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Expanding Surgical Treatment of Pancreatic Cancer: The Role of Regional Chemotherapy

Jeremy L. Davis, MD, **Prakash K. Pandalai, MD**, **R. Taylor Ripley, MD**, **Russell C. Langan, MD**, and **Itzhak Avital, MD**
Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Objectives—Pancreatic cancer is a lethal disease that offers little chance of long-term survival for patients with unresectable tumors. Surgery remains the most effective means of attaining prolonged survival, yet its role remains limited. Regional chemotherapy has been described for patients with pancreatic cancer, including reports of objective tumor regression allowing for tumor resection in previously unresectable cases, however comprehensive data have not been reviewed to date.

Methods—A review of the literature from 1995 to 2010 was performed to analyze the results of regional chemotherapy administered to patients with advanced pancreatic cancer. Reports of individual cases, post-operative regional therapy and treatment of mixed tumor types were excluded.

Results—Twenty-one reports of 895 total patients with pancreatic cancer were reviewed. Greater than 95% of patients had stage III or IV adenocarcinoma. Objective response rates ranged from nil to 58%, with associated median survivals of 4 to 22 months. Low grade gastrointestinal and hematologic toxicities were not uncommon.

Conclusions—Regional chemotherapy can be administered safely to patients with pancreatic cancer, but with unclear benefit. Advanced pancreatic tumors converted to resectable status by the use of regional chemotherapy may improve patient survival.

Keywords

Pancreatic cancer; chemotherapy; cancer; regional perfusion; infusion; intra-arterial

Introduction

Every year in the United States alone an estimated 43,140 cases of pancreatic cancer are diagnosed and 36,800 patients die of the disease, making it one of the most lethal forms of cancer in adults.[1] Overall survival is poor, with approximately 23% of patients living 12

Corresponding Author and To Whom Reprint Requests Should Be Sent: Itzhak Avital, M.D., Assistant Professor of Surgery, USUHS, Head GI and Hepatobiliary Malignancies Section, Surgery Branch, National Cancer Institute, National Institutes of Health, 10 Center Drive, CRC Room 4-3961, Bethesda, MD 20892, avitali@mail.nih.gov, Office: 301-402-0083, Fax: 301-451-6933.

Conflicts of Interest
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months after diagnosis.[2] Patients who undergo complete tumor resection survive 18 to 20 months in most series, with or without the addition of single-agent chemotherapy.[3] Unfortunately, less than 20% of patients with pancreatic cancer have resectable tumors at the time of diagnosis, most often due to invasion of adjacent vasculature or metastatic disease. In cases which tumors are detected early enough to allow resection, the choice of adjuvant chemotherapy is based on a randomized clinical trial that demonstrated significant improvement in median disease-free survival favoring gemcitabine over observation alone.[3] The addition of targeted molecular agents or cytotoxic drugs to gemcitabine adds little or no clinical benefit to patients with this disease.[4, 5] Likewise, current data are equivocal regarding the benefit of adjuvant chemoradiotherapy. For patients with inoperable pancreatic cancer systemic chemotherapy may prolong survival and improve quality of life, yet it can only be considered truly palliative in patients without a surgical treatment option.[6]

It can be estimated from population-based data that approximately 20 - 30% of patients with pancreatic cancer present with locally advanced disease, defined generally by tumor extension beyond the pancreas with or without regional lymph node metastases.[7] The term “locally advanced” has been applied liberally to patients with regional disease most often ascribed to advanced tumor stage (T3 and T4) that corresponds with American Joint Committee on Cancer (AJCC) stage II or III.[8] Advanced tumor stage that involves adjacent mesenteric vasculature is subdivided further into three categories based on pre-operative computed tomography: resectable, borderline resectable, and unresectable (Supplemental Table A). The accepted definitions of resectability are based on the type and degree of arterial and venous involvement and the presence of peritoneal or distant metastases.[9, 10]

Increasing the rate of complete tumor resection among patients with pancreatic cancer represents a practical approach to improving survival for those patients who present with advanced stage disease and currently have no surgical treatment option. Achieving this goal requires neoadjuvant therapy that mediates substantial tumor regression, allowing for complete resection in previously unresectable patients. Administration of regional chemotherapy is used currently to treat local-regional and metastatic disease for many cancer histologies. The pharmacologic rationale for regional drug delivery is to increase drug concentrations at tumor sites and limit systemic drug exposure and its toxicity.[11] The role of regional chemotherapy as an adjunctive therapy in patients with local-regional disease has been well documented since Creech et al. employed an extracorporeal circuit for regional isolation perfusion of nitrogen mustard compounds in the treatment of 24 patients with a variety of cancers.[12] Examples of effective contemporary regional therapy include isolated limb perfusion for cutaneous melanoma and hyperthermic intraperitoneal chemotherapy for primary peritoneal mesothelioma and carcinoma of ovarian, appendiceal and colorectal origin.[13–17]

The purpose of this review is to evaluate the available evidence for regional chemotherapy in advanced stage pancreatic cancer. We use these data to understand the potential benefits of tumor response and patient survival as well as the toxicity of this treatment strategy. We also explore the rationale for prospective investigation of this strategy with the intent of minimizing toxicity and increasing treatment efficacy, as measured by tumor response and increased rates of tumor resection.

Methods

A search of the Medline database was performed to identify published reports of regional chemotherapy for pancreatic cancer in the English language literature from January 1995 to January 2010. Medical subject heading (MeSH) terms used included (1) pancreatic

neoplasm, (2) infusion, intra-arterial, and (3) chemotherapy, cancer, regional perfusion. We focused the search by excluding the following: case reports, dose-escalation (phase I) trials, combined chemotherapy and radiation trials, and studies of perioperative or adjuvant regional chemotherapy. Reports that included multiple gastrointestinal histologies were also excluded. I n instances which institutions published updated patient data or combined analyses, we used the most recent publications. Data collected included the year of publication, patient sample size, age and gender, tumor histopathology and stage, type of regional therapy, toxicity and complications, response rate, and survival rate when available.

Patients

Twenty-one different studies published between 1995 and 2010 reported results of regional chemotherapy administered to 895 patients with advanced stage pancreatic cancer (Table 1).[18–38] Included were 62% (389/630) males and 38% (241/630) females in 20 studies reporting gender data. The mean age was 60 years in ten reports, and the median age ranged from 55 to 66 years (median 62) in eight other reports; three studies did not provide patients' age. Median time to follow-up was not reported in any series.

Clinicopathologic features of the primary pancreatic cancer

Eleven studies provided data on tumor type for all patients (n=425) whereas three studies reported histopathology for only a fraction (n=39); tumor pathology was either not confirmed or not reported in 431 of 895 (48%) patients (Table 2). Among 464 patients with histopathologic data, 96% (447/464) had adenocarcinoma, 2% (7/464) mucinous carcinoma, 1% (3/464) cystadenocarcioma, <1% (1/464) anaplastic carcinoma, and 1% (6/464) were classified as undifferentiated or "other". Pancreatic cancer staging was clearly specified in nine studies encompassing 633 patients (71%, 633/ 895). Eight reports utilized UICC (International Union Against Cancer) staging, and one study cited the Japan Pancreas Society staging system while also providing the TNM (*t*umor, *n*ode, *m*etastasis) classification. Of the nine studies reporting tumor stage using a defined system, 46% (290 of 633) were stage III, 54% (339 of 633) stage IV, and less than 1% (4 of 633) stage I–II. Reports that did not specify a staging system simply described patients as having "locally advanced", "unresectable" or "inoperable" pancreatic cancer with or without metastases. Other reports stated that patients had stage III or IV disease without providing additional information. The term "locally advanced" often was used interchangeably with stage III disease, while metastatic disease was synonymous with stage IV. Therefore, despite the deficiencies in reporting, if ancillary information was used to decipher tumor stage based on current AJCC staging (e.g. "T4 tumor without metastases"), 41% (363 of 875) were stage III and 58% (508 of 875) were stage IV. Only one study, by Sasada et al., provided criteria for declaring tumors unresectable based on invasion of the superior mesenteric or celiac artery and/or occlusion or stenosis of the portal or superior mesenteric vein. The remaining studies in this review provided no information regarding criteria used for determining the resectability of non-metastatic tumors.

Prior therapy

Seventeen studies provided information on 277 patients receiving treatment prior to regional chemotherapy. Fourteen studies described 196 patients as having had prior surgery; 14 patients were described as having a prior curative resection, 122 had a bypass or other palliative procedure, and the remaining 60 patients were not further specified. Eighty-one of the 277 patients received systemic chemotherapy and/or radiation treatment prior to regional chemotherapy. Three authors disclosed that no patients received systemic chemotherapy prior to regional chemotherapy.[29, 35, 38]

Regional chemotherapy

Catheter-based arterial infusion and perfusion techniques, with and without hemofiltration, were used to deliver regional chemotherapy in these studies. Briefly, arterial perfusion generally referred to the use of a closed circuit incorporating arterial and venous catheters, whereas infusion techniques did not utilize venous return catheters and therefore the chemotherapeutic agents were open to the effects of systemic circulation. Abdominal perfusion and arterial infusion were performed commonly via access to the femoral vessels whereby arterial catheters were positioned with fluoroscopic guidance in the celiac trunk for celiac axis infusion (CAI) and into peri-pancreatic arteries for selective arterial infusion (SAI). In three reports, arterial catheters were placed at the time of laparotomy to obtain more selective pancreatic infusion. For abdominal perfusion with or without isolation of the abdominal compartment, also referred to as hypoxic abdominal perfusion (HAP) or aortic stop-flow infusion, balloon catheters were inserted into the femoral artery and vein and advanced into the aorta and vena cava, respectively, with occluding balloon cuffs placed at the level of the diaphragm. Arterial and venous catheters were attached to a roller pump or extracorporeal circuit with or without a filtration device. In order to isolate the abdomen tourniquets were applied to the thighs to exclude perfusion of the legs.

Celiac axis infusion (CAI) was used in a majority of studies (52%, 11/21) whereas selective arterial infusion (SAI; 29%, 6/21) and hypoxic abdominal perfusion (HAP: 29%, 6/21) were used less often. Two series reported using hemofiltration in the extracorporeal circuit, whereas four studies of HAP did not use hemofiltration. In two studies, CAI and HAP were utilized sequentially.[27, 28] In an attempt to direct blood flow to tumor or pancreas only, four studies (19%, 4/21) utilized selective arterial embolization prior to arterial chemotherapy infusion.[24, 29, 34, 38] Technical variations in arterial catheterization, including percutaneous versus open surgical approach, appeared to reflect changes in procedural experience over time and the method of patient selection. A variety of chemotherapeutic agents were used alone or in combination (Table 1). 5-fluorouracil (5-FU) was used most often (57%) followed by mitomycin-C (MMC; 48%), cisplatinum (CDDP; 38%), gemcitabine (24%), mitoxantrone (19%), epirubicin and carboplatin (14%), methotrexate (5%) and melphalan (5%). Three studies also included adjuncts to chemotherapy: warfarin, angiotensin-II, and degradable starch microspheres.[26, 28, 37]

Response Rates

Tumor response rate and patient survival were reported as study endpoints; 19 studies reported tumor responses, 10 reported survival, and 9 reported both response and survival rates. Objective response criteria were defined in 17 of 21 (81%) studies (Table 3). World Health Organization (WHO) response criteria were used by 71% (15/21) of studies; nine authors (43%, 9/21) specifically referenced WHO, whereas six (29%, 6/21) provided definitions for partial and complete responses and progressive disease that were synonymous with WHO criteria. One study utilized Southwest Oncology Group (SWOG) criteria, while another used Response Evaluation Criteria In Solid Tumors (RECIST) criteria. The average response rate reported was 26% (range 0 to 58%) for 19 of 21 studies reporting response data, regardless of criteria. For 17 of 21 studies (564/895 patients) utilizing defined response criteria, the response rate was 25%. Two studies reported tumor response rate without defining response criteria, and two additional studies neither defined nor reported response rate. Studies by van Ijken, Milandri and Sasada et al. provided response data for only a subset of total patients treated (16 of 21, 16 of 19 and 12 of 16 patients, respectively), and these are included in the average response rates reported above.

Toxicity

General toxicity was reported in either a graded format or simply with descriptive text. WHO and National Cancer Institute (NCI, Common Terminology Criteria for Adverse Events) criteria were at least noted in the text of 17 reports, however only 14 of 21 (67%) studies provided comprehensible toxicity data amenable to interpretation (Supplemental Table B). Of 895 total patients, toxicity data were available for 288 (32%). Grade I to II gastrointestinal toxicity occurred in 48% (139 of 288), and grade III to IV in 13% (38 of 288). The incidence of hematologic toxicity was similar with 46% (133 of 288) grade I to II, and 22% (62 of 288) grade III to IV. Link et al. reported toxicity as percentage of total cycles of infusion performed; the incidence of gastrointestinal toxicity was 54% grade I to II and 10% grade III to IV, and 9% for grade I to II and 1% for grade III to IV hematologic toxicity. Specific examples of procedure-related morbidity included arterial dissection (n=3), catheter dislocation (n=6), duodenal or gastric ulcer (n=4), hepatic abscess (n=2), port site dysfunction (n=2), groin lymphatic fistula (n=6), and deep vein thrombosis (n=6). Meyer et al. reported a 30-day mortality of 17.6 % (3 of 17 patients) and van Ijken et al. described a treatment related mortality attributed to acute mesenteric ischemia; total treatment-related mortality was 0.04% (4/895).

Survival

The average 1-year survival was 38.8% (range 6% to 83%, n=10 studies reporting), with a median survival of 4 to 22 months (median 8.5 months, n=17 studies reporting). Few studies analyzed survival by tumor stage. Link et al. reported 12 months median survival for patients with stage III disease compared to 4 months median survival for patients with stage IV disease.[20] Mambrini et al. reported 10.5 and 6.6 months median survival and Maurer et al. reported 8.5 and 5 months median survival for patients with stage III and IV disease, respectively.[22, 31] In a subsequent report by Mambrini et al., prognostic factors associated with improved survival were sought for the original cohort of 211 patients. Factors associated with improved survival were pain reduction during treatment greater than 30% of baseline, non-metastatic disease, and greater than 3 cycles of regional chemotherapy received.[39] Meyer et al. reported median survival of 3.2 months for patients without metastases and 4.7 months for those without.[32]

Progression to surgery following chemotherapy

Eighty-five patients (9%, 85/895) underwent exploratory surgery following regional chemotherapy. One patient was explored despite having progressive disease and underwent resection.[21] Nakbachandi et al. reported “downstaging” of tumor in three patients, resulting in resection and prolonged survival (8.2, 10.7 and 17.5 months).[37] In three additional studies, 7 patients were re-explored, one of which underwent a pancreaticoduodenectomy, one was unresectable, and the remaining five had a procedure not otherwise specified.[19, 22, 36] In the largest series to report re-exploration of patients following regional chemotherapy, Aigner et al. provided data on 80 patients surviving greater than 12 months beyond treatment, of which 74 underwent surgical exploration; 31 of 74 (42%) underwent resection via pancreaticoduodenectomy, partial pancreatectomy, or evacuation of tumor necrosis.[28]

Discussion

Approximately 80% of pancreatic cancer patients have no option for curative resection at the time of diagnosis. Half of all patients are diagnosed with metastatic disease, while approximately 25% present with advanced tumor stage considered unresectable due to involvement of adjacent mesenteric vasculature.[7, 40] Patients with unresectable tumors have only a 20% chance of surviving one year following diagnosis and treatment with single

agent chemotherapy.[41] For the relatively small number of patients with tumors amenable to resection, the most common sites of recurrence are the local resection bed, liver and peritoneum. For these reasons the application of regional chemotherapy for advanced pancreatic cancer has been posited not only as a method for treating unresectable disease, but also as prevention of local and hepatic recurrences in the adjuvant setting. In this review of 21 published reports representing 895 patients with both locally invasive and metastatic pancreatic cancer, regional chemotherapy offers an average one-year survival rate of 39% and median survival of 8.5 months, which approximates survival for advanced (unresectable) pancreatic cancer patients receiving systemic chemotherapy with or without radiation therapy.[42–44]

Although previous classification systems have described the extent of vascular involvement in order to guide pre-operative decision making, only within the last decade have patients benefited from consensus criteria used to determine tumor resectability.[9, 45, 46] In this review, the often used description of locally advanced (non-metastatic) pancreatic cancers as “inoperable” provides inadequate information regarding patient selection, thus weakening the conclusions taken from these studies. Different tumor resectability criteria used among investigators and increasing allowance for venous resection over time accounts for a heterogeneous population of patients from which these conclusions are drawn. Going forward, clinical trials must utilize current preoperative cross-sectional imaging criteria that allow for standardized classification of resectable and unresectable pancreatic tumors.

Even so, a category of borderline resectable tumors remains a topic of controversy with regard to best treatment strategy. Patients with borderline resectable tumors are at high risk for margin-positive (R1/R2) resections and may benefit from a neoadjuvant treatment strategy designed to achieve objective tumor regression and subsequent complete resection. Pre-operative radiographic criteria for determining resectability have been accepted as a means of identifying patients who might benefit from neoadjuvant therapy.[10] The rationale offered for a neoadjuvant treatment strategy in patients with borderline respectable or unresectable disease is (a) the so-called “biologic test” to gauge the aggressiveness of the tumor, (b) treatment of micrometastatic disease, (c) administration of chemotherapy in the neoadjuvant setting may be better tolerated than postoperative therapy and (d) the potential for tumor destruction to maximize the potential for a complete (R0) resection. This determined approach to patients with advanced disease may yield improved survival due to an effective neoadjuvant strategy and the application of well-defined pre-operative resection criteria.

Morganti and colleagues performed a review of thirteen studies evaluating patients undergoing surgery following neoadjuvant chemoradiotherapy for unresectable pancreatic cancer.[47] The resection rates in these studies ranged from 8.3% to 64.2%, while the median survival ranged from 9 to 23 months. The rate of surgical exploration following neoadjuvant therapy ranged from 25% to 67%, and included patients without a radiographic response to treatment. Comparatively, the rate of re-exploration in the largest series of regional chemotherapy by Aigner et al. was 28% (74/265).[28] The rate of resection was 36% (27/74) for those undergoing re-exploration, and 10% (27/265) for the entire cohort. Without resectability clearly defined prior to regional chemotherapy, it is unclear if patients that ultimately underwent re-exploration and resection were more likely to have had borderline resectable versus unresectable tumors on pre-treatment imaging. While this potentially confounds the interpretation of rates of conversion to resectable status, these results reinforce the concept that regional chemotherapy, similar to neoadjuvant chemoradiotherapy, may provide benefit to a subset of patients currently not offered tumor resection.

Progressive surgical techniques combined with current neoadjuvant chemoradiotherapy strategies have already yielded emerging support for a multimodality approach to treatment. The treatment algorithm advocated by Katz et al. has resulted in the highest reported 5-year survival rates likely due to tumor response to neoadjuvant therapy and improved patient selection afforded by precise pre-operative selection criteria.[48] Furthermore, the belief that vascular invasion is a harbinger of poorer survival has been countered with mounting evidence that en bloc vascular resection for locally advanced pancreatic cancer matches outcomes for standard pancreaticoduodenectomy. In a study by Yekebas and colleagues, patients undergoing pancreatectomy with en bloc vascular resection compared to pancreatectomy without vascular resection had equivalent perioperative mortality and median overall survival.[49] This convergence of data supporting multimodality adjuvant therapy and progressive surgical technique highlights the attributes of patient selection, standard operative approach and routine use of multimodality therapy. Thus, the addition of radiation therapy to regional chemotherapy has the potential to improve further tumor response and resectability conversion rates and warrants consideration.

This review is encumbered by additional factors such as the heterogeneity of reports, inconsistent use of standard chemotherapeutic agents (i.e. gemcitabine), ill-defined inclusion and exclusion criteria, and non-standardized chemotherapy administration techniques. The inclusion of data for patients receiving regional chemotherapy after pancreatic resection, although representing less than one quarter of all patients in this review, potentially confounds the interpretation of results by introducing a subset of patients for whom the trials were not necessarily meant to address. Future studies should address separately neoadjuvant and adjuvant regional chemotherapy, as these represent two distinct strategies. Similarly, the inclusion of patients with stage IV pancreatic cancer deserves special consideration. Although the future application of this treatment strategy will likely be directed to patients with unresectable disease due solely to advanced T stage, the data related to toxicity, survival and tumor response gathered from patients with metastases has worth. Therefore these patients were not considered for exclusion from this review because of the value they provide to developing future investigation of regional chemotherapy.

Conclusion

The unacceptably high death rate due to pancreatic cancer is attributed to aggressive tumor biology, late stage diagnosis and relatively in-effective systemic therapy. Without the ability to affect tumor biology, the current approach to improving patient survival is through timely diagnosis and discovery of meaningful targeted therapy. Until then, complete tumor resection offers patients the only chance at long-term survival. Regional chemotherapy may provide patients currently without the option of resection that chance. Within the past two decades patients have been treated safely with regional chemotherapy in the setting of advanced, unresectable pancreatic cancer. In the modern era, novel treatment strategies for pancreatic cancer should be pursued in the setting of prospective clinical trials. Therefore, further investigation of regional chemotherapy is warranted with the goals of minimizing toxicity through the use of relevant agents and increasing treatment efficacy as measured by tumor response and increased rates of tumor resection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Trials of Regional Chemotherapy for Pancreatic Cancer: Patient Demographics, Technical Approach, and Chemotherapy

Author (Year)	Country	Patients	Mean Age[1]	Gender (M:F)	Procedure[□]	Chemotherapeutic agents
Fiorentini (1996)	Italy	20	NR	16:4	HAP	MMC
Muchmore (1996)	USA	12	56	3:9	CAI	MMC, 5-FU, Folinic acid
Link (1997)	Gemany	32	60	19:13	CAI	CDDP, Mitoxantrone, 5-FU, Folinic acid
Lorenz (1998)	Germany	17	61*	12:5	HAP	MMC
Maurer (1998)	Switzerland	12	59.9	9:3	CAI	CDDP, Mitoxantrone, 5-FU, Folinic acid
Klapdor (1999)	Germany	28	NR	17:11	CAI	Gemcitabine, MMC
Homma (2000)	Japan	31	61.5	18:13	SAI	CDDP, 5-FU, Folinic acid
Bayar (2003)	Turkey	14	55*	8:6	CAI	CDDP, MMC, 5-FU, Folinic acid
Ohigashi (2003)	Japan	32	60	20:12	SAI	Angiotensin-II, Methotrexate
van Ijken (2004)	Netherlands	21	59	12:9	CAI[2] / HAP	Melphalan, MMC
Aigner (2005)	Germany	265	NR	NR	CAI / HAP	CDDP, Mitoxantrone, MMC, degradable startch microspheres
Takamori (2005)	Japan	24	62.6*	16:8	CAI[3]	Gemcitabine, 5-FU, Folinic acid
Barletta (2006)	Italy	32	62*	22:10	SAI[4]	Carboplatin, Epirubicin, 5-FU, Folinic acid
Mambrini (2006)	Italy	211	61*	130:81	CAI	Carboplatin, Epirubicin, 5-FU, Folinic acid
Meyer (2006)	Germany	17	54.5	11:6	HAP	MMC
Guadagni (2007)	Italy	22	66*	12:10	HAP	CDDP, MMC
Ikeda (2007)	Japan	33	60	22:11	SAI[5]	Gemcitabine, 5-FU, Folinic acid
Ishikawa (2007)	Japan	20	63.7*	9:11	CAI	Angiotensin-II, CDDP, Gemcitabine, 5-FU, Folinic acid
Milandri (2007)	Italy	19	62*	12:7	SAI[4]	Carboplatin, Epirubicin, 5-FU, Folinic acid
Nakchbandi (2008)	Germany	17	65.7	11:6	CAI	Gemcitabine, MMC, Warfarin
Sasada (2008)	Japan	16	61.2	10:6	SAI[5]	CDDP, 5-FU, Folinic acid

□HAP, hypoxic abdominal perfusion; CAI, celiac axis infusion; SAI, selective arterial infusion; MMC, mitomycin C; 5-FU, 5-fluorouracil; CDDP, cis-platinum;

[1]NR, not reported;

*Studies reporting median age.

[2]CAI performed in 9 of 21 patients that underwent HAP.

[3] CAI performed after selective peri-pancreatic artery embolization.

[4] Patients with liver metastases received half of chemotherapy dose via hepatic artery.

[5] SAI preceded by selective arterial embolization.

Table 2

Clinicopathologic Details

		Histology			Stage				
Author	**Patients**	**Adenocarcinoma**	**Other**	**Unknown[1]**	**Stage I/II**	**Stage III**	**Stage IV**	**Unknown[1]**	**Staging System**
Fiorentini	20	20	-	-	-	12	8	-	NR
Muchmore	12	11	1	-	-	-	-	12	NR
Link	32	28	4	-	-	17	15	-	UICC
Lorenz	17	17	-	-	2	10	5	-	UICC
Maurer	12	12	-	-	-	6	6	-	UICC
Klapdor	28	-	-	28	-	-	20	8	NR
Homma	31	31	-	-	-	-	31	-	UICC
Bayar	14	-	-	14	-	5	9	-	NR
Ohigashi	32	-	-	32	-	32	-	-	UICC
van Ijken	21	-	-	21	-	15	6	-	NR
Aigner	265	-	-	265	-	112	153	-	UICC
Takamori	24	-	-	24	-	3	21	-	NR
Barletta	32	32	-	-	-	7	25	-	NR
Mambrini	211	203	8	-	-	99	112	-	UICC
Meyer	17	-	-	17	-	7	10	-	NR
Guadagni	22	20	2	-	-	14	8	-	NR
Ikeda	33	19	-	14	-	-	33	-	NR
Ishikawa	20	-	-	20	-	-	20	-	NR
Milandri	19	17	2	-	-	10	9	-	NR
Nakchbandi	17	17	-	-	2	2	13	-	UICC
Sasada	16	9	-	7	-	12	4	-	JPS[3]/TNM

[1]Unreported or not confirmed prior to therapy; not discernible from manuscript

[2]UICC, International Union Against Cancer

[3]Japan Pancreas Society; TNM, *t*umor, *n*ode, *m*etastasis.

NR, not reported.

Table 3

Response Rate and Survival

Author	Response Criteria	Response Rate[1] (%)	1-yr Survival (%)	Median Survival (months)
Fiorentini	NR	50	NR	NR
Muchmore	WHO*	46	NR	NR
Link	WHO	19	NR	12 (Stage III) 4 (Stage IV)
Lorenz	WHO	0	NR	4.2
Maurer	WHO	8	NR	6
Klapdor	WHO	46	NR	9
Homma	WHO	58	67	NR
Bayar	WHO*	36	NR	8
Ohigashi	WHO*	6	56	13
van Ijken	WHO	5^	NR	6
Aigner	NR	NR	NR	9
Takamori	WHO	21	51	14
Barletta	WHO*	22	50	6.1
Mambrini	SWOG	8	NR	9.2
Meyer	NR	18	6	4.1
Guadagni	WHO*	18	9	6
Ikeda	WHO*	24	NR	13
Ishikawa	WHO	25	45	12
Milandri	WHO	25^	16	6
Nakchbandi	NR	NR	6	6.8
Sasada	RECIST	58^	83	22

[1] Response rate reflects partial and complete responses; mixed or minor responses not included

* WHO criteria as described in methods, however WHO criteria reference not cited.

^ response rate based on fraction of total number of patients treated

WHO, World Health Organization; SWOG, Southwest Ongology Group; RECIST, Response Evaluation Criteria In Solid Tumors.