10 yr could not reproduce clinically promising experimental results. In clinical trials, immunotherapy with cytokines like TNF or interferon and monoclonal antibodies could not show any significant improvement concerning life quality and survival rate of this disease (3,4). Only palliative treatments, for example, by endoscopic stenting in case of obstructive jaundice or by the use of regional chemotherapy in nonresectable stages, have proven to be noninvasive procedures improving only the life quality of the patients and not their survival period. Therefore, extended surgical procedures still offer the only curative form of treatment especially since the perioperative mortality has decreased from 20% to under 5% in the last two decades (5–7).

Since the symptoms of pancreatic carcinoma are unspecific, reliable screening methods are not available, and risk groups of patients developing pancreatic carcinoma are not yet identified. Therefore 60% of the patients with a malignant disease of the pancreatic gland are already unresectable at diagnosis (8,9). This clinical situation and the patient characteristics collectively imply that the preoperative clinical staging should be simple, sensitive, and meet the growing demand for more economical diagnostic procedures.

Diagnosis. Currently, most patients with pancreatic cancer are identified on the basis of their symptoms. Patients with gastric pain, weight loss over 10% of their ideal body weight, jaundice, or combinations of these symptoms are present in over 90% of the patients (10). The first step of diagnosis should evaluate the patients' medical history and the likelihood of a malignant disease in the pancreatic gland. Medical history and the aforementioned clinical signs of the disease together with a high concentration of the tumor marker CA 19-9 prompts further and more invasive diagnostic procedures. The sensitivity of the tumor marker CA 19-9 in distinguishing pancreatic cancer was in our experience 87% considering 37 U/mL as the threshold value. The specificity and the total accuracy was 86% (11) (Table 1). In order to differentiate between other diseases within the pancreatic gland (chronic and acute pancreatitis), the first diagnostic procedure should include routine laboratory data including serum amylase as well as plain X-ray of the abdomen and thorax. Thereby calcifications within the pancreatic head are an easy way to differentiate between pancreatic carcinoma and chronic pancreatitis since in these aforementioned cases 90% of the patients are suffering from chronic calcifying pancreatitis (12).

Ultrasonography and CT are the methods most frequently used to confirm a clinical suspicion of pancreatic cancer. Both methods are able to detect pancreatic masses as small as 2 cm, in some patients the enlarged pancreatic duct and bile duct, hepatic metastases, and extrapancreatic spread can be seen. Thereby,

Table 1
Results of the 18-FDG-PET of 25 Patients
with Pancreatic Carcinoma and 17 with Chronic Pancreatitis

	PET positive	PET negative
Chronic pancreatitis, <i>n</i> = 17	4	13
Pancreatic carcinoma, <i>n</i> = 25	23	2
Sensitivity	92%	
Specificity	76.5%	
Positive predictive value	85.2%	
Negative predictive value	86.7%	

ultrasonography remains the most available and least expensive of the imaging modalities used in the assessment of the upper abdomen (13). Moreover, this imaging procedure distinguishes accurately between obstructive from nonobstructive jaundice, which is one of the leading symptoms in 50% of the patients suffering from pancreatic carcinoma (10). On the other hand, CT-scan (preferably also contrast-enhanced CT scan) provides a more accurate imaging of the tumor itself and its surrounding structures. Moreover, CT-imaging procedures are more objective, whereas the accuracy of ultrasonography relies on the experience of the examiner as well as the preparation and the habitus of the patient (14).

Besides these imaging procedures containing ultrasound examination and contrast-enhanced CT-scan the endoscopic retrograde cholangiography (ERCP) has become essential for the differential diagnosis of tumors of the pancreaticobiliary system. ERCP procedure is instrumental for differentiation whether the tumor is in the pancreatic head (85% of patients) or in the distal common bile duct (6% of the patients). In 4.5% of the patients undergoing ERCP, the tumor is found in the ampullary region (15). These findings are extremely important since the 5-yr-survival rate of patients suffering from ampullary carcinoma amounts to 50% after successful resection of the tumor thus being two to three times higher than in patients with pancreatic duct carcinoma (16).

Sometimes it is difficult to distinguish between pancreatic cancer and chronic pancreatitis since the two diseases show similar ERCP abnormalities. It has been suggested that the presence of a pancreatic duct stricture longer than 10 mm, especially if this stricture exhibits irregularities, is a fairly accurate sign of a pancreatic carcinoma instead of chronic pancreatitis in which the stenosis should not exceed 5 mm (17).

All other diagnostic measures in line with the ERCP examination (cytology from the pancreatic juice, brushing within the pancreatic duct, and so forth) have not been proven feasible for the diagnosis of pancreatic cancer. Regarding the sensitivity of all diagnostic procedures a comparative study could show that the imaging procedures alone did not have satisfactorily high sensitivity rates. Moreover, the results implied that all three methods are complementary and should be used together in order to distinguish between benign and malignant diseases within the pancreatic gland (18).

Percutaneous Aspiration Cytology. Despite the high sensitivity of the combination of various imaging procedures the clinical

cal and radiological diagnoses should be confirmed by fine needle aspiration cytology or biopsy. Although the pitfalls concerning the cytological and/or histological confirmation are well-recognized, the importance of this essential diagnostic procedure cannot be overemphasized. The number of benign conditions can certainly masquerade a cancer, and it is therefore unforgivable to start a potentially dangerous and inappropriate pancreas resection for a misdiagnosed benign disease solely on the basis of imaging procedures for diagnostics. Furthermore, a number of neoplasms masquerading a pancreatic adenocarcinoma carry a much more optimistic outlook if appropriate treatment is instituted. For example, lymphomas obstructing the biliary system are better treated by chemotherapy than operative therapy. Moreover, primary pancreatic neoplasms, such as cystoadenocarcinomas and cystadenomas as well as APUDomas, have a much better prognosis once the true nature of the disease is recognized (9). This procedure has been regarded as safe, however, the sensitivity ranges from 57–96%. There are two major drawbacks of percutaneous aspiration cytology. First, negative results cannot exclude the possibility of a malignant disease in the pancreatic gland. Secondly, a recent report indicates that in patients undergoing percutaneous needle biopsy a significantly higher number had a positive cytological finding in peritoneal washing during staging as compared to those without biopsy. Therefore, fine needle biopsy has to be evaluated further for its practicability in diagnosis of pancreatic carcinoma (18).

Lately we perform in all patients an 18 FDG-PET (fluorodeoxyglucose-positronemissions-tomography). So far, 42 patients underwent this new diagnostic procedure, the sensitivity for FDG-PET was 92% and the positive predictive value was 85.2%. Therefore, PET with 18 FDG seems to be a new suitable noninvasive diagnostic procedure to differentiate again between chronic pancreatitis and neoplasms of the pancreatic gland (19).

Preoperative Staging of Pancreatic Carcinoma. After the malignant disease has been diagnosed and confirmed by fine-needle aspiration cytology or biopsy, it is essential to determine which patients with pancreatic cancer should be offered which form of treatment. Twenty years ago, surgical laparotomy (thus exploration) was recommended for most patients since it provided an opportunity to obtain adequate diagnosis by biopsy and to assess resectability. If found unresectable, the patient underwent palliative procedures such as biliary and duodenal bypass (19). This strategy is no longer justifiable since improved preoperative staging can clarify in most cases the optimal treatment for the patient. Computed tomography and ultrasonography are widely used to assess not only the diagnosis but also the resectability of the tumor. The CT criteria for unresectability include evidence of hepatic or more distant metastases and/or local signs of tumor extension of the neighboring structures especially vascular encasement or invasion and local lymphadenopathy. However, in our experience, these radiological diagnostic procedures are not sufficient. Therefore, most patients undergo selective angiography in order to exclude significant vascular invasion in the arteries and relevant veins (portal vein, superior mesenteric vein). In borderline cases, we have recently submitted the patient to laparoscopic diagnosis, which has proven useful in evaluating resectability prior to laparotomy. In a prospective study, Fernandez del Castillo and Warshaw show that preoperative laparoscopy was useful for identifying small perito-

neal and liver implants, which were present in 27% of the patients with tumors of the pancreatic head and in 65% of those with cancer of the body and tail of the pancreas. Moreover, the authors performed peritoneal cytology and found in 20–30% of the patients malignant cells indicating a very bad prognosis (20).

Perioperative Risks. After exact diagnosis and evaluation of its technical resectability, the patients undergo extensive cardiopulmonary examinations in order to determine their perioperative risks. The patient's age in itself is no longer a contradiction to surgery and specialized centers are able to undertake resections in older patients if they are considered fit for major surgery. Therefore, in all patients besides the routine perioperative examinations it is important to obtain and exercise ECG, possibly cardioulttrasound examination and various pulmonary function tests. As in all surgical procedures in the upper abdomen chronic obstructive pulmonary diseases and/or severe cardiovascular alterations endanger the success of the operative procedure. Moreover, since pancreatic duodenectomy in unexperienced hands can cause considerable morbidity and up to 50% mortality, it may be appropriate to perform staging in the local hospital but to consider transferring the patient to a referral center if resection seems likely. In specialized centers as mentioned above the perioperative morbidity and mortality could be reduced considerably in the last 20 yr.

Summary. With these differentiated procedures, the sensitivity of tumor diagnosis and resectability amounts in our clinic to 92%. The assessment of perioperative risks has decreased the overall hospital lethality to 4.1% in our institution. These data suggest that preoperative diagnosis, clinical staging, and assessment of perioperative risks is only successful if an experienced cooperative staff takes over this task, thus improving the sensitivity of diagnosis and avoiding perioperative complications. Hopefully, timely diagnosis, adequate clinical staging, and operative procedures in experienced hands will also improve the survival rate, which until now is still depressingly low.

References

- 1 Gordis L, Gold EB. Epidemiology and etiology of pancreatic cancer, in *The Exocrine Pancreas: Biology, Pathobiology and Diseases*, Go VLW, ed., Raven, New York; 1986, p. 621.
- 2 National Cancer Institute. *Annual Cancer Statistics Review 1973–1988*. Department of Health and Human Services, Bethesda, MD, 1991 (NIH publication no. 91-2789).
- 3 Klapdor R, Montz R. Clinical and immunological response to the therapy of pancreatic cancer with murine monoclonal antibodies, in *Immunotherapy and Scintigraphy of Tumors with Monoclonal Antibodies*, Aktuelle Onkologie Nr. 41, Epenetos AA, Oberhausen E, Reisfeld LRA, eds., Zuckschwerdt, München: 1988; p. 87.
- 4 Klapdor R. Interaction of monoclonal antibodies with biological response modifiers and cytostatics, in *Cancer Therapy. Monoclonal Antibodies, Lymphokines, New Development in Surgical Oncology, Chemo- and Hormonal Therapy*, Beger H, ed., Springer, Berlin, 1989; p. 56.
- 5 Moosaa AR, Gadd M, Lavelle-Jones M. Surgical treatment of exocrine pancreatic cancer, in *The Exocrine Pancreas: Biology, Pathobiology and Diseases*, Go VLW, ed., Raven, New York, 1986; p. 713.

- 6 Tsuchiya R, Noda T, Harada N, Miyamoto T, Tomioko T, Yamamoto K. Collective review of small carcinomas of the pancreas. *Ann Surg* 1986; 203: 77.
- 7 Beger HC, Büchler MW, Friess H. Chirurgische Ergebnisse und Indikation zu adjuvanten Maßnahmen beim Pankreaskarzinom. *Chirurg* 1994; 65: 246–252.
- 8 Trede M. The surgical treatment of pancreatic carcinoma. *Surgery* 1985; 97: 28–35.
- 9 Warshaw AL, Fernandez-Del Castillo C. Pancreatic carcinoma. *New Engl J Med* 1992; 326: 455–465.
- 10 Kalser MH, Barkin J, MacIntyre JM. Pancreatic cancer: assessment of prognosis by clinical presentation. *Cancer* 1985; 56: 397–402.
- 11 Safi F, Roscher R, Beger HC. The clinical relevance of the tumor marker CA 19-9 in the diagnosing and monitoring of pancreatic carcinoma. *Bull Cancer* 1990; 77: 83–91.
- 12 Beger HG, Bittner R, eds. *Das Pankreaskarzinom*. Springer, Berlin, 1986.
- 13 Campbell JP, Wilson SR. Pancreatic neoplasms: how useful is evaluation with US? *Radiology* 1988; 167: 341–344.
- 14 Balthazar EJ, Chako AC. Computed tomography of pancreatic masses. *Am J Gastroenterol* 1990; 85: 343–349.
- 15 Michelassi F, Erroi F, Dawson PJ, et al. Experience with 647 consecutive tumors of the duodenum, ampulla, head of the pancreas, and distal common bile duct. *Ann Surg* 1989; 210: 544–554.
- 16 Tarazi RY, Hermann RE, Vogt CP, et al. Results of surgical treatment of periampullary tumors: a thirty-five-year experience. *Surgery* 1986; 100: 716–723.
- 17 Shemesh E, Czerniak A, Nass S, Klein E. Role of endoscopic retrograde cholangiopancreatography in differentiating pancreatic cancer coexisting with chronic pancreatitis. *Cancer* 1990; 65: 893–896.
- 18 Pasanen PA, Partanen KP, Pikkarainen PH, Alhava EM, Janatuinen EK, Pirinen AE. A comparison of ultrasound, computed tomography and endoscopic retrograde cholangiopancreatography in the differential diagnosis of benign and malignant jaundice and cholestasis. *Eur J Surg* 1993; 159(1): 23–29.
- 19 Isenmann R, Büchler M, Frieß H, Ebert M, Langhans J, Beger HG. Positronen-Emissions-tomographie—ein neues Verfahren in der Diagnostik des Pankreaskarzinoms. *Langenbecks Arch (Chirurg Forum, Suppl.)* 1993.
- 20 Fernandez-del-Castillo C, Warshaw AL. Laparoscopy for staging in pancreatic carcinoma. *Surg Oncol* 1993; 2: 25–29.

Preoperative Staging of Pancreatic Ductal Cancer in the USA

Eugene P. DiMagno

Mayo Clinic, Gastroenterology Unit, Rochester, MN

Introduction. Of the diagnostic tests for pancreatic cancer, only tests to image the pancreas and other intra-abdominal structures are useful for staging. Hence, the following tests, although of some use in the diagnosis of pancreatic cancer, have no role in staging of this disease: clinical findings, which are nonspecific

and have low sensitivity; routine laboratory tests, which are nonspecific; and serum markers and pancreatic function tests. Thus, the only tests I will discuss are usual imaging tests, including abdominal ultrasound (US), computed tomography (CT), angiography, endoscopic retrograde pancreatography (ERCP), and laparoscopy, as well as some newer tests, such as endoscopic ultrasonography (EUS), magnetic resonance imaging (MRI), and positron emission tomography (PET).

Ultrasound (US) and Computed Tomography (CT). Both US and CT are widely used to diagnose pancreatic cancer. Previously, we recommended that US be the first test (1) because it is only slightly less sensitive than CT (65–75 vs 69–80%) (1–7), is less expensive, and does not expose patients to ionizing radiation. However, in 10% of patients, US is technically unsatisfactory, and dynamic CT scanning can visualize smaller pancreatic cancers by enhancing the surrounding pancreatic parenchyma and provide information about vascular invasion by the tumor (8) and local and distant metastases. Because these additional data are essential in determining resectability, in most centers, CT is an indispensable test prior to considering surgery. Thus, at present the single best test to diagnose and stage pancreatic cancer is CT.

Endoscopic Retrograde Cholangiopancreatography. Endoscopic retrograde pancreatography (ERP) has a sensitivity and specificity of 90% for the diagnosis of pancreatic cancer (1,3,9). ERP signs of pancreatic cancer are the double-duct sign, solitary irregular pancreatic ductal stenosis, abrupt or gradual occlusion of the main duct, focal acinar destruction, displacement of the pancreatic duct, and pooling of contrast in irregular pockets of a necrotic tumor mass (10). However, chronic pancreatitis is sometimes difficult to differentiate from cancer, because fibrosis or pseudocysts may produce some of the radiologic features of pancreatic cancer.

Cytologic examination of cells in pancreatic juice obtained during ERCP with secretin stimulation generally is less accurate than the early report of Endo et al. (11). Sensitivity is low because pancreatic enzymes may partially digest cells, which hinders histologic interpretation. Endoscopic retrograde brush cytology to obtain cells directly from the pancreatic duct (12,13) may improve sensitivity.

Cytology or Biopsy by CT or US Guided-Needle Aspiration. Fine-needle aspiration cytology or biopsy is 90% sensitive for the diagnosis of pancreatic cancer (14,15). However, this procedure should not be done in a patient with a potentially resectable tumor, because the procedure may seed neoplastic cells within the abdominal cavity (16) or along the needle tract (17–19). When there is an unresectable tumor, aspiration cytology to confirm the diagnosis should prevent fruitless further investigation. Cytology rarely discloses a curable disease, such as lymphoma (20) or tuberculosis (21).

Endoscopic Ultrasonography (EUS). Since our introduction of endoscopic ultrasonography (EUS) (22), its use in diagnosing pancreatic cancer has gradually increased (3–6,23,24), particularly with the introduction of commercially available instruments. In comparison to other imaging tests, interpretations of EUS images appear more sensitive (>90%) in detecting small tumors (3,5,7) and in accurately predicting nonresectability by detecting extension of the tumor into vessels, particularly the portal vein (4,7,25). Vascular involvement is suspected when

tumor protrudes into the vascular lumen, or when the hyperechoic interface between the vascular lumen and vascular wall disappears. Lymph nodes are easily seen by EUS, but it is difficult to determine if they contain metastases or are reactive.

Angiography. Angiography is no longer widely used to diagnose or stage pancreatic cancer. Previously, it was used to detect vascular involvement, but CT with contrast or EUS is a better method to assess vascular involvement than angiography (4,8).

New or Future Imaging Techniques. Several imaging tests hold promise for detecting small pancreatic cancers and for better staging the tumor. The next imaging test that may be applied widely to diagnosing pancreatic cancer is magnetic resonance imaging (MRI). Although current evaluations indicate that MRI is not superior CT (26), there is a strong likelihood that MRI may better detect small lesions and vascular involvement, and thus enter into our armamentarium to diagnose and stage pancreatic cancers. Single-photon-emission computed tomography (27) (positron emission tomography) is not widely available, and it has not been used extensively in pancreatic cancer. To date, it has no particular advantage over current imaging tests, but it needs further evaluation.

Innovative modifications of outmoded or current tests may improve the diagnosis of early cancers. Although scintigraphy of the pancreas with selenomethionine Se75 is no longer used because it is inaccurate (1,28), immunoscintigraphy using a radiolabeled monoclonal antibody seems promising (29). Several investigators are testing miniature endoscopes or ultrasonic probes to detect small intrapancreatic lesions (30). These instruments are inserted into the lumen of the pancreatic duct through conventional endoscopes.

Evaluation of Resectability. Preoperative staging of pancreatic cancer to determine resectability is important to avoid unnecessary surgery and to offer the patient other choices, such as endoscopic placement of a stent, laparoscopic cholecystojejunostomy (31), or other palliative surgery. Pancreatic cancer is resectable if there are no metastases and no portal vein or aortic (celiac axis) involvement. Splenic vein involvement and lymph node involvement are not necessarily contraindications to resection.

The common preoperative test to determine resectability is CT. Angiography was used in the past, and laparoscopy and EUS are used increasingly. Warshaw et al. compared CT, angiography, and laparoscopy, and found that in patients judged to be operable by conventional CT, more than 40% of them had small intraperitoneal metastases by laparoscopy (32). Consequently, they recommended using laparoscopy (15,32) routinely to assess resectability. EUS is better than angiography to detect vascular involvement, especially of the portal system (4-7), and EUS is also useful to assess lymph node involvement (4,6,7).

Summary of Tests to Diagnose and Stage Pancreatic Cancer. Current data suggest that CT is the best test to diagnose and stage pancreatic cancer. EUS and laparoscopy will have an increasing role in staging of the tumor. We suggest that CT should be the first test. If the tumor is resectable, EUS should be the next test to stage the tumor. If the tumor is still judged to be resectable, laparoscopy should be performed. In the future, EUS may become the single best test to diagnose and stage the tumor simultaneously. Currently, however, it is an expensive test and requires expertise. If an accurate and cost-effective screening

test, such as a tumor marker, becomes available, EUS may play an important role in detecting small cancers.

References

- 1 DiMagno EP, Malagelada J-R, Taylor WF, Go, VLW. A prospective comparison of current diagnostic tests for pancreatic cancer. *New Engl J Med* 1977; 297: 737-742.
- 2 Gowland M, Kalantzis N, Warwick F, Braganza J. Relative efficiency and predictive value of ultrasonography and endoscopic retrograde pancreatography in diagnosis of pancreatic disease. *Lancet* 1981; 2: 190-193.
- 3 Rösch T, Reinhard L, Braig C, Feuerbach S, Siewert R, Schusdziaira V, Classen M. Endoscopic ultrasound in pancreatic tumor diagnosis. *Gastrointest Endosc* 1991; 37: 347-352.
- 4 Rösch T, Braig C, Gain T, Feuerbach S, Siewert JR, Schusdziaira V, Classen M. Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography: comparison with conventional sonography, computed tomography, and angiography. *Gastroenterology* 1992; 102: 188-199.
- 5 Snady H, Cooperman A, Siegel J. Endoscopic ultrasonography compared with computed tomography with ERCP in patients with obstructive jaundice or small peripancreatic mass. *Gastrointest Endosc* 1992; 38: 27-34.
- 6 Tio TL, Tytgat GNJ, Cikot RJLM, Houthoff HJ, Sars PR. Ampullopapillary carcinoma: preoperative TNM classification with endosonography. *Radiology* 1990; 175: 455-461.
- 7 Palazzo L, Roseau G, Gayet B, Vilgrain V, Belghiti J, Fekete F, Paolaggi JA. Endoscopic ultrasonography in the diagnosis and staging of pancreatic adenocarcinoma: results of a prospective study with comparison to ultrasonography and CT scan. *Endoscopy* 1993; 25: 143-150.
- 8 Freeny PC, Marks WM, Ryan JA, Traverso LW. Pancreatic ductal adenocarcinoma: diagnosis and staging with dynamic CT. *Radiology* 1988; 166: 125-133.
- 9 Moosa AR, Levin B. The diagnosis of "early" pancreatic cancer: The University of Chicago experience. *Cancer* 1981; 47: 1688-1697.
- 10 Kawanishi H, Pollard HM. Endoscopic evaluation of cancer of the pancreas. *Semin Oncol* 1979; 6: 309-317.
- 11 Endo Y, Morii T, Tamura H, Okuda S. Cytodiagnosis of pancreatic malignant tumors by aspiration under direct vision, using a duodenal fibroscope. *Gastroenterology* 1974; 67: 944-951.
- 12 Venu RP, Geenen JE, Kini M, Hogan WJ, Payne M, Johnson GK, Schmalz, MJ. Endoscopic retrograde brush cytology: a new technique. *Gastroenterology* 1990; 99: 1475-1479.
- 13 Nakaizumi A, Tatsuta N, Uehara H, Yamamoto R, Takenaka A, Kishigami Y, Takemura K, Kitamura T, Okada S. Cytologic examination of pure pancreatic juice in the diagnosis of pancreatic carcinoma. *Cancer* 1992; 70: 2610-2614.
- 14 Beazley RM. Needle biopsy diagnosis of pancreatic cancer. *Cancer* 1981; 47: 1685-1687.
- 15 Jennings PE, Donald JJ, Anthony C, Carol A, Rode J, Lees WR. Ultrasound-guided core biopsy. *Lancet* 1989; 1: 1369-1371.

- 16 Warshaw AL, Gu Z-Y, Wittenberg J, Waltman AC. Pre-operative staging and assessment of resectability of pancreatic cancer. *Arch Surg* 1990; 125: 230-233.
- 17 Ferrucci JT Jr, Wittenberg J, Margolies MN, Carey RW. Malignant seeding of the tract after thin-needle aspiration biopsy. *Radiology* 1979; 130: 345-346.
- 18 Rashleigh-Belcher HJC, Russell RCG, Lees WR. Cutaneous seeding of pancreatic carcinoma by fine-needle aspiration biopsy. *Br J Radiol* 1986; 59: 182,183.
- 19 Weiss SM, Skibber JM, Mohiuddin M, Rosato FE. Rapid intraabdominal spread of pancreatic cancer: influence of multiple operative biopsy procedures. *Arch Surg* 1985; 120: 415,416.
- 20 Webb TH, Lillemoie KD, Pitt HA, Jones RJ, Cameron JL. Pancreatic lymphoma: is surgery mandatory for diagnosis or treatment? *Ann Surg* 1989; 209: 25-30.
- 21 Fernández del Castillo C, González-Ojeda A, Reyes E, Quiroz-Ferrai F, Uribe M, Robles-Díaz G. Case report: tuberculosis of the pancreas. *Pancreas* 1990; 5 (6): 693-696.
- 22 DiMagno EP, Buxton JL, Regan PT, Hattery RR, Wilson DA, Suarez JR, Green PS. Ultrasonic endoscope. *Lancet* 1980; 2: 629-631.
- 23 DiMagno EP, Regan PT, Cain JE, James EM, Buxton JL. Human endoscopic ultrasonography. *Gastroenterology* 1982; 83: 824-829.
- 24 Yasuda K, Mukai H, Fujimoto S, Nakajima M, Kawai K. The diagnosis of pancreatic cancer by endoscopic ultrasonography. *Gastrointest Endosc* 1988; 34: 1-8.
- 25 Yasuda K, Mukai H, Nakajima M, Kawai K. Staging of pancreatic carcinoma by endoscopic ultrasound. *Endoscopy* 1993; 25: 151-155.
- 26 Steiner E, Stark DD, Hahn PF, Saini S., Simeone JF, Mueller PR, Wittenburg J, Ferrucci JT. Imaging of pancreatic neoplasms: comparison of MR and CT. *AJR* 1989; 152: 487-491.
- 27 Yamamoto K, Shibata T, Saji H, Kubo S, Aoki E, Fujita T, Yonekura Y, Konishi J, Yokogama A. Human pancreas scintigraphy using iodine-123-labeled HIPDM and SPECT. *J Nucl Med* 1990; 31: 1015-1019.
- 28 Fitzgerald PJ, Fortner JG, Watson RC, Schwartz MK, Sherlock P, Benua RS, Cubilla AL, Schottenfeld D, Miller D, Winawer SJ, Lightdale CJ, Leidner SD, Nisselbaum JS, Menendez-Botet CJ, Poleski MH. The value of diagnostic aids in detecting pancreatic cancer. *Cancer* 1978; 41: 868-879.
- 29 Baum BP. Review: Immunoscintigraphy as a diagnostic tool in pancreatic cancer. *Hepatogastroenterology* 1989; 36: 459-461.
- 30 Mukai H, Mizuno S, Hayakumo T, Yasuda K, Nakajima U. Clinical evaluation of an ultrasonic probe in the diagnosis of biliary and pancreatic tumors. *Gastrointest Endosc* 1991; 37: 275 (abstract).
- 31 Shimi S, Banting S, Cuschieri A. Laparoscopy in the management of pancreatic cancer: endoscopic cholecystojejunostomy for advanced disease. *Br J Surg* 1992; 79: 317-319.
- 32 Warshaw AL, Tepper JE, Shipley WU. Laparoscopy in the staging and planning of therapy for pancreatic cancer. *Am J Surg* 1986; 151: 76-80.

Methods of Tissue Sampling for Staging

Tsutomu Tomioka and Takashi Kanematsu

Second Department of Surgery, Nagasaki University
School of Medicine, Nagasaki City, Japan

Introduction. The diagnosis and staging of pancreatic cancer require careful examination and sampling of tissue for staging. Although several methods can be used for tissue sampling in the world, it is advisable to use a standard, internationally accepted method that should be simple, but adequate to obtain the most possible information for assessment of curative value and prognosis, and for statistical evaluation. We introduce the gross and lymph nodes sampling method for staging, according to the general rules adopted by the Committee of the Pancreas Society of Japan (1).

Tissue Examination for the Staging. Adequate examination of the pancreas requires knowledge of the anatomical relationship between the common bile duct, pancreatic duct, and papilla of Vater. Because of the higher pancreatic cancer incidence in the pancreas head, most surgical specimens include part of the common ducts and papilla of Vater. However, this anatomical relationship is sometimes complicated and makes it difficult to establish a procedure for tissue examination that is both universal and comprehensive (2).

The requirements for adequate examination include:

1. The whole pancreas (or resected specimen) should be available for gross examination;
2. Tumor cross-sections should be obtained for histopathological evaluation;
3. Regional lymph nodes should be available for study; every pancreatic specimen should be examined grossly in the following order:
 - a. Determine the metastases or invasion of the surrounding tissue;
 - b. Describe the surface appearance of the tumor;
 - c. Measure the external size of the specimen;
 - d. If lymph nodes are attached to the specimen, identify them individually and mark them according to the anatomic-topographic classification. *In situ* specimen autopsy) or pancreaticoduodenectomized specimen should be sectioned as follows:
 - i. Open the stomach along the greater curvature;
 - ii. Open the duodenum at the opposite side of the papilla of Vater. Examine the mucosa of the duodenum and the papilla of Vater;
 - iii. If necessary, open the duodenum of the dorsal side of the pancreas and examine the intrapancreatic bile duct by a tube sonde;
 - iv. Pin the margins of the opened stomach, duodenum, and gallbladder with the mucosal surface up, as well as the pancreas, on a cork board with stainless-steel needles;
 - v. Slice the pancreas from the papilla of Vater to the specimen serially at 3-5 mm intervals vertically. Cut line number 0 is on the papilla of Vater. In pancreaticoduodenectomized specimen, the cut line should be parallel to Kerckring folds. Marginal resection of the duodenum can be made to examine

Fig. 1. Pancreatic tissue preparation for routine and investigative purposes.

Fig. 2. Lymph nodes of the pancreas. ACM: *A. colica media*; AJ: *A. jejunalis*; AMS: *A. mesenterica superior*, APDI: *A. pancreaticoduodenalis inferior*.

tumor invasion. For body and tail resection, the specimen should be cut at right angles longitudinal to the pancreas; for total pancreatectomy or autopsy, both of the above procedures should be used;

- vi. Examine and describe the appearance of the cut surface of the tumor according to established criteria;
- vii. Immerse the tissue-fixation board in a tank containing buffered 10% formalin or Bouin's solution for 24 h. A longer fixation time should be avoided.

To prevent postmortem autolysis, both autopsy and fixation of tissues should be done as soon as possible if specimens for

cytology or biochemical and electron microscopic examinations are not considered. The injection of formalin solution from the papilla of Vater into the pancreatic duct provides excellent preservation of the pancreatic duct system. It can prevent damage to the epithelium and also prevent tumor cell exfoliation. It is especially useful in cases that require a meticulous histological examination. However, care should be taken not to inject the fixatives with force and high pressure, which may damage the ductal walls and wash away tumor cells.

These procedures are also applicable to surgical specimens that are prone to autolysis. Because of the presence of tumors and possible preneoplastic lesions in surgical specimens and because

Fig. 3. Para-aortic lymph nodes.

difficulties arise in differentiating nuclear atypism in postsurgical autolytic changes from that in cancer, surgical tissues must be properly handled and fixed as described above.

In addition to routine histological evaluation of pancreatic cancer, many new technologies are now available for detailed investigation of morphology, phenotypes and genetic alterations of pancreatic cancer. Figure 1 summarizes the possibilities for tissue reparation for investigative purposes.

Sampling of Lymph Nodes. Lymph node sampling is very important to determine the stage of the cases. Figure 2 shows the distribution and border of the regional lymph nodes of the pancreas (1). Figure 3 also shows the border of each lymph node surrounding the aorta. We presented the methods of tissue sampling for staging according to the Japanese general rules for the study of pancreatic cancer.

References

- 1 *General Rules for the Study of Pancreatic Cancer*, 4th ed. Japan Pancreas Society, Kanehara Co., P25-35, 1993.
- 2 *Atlas of the Pancreas Cancer. Sampling Method for Pancreatic Tissue Examination*. Springer-Verlag, Tokyo, 1994.

The Method of Preoperative Clinical Staging Japanese Experience

Joe Ariyama

Department of Gastroenterology, Juntendo University, Tokyo, Japan

Introduction. Imaging procedures must be able not only to depict pancreatic ductal adenocarcinoma, but also to allow evaluation of parameters that may influence prognosis and modify treatment. The staging system for pancreatic carcinoma is of proven value, and the Japanese classification system is repro-

duced in Table 1. Recent advance in the imaging diagnosis of pancreatic carcinoma have had impact on the survival rate in Japan. The purpose of this article is to show how the imaging procedures can be used to evaluate preoperative staging of pancreatic carcinoma.

Subjects and Methods. During a period of 20 yr, 285 pancreatic ductal adenocarcinomas were studied. All patients had histological confirmation either by operation, biopsy, or autopsy. The male-to-female ratio was 179:106, with an average age of 62 yr.

Ultrasound (US) was used as a screening procedure. When US demonstrated a large tumor, computed tomography (CT) was performed for staging. If US was negative or equivocal and there was still clinical suspicion of pancreatic carcinoma, endoscopic retrograde cholangiopancreatography (ERCP) was indicated. If ERCP revealed abnormality, then endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), angiography, peroral pancreatoscopy, and/or peroral pancreatic ductal biopsy was performed.

US was performed using Toshiba SSA-270A. Toshiba X-peed was used for CT. CT scan was obtained using 5-mm collimation at 5-mm intervals immediately after a bolus injection of 150 mL of nonionic contrast material (ioversol 320) at 3.0 mL/s. MR images were obtained with 1.5-T unit (Toshiba MRT-2000RX). For pancreatic imaging axial spin-echo T_1 -weighted imaging (TR/TE = 500/20ms) and T_2 -weighted imaging (TR/TE = 2000/80ms) were used. EUS was performed with Olympus GF-UM20 or Toshiba EPL-703. A 1-mm "skinny" pancreatoscope with 4000 fiberoptic bundles (Fujinon PO-10M) was introduced into the main pancreatic duct without performing endoscopic sphincterotomy.

Results. Primary Mass. The large unresectable pancreatic carcinoma was demonstrated by US and CT without difficulty. Tumor appeared as a hypoechoic or hypoattenuating compared with the surrounding pancreatic parenchyma. Pancreatic carcinoma resulted in several secondary imaging findings, including atrophy of the proximal gland, or dilatation of the pancreatic and/or bile ducts. In seven patients with a tumor smaller than 1 cm,

Table 1
Surgical Stage of Pancreatic Cancer^a

	P ₀ , H ₀ , M ₀				P ₁ , H ₁ or M ₁
	N ₀	N ₁	N ₂	N ₃	
T _{1a} Tumor <2.0 cm S ₀ + RP ₀ + PV ₀ + A ₀ + DU ₀ + CH _{0,1}	I	II	III		IVa
T _{1b} Tumor >2.0 cm S ₀ + RP ₀ + PV ₀ + A ₀ + DU ₀ + CH _{0,1}	II	II	III		
T ₂ Any tumor size. Tumor invasion to one or more of following: S ₁ , RP ₁ , PV ₁ , A ₁ , DU _{1,2,3} , CH _{2,3}	III	III	IVa		IVb
T ₃ Any tumor size. Tumor invasion to one or more of following: S _{2,3} , RP _{2,3} , PV _{2,3} , A _{2,3}		IVb			

^aJapan Pancreas Society: *General Rules for the Study of Pancreatic Cancer*, 1993.

S, capsular invasion; RP, retroperitoneal invasion; PV, portal vein invasion; DU, duodenal invasion; CH, common bile duct invasion; A, arterial invasion (invasion to common hepatic, superior mesenteric, splenic, celiac artery, and/or aorta); H, hepatic metastasis; P, peritoneal dissemination; M, distant metastasis; 0, no evidence of invasion or metastasis; 1, suspected invasion or metastasis; 2, definite invasion or metastasis; 3, marked invasion or metastasis; N₀, no lymph node involvement; N₁, involvement of regional lymph nodes close to the primary tumor; N₂, involvement of regional lymph nodes distant from the primary tumor; N₃, involvement of juxta-regional lymph nodes.

two tumors were recognized by US and incremental dynamic CT. In three of the remaining five patients, a dilated pancreatic duct system was depicted. ERCP and EUS were found to be highly accurate in the diagnosis of small pancreatic carcinoma. ERCP showed obstruction, stenosis, or irregular cystic dilatation of the pancreatic duct system even in a small tumor. EUS was successful in delineating tumors as small as 1 cm and was accurate in determining tumor size.

Liver Metastases. Liver metastases were appreciated by US, CT, and MRI. US showed metastases as hypoechoic or hyperechoic masses. "Target sign" and "cluster sign" were frequently identified. On CT, metastases appeared as hypoattenuating nodular masses. On MRI, metastases appeared as masses of lower signal intensity on T₁-weighted images and of higher signal intensity on T₂-weighted images. MRI was equal in accuracy to CT for detecting metastases. It was difficult to detect small metastases on the liver surface by imaging procedures.

Lymphadenopathy. US and CT demonstrated enlargement of lymph nodes larger than 1 cm in the porta hepatis and peripancreatic region. Enlargement of lymph nodes appeared as hypoechoic or hypoattenuating homogenous soft-tissue masses. EUS was shown to be superior to US and CT in demonstrating enlargement of lymph nodes in the peripancreatic region. Enlargement of lymph nodes might be the result of reactive hyperplasia, and unenlarged nodes might harbor an occult tumor not palpable to the operating surgeon.

Vascular Involvement. Extraglandular extension of pancreatic carcinoma with invasion of adjacent major arterial and venous structures was depicted by US and CT, and there was little benefit in using angiography to determine major vessel encasement. CT had an advantage of showing perivascular adventitial changes. Involvement of adventitia appeared as thickening of the caliber of the vessel or as a soft-tissue mantle obscuring the normal sharp margin of the vessel with the perivascular fat. Color doppler ultrasound was sensitive in demonstrating minor arterial involvement, including the gastroduodenal artery and proximal superior mesenteric artery in which the finding was not shown by CT. Intrapaneatic vessel encasement was demonstrated only by superselective angiogram. Involvement of the portal vein was identified as a result of invasion by a contiguous pancreatic carcinoma by CT. Another manifestation of portal vein invasion was the presence of collateral vessels. EUS was useful in the diagnosis of tumor invasion to adventitia of the portal vein in which color doppler ultrasound, CT, and arterial portogram revealed normal patterns. On EUS, involvement of adventitia of the portal vein appeared as a lack of fat plane between tumor and the vessel.

Prognosis of Pancreatic Carcinoma. In followup of 66 patients with pancreatic ductal adenocarcinoma in whom the tumor was resected, survival depended on tumor size. The 5-yr survival rate of patients with tumor smaller than 1 cm was 100%. Histologically, these tumors were limited to the duct epithelium.

Resected specimens were sectioned every 5 mm and histologically examined. There was no evidence of capsular invasion, lymph node metastasis, lymphatic invasion, or perineural invasion. Statistically, there was no difference in survival rate after resection in patients with tumor larger than 1.1 cm with parenchymal invasion. In 33% of patients with tumor between 1.1 and 2 cm and in 73% of patients with tumor between 2.1 and 3 cm, histology of resected specimen verified capsular invasion, lymph node metastasis, and perineural invasion. Pancreatic carcinomas smaller than 1 cm without parenchymal invasion were considered as early cancer.

References

- 1 Ariyama J, Suyama M, Ogawa K, et al. The detection and prognosis of small pancreatic carcinoma. *Int J Panc* 1990; 7: 37-47.
- 2 Tsuchiya R, Tsunoda T. Tumor size as a predictive factor. *Int J Pancreatol* 1990; 7: 117-123.
- 3 Freeny PC, Marks WM, Ryan JA, et al. Pancreatic ductal adenocarcinoma: diagnosis and staging with dynamic CT. *Radiology* 1988; 166: 125-133.
- 4 Megibow AJ. Pancreatic adenocarcinoma: designing the examination to evaluate the clinical questions. *Radiology* 1992; 183: 297-303.

Relationship Between Survival and Cancer Extension

Masahiro Yamamoto, Osamu Ohashi, Hidehumi Ishida, Takashi Kamigaki, Hirohiko Onoyama, and Yoichi Saitoh

The First Department of Surgery, Kobe University School of Medicine, Kobe City, Japan

The annual number of deaths from pancreatic cancer in Japan exceeds 13,000, and pancreatic cancer is one of the cancers that is showing an annual increase in mortality. The mortality rate showed an increase of 2.4- to 2.7-fold during the past 20-yr period. The recent development of medical examinations for pancreatic diseases in Japan has been remarkable. With regard to pancreatic cancer, however, since most cases on detection are advanced, this cancer carries the impression of very poor prognosis in comparison with other gastrointestinal cancers.

For the purpose of improving such therapeutic results for pancreatic cancer and as a means of assessing data on the basis of common criteria, the *General Rules for the Study of Pancreatic Cancer* were established by the Japanese Pancreatic Society in 1980 (1,2). On the basis of these rules, a nationwide pancreatic cancer registration has been undertaken by the Pancreatic Cancer Registration Committee of the society every year since 1981. It has been performed for 12 yr, and by obtaining cooperation from departments of internal medicine and surgery of 345 cardinal institutions throughout Japan, a total of 13,498 cases of pancreatic cancer have been collected.

In this study, the results of a nationwide survey and the total-ity of data, which have been performed by the Pancreatic Cancer

Registration Committee of the Japanese Pancreatic Society, and also the relationship between survival and cancer extension will be described.

The male-to-female ratio of the registered patients was 1.6 to 1, and the number of patients in their 60s was the largest.

Among various test methods, ultrasonography (US) and computed tomography (CT) have become increasingly important as the methods for first detecting a lesion of the pancreas. The frequency of US, particularly, has recently reached 49.7%, although it was 24.5% at the beginning of the survey.

Although small pancreatic cancers, at most 2 cm in tumor diameter, are not necessarily early pancreatic cancers, the rates of resection and prognosis are better than those of pancreatic cancers of 2 cm or more. Owing to the recent development of diagnostic techniques, such as diagnostic imaging, there is a slight tendency for detection of small pancreatic cancers to increase. The incidence of small pancreatic cancers among the registered patients in fiscal 1981, 2.9%, was increased to 5.7% in fiscal 1992.

According to the treatment method, the total number of 13,498 registered patients consisted of 4597 (34.1%) patients who underwent resection, 4699 (34.8%) who underwent palliative operation, 921 (6.8%) who underwent exploratory laparotomy, 2940 (21.8%) without operation, and 341 (2.5%) without operation who were autopsied.

In connection with this, 24.5% of all patients underwent resection in 1981 when the nationwide survey was initiated, but this number had increased to include 37.6% by 1992. Such improvement in the rate of resection may be attributed mainly to the increase in detection of resectable pancreatic cancer and the active introduction of extended surgery.

Among the patients with resection, 706 (15.4%), 2810 (61.1%), and 976 (21.2%) underwent total pancreatectomy (TP), pancreatoduodenectomy (PD), and caudal resection of the pancreas (DP), respectively. The annual changes in pancreatectomy procedures showed that the proportions of patients who underwent TP, PD, and DP (28.8, 53.8, and 15.4%, respectively) in 1981 had changed to 5.5, 66.4, and 26.6, respectively, by 1992, as a result of the gradual decrease in TP.

The lymph node stations 1-18 according to the Japanese classification have been divided into three groups, namely Group 1 of nodes closest to the tumor and Groups 2 and 3 of more distant groups. With regard to lymph node dissection in the resected cases, the Group 1 lymph nodes were not dissected or dissected insufficiently in 14.5% (D_0), the Group 1 lymph nodes alone were dissected in 31.9% (D_1), and the Group 1 and 2 lymph nodes were dissected in 46.4% (D_2).

The organs resected with the lesion were the colon in 7.8%, a portion of the liver in 1.9%, the spleen in 25.9%, the stomach (total gastrectomy) in 5.5%, portal vein in 22.0%, and artery in 4.9%. Among the recent tendencies in organ resection with pancreatic lesions, the frequency of combined resection of the portal vein has been increasing little by little, and this combined resection seems to contribute to improvement in the rate of resection.

Cumulative survival rate was calculated by the actuarial method for 3692 patients undergoing resection, 3862 patients undergoing palliative operation, 736 patients undergoing exploratory laparotomy, and 2444 patients without resection, for whom followup data were available among the registered patients.

Table 1
Surgical Stage Classification According to the Japan Pancreas Society (1993)

	P_0, H_0, M_0				$P_{1,2,3}, H_{1,2,3}, \text{ or } M_1$
	N_0	N_1	N_2	N_3	
T_1a Tumor size of <2 cm and $S_0 + RP_0 + PV_0 + A_0 + DU_0 + CH_{0,1}$	I	II	III		IVa
T_1b Tumor size of >2 cm and $S_0 + RP_0 + PV_0 + A_0 + DU_0 + CH_{0,1}$	II	II	III		
T_2 Regardless of tumor size and one more positive of $S_1, RP_1, PV_1, A_1, DU_{1,2,3},$ and $CH_{2,3}$	III	III	IVa		IVb
T_3 Regardless of tumor size and one more positive of $S_{2,3}, RP_{2,3}, PV_{2,3},$ and $A_{2,3}$		IVa			

S_0 , no capsular invasion; S_1 , suspected invasion to the capsule; S_2 , definite invasion to the capsule; S_3 , Invasion to the adjacent viscera; RP, PV, A, DU, and CH factors are subdivided and defined in the same manner; P_0 , no evidence of peritoneal dissemination; P_1 , dissemination to the peritoneum adjacent to the pancreas; P_2 , sporadic dissemination to the peritoneum distant from the pancreas; P_3 , multiple dissemination to the peritoneum distant from the pancreas; H_0 , no evidence of hepatic metastasis; H_1 , metastasis to a single lobe of the liver; H_2 , sporadic metastases to both lobes of the liver; H_3 , multiple metastases to both lobes of the liver; N_0 , no evidence of lymph node involvement; N_1 , evidence of lymph node involvement within Group 1; N_2 , evidence of lymph node involvement within Group 2; N_3 , evidence of lymph node involvement within Group 3.

According to the therapeutic method, cumulative 1-, 3-, and 5-yr survival rates were 52.7, 23.2, and 17.5% of the patients with resection, respectively. On the other hand, 1-yr survival rates in the patients undergoing palliative operation, exploratory laparotomy, and without operation were 14.0, 12.1, and 10.1%, respectively.

As in other gastrointestinal cancers, only the patients undergoing resection have the possibility of prolonged survival. In connection with this, the data in 1985, when the 5-yr survival rate was calculated for the first time showed a 5-yr survival rate of 10.1% in the patients with resection. The recent improvement in results of surgical treatment can be estimated from the improvement in the prognosis.

According to the histological classification of patients undergoing resection, the prognosis of tubular adenocarcinoma corresponding to ductal adenocarcinoma generally used, which constitutes the majority of pancreatic cancer cases, is the worst. Papillary adenocarcinoma, cystadenocarcinoma, and islet cell carcinoma showed relatively favorable prognoses, despite being in the category of pancreatic cancer. Some cases of so-called mucin-producing pancreatic cancer, which is noted as a pancreatic cancer with a good prognosis, may be included in papillary adenocarcinoma in the nationwide totality because its pathologic classification has not been established.

The *General Rules for the Study of Pancreatic Cancer* contain rules for the description of operative findings. The stage of pancreatic cancer is expressed by peripancreatic invasion (T), hepatic metastasis (H), peritoneal dissemination (P0), lymph

node metastasis (N), and metastasis to other distant extra-peritoneal organs (M). T is also defined with infiltration to the anterior capsule of the pancreas (S), infiltration to tissue adjacent to the posterior surface of the pancreas (RP), infiltration to the intrapancreatic bile duct (CH), infiltration to the duodenal wall (DV), infiltration to the portal vein system (PV), and infiltration to the arterial system (A).

The results of calculation of the cumulative survival rate according to each factor in the patients who underwent resection, except for patients with cystadenocarcinoma and islet cell carcinoma, suggest that all of these are important prognostic factors.

In the relationships between tumor size and each of these factors, when the tumor size increased, the incidence and degree of infiltration to the pancreatic capsule and the peripancreatic tissue increased, and the incidence and extent of lymph node metastasis also increased.

On the basis of the results of such assessments, the *General Rules for the Study of Pancreatic Cancer* were recently revised in 1993, and the new stage classification as shown in Table 1 was presented; criteria resembling the TNM classification were adopted for T categories, and the Japanese N classification, which has conventionally been used (classification by regional lymph node group with slight modification) was adopted for N categories.

Then, the cumulative survival rate was calculated according to the new stage classification, with regard to the prognosis of resected cases (except for cystadenocarcinoma and islet cell carcinoma).

The 1-, 3-, and 5-yr survival rates were 92.6, 71.1, and 59.7% for patients with T_{1a} , respectively, and the corresponding rates in those with T_{1b} were 75.2, 53.4, and 46.2%. Thus, the prognosis in patients without invasion to the peripancreatic tissue was good regardless of tumor size. However, the 1-, 3-, and 5-yr survival rates in patients with T_2 were 48.1, 16.4, and 11.3%, respectively, and the corresponding rates in patients with T_3 were 36.0, 12.9, and 11.2%, showing that the prognosis in patients with invasion to the surrounding organs or large blood vessels was very poor. The lymph node metastasis and distant metastasis were also definitive influences on the prognosis following resection.

Accordingly, in the patients with stage I, the survival rates were 97.1% at 1 yr, 78.4% at 3 yr, and 68.3% at 5 yr, whereas they were 78.6% at 1 yr, 55.8% at 3 yr, and 49.7% at 5 yr in those with stage II. These rates were markedly better than the corresponding rates of 58.7, 21.6, and 13.6% in those with stage III, 45.0, 14.3, and 11.3% in those with stage IVa, and 40.2, 6.6, and 2.3% in those with stage IVb, showing that the prognosis in patients with advanced stage was very poor (Fig. 1).

In the nationwide totality as well, registration will follow the new rules as of 1993, prognostic factors will be elucidated, and various therapeutic methods will be evaluated for more detailed assessment. This study has been supported by the Japanese Pancreatic Society and pushed forward by the cooperation of a large number of earnest surgeons in Japan.

References

- 1 Pancreatic Cancer Registration Committee of the Japan Pancreas Society: Report of nationwide registration of pancreatic cancer patients in 1981–1992. 1982–1993.

Fig. 1. Postoperative cumulative survival rates of patients who received resection according to state grouping proposed by the Japan Pancreas Society. (○), stage I ($n = 78$), (●), stage II ($n = 119$), (□), stage III ($n = 1002$), (■), stage IVa ($n = 347$), (△), stage IVb ($n = 1142$).

- 2 Japan Pancreas Society. *General Rules for the Study of Pancreatic Cancer*, the 4th ed., Kanehara Shuppan Co., Ltd., Tokyo, 1993.