Chinese-German Journal of Clinical Oncology April 2007, Vol. 6, No. 2, P162–P169
DOI 10.1007/s10330-007-0046-z

Pancreatic cancer – Neoadjuvant therapy

R. Krempien, M. W. Munter, W. Harms, J. Debus

Department of Radiation Oncology, University of Heidelberg, INF 400, 69120 Heidelberg, Germany

Received: 14 February 2007 / Revised: 28 February 2007 / Accepted: 6 March 2007

Abstract In spite of the high mortality in pancreatic cancer, significant progress is being made. This review discusses multimodality therapy for patients with pancreatic cancer. Surgical therapy currently offers the only potential monomodal cure for pancreatic adenocarcinoma. However only 10%–20% of patients present with tumors that are amenable to resection, and even after resection of localized cancers, long term survival is rare. The addition of chemoradiation therapy significantly increases median survival. To achieve long-term success in treating this disease it is therefore increasingly important to identify effective neoadjuvant/adjuvant multimodality therapies. Preoperative chemoradiation for potentially resectable pancreatic cancer has the following advantages: (1) neoadjuvant treatment would eliminate the delay of adjuvant treatment due to postoperative complications; (2) neoadjuvant treatment could avoid unnecessary surgery for patients with metastatic disease evident on restaging after neoadjuvant therapy; (3) downstaging after neoadjuvant therapy may increase the likelihood for negative surgical margins; and (4) neoadjuvant treatment could prevent peritoneal tumor cell implantation and dissemination caused during surgery. This review systematically summarizes the current status, controversies, and prospects of neoadjuvant treatment of pancreatic cancer.

Key words pancreatic cancer; neoadjuvant therapy; advantage

Pancreatic cancer is the fourth commonest cause of death from cancer in men and women [1, 2]. Surgical therapy currently offers the only potential monomodal cure for pancreatic adenocarcinoma [3]. However only a few patients present with tumors that are amenable to resection, end even after resection of localized cancers, long term survival is rare. At presentation, only 10%–20% of patients with pancreatic adenocarcinoma have potentially resectable cancers, 40% have locally advanced unresectable tumors, and 40% have metastatic disease. Adenocarcinoma of the pancreas has a 5-year survival rate of only 4% [2]. In spite of the progress in surgical treatment, resulting in increased resection rates and a decrease in treatment-related morbidity and mortality, resection has failed to improve long-term survival [3]. By histological evaluation less than 15% of the patients undergoing R0 resection have a pN0 status, more than 50% suffer from lymphangiosis carcinomatosa, and more than 50% suffer from extrapancreatic nerve plexus infiltration [4, 5].

Pretreatment staging

Optimally, the initial goals in the evaluation and treatment of patients with suspected pancreatic cancer are to determine resectability, obtain a histologic diagnosis, safely establish biliary decompression, and to develop a stage specific treatment strategy. The most important initial step is to accurately classify patients into resectable (stages I and II), unresectable (stage III), and metastatic (stage IV) groups based on radiographic imaging. Changes in the most recent American Joint Committee on Cancer staging system for pancreatic adenocarcinoma reflect a clinical definition of resectability based on computed tomographic assessment. The T-stage designation classifies T1–T3 tumors as potentially resectable and T4 tumors as locally advanced (unresectable). Tumors with any involvement of the superior mesenteric artery (SMA) or the celiac artery are classified as T4. However tumors that involve the superior mesenteric, splenic, or portal veins are classified as T3 because these veins can be resected and reconstructed, providing that they are patent. Therefore, three criteria are necessary for resectability: (1) localized disease, (2) lack of involvement of the celiac axis or superior mesenteric artery, and (3) patency of the superior mesenteric/portal venous confluence.

In clinical practice today, imprecise pre-operative assessment of the feasibility of complete gross tumor resection commonly leads to futile surgery as vessel involving tumor is discovered intraoperativly. This often leads to incomplete gross removal of tumor, and eventual tumor-related death. The variation in the quality of preoperative assessment and surgery (frequency of complete gross resection) from center to center created considerable heterogeneity among patients accrued to clinical trials, and makes the interpretation of the value of either adjuvant

Correspondence to: R. Krempien.
Email: robert_krempien@med.uni-heidelberg.de

systemic therapy or chemoradiation exceedingly difficult. Clinical trials cannot accurately evaluate the value of adjuvant therapy if significant numbers of patients with incurable gross residual disease are included.

Achievements of surgery

Although surgery offers a low cure rate, it is also the only chance for cure. Regarding long-term survival after R0 resection, only 3%–16% of the patients from selected series survived 5 years or more. Loco-regional recurrence and/or metastatic disease develop in the majority of patients who undergo pancreatic resection. Relapse occurs within 9–15 months after initial presentation and patients have median life expectancies of only 12–15 months without adjuvant therapy. The 5-year survival rate of patients with resected pancreatic adenocarcinoma is approximately 10% [3]. The statistics for the 80% to 90% of patients who present with locally advanced and metastatic pancreatic cancer are even more dismal. Rarely do such patients achieve a complete response to treatment; median survival is 5–10 months and 5-year survival is near zero [6].

The cardinal rule in improving the prognosis in patients with pancreatic cancer proved to be complete tumor removal in patients undergoing oncological resection [3, 4]. In most recent published prospective trials, R0 resection results in an increase of survival in comparison to patients with a residual tumor [7, 8]. However, R0 resection fails to improve long-term survival [4]. More than 95% of the patients undergoing surgical resection are in an advanced stage of cancer. Potentially curative resection is hampered by a failure to include remote cancer cell-positive tissues in the operative specimen, i.e. N2 lymph nodes, nerve plexus, and perivascular tissue [9, 10]. Cancer recurrence after resection with curative intent is the consequence of cancer cell-positive tissues left behind. However, comparison of the survival times after standard and extended resection of pancreatic cancers indicated that no significant long-term survival benefit resulted from extended R0 resection [11, 12].

Dissemination pattern of pancreatic cancer

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 lymph nodes previously seen as microscopically free of cancer showed micrometastasis by RT-PCR even in UICC stage I or II cancers [5, 13]. Nerve plexus invasion outside of the pancreas has been observed in 43%–72% of patients [14, 15]. Further, careful histopathological evaluation of cancer dissemination have demonstrated that even in stage I and II cancers, lymph vessels surrounding the pancreas are cancer cell infiltrated in most of the cases [5, 14]. In bone marrow specimens micrometastasis was found in 36% to 63% of the patients investigated [5]. Among patients in cancer stage UICC I and II undergoing surgery, 46% had positive immunostaining for cancer cells in the bone marrow [16]. 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 [17].

This knowledge about cancer cell dissemination early in the course of pancreatic cancer, including early stage cancers explains why true R0 resection in pancreatic cancer is difficult to achieve, and explains the observed frequency of recurrence in more than 95% of patients undergoing surgical resection with curative intent.

Combined modality treatment

Chemoradiation has been shown to reduce the probability of local tumor recurrence in patients with gastrointestinal malignancies who have undergone potentially curative surgery [18–21]. Locoregional control rates of 90% or grater are achieved in virtually every tumor site where combined modality approaches are the standard (head and neck cancer, breast cancer, sarcoma, rectal cancer). Improved local tumor control with the use of postoperative chemoradiation has also been shown to improve overall survival in many gastrointestinal tumor sites, including pancreatic cancer [18–20]. Chemoradiation accomplishes this by eradicating microscopic residual disease in the tumor bed after complete resection or through the reduction in regional lymph node recurrence. Indeed, patients with microscopically close or positive margins to seem benefit the most. Chemoradiation may be overtreatment for tumors with wide negative margins and conversely, may be futile in those with gross residual disease. In the case of pancreatic cancer, the retroperitoneal margin is nearly always close and often positive. Therefore, it is reasonable to conclude that locoregional therapy in pancreatic cancer can be optimized with complete resection and treatment of microscopic disease at the retroperitoneal margin with chemoradiation.

Both distant and local/regional patterns of recurrence are common, and this suggests that most patients have occult metastatic or local/regional disease (or both) at the time of resection. According to several phase II or III trials combined modality treatment approaches using chemotherapy or chemoradiation in addition to surgery improvement in locoregional control and survival can be achieved.

The data from randomized trials in pancreatic cancer [7, 8, 20, 22] are exceedingly difficult to interpret due to many factors such as inadequate dose and schedule of radiotherapy and chemotherapy, lack of protocol compliance, inadequate statistical power, and particularly lack

of surgical quality control. The most revealing indicator of the latter is the high local tumor recurrence rates in the reported randomized trials evaluation postoperative chemoradiation [7, 8, 20]. Preenrolment computed tomography to exclude obvious residual disease was not required on these studies. Local tumor recurrence (or more likely) persistence was identified as a component of the first site of failure in 39% of patients enrolled on the GITSG trial [20], 53% of the patients enrolled on the EORTC trial [7], and 62% of the patients enrolled on the ESPAC-I trial [8]. Given the universally recognized propensity for early and frequent distant disease recurrence in pancreatic cancer patients, first-site local recurrence rates this high can only mean that significant numbers of patients with incomplete gross resection – incurable tumors – were enrolled in these trials. Including large numbers of incurable patients makes clinical trials designed to assess the benefit of an adjuvant treatment in potentially curable patients a futile endeavor. In order to properly address the value of adjuvant therapy in potentially resectable pancreatic cancer in the future preoperative imaging with well defined resectability criteria and surgical quality control must be introduced into clinical trial design.

Postoperative chemoradiation therapy (CRT) has been shown to improve survival in patients with resected pancreatic adenocarcinoma [7, 20, 23], although there is debate over whether radiotherapy is a beneficial component [8]. The problems with the postoperative adjuvant approach include the fact that at least 25% of patients do not actually receive adjuvant therapy because of complications of surgery or patient refusal [7, 24]. A primary advantage of preoperative therapy is therefore the assurance that CRT is received by all patients with resected disease in a timely fashion. Other benefits are the delivery of radiation to well-oxygenated tissues and the avoidance of radiation to fixed loops of intestine within the operative field. Another rationale for neoadjuvant treatment is that occult metastatic disease is given the opportunity to manifest, thus allowing patients to avoid the morbidity of resection or laparotomy. Finally, the potential for preoperative CRT to convert locally advanced lesions to resectable lesions could greatly increase the number of patients with pancreatic cancer who might be offered a chance of cure [25].

To achieve long-term success in treating this disease it is therefore increasingly important to identify effective neoadjuvant/adjuvant multimodality therapies.

General oncologic advantages of preoperative chemoradiation in pancreatic cancer

The theoretical advantages of preoperative chemoradiation compared to postoperative chemoradiation for pancreatic cancer include increased efficacy and reduced toxicity related to (i) more effective chemotherapy delivery with an intact blood supply, (ii) the avoidance of hypoxia-related chemoradiation resistance and the avoidance of late radiation-related toxicity. (1) neoadjuvant treatment would eliminate the delay of adjuvant treatment from postoperative recovery; (2) neoadjuvant treatment could spare unnecessary surgery for patients with metastatic disease evident on restaging after neoadjuvant therapy; (3) downstaging after neoadjuvant therapy may increase the likelihood for negative surgical margins; and (4) neoadjuvant treatment could prevent peritoneal tumor cell implantation and dissemination during surgery.

Clinical trials in neoadjuvant treatment for pancreatic cancer

The goal of neoadjuvant treatment is downstaging, and in combination with an oncological resection, increasing the chances of survival [26]. Since R0 resection is a prerequisite for cure, the aim of any multimodal treatment should be to improve the R0 resection rate. A protocol for neoadjuvant, multimodal treatment of pancreatic cancer is not yet established. Results from uncontrolled prospective mono-institutional series applying chemoradiation to patients with pancreatic cancer II and III (UICC) resulted in downstaging in 15%–30% of the patients and a resection rate of the downstaged patients between 50% and 83%. The median survival of these patients ranged between 15–32 months (Table 1 [24, 27–40]).

In a case control study Ishikawa *et al* [28] found that neoadjuvant chemoradiation led in 17 out of 23 patients to downstaging of pancreatic cancers and to the possibility of oncologic resection. Evans *et al* [27] and Hoffman *et al* [41] have pioneered preoperative chemoradiation for pancreatic cancer. In the initial preoperative trial, reported by Evans, 28 patients with cytologic or histologic proof of localized adenocarcinoma of the pancreatic head received preoperative radiation (50.4 Gy) and concurrent continuos infusion (CI) 5-FU 300 /m^2/day. Patients were restaged 4 to 5 weeks after completion of chemoradiation. 5 patients were found to have metastasis, and 23 patients without evidence of disease progression underwent laparotomy. At laparotomy, three patients were found to have metastasis, three patients had unresectable locally advanced disease, and 17 patients underwent pancreaticoduodenectomy. This study showed that tumor resection could be performed with a low incidence of complications after chemoradiation in patients with pancreatic cancer.

In a pilot study by Hoffman *et al* [41], patients received preoperative CI 5-FU (1000 mg/m^2/day on days 2 through 5 and 29 through 32), mitomycin-C (10 mg/m^2/day on day 2), and radiation (50.4 Gy). For patients with curative resection, the median survival (from the time of tissue diagnosis) was 45 months, with a median disease-free survival of 27 months. Based on these encouraging results, the

Table 1

	Year	*n*	Neoadjuvant therapy	Resection rate	Median survival all patients (months)	Median survival resected patients (months)
Evans *et al* [27]	1992	28	EBRT + 5-FU (± IORT)	17/28 (61%)	N. R.	N. R.
Ishikawa *et al* [28]	1994	23	EBRT	17/23 (74%)	N. R.	N. R.
Coia *et al* [29]	1994	27	EBRT + 5-FU/MMC	13/27 (48%)	19% (3-yr SR)	43% (3-yr SR)
Staley *et al* [30]	1996	39	EBRT + IORT + 5-FU	39/39 (100%)	19	k. A.
Spitz *et al* [24]	1997	91	EBRT + 5-FU (± IORT)	41/91 (45%)	19	19.2
Hoffmann *et al* [31]	1998	53	EBRT + 5-FU/Mit	24/53 (45%)	9.7	15.7
White *et al* [32]	2001	111	EBRT + 5-FU/MMC/Cis	39/111 (35%)	N. R.	N. R.
Wanebo *et al* [33]	2000	14	EBRT + 5-FU/Cis	9/14 (64%)	9	19
Snady *et al* [34]	2000	68	EBRT + 5-FU/Cis/Strep	20/68 (29%)	23.6	32.3
Mehta *et al* [35]	2001	15	EBRT + 5-FU	9/15 (60%)	N. R.	30
Wilkowski *et al* [36]	2003	33	EBRT + Cis/Gem	11/33 (48%)	10	11.7
Magnin *et al* [37]	2003	32	EBRT + 5-FU/Cis	19/32 (59%)	37.2% (2-yr SR)	59.3% (2-yr SR)
Aristu *et al* [38]	2003	47	EBRT + CHT	9 (19%)	10	23
Calvo *et al* [39]	2004	15	EBRT + Tegafur	9 (60%)	17	23
Joensuu *et al* [40]	2004	34	EBRT + Gem	21 (60%)	N. R.	25

SR: survival rate; MMC: Mitomycin-C; Cis: Cisplatin; Strep: Streptozotocin

ECOG conducted a trial testing this regime [31]. Of 53 patients, 12 did not proceed to surgery because of intercurrent illness, toxicity, local progression, distant metastasis, or death. 17 patients underwent surgical exploration but could not be resected because of unresectable locally advanced disease or distant metastasis. 24 patients showed downstaging and underwent resection with a median survival of 15.7 months compared with 9.7 months for the entire group.

So far two studies showed exceptional median survival rates of 31 and 32 months, respectively. Snady *et al* [34] reported a median survival of 32 months in 20 patients (29%) who had resection from an original group of 68 patients treated neoadjuvant with concurrent split course radiation therapy and 5-FU, streptozotocin and cisplatin. The median survival of the whole group was 23.6 months, and 32 months in the resected patients. During the same period another group of 91 patients underwent resection, of whom 63 received adjuvant chemotherapy or chemoradiation. The median survival in patients who had oncological resection and adjuvant treatment was 16 months, compared with 11 months in those that did not have adjuvant treatment after resection. The median survival of the neoadjuvant treated group was significantly better than in the initially operated group (32 months versus 14 months, $P = 0.006$). Mehta *et al* [35] have recently reported a median survival of 30 months with neoadjuvant treatment but only in 9 patients.

Pisters *et al* [42] evaluated preoperative rapid-fractionation chemoradiation in a phase II trial of 35 patients. The preoperative chemoradiation consisted of a 2 weeks course of 5-FU (300 mg/m^2/day, 5 days per week) and concurrent radiotherapy (30 Gy over two weeks, 3 Gy/fraction). Following resection patients received intraoperative radiation therapy (10 to 15 Gy). Median survival for patients was 25 months, and 3-year actuarial overall survival rate was 23%.

Recently, initial results of preoperative gemcitabine based chemoradiation for resectable pancreatic cancer were reported [43]. 86 patients received seven weekly infusions of gemcitabine 400 mg/m^2 on concurrent radiation therapy (30 Gy over 2 weeks with 3 Gy/fraction). Patients underwent restaging 4 to 6 weeks after the last dose of gemcitabine. Of the 83 patients, 12 (14%) did not underwent surgery. Of the 71 patients undergoing laparotomy, 10 (12%) were found to have metastatic disease. Thus 61 patients (73%) underwent complete resection. Another trial [40] using gemcitabine applied 50.4 Gy in 28 fraction neoadjuvant with concomitant twice-weekly gemcitabine (50 mg/m^2) in locally advanced potentially resectable pancreatic cancers. Of the total of 34 patients 21 underwent surgery. In the group of resected patients the estimated median survival was 25 months. Calvo *et al* [39] evaluated neoadjuvant chemoradiation (total dose of 45 to 50.4 Gy with daily fractions of 1.8 Gy) with tegafur in potentially resectable pancreatic cancers. Tegafur dose was 1200 mg/d along the external beam radiation therapy (EBRT) period. Of the 15 enrolled patients a total of 9 patients underwent surgery. Median survival of the resected patients was 23 months (completely resected patients 28 months) compared to 8 months in the unresected patients.

Impact of neoadjuvant treatment for potentially resectable pancreatic cancer

Preoperative chemoradiation for potentially resectable pancreatic cancer has the following advantages: (1) neoadjuvant treatment would eliminate the delay

of adjuvant treatment from postoperative recovery; (2) neoadjuvant treatment could spare unnecessary surgery for patients with metastatic disease evident on restaging after neoadjuvant therapy; (3) downstaging after neoadjuvant therapy may increase the likelihood for negative surgical margins; and (4) neoadjuvant treatment could prevent peritoneal tumor cell implantation and dissemination during surgery. In recent controlled clinical trials comparing historical and prospective control groups, the frequency of downstaging was observed to be between 13% and 45%. Neoadjuvant chemoradiation resulted in a decrease in the frequency of cancer-positive margins. Oncological resection after neoadjuvant chemoradiation resulted in a median survival between 15 and 32 months. During neoadjuvant therapy, disease progression occurs in 15% to 25% of the patients with the appearance of liver metastases and/or peritoneal carcinosis. These patients are spared unnecessary operation. After neoadjuvant treatment no increase of postoperative complications has been reported. Unfortunately, many reports of neoadjuvant therapy for pancreatic cancer have included heterogeneous patient populations, enrolling patients with resectable, marginally resectable and locally advanced pancreatic cancer (Table 1 [29, 31–33, 35, 36, 40]). This confounds reports of resection rates and complicates comparison with other studies. Therein lays the importance of using accurate, reproducible anatomic definitions for resectability.

Impact of neoadjuvant treatment for locally advanced pancreatic cancer

Because surgical resection of the primary tumor remains the only potentially curative treatment for pancreatic cancer, preoperative chemoradiation has been investigated in locally advanced pancreatic cancer to downstage locoregional disease to facilitate surgical resection and to improve the rate of complete (R0) resections. Locally advanced pancreatic cancer describes pancreatic cancer without evidence of distant metastasis but unresectable situation because of tumor encasement of major vessel structures such as celiac and superior mesenteric arteries or adherence to the portal vein. Downstaging in this group of locally advanced pancreatic cancer leads to a separation between tumor and vessel wall and to an increase of resection rates between 29% and 80% and a survival benefit after oncological resection (Table 1).

In evaluating the results of multimodality approaches in locally advanced pancreatic cancer, it is useful to remember that a median survival of 3 to 6 months has been reported for this subset of patients undergoing palliative gastric or biliary bypass only [44].

Despite the potential benefits for patients with locally advanced pancreatic cancer receiving chemoradiation, those gains are modest. Rarely do such patients achieve a complete response to treatment. In case no downstaging with secondary resectability can be achieved, median survival is around 10 months and 5-year survival is near zero [6]. Despite this, significant palliative benefit can be achieved by chemoradiation. Complete pain relief can be obtained in as much as 50%–80% of patients as well as some improvement in wasting, obstructive symptoms, performance status and anorexic symptoms [45].

Although local control rates have been improved by radiation therapy, systemic failure remains a major obstacle in improving the long-term survivorship. Because of the high rates of distant metastasis and poor overall survival results, the value of secondary resection after conversion of unresectable disease to resectable disease is questioned in the treatment of this subgroup. As this issues are so far not addressed in larger published studies the question remains controversial. Regarding the available smaller phase I and II studies (Table 1) secondary resectability results in median survival between 15% and 32% compared to 9% to 20% for all patients. As these are only small, mostly, non randomized, single institution studies they may be subject to selection bias. Following neoadjuvant therapy the patient undergoes restaging (usually several months after the initial diagnosis) and patients who have developed interval metastases are excluded. Further interpretation of these data is difficult because of different criteria for resectability. The reported resection rates vary between 45% to 100% in patients with tumors initially deemed resectable and from 29% to 80% in those with unresectable disease (Table 1), indicating that primary resectability has been defined different. A specialist pancreatic cancer surgery team can often resect what is considered by another team to be unresectable locally advanced disease. For example the John Hopkins group was able to carry out resection on 52 of 78 patients (67%) operated upon elsewhere and thought to have irresectable disease [46]. For future trials, it will be important to identify locally advanced patients as a unique subset requiring careful diagnostic work-up and definition of common resectability criteria.

Radiation therapy dose escalation

Several trials could show that dose escalation in radiation therapy using either EBRT [23] or IORT [47, 48] resulted in improved local control in combination with potentially curative resection. The efficacy of EBRT in pancreatic cancer is limited by the inability to deliver adequate doses of irradiation secondary to the dose tolerance limits of small bowel, spinal cord, stomach, kidney, and liver. Further, the use of combined modality approaches in pancreatic cancer is associated with increased gastrointestinal toxicity. Technical developments like intensity-modulated radiation therapy (IMRT) have the potential to significantly improve radiation therapy of pancreatic cancers by reducing normal tissue dose, and simultane-

ously allow escalation of dose to further enhance locoregional control [49].

Future directions in neoadjuvant therapy

Currently perhaps the most poorly defined parameter in the treatment of pancreatic cancer is patient selection for therapy. Whereas in other cancers assessment of aberrations in gene expression that correspond with therapeutic response and outcome are being adopted routinely to increase predictive power (e.g. HER-2/neu in breast cancer), there are only preliminary data of molecular markers of clinical utility in pancreatic cancer. A bewildering number of biomarkers are currently under evaluation [50, 51]. For most part, the evidence regarding their application as prognostic indicators is conflicting.

Current choice of therapy is based on histopathological assessment of the tumor. Recent advances in molecular biology have provided a detailed understanding of molecular events in pancreatic carcinogenesis and may offer new approaches to the treatment of pancreatic cancer [52]. The development, progression, and metastasis of pancreatic cancer are determined by accumulation of multiple genetic and epigenetic changes, including inactivation of tumor-suppressor genes and overexpression of proto-oncogenes [53].

Within the last years, chemoradiation has evolved as the standard treatment for locally advanced pancreatic carcinoma. The rationale for concurrent administration of chemotherapy is to improve locoregional control by sensitizing the tumor for radiotherapy (radiosensitization), and to treat potential distant micrometastases. Recently, new biological treatment options have emerged that target specific pathways of either tumor cells or normal cells within the tumors [25, 54].

New therapeutic strategies exploit a critical function or genetic abnormality of cancers. These strategies are directed at key proteins or genes responsible for various aspects of cell proliferation, differentiation and function, as well as angiogenesis and invasion [53–55]. For example there are various tyrosine kinase-dependent pathways of great interest in the treatment of pancreatic cancer. The epidermal growth factor receptor (EGFR) is involved in such carcinogenic cellular processes as invasion, metastasis, angiogenesis, and radiation resistance [55, 56]. In a recently completed phase II trial the monoclonal EGFR antibody cetuximab in combination with gemcitabine for patients with advanced pancreatic cancer showed considerably better results than that achieved using gemcitabine alone as documented in a previous phase III trial [57, 58]. Recently a phase three study could demonstrate the benefit of the combination of an EGFR tyrosine kinase inhibitor in combination with chemotherapy in pancreatic cancer [59]. A total of 569 patients with advanced pancreatic cancer were randomized to receive standard dose gemcitabine, 1000 mg/m^2 iv weekly in 7 out of 8 weeks, then weekly 3 out of four weeks plus either erlotinib 100 mg daily (n = 285) or placebo (n = 284). Combined erlotinib therapy with gemcitabine resulted in a 24% improvement in survival as compared to placebo (P= 0.025) with corresponding 1-year survival rate of 24% and 17% (erlotinib and placebo arm, respectively). A current study addresses the effect of a triple therapy using intensity modulated radiation therapy with concurrent gemcitabine based chemotherapy and EGFR blockade using cetuximab in locally advanced pancreatic adenocarcinoma [60]. Preliminary results showed that this combination is feasible and safe. Preliminary efficacy data of 20 pts revealed tumor regression (according to CT-imaging) of > 50% after 6 months in 40% of pts and a resectability rate of 25% [61]. Also vascular endothelial growth factor (VEGF) receptor inhibitors or plateled-derived growth factor (PDGF) receptor inhibitors are currently being tested in combination with other cytotoxic drugs in pancreatic cancers [52, 53].

Treatment related primary and acquired chemo- radioresistance presents a significant hindrance for all current therapy regimes in pancreatic cancer patients [27, 28]. Multiple factors such as genetic instability of tumors and high inter- and intratumoral heterogeneity contributes to the hardly predictable therapy resistance [26]. To understand patterns of therapy response genome expression profiling and detection of genetic polymorphisms enables to identify key mechanisms in systems biology.

Conclusion

Pancreatic cancer remains one of the most formidable challenges in oncology. The length and quality of life will be maximized by accurate preoperative staging, assessment of resectability, and the use of protocol-based multimodality treatments. Surgical therapy currently offers the only potential monomodal cure for pancreatic adenocarcinoma. However only a few patients present with tumors that are amenable to resection, end even after resection of localized cancers, long term survival is rare. Therefore surgery should always be performed as part of a multimodality approach involving neoadjuvant and/or adjuvant treatment. Continued efforts to enroll patients into well designed clinical trials should remain a high priority for oncologists across all disciplines. For future trials, it will be important to identify patients with primary irresectable, locally advanced pancreatic cancer as a unique subset requiring careful diagnostic work-up and definition of common resectability criteria.

Currently perhaps the most poorly defined parameter in the treatment of pancreatic cancer is patient selection for therapy. The objectives of future studies are to correlate and potentially predict therapy response using tumor genomic fingerprints. Significant improvements in long-term survival will likely be achieved through exploita-

tion of the basic biologic anomalies of this malignancy. Recently, new biological treatment options have emerged that target specific pathways of either tumor cells or normal cells within the tumors. These strategies are directed at key proteins or genes responsible for various aspects of cell proliferation, differentiation and function, as well as angiogenesis and invasion.

References

1. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. Eur J Cancer, 2001, 37 (Suppl 8): S4–S66.
2. Jemal A, Murray T, Ward E, *et al*. Cancer statistics, 2005. CA Cancer J Clin, 2005, 55: 10–30.
3. Wagner M, Redaelli C, Lietz M, *et al*. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg, 2004, 91: 586–594.
4. Stocken DD, Buchler MW, Dervenis C, *et al*. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. Br J Cancer, 2005, 92: 1372–1381.
5. Beger HG, Rau B, Gansauge F, *et al*. Treatment of pancreatic cancer: challenge of the facts. World J Surg, 2003, 27: 1075–1084.
6. Tsai JY, Iannitti DA, Safran H. Combined modality therapy for pancreatic cancer. Semin Oncol, 2003, 30 (Suppl 9): 71–79.
7. Klinkenbijl JH, Jeekel J, Sahmoud T, *et al*. 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: 776–782.
8. Neoptolemos JP, Stocken DD, Friess H, *et al*. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med, 2004, 350: 1200–1210.
9. Beger HG, Poch B, Schwarz M, *et al*. Pancreatic cancer: the relative importance of neoadjuvant therapy. Chirurg, 2003, 74: 202–207.
10. Smeenk HG, Tran TC, Erdmann J, *et al*. Survival after surgical management of pancreatic adenocarcinoma: does curative and radical surgery truly exist? Langenbecks Arch Surg, 2005, 390: 94–103.
11. Pedrazzoli S, DiCarlo V, Dionigi R, *et al*. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg, 1998, 228: 508–517.
12. Yeo CJ, Cameron JL, Lillemoe KD, *et al*. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg, 2002, 236: 355–366.
13. Demeure MJ, Doffek KM, Komorowski RA, *et al*. Adenocarcinoma of the pancreas: detection of occult metastases in regional lymph nodes by a polymerase chain reaction-based assay. Cancer, 1998, 83: 1328–1334.
14. Hermanek P. Pathology and biology of pancreatic ductal adenocarcinoma. Langenbecks Arch Surg, 1998, 383: 116–120.
15. 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: 2485–2491.
16. Juhl H, Kalthoff H, Kruger U, *et al*. Immunocytologic detection of disseminated tumor cells in the peritoneal cavity and bone marrow in patients with pancreatic carcinoma. Chirurg, 1994, 65: 1111–1115.
17. Inoue S, Tezel E, Nakao A. Molecular diagnosis of pancreatic cancer. Hepatogastroenterology, 2001, 48: 933–938.
18. Macdonald JS, Smalley SR, Benedetti J, *et al*. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med, 2001, 345: 725–730.
19. Krook JE, Moertel CG, Gunderson LL, *et al*. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med, 1991, 324: 709–715.
20. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Cancer, 1987, 59: 2006–2010.
21. Kapiteijn E, Marijnen CA, Nagtegaal ID, *et al*. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med, 2001, 345: 638–646.
22. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Ann Surg, 2003, 237: 74–85.
23. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg, 1985, 120: 899–903.
24. Spitz FR, Abbruzzese JL, Lee JE, *et al*. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. J Clin Oncol, 1997, 15: 928–937.
25. Fogelman DR, Chen J, Chabot JA, *et al*. The evolution of adjuvant and neoadjuvant chemotherapy and radiation for advanced pancreatic cancer: from 5-fluorouracil to GTX. Surg Oncol Clin N Am, 2004, 13: 711–735.
26. Chandler NM, Canete JJ, Stuart KE, *et al*. Preoperative chemoradiation in resectable pancreatic cancer. J Hepatobilary Pancreat Surg, 2003, 10: 61–66.
27. Evans DB, Rich TA, Byrd DR, *et al*. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. Arch Surg, 1992, 127: 1335–1339.
28. Ishikawa O, Ohigashi H, Imaoka S, *et al*. Is the long-term survival rate improved by preoperative irradiation prior to Whipple's procedure for adenocarcinoma of the pancreatic head? Arch Surg, 1994, 129: 1075–1080.
29. Coia L, Hoffman J, Scher R, *et al*. Preoperative chemoradiation for adenocarcinoma of the pancreas and duodenum. Int J Radiat Oncol Biol Phys, 1994, 30: 161–167.
30. Staley CA, Lee JE, Cleary KR, *et al*. Preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for adenocarcinoma of the pancreatic head. Am J Surg, 1996, 171: 118–124.
31. Hoffman JP, Lipsitz S, Pisansky T, *et al*. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an Eastern Cooperative Oncology Group Study. J Clin Oncol, 1998, 16: 317–323.
32. White RR, Hurwitz HI, Morse MA, *et al*. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. Ann Surg Oncol, 2001, 8: 758–765.
33. Wanebo HJ, Glicksman AS, Vezeridis MP, *et al*. Preoperative chemotherapy, radiotherapy, and surgical resection of locally advanced pancreatic cancer. Arch Surg, 2000, 135: 81–87.
34. Snady H, Bruckner H, Cooperman A, *et al*. Survival advantage of combined chemoradiotherapy compared with resection as the initial treatment of patients with regional pancreatic carcinoma. An outcomes trial. Cancer, 2000, 89: 314–327.
35. Mehta VK, Fisher G, Ford JA, *et al*. Preoperative chemoradiation for

marginally resectable adenocarcinoma of the pancreas. J Gastrointest Surg, 2001, 5: 27–35.
36. Wilkowski R, Thoma M, Heinemann V, *et al*. Radiochemotherapy with gemcitabine and cisplatin in pancreatic cancer – feasible and effective. Strahlenther Onkol (German), 2003, 179: 78–86.
37. Magnin V, Moutardier V, Giovannini MH, *et al*. Neoadjuvant preoperative chemoradiation in patients with pancreatic cancer. Int J Radiat Oncol Biol Phys, 2003, 55: 1300–1304.
38. Aristu J, Canon R, Pardo F, *et al*. Surgical resection after preoperative chemoradiotherapy benefits selected patients with unresectable pancreatic cancer. Am J Clin Oncol, 2003, 26: 30–36.
39. Calvo FA, Matute R, Garcia-Sabrido JL, *et al*. Neoadjuvant chemoradiation with tegafur in cancer of the pancreas: initial analysis of clinical tolerance and outcome. Am J Clin Oncol, 2004, 27: 343–349.
40. Joensuu TK, Kiviluoto T, Karkkainen P, *et al*. Phase I–II trial of twice-weekly gemcitabine and concomitant irradiation in patients undergoing pancreaticoduodenectomy with extended lymphadenectomy for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys, 2004, 60: 444–452.
41. Hoffman JP, Weese JL, Solin LJ, *et al*. A pilot study of preoperative chemoradiation for patients with localized adenocarcinoma of the pancreas. Am J Surg, 1995, 169: 71–77.
42. Pisters PW, Abbruzzese JL, Janjan NA, *et al*. Rapid-fractionation preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for resectable pancreatic adenocarcinoma. J Clin Oncol, 1998, 16: 3843–3850.
43. Wolff RA, Evans DB, Gravel DM, *et al*. Phase I trial of gemcitabine combined with radiation for the treatment of locally advanced pancreatic adenocarcinoma. Clin Cancer Res, 2001, 7: 2246–2253.
44. Gunderson LL, Haddock MG, Burch P, *et al*. Future role of radiotherapy as a component of treatment in biliopancreatic cancers. Ann Oncol, 1999, 10 (Suppl 4): 291–295.
45. Willett CG, Czito BG, Bendell JC, *et al*. Locally advanced pancreatic cancer. J Clin Oncol, 2005, 23: 4538–4544.
46. Sohn TA, Lillemoe KD, Cameron JL, *et al*. Reexploration for periampullary carcinoma: resectability, perioperative results, pathology, and long-term outcome. Ann Surg, 1999, 229: 393–400.
47. Crane CH, Beddar AS, Evans DB. The role of intraoperative radiotherapy in pancreatic cancer. Surg Oncol Clin N Am, 2003, 12: 965–977.
48. Kinsella TJ, Sindelar WF. Intraoperative radiotherapy for pancreatic carcinoma. Experimental and clinical studies. Cancer, 1996, 78: 598–604.
49. Landry JC, Yang GY, Ting JY, *et al*. Treatment of pancreatic cancer tumors with intensity-modulated radiation therapy (IMRT) using the volume at risk approach (VARA): employing dose-volume histogram (DVH) and normal tissue complication probability (NTCP) to evaluate small bowel toxicity. Med Dosim, 2002, 27: 121–129.
50. Garcea G, Neal CP, Pattenden CJ, *et al*. Molecular prognostic markers in pancreatic cancer: a systematic review. Eur J Cancer, 2005, 41: 2213–2236.
51. Segara D, Biankin AV, Kench JG, *et al*. Expression of HOXB2, a retinoic acid signaling target in pancreatic cancer and pancreatic intraepithelial neoplasia. Clin Cancer Res, 2005, 11: 3587–3596.
52. Awada A, Mano M, Hendlisz A, *et al*. New anticancer agents and therapeutic strategies in development for solid cancers: a clinical perspective. Expert Rev Anticancer Ther, 2004, 4: 53–60.
53. Xiong HQ. Molecular targeting therapy for pancreatic cancer. Cancer Chemother Pharmacol, 2004, 54 (Suppl 1): S69–S77.
54. Willett CG, Clark JW. Update on combined-modality treatment options for pancreatic cancer. Oncology (Williston Park), 2003, 17 (12 Suppl 13): 29–36.
55. Lawrence TS. Radiation sensitizers and targeted therapies. Oncology (Williston Park), 2003, 17 (12 Suppl 13): 23–28.
56. Baumann M, Krause M. Targeting the epidermal growth factor receptor in radiotherapy: radiobiological mechanisms, preclinical and clinical results. Radiother Oncol, 2004, 72: 257–266.
57. Xiong HQ, Abbruzzese JL. Epidermal growth factor receptor-targeted therapy for pancreatic cancer. Semin Oncol, 2002, 29 (5 Suppl 14): 31–37.
58. Xiong HQ, Rosenberg A, LoBuglio A, *et al*. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II trial. J Clin Oncol, 2004, 22: 2610–2616.
59. Moore MJ, Goldstein D, Hamm J, *et al*. Erlotinib plus gemcitabine compared to gemcitabine alone in patients with advanced pancreatic cancer. A phase III trial of the National Cancer Institute of Canada Clinical Trials Group [NCIC-CTG]. ASCO Meeting Abstracts, 2005, 23: 1.
60. Krempien R, Muenter MW, Huber PE, *et al*. Randomized phase II – study evaluating EGFR targeting therapy with cetuximab in combination with radiotherapy and chemotherapy for patients with locally advanced pancreatic cancer – PARC: study protocol [ISRCTN56652283]. BMC Cancer, 2005, 5: 131.
61. Krempien R, Munter MW, Huber PE, *et al*. Phase II – study evaluating trimodal therapy with Cetuximab, intensity modulated radiotherapy (IMRT) and gemcitabine for patients with locally advanced pancreatic cancer [ISRCTN56652283]. ASCO 2006, Abstract 4100.