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Editorial Update

Treatment of Pancreatic Cancer: Challenge of the Facts

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Abstract. Adenocarcinoma of the pancreas is associated with the worst survivalof any form of gastrointestinal malignancy. In spite of the progress in surgical treatment, resulting in increasing resection rates and a decrease in treatment-related morbidity and mortality, the true figures of cure are even today below 3%. The dissemination of pancreatic cancer behind the local tissue compartments restricts the short-term (< 3 years) and long-term outcome for patients who have undergone resection. By histological evaluation, less than 15% of the patients undergoing R_0 resection have a pN_0 status, more than 60% suffer from lymph angiosis carcinomatosa, and more than 50% suffer extrapancreatic nerve plexus infiltration. Hematoxylin and eosin–negative lymph nodes were found to be cancer positive when reverse transcriptase polymerase chain reaction (RT- PCR) or immunostaining was applied to the HE-negative lymph nodes. Cancer of the uncinate process has a very poor prognosis because there are no early symptoms; vessel wall involvement occurs early and frequently; a high association of liver metastasis exists as well. Surgery offers a low success rate, but it provides the only chance of cure. Ductal pancreatic cancer is diagnosed in more than 95% of the cases in an advanced stage; potentially curative resection can be performed only in about 10%–15% of these patients. Major contributions of surgery to improved treatment results are the reduction of surgical morbidity—e.g., early postoperative local and systemic complications—and a decrease of hospital mortality below 3%–5%. In most recently published prospective trials, R_0 resection has been reported to result in an increase in short-term survival beyond that recorded for patients with residual tumor. However, R_0 resection fails to improve long-term survival. In many published R_0 series, standard tissue resection of pancreatic head cancer with the Kausch-Whipple procedure failed to include remote cancer cell–positive tissues in the operative specimen; e.g., N_2-lymph nodes, nerve plexus, and perivascular extrapancreatic and retropancreatic tissues were not excised. Cancer recurrence after so-called R_0 resection with curative intent is frequently the consequence of cancer left behind. Thus, long-term survival (> 5 years) is observed in a very small group of patients, contradicting the published 5-year actuarial survival rates of 20%–45% for resected patients. The assessment of clinical benefit from surgical or medical cancer treatment should therefore be based on several end points, not only on actuarial survival. Publication of actuarial survival figures must include the number of observed (actual) survivals, the definition of the subset of patients followed after resection, and the total number of patients in the study group; anything less is misleading. In reporting pancreatic cancer treatment trial results after oncological resections, more convincing primary end points to evaluate treatment efficacy are median survival (in months), actual survival at 1–5 years, and progression-free survival (in months). In series with multimodality treatment, clinical benefit response as well as quality of life measurements using the EORTC Quality of Life index C30 (QLQ-C30) are of importance in evaluating survival data. Adjuvant treatment improves survival after oncological resection; however, the short-term and long-term benefit after adjuvant chemotherapy in R_0 as well as in R_1-$_2$ resected patients has not yet been underscored by data from controlled clinical trials. The survival benefit (median survival time) of adjuvant chemotherapy or radiochemotherapy has been demonstrated to be 6–10 months. Therefore, after oncological resection of pancreatic cancer each patient should be offered adjuvant treatment. A neoadjuvant treatment protocol for pancreatic cancer, however, has not been established.

Of all forms of gastrointestinal malignancy, adenocarcinoma of the pancreas is associated with the worst survival. Most patients die within a year after establishment of the diagnosis. Epidemiological studies, underlined by animal experiments, reveal that cigarette smoking and alcohol consumption contribute to the increase of the incidence of pancreatic cancer in industrialized countries; hereditary cancer syndromes are implicated in less than 8% of malignant lesions of the pancreas [1].

In spite of the progress in surgical treatment, resulting in increasing resection rates and a decrease in treatment-related morbidity and mortality, the true figures of cure are even today below 3% [2]. In this article present knowledge about dissemination roots of pancreatic cancer is re-evaluated in the light of results of current treatment protocols including surgery, adjuvant chemotherapy and radiotherapy, and neoadjuvant treatment modalities.

Dissemination Pattern of Pancreatic Cancer: Limitation of Surgical Treatment

The international classification systems of pancreatic cancer [International Union Against Cancer (UICC), American Joint Cancer Committee (AJCC), Japanese Pancreatic Society (JPS)] rely on tumor size, lymph node (LN) involvement, stage of infiltration into

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Table 1. Ductal cancer of the pancreas: factors of tumor biology favorably influencing survival after resection.

Size of the tumor (cm)	< 2–3	Tsuchiya et al., 1985 [3]
LN metastasis	Negative	Cameron et al., 1991 [4]
Nerve infiltration	Negative	Nagakawa et al., 1991 [5]
Infiltration of vessel wall	Negative	Ishikawa, 1996 [6]
Cell differentiation	G1 (well differentiated)	Geer and Brennan, 1993 [7]
DNA content	Diploid	Yeo et al., 1997 [8]
Gene aberration	Wild-type of p53, p16, DPC4, K-ras	

LN: lymph node.

surrounding tissues, and presence of metastasis. The cardinal rule in improving the prognosis proved to be complete tumor removal in patients undergoing oncological resection; in recent published series, the absence of residual tumor is associated with an increased chance of survival. The prognosis of patients undergoing a resection of pancreatic cancer is determined by the state of lymph node (LN) metastasis, tumor size, invasion of blood vessel walls, and number of units of blood transfused during surgery and in the early postoperative course. Furthermore, factors of tumor biology have also been found to have a prognostic effect; these include DNA ploidy status, cell differentiation, and the absence of aberrations of oncogenes and suppressor genes (Table 1). A patient without LN metastases and a tumor size < 2 cm, without vessel wall involvement or distant metastases, has a significant survival benefit after a R_0 resection [9].

Unfortunately preoperative staging is unreliable regarding the presence and extent of LN involvement. The N-factor can only be clarified after surgical resection by histological examination. The reliability of LN negativity is related to the size of the operative specimen sent for pathological examination, which is determined by the extent of the lymphadenectomy performed. Patients undergoing a standard Kausch-Whipple resection for pancreatic head cancer without clearance of the more distant LN stations are at risk of being classified as false-negative for N-status; metastasis to LN in the hilum of the liver, the inter-aortocaval spaces, and the left side of the superior mesenteric artery is frequent [10]. Among patients with pancreatic head cancer, histological examination techniques have demonstrated that about 30% of the LN in the inter-aortocaval space are cancer infiltrated [11]. The posterior hepatic LN, the LN of the hepatoduodenal ligament, and the posterior pancreatic head LN drain primarily to the LN in the inter-aortocaval space below the left renal vein. These roots are the major origin of the thoracic duct [12]. In a collective series of patients with a small tumor (< 2 cm), LN metastases were discovered in one third [13]. Careful histopathomorphological evaluations of cancer disseminations have demonstrated that in cancer stage I and II, lymph vessels surrounding the head of the pancreas are cancer cell infiltrated (Table 2).

Using molecular biological methods like reverse transcriptase polymerase chain reaction (RT-PCR) or immunostaining, a new dimension of micrometastasis has been objectified. With the higher sensitivity of these molecular-biological methods, up to 60% of LN previously seen as microscopically free of cancer cells showed micrometastasis by RT-PCR (Table 3). In bone marrow specimens micrometastasis was found in 36% to 65% of the patients investigated (Table 4). Among patients in cancer stage I and II (UICC) undergoing surgery, 46% had positive immunostaining for cancer cells in the bone marrow. Using RT-PCR techniques 13 of 17 investigated patients showed micrometastases in the liver; some but not all of these patients later developed metastatic liver disease macroscopically [24].

Present knowledge about cancer cell dissemination early in the course of pancreatic disease, including UICC stages I and II, explains the observed frequency of recurrence in more than 95% of the patients undergoing surgical resection.

Nerve plexus invasion outside of the pancreas has been observed in 43%–72% of patients, occurring most often in the right plexus mesentericus II and the nerve plexus around the superior mesenteric artery [29] (Table 5).

Cancer of the Uncinate Process Bears the Worst Prognosis

The uncinate process arises from the embryological ventral bud of the pancreas. The development of a malignancy within this area of the pancreas is frequent. Because of the lack of early symptoms like jaundice, patients with cancer of the uncinate process have a poor prognosis. Vessel wall involvement occurs early in the course of the disease, and is present in almost all patients with advanced uncinate cancer due to the proximity of the malignant lesion to the mesenteric vessels. At the time of diagnosis, liver metastases are present macroscopically in more than one third of these patients [30]. Lymph node involvement has been observed in 20% in the inter-aortocaval spaces and in 65% on both sides of the superior mesenteric artery and the mesentery of the small bowel. Because of the dissemination pattern of cancer of the uncinate process, after oncologic resection patients have shorter survival chances than patients with pancreatic head cancer arising from the dorsal bud of the pancreas [9].

Pancreatic Cancer Treatment: Achievements of Surgery

Although surgery offers a low cure rate, it is also the only chance for cure. Ductal pancreatic cancer in an advanced stage is diagnosed in ≥ 95% of patients; potentially curative resection can be performed only in about 10%–15% of them. Contraindications for resective surgery are the presence of liver metastases or distant metastases, peritoneal seedings, circular tumor infiltration into mesenteric vessel walls, and extension of the tumor into the mesentery of the jejunum or the mesocolon transversum. Lymph node enlargement near and remote from the primary tumor is not considered a criterion for non-resective management.

Major contributions to improved surgical treatment results are the reduction of hospital mortality and treatment in high-volume centers (Table 6). After the first article reporting a large series of Whipple resections without any deaths [39], the hospital death rate in experienced centers is now < 3%–5%. Postoperative morbidity has also decreased dramatically as a result of standardization of surgical techniques with well-defined steps of tissue clearance. With both standard and extended oncological resections, the early postoperative complication rate in experienced institutions is < 30%–40%. Standardized surgical techniques for suturing anastomoses have led to a decrease in severe local complications such as pancreatic fistula, intraabdominal bleeding, and leakage at the site of intestinal anastomoses, minimizing local septic complications. After a Kausch-Whipple resection, 60%–75% of the patients are

Table 2. Dissemination pattern of pancreatic cancer.

	Methods	Patients (*n*) positive/total	Frequency (%)	Cancer stage	Study
LN metastases (mm)					
T—20	HE/histology	10/16	64		Hermanek, 1991 [14]
T 21–40	HE/histology	99/126	78		Hermanek, 1991 [14]
T 41–60	HE/histology	43/53	81		Hermanek, 1991 [14]
Lymphangiosis carcinomatosa	HE/histology	44/65	67	I-II[a]	Takahashi et al. 1992 [15]
Intrapancreatic nerve infiltration	HE/histology	116/129	90	I-IV[b]	Nakao et al., 1996 [16]
Extrapancreatic nerve infiltration	Histology	27/39	69	II-IV[b]	Kayahara et al., 1996 [17]
Infiltration of retroperitoneal tissue	HE/histology	38/44	88	II + IV[b]	Kayahara et al., 1996 [17]
Free, viable carcinoma cells in peritoneal fluids	Cytology	12/36	33	II + III[a]	Heeckt et al., 1992 [18]

[a]International Union Against Cancer (UICC).
[b]Japan Pancreatic Society (JPS).
HE: hematoxylin and eosin staining.

Table 3. Micrometastasis in HE-negative lymph nodes.

Study	Patients (*n*) positive/total	Cancer stage	Frequency MM positive (%)	Methods	Location of LN
Ando et al., 1997 [19]	8/15		53	RT-PCR/K-ras	Paraaortic
Hosch et al., 1997 [20]	13/18	II ($9pN_0$)	72	Immunohistology	N_1
Demuere et al., 1998 [21]	16/22	I[a]	73	RT-PCR/K-ras	N_1/N_2
Mühling et al., 2002 [22]	6/9	I-III[a]	66	RT-PCR/K-ras	N_2

[a]UICC.
MM: micrometastasis; RT-PCR: reverse transcriptase-polymerase chain reaction.

Table 4. Pancreatic cancer micrometastasis.

Study	Patients (*n*) positive/total	Frequency MM positive (%)	Cancer stage	Tissue	Methods
Juhl et al., 1994 [23]	26/34	46	I + II[a]	Bone marrow	Immunohistology
		65	III + IV	Bone marrow	Immunohistology
Inoue et al., 1995 [24]	13/17	76.5	III–V[b]	Liver	RT-PCR, K-ras
Soeth et al., 1996 [25]	4/11	36		Bone marrow	RT-PCR, CK-20
Thorban et al., 1996 [26]	14/24	58.3		Bone marrow	Immunohistology

[a]UICC.
[b]JPS.

Table 5. Nerve plexus invasion outside of the pancreas.

Study	Patients (*n*) positive/total	Frequency (%)	Nerve plexus	Methods	Carcinoma stage
Kayahara et al., 1991 [27]	27/39	69	PlxM II 63%	HE/EvG	t_1-t_3 (JPS)
Nagakawa et al., 1992 [28]	21/29	72	PlxM II 66%	Histology	t_1-t_3 (JPS)
Takahashi et al., 1992 [15]	28/65	43		HE/EvG	
Nakao et al., 1996 [16]	80/116	69		Histology	
Ohigashi et al., 2000 [29]	9/24	37.5	AMS	RT-PCR/K-ras	I–III (JPS)

PlxM II: plexus mesentericus II (right); AMS: plexus around arteria mesenterica superior; EvG: elastica van Giesen.

discharged from the hospital between the 8th and 15th postoperative day [40]. Present knowledge about the survival benefits yielded by a more extended tissue clearance does not support an oncological extended Kausch-Whipple resection in pancreatic head cancer [41] [42]. However, the extent of tissue resection remains to be determined on the basis of knowledge about the degree of dissemination, even in cancer at stages (UICC) I and II. Presumably patients with local lymph node involvement [node stage 13, 17 (JPS)], and with an N0-LN status of the N_2 LN and no vessel and nerve-plexus involvement, may gain a long-term survival benefit from extended oncological resection [43]. More than half of the few patients observed to survive > 5 years after pancreatic cancer resection had an advanced cancer stage with positive lymph nodes, serosal involvement, and vessel wall involvement (Table 7). Extended resection including resection of vessel wall can be performed without increased hospital morbidity and mortality (Table 8). Portal vein and/or superior mesenteric vein resection in patients with limited vessel wall infiltration results in a downstaging of the cancer and therefore a survival benefit; in about 50% of the patients in which the surgeon considered the vessel wall to be infiltrated, there was actually an

Table 6. Pancreatic carcinoma: hospital mortality after pancreaticoduodenectomy—results of low- and high-volume hospitals.

State and country	Year	Hospital mortality (%)[a]	
		High-volume centers	Low-volume centers
Maryland, USA [31]	1995	2.2	19.0
New York, USA [32]	1995	5.5	18.9
Netherlands [33]	1997	1.5	159
UK[b] [34, 35]	1995/1997	5.9	28.0
Maryland[c], USA [36]	1997	1.8	14.2
Finland [37]	1996	4.8	11.0
Nationwide, USA [38]	1999	4.1	16.1

[a]Different criteria are used for high-volume and low-volume hospitals.
[b]Specialized units versus multi-institutional survey.
[c]Recent data compared with previous study.

adherence of the tumor but microscopically no cancer infiltration into the adventitia (Table 8).

R_0 Resection Fails to Improve Long-term Survival

The stage of residual tumor R_0–R_2 is determined by histological examination of tissue of the resection margins of the pancreas, common bile duct,stomach, and duodenum, respectively. In most recent published prospective trials, R_0 resection results in an increase of survival in comparison to patients with a residual tumor; after R_1 or R_2 resection, no long-term survivors are reported. The achievement of R_0 resection is determined by the extent of tissue dissection. Considering present knowledge of dissemination patterns of pancreatic cancer, it is a mistake to identify R_0 resection with absence of residual tumor. Many R_0 series published after standard tissue resection of the pancreatic head cancer by means of a Kausch-Whipple procedure are hampered by a failure to include remote cancer cell–positive tissues in the operative specimen—e.g., N_2 LN, nerve plexus, and perivascular tissues. Cancer recurrence after so-called resection with curative intent is frequently the consequence of cancer cell–positive tissues left behind (Table 9).

More than 95% of the patients undergoing surgical resection are in an advanced stage of cancer. R_0 resection established by histological examination of resection margins is reliable only in cases in which a full tissue specimen is histologically investigated. However, using a standard Kausch-Whipple resection in pancreatic head cancer, the N_2 LN as well the nerve plexus on the right side of the aorta are not part of the operative specimen. Cancer infiltration in N_2 LN is present in 30%–60% of stage II and III cancers. Recurrence of the cancer develops in 40% of the patients within 6 months and in 60%–80% within 12 months of surgical resection. The progression-free period varies between 8 and 12 months (median) [64–67]. In one third of the patients undergoing R_0 resection, liver metastasis is the first sign of recurrence. In these patients liver metastases have been overlooked during surgery.

Regarding long-term survival after R_0 resection, only 3%–16% of the patients from selected series survived 5 years or more (Table 7). Comparing the survival times after standard and extended resection of pancreatic head cancer no significant long-term survival benefit results from extended R_0 resection [41, 42, 68].

Survival Statistics and the Definition of Treatment End Points in Pancreatic Cancer Surgery

Long-term survival $\geq$ 5 years is observed in a very small group of pancreatic cancer patients, contradicting the published 5-year actuarial survival rates of 20%–45% among resected patients. Over the period of 65 years of resective cancer treatment Gudjonson claims that not more than 300–350 individuals with observed and well documented 5-year survival have been reported in the international literature [69]. The Kaplan-Meier calculations of survival result in misleading survival figures if, in the subgroup of patients treated by surgical resection, the hospital deaths and the patients lost to follow-up are excluded. Publication of actuarial survival figures should be considered as unacceptable without information on the total number of patients in the study group, the number of observed (actual) survivors, and definition of the subset of patients followed after resection.

A few end point evaluations have been conducted in pancreatic cancer treatment trials. Evidence from studies shows that surgical resection as well as chemotherapy can prolong survival and improve quality of life in advanced pancreatic cancer. The number of patients who benefit from treatment is, however, still limited. The assessment of clinical benefit from surgical or medical cancer treatment should be based on several end pointsbeyond actuarial survival only. Besides the well-defined actual survival, the *observed median survival* has been employed as a simple, reliable, and well-evaluated criterion. In addition, *progression- free survival* has recently been introduced in surgical series as one of the most appropriate primary end points from which to measure the treatment benefits.

In the palliative setting, as in most cases of pancreatic cancer, treatment-related *survival prolongation* is of greatest importance; single or combined chemotherapy as well as multimodality regimen have shown only modest effectiveness, with objective response rates of most protocols in the range of 10%–20%. Response evaluations rely on the application of sensitive staging methods. Response rates to chemotherapy are not strongly correlated to a survival benefit. Doubts have been raised regarding whether response rate is an independent prognostic factor for survival [70]. *Clinical benefit response* has been introduced as an additional end point to evaluate the efficacy of chemotherapeutic agents; a combination of improvements in pain (reductions in pain intensity and/or analgesic requirements), performance status, and weight gain is used to objectify clinical benefit [71]. Clinical benefit response, however, can underestimate the effects of chemotherapy because it does not include the assessment of other symptoms. Further, it can overestimate the results of chemotherapy, as it does not properly assess the side effects. The assessment of quality of life (QOL) aspects using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Index C30 (QLQ-C30) [72] or a standard functional assessment of hepatobiliary cancer treatment (FACT-Hep) [73] has now been incorporated in cancer trials to accomplish the more traditional assessment. In advanced pancreatic cancer QOL was significantly better in patients receiving chemotherapy than in those receiving best supportive care. The level of QOL after pancreatic cancer resection is strongly determined by the presence (low QOL) or absence (high QOL) of cancer recurrence.

In pancreatic cancer treatment trials reporting results after oncologic resections, the primary end points to evaluate treatment

Table 7. Long-term survival after resection: observed 5-year survivors.

	Year	Survivors resected versus total group	Observed 5-year survivors (%)	Cancer dissemination of survivor	Cancer stage
Tsuchiya et al. [44]	1988	34/?		T_2 43%, T_3 17%, T_4 11%, N + 37%, S +27%	I 14, 3%, II 48%, III 23%, IV 11% (JPS)
Trede et al. [45]	1990	18/130	13.8		
Nagakawa et al. [46]	1991	7/49	14.3		
Takahashi et al. [47]	1995	10/61	16.4		
Klempenauer et al. [48]	1995	38/306	12.4		
Yeo et al. [49]	1995	11/201	5.5	$R_1$8%, T > 3 cm, 15%	
Takahashi et al. [50]	1995	10/149	67	N + 30%, V + 10%	I6, II1, III3 (UICC)
Nitecki et al. [51]	1995	12/174	6.9	N + 15%	I14%, III1% (UICC)
Hanyu et al. [52]	1997	11/295	3.7	Rp + 4, PV + 3, N + 6	I5, II3, III2, IV1 (JPS)

Table 8. Pancreatic head resection: portal (PV) and superior mesenteric vein (SMV) resection.

	Patients (*n*)	Hospital mortality (%)	PV/SMV cancer infiltration		Survival actuarial 2 years (%)	Median months
			Positive (%)	Negative (%)		
1991–2002	406	5.4	57	43	16–39.7	8.75

This table summarizes data from the following published articles: Tashiro et al. [53]; Ishikawa et al. [54]; Allema et al. [55]; Takahashi et al. [56]; Nakao et al. [57]; Roder et al. [58]; Harrison et al. [59]; Evans et al. [60]; Launois et al. [61]; Shibada et al. [62]; Kawada et al. [63].

efficacy are median survival (months), actual survival at 1 to 5 years, and progression-free survival (months). Reporting only actuarial or cumulative survival figures is inadequate. In series with multimodality treatment, clinical benefit response as well as QOL measurements using EORTC, QLQ-C30 are of greatest importance in addition to observed survival data.

Adjuvant Treatment Improves Survival

The limits of surgery are defined by low resectability rates and the biology of the disease, which determines the patients' poor prognosis even after R_0 resection at an average median survival of 11 to 24 months (Table 10). Multimodality treatment concepts have applied radiotherapy and chemotherapy either alone or in combination before, during, or after surgical resection. Two carefully controlled prospective series conducted by the Gastrointestinal Tumor Study Group (GITSG) (1985, 1987) [74, 75] were able to extend survival in patients with ductal pancreatic cancer with postoperative 5-fluorouracil, doxorubicin, and mitomycin C (FAM)-chemotherapy versus surgery alone. Patients receiving adjuvant chemotherapy had a median survival of 20 months versus 11 months among patients who had surgical treatment alone. In the GITSG studies the survival benefit persisted; after 10 years 19% of the patients treated with radiochemotherapy were still living, whereas no patients from the surgery-alone group survived. In a European adjuvant treatment trial (EORTC-GITCCG) patients with curatively resected pancreatic head cancer were randomized into two groups, one receiving 40 Gy + 5-FU for radiosensitization and the other receiving surgery alone. The median survival in the two groups was 23.5 months for the radiosentized patients versus 19.1 months for those who received surgery alone. Although the difference was not significant, the adjuvant treatment seemed to be effective in pancreatic head cancer patients (Table 10).

In a prospective case control study, Yeo et al. [76] confirmed the benefits of postoperative adjuvant radiochemotherapy; the Baltimore trial resulted in an increase in median survival to 19.5 months versus 13.5 months in the surgery-alone group. The European Study Group of Pancreatic Cancer recently finished the largest randomized controlled clinical trial evaluating the benefits of adjuvant chemotherapy using 5-FU/folinic acid. The median survival of the patients who had oncological cancer resection and postoperative 5-FU/folinic acid treatment was 19.7 months in 238 patients versus 14 months in the surgery-alone group [78]. The median survival was highly significant; a significant difference was observed for the 2-year actuarial survival. The results of the three prospective controlled studies, two of them randomized series, evaluating the benefits of adjuvant treatment with large patient allocation and sufficient observation periods demonstrated a significant benefit of 6–10 months with regard to the median survival time.

Regional adjuvant chemotherapy has been shown to improve the survival time in studies comparing intraarterial chemotherapy using celiac artery infusion versus historical controls. The median survival time improved after regional adjuvant chemotherapy to 21 months versus 19.3 months in historical controls [79]. Celiac artery infusion exposes the rest of the pancreas and the upper abdominal organs, and particularly the liver, via the hepatic artery and splenic–portal vein, to chemoactive drugs. The preliminary data deriving from prospective clinical trials, comparingintraarterial regional adjuvant chemotherapy with historical controls, reveal that disease progression was significantly reduced in the liver. In fact, tumor recurrence occurred either locally or in the peritoneum, but it occurred in the liver in < 20% of the cases (Table 11) [79, 81].

The effect of radiation alone is still under discussion. Local disease control and longer survival were achieved by Zerbi et al., who administered a high dose of intraoperative radiation therapy (IORT) [82]. In contrast, the local relapse rate in the GITSG patient group receiving 40 Gy radiotherapy was 33% versus 47%–55% in the control group. In the Mayo trial, patients were treated with 54 Gy; only 9% had a local relapse, but the disease progression in the liver was 52%, resulting in a limited survival benefit for the

Table 9. Recurrence after R_0 resection.

Study	Year	Patient (*n*)	Extent of resection	Cancer stage	Localization of first recurrence				Time of recurrence			Survival	
					Local (%)	Liver (%)	Peritoneum (%)	loc +/− liver (%)	< 6 months (%)	< 12 months (%)	> 12 months (%)	PFS (median), months	5-year actuarial survival (%)
Griffin et al. [64]	1990	26	Standard	T_1-T_3[a]	27	15	31					8	17
Westerdahl et al. [65]	1993	74	Standard		8	14		78		92	8		
Kayahara et al. [66]	1993	30	Extended	II–IV[b]								9.1	
Sperti et al. [67]	1997	78	Standard	I–III[a]	33	36	10		44	71		8	3

[a]UICC.
[b]JPS.
PFS: progression free survival; loc: localization.

adjuvant-treated patients in spite of the improved local disease control [83].

A positive effect of intraoperative radiotherapy after resection as a single treatment modality has not been unanimously confirmed; however, in a prospective controlled clinical trial, a median survival time of 13 months was achieved in the treated patients versus 8 months in the control group [82]. The combination of extended radical resection and IORT improved the actuarial 5-year survival rate to 29% versus 0% [84]. Taking the results of the prospective trials together—although they are on a lower level controlled—IORT in combination with oncological resection leads to a significant reduction in local recurrence and a prolongation of survival to 12.8–16 months in comparison to a survival of 7–8 months in control groups [85, 86].

Impact of Neoadjuvant Treatment

A protocol for neoadjuvant, multimodal treatment of pancreatic cancer is not yet established. Results from uncontrolled, prospective mono-institutional series applying radiochemotherapy to patients with pancreatic cancer stage II and III (UICC) resulted in a frequency of downstaging of 15%–30% and a resection rate of the downstaged patients between 50% and 83% [87–89]; the median survival rates of these patients ranged 15–32 months. The use of preoperative chemoradiation is supported by the following considerations: (1) The goal of neoadjuvant treatment is downstaging of the patient and, in combination with an oncological resection, increasing the chances of survival. A certain percentage of potentially unresectable tumors are downstaged to enable surgical resection. (2) Radiation therapy is more effective on well-oxygenated cells that have not been devascularized by surgery. (3) Pretreatment before surgery may prevent implantation and dissemination of tumor cells at laparotomy. (4) Patients with evidence of disseminated disease on re-staging after chemoradiation will not be subjected to unnecessary laparotomy. (5) Delayed postoperative recovery will not affect the delivery of multimodality therapy as it does in one third of the patients receiving adjuvant chemotherapy.

In recent published controlled clinical trials comparing historical and prospective control groups, the frequency of downstaging was observed to be between 13% and 45% [88, 89]. Oncological resection after neoadjuvant radiochemotherapy resulted in a median survival between 15 and 32 months [84–86]. Patients with UICC stages II and III pancreatic cancer are candidates for neoadjuvant treatment. Neoadjuvant multimodal treatment including radiotherapy with 54 Gy and chemosensitization using 5-FU/folinic acid or gemcitabine had a survival benefit after resection in comparison to non-resected patients of the same cancer stage. Between 10% and 25% of the patients with resectable cancer are downstaged [86].

During neoadjuvant chemotherapy, disease progression occurs in 15%–25% of the patients with the appearance of liver metastases or peritoneal carcinosis. These patients are spared a laparotomy. After neoadjuvant radiochemotherapy, patients who were not considered candidates for surgical resection because of adherence of the cancer to the wall of the portal vein or the superior mesenteric vein show a separation between tumor and vessel wall [89]. Downstaging in this group of advanced pancreatic cancer patients resulted in a survival benefit after oncological resection. Neoadjuvant radiochemotherapy also resulted in a decrease in the frequency of cancer-positive resection margins. Finally, after neoadjuvant radio-

Table 10. Pancreatic cancer: adjuvant treatment: results of controlled clinical trials.

					Survival			
						Actuarial		
Study	Year	Patients (*n*)	Adjuvant treatment	Patients in study (*n*)	Months (median)	1 Year (%)	2 Year (%)	5 Year (%)
GITSG [74, 75]	1985, 1987	43	S + RT + 5-FU	21	20		42	19
			S alone	22	11			
Yeo et al. [76]	1997	120	S + RT + FU	21	19.5			
			S alone	99	13.5			
EORTC-GITCCG [72]	1997[a]	228	S + RT + CHT	108	23.5			
			S alone	110	19.1			
Nukui et al. [77]	2000	33	S + RT + FU + Cis + IFNα	17	> 24.0		84	
			S + RT + FU	16	18.5		54	
Neoptolemos et al. [78]	2001	473	S + FU/FA	238	19.7			
			S alone	235	14.0			

S: oncological resection; RT: radiotherapy; CHT: chemotherapy; 5-FU: 5-fluorouracil; FA: folinic acid; Cis: cisplatin; IFNα: interferon α.
[a]Periampullary tumor included.

Table 11. Ductal pancreatic cancer: options to prevent/reduce occurrence of liver metastases using regional adjuvant chemotherapy.

	Patients (*n*)	Cancer stage	Mode of treatment	Drug	Recurrence pattern liver metastases (%)	Survival probability		
						3 years	4 years	5 years
Ishikawa et al., 1994 [79]	20	JPS I-III	R + HAI + PV	5-FU	8	54		54
Takahashi et al., 1995 [80]	25	JPS I-III	R_0 + PV	5-FU	32			15
Beger et al., 1999 [81]	26	UICC I-III	R + CAI	5-FU + FA/M/CPPD	17		48	

R: resection; HAI: hepatic artery perfusion; PV: portal vein infusion; CAI: celiac artery perfusion; M: mitoxantrone; CPPD: cisplatin; R_0: curatively resected.

chemotherapy and surgical resection no increase in postoperative complications has been reported [89].

Summary

The prognosis of patients suffering pancreatic cancer who undergo surgical resection is determined by the state of lymph node metastasis, invasion of blood vessel walls, infiltration of extrapancreatic nerve plexus, and the degree of micrometastasis into the surrounding tissues and remote organs. More than 95% of such patients are in an advanced stage of cancer. Major contributions of surgery to improve treatment results are reduction of hospital morbidity and mortality. In high-volume centers the hospital mortality is considered to be < 5%. Regarding long-term survival after R_0 resection, < 10% of patients in selected surgical series were observed surviving 5 years and more without cancer recurrence. Long-term survival is observed in a very small group of patients, contradicting the published 5-year actuarial survival rates of 20%–45% of resected patients. Kaplan-Meier analyses of survival results in misleading survival figures in the subgroup of patients treated by surgical resection if patients who died in the hospital and those lost to follow-up are excluded from the calculations. R_0 resection alone fails to improve long-term survival. Besides the well-defined actual survival, other reliable criteria to measure treatment results including observed median survival, progression-free survival, treatment-related survival prolongation, and quality of life data are accepted and reliable criteria to assess treatment results. Adjuvant treatment improves survival after oncological resection. The survival benefit by applying chemotherapy or radiochemotherapy in an adjuvant setting has been demonstrated to be 6–10 months in terms of median survival time. After oncological resection of pancreatic cancer each patient should be offered adjuvant treatment. A neoadjuvant treatment protocol for pancreatic cancer is presently not established. However, after neoadjuvant radiochemotherapy about 15% of downstaged patients have a survival benefit in combination with an oncological resection.

Résumé. En dépit des progrès réalisés dans le traitement chirurgical, essentiellement une augmentation du taux de la résécabilité et une diminution de la morbidité et de la mortalité, le taux de cure après résection pour cancer du pancréas reste, même aujourd'hui, en dessous de 3%. La dissémination locale du cancer du pancréas limite le taux de survie à court terme (< 3 ans) et à long terme des patients ayant eu une résection. Selon une évaluation histologique, moins de 15% des patients ayant eu une résection R_0 étaient pN_0, avec plus de 60% qui avaient un envahissement lymphatique; > 50% des patients ont une infiltration extrapancréatique plexique nerveuse. En fait, les ganglions HE négatifs s'étaient montrés cancéreux lorsque la coloration PCR ou l'immuno-coloration ont été utilisées au niveau de ces ganglions HE négatifs. Les cancers du petit pancréas ont un très mauvais pronostic en raison d'une absence de signes précoces; l'envahissement vasculaire, fréquent, est habituellement précoce; il y a souvent également des métastases hépatiques. La chirurgie est souvent la seule chance de cure, quoique faible. Le diagnostic de cancer canalaire est fait dans plus de 95% des cas à un stade avancé; une résection potentiellement curatrice peut être réalisée chez seulement environ 10–15% des patients. Le pas important de la chirurgie pour améliorer les résultats du traitement a été la réduction de la morbidité chirurgicale, c'est-à-dire les complications postopératoires locales et systémiques ainsi qu'une diminution de la mortalité hospitalière arrivant en-dessous de 3–5%. Selon les résultats des essais prospectifs les plus récents, la réalisation d'une résection R_0, comparée à une résection laissant de la tumeur en place, augmente la survie. Cependant, ceci n'est pas toujours vrai. Dans beaucoup de séries de résection R_0 publiées après résection standard des cancers de la tête du pancréas selon le procédé de Kausch-Whipple, on a noté l'absence de tissus comprenant des cellules cancéreuses dans les

pièces de résection, c'est-à-dire au niveaux des ganglions lymphatiques N_2, des plexus nerveux et des tissus périvasculaires extrapancréatiques et rétropancréatiques. La récidive après des résections soi-disant R_0 avec intention de cure est souvent la conséquence du tissu cancéreux laissé en place. La survie à long terme (> 5 ans) peut être observée dans un groupe de patients extrêmement petit, avec des taux de survie actuarielle à 5 ans de 20–45% chez les patients réséqués. L'évaluation des bénéfices cliniques provenant d'un traitement chirurgical or médical devrait être basée sur plusieurs points, pas seulement sur la survie actuarielle. Les publications concernant la survie actuarielle sans information en ce qui concerne le nombre de patients en survie réel (actuel), la définition d'un sous-groupe de patients suivis après résection et le nombre total de patients dans le groupe d'étude dans les essais thérapeutiques du cancer du pancréas peuvent prêter à confusion: on a en effet besoin de critères de jugement plus convaincants pour évaluer l'efficacité thérapeutique après résection oncologique, tels que la médiane de survie (en mois), la survie actuelle à 1–5 ans et la survie sans progression de la maladie (en mois). Dans les séries de traitement multi modalité, l'évaluation de la réponse clinique ainsi que la qualité de vie utilisant des instruments de mesure comme les questionnaires EORTC ou QLQ-C30 sont également très importants en plus des chiffres de survie. Le traitement adjuvant améliore la survie après résection oncologique. Cependant, les bénéfices à court et à long terme après chimiothérapie adjuvante en cas de résection R_0 ou R_1-$_2$ sont jusqu'à présent sans conviction à partir des essais cliniques contrôlés. Le bénéfice de survie par la chimiothérapie ou par la radio chimiothérapie est de l'ordre de 6–10 mois en ce qui concerne la médiane de survie. Après résection oncologique d'un cancer du pancréas, chaque patient a droit à un traitement adjuvant. Il n'existe pas, à l'heure actuelle, de traitement néoadjuvant bien établi pour cancer du pancréas.

Resumen. Los progresos registrados en el tratamiento quirúrgico del adenocarcinoma de páncreas han propiciado un incremento en el número de resecciones y un descenso en las tasas de morbi-mortalidad inherentes a la intervención quirúrgica; sin embargo, el número real de pacientes curados no supera el 3%. La rápida diseminación del cáncer al espacio retropancreático es responsable de la escasa supervivencia, a corto (< 3 años) y largo plazo, de los pacientes resecados. Utilizando criterios histológicos, menos del 15% de los pacientes sometidos a una resección curativa (R_0) pertenecen al estadio pN_0 y más del 60% presentan una linfangitis carcinomatosa; cerca del 50% de los pacientes muestran infiltración carcinomatosa en los plexos nerviosos extrapancreáticos. Los ganglios linfáticos negativos con la tinción de hematoxilina-eosina (HE) resultan positivos, con micrometástasis, si se utilizan otras técnicas como la RT-PCR o la inmunotinción. El cáncer del proceso uncinado tiene muy mal pronóstico pues cursa inicialmente de forma asintomática; con frecuencia, la invasión de las paredes vasculares se produce muy precozmente y las metástasis hepáticas también. El tratamiento quirúrgico constituye la única terapéutica efectiva, pero sólo en pocos casos tiene carácter curativo. En más del 95%, el adenocarcinoma ductal pancreático se diagnostica en estadios avanzados y una resección, potencialmente curativa, se realiza sólo en un 10–15% de los pacientes. El progreso de la técnica quirúrgica ha reducido exclusivamente la morbilidad, p. ej. las complicaciones locales o sistémicas postoperatorias, disminuyendo la mortalidad intrahospitalaria por debajo del 3–5%. En estudios prospectivos recientes se ha demostrado un aumento de la supervivencia a corto plazo en pacientes con resecciones radicales curativas R_0, con respecto a aquellos en los que persiste un resto tumoral. Sin embargo, las resecciones R_0 no han mejorado la supervivencia tardía. Estudios casuísticos publicados han demostrado que tras resección R_0 (efectuando la duodenopancreatectomía estándar a lo Kausch-Whipple), persisten restos tumorales tales como: micrometástasis en los ganglios linfáticos N_2, nidos de células cáncerosas extrapancreáticas en tejido retroperitoneal, perivasculares o a lo largo de los plexos nerviosos. La recidiva, tras la así llamada resección R_0 curativa, se debe, con frecuencia, a estos restos neoplásicos abandonados, por desapercibidos, en la operación estándar. Supervivencias > 5 años se constatan sólo en un reducido grupo de pacientes, lo que contrasta con las cifras publicadas basadas en la curva actuarial que alcanza hasta el 20–45% de los pacientes resecados. Para averiguar la variable predefinida que permite cuantificar los efectos del tratamiento quirúrgico o médico del cáncer de páncreas, han de utilizarse otros criterios de valoración distintos a la supervivencia actuarial. Las publicaciones de supervivencia actuarial sin cifras que informen sobre el número de casos actualmente vivos ni que expliciten el número de pacientes revisados tras la resección, en relación con el número total de los estudiados, conducen a conclusiones erróneas. En los ensayos sobre el tratamiento del cáncer de páncreas los resultados, por lo que a la eficacia de las resecciones oncológicas se refiere, han de basarse en criterios de valoración principales tales como: supervivencia media (en meses), supervivencia actual al 1–5 años, y el curso evolutivo de la supervivencia sin enfermedad (en meses). En series en las que se aplican tratamientos multimodales han de valorarse además la respuesta clínica al tratamiento así como la calidad de vida de los pacientes evaluados mediante tests tales como el EORTC, y el QLQ-C30. El tratamiento adyuvante aumenta la supervivencia tras resecciones oncológicas. Sin embargo, en la actualidad no existen estudios controlados que demuestren fehacientemente, que el tratamiento con quimioterapia adyuvante, tras resecciones R_0 y $R_{1–2}$ sea beneficioso para los pacientes ni a corto ni largo plazo. Lo único que se ha demostrado es que la administración de quimio o radio-quimioterapia adyuvante prolonga en 6–10 meses la vida de los pacientes con respecto a la supervivencia media. Tras una resección oncológica por cáncer de páncreas cada paciente a de ser sometido a un tratamiento adyuvante, pero hasta el momento no se ha podido definir el tratamiento neoadyuvante más idóneo para el cáncer de páncreas.

References

1. Hruban RH, Offerhaus GJA, Kern SE. Familial pancreatic cancer. In Cameron JL, editor, Pancreatic Cancer Hamilton, London, Ontario, BC Decker, Inc., 2001;25–36
2. Gudjonsson B. Cancer of the pancreas. 50 years of surgery. Cancer 1987;60:2284
3. Tsuchiya R, Oribe T, Noda T. Size of the tumor and other factors influencing prognosis of carcinoma of the head of the pancreas. Am. J. Gastroenterol. 1985;80:459
4. Cameron JL, Crist DW, Sitzmann JV, et al. Factors influencing survival after pancreaticoduodenectomy for pancreatic cancer. Am. J. Surg. 1991;161:120
5. Nagakawa T, Kayahara M, Ohta T, et al. Patterns of neural and plexus extensive invasion of human pancreatic cancer and experimental cancer. Int. J. Pancreatol. 1991;10:113
6. Ishikawa O. Surgical technique, curability and postoperative quality of life in an extended pancreatectomy for adenocarcinoma of the pancreas. Hepatogastroenterology. 1996;43:320
7. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of adenocarcinoma of the pancreas. Am. J. Surg. 1993;165:68
8. Yeo C, Abrams R, Grochow L, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. Ann. Surg. 1997;225:621
9. Birk D, Fortnage G, Formentini A, et al. Small carcinoma of the pancreas. Factors of prognostic relevance. J Hepatol. Biliary Pancreat. Surg. 1998;23:234
10. Beger HG, Gansauge F, Birk D. Lymph node dissection. In Cameron JL, editor, Pancreatic Cancer Hamilton, London, Ontario, BC Decker, Inc., 2001;123–132
11. Ishikawa O, Ohigashi H, Sasaki Y, et al. Practical grouping of positive lymph nodes in pancreatic head cancer treated by an extended pancreatectomy. Surgery 1997;121:244–249
12. Hirai I, Murakami G, Kimura W, et al. Origin of the thoracic duct and pancreaticoduodenal lymphatic pathways to the para-aortic lymph nodes. J. Hepatobiliary. Pancreat. Surg. 2001;8:441–448
13. Tsuchiya R, Takatoshi N, Harada N, et al. Collective review of small carcinomas of the pancreas. Ann. Surg. 1986;203:77–81
14. Hermanek P. Staging of exocrine pancreatic carcinoma. Eur. J. Surg. Oncol. 1991;17:167–172
15. Takahashi T, Ishikara H, Kato H, et al. Intra-pancreatic, extratumoral perineural invasion. Acta Pathol. Jpn. 1992;42:99–103
16. Nakao A, Harada A, Nonami T, et al. Clinical significance of carcinoma invasion of the extrapancreatic nerve plexus in pancreatic cancer. Pancreas 1996;12:357–361
17. Kayahara M, Nagakawa T, Futagami F, et al. Lymphatic flow and neural plexus invasion associated with carcinoma of the body and tail of the pancreas. Cancer 1996;78:2485
18. Heeckt P, Safi F, Binder T, et al. Free intraperitoneal tumor cells in pancreatic cancer—significance for clinical course and therapy. Chirurgie 1992;78:2485

19. Ando N, Nakao A, Nomoto S, et al. Defection of mutant K-ras in dissected paraaortic lymph nodes of patients with pancreatic adenocarcinoma. Pancreas 1997;15:374–378
20. Hosch SB, Knoefel WT, Metz S, et al. Early lymphatic tumor cell dissemination in pancreatic cancer: frequency and prognostic significance. Pancreas 1997;15:154–159
21. Demuere MJ, Doffek KM, Komoiowski RA, et al. Adenocarcinoma of the pancreas. Detection of occult metastases in regional lymph nodes by PCR-based assay. Cancer 1998;83:1328–1334
22. Mühling B, Dehner C, Steiger. Micrometastasis in pancreatic head cancer: use of polymerase chain reaction for precise tumor staging. J. Gastrointest. Surg., in press
23. Juhl H, Stritzel M, Wroblewski A, et al. Immunocytological detection of micrometastatic cells. Int. J. Cancer 1994;57:330–335
24. Inoue S, Nakao A, Kasai Y, et al. Detection of hepatic micrometastasis in pancreatic adenocarcinoma patients by two-stage polymerase chain reaction/restriction fragment length polymorphism analysis. Jpn. J. Cancer Res. 1995;86:626–630
25. Soeth E, Röder C, Juhl H, et al. The detection of disseminated tumor cells in bone marrow from colorectal-cancer patients by a cytokeratin-20-specific nested reverse-transcriptase-polymerase-chain reaction is related to the stage of disease. Int. J. Cancer 1996;69:278–282
26. Thorban S, Roder JD, Pantel K, et al. Immunocytochemical detection of isolated epithelial tumor cells in bone marrow of patients with pancreatic carcinoma. Am. J. Surg. 1996;172:297–298
27. Kayahara M, Nagakawa T, Konishi I, et al. Clinicopathological study of pancreatic carcinoma with particular reference to the invasion of the extrapancreatic neural plexus. Int. J. Pancreatol. 1991;10:105–111
28. Nagakawa T, Kayahara M, Ueno K, et al. A clinicopatholgic study on neural invasion in cancer of the pancreatic head. Cancer 1992;69:930–935
29. Ohigashi H, Ishikawa O, Sasaki Y, et al. K-ras point mutation in the nerve plexus around superior mesenteric artery in resectable adenocarcinoma of the pancreatic head. Arch. Surg. 2000;135:1450–1455
30. Birk D, Fortnage G, Formentini A, et al. Carcinoma of the pancreas arising from the uncinate process. Br. J. Surg. 1998;85:498
31. Gordon TA, Burleyson G, Tielsch JM, et al. The effects of regionalization on cost and outcome for one high-risk general surgical procedure. Ann. Surg. 1995;221:43–49
32. Liebermann MD, Killborn H, Lindsey M, et al. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann. Surg. 1995;222:638–645
33. Gouma DJ, van Geenen RCI, van Gulik THM. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann. Surg. 2000;232:786–794
34. Bramhall SR, Allum WH, Jones AG, et al. Treatments and survival in 13.560 patients with pancreatic cancer, and incidence of the disease, in the West Midlands: an epidemiological study. Br. J. Surg. 1995;82:111–115
35. Neoptolemos JP, Russel RCG, Bramhale S, et al. Low mortality following resection for pancreatic and periampullary tumours in 1026 patients. Br. J. Surg. 1997;84:1370
36. Gordon TA, Bowman HM, Bass EB, et al. Complex gastrointestinal surgery: impact of provider experience on clinical and economic outcomes. J. Am. Coll. Surg. 1999;189:46–56
37. Scand J Finnish Surg Society Annual Meeting. (1996) 17-45
38. Birkmeyer JD, Finlayson SRG, Tosteson ANA, et al. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. Surgery 1999;125:250–256
39. Howard J. Pancreaticoduodenectomy: forty-one consecutive Whipple resections without an operative mortality. Ann. Surg. 1968;168:629–640
40. Beger HG, Gansauge F, Ramadani M, et al. Morbidity and mortality after pancreatic head resection— monoinstitutional results of 1200 patients. Ann. Surg. 2003, in press
41. Pedrazzoli S, Di Carlo V, Dionigi R, et al. Standard versus extended lymphadenectomy associated with pancreaticoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas. Ann. Surg. 1998;228:508–517
42. Yeo CL, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma. Ann. Surg. 2002;236:355–368
43. Pedrazzoli S, Beger HG, Obertop H, et al. A surgical and pathological based classification of resective treatment of pancreatic cancer. Dig. Surg. 1999;16:337–345
44. Tsuchiya R, Karada N, Tsunoda T, et al. Long-term survivors after operation on carcinoma of the pancreas. Int. J. Pancreatol. 1988;3:401–406
45. Trede M, Schwall G, Seger HD. Survival after pancreatoduodenectomy. 118consecutive resections without an operative mortality. Ann. Surg. 1990;211:447–458
46. Nagakawa T, Kayahar M, Ohta T, et al. Patterns of neural and plexus invasion of human pancreatic cancer and experimental cancer. Int. J. Pancreatol. 1991;10:113–119
47. Takahashi S, Ogata Y, Miyazaki H, et al. Aggressive surgery for pancreatic duct cell cancer: feasibility, validity, limitations. World J. Surg. 1995;19:653–660
48. Klempnauer J, Ridder GJ, Pichlmayr R. Prognostic factors after resection of ampullary carcinoma: multivariate survival analysis in comparison with ductal cancer of the pancreatic head. Br. J. Surg. 1995;82:1686–1691
49. Yeo CL, Sohn TA, Caeron JL, et al. Periampullary adenocarcinoma: analysis of 4-year survivors. Ann. Surg. 1998;227:821–831
50. Takahashi T, Nizno N, Ishikura H, et al. Predictive factors for long-term survival in patients with pancreatic carcinoma. Hepatogastroenterology. 1997;44:1463–1468
51. Nitecki S, Sarr MG, Thomas VC, et al. Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? Ann. Surg. 1995;221:59–66
52. Hanyu F, Imaizumi T. Extended radical surgery for carcinoma of the head of the pancreas—Japanese experience. In Beger HG, Büchler M, Schoenberg MH, editors, Cancer of the Pancreas Ulm (Germany), Universitätsverlag, 1996;389–401
53. Tashiro S, Kochino R, Hiraoka T, et al. Surgical indications and significance of portal vein resection in biliary and pancreatic cancer. Surgery 1991;109:481–487
54. Ishikawa O, Ohigashi H, Imaoka S, et al. Preoperative indications for extended pancreatectomy for locally advanced pancreas cancer involving the portal vein. Ann. Surg. 1992;215:231–236
55. Allema JH, Renders ME, van Gulik TM, et al. Portal vein resection in patients undergoing pancreatoduodenectomy for carcinoma of the pancreatic head. Br. J. Surg. 1994;81:1642–1646
56. Takahashi S, Ogata Y, Tsuzuki T. Combined resection of the pancreas and portal vein for pancreatic cancer. Br. J. Surg. 1994;81:1190–1193
57. Nakao A, Harada A, Nonami T, et al. Clinical significance of portal vein invasion by pancreatic head carcinoma. Surgery 1995;117:50–55
58. Roder JD, Stein HJ, Siewert JR. Carcinoma of the periampullary region: who benefits from portal vein resection? Am. J. Surg. 1996;171:170–175
59. Harrison LE, Klimstra DS, Murray FB. Isolated portal vein involvement in pancreatic adenocarcinoma. A Contraindication for resection? Ann. Surg. 1996;224:342–349
60. Evans DB, Pisters PWT, Lee JE, et al. Preoperative chemoradiation strategies for localized adenocarcinoma of the pancreas. J. Hepatobil. Pancreat. Surg. 1998;5:242–250
61. Launois B, Franci J, Bardayoglou E, et al. Total pancreatectomy for ductal adenocarcinoma of the pancreas with special reference to resection of the portal vein and multicentric cancer. World J. Surg. 1999;17:122
62. Shibada C, Kobari M, Tsuchiya T, et al. Pancreatectomy combined with superior mesenteric-portal vein resection for adenocarcinoma in pancreas. World J. Surg. 2001;25:1002–1005
63. Kawada M, Kondo S, Okushiba S, et al. (2003) ″Re-evaluation on indication of radical pancreatectomy for pancreatic carcinoma—is portal vein infiltration a contraindication?″ Langenbecks Arch. Surg., in press
64. Griffin JF, Smallay SR, Jewel W, et al. Patterns of failure after curative resection of pancreatic carcinoma. Cancer 1990;66:56–61
65. Westerdahl J, Andrew-Sandberg A, Ihse I. Recurrence of exocrine pancreatic cancer: local or hepatic? Hepatogastroenterology. 1993;40:384
66. Kayahara M, Nagakwa T, Keno K, et al. An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined by autopsy and diagnostic imaging. Cancer 1993;72:2118
67. Sperti C, Pasquali C, Piccoli A, et al. Survival after resection for ductal adenocarcinoma of the pancreas. Br. J. Surg. 1996;83:625–631

68. Iacono C, Bortolasi L, Facci E. Does extended pancreaticoduodenectomy increase operative morbidity and mortality vs. standard pancreatoduodenectomy? J. Gastrointest. Surg. 1997;1:446–453
69. Gudjonsson B. Survival statistics gone awry. Pancreatic cancer, a case in point. J. Clin. Gastroenterol. 2002;35:180–184
70. Glimelius B. Efficacy endpoints in pancreatic cancer trials: an expert's view CRP. The Remedy Ltd, London
71. Storniolo AM, Enas NH, Brown CA, et al. An investigational new drug treatment programme for patients with gemcitabine. Cancer 1999;85: 1261–1268
72. Klinkenbijl JH, Jeekel J, Sahmoud T. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann. Surg. 1999;230:776–784
73. Nguyten TC, Sohn TA, Cameron JL, et al. Standard vs. radical pancreaticoduodenectomy for periampullary adenocarcinoma: a prospective, randomized trial evaluating quality of life in pancreaticoduodenectomy survivors. J. Gastrointest. Surg. 2003;7:1–11
74. Kalser MH, Ellenberg SS. Pancreatic cancer: adjuvant combined radiation and chemotherapy following curative resection. Arch. Surg. 1985; 120:899–903
75. GITSG. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Cancer 1987;59:2006–2010
76. Yeo CJ, Abrams RA, Grochow LB, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. Ann. Surg. 1997;225:621–636
77. Nukui Y, Picozzi VJ, Traverso LW. Interferon-based adjuvant chemoradiation therapy improves survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Am. J. Surg. 2000;179:367–371
78. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet 2001;358:1576–1585
79. Ishikawa O, Ohigashi H, Sasaki Y, et al. Liver perfusion chemotherapy via both the hepatic artery and portal vein to prevent hepatic metastasis after extended pancreatectomy for adenocarcinoma of the pancreas. Am. J. Surg. 1994;168:361–364
80. Tahakashi S, Ogata Y, Miyazaki H, et al. Aggressive surgery for pancreatic duct cell cancer: feasibility, validity, limitations. World J. Surg. 1995;19:653
81. Beger HG, Gansauge F, Büchler MW, et al. Intraarterial adjuvant chemotherapy after pancreaticoduodenectomy for pancreatic cancer: significant reduction in occurrence of liver metastasis. World J. Surg. 1999;23:946–949
82. Zerbi A, Fossati U, Perolini D, et al. Intraoperative radiation therapy adjuvant to resection in the treatment of pancreatic cancer. Cancer 1994;73:2930–2935
83. Foo ML, Gunderson LG, Nagorney DM, et al. Patterns of failure in grossly resected pancreatic ductal adenocarcinoma treated with adjuvant irradiation + 5 fluorouracil. Int. J. Radiat. Oncol. Biol. Phys. 1993; 26:483–489
84. Hiraoka T. Extended radical resection of cancer of the pancreas with intraoperative radiotherapy. Baillieres Clin. Gastroenterol. 1990;4:985
85. Hosotani R, Kogire M, Arii S, et al. Results of pancreatectomy with radiation therapy for pancreatic cancer. Hepatogastroenterology. 1997; 44:1528–1535
86. Farrell TJ, Barbot DJ, Rosato FE. Pancreatic resection combined with intraoperative radiation therapy for pancreatic cancer. Ann. Surg. 1997;226:66–69
87. Jessup JM, Steele C, Mayer RJ, et al. Neoadjuvant therapy for unresectable pancreatic adenocarcinoma. Arch. Surg. 1993;128:559
88. Spitz F, Abbruzzose J, Janjan N, et al. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. J. Clin. Oncol. 1997;15: 928
89. Snady H, Bruckner H, Coopermann A, et al. Survival advantage of combined chemoradiotherapy compared with resection as the initial treatment in patients with regional pancreatic carcinoma. Cancer 2000; 89:314