Colin D. Johnson
Clement W. Imrie
*Editors*

# Pancreatic Disease

## Protocol and Clinical Research

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# Introduction

**Clem Imrie and Colin Johnson**

This book stems from an unusual meeting held in The Royal College of Physicians and Surgeons of Glasgow in March 2007.

Enthusiastic doctors in the diagnosis and treatment of pancreatic diseases were arranged in small groups to discuss specific unsolved/partially clinical problems and suggest the way forward. In some instances, the recommendations were initial improved longitudinal studies, while in others better double-blind randomized studies. The recommendations were then presented on the second day before the total 40 plus participants who added their input. Finally, the mechanics of initiating the proposals were arranged.

The editors are most thankful to the authors from the meeting, who have assembled the various contributions to this stimulating volume.

# Part I
# Potential Trials in Acute Pancreatitis

# Chapter 1
# Acute Pancreatitis in Intensive Care

**John Kinsella, Barry Clements, Euan Dickson, Thierry Dugernier, and Martin Hughes**

## 1.1 Introduction

Severe acute pancreatitis is associated with the development of the systemic inflammatory response syndrome (SIRS).

Hypoxemia is a hallmark of acute pancreatitis and respiratory failure is the most common single organ failure in this disease. In the most severely ill patients multi-organ dysfunction syndrome (MODS) and multi-organ failure (MOF) occur. Intensive care with multiple organ support is necessary.

In this review, we have considered the key issues relevant to acute pancreatitis in the intensive care unit (ICU). We have identified areas that may merit further research, specifically in patients with severe acute pancreatitis, who are receiving intensive care or have a high risk of developing multi-organ failure.

## 1.2 Nutrition

Patients with acute pancreatitis have a prolonged illness, with increased metabolic and nutritional demands. Traditionally, nutrition was provided parenterally because of the perceived potential hazard of stimulating pancreatic secretion, which might increase the severity of pancreatitis. In addition, enteral nutrition had a relatively high failure rate compared with parenteral nutrition; pancreatitis is also associated with gastrointestinal failure, and patients are prone to gastrointestinal bleeding and bacterial translocation, as well as nutritional depletion.

Many of these problems are not unique to pancreatitis. Enteral nutrition in the critically ill is now the preferred method of meeting the nutritional requirements, as well as providing protection against gastrointestinal bleeding and bacterial

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translocation. Furthermore, feeding is an issue for patients with pancreatitis even if they do not require intensive therapy.

Several trials have now been published examining the routine use of enteral feeding in pancreatitis (Kalfarentzos et al. 1997, 1998; Olah et al. 2002; Windsor et al 1998). The majority of the studies used postpyloric feeding, avoiding pancreatic stimulation and bypassing the problems of gastric stasis and gastric outlet obstruction. Further work has suggested that nasogastric feeding is possible, and that feeding success rates and mortality are similar to those in jejeunal feeding (Eatock et al. 2005). These trials have demonstrated that enteral feeding is cheaper than total parenteral nutrition (TPN), has fewer infective complications, and does not change mortality.

There is now, therefore, a broad consensus that supports the routine use of enteral feeding in pancreatitis, wherever possible.

It has been demonstrated that tight glucose control in ICU reduces mortality, but this was not confirmed in further studies (Van den Berghe et al. 2001). Patients with acute pancreatitis are very susceptible to poor glucose homeostasis, and TPN exacerbates this problem. It is possible that the parenteral feeding groups in the above trials were relatively disadvantaged by unrecognized or at least untreated hyperglycemia, and that the current regimens of glucose control in ICU would improve the outcome from parenteral nutrition. Although it is unlikely that a study could be carried out to compare tight glucose control to poor glucose control in acute pancreatitis, it should be possible to employ tight glucose control in future studies comparing different methods of nutritional support.

There appears to be little scope for a study comparing routes of administration of nutrition in pancreatitis patients in ICU. Although there is some interest in whether tight glucose control would have led to improved outcome in the patients with TPN, this study would be difficult to perform, and not likely to be productive.

## 1.3 Sepsis

Severe acute pancreatitis is associated with the features that define the systemic inflammatory response, i.e., abnormal white cell count, abnormal temperature, tachycardia, and respiratory failure. Subsequent development of infection, which may be in the necrotic pancreas or in other areas such as the respiratory tract, is associated with a worsening clinical picture, increased complications, and worse outcomes. Prognosis progressively deteriorates with sepsis, severe sepsis, and septic shock.

Measures to identify the development of infection have been thoroughly investigated in pancreatitis. When there is a strong clinical and radiological suspicion of infection, computed tomography (CT)-guided drainage and the culture of the collections can be used to diagnose and treat the peripancreatic infection. An alternative approach is repeated fine needle aspiration, even in the absence of systemic sepsis to make an early diagnosis of the developing infection. The early use of antibiotics or antifungals either as prophylaxis or early treatment has been investigated

in several studies (Eggimann et al. 2006). Meta-analysis of these studies provides support for the hypothesis that prophylaxis reduces mortality but the studies are all small and a single large trial has not yet confirmed this (Villatoro et al. 2006). As most patients with pancreatitis do not require multiorgan support, at least in the initial stages, future studies that define the value of antibiotics are likely to be performed in patients who are not in intensive care.

## 1.4 Clinical Trials of Specific Interventions in Critical Care

In the last 5 years several interventions, which can be applied to a large portion of the patients with multiorgan failure, have been shown to be of benefit. These measures can be applied to patients with pancreatitis but as yet have not been evaluated specifically in patients with pancreatitis.

### *1.4.1 Ventilation*

Acute respiratory distress syndrome (ARDS), which is associated with a high mortality, is a recognized complication of acute pancreatitis. Although no specific drug treatment is known to reduce mortality, there have been significant developments in ventilatory management strategies, which have reduced mortality. The ARDSnet study demonstrated the benefits of a ventilatory strategy characterized by reduced intrathoracic pressure and relatively small tidal volume ventilation (ARDSnet 2000). The recommendations that followed from this study have been widely adopted. There is no reason to assume that a patient with pancreatitis and ARDS will not benefit from this strategy. However, some questions remain unanswered.

Respiratory failure in pancreatitis also occurs because of pleural effusions, pulmonary infections, and abdominal distension with resultant diaphragmatic splinting. An optimal ventilatory strategy for these disorders is much less clear. Even in patients with ARDS, abdominal distension may have a significant effect on pulmonary mechanics, which may invalidate application of the ventilatory pressures from the ARDSnet study. Therefore large studies of ventilatory strategy in respiratory failure related to pancreatitis are likely to be difficult to perform, and we do not consider such studies to be feasible.

### *1.4.2 Intra-abdominal Pressure*

Raised intra-abdominal pressure in pancreatitis may be associated with a poor outcome due to the effects on organ perfusion. Measurement of abdominal pressure in pancreatitis would be of great interest to clinicians. Such measurements would

allow the investigation of the relationship between intra-abdominal pressure and outcome and perhaps facilitate planning of intervention studies. We would support the collection of daily intra-abdominal pressure measurements in pancreatitis, either as part of an ongoing international audit or as part of a multicentre study

### *1.4.3 Renal Replacement Therapy*

There is considerable evidence that the dose of renal replacement therapy affects outcome in multi-organ failure. This applies to both renal dialysis and hemofiltration. The use of low-dose replacement therapy is associated with a worse outcome (Ronco et al. 2000). Although hemofiltration has some theoretical benefits this has not been shown to be superior to dialysis in outcome studies (Vinsonneau et al. 2006). Hemofiltration may be associated with superior clearance of cytokines and therefore alter the profile of the inflammatory response in pancreatitis, but this has not been studied (Wang et al. 2003).

### *1.4.4 Steroid Therapy*

Steroid replacement therapy has been shown to reduce mortality in vasopressor-dependent septic shock (Annane et al. 2002). No trials in pancreatitis have been performed. It is unclear whether there is benefit in vasopressor-dependent systemic inflammatory response syndrome (SIRS) (rather than sepsis) or whether steroid administration directly influences the inflammatory process in the pancreas. However, a trial with a relative risk reduction (RRR) of 20% on mortality would need approximately 4,000 patients and we do not consider this trial to be of sufficient importance to justify the huge resources required.

### *1.4.5 Glucose Control*

Providing tight glucose control is now known to be of value in many clinical situations including myocardial infarction and head injury. There are no studies that demonstrate its effect on pancreatitis, and although pancreatitis influences glucose control, it is not clear whether glucose control influences pancreatitis. However, tight glucose control has been shown to significantly reduce mortality in a large surgical ICU (Van den Berghe et al. 2001). The benefit of intensive insulin therapy was attributable to its effect on mortality among patients who remained in the intensive care unit for more than 5 days (20.2% with conventional treatment, as compared with 10.6% with intensive insulin therapy; $P = 0.005$). The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven

septic focus. It would seem likely that patients with pancreatitis will benefit from such a regime.

Recently, the results of a trial of tight glucose control in patients with medical (rather than surgical) conditions have cast some doubt about its value in all critically ill patients and the results of further studies are awaited. In addition, there are considerable risks in employing very tight glucose control, specifically the development of biochemical and symptomatic hypoglycemia. It is unlikely to safely use very tight control in patients, who are not in intensive care, due to the unpredictable course of the disease, difficulties in establishing feeding, and the need for very close observation. Given the difficulties involved, and the likely benefit of tight glucose control in pancreatitis, we do not recommend a further study in this area.

### *1.4.6 Other Treatments*

There is no evidence that novel therapies reduce either the severity of severe sepsis or pancreatitis. These include platelet-activating factor (PAF) antagonists, anti-tumor necrosis factor (TNF) therapies, somatostatin analogs, aprotonin, probiotics, and nitric oxide inhibition (Liu et al. 2006). Although activated protein C has been shown to reduce mortality in severe sepsis, concerns about bleeding limit its use in pancreatitis (Jamdar and Siriwardena 2005). As a further large trial is proposed in sepsis, it is unlikely that a study in pancreatitis could be realistic in the near future.

### *1.4.7 Resuscitation*

At present there is no conclusive evidence that the type of fluid used in resuscitation affects the outcome of patients with critical illness, and therefore no recommendations can be made for pancreatitis patients. There was a considerable controversy regarding the potential deleterious effects of albumin. A meta-analysis appeared to show that albumin was associated with a worse outcome. A large randomized controlled trial in 7,000 patients, which compared saline to albumin, did not support the finding of the meta-analysis (The SAFE study investigators 2004). In this study there was no effect of the type of fluid on mortality or organ failure. There is now evidence that early resuscitation does influence outcome. A prospective study of 263 patients presenting with diagnostic criteria for the systemic inflammatory response syndrome plus low blood pressure or lactic acidosis were given standard therapy or aggressive resuscitation to improve oxygen delivery (Rivers et al. 2001). Therapy was directed to increase evidence of adequate tissue oxygen delivery as measured by mixed venous oxygen tensions. The measures used to improve oxygen delivery included 6 h of fluids, blood transfusion, and inotropic therapy. Oxygen consumption was reduced where required with sedation, paralysis, and ventilation.

There was a significant reduction in in-hospital mortality from 44% to 29% with these interventions. Once multiple organ failure has developed the role of aggressive fluid therapy is less clear as a negative fluid balance was associated with an improvement in outcome in patients who had severe acute respiratory distress syndrome (ARDS) (ARDSnet 2000).

Pancreatitis has clear clinical and pathophysiological similarities to severe sepsis. Early aggressive resuscitation forms part of the routine treatment of severe pancreatitis and the severity of the physiological disturbance correlates with the clinical outcome (Garcea et al. 2006). We believe that testing the hypothesis of early goal-directed therapy in acute pancreatitis, using central venous oxygen saturation as part of the resuscitation goals, would have considerable merit. A trial with similar mortality reduction to that reported in general intensive treatment unit (ITU) patients would require approximately 300 patients. We believe this in an achievable goal in the setting of an international multicentre study.

## 1.5 Conclusion

There are several new therapies of proven efficacy in critically ill patients. Few of these have been directly tested on pancreatitis. Studies able to recruit the number of patients required to demonstrate modest benefit are unlikely to be practical. Even studies of therapies expected to show a large advantage will need international cooperation to perform multicentre investigations. We believe that the two areas of utmost importance at present are the measurement of intra-abdominal pressure and the use of goal-directed therapy in the early stages of treatment.

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# Chapter 2
# Antibiotic Prophylaxis in Acute Severe Pancreatitis: Should We Have a Further Study?

**Jens Werner, Kevin C.P. Conlon, Hjalmar C.van Santvoort, Caroline S. Verbeke, and Sakhawat H. Rahman**

The most significant change in the clinical course of acute pancreatitis over the past decades has undoubtedly been the decrease in mortality. Almost all deaths caused by acute pancreatitis are observed in patients with severe acute pancreatitis. Today, there is no doubt that pancreatic infection is the major risk factor in necrotizing pancreatitis with regard to morbidity and mortality in the later phase of the disease (Beger et al. 1986; Buchler et al. 2000; Werner et al. 2005). While pancreatic necrosis develops within the first week, superinfection of pancreatic and peripancreatic necrosis is usually observed 2–3 weeks after the onset of the disease (Beger et al. 1986; Werner et al. 2003). The frequency of infection correlates with the extent of necrosis. The profile of the organisms suggests an origin in the gastrointestinal tract. The ways in which microorganisms reach the pancreas include transperitoneal spread and the spread along the pancreatic duct ascending from the duodenum or descending from the bile duct, as well as via lymph or the bloodstream.

Attempts to decrease infection-related mortality in severe acute pancreatitis have focused on the prophylactic administration of antibiotics. Since the early 1970s, several clinical trials have evaluated whether prophylactic antibiotic administration will reduce the likelihood of pancreatic infection, development of sepsis, complications, and mortality in severe necrotizing pancreatitis. Some early trials were flawed as the majority of the patients evaluated had only mild disease, and so pancreatic infection was very unlikely to develop. Moreover, the antibiotic agent used in these first trials was ampicillin. However, it has been demonstrated that the pancreas is highly impenetrable for antibiotics, and that most antibiotics including ampicillin do not reach sufficient tissue concentrations to inhibit bacteria usually found in pancreatic infections (Buchler et al. 1992). The antibiotics with the greatest penetrance into the pancreatic tissue and with the best bactericidal properties are the carbapenems, followed by the fluoroquinolones and cephalosporins. Therefore, later clinical trials have used these antibiotic agents. In addition, several randomized controlled trials have compared the clinical efficiency of different

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antibiotics in the treatment of severe acute pancreatitis. In one of these trials from Italy, 60 patients with severe necrotizing pancreatitis were randomly allocated to receive either intravenous pefloxacin, a fluoroquinalone with good pancreatic penetration and an appropriate spectrum of antimicrobiocidal activity, or imipenem (Bassi et al. 1998). Pancreatic infections were significantly reduced in patients treated with more imipenem than in those treated with pefloxacin (10% versus 34%, $p < 0.05$), while extrapancreatic infections (20% versus 43%), the need for surgical intervention (3% versus 10%), and mortality (3% versus 5%) were also lower in the imipenem group, without reaching statistical significance. In a recent randomized trial, the effectiveness of meropenem in preventing pancreatic infectious complications was reported to be identical to that of imipenem (Manes et al. 2003). Thus, if antibiotics are to be used in the management of severe necrotizing pancreatitis, it would seem sensible to start with betalactam antibiotics.

Four randomized controlled trials evaluating the effectiveness of antibiotics in the treatment of severe acute pancreatitis were conducted between 1993 and 2000 (Pederzoli et al. 1993; Sainio et al. 1995; Delcenserie et al. 1996; Schwarz et al. 1997). Altogether 186 patients were included in these trials. The infection rate of pancreatic necrosis in these series was 21%, which is lower than the expected 40–70% in the natural course. Of those trials, Pederzoli et al. could demonstrate a significant reduction of infection (30% versus 12%, control group versus antibiotics), and the Finnish trial by Sainio et al. showed a reduction of mortality (23% versus 3%, controls versus antibiotics). However, all the trials recruited only a small number of patients; therefore, all of them were statistically underpowered. In addition, none of these early trials was placebo-controlled or double-blinded. Two meta-analyses on the basis of the data of these four trials were published in 1998 (Golub et al. 1998) and 2001 (Sharma and Howden 2001). The meta-analysis of Golub included all four trials and demonstrated a significant reduction of mortality in patients who received prophylactic antibiotics when compared with controls who did not receive them. Sharma excluded the study by Delcenserie et al., as patients with pancreatic fluid collections rather than patients with pancreatic necrosis were included in that trial. According to both meta-analyses, infection, pancreatic infection, and mortality were significantly reduced by prophylactic antibiotics in severe necrotizing pancreatitis.

In 2001, another single-center randomized study was published by Nordback et al. (Nordback et al. 2001). In this trial, imipenem was used prophylactically and the results compared with those of a control group that did not receive early antibiotics. A high percentage of the patients included had more than 30% necrosis, and it was demonstrated that the need for surgery and the overall number of major organ complications were significantly reduced by early prophylactic antibiotics. Mortality was reduced from 15% to 8%, but this was not statistically significant. Again, the trial by itself was statistically underpowered and there were some methodological drawbacks. However, this study demonstrated for the first time that patients with suspected or proven infected pancreatic necrosis benefited from antibiotic treatment and did not have to be operated on immediately. Fourteen of 33 patients in the control group developed septic symptoms, but after the initiation of

antibiotic treatment, nine improved and only five of the 14 actually needed surgery. Thus, this trial not only showed that prophylactic antibiotic treatment improves the outcome of necrotizing pancreatitis, but that antibiotics treatment even after establishment of infection is helpful and can help to postpone surgery.

In 2004, the first double-blinded, placebo-controlled clinical trial evaluating the effectiveness of prophylactic antibiotics in severe acute pancreatitis was published (Isenmann et al. 2004). This trial had the highest methodological quality of all clinical trials published on this topic so far. In this study, the prophylactic antibiotic treatment with ciprofloxacin/metronidazole did not reduce the development of infectious complications, infected pancreatic necrosis, extrapancreatic infections, or mortality. The only significant result was that patients in the placebo group needed to switch their study medication to another antibiotic more often (46% versus 28%, placebo versus antibiotic). The indications for stopping the study drug and starting an open antibiotic treatment were the new development of sepsis, multiple organ failure, pancreatic or extrapancreatic infection, or a clinically suspected pancreatic infection as indicated by an increase of C-reactive protein (CRP). Therefore, the trial demonstrated that the prophylactic administration of antibiotics significantly reduced these conditions. However, there was no significant effect with regard to the length of hospital stay, mortality, or any other secondary outcome parameters. This, however, may be secondary to the small numbers of patients in each group, and so the study was underpowered to detect differences in these secondary endpoints. In fact, the study was terminated after an interim analysis before the calculated sample size of 100 patients per group was reached. Other weaknesses of the study by Isenmann were that only a small percentage of the patients included actually had necrotizing pancreatitis, which was probably due to the inclusion criteria of predicted severity based on CRP. Moreover, many of the patients included did not develop severe pancreatitis since the mortality rate even in the placebo group was very low at 7%. Thus, the conclusion of Isenmann et al. that antibiotic prophylaxis has no beneficial effect on the course of necrotizing pancreatitis is not proven by the data.

Although the heterogeneity of the methods and patients included in the trials published so far makes it difficult to combine the results for meta-analysis, it seems that this is the only way to gather enough information to evaluate whether prophylactic antibiotics are useful or not, since all individual trials published are underpowered. Therefore, a Cochrane review was performed in 2003 and has been updated on a regular basis, at last in 2006 (Villatoro et al. 2006). The five studies included a total of 294 patients (Pederzoli et al. 1993; Sainio et al. 1995; Delcenserie et al. 1996; Schwarz et al. 1997). The analysis suggests a significant reduction of mortality with prophylactic administration of antibiotics (antibiotic prophylaxis 6% versus control 15.3%). In contrast, extrapancreatic infections, infected pancreatic necrosis, operative treatment rates, or fungal infections were not different between those patients who received antibiotic prophylaxis and who did not. However, the subgroup analysis of those trials which used a beta-lactam prophylaxis (192 patients in three trials) (Pederzoli et al. 1993; Sainio et al. 1995; Delcenserie et al. 1996; Schwarz et al. 1997) demonstrated that mortality

(6.3% versus 16.7%, $p = 0.03$) and infected pancreatic necrosis (15.6% versus 29.2%, $p = 0.02$) were decreased significantly. However, there was only a nonsignificant reduction of extrapancreatic infection rates and operative treatment rates in the betalactam groups, and no difference of the frequency of fungal infections between the groups. Subgroup analysis for quinolones did not show any effect of the treatment which might be due to the effect of the smaller number of patients included in the quinolone group or the agent itself.

Thus, published results show that intravenous antibiotic prophylaxis is associated with significantly decreased mortality in patients with pancreatic necrosis. However, most other outcome parameters are not different compared to the control groups. From the subgroup analysis, it appears that betalactam agents are superior to other antibiotic regimens including quinolones. Nevertheless, it has to be considered that there is a wide variation of methodological quality and treatment regimens between the studies, and additionally a lack of data on potential adverse effects still exists. The authors of the Cochrane review concluded that more trials to confirm the benefits of antibiotic prophylaxis were needed.

A new double-blind, placebo-controlled randomized multicenter prospective study evaluated the effectiveness of antibiotic prophylaxis with meropenem in 32 centers (Dellinger et al. 2007 May). One hundred patients were included, 41 of 50 with necrotizing pancreatitis in each group, and about 50% of the patients had more than 30% necrosis. The results of this trial demonstrate no significant difference between the placebo group and the patients who received prophylactic antibiotics with regard to mortality (placebo 18% versus antibiotics 20%), pancreatic infection (12% versus 18%), operative treatment (20% versus 26%), or extrapancreatic infection rate (48% versus 32%). Thus, antibiotic prophylaxis did not exert any benefit compared to placebo and antibiotic treatment on demand. However, although this trial has a high methodological standard, since it is placebo-controlled and double-blinded, several critical points have to be mentioned. Patients were included up to 120 h after the onset of the symptoms, and so antibiotic treatment was started late compared to other trials. In fact, pancreatic necrosis is completely developed at that time point (Beger et al. 1986). Moreover, although the study was performed in 32 centers, the calculated number of patients ($n = 240$) was not reached and the study terminated early. Another weakness of this study is the high number of patients in both arms who received nonstudy antibiotics at some time during the trial (placebo 54%, antibiotics 50%). While the number of antibiotics needed in the placebo group is in accordance with the trial by Isenmann et al. (Isenmann et al. 2004), the nonstudy antibiotics used in the treatment group seems exceptionally high. Thus, this new trial suggests that prophylactic antibiotic treatment in necrotizing pancreatitis does not have any beneficial effect. However, the power of the study to reject the benefit of early antibiotics is lacking.

Another trial published recently by Rokke et al. is a randomized controlled multicenter trial (Rokke et al. 2007). Seventy-three patients with predicted severe pancreatitis (defined as CRP > 120 mg/l within 24 h, or CRP > 200 mg/l within 48 h) were treated in seven centers in Norway between 1997 and 2002. The patients in the imipenem group experienced significantly lower rates of complications

(33% versus 59%, $p < 0.05$) and pancreatic and extrapancreatic infections (14% versus 43%). However, mortality, organ failure, and the rate of interventions, as well as the need for intensive care unit (ICU), length of hospital stay did not differ between the two groups. The onset of infection was significantly postponed in patients who received antibiotic prophylaxis. While all infections in the control group occurred within the first 2 weeks, all infections of the imipenem group were not evident before the third week of the disease. Thus, infectious complications were reduced and postponed by prophylactic administration of antibiotics. This study has some methodological weaknesses. Like the other publications on this topic, it is underpowered and the study was terminated because of slow recruitment. In addition, patients with predicted severe pancreatitis as assessed by CRP were included, but only a small proportion of the patients (23%) actually developed pancreatic necrosis of more than 30% and one third had no necrotizing disease at all.

Taken together all the results published, it is clear that prophylactic administration of antibiotics does not reduce mortality of severe necrotizing pancreatitis. While the meta-analysis of the Cochrane review which included four trials (Pederzoli et al. 1993; Sainio et al. 1995; Delcenserie et al. 1996; Schwarz et al. 1997) still demonstrated a decreased mortality in the antibiotic groups, especially in the subgroup analysis of the betalactam antibiotics, the mortality is not different between the groups when the data of the last two trials by Dellinger et al. and Rokke et al. are included in this analysis. In fact, the trial by Sainio et al. (Sainio et al. 1995) was the only trial which showed a significant reduction of mortality. Although most of the other studies demonstrated a nonsignificant tendency toward a reduced mortality in the antibiotic prophylaxis group, it is striking that the two placebo-controlled and double-blinded studies do not.

The trials by Pederzoli et al. and Rokke et al. demonstrated the reduction of infection, as does the Cochrane meta-analysis. However, the two larger placebo-controlled trials could not demonstrate this effect. This might be a consequence of the small proportion of patients with necrotizing pancreatitis (12% > 30% necrosis) in the one trial, and the late onset of the antibiotic treatment (<120 h after the onset of the disease) in the other. Moreover, the high proportion of nonstudy antibiotics administered in these two placebo-controlled trials also may have influenced the results. The study by Rokke et al. nicely demonstrates that prophylactic antibiotic treatment postpones the onset of infection. This is of special benefit for patients who need surgical intervention, since necrosis is demarcated better and necrosectomy can be performed more safely after the third week of the onset of the disease. Thus, there are contradicting results on the effectiveness of antibiotics on infectious complications.

There is a general agreement that antibiotic treatment increases the incidence of gram-positive strains. However, there is no evidence from the studies so far for an increase in multiresistant strains or fungal infections after antibiotic treatment. This is of importance since it has been shown that the infection with multiresistant organisms in acute pancreatitis is correlated with a negative outcome, including longer stays on the ICU.

In addition, the trials by Isenmann et al. and Rokke et al. demonstrate the potential economic effects of treatment on demand rather than prophylactic treatment (Dellinger et al. 2007). Both calculate a reduction of costs for antibiotics by 50% if antibiotics are used on demand. However, it has to be mentioned that overall costs need to be reflected by treatment outcomes when considering cost–benefit ratios. In fact, costs for ICU treatment, septic complications treatment, and radiological and surgical interventions easily outweigh the costs of antibiotics. Since economical aspects are more and more important in health care systems all over the world, it seems that more data on this matter need to be collected, and the analysis of costs need to be performed in greater detail as well and should not only focus on the costs of the study medication as has been done in the past (Dellinger et al. 2007). Since costs of treatment vary significantly even within Europe, different countries probably will come to different conclusions about whether antibiotic prophylaxis is justified in the treatment of necrotizing pancreatitis.

In determining whether or not a further trial of antibiotics should be undertaken largely depends on an understanding of the inadequacy of the previous studies. Conceptually, all the previous trials have been designed with a key endpoint; reduction in mortality. However, such endpoints in acute pancreatitis are unlikely to be dependent on single-factor adjustment alone, and increasingly heterogeneity in the overall management of these patients throughout the world, let alone within individual countries, does not easily lend itself, perhaps, to study a reduction in mortality as an achievable endpoint. The expert review that met in Glasgow 2007 felt that the evidence base for the management of severe acute pancreatitis is in itself lacking, and this has been highlighted by the extensive debate contained within this edition. It is therefore, unlikely that until an "ideal" protocol of management of this disease is adopted throughout the world, a new study designed to address the use antibiotics to reduce mortality can ever be achieved.

But, can we define potentially achievable endpoints? Super-infection of pancreatic necrosis is without doubt associated with a significantly increased risk of mortality (Beger et al. 1986; Buchler et al. 2000; Werner et al. 2005), and a number of trials of antibiotics have suggested reduced infective complications. Furthermore, operative intervention is often based on clinically proven infected necrosis. It was felt by the expert review that it may therefore be feasible to investigate whether antibiotic prophylaxis reduces super-infection of pancreatic necrosis, and whether antibiotics could delay surgery in cases of proven infected necrosis.

Previous studies have based power calculations on historical data, in which the rate of infected pancreatic necrosis was 50%. However, it is clear that the rate of infection is determined by the extent of necrosis (Werner et al. 2003), with the crude rate of infection for 30–50% necrosis being about 10–20%, and this rises to almost 70% when more than 50% necrosis is present. It is evident from the literature review that in the majority of studies, almost a third of the patients had no necrosis, and at most, less than a quarter had greater than 30% pancreatic necrosis.

Power calculations, therefore, should be based on an infection rate of 20%, in order to take into account that the majority of the patients will have less than 50%

pancreatic necrosis. This would mean 200 patients with proven >30% pancreatic necrosis in each arm of a RCT. Even if mortality was to be considered as an endpoint, current data suggests that overall mortality has reduced from 40% to almost 20%, and prior studies have seriously underestimated sample-size calculations. In order to achieve 80% power ($\alpha < 0.05$), 1,525 patients with proven pancreatic necrosis are required in each arm, which is clearly difficult or nearly impossible to achieve given the heterogeneity in patient management.

In previous studies, the fall-out rate ranges from 30–50% of patients who do not have extensive necrosis. It is currently not possible to predict disease severity with 100% accuracy, let alone pancreatic necrosis. A review of prognostic markers is beyond the scope of this chapter and is dealt with elsewhere; however, it is clear that in the absence of a good prognostic marker, a 50% dropout rate should be expected, not only for the prediction of severe disease but also pancreatic necrosis. All patients likely to develop pancreatic necrosis would have done so by day 5, and this should be considered an important landmark for randomization and/or exclusion of those patients already included. It was therefore suggested by the expert panel, given the current selection criteria, that over 3,000 patients are required in each arm of an RCT if patients are recruited with an early cut-off day.

One of the other major drawbacks highlighted in the review was not only the choice of antibiotic, but also the variance in treatment onset, duration of treatment, and also the number of changes made to the regime. A study examining antibiotic *prophylaxis* using a betalactam is yet to be achieved and would be most *desirable*, given that the mean time to administration of study drug was 3–3.3 days from the onset of the symptoms in Dellingers' study (Dellinger et al. 2007). The expert review felt that the current evidence suggests that altered gut permeability may give rise to bacterial translocation, and that this happens early in the course of the disease, and that all prior studies have failed to take this into account. Without, further clinical evidence, this notion remains a hypothesis.

In line with the outcomes of the Cochrane review, duration of treatment has not been standardized and little attention has been paid to the indications for altering antibiotic regimes (Villatoro et al. 2006). The expert review concluded that a standard course of 10–14 days should be considered in any future trial, and the regime should only be altered on the basis of microbial evidence. Similarly, patients randomized to the nontreatment arm should be given best medical care; this includes the use of appropriate antibiotics in the presence of culture-proven infection.

And finally, how is the endpoint defined? – in this case infected pancreatic necrosis. It was felt that serial fine needle aspiration (FNA) of pancreatic necrosis was inappropriate unless clinically indicated, and in any future study, well-defined criteria should be adopted. Unfortunately, the radiological expertise may not be available in many centers and the only evidence may follow surgical debridement. The expert panel felt that the indications for surgical intervention and indeed the type of surgery must be clearly defined in future protocols, and the role of percutaneous radiological drainage of peripancreatic collections needs to be standardized. Secondary endpoints must include the potential economic benefit, and address the concern of emerging resistant multiorganisms. The former is particularly

pertinent given that the costs for antibiotics in the placebo group were 50% of the antibiotics prophylaxis group in the Rokke and Isenmann trials. If antibiotic prophylaxis is beneficial, this expense may be outweighed by the benefits of the decreased need for ICU care or surgical interventions; however, these data are currently not available.

In conclusion, the meeting of the expert panel expressed a number of concerns about any future trials of antibiotics in acute pancreatitis. Although future studies may be desirable to answer the unanswered questions, whether or not any large multinational drug company is likely to fund any future work remains uncertain, especially given the failure of benefit demonstrated by Dellingers' study. The heterogeneity in management of acute pancreatitis makes recruitment of an adequately powered study impossible, and efforts for at least the foreseeable future should be directed at achieving the "ideal" protocol of care. The current evidence suggests a lack of benefit of antibiotic prophylaxis, albeit limited by underpowered studies. Prophylactic antibiotics and their usage on demand is likely to continue despite this current evidence base, largely dictated by past experience and economic pressures within individual health care systems.

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# Chapter 3
# Designing an Optimal Study for the Management of Infected Pancreatic Necrosis

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## 3.1 Introduction

One of the greatest challenges facing those treating pancreatic disease is the optimum treatment of infected pancreatic necrosis (IPN). IPN may consist of either infected necrotic pancreatic tissue and/or infected peripancreatic fat necrosis. Despite many improvements in management, the treatment algorithm for IPN remains for the most part defined by "expert opinion" rather than based on data from randomized controlled trials (Nieuwenhuijs et al. 2003; Werner et al. 2005). In the past decade, the most important developments in the management of IPN have arguably been minimally invasive (peri-) pancreatic necrosectomy (MIPN) and the trend toward delayed intervention. The drive toward the use of less invasive techniques has been fueled by the high morbidity and mortality rates (up to 25%) (Besselink et al. 2006a) associated with necrosectomy by laparotomy (Windsor 2007). The timing of surgical intervention has been addressed frequently in recent

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years. Early proponents of delayed intervention reasoned that operative intervention should be avoided during the initial 1–2 weeks, the "systemic inflammatory response syndrome (SIRS)-phase," but recently, it has been suggested that intervention in IPN should be delayed even further to allow for encapsulation of the infected necrosis. This latter approach greatly facilitates the use of minimally invasive techniques (Forsmark and Baillie 2007). In order to design adequate future prospective studies we performed a systematic literature review and critical appraisal of the available evidence on the use of MIPN and delayed intervention in IPN.

## 3.2 Methods

We used the results of a previously published MEDLINE database search that focused on the timing of intervention in IPN (Besselink et al. 2007a). To qualify for inclusion, studies had to originate from a single center (the most recent publication of each center being selected) and had to present data regarding the timing of surgical intervention. In order to minimize the effects of selection bias, a series describing a surgical technique incorporating laparotomy had to present data on at least 25 patients. For MIPN and transgastric necrosectomy studies, only series with more than five patients were included. Here, a lower cut-off was used as it was anticipated that fewer studies had been published on the latter subject. Only papers written in English were included.

From the included studies, data on study design, patient numbers, annual patient volume, preoperative organ failure, infection of pancreatic necrosis, timing of first intervention, and mortality were collected. Preoperative organ failure was considered the most relevant preoperative characteristic. When data on preoperative organ failure were lacking, data on preoperative intensive care unit (ICU) stay were disregarded because mere admission to the ICU may not reflect the presence of organ failure; sometimes patients may be admitted to ICU only for monitoring purposes.

### *3.2.1 Statistical Analysis*

Categorical data were compared using Fisher's exact test. Comparison of continuous variables with skewed distribution was performed using the Mann–Whitney-U test. Correlations between continuous outcomes were explored by linear regression. A two-tailed $P < 0.05$ was considered statistically significant.

## 3.3 Results

### *3.3.1 Surgical Strategies*

No randomized controlled trials that compared surgical treatment strategies for IPN were identified. A total of 18 studies were included; 11 studies described the results of laparotomy (Table 3.1), six studies on minimally invasive retroperitoneal

**Table 3.1** Laparotomy for infected pancreatic necrosis

| First author | Year | Design | *N* | Pts per year | Preoperative organ failure (%)* | Infection (%) | Timing (days) | Mortality (%) |
|---|---|---|---|---|---|---|---|---|
| Mier et al. 1997 | 1997 | RCT-arm | 25 | 8.3 | – | 60 | 2 | 56 |
| Fernandez-del Castillo et al. 1998 | 1998 | Retro | 64 | 9.1 | 31 | 56 | 31 | 6 |
| Branum et al. 1998 | 1998 | Retro | 50 | 8.3 | – | 84 | 27 | 12 |
| Farkas et al. 1998 | 1998 | Retro | 203 | 11.3 | – | 100 | 20 | 15 |
| Buchler et al. 2000 | 2000 | Pro | 28 | 5.6 | 90–95 | 96 | 22 | 21 |
| Ashley et al. 2001 | 2001 | Retro | 36 | 7.2 | – | 92 | 27 | 11 |
| Beattie et al. 2002 | 2002 | Retro | 54 | 6.8 | – | 68 | 26 | 43 |
| Gotzinger et al. 2003 | 2003 | Pro | 250 | 15.6 | – | 74 | 15 | 39 |
| Connor et al. 2005 | 2005 | Pro | 41 | 6.8 | – | 76 | 36 | 39 |
| Rau et al. 2005 | 2005 | Retro/pro | 285 | 15 | 60–70 | 49 | 13 | 25 |
| Besselink et al. 2007a | 2007 | Retro | 53 | 5.3 | 57 | 83 | 28 | 36 |
| Average | | | 99 | 9.0 | 60–63 | 76 | 22 | 28 |

*Organ failure for the entire hospital admission were not accepted since organ failure may have occurred after the initial surgical intervention.

Only series published in the previous decade that present data on timing for the entire group, with at least 25 patients from a single center are depicted.

necrosectomy (Table 3.2), and two studies on endoscopic transgastric necrosectomy (Table 3.3). One study (Connor et al. 2005) presented data on >25 patients treated by laparotomy and >5 patients with minimally invasive retroperitoneal necrosectomy: these data are presented separately in Tables 3.1 and 3.2. One randomized trial studied timing of intervention (Mier et al. 1997); only the "early" arm of the trial comprised of more than 25 patients and was included.

The mean mortality rate in 11 studies describing the results of necrosectomy by laparotomy was greater than in six studies on minimally invasive retroperitoneal necrosectomy (mean 28% versus 11%, $P = 0.062$) but the difference was not statistically significant. The studies on minimally invasive retroperitoneal necrosectomy had a greater percentage of infected pancreatic necrosis (mean 97% versus 67%, $P = 0.007$). However, it has to be stressed that the studies on minimally invasive

**Table 3.2** Minimally invasive pancreatic necrosectomy

| First author | Year | Design | *N* | Pts per year | Preoperative organ failure (%)* | Infection (%) | Timing (days) | Mortality (%) |
|---|---|---|---|---|---|---|---|---|
| Carter et al. 2000 | 2000 | Retro | 14 | – | – | 100 | 40 | 14 |
| Horvath et al. 2001 | 2001 | Retro | 6 | 1.5 | – | 100 | 41 | 0 |
| Risse et al. 2004 | 2004 | Retro | 6 | 3.0 | – | 100 | 48 | 0 |
| Castellanos (Mckay et al. 2007) | 2005 | Pro | 11 | – | – | 100 | 13 | 27 |
| Connor et al. 2005 | 2005 | Pro | 47 | 7.4 | – | 89 | 28 | 19 |
| Van Santvoort et al. 2007a | 2007 | Retro | 15 | 3.0 | 80 | 93 | 49 | 7 |
| Average | | | 17 | 3.7 | – | 97 | 37 | 11 |

Only series published in the previous decade that present data on timing for the entire group, with at least five patients from a single center are depicted.
* Organ failure for the entire hospital admission were not accepted since organ failure may have occured after the initial surgical intervention.

**Table 3.3** Endoscopic transgastric necrosectomy

| First author | Year | Design | *N* | Pts per year | Preoperative organ failure (%)* | Infection (%) | Timing (days) | Mortality (%) |
|---|---|---|---|---|---|---|---|---|
| Seewald et al. 2005 | 2005 | Retro | 13 | 1.8 | – | x | x | 0 |
| Charnley et al. 2006 | 2006 | Retro/pro | 13 | 5.4 | – | 85 | 24 | 18 |
| Average | | | 24 | 3.6 | – | 85 | 24 | 9 |

Only series published in the previous decade that present data on timing for the entire group, with at least five patients from a single center are depicted.

retroperitoneal necrosectomy are smaller than the studies on necrosectomy by laparotomy (mean 17 versus 99 patients per study, $P = 0.002$) and that surgical intervention was performed generally 15 days later than in the laparotomy studies (mean 37 versus 22 days after admission, $P = 0.037$). Furthermore, in the minimally invasive retroperitoneal necrosectomy and transgastric necrosectomy groups, only one of the eight studies explicitly reported on preoperative organ failure (Van Santvoort et al. 2007a). Hence, it is not possible to truly compare the study populations as selection bias and confounding will have played a substantial role.

Only two studies that reported on transgastric necrosectomy in IPN were identified. Although results are favorable with 0% and 18% mortality, larger prospective series are needed.

### 3.3.2 Timing of Intervention

Five studies were identified that presented data on timing of intervention in IPN (Table 3.4). These studies provided some evidence for the delay before surgical intervention. In 1997, the landmark randomized trial by Mier et al. demonstrated that intervention after 12 days is superior to intervention less than 72 h from the onset of symptoms (Mier et al. 1997). In 2002, a retrospective study demonstrated similar results with lower mortality for surgical intervention >72 h (as compared to <72 h) (Hartwig et al. 2002). A large prospective study on 250 patients, published in 2003, demonstrated that intervention >3 weeks (as compared to <3 weeks) was associated with a lower mortality (Gotzinger et al. 2003). In 2006, this finding was confirmed by a Dutch study showing a lower mortality for intervention >29 days (as compared to intervention between day 14–29) (Besselink et al. 2007a). The concept of reduced mortality in patients undergoing delayed intervention was documented in 1998, by Fernandez-del Castillo et al. who demonstrated a mortality for intervention >6 weeks of only 3.7%. This reduction in mortality was not statistically

**Table 3.4** Studies on delayed intervention for infected necrotizing pancreatitis

| First author | Year | Design | *N* | Summary | *P* |
|---|---|---|---|---|---|
| Mier et al. 1997 | 1997 | RCT | 36 | Timing >12 days versus <72 h<br>Mortality 27% versus 56% | NS, OR 3.4 |
| Fernandez-del Castillo et al. 1998 | 1998 | Retro | 64 | Timing > 6 weeks versus < 6 weeks<br>Mortality 3.7% versus 8.1% | NS |
| Hartwig et al. 2002 | 2002 | Retro | 62 | Timing >72 h versus <72 h<br>Mortality 22% versus 53% | 0.02 |
| Gotzinger et al. 2003 | 2003 | Pro | 250 | Timing > 3 weeks versus < 3 weeks<br>Mortality 25% versus 46% | 0.002 |
| Besselink et al. 2007a | 2007 | Retro | 53 | Timing < 14 versus 15–29 versus > 29 days<br>Mortality 75% versus 45% versus 8% | 0.0001. Similar results after stratification for preoperative organ failure |
| | | Syst. review | 1136 | Eleven studies were reviewed: the later the intervention, the better the outcome | 0.050, R =−0.603, 95% CI −2.10 to −0.02 |

significant, which may be due to their impressive low mortality of 8.1% for intervention <6 weeks (Fernandez-del Castillo et al. 1998).

A review of the studies listed in Table 3.1 showed that the more surgery is postponed, the lower the mortality tends to be ($R = -0.603$, $P = 0.050$, 95% CI −2.10 to −0.02) (Figure 3.1) (Besselink et al. 2007a). Except for the study by Mier et al., the studies had no randomized design and therefore confounding by selection most probably plays a role, because of the phenomenon that the sickest patients do not survive long enough to undergo delayed intervention or that early operation may have been performed on patients with more severe disease. Of the data from the 11 studies on laparotomy presented in Table 3.1, no correlation between preoperative organ failure and timing of intervention ($P = 0.502$) could be extracted and more data on the relation between preoperative organ failure and outcome are needed.

## 3.4 Discussion

The main developments in the management of IPN in the last decade have been the increase in use of MIPN and the further postponing of surgical intervention. Our review highlights a need for well-designed randomized controlled trials. To date, there are no randomized trials that compared MIPN with open necrosectomy. In the operative treatment of IPN, there has only been one randomized study which compared intervention <3 days with delayed intervention (>12 days) (Mier et al.

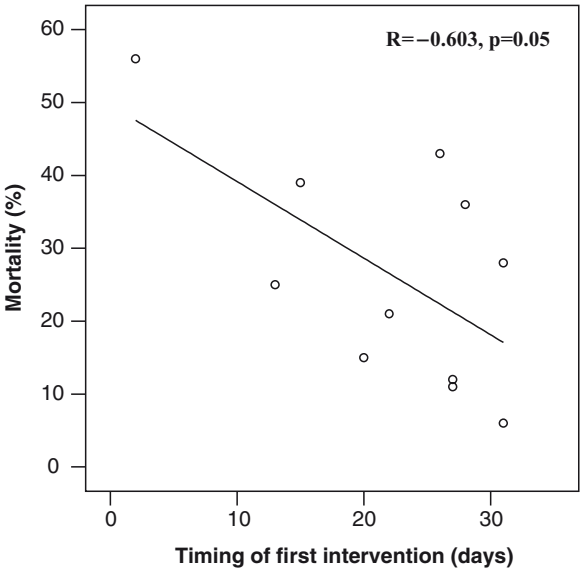


**Fig. 3.1** Correlation for timing of laparotomy and mortality (With permission of the American Medical Association, reprinted from Besselink, Arch Surg 2007)

1997). But, the definition of "delayed intervention" has changed considerably since 1997, with intervention after 12–14 days considered "early" by most pancreatologists today.

Reports of larger series of patients undergoing MIPN are now becoming available. Recently, McKay et al. presented 106 patients treated with "percutaneous pancreatic necrosectomy" (PPN). Both the Glasgow (Carter et al. 2000; and Liverpool (Connor et al. 2005) units report that MIPN may be used with consistent results. Furthermore, Horvath et al. performed a multicenter prospective single-arm trial on videoscopic-assisted retroperitoneal debridement (VARD) in 40 patients with IPN in the USA and Canada (VARD trial 2005). Recently, a relatively large randomized multicenter study on the use of MIPN in patients with IPN was completed, in the Netherlands. In 2006, the Dutch Acute Pancreatitis Study Group reported on the start of the *pa*ncreatitis *n*ecrosectomy versus s*te*p-up app*r*oach (PANTER) trial which compares a minimally invasive "step-up approach" with primary maximal necrosectomy by laparotomy (Besselink et al. 2006b). The "step-up" approach consists of percutaneous drainage, if necessary followed by VARD (Van Santvoort et al. 2007b). Eighty-eight patients with documented or suspected IPN will be randomized in 19 centers in a 3-year period, results became available in 2009. Data on the use of endoscopic transgastric necrosectomy are still scarce (Seewald et al. 2005; Charnley et al. 2006), and larger prospective series are needed.

Although it is likely that necrosectomy performed in the first 12–14 days following an attack of acute pancreatitis is associated with higher mortality, the optimal timing of surgical intervention in IPN remains unclear. Although evidence is accumulating to suggest that postponing intervention for at least 4 weeks after an attack of acute pancreatitis is associated with improved outcome, there are no randomized studies comparing intervention in the third or fourth week after the onset of symptoms (day 15–28) with intervention after day 28. Such a randomized trial would be very interesting as arguments exist both in favor and against delaying intervention once infection is proven or suspected (Connor et al. 2006). In addition, better data are needed to see whether the varying outcome for severe acute pancreatitis and IPN for different centers is caused by a variance in "case-mix," by different treatment algorithms or both. In these studies, the focus should be on the timing of surgical intervention and preoperative organ failure scores.

There are several factors which contribute to the paucity of randomized studies on IPN, including the relatively low incidence of the severe form of the disease (Table 3.1: average nine patients per center per year requiring surgery) and the heterogeneity both in the severity of the disease and in the extent of the (peri-) pancreatic collections. Although current guidelines state that IPN patients are best treated in specialized centers (UK guidelines for the management of acute pancreatitis, 2005; Baillie 2007), in everyday clinical practice, these patients are often not referred (Besselink et al. 2006a). It is possible that randomized studies with a multicenter set-up will raise the tendency to refer patients. For an adequately powered study to ascertain whether MIPN is associated with a reduction in *mortality* from 25% to 15%, with a significance, alpha, set at 0.05 and 80% power (beta = 0.20), a total sample size of 540 patients (2 × 270 patients) would be required. It would take

the cooperation of 20 of the largest centers worldwide for 3 years to reach this number of patients. Furthermore, not every patient with IPN is eligible for MIPN. In a recent study, five radiologists reviewed 80 CT scans of patients operated on for IPN. In retrospect, it appeared that 56% of the patients would have been eligible for retroperitoneal MIPN and 84% of the patients had collections potentially amenable to percutaneous or transgastric drainage (Besselink et al. 2007b). This limitation further increases the number of participating centers needed for a randomized study on MIPN. Potentially, the use of a composite primary endpoint or the use of a continuous endpoint with low standard deviation could greatly reduce the sample size needed to demonstrate superiority. However, these endpoints should be chosen in such a way that clinicians are universally willing to accept them as sufficient evidence for changing their clinical practice.

A randomized study on timing of intervention would face similar difficulty in recruiting sufficient patients to demonstrate a reduction in mortality. A sample size calculation shows that if postponed intervention (>29 days) is able to reduce mortality from 30% to 10% (alpha = 0.05 and beta = 0.20), a total of 144 patients (2 × 72 patients) would be required. Again, not all patients with IPN would be eligible for such a trial.

Large-scale collaborative studies of pancreatic conditions where recruitment is difficult are certainly possible. The European Study group for Pancreatic Cancer (ESPAC) (Neoptolemos et al. 2001) and the previously mentioned PANTER trial of the Dutch Acute Pancreatitis Study Group (Besselink et al. 2006b) have clearly demonstrated this. At the 2007 Glasgow meeting, it was decided by attendants of virtually all leading European pancreatitis centers that international collaboration is the best way forward. It was agreed to start a prospective registration of patients with necrotizing pancreatitis. This collaboration was termed: European Pancreatic Necrosis Network (E-PANN). E-PANN will focus on the relationship between the extent of preoperative organ failure, MIPN, and timing of intervention versus outcome. The outcome of this analysis may precipitate a large-scale international randomized controlled trial. We believe that through truly collaborative ventures, it will be possible to improve the outcome of IPN.

## *Communicated By*

### Author Contributions

MGHBesselink performed the systematic review and wrote the manuscript.
MGHBesselink, R Carter, RM Charnley, and DJ Mole formed the working party on future studies on infected necrotizing pancreatitis at the 2007 “Pancreatic Diseases – The Challenges” meeting in Glasgow, UK.
All the authors participate in the European Pancreatic Necrosis Network (E-PANN) collaboration.
All the authors edited the manuscript and read and approved the final manuscript.

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# Chapter 4
# Nutrition in Acute Pancreatitis

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## 4.1 Background

Acute pancreatitis is one of the most common diseases in gastroenterology/surgery. The incidence of acute pancreatitis ranges from 10 to 46 per 100,000 people per year. Recent studies have suggested a slightly higher incidence of acute pancreatitis at 56.5 per 100,000 people, which may be linked to socioeconomic deprivation (Ellis et al. 2009). Two percent of all hospital admissions are due to acute pancreatitis. During the last decade, there has been an increase in incidence, mostly due to a higher sensitivity of diagnostic tests. With regard to the clinical course of the disease, it is important to distinguish between mild edematous disease (approximately 85% of all cases) with mortality below 1% and severe necrotising pancreatitis (approximately 15% of all cases) with a fatal outcome in 10–24%. Either clinical course is possible regardless of the underlying etiology of the disease. Up to 90% of all cases of acute pancreatitis are etiologically linked to gallstone disease or alcohol abuse; pancreatitis due to other causes such as hypercalcemia, hyperlipidemia, or infectious agents is rare.

Acute pancreatitis causes an inflammatory response. Severe acute pancreatitis (SAP) can lead to sepsis, multiple organ failure, and death. There is no specific therapy directed against the underlying pathophysiological mechanisms, and the management of SAP focuses on treatment of symptoms and prevention of complications (Uhl et al. 2002; Isaji et al. 2006; Toouli et al. 2002; Ihse et al. 2003). Nutritional support plays an important role in the management of acute pancreatitis. Previously, none of the major institutional guidelines specified the preferred mode of nutrition in patients with severe acute pancreatitis, though the recent UK guidelines do suggest that enteral nutrition (EN) may be preferred (Uhl et al. 2002; Isaji et al. 2006; Toouli et al. 2002; Ihse et al. 2003; UK guidelines for the management of acute pancreatitis 2005; Meier et al. 2006). Benefits from the use of EN have

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previously been shown in critically ill patients, including those with burns, trauma, and sepsis (Moore and Moore 1991; Moore et al. 1992; Kudsk et al. 1992).

## 4.2 Nutrition in Acute Pancreatitis

Traditionally, patients with acute pancreatitis were kept nil by mouth. It was believed that any stimulation of the exocrine pancreas by fluid or solid nutrients would negatively affect the course of the disease. The pancreas would be "at rest" during pancreatitis and is unresponsive to stimulation. Table 4.1 summarizes all the clinical trials conducted with regard to nutrition in acute pancreatitis, while Table 4.2 summarizes the meta-analysis conducted in this regard.

Enteral feeding can serve a dual purpose: early, to prevent mucosal permeability impairment, and later as an alternative to PN. In the later phase of the illness, it may not be possible to meet the required caloric intake via EN alone in order to prevent catabolism. Some suggest that EN should still be given to some extent via nasogastric or nasojejunal feeding tube to prevent atrophy of the intestinal mucosa and loss of barrier function. In addition the required calories should be supplemented parenterally. Though most studies have suggested a lower complication rates for EN, Eckerwall et al. have recently suggested that NG route of EN may result in higher pulmonary complications (Eckerwall et al. 2006). Gupta and coworkers found decreased CRP levels in patients with EN (Gupta et al. 2003). A randomized controlled trials (RCT) from Glasgow and New Delhi (Eatock et al. 2005; Kumar et al. 2006) compared EN via a nasojejunal tube versus nasogastric tube. No disadvantages were found for the group receiving nutrition via a nasogastric tube. Taking into account the frequent rate of nasojejunal tube dislocation and the required endoscopic replacements, nasogastric enteral feeding seems to be the most feasible option in daily clinical practice and indeed is cheaper (Eatock et al. 2005; Kumar et al. 2006). It is quicker and safer to place a nasogastric tube as endoscopy or radiology is involved in placement of nasojejunal tube. If a nasojejunal tube is required than the 7 Ch nasobiliary tube (Wilson Cook, Winston–Salem, NC, USA) seems to serve the purpose best, since it does not "stick" to the endoscopy channel on withdrawal of the endoscope, thus reducing the risk of its dislodgement immediately after placement (Eatock et al. 2005).

It has been shown that fasting leads to impaired intestinal mucosal integrity thus increasing gut permeability and bacterial translocation (Powell et al. 2000; Eatock et al. 2005). An early increase in gut permeability is described in clinical studies in SAP (Windsor et al. 1998; Pupelis et al. 2000) and one of these studies found a correlation with systemic endotoxin levels. Endotoxin and other bacterial products stimulate endogenous cytokines responsible for the acute-phase response. Gut barrier failure may contribute to the severity of acute pancreatitis and probably represent an important factor in the development of late and septic complications (McClave et al. 1997). Pancreatic infection is a common cause of mortality in severe acute pancreatitis and it is suggested that the infection occurs due to bacterial

**Table 4.1** Role of nutrition in acute pancreatitis

| Year | Author (ref) | Severity | *N* | Comparison | Outcome |
|---|---|---|---|---|---|
| 1987 | Sax et al. 1987 | All | 54 | NBM versus PN | PN worse |
| 1996 | Hernandez-Aranda et al. 1996 | SAP | 22 | EN versus PN | EN cheaper |
| 1997 | Kalfarentzos et al. 1997 | SAP | 38 | EN versus PN | EN better |
| 1997 | McClave et al. 1997 | Mixed | 30 | EN versus PN | EN better |
| 1998 | Windsor et al. 1998 | Mixed | 34 | EN versus PN | EN better |
| 2000 | Olah et al. 2000 | Mixed | 89 | EN versus PN | EN better |
| 2000 | Powell et al. 2000 | SAP | 27 | NBM versus EN | None better |
| 2000 | Pupelis et al. 2000 | Operated SAP | 29 | NBM versus EN | EN better |
| 2002 | Abou-Assi et al. 2002 | Mixed | 53 | EN (NJ) versus PN | EN better |
| 2002 | Ockenga et al. 2002 | Mixed | 28 | PN versus PN (Glut) | Glut better |
| 2003 | Gupta et al. 2003 | SAP | 17 | EN versus PN | EN better |
| 2003 | Zhao et al. 2003 | SAP | 96 | PN versus PN and EN | EN better |
| 2004 | Pandey et al. 2004 | Mixed | 28 | Oral versus NJ | NJ better |
| 2004 | Sun et al. 2004 | SAP | 100 | PN versus staged[a] | Staged better |
| 2005 | Eatock et al. 2005 | SAP | 50 | NG versus NJ | NG cheaper |
| 2005 | Lasztity et al. 2005 | SAP | 28 | PUFA versus no | Equivalent |
| 2005 | Louie et al. 2005 | SAP | 28 | EN versus PN | EN better |
| 2006 | Eckerwall et al. 2006 | Mixed | 50 | Early EN versus PN | EN worse |
| 2006 | Kumar et al. 2006 | SAP | 31 | NG versus NJ | Equal |
| 2006 | Pearce et al. 2006 | SAP | 31 | Immunonutrition[b] | Worse? |
| 2006 | Petrov et al. 2006 | SAP | 70 | EN versus PN | EN better |
| 2006 | Tiengou et al. 2006 | Mixed | 30 | Semi-elemental versus polymeric EN | Equal |
| 2007 | Casas et al. 2007 | SAP | 33 | EN versus PN | EN better |
| 2007 | Eckerwall et al. 2007 | Mild | 60 | NBM versus oral | Oral better |
| 2007 | Jacobson et al. 2007 | Mild | 121 | Clear liquids versus low fat solid | Equal |
| 2008 | Fuentes-Orozco | SAP | 44 | Glut versus Std PN | Glutamine better |
| 2008 | Wang et al. 2008 | SAP | 40 | PN versus PN (omega-3 fatty acids) | Omega-3-fatty acids better |

*N*, total number of patients in the study
NBM, nil by mouth
NG, Nasogastric feed
NJ, Nasojejunal feed
EN, Enteral nutrition
PN, Parentral nutrition
Glut, Glutamine
[a] Staged means a combination of EN (as tolerated) and PN
[b] Glutamine, arginie, and omega-3 fatty acids

**Table 4.2** Meta-analysis for nutrition in acute pancreatitis

| Year | Author (ref) | Severity | *N* | Comparison | Outcome |
|---|---|---|---|---|---|
| 2004 | Marik and Zaloga 2004 | Mixed | 6 | PN versus EN | EN better |
| 2008 | Petrov et al. 2008a | Mixed | 3 | Immunonutrition with EN | No benefit |
| 2008 | Petrov et al. 2008b | Severe | 4 | Role of NG feed | Not detrimental |
| 2008 | Petrov et al. 2008c | Severe | 5 | EN versus PN | EN better |

*N*, number of studies

translocation from the gut (Sax et al. 1987). Increasing evidence suggests that EN is safe and may reduce complications by maintaining the intestinal barrier function (Buchman et al. 1995; Juvonen et al. 2000) and by preventing/reducing bacterial translocation from the gut (Ammori et al. 1999; Alverdy et al. 1988).

Furthermore, EN eliminates some complications of parenteral nutrition (PN), such as hyperglycemia and catheter sepsis (2% even if the catheter is managed appropriately), as well as less common line-related complications such as arterial laceration, pneumothorax, thrombosis, thrombophlebitis, and catheter embolism. In several prospective randomized clinical trials involving EN (Table 4.1), it has emerged that EN is most likely superior to PN in preventing complications of the acute pancreatitis. Also the cost of EN is only 15% of the cost of PN. This and the fact that EN is clearly not harmful in pancreatitis make it an increasingly accepted treatment modality.

## 4.3 Probiotics in Severe Acute Pancreatitis

Early studies had suggested a beneficial role for probiotics in ameliorating the infectious complications associated with severe acute pancreatitis (Table 4.3) (Olah et al. 2002, 2005; Karakan et al. 2007) and other conditions (Rayes et al. 2005; Rayes et al. 2007). Investigations by the Dutch Acute Pancreatitis Study Group have suggested that probiotics may in fact be detrimental to these patients, due to an increase in nonocclusive mesenteric ischemia; though no mechanism has been provided (Besselink et al. 2008). In a large, well-powered, well-designed, multicenter randomized, double-blind, placebo-controlled trial study they recruited 298 patients with predicted severe acute pancreatitis (based on Acute Physiology and Chronic Health Evaluation (APACHE II) score ≥ 8, Imrie score ≥ 3, or C-reactive protein > 150 mg/l). Patients were given either probiotics (containing six different strains of freeze-dried, viable bacteria: *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus salivarius, Lactococcus lactis, Bifidobacterium bifidum*, and *Bifidobacterium lactis* in a total daily dose of $10^{10}$ bacteria, plus cornstarch and maltodextrins) or placebo only.

One hundred and fifty-two patients in the probiotics group and 144 in the placebo group were similar in baseline characteristics and disease severity. Overall infectious

**Table 4.3** Role of probiotics in acute pancreatitis

| Year | Author (ref) | Severity | *N* | Comparison | Outcome |
|---|---|---|---|---|---|
| 2002 | Olah et al. 2002 | Mixed | 45 | EN, L plantarum, and oat versus EN | Probiotics better |
| 2005 | Olah et al. 2005 | SAP | 60 | EN, mixed (four strains) versus EN | Probiotics better |
| 2007 | Karakan et al. 2007 | SAP | 30 | EN, Fiber versus EN | Fiber better |
| 2008 | Qin et al. 2008 | Mixed | 76 | EN (with L plantarum) versus PN | EN better |
| 2008 | Besselink et al. 2008 | SAP | 292 | EN, mixed (six strains) versus EN | Worse |

EN, enteral nutrition
PN, parentral nutrition
*N*, total number of patients in the study

complications were unchanged (46 (30%) patients in the probiotics group and 41 (28%) of those in the placebo group had infectious complications (relative risk 1.06, 95% CI 0.75–1.51)) However, there were significantly more deaths in the probiotics group (24 (16%), compared to nine (6%) in the placebo group (relative risk 2.53, 95% CI 1.22–5.25)) mainly due to nonocclusive mesenteric ischemia (nine in the probiotics group (eight with fatal outcome) and none in the placebo group ($p = 0{\cdot}004$)).

The cause of these unexpected findings was speculated. The administration of 10 billion probiotic bacteria per day on top of enteral nutrition may have increased local oxygen demand, with a combined deleterious effect on an already critically reduced blood flow. A second possible explanation could be that the presence of probiotics caused local inflammation at the mucosal level. This trial has effectively stopped the use of probiotics in routine clinical practice for patients with severe acute pancreatitis.

## 4.4 Future Research

Nevertheless, all the previous studies conducted to test the efficacy of early EN in SAP were largely underpowered according to the criteria of evidence-based medicine. Recent meta-analyses of the trials on nutrition in acute pancreatitis point to the poor quality of data and heterogeneous studies with patients suffering from various degrees of severity of pancreatitis (Marik and Zaloga 2004; Petrov et al. 2008c). However, they do emphasize the deleterious role of PN. It also paves a way for further study in the role of *early* EN in acute pancreatitis to extend from previous experimental work (Ammori et al. 1999; Alverdy et al. 1988). It is necessary to further evaluate this subject in a prospective, well-powered, randomized multicenter trial to prevent late and septic complications. The presumed mechanism of action of early EN to prevent these changes is by maintaining gut mucosal barrier

function. Thus, it is logical to test the effect of early EN on gut barrier failure in severe acute pancreatitis, as this will provide reliable evidence on the supposed mechanism, and will serve as a surrogate for clinical efficacy.

In this context, a clinical trial proposal, put forward by the Pancreas 2000 ENSAP group, was discussed. This group met between 2002 and 2005 under the Pancreas 2000 European Research Programme and registered their study as ISRCTN 12838128. Group members include Hemant Kocher (London), Julia Mayerle (Greifswald), Hana Algul (Munich), Marko Marruste (Tartu), Eduardo Villatoro (Derby), Colin McKay (Glasgow), and Colin Johnson (Southampton). The University of Lund contributors has thier own study (Eckerwall et al 2006). The new study suggested here results from group discussions.

There are different markers available to measure intestinal permeability such as polyethylene glycol (PEG) ratio, EndoCAb, soluble TNF receptor amongst others. PEG ratio has an established safety profile and has been used effectively in patients with severe acute pancreatitis (Ammori et al. 1999). Briefly, PEG 3350 acts as a permeability probe with PEG 400 as an internal control. A prespecified ratio of PEG 3350/400 is administered and urinary excretion of the two markers is measured over 24 h. PEG 3350 is a macromolecule approximating the size of gram-negative endotoxin. It is not metabolized in the intestine and is not absorbed unless the gut barrier is permeable. When absorbed it is readily excreted in urine without any metabolism. PEG 400 is similar to PEG 3350, but is normally readily absorbed by the intestine because of small molecular size (similar to monosacharide, lactulose 340 Da). PEG can be readily measured by high-performance liquid chromatography (HPLC) (Ryan et al. 1992). Moreover, PEG has an established safety profile and is nontoxic, with clinical use in bowel preparation (high doses), and as a component in some drugs and processed food products.

Pancreas 2000 ENSAP is a pragmatic, prospective, multicenter, open-label randomized phase III, trial in patients diagnosed with severe acute pancreatitis. A total of 66 patients with severe acute pancreatitis will be randomized to one of the two treatment groups (early enteral nutrition versus standard fluid replacement for the first 3 days after onset of symptoms) in order to compare the effect of early enteral versus delayed enteral nutrition. Patient randomization would be stratified by the center due to difference in local policies (standard operating procedures submitted beforehand), which would remain unchanged (and therefore a pragmatic approach) and specific for each center.

## 4.5 Inclusion Criteria

The criteria includes patients aged 18 or over with a proven diagnosis of acute pancreatitis (pain and raised enzymes or CT evidence) together with systemic inflammatory response syndrome (SIRS) or organ failure (Marshall score [Bone et al. 1992] two or more for any organ system except liver) present for 24 h or more, or (if available) a CT with Balthazar Severity Index > 4 (Balthazar 2002) i.e., >30% necrosis and/or two

extra-pancreatic fluid infiltrates. Randomization must be within 72 h of onset of symptoms. SIRS is defined as any two or more of the following features: temperature outside the range 36–38°C, white blood count > 12%, <4% or >10% of immature cells, respiratory rate > 20, $PaCO_2$ > 4.3 kPa, and pulse rate > 90 (Bone et al. 1992).

## 4.6 Primary Endpoint

The return of gut permeability to the normal state after being rendered permeable by SAP will be measured by the return of polyethylene glycol (PEG) ratio to normal range after institution of early enteral nutrition by day 3/day 7. PEG ratio is a surrogate marker of gut permeability and will be measured on days 1 (baseline), 3, and 7. It is expected that at least 80% of the patients included in this trial will have gut permeability in the range quoted for severe acute pancreatitis (PEG ratio; median 0.06, interquartile range 0.01–0.19) (Ammori et al. 1999). We anticipate that with early enteral nutrition the gut permeability will be restored to the range for mild acute pancreatitis (PEG ratio: median 0.008, interquartile range 0.005–0.013) in at least half the patients. Only 40% of patients should have gut permeability by day 3/7 in the severe acute pancreatitis range. Thus, the primary outcome would be defined as the reduction in the number of patients from 80% to 40% with gut permeability in the severe acute pancreatitis range. A sample size of 27 patients per group will be sufficient to show a significant difference between early EN and no nutrition (in first 3 days), with at least 90% power, using a significance level of 0.05. Allowing for a 20% dropout rate we will need 33 patients in each group. Thus a total of 66 patients will be required.

## 4.7 Secondary Endpoint

Many probable secondary endpoints were put forward. These included development, presence, severity, and duration of organ failure and other clinical outcomes: complications, intensive care unit (ICU) stay, length of hospital stay, or time of return of GI function (defined as passage of flatus). Other markers of gut permeability (EndoCAb, soluble TNF receptor), markers of intestinal ischemia (IFABP), and markers of inflammatory response (cytokines such as IL-8, IL-6, IL-10, IL-1ra, sTNFR, CRP, PMN-elastase, and Pro-calcitonin) were also considered.

## 4.8 Conclusion

Much progress has been made in investigating the role of nutrition in severe acute pancreatitis. The advantage of enteral over-parenteral nutrition is now well established; while the putative benefits of adding probiotics can now be discounted because of the results of the Dutch Multicentre Prospective Study. More well-designed

trials are now required to investigate the role of early enteral nutrition to reduce or prevent bacterial translocation and thus infectious complications in severe acute pancreatitis.

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# Chapter 5
# An Optimal Randomized Study for Pain Control in Acute Pancreatitis

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## 5.1 Introduction

The diagnosis of acute pancreatitis is, in most cases, based on an acute onset of abdominal pain (upper abdominal pain, sometimes radiating to the back or the shoulders) and the absence of other acute pain-inducing abdominal conditions (e.g., peptic ulcers, bile duct diseases, or intraabdominal vascular occlusions), paired with significantly increased serum amylase or lipase (usually three times over the upper reference value). However, pain is the symptom that brings the patient to seek medical attention and the cardinal symptom that makes the doctor suspect the diagnosis of acute pancreatitis (Keller et al. 2007). Moreover, effective management of severe pain in acute pancreatitis is one of the most important issues in therapy, as pain reflexes may contribute to the development of secondary complications and are the most distressing complaint of the patient.

## 5.2 Clinical Aspects of Pain in Acute Pancreatitis

Pain in acute pancreatitis is often of sudden onset with frequent excruciatingly severe pain or may be a more gradual onset with moderate abdominal pain several hours after a large meal. There are also reported cases of acute pancreatitis without pain, but these are rare – or at least rarely diagnosed. Mild, alcohol-induced pancreatitis is sometimes recognized by the patient not until "the day after the day after" – when all other symptoms related to hangover have resolved – which means that pancreatitis pain was obscured by alcohol confusion when it was at its peak.

According to some authors, there can be some localization of the pain depending on the part of the pancreas that is most severely affected by the inflammation. Painful stimuli in the head of the pancreas may thus be perceived as pain in the right

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upper abdominal quadrant; there is a radiation from the body of the pancreas to the epigastrium and from the tail to the left upper quadrant and shoulder. However, pain is localized to the epigastrium and periumbilical regions in about two thirds of the patients, whereas in most other cases, pain is diffuse and difficult to localize. This is probably due to general panpancreatic inflammation and a peripancreatic retroperitoneal edema and inflammation. About one third of the patients report that the pain is radiating to the back.

The pain is often continuous for hours (e.g., biliary pancreatitis) or days (alcoholic pancreatitis and more severe forms of biliary pancreatitis), but can be intermittent in less than 15% of patients. The intensity is reported from "as severe as possible" to "well tolerable". In most cases, a patient with acute pancreatitis will require potent analgesics for treatment (Kune et al. 1975).

There is little correlation between the severity of pancreatitis and the severity of pain and its localization. However, in the most severe cases of pancreatitis the patient may already be in shock or preshock when admitted to the emergency ward, which means that the patient will not express pain as his or her leading complaint or may not even experience pain at all. Absence of pain in a severely ill patient with acute pancreatitis is an ominous sign.

## 5.3 Pathophysiology of Pain in Acute Pancreatitis

There seems to be no single cause of pain in acute pancreatitis, but several factors contribute. Pain can be due to the inflammation with direct inflammatory stimulation of pancreatic and peripancreatic nerve endings and the production of noxious and pain-inducing substances in the sensitive peritoneum. This is likely to be a local process as most patients with acute pancreatitis have localized pain in the epigastrium and the surrounding upper part of the abdomen. On the other hand, as patients can also have pain in the back, this may represent neural referred pain, or spread of noxious stimuli through a large part of the upper retroperitoneum.

The swelling of the gland is unlikely to cause intrapancreatic pain as there are few sensory nerves inside the pancreas, but the pressure affected on the surrounding tissues may well be generating pain. However, there is no demonstrable correlation between pain and the size or grade of pancreatic swelling and no correlation with compression or distension of the biliary tract, duodenum, or pancreatic "capsule" by an inflammatory mass, or by pseudocysts. Hypertension within the ducts due to obstruction has not been shown to be generally present in acute pancreatitis.

There is probably relative ischemia of the pancreatic gland at some point of the inflammation and a low pH, but whether this is of significance for pain sensations is not known.

At present it is probably correct to assume that the origin of pain in acute pancreatitis is multifactorial, and more research is needed to clarify which cause of pain is most important and most likely to benefit from intervention. However, compared to

other questions regarding the pathophysiology of acute pancreatitis, the answer has presently little impact on the choice of pain medication and has therefore attracted limited attention from researchers.

From the patients' points of view today there are already several acceptable options for treatment of pain in acute pancreatitis.

## 5.4 Literature Review

A PubMed query in 2007 with the MeSH headings "Treatment and pain + acute pancreatitis" identified 1,119 articles, and among them there were 102 on "Narcotics and pancreatitis," 91 on "Procaine and pancreatitis," and 22 on "Peridural/Epidural analgesia and pancreatitis." However, the majority of those were reviews, case reports, or uncontrolled treatment reports in nonEnglish languages.

### *5.4.1 Procaine and Novocain*

In German speaking countries a "teutonic dogma" has long been advocated, stating that it is obsolete to use opiates to treat abdominal pain in patients with acute pancreatitis because it induces spasm of the sphincter of Oddi. Continuous systemic infusion of procaine hydrochloride (Procaine or Novocain) has instead been recommended by various authors and the German Society of Gastroenterology and Metabolic Diseases for pain treatment in patients with acute pancreatitis (Kahl et al. 2004).

In an open, randomized, controlled trial, 107 patients were recently randomized to receive either procaine ($n = 55$) or pentazocine ($n = 52$) for pain relief. Procaine 2 g per 24 h was administered by continuous intravenous infusion, and pentazocine 30 mg was administered every 6 h as a bolus intravenous injection. Pentazocine was additionally administered on demand whenever required in patients of both treatment groups. Patients receiving procaine were significantly more likely to request additional analgesics compared to patients treated with pentazocine alone, 98% versus 44%, respectively. Procaine infusion did not reduce the amount of pentazocine required for pain control. The amount of pentazocine given in both groups was not statistically different. Recorded pain scores were significantly lower in patients of the pentazocine group during the first 3 days of analgesic treatment. From day 4 onwards, there was no significant difference in pain scores between the two groups. Thus, the authors drew the conclusion that intravenous procaine treatment was not effective for pain control in patients with acute pancreatitis (Kahl et al. 2004).

In another prospective randomized study 40 patients with acute pancreatitis or an acute bout of chronic pancreatitis received either buprenorphine or procaine for

pain relief. Both analgesics were administered as constant intravenous infusions, and additional analgesics were given on demand. Pain scores were assessed on a visual analog scale during the 3-day study period. Patients receiving buprenorphine were significantly less likely to request additional analgesics (one versus 14 patients), and the pain scores for patients in the buprenorphine group were significantly lower in the treatment period in comparison to procaine. Side effects were comparable for both groups with the exception of a slightly higher sedation rate under buprenorphine (Jakobs et al. 2000).

Treatment of acute abdominal pain in acute pancreatitis by the systemic infusion of a local anesthetic is neither supported by randomized trials nor by published case series, and it is, therefore, difficult to recapitulate on what basis this treatment modality found its way into the medical armamentarium 30 years ago – at least in the German-speaking world. Two recent studies show that systemic Procaine is vastly inferior to opiates in one study and not at all an effective pain treatment in the second study. The meeting consensus was that no further trials would be needed to evaluate Procaine infusion in pancreatitis.

### *5.4.2 Systemic Opiates*

Traditional opinion suggested that morphine can induce "spasm" of the sphincter of Oddi and should not be used in acute pancreatitis and that alternative analgesics should be chosen. A literature search and review of this item was published in 2001. It was found that initial studies measured biliary pressure after narcotic administration in animals and postoperative and intraoperative cholecystectomy patients. All narcotics invariably increased biliary pressure, but morphine was associated with the greatest elevation. Later studies using endoscopic retrograde cholangiopancreatography with direct sphincter of Oddi manometry demonstrated that this sphincter is exquisitely sensitive to all narcotics including meperidine and that a small increase in biliary sphincter pressure is seen with higher doses of morphine. All narcotics increased the phasic wave frequency of the sphincter and interfered with its peristaltic. No studies directly compared the effects of different opioids by manometry and only one comparative study exists in patients with acute pancreatitis. No outcome-based studies comparing these drugs have been performed in patients with acute pancreatitis. Moreover, no studies or other evidence exist to indicate that morphine is contraindicated or harmful for patients with acute pancreatitis (Thompson 2001).

A short note from 1984 in the *British Medical Journal* reported a series of 32 consecutive patients receiving either buprenorphine ($n = 17$) or pethidine ($n = 15$) for pain treatment in acute pancreatitis. Outcome measurement of pain was using a visual analog scale, the mean number of pain-free intervals, and the patient's request of additional analgesics. The authors found no differences concerning efficacy of pain relief, or duration of pain relief, or side effects; both drugs were equally effective (Blamey et al. 1984).

### 5.4.3 Pancreatic Enzyme Supplementation for Pain Control

According to the theory of negative feedback regulation of pancreatic enzyme secretion by intraluminal proteases, treatment with pancreatic extracts has been proposed to lower pain in pancreatitis – predominantly chronic pancreatitis – by resting the pancreas, but a randomized trial found no effect of enzyme replacement therapy on pain in pancreatitis decreasing pancreatic duct pressure. However, there is little clinical evidence that this works in acute pancreatitis (Mössner 1993; Mössner et al. 1992; Patankar et al. 1995).

### 5.4.4 Celiac Plexus Block

A retrospective study (Rykowski and Hilgier 1995) has assessed the effect of continuous celiac plexus block as an alternative analgesic method in patients with acute pancreatitis. Of 43 patients admitted to the intensive care with acute pancreatitis, seven who did not respond to routine segmental T5-L2 epidural block received a continuous celiac plexus block performed in the right lateral position as an alternative method of pain relief. This was found to be an effective alternative treatment for pain in acute pancreatitis. Despite this positive report from 1995, the method of celiac plexus block has not received wide acceptance for the treatment of pain in acute pancreatitis.

### 5.4.5 Epidural Analgesia

The direct interruption of afferent nociceptive visceral stimulation by segmental epidural block has been claimed to be an effective method of pain relief in acute pancreatitis with additional positive side effects, e.g., increased gastrointestinal perfusion. A recent study in a rat model (Freise et al. 2006) was based on the fact that acute pancreatitis has been linked to intestinal barrier dysfunction and a systemic inflammatory response and that thoracic epidural analgesia could improve intestinal perfusion. In untreated pancreatitis, decreased total capillary perfusion increased the total intercapillary area by 24%. Furthermore, loss of continuous perfusion greatly increased continuous intercapillary area. After immediate and delayed epidural analgesia, continuous perfusion was significantly restored. Blood flow decreased by 50% in untreated pancreatitis but could be preserved by epidural analgesia at a significant rate. Biochemical and histological signs of pancreatitis were not affected by epidural analgesia. Lactate and interleukin-6 levels increased in untreated pancreatitis, but this increase was prevented in the treatment group. Epidural analgesia significantly increased at 7-day survival from 33% to 73%. This means that thoracic epidural analgesia attenuated the systemic response and

improved survival in severe acute pancreatitis in the rat and that these effects might be explained by improved mucosal perfusion.

In a large case series (Bernhardt et al. 2002), the effectiveness and safety of epidural analgesia were demonstrated in patients with severe acute pancreatitis, who were admitted to an intensive care unit. Epidural analgesia alone produced excellent pain relief on 1,083 of 1,496 observation days (72%) without need for the systemic use of additional analgesic substances. Even in patients with marginal cardiovascular stability, epidural injection of the local anesthetic was tolerated well. Only 8% of all local anesthetic injections were associated with a hemodynamic reaction that required pharmacological intervention. There was no case of a septic or neurological complication from epidural analgesia. Elevated serum amylase and lipase levels were normalized after 17 days (minimum 1 day, maximum 19 days). Mortality was 2.5% (three patients). All three patients suffered from severe acute pancreatitis. The average duration of ICU treatment was 12 days (minimum 2 days, maximum 101 days).

### *5.4.6 Thoracoscopic Splanchnicectomy*

Refinement of thoracoscopic technique has led to the introduction of thoracoscopic splanchnicectomy as a treatment of pancreatic pain. Bilateral thoracoscopic splanchnicectomy has been shown to eradicate pancreatic pain without associated deterioration of pancreatic function (Andrén-Sandberg et al. 1996; Ihse et al. 1999). However, this has not been attempted in acute pancreatitis despite being regarded as useful and as an effective pain treatment in chronic pancreatitis today.

### *5.4.7 Refeeding Pancreatitis*

The timing of oral refeeding in patients with acute pancreatitis is critical because they may experience pain relapse. A multicenter, multidimensional, prospective study involving a total of 116 patients has shown that during the oral refeeding period, 21% of patients had pain-relapse(Lévy et al. 1997). This occurred on days 1 and 2 in half of the patients. Using multidimensional analysis, Balathazar's CT score, period of pain, and serum lipase concentrations on the day before refeeding were independently associated with an increased risk of pain relapse. Pain relapse nearly doubled total hospital stay and hospital stay after the first attempt at oral refeeding.

A recent study was performed to assess the frequency of pain relapse in patients with acute necrotizing pancreatitis after treatment with one intramuscular injection of lanreotide (30 mg) on the day before refeeding (Lévy et al. 2004). The refeeding procedure was standardized and progressive. Twenty-three patients were included in four centers. Balthazar's score was D or E in seven and 16 patients, respectively.

Median duration of pain and interruption of oral feeding were 11 (3–23) and 16 (5–34) days, respectively. Median hospital stay was 22 (9–41) days. Only one patient (4%) had pain occurring 3 days after refeeding. The authors concluded that this figure is significantly lower than the expected 35% rate which was previously reported without preventive treatment. This suggests that one intramuscular injection of lanreotide 30 mg on the day before refeeding could decrease the frequency of pain relapse in patients with acute necrotizing pancreatitis, but this conclusion needs to be confirmed in a randomized, controlled phase III study.

## 5.5 Will Randomized Studies Give Us Additional Answers?

Before discussing new trials it is useful to summarize the present clinical status regarding pain control in acute pancreatitis – the combination of clinical experience and scientific evidence:

- Intensity of pain is not directly related to the severity or prognosis of acute pancreatitis.
- Pain control in nonsevere acute pancreatitis does not differ significantly from other acute abdominal conditions.
- It has not been demonstrated that severe acute pancreatitis is sufficiently different from other conditions causing acute abdominal pain to warrant a specific protocol for pain control.
- There is only limited evidence available for, or against, the use of opiates in pain control, and the fear of exacerbating pancreatitis as a result of spasm of the sphincter of Oddi induced by morphine may be unwarranted or of little clinical importance.
- Opiate-based patient-controlled analgesia (PCA) is now an accepted practice in most parts of the world, but only few pancreatitis studies have been performed.
- Epidural analgesia is commonly used when the patient is treated in an ICU and there is evidence from uncontrolled studies to support this.

Although a clinical pain management strategy is reasonably well established for patients with acute pancreatitis, there are several questions that ought to be answered in order to improve patients' care and pain control.

- Is the tendency of opiates to contract the sphincter of Oddi a clinical problem during acute pancreatitis and are there clinically significant differences between different opiates?
- Is the cheaper morphine equal to other opioids regarding its efficacy and side effects?
- Is peridural analgesia superior in comparison to intravenous or intramuscular opioids?
- Is patient-controlled analgesia equal to, or better than, epidural block?
- Is there a role for somatostatin analogs as routine prophylaxis against refeeding pancreatitis (lanreotide or octreotide versus placebo)?

All these questions are well suited for randomized controlled studies. However, as the expected differences between treatment arms are limited, a substantial number of patients in clinical studies of this kind will be needed, which, in turn, means that they can only be done as multicenter studies, which are labor- and time-consuming. Moreover, it is probably not overly interesting to perform such studies in patients with mild pancreatitis as, by definition, they heal without complications. Empirically, it is also known that in these patients the pain problem can be managed with simple strategies based on paracetamol, dextropropoxiphen, and morphine – and in most cases strong analgesics are needed only for a day or two (if morphine is required for a longer period, the diagnosis should be reevaluated, or at least an acute episode of chronic pancreatitis must be considered).

If only *a single most promising* study should be recommended, it is probably that of opioid analgesia versus epidural analgesia in "moderate" and severe acute pancreatitis as there are more components than "only" pain in this issue. For example, it is well documented that epidural analgesia may modify splanchnic perfusion and therefore may influence the risk of subsequent necrosis or its risk of becoming infected. Also, epidural analgesia may reduce the need for ventilatory support. On the other hand, epidural analgesia is an invasive intervention in patients at risk of infectious complications, and requires considerably more resources and impairs the mobilization of the patient.

Taken together it seems that there are several easily defined and limited clinical questions on pain management in acute pancreatitis that could be answered by well-planned randomized studies. However, all of them need a multicenter approach and are labor- and time-consuming. It is therefore important to define whether studying pain control is the most urgent question to be addressed in acute pancreatitis trials if only limited resources are available.

The authors of this overview feel that more pressing issues like control of inflammatory process, a redefinition of the role of surgery, and the need and use of nutrition and antibiotics may have greater impact on patient care than a head-to-head comparison of different treatment regimens for pain control.

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# Part II
# Potential Trials in Chronic Pancreatitis

# Chapter 6
# Endoscopic Versus Surgical Drainage for Chronic Pancreatitis

**Stephen P. Pereira, Shivi S. Siva, and Colin D. Johnson**

## 6.1 Introduction

In patients with acute relapsing and chronic pancreatitis, a variety of endoscopic and surgical therapies have been described. After endoscopic pancreatic sphincterotomy, stones can be removed from the pancreatic duct, and strictures can be stented or balloon-dilated.

Operations for chronic pancreatitis include pure duct drainage procedures (Partington-Rochelle or Puestow procedure), pure resection procedures (left pancreatectomy, pancreaticoduodenectomy, or total pancreatectomy with islet autotransplantation), combined duct drainage/resection procedures (Frey procedure), duodenum-preserving subtotal resection of the head of the pancreas (Beger procedure), and neuroablative procedures (thoracoscopic splanchicectomy).

The results of uncontrolled studies suggest that pancreatic endotherapy at the time of endoscopic retrograde cholangiopancreatography (ERCP) provides similar rates of both early and long-term pain relief compared with surgical drainage, with equivalent or reduced morbidity and mortality. However, there have been few randomized comparisons of these ERCP techniques with surgery.

The purpose of this review is to examine the available evidence on the efficacy of endoscopic and surgical drainage for chronic pancreatitis, with a particular emphasis on the results of randomized studies.

## 6.2 Pain in Chronic Pancreatitis

In patients affected with chronic pancreatitis, there is a significant deterioration in the quality of life compared with the general population (Wehler et al. 2003). Pain is the most important factor affecting quality of life indices (Pezzilli et al. 2005),

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leading to physical, psychological, and social impairment (Lankisch et al. 1993a). In a study of 190 patients with chronic pancreatitis (Pezzilli et al. 2005), main pancreatic duct dilatation, diabetes, and body mass index were studied in association with physical and mental domains. Dilatation of the main pancreatic duct correlated negatively with physical function, general health, vitality, and social function. In addition, the patients' perception of their health negatively correlated with the main pancreatic duct dilatation ($p < 0.025$) and abdominal pain ($p < 0.001$).

Early in the course of disease, acute attacks of pain may occur, with a progression to continuous pain over time in some patients and a gradual decline thereafter. In one study of 245 patients with alcohol-related chronic pancreatitis, 85% became pain-free at a median of 4.5 years after presentation (Ammann et al. 1984). Many studies have reported that resolution of pain often occurred in parallel to the development of pancreatic exocrine insufficiency. In a study by Mullhaupt et al. (2005), 240 of 251 patients (95%) with alcohol-related chronic pancreatitis achieved pain relief over a period of 14–36 years, usually in conjunction with the development of exocrine and endocrine pancreatic insufficiency.

Layer et al. (1994) were the first to describe a different clinical course in idiopathic chronic pancreatitis as compared to alcoholic pancreatitis. In a retrospective study of patients with alcoholic chronic pancreatitis ($n = 249$), or early or late onset idiopathic pancreatitis ($n = 66$), endocrine and exocrine insufficiency with calcification developed more slowly in early onset pancreatitis as compared to late onset or alcoholic pancreatitis ($p = 0.03$). However, pain was a more prominent feature in early onset pancreatitis compared to the other two etiologies ($P = 0.003$ early versus alcohol) and was more severe ($P = 0.004$ early versus late). This variable outcome confirmed a previous observation made by Ammann et al. (1987). Conversely, this "pancreatic burnout" effect was less pronounced in another study of 335 mixed alcoholic and nonalcoholic patients, where pain declined at a similar rate in the two groups and less than 50% had resolution of pain during 10-year follow-up (Lankisch et al. 1995). Thus, there is conflicting evidence that the pain of chronic pancreatitis resolves during long-term follow-up, due in part to differences in the patient populations studied, disease etiology, and the multifactorial causes of pain in chronic pancreatitis (Table 6.1).

**Table 6.1** Causes of pain in chronic pancreatitis

| |
|---|
| Pancreatic |
| • Acute inflammation |
| • Increased intrapancreatic pressure |
| – Intraductal |
| – Parenchymal (compartment syndrome) |
| – Pseudocyst |
| – Neural inflammation, fibrosis, neuropathy |
| Extra pancreatic |
| • Bile duct obstruction |
| • Duodenal stenosis |
| • Peptic ulcer |
| • Colonic stenosis |

## 6.3 Endoscopic Treatment of Chronic Pancreatitis

A variety of endoscopic therapies have been described for the management of painful chronic pancreatitis. In 1976, Cremer performed the first pancreatic sphincterotomy to treat a patient with acute cholangitis to remove an impacted pancreatic stone in the major papilla. Pancreatic stenting and extracorporeal shock wave lithotripsy (ESWL) for pancreatic stones followed in 1985 and 1987, respectively.

### *6.3.1 Sphincterotomy*

Pancreatic sphincterotomy improves access into the pancreatic duct, enabling removal of stones, insertion of stents, balloon dilatation of strictures, and, in pancreas divisum, drainage of the dorsal duct. In a retrospective study (Okolo et al. 2000), 55 patients with pancreatobiliary-type pain were followed for a median period of 16 months after pancreatic sphincterotomy. Before treatment, all patients had undergone either an elevated pancreatic sphincter of Oddi pressure of ≥40 mm Hg or Type 1 pancreatic sphincter of Oddi dysfunction, as defined by Sherman et al. (1991). Thirty-four of 55 patients (62%) reported significant improvement in their pain scores, from a median of 8.8 ± 1.8 before spincterotomy to 3.6 ± 3.4 after sphincterotomy ($p < 0.01$). The most frequently reported complications were acute pancreatitis (9.0%), bleeding (3.6%), and early stent occlusion (9.0%).

### *6.3.2 Stents*

The technical success rates of pancreatic stent insertion across a dominant stricture are reported to be 70–95% (Williams et al. 2007; Lohr et al. 1997). Overall, procedural complications range between 4–30% (Suissa et al. 2005; Cahen et al. 2005), including acute pancreatitis (3.9–39%) (Freeman 1996; Freeman et al. 2001; Andriulli et al. 2002; Friedland et al. 2002), bleeding (3.9%) (Suissa et al. 2005), stent occlusion (20%) (Cremer et al. 1991; Binmoeller et al. 1995; Smits et al. 1995; Ponchon et al. 1995), stent migration (10%) (Lohr et al. 1997; Smits et al. 1995; Rosch et al. 2002), and infection (Deviere et al. 1990; Harsch et al. 2001).

### *6.3.3 Extracorporeal Shock Wave Lithotripsy (ESWL)*

Extracorporeal shock wave lithotripsy (ESWL) may be useful/indicated in 36–44% of patients with chronic pancreatitis and stones in the main pancreatic duct (Delhaye et al. 1992), and facilitates stone fragmentation and duct clearance. ESWL is associated

with minor complications including acute pancreatitis and there has been no reported mortality. Based on largely retrospective studies of combined ESWL and ERCP (in more than 1,000 patients), stone fragmentation can be achieved in 54–100% of patients, with complete duct clearance in 44–74% of patients, and complete or partial pain relief in 48–85%, during a mean follow-up of 7–40 months (Delhaye et al. 1992; Costamagna et al. 1997; Adamek et al. 1999; Farnbacher et al. 2002). In these studies, surgery was required in 3–20% of the patients due to persistent or recurrent symptoms.

In a pilot study of ESWL alone in 32 patients with chronic pancreatitis (Ohara et al. 1996), complete clearance of stone fragments and resolution of pain was achieved in 24 patients (79%) after a mean follow-up period of 44 months. In a recently reported prospective trial of 55 patients randomized to ESWL alone ($n = 26$) or ESWL in combination with endoscopy ($n = 29$) (Dumonceau et al. 2007), pain relapse at 2 years occurred in 38% and 45% of patients, respectively (n.s.). In the two treatment groups, there was a similar reduction in diameter of the main pancreatic duct (mean decrease 1.7 mm, 95% CI 0.9–2.6; $p < 0.01$), and the number of pain episodes per year (mean decrease 3.7 (95% CI 2.6–4.9; $p < 0.01$)). The cost of combination therapy per patient was three times higher than for ESWL alone (Table 6.2).

## 6.4 Surgical Drainage for Chronic Pancreatitis

There are several randomized trials of different surgical approaches for the management of chronic pancreatitis, and particularly, for the relief of pain. The majority concern resection, and deal with patients not usually considered for endoscopic therapy: those with an inflammatory mass in the head of the pancreas (with or without obstruction of the bile duct or duodenum, and those with small (nondilated) pancreatic ducts). The results of surgical treatment are generally good in the short and long term (Table 6.3).

The conclusion of comparisons of pancreaticoduodenectomy and duodenum-preserving operations (Beger or Frey procedure) (Muller et al. 2008; Strate et al. 2005; Strate et al. 2008) are that both procedures provide adequate pain relief and quality of life after long-term follow-up with no differences regarding exocrine and endocrine function. However, short-term results favor the organ-sparing procedure.

**Table 6.2** Factors favoring endoscopic pancreatic stone removal

| |
|---|
| • Main duct stones |
| • Confined to head/body<br>• No stricture<br>• <3 stones<br>• <0 mm<br>• Not impacted |

**Table 6.3** Summary of the outcome in RCT of various surgical techniques for the treatment of painful chronic pancreatitis

| | Operation | *n* | Complications | Less pain or pain-free | QoL | Weight gain |
|---|---|---|---|---|---|---|
| Izbicki | LPJ/LPHE | 31 | 19% | 94% | 86 | 82% |
| 5 years (Wehler et al. 2003; Pezzilli et al. 2005; Lankisch et al. 1993a; Ammann et al. 1984; Mullhaupt et al. 2005; Layer et al. 1994; Ammann et al. 1987; Lankisch et al. 1995; Okolo et al. 2000; Sherman et al. 1991) | PP Whipple | 30 | | 95% | 57 | 40% |
| Buchler | Beger | 20 | 15% | 75% | | 88% |
| 6 months | PPW | 20 | 20% | 40% | | 67% |
| Farkas | LPJ/LPHE | 20 | 0 | 85% | | 7.8 kg |
| 1–3 years | PPW | 20 | 40% | 90% | | 3.2 kg |

QoL: quality of life; LPJ: lateral pancreaticojejunostomy; LPHE: LPJ with head excision; PPW: pylorus-preserving Whipple.

The management of patients with dilated ducts who are suitable for a pancreatic drainage procedure centers on the choice and timing of the operation. There is a general agreement, based on the poor results of other procedures, that when there is evidence of duct obstruction, a full-length drainage (Partington-Rochelle) is required. The Frey variant of this is often considered as a resection procedure, but the essential principle is that the whole pancreas is decompressed. Indeed, drainage and resection procedures can be regarded as a continuum designed to achieve the same goal – decompression of the whole pancreas (Figure 6.1). The conclusion to be drawn from the literature on the selection of type of operation is that good results can be achieved by offering each patient the procedure that best fits the state of their pancreas. Bassi's group has shown that excellent results can be achieved by pancreatic drainage (Talamini et al. 1996), if patients are appropriately selected (Figure 6.2).

The surgeon operating on patients with chronic pancreatitis should be equipped to deal with all options by means of pancreaticojejunostomy, Frey or Beger procedure, or V-resection of the body of pancreas, to achieve decompression without removal of the duodenum in the majority of the cases. In some circumstances, for example, groove pancreatitis, it may be necessary to perform a Whipple operation because of the involvement of the duodenal wall, but often subtotal excision of the head of pancreas (Beger procedure) will free the duodenum form encasing inflammatory fibrous tissue, and allow preservation of the duodenum.

Nealon et al. showed in an observational study (Nealon et al. 1988) that there might be benefit for patients with a dilated pancreatic duct and need for the preservation of pancreatic function to have an operation early in the course of the disease.

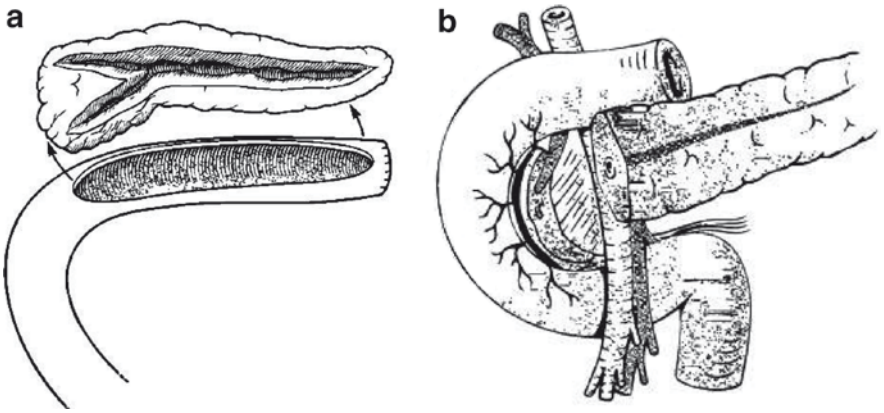


**Fig. 6.1** Panel **a** shows full-length decompression (Partington-Rochelle). If the central core of the tissue in the head of pancreas is removed, a frey procedure has been performed. In Panel **b**, removal of the head of pancreas and lateral pancreaticojejunostomy of the body and tail (Beger operation) combines the concept of pancreatic decompression with resection of inflammatory tissue and duodenal preservation

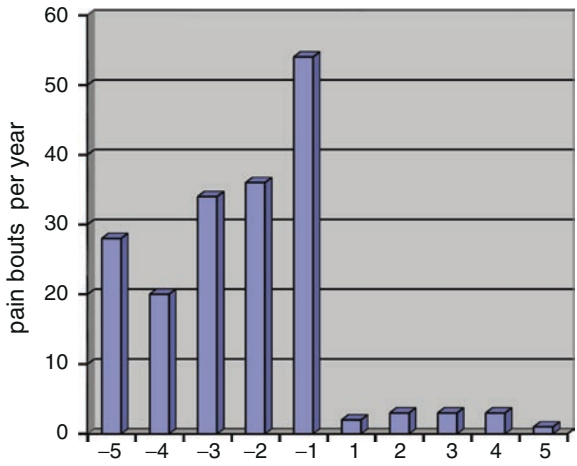


**Fig. 6.2** Number of pain episodes recorded each year in 180 patients before and after drainage operation for painful chronic pancreatitis from Talamini et al. (1996)

They found preservation of pancreatic function in patients operated early, but progressive loss of function if surgery was delayed. They followed this up with an impressive study, part observational, part randomized trial, which confirms the benefit, in terms of preserving function, of early surgery, when the patient is suitable for a drainage procedure (Table 6.4).

The excellent results achieved in the studies set a high standard against which studies of endoscopic therapy should be judged.

**Table 6.4** Preservation of pancreatic function in patients with mild or moderate painful chronic pancreatitis who underwent early operation for pain relief

| | Follow-up mild/moderate ($n$ = 83) | | |
|---|---|---|---|
| | Initial Evaluation | Follow-up | Progressed To severe |
| Operated | 47/47 | 41/47 (87%) | 6/47 (13%) |
| Nonoperated | 38/36 | 8/36 (22%) | 28/36 (78%) |

## 6.5 Pain Relief After Endoscopic or Surgical Drainage

The results of largely uncontrolled studies indicate that both endoscopic and surgical drainage procedures are associated with high technical success rates and early and medium-term pain relief. In one study, 70 patients with chronic pancreatitis and stones in the main pancreatic duct underwent therapeutic endoscopy (Dumonceau et al., 1996, 2007). Clearance of the main pancreatic duct stones was achieved in 55 of 70 patients (complete in 35, partial in 20). In the 56 patients who had pain on admission, immediate pain relief was noted in 95% of patients (pain-free in 41, >50% pain reduction in 12). At 2 years follow-up, 25/46 patients (54%) remained completely pain-free.

Delhaye et al. studied the efficacy of pancreatic endotherapy in 56 patients followed up for a mean of 14.4 years (Delhaye et al. 2004). Complete or partial technical success was achieved in 48 of 56 patients, and there was a significant reduction in the annual rate of hospitalization for pain, from 0.98 admissions/year before endotherapy to 0.40 for 3 years thereafter, and to 0.14 for the last 11 years. In addition, 44 of 56 did not require surgery.

By comparison, many surgical series have reported significant pain relief after surgical intervention. In a study of 335 patients with a median follow-up of 9.8 years (Lankisch et al. 1993b), pancreatic surgery led to immediate pain relief but later on the pain course between operated and nonoperated patients was not significantly different. In a prospective study of 207 medical-surgical patients with alcoholic chronic pancreatitis followed up for 12.7 ± 5.8 years (Lankisch et al. 1993b), complete pain relief eventually occurred in all medical ($n$ = 91) and surgically treated ($n$ = 116) patients. In addition, development of exocrine and endocrine insufficiency was identical in both groups (Figure 6.3). These results were similar to those of another prospective study of mixed medical-surgical patients ($n$ = 265).

## 6.6 Randomized Studies of Endoscopic Versus Surgical Drainage

Several uncontrolled studies have reported outcomes after endoscopic or surgical drainage in the treatment of chronic pancreatitis (Binmoeller et al. 1995; Smits et al. 1995; Hammarstrom et al. 1997; Gabbrielli et al. 2002), with both modalities appearing to be effective in achieving pain control in most patients (Binmoeller

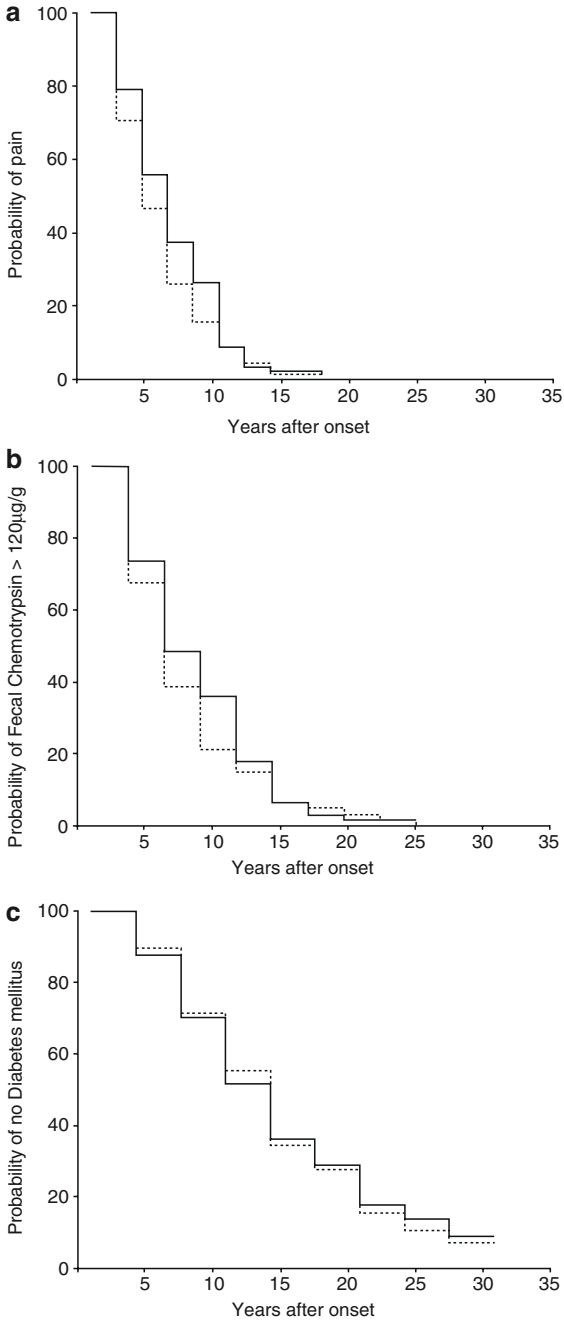


**Fig. 6.3** Probability of remaining free from: (**a**) pain recurrence, (**b**) exocrine insufficiency, and (**c**) diabetes mellitus for surgical (---) and nonsurgical (...) patients. A fecal Chymotrpsin level of >120 µg/g is indicative of normal exocrine function (From Ammann et al. (Ammann and Muellhaupt 1999))

et al. 1995; Smits et al. 1995; Hammarstrom et al. 1997; Gabbrielli et al. 2002; Izbicki et al. 1998; Hakaim et al. 1994). However, limitations of many studies have been their retrospective nature, lack of a validated pain scoring system, and limited follow-up period.

Two randomized trials have evaluated the medium-term results of endoscopic versus surgical therapy in patients with chronic pancreatitis.

In the first study by Dite et al. (2003) on 140 patients with painful obstructive chronic pancreatitis, 72 were randomized to either endoscopic or surgical treatment ($n$ = 36 in each group), with the remaining 68 opting for either surgical ($n$ = 40) or endoscopic treatment ($n$ = 28). All 140 patients met the following inclusion criteria: (a) a diagnosis of chronic pancreatitis confirmed by imaging studies, (b) an obstructive form of chronic pancreatitis with a dilated main pancreatic duct, strictures, and/or stones predominantly in the pancreatic head or body, (c) a Melzack's pain score > 3, (d) refractory to conservative management > 3 years, (e) clinical disease > 5 years, and (f) indication for intervention.

In the endoscopy group ($n$ = 64), pancreatic sphincterotomy was performed in all patients and pancreatic stents were placed in 33 (52%). Stone extraction was attempted in 15 patients (23%). The procedure was technically successful in 62 of 64 patients (97%). The mean duration of stenting was 16 months with an average of six stent exchanges per patient. Complications were classified as minor and included bleeding (Pezzilli et al. 2005), acute pancreatitis (Pezzilli et al. 2005), and pancreatic abscess (Wehler et al. 2003), with an overall post-ERCP complication rate of 8%. There was no surgical intervention or treatment-associated mortality.

In the surgical group ($n$ = 76), 61 (80%) underwent resection including duodenum-preserving pancreatic head resection ($n$ = 33), hemi pancreaticoduodenectomy ($n$ = 23), distal pancreatectomy ($n$ = 5), and lateral jejunostomy ($n$ = 15). Postoperative complications included acute pancreatitis (Pezzilli et al. 2005), fistula (Pezzilli et al. 2005), ileus (Wehler et al. 2003), anastomotic leak (Wehler et al. 2003), and repeat surgery for complications (Pezzilli et al. 2005), with an overall complication rate of 8%. There was no treatment-related mortality.

At 1 year, success rates as measured by the absence or partial relief of pain were similar for the endoscopic and surgical groups. However, at 5 years follow-up, significantly more patients in the surgical group reported complete absence of pain compared with the endoscopic group – both in the total group ($n$ = 140, 37% versus 14% $p$ = 0.002) as well as in the randomized group ($n$ = 72, 34% versus 15% $p$ = 0.002; Figure 6.4). In addition, there was a significantly better improvement in body weight in the total and randomized surgical groups compared to the endoscopic groups (total $n$ = 140; 52% versus 27%, $p$ = 0.002 and randomized $n$ = 72; 47% versus 29%, $p$ = 0.002).

In summary, this was the first prospective randomized study to compare the efficacy of endoscopic and surgical drainage in painful chronic pancreatitis, with similar complication rates in the two groups but better symptom control in those undergoing surgery. However, this study did have some limitations including the choice of treatment being tailored to patients' preference (although outcomes were comparable between the randomized and nonrandomized groups), lack of repeated

endoscopic procedures despite persistent or recurrent symptoms, the lack of extracorporeal shock wave lithotripsy, and surgery comprising mostly of resection rather than ductal drainage procedures.

The second prospective study was conducted by researchers in Amsterdam (Cahen et al. 2007) and was terminated early by the safety committee due to significant differences in outcome in the 39 patients with chronic pancreatitis who were randomized to endoscopic ($n$ = 19) or surgical ($n$ = 20) drainage.

In the endoscopic group, 16/19 patients underwent ESWL followed by an endoscopic procedure (stent insertion in 16/19, balloon dilatation in 15/19), with insertion of cumulative stents as required. A median of five (range 1–11) therapeutic procedures were performed and the median period of stenting was 27 weeks. Minor complications occurred in 58% of patients, and included stent occlusion (Mullhaupt et al. 2005), pancreatitis (Wehler et al. 2003), cholecystitis (Wehler et al. 2003), and wound infection (Wehler et al. 2003), and there was one death. In four of the 19 patients, surgical drainage was subsequently performed for intractable abdominal pain.

In the surgical group, 18/20 patients underwent lateral pancreatojejunostomy (modified Puestow procedure), with one patient each undergoing pancreaticoduodenectomy (for peripancreatic inflammation) or a Frey procedure (for stone extraction). Minor complications occurred in 35%, and included wound infection (Lankisch et al. 1993a), hemorrhage (Pezzilli et al. 2005), pneumonia (Wehler et al. 2003), and a need for repeat laparotomy (Wehler et al. 2003).

The median number of therapeutic procedures was significantly higher in the endoscopic group compared to that of the surgical group (8:3, $P < 0.001$). The technical success rates were 53% and 100% for endoscopic and surgical procedures, respectively ($p < 0.001$).

A validated pain score system based on subjective and objective criteria for chronic pancreatitis (Bloechle et al. 1995) was used to evaluate pain relief during,

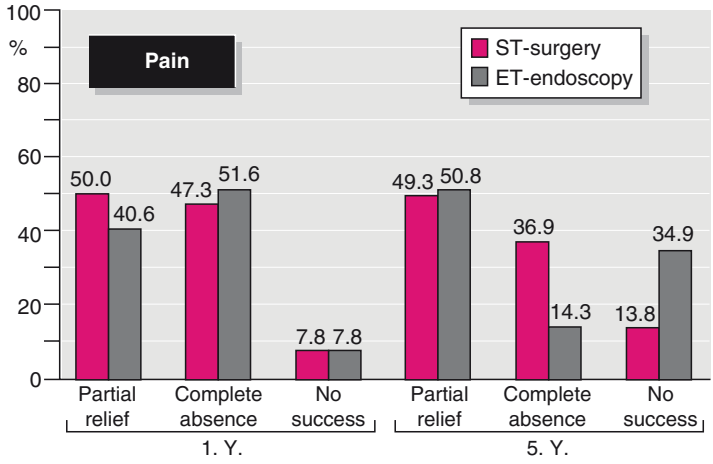


**Fig. 6.4** Comparison of the 1-year and 5-year follow-up results for pain between endotherapy (ET) and surgery (ST). From Dite et al. (2003)

and at the end of, the 2-year follow-up, which revealed a rapid and sustained pain relief among the surgical group (Figure 6.5). Complete or partial pain relief was achieved at the end of the 2-year follow-up among 32% of the endoscopic group and 75% of the surgical group ($p = 0.007$). In addition, the quality of life score for physical health was significantly lower in the endoscopic group compared to the surgical group ($p = 0.003$).

## 6.7 Conclusions

The data reviewed here show that both endoscopic and surgical approaches can give good outcomes in selected patients with painful chronic pancreatitis, managed in expert centers. Only two trials have compared endoscopic and surgical drainage for pain relief in patients with evidence of pancreatic duct obstruction in a randomized fashion. Both techniques are associated with good early results, with similar rates of

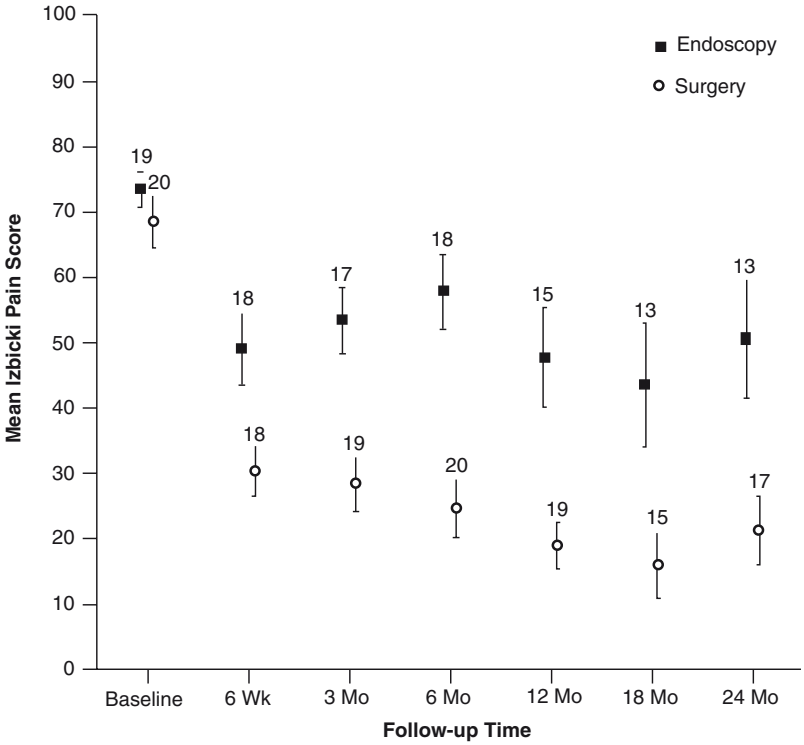


**Fig. 6.5** Mean Izbicki pain scores at baseline and at 6 weeks, 3, 6, 12, 18, 24 months after endoscopic or surgical drainage. Bars represent standard errors. The number of observations is shown above each bar. The Izbicki pain score ranges from 0 to 100, with higher scores indicating more severe pain. From Cahen et al. (2007)

pain relief in the first year. However, endoscopic treatment is more often followed by symptom relapse, which requires further intervention, including surgery, to improve symptoms and prevent deterioration in pancreatic function. The two randomized comparisons of endoscopic and surgical treatment have been small, but both suggest that surgery gives better long-term pain relief at 2–5 years.

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# Chapter 7
# Duodenum-Preserving Pancreatic Resection with Pancreatic Duct Drainage: What Is the Role of Supraduodenal Biliary Drainage?

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Biliary stricture due to severe pancreatic disorders such as inflammatory masses or chronic pseudocysts is a recognized complication of chronic pancreatitis (CP). The anatomical relationship of the distal common bile duct with the head of the pancreas is the main factor for its involvement in CP.

Surgical series addressing CP-induced extrapancreatic pathologies report an incidence of duodenal obstruction of approximately 12% (range: 2–36%) (Izbicki et al. 1994; Taylor et al. 1991; Beger et al. 1990; Sugerman et al. 1986; Bradley 1986; Prinz et al. 1985; Warshaw 1985; Grodsinsky and Block 1980; Frey 1978; Frey et al. 1976; Guillemin et al. 1971), whereas that of CBD stenosis is substantially higher at about 30% (range: 15–46%) (Sugerman et al. 1986; Prinz et al. 1985; Grodsinsky and Block 1980; Frey 1978; Huizinga and Baker 1993; Pereira-Lima et al. 1989; Wislooff et al. 1982; Stabile et al. 1987; da Cunha et al. 1984; Lygidakis, 1983 Jun; Gall et al. 1982; Traverso et al. 1979).

The therapeutic approach to CP-related CBD stenosis depends on the clinical symptoms, in particular on whether or not a chronic pain syndrome exists. One previous study investigated whether endoscopic stenting of CBD stenosis without surgically addressing parenchymal lesions due to CP results in effective pain relief. Although after a 1-year follow-up period the entire cohort of 61 patients subjected to endoscopic stenting experienced complete resolution of biliary obstruction; this had no influence on pain intensity. Pain score even slightly increased from 6.8 ± 6.3 before stenting to 7.7 ± 7.7 after stenting (Kahl et al. 2004). Studies comparing endoscopic stenting versus surgical choledocho-jejunostomy for treatment of the unusual, rather theoretical, clinical setting of CP-related painless CBD stenosis have not been published so far.

In contrast, when distal CBD obstruction is associated with chronic upper abdominal pain, any surgery limited to the treatment of CBD stenosis will, with regard to pain control, most likely fail. Therefore, a customized surgical treatment should consider the following aspects:

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a. The site of CBD stenosis, i.e., whether it is located distally or cranially to the first part of the duodenum
b. The length of the stenotic segment
c. The nature of the CBD pathology, i.e., whether the stenosis is due to extrinsic reasons, such as inflammatory tumors, cephalic pseudocysts, periductal pancreatic scarring, or whether the CBD itself has been chronically damaged. This may occur as a result of an ongoing biliary obstruction with recurrent episodes of cholangitis

Usually, CBD strictures are restricted to the intrapancreatic course of the CBD. Therefore, differential diagnosis of atypical, CP-related long-segment strictures involving the supraduodenal CBD should also always consider the possibility of malignant transformation.

Although surgical treatment of CBD strictures which do not "spontaneously" resolve after the removal of pancreatic head pathology depends basically on the site of the stricture, it has also to be emphasized that decision making in the individual patient must be based on institutional experiences, due to the lack of controlled comparative studies. It has also been suggested, controversially, that duodenum-preserving pancreatic head resection (DPPHR) loses its benefits compared to pylorus-preserving (PPPD) or classical partial pancreato-duodenectomy (cPD), if the continuity of the bile duct has to be interrupted.

In patients in whom the removal of the pancreatic head does not result in decompression of the intrapancreatic CBD, the restoration of biliary flow represents the second, equally important, part of the operation. What is the adequate surgical treatment when distal CBD stricture is not due to "simple" extrinsic compression but originates from a chronically injured ductal epithelium?

In principle, depending on the site of CBD stricture, pancreatic head resection can be combined with the following procedures to restore bile flow:

Typical, intrapancreatic localization of CBD stenosis ("infraduodenal"):

a. DPPHR with reinsertion of the pre-stenotic CBD in the resection cavity (Hamburg procedure) (Izbicki et al. 1997)
b. Extended coring of the pancreatic head resulting in an entire decompression of the intrapancreatic CBD (Bern procedure) (Gloor et al. 2001)
c. DPPHR with transsection of the pancreas above the portal vein + infraduodenal choledocho-jejunal anastomosis of the pre-stenotic CBD with the jejunal loop used for the pancreatico-jejunostomy (Beger procedure) (Beger et al. 1985)

Atypical biliary obstruction extending to the retro- and supraduodenal CBD:

d. Roux-en Y choledocho-jejunostomy between the supraduodenal CBD and the oral stump of the jejunal loop used for the pancreatico-jejunostomy (Sugerman procedure I) (Sugerman et al. 1986)
e. Roux-en Y pancreatico-choledochostomy combined with supraduodenal side-to-side choledocho-duodenostomy (Sugerman procedure II) (Sugerman et al. 1986)
f. PPPD/cPD

Whereas both DPPHR with CBD reinsertion and the modified Beger operation combine decompression of the pancreatic head with an internal biliary drainage,

PPPD, cPD, and both Sugerman procedures represent classical, extrapancreatic ("supraduodenal") bilio-enteric anastomosis.

What is the incidence of patients who require any kind of concomitant biliary drainage during surgery for CP? Although CBD stricture is one of the major complications of CP, this question has so far not been systematically evaluated. Nor has been any study published which addresses the rate of secondary salvage procedures for treatment of biliary obstruction after previous surgery for CP. This lack of data concerns patients with a normal ductal diameter who develop "de novo" CBD stricture after primary surgery as well as those in whom biliary obstruction is addressed at the time of primary surgery, but develop recurrent CBD stricture after the index operation. It is most likely that the incidence of postoperative CBD stricture after surgery for CP is rather higher than that after Whipple resection which, according to the recently published Johns Hopkins series evaluating the outcome in 1,595 pancreatoduodenectomy patients, accounts for 2.6% (House et al. 2006). In any case, this percentage is substantially lower than the anastomotic stricture rate associated with the Hamburg procedure of CBD reinsertion in the resection cavity (18%, Cataldegirmen et al. 2008.

In summary, until procedures, such as the Frey and the Beger operations have been critically evaluated with regard to postoperative CBD stricture rates, "best treatment" recommendations with respect to possible indications for supraduodenal biliary drainage are difficult to formulate. This concerns especially CBD strictures due to a chronically injured ductal epithelium and the rare cases of long-segment pathologies extending up to the supraduodenal bile duct. At the moment, intraoperative decision-making on how to manage a supraduodenal CBD stricture complicating chronic pancreatitis is based on institutional experiences or even the individual surgeon's discretion rather than on any evidence provided by controlled studies. Such an analysis should especially focus on the following aspects: What is the overall rate of CBD stricture in chronic pancreatitis patients? What is the rate of patients whose CBD involvement extends up to the supraduodenal part of the CBD? What are the institutional experiences of specialized pancreatic centres regarding the surgical management of the aforementioned pathologies? A meticulous analysis of these questions based on databases which already exist in several specialized centers is mandatory before any recommendation concerning the "best" surgical procedure for CBD stricture due to CP and possible indications for supraduodenal bilio-enteric anastomosis.

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# Part III
# Potential Trials in Pancreatic Cancer

# Chapter 8
# Pain Management and Nutritional Support in Nonresectable Pancreatic Cancer

**David P. Berry, Richard M. Charnley, Christos Dervenis, Gareth R. Kirk, Francis Regan, Emre F. Yekebas, and Clement W. Imrie**

Despite the fact that 80–85% of the patients with pancreatic cancer present with nonresectable disease and are therefore a large patient cohort (approximately 5,500 patients with pancreatic cancer per annum in the UK alone), the available literature is sparse and there have been few good-quality studies in this patient group. The specific topics of pain relief and nutritional support in these patients with unresectable pancreatic cancer have received very little interest in the literature over many years. We present our review of the relevant literature and discussions regarding future investigations of these two important topics, as discussed at the meeting at the Royal College of Physicians and Surgeons in Glasgow, entitled "Pancreatic Diseases, the Challenges," in March 2007.

## 8.1 Pain Management

Pain in pancreatic cancer is widely reported as being a frequent event. The evidence base for this is poor, and as long ago as 1991, Hudis et al. (1991) at the Memorial Sloan Kettering Cancer Center showed that 40% of the patients with pancreatic cancer had no pain at the time of referral and that a further 30% had only minimal complaints of pain. Moderate to severe pain was present only in 30% of the patients and indeed severe pain only in 10% of the patients. These figures were supported by Lillemoe et al. (1993) in the *Annals of Surgery* when they reported that only 20% of the patients with pancreatic cancer had significant pain at the time of assessment. The widely held belief that significant (opioid-dependent) pain is a frequent symptom in pancreatic cancer is not supported by the available literature and whilst there is no doubt that intractable pain can occur in this patient group, the prevalence of pain and its duration in the terminal phases of pancreatic cancer remain to be elucidated.

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When pain occurs and is not managed by analgesics, several methods of pain relief have been described including celiac plexus block, splanchnic nerve block, and surgical splanchnicectomy (more recently using a thoracoscopic approach).

In 1995, Eisenberg et al. (1995) described a meta-analysis of 1,145 patients who had undergone neurolytic celiac plexus blocks for the treatment of cancer pain. They reported 80% good pain relief extending from 2 weeks to greater than 3 months, with the assessment of pain relief on pain scores. In addition to these radiological-guided methods, Gunaratnam et al. (2001) reported 58 patients treated with endoscopic ultrasound-guided celiac plexus neurolysis in 2001 with a 78% reduction in pain score. Following these studies in 2004, Wong et al. (2004) reported 100 patients in a double-blind randomized trial comparing celiac plexus block with opioid. Whilst the pain scores were improved in the celiac plexus block group compared to the opioid group, there was no difference in opioid consumption between the groups. In addition there was no effect on quality of life or survival between the two groups. When comparing different methods of pain block, Ihse et al. (1999) reported 61 patients who were subjected to three different techniques. Two groups underwent celiac plexus block and one a splanchnic nerve block. They reported 60–75% good pain relief; it was noticeable that the earlier the block was performed, the more effective this was as judged by reduction in pain scores. There was no difference between the various techniques reported in this study.

Lillemoe et al. (1993) reported a prospective randomized double-blind trial of 137 patients with unresectable pancreatic cancer at the time of laparotomy receiving either intraoperative chemical splanchnicectomy versus placebo. Interestingly, only 34 patients had significant pain at the time of diagnosis. Postoperatively there were lower pain scores in the treatment group and good pain relief was associated with improved survival. Improved pain control in the postoperative period was also reported in those patients who did not have pain at the time of diagnosis and entry into the trial, suggesting again that early intervention was more effective.

In 1993, Worsey et al. (1993) reported thoracoscopic pancreatic denervation for pain control in unresectable pancreatic cancer. This was a case report but identified thoracoscopic splanchnicectomy as an alternative to a radiological procedure. The advantage of thoracoscopic splanchnicectomy is that it is permanent and the nerves are visualized; however, the disadvantages are that it requires a general anesthetic and there is a small risk of open thoracotomy reported for bleeding. In 1999, Ihse et al. (1999) reported 44 patients undergoing thoracoscopic splanchnicectomy, 23 of whom had pancreatic cancer. They reported a 50% reduction in visual analog scores following thoracoscopic splanchnicectomy suggesting this procedure as an alternative to celiac plexus block and splanchnic nerve blocks.

## 8.2 Nutritional Support

A well-recognized feature of patients with advanced cancer is the so-called cancer cachexia syndrome resulting in profound weight loss. Many patients with pancreatic cancer suffer with cancer cachexia, which is the result of either altered metabolism

or reduced food intake. It is widely reported in the literature that most pancreatic cancer patients lose at least 3 kg a month of body weight and there have been some reports investigating whether or not this trend can be reversed. Wigmore et al. (1996) and Barber et al. (1999) both reported small studies. These were two studies from the same unit reporting the administration of nutritional supplements in the form of small volume drinks to patients with unresectable pancreatic cancer. The supplements contained 620 kcal, 32 g of protein, and 2.2 g of eicosapentaenoic acid (EPA). These two studies reported weight gain in patients of 2 kg at 7 weeks (expected weight loss 6 kg) and importantly the weight gain represented gain of lean body mass. Fearon et al. (2003) published a randomized series of 200 patients receiving the same supplements with or without EPA. Both groups gained weight without a significant difference between groups suggesting that the addition of EPA was not as important as the additional calories and protein.

In 2004, Davidson et al. (2004) reported 107 patients analyzed with a post hoc analysis. They reported that the addition of supplements on the above scheme lead to stable weight and this improved survival and increased quality of life. Bauer et al. (2005) reported the same 200 patients as in the Fearon report of 2003 highlighting that the intake of the supplements resulted in increased intake of calories and protein, but did not replace normal eating.

As most pancreatic cancer occurs in the head of the gland these patients may develop pancreatic insufficiency. The prevalence of pancreatic insufficiency is unclear and the only report to date of pancreatic enzyme supplements is by Bruno et al. (1998). Twenty-one patients with unresectable pancreatic cancer underwent an 8-week randomized double-blind trial. Patients were given 200,000 units of Lipase per day and in the enzyme group, body weight increased by 1.2%, whereas in the control group, body weight reduced by 3.9%. No nutritional supplements were given suggesting that pancreatic enzyme supplementation alone can reverse some of the weight loss in these patients.

## 8.3 Discussion

These aforementioned papers represent the most significant contributions to the literature on the topics of pain management and nutritional support in patients with unresectable pancreatic cancer. The authors considered all the available evidence and after discussion of the evidence in a small group setting presented their findings to the main meeting for further discussion.

With regard to pain management, the discussion first centered on the prevalence and duration of pain in the course of patients with unresectable pancreatic cancer. There was a consensus agreement that neither question could be answered on the available data. The discussion of pain management was expanded to consider all other factors that might influence pain, such as biological factors (anatomical and functional abnormalities), psychological factors (mood, sleep pattern, and coping mechanisms), and social factors (domestic situation, work and finances and social interaction), and there was an agreement that these components of the so-called

biopsychosocial model of pain had not been addressed in previous studies. With regard to interventions for pain relief, there was a consensus agreement that the current data are unclear as to whether intervention is desired, and if so, which intervention is the best, although some studies suggest earlier intervention to be more effective. There was much discussion as how best to assess the effect of the pain interventions with clinical significance and recognition that pancreatic cancer is a progressive disease, and once pain was present, it was unlikely that the pain would be completely alleviated, and so in future studies, it would be desirable to investigate the concept of "manageable" pain.

With regard to body weight and nutritional support in patients with unresectable pancreatic cancer, there was a consensus agreement that compelling evidence exists to support the use of nutritional supplements and pancreatic enzyme supplementation.

The discussion was expanded and there was a consensus agreement that the palliative care of these patients should be linked to biochemical data, such as C-reactive protein (CRP) (see chapter 11 for more details) to try and identify patients who will survive long term and those who will demise rapidly.

The proposal of the study group was for an observational study. It was suggested that simple data be collected on a national basis. These data should include all nonresection patients with pancreatic cancer and include data on pain (at presentation and the timing of onset during the course of the disease and the presence of manageable pain), pain management (interventions and medication), weight loss, dietary and pancreatic enzyme supplements, chemotherapy, and survival. In addition, these data should be cross-referenced to biochemical data. The proposal was that a simple data set be collected in a multicenter study of consecutive patients. It is anticipated that this would provide sufficient information to assess the prevalence of pain and current practice with regard nutritional support and the prescribing of pancreatic enzyme supplementation. Discussions also centered on a trial of pancreatic enzyme supplementation and it was agreed that this should be explored further with interested parties. There was a consensus agreement that prospective trials on these topics were not indicated at present until the observational data were obtained and analyzed.

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# Chapter 9
# Endoscopic Therapy in the Palliation of Nonresectable Pancreatic Cancer

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Biliary obstruction and duodenal stenosis are common complications of pancreatic head cancer. In patients who are not candidates for surgical resection both surgical and endoscopic procedures can be used to palliate jaundice or gastric outlet obstruction.

## 9.1 Obstructive Jaundice

The first meta-analysis which compared endoscopic biliary stenting with surgical bypass in patients with nonresectable malignant distal bile duct obstruction was published by Taylor et al. (2000). The inclusion criteria for the evaluated studies, published in English, were randomized patient assignment and 20 or more patients per group, which were followed up until death. Only three trials met the inclusion criteria. All of them compared surgery with plastic biliary stents. The final analysis concluded that more treatment sessions were required after endoscopic stent placement than after surgery. Thirty-day mortality was not significantly different (*OR* = 0.522; 95% CI, 0.263–1.036).

Further meta-analysis was published in 2006. Moss et al. reviewed randomized, controlled trials comparing surgery and endoscopic stenting, endoscopic metal stents and plastic stents, and different types of endoscopic plastic and metal stents (Moss et al. 2006a). Altogether 21 trials were evaluated involving 1,454 patients. Based on meta-analysis, endoscopic stenting with plastic stents appears to be associated with a reduced risk of complications (RR 0.60, 95% CI, 0.45– 0.81). However, the risk of recurrent biliary obstruction prior to death was higher in the stented patients (RR 18.59, 95% CI, 5.33–64.86). There was a trend towards higher 30-day mortality in the surgical group but the difference was statistically not significant ($p$ = 0.07, RR 0.58, 95% CI, 0.32–1.04). In endoscopic stent comparisons, metal stents had a lower risk of recurrent biliary obstruction than plastic stents (RR

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0.52, 95% CI, 0.39–0.69). The meta-analysis failed to find significant statistical difference in technical success, therapeutic success, complications, or 30-day mortality. Based on these data the authors concluded that endoscopic metal stents should be the intervention of choice in patients with obstructive jaundice due to nonresectable pancreatic cancer except for cases with very short predicted survival where the patency benefits of a metal stent over a plastic stent may not be realized.

The most recent meta-analysis by the same authors was published in December 2006 (Moss et al. 2006b) with the addition of almost 1,000 patients. The results of this analysis were very similar. Endoscopic biliary stenting with a plastic stent was found to be associated with a lower risk of complications but a higher risk of recurrent biliary obstruction than surgical bypass procedures. Seven studies were found comparing self-expanding metal stents with plastic stents. Metal stents were associated with a significantly reduced risk of recurrent biliary obstruction at 4 months (RR 0.44, 95% CI, 0.3–0.63), prior to death or end of study (RR 0.52, 95% CI, 0.39–0.69). No statistically significant differences were detected in technical success, therapeutic success, mortality, or complications. The cost-effectiveness outcomes were not suitable for meta-analysis.

It is generally accepted that metallic stents have a greater initial cost, but provide an overall cost saving in patients with expected survival duration of over 6 months (Andtbacka et al. 2004). Other workers have concluded that biliary self-expanding metal stents should be placed, if expected survival is more than 6 months, and plastic stents, if expected survival is less than 6 months (Srikureja and Chang 2005). How this decision is reached has not been defined accurately.

Very few studies have compared endoscopic metallic stents with surgical bypass. A retrospective analysis was published in 2001 from Japan (Maosheng et al. 2001). The prevalence of late complications was lower after surgical bypass, but a shorter hospitalization period and lower treatment cost were found using endoscopic metallic stents.

A small but unique study was published from Amsterdam in 2003 (Nieveen van Dijkum et al. 2003). The objective of the primary study was to evaluate the efficacy of laparoscopic staging in patients with pancreatic cancer. In a secondary study, 27 patients, who underwent laparoscopy and were defined as having nonresectable disease, were randomized into two groups. Thirteen patients underwent a surgical bypass procedure while 14 patients had a self-expanding metal biliary stent inserted at duodenoscopy. Both the mean survival (116 versus 192 days) and the mean hospital-free survival (94 versus 164 days) were significantly shorter in the stented group. The difference in survival was 70 days ($p < 0.05$).

The first primary, prospective, randomized trial comparing surgical bypass with metallic biliary stenting in nonresectable pancreatic cancer was published in 2006 (Artifon et al. 2006). Artifon et al. from Brazil randomized 30 patients with metastatic pancreatic cancer without gastric outlet obstruction. Both surgical and endoscopic drainage procedures were successful without any mortality in the first 30 days. The cost of the biliary drainage procedure (US$2,832 versus US$3,821), the cost of care during the first 30 days (US$3,100 versus US$6,500), and the overall total cost of care (US$4,200 versus US$8,300) were significantly lower in the

endoscopy group. In addition, the quality of life scores were better in the endoscopy group at 30 days ($p = 0.042$) and at 60 days ($P = 0.05$). There was no difference between the groups in complication rate, readmissions for complications, and duration of survival. Based on this randomized, controlled trial the authors concluded that endoscopic drainage with a metallic biliary stent is more cost-effective and provides a better quality of life than a surgical bypass procedure in patients with obstructive jaundice due to nonresectable pancreatic cancer.

The international group who met in Glasgow between March 1–3, 2007 discussed the literature referred to above and concluded that patients presenting with obstructive jaundice due to extra-hepatic bile duct compression arising from nonresectable cancer of the pancreas should receive palliation of their jaundice using trans-duodenal endoscopic biliary stenting where possible. When a decision has been made not to proceed to surgical resection a self-expanding metallic biliary stent should be used unless there is convincing evidence that survival will be less than 12 weeks when a plastic biliary stent of at least 10 FG will be cost-effective. It is recognized that it is usually difficult to make an accurate prediction as to length of survival in any one individual and because of this the use of metallic biliary stents is to be encouraged. Patients, carers, and primary physicians should be made aware of the possibility of stent blockage and re-referral should be advised if appropriate signs/symptoms arise.

## 9.2 Duodenal Obstruction

The other possible application of endoscopic therapy in nonresectable pancreatic cancer is the use of stents for duodenal obstruction presenting as symptomatic gastric outlet obstruction. Endoscopic placement of self-expanding metallic stents has been used as palliative treatment of patients with malignant obstruction of the gastrointestinal tract for over a decade. The first systematic review of their clinical effectiveness was published by Dormann et al. (2004). A total of 136 relevant publications were found in the literature between January 1992 and September 2003. The analysis included 32 case series evaluating technical success (successful stent placement and deployment), clinical success (relief of symptoms such as nausea and vomiting, and/or improvement of food intake), and complications. Only ten of the studies were prospective and none of them were controlled. Based on data from 606 stent insertions a technical success rate of 97% was reported. Clinical success was achieved in 526 patients (87% of the entire group). Oral fluid intake became possible in all of the patients in whom a successful procedure was carried out. There was no procedure-related mortality. Bleeding or perforation was observed after only 1.2% of the procedures reported. The rate of stent migration was low (5%). Obstruction of the stent – mainly due to tumor infiltration – occurred in 18%. The mean survival of the patients was 12 weeks. Based on the data from this review the procedure appears to be a safe and effective treatment option in patients with a short remaining lifespan.

Reviewing the literature reveals that no randomized, controlled trials on this subject have been published to date. Only five retrospective case series and a prospective study from the UK were found. A Japanese group retrospectively compared stent insertion and surgical bypass over a 9-year period in 20 and 19 patients, respectively (Maetani et al. 2004). No differences were detected with regard to technical and clinical success, survival, and the incidence of complications. There was no procedure-related mortality in either group. However, the time from the procedure to resumption of food intake was significantly shorter in the stent group (1 day versus 9 days) and improvement in the performance score after the procedure was observed more frequently in the stent group (65% versus 26.3%).

Lindsay et al. evaluated the data of 40 patients with malignant gastric outlet obstruction who were unsuitable for surgical bypass and underwent gastroduodenal metallic stent insertion (Lindsay et al. 2004). The primary tumor was pancreatobiliary in 15 cases. A stent was successfully placed in all the cases. Altogether 82.5% of the patients were discharged from hospital. In a multicenter, retrospective study from Boston, 176 gastroduodenal metal stent insertions were analyzed (Telford et al. 2004). In this series 84% of the patients resumed oral intake for a median time of 146 days. A retrospective evaluation of metallic stenting for duodenal obstruction by an Italian group included a significant number of patients with pancreatic cancer – 27 from 33 cases (Fiocca et al. 2006). The authors detected improvement in the quality of life in all patients.

Mosler et al. reviewed data from 36 patients offered stenting for duodenal obstruction (Mosler et al. 2005). The technical success was high (92%) and clinical improvement was detected in 75%. However, there was a significant incidence of stent dysfunction (36%) which required subsequent intervention. The authors suggested that due to these complications and the short life expectancy of the patient group gastroduodenal metallic stent placement should only be offered to selected individuals.

A prospective study was published from Birmingham in 2004 (Holt et al. 2004). Self-expanding metallic stent placement was successful in 26 of 28 patients with nonresectable gastric or pancreatic cancer. After stenting 24 patients resumed an adequate liquid and semisolid diet. The stent insertion facilitated hospital discharge for 20 of the 28 patients.

In the largest reported series to date, Lowe et al. (2007) described gastroduodenal stent placement in 87 patients, with 97% successful positioning, and 87% resumption of oral intake. Successful stenting was associated with improvement in performance status, and a mean survival of 107 days.

The experts attending the Glasgow meeting concluded that gastroduodenal stenting using an endoscopically placed uncovered self-expanding metallic stent appears to be a feasible option for the palliation of gastric outlet obstruction due to duodenal compression from nonresectable pancreatic cancer. It must be recognized, however, that oral intake will not be normalized by this technique due to the inherent limitations of the stent and techniques such as laparoscopic gastrojejunostomy should also be evaluated in this situation. The consensus from the Glasgow meeting of experts was that what is required in the first instance is an international, multicenter,

prospective, web-based observational study to accurately record the efficacy of techniques currently used to palliate symptomatic duodenal obstruction due to nonresectable pancreatic cancer. Data accrual should not take too long due to the natural history of the condition being studied.

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# Chapter 10
# Pancreatic Endocrine Tumors

**Damian J. Mole, Caroline S. Verbeke, and Nicholas S. Reed**

## 10.1 Introduction

Pancreatic endocrine tumors are relatively uncommon, accounting for approximately five to ten cases per million persons per year (Heitz et al. 2004). They may be classified as functioning or nonfunctioning. Functioning tumors (those with secretory neuropeptide function) are usually associated with classical syndromes. These include VIPomas, gastrinomas, glucagonomas, and insulinomas (Ramage et al. 2005). At least one third of the tumors may be nonfunctioning, despite typical pathological appearances of well-differentiated endocrine tumors or carcinomas (Clarke et al. 1997). Circulating levels of gut hormones may be detected even in the absence of symptoms (Clarke et al. 1997; Rindi et al. 2006).

The primary management of these tumors should be surgical resection wherever possible, as this offers the only chance of cure (Ramage et al. 2005). Given the rarity of these tumors, and the potential complexity of surgery, a multidisciplinary team approach in a small number of regional or supraregional units is likely to result in optimal management (Ramage et al. 2005). Accurate preoperative imaging is essential for the planning of the correct procedure and at a minimum will include CT or MRI (Oberg 2000). If the clinical course permits, radionuclide scintigraphy with Octreoscan imaging and the emerging use of PET CT with $^{18}$FDG PET or $^{18}$F-DOPA may contribute important details (Oberg 2000). Surgery may still be considered if there are regional lymph nodes and liver metastases, which could be resected at the time of the primary surgery; however, each case should be assessed on its own merit. Other techniques, including radio-frequency ablation, may be considered. After operation, the suitability of adjuvant treatment may be discussed in the light of the operative and histopathological findings. Review of the pathology and risk factors is best carried out by a dedicated histopathologist with an interest in pancreatic endocrine tumors (Rindi et al. 2006).

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## 10.2 Histopathology

To date, the WHO classification of pancreatic endocrine tumors (Heitz et al. 2004) provides the most reliable and accurate prediction of the biological behavior of pancreatic endocrine tumors (Table 10.1). It provides guidance to distinguish between poorly differentiated and well-differentiated tumors and to distinguish well-differentiated tumors likely to metastasize from those with little or no metastatic potential. The classification is based on the following morphological criteria: tumor size, vascular invasion, proliferative activity, histological differentiation, invasion of adjacent organs, and presence of metastases, combined with the hormonal activity of the tumor.

In everyday practice, however, the ability to predict whether a particular endocrine tumor will metastasize may be redundant, as approximately one third of the patients have liver metastases at presentation. The rate of tumor growth, disease progression, and survival vary, and many patients often maintain a good quality of life for long periods.

As outlined below, treatment planning for these patients is challenging, as there is currently no evidence-based consensus regarding the therapeutic options that are to be offered at any particular stage of the disease. The WHO classification offers no guidance in this context (Bajetta et al. 2005), and unfortunately, so far, only a few studies have aimed at identifying patient- or tumor-related prognostic factors in these settings. The recent proposal of a TNM staging system for pancreatic endocrine

**Table 10.1** WHO classification of pancreatic endocrine tumors (Heitz et al. 2004)

| |
|---|
| 1. Well-differentiated endocrine tumour |
| 1.1 “Benign” behaviour |
| Confined to the pancreas |
| Not angioinvasive |
| No perineural invasion |
| <2 cm diameter |
| <2 mitoses per 10 high power fields |
| <2% Ki-67 positive cells |
| 1.2 Uncertain behaviour |
| Confined to the pancreas and one or more of: |
| >2 cm diameter |
| 2–10 mitoses per high-power fields |
| >2% Ki-67 positive cells |
| Angioinvasion |
| Perineural invasion |
| 2. Well-differentiated endocrine carcinoma |
| Low-grade malignant |
| Gross local invasion and/or metastases |
| 3. Poorly differentiated endocrine carcinoma |
| High-grade malignant |
| >10 mitoses per high-power field |

tumors by the European Neuroendocrine Tumor Society (ENETS) addresses the urgent need for standards in the stratification and treatment of patients with regional or distant tumor spread (Rindi et al. 2006).

The lack of consensus on the best treatment at different disease stages partially results in our limited understanding of the biological behavior of pancreatic endocrine tumors. Data in the literature suffer from low series numbers, the inclusion of patients with tumors from different sites, and poor standardization of histopathology. While the occurrence of liver metastases is generally believed to mark a point of acceleration in disease progression and a limitation of patient survival, little to no research has gone into the identification of morphological or molecular markers that reflect disease progression and could therefore be of potential use as prognostic factors.

The proliferative activity of the tumor, based on Ki-67 immunostaining, seems an obvious candidate parameter. Despite some controversy over the optimal cut-off levels (Clarke et al. 1997; Gentil Perret et al. 1998; Hochwald et al. 2002; Pelosi et al. 1996), the correlation of the proliferative activity with clinical outcome has been well established. It is an essential criterion in the WHO classification of pancreatic endocrine tumors without distant metastasis, although its extended use for the prediction of the development of distant metastases and their further clinical course has not been formally investigated to date. Despite being hampered by small case numbers and inclusion of cases of both distant and regional lymph node spread, existing studies suggest that although the proliferative activity in primary and metastatic tumors is similar, the Ki-67 index is negatively associated with survival (Hochwald et al. 2002; Pelosi et al. 1996; Jorda et al. 2003). These results are interesting in that they suggest that outcome in patients with pancreatic endocrine tumors may be dependent more on the biological behavior of the tumor than on the stage of tumor evolution at presentation. It is speculated that tumor kinetics may evolve with time, ultimately becoming more aggressive, perhaps with a change in proliferation index. These findings need to be tested in large controlled studies.

## 10.3 Treatment

Because of the rarity of these tumors, few clinical trials and virtually no randomized studies of adjuvant therapy exist. Recommendations are therefore largely based on expert opinion (Ramage et al. 2005), and are summarized in Table 10.2. It is probably safe to recommend that no adjuvant treatment will be required when there has been optimal surgery and minimal residual disease of less than 1 cm. For patients with close excision margins, external beam radiotherapy may be considered, but there is no evidence base to support the routine use of radiotherapy in this tumor group. It may be better reserved for localized relapse. For patients with gross macroscopic residual disease (>1 cm diameter), adjuvant treatment could be considered, and for patients with unresectable disease or where there is bulky residual disease, systemic treatment will be considered (Ramage et al. 2005).

**Table 10.2** Recommendations for adjuvant treatment based on risk category

| Risk | Defining characteristics | Recommended adjuvant treatment |
|---|---|---|
| Low | No residual disease<br>Elevated gut hormone profile only<br>Close excision margins (exact distance unspecified) | No definite indication |
| Intermediate | Minor residual disease (<1 cm diameter)<br>Residual disease (>1 cm diameter) | Uncertain indication |
| High | Inoperable/residual disease<br>Relapsed disease – (potentially resectable but high risk)<br>Relapsed disease – unresectable | Adjuvant treatment advised |

As pancreatic endocrine tumors are generally slow-growing, and although there will be exceptional cases where a much more rapid pattern of growth and metastasis is present, the indolence of these tumors often allows a period of monitoring for several months to try and assess the rate of growth. The use of imaging and biochemical tumor markers such as gut hormones may be helpful in this context. In a patient with a relatively slow-growing tumor it may be appropriate to withhold treatment until there is evidence of tumor progression or the development of symptoms. If recurrence is local or regional then further consideration of surgery should be given. Patients who have a small amount of residual disease with a slow-growing tumor pose the greatest dilemma. There is no consensus on how best to manage these patients and we propose (vide infra) that a retrospective review of this patient group may contribute to our knowledge base of prognostic factors which may help to predict likely outcome and behavior.

## 10.4 Treatment Options

Following surgery, treatment options include:

a. Observation only
b. Chemotherapy
c. Biological agents (e.g., somatostatin analogs and interferon)
d. External beam radiotherapy
e. Combined multimodality therapy
f. Newer conventional drugs
g. Targeted anticancer agents
h. Hepatic artery embolization with or without chemotherapy
i. Targeted radionuclide therapy
j. Radio-frequency ablation

Choice of therapy will depend upon local expertise and practice; however, there should be locally agreed clinical protocols for management in order to standardize the approach to systemic treatment at a regional level, as current postoperative management varies hugely depending on local prejudices, policies, and expertise. The authors believe strongly that multidisciplinary care networks, for example, the UK and Ireland neuroendocrine tumor network, UKINET, and the European neuroendocrine tumor network, ENET, constitute the strategy for the future.

## 10.5 Systemic Treatment

In most centers, systemic management is focused on biological therapies or chemotherapy (Table 10.3). In this context, biological therapies include somatostatin analogs, for example, octreotide and lanreotide, and interferons. Somatostatin analogs may be prescribed in patients with symptoms, but for nonfunctioning, asymptomatic patients, their role has yet to be defined. Interferon may be considered for patients with progressive disease who are already on sandostatin. Interferon therapy is more popular in Scandinavia and Germany than in the UK, despite a failure of sandostatin or interferon singly or in combination to show any advantage in carcinoid tumors. A current trial organized by E-NET, coordinated by Bertram

**Table 10.3** Systemic treatments for pancreatic endocrine tumors. Need to add anti-angiogenesis/VEGFR blocker bevacizumab to above table

| Category | Class of agent | Individual drugs |
|---|---|---|
| Biologicals | Somatostatin analogs | Octreotide |
| | | Lanreotide |
| | Interferons | Interferon α2b |
| Chemotherapy | Conventional agents | Streptozocin |
| | | Adriamycin |
| | | Epirubicin |
| | | DTIC (dacarbazine) |
| | | 5-fluorouracil |
| | | Capecitabine |
| | | Cisplatin |
| | Newer agents | Taxol |
| | | Taxotere |
| | | Irinotecan |
| | | Gemcitabine |
| | | Temozolamide |
| Targeted anticancer agents | EGFR kinase inhibitors | Gefitinib |
| | VEGFR kinase inhibitor | Sorafenib |
| | PDGFR kinase inhibitor | Sorafenib |
| | mTOR pathway inhibitors | Temsirolimus (CC1779) |
| | | Everolimus (RAD001) |

Wiedenmann (Berlin), will compare sandostatin LAR with a chemotherapy combination of streptozotocin and 5-fluorouracil.

## 10.6 Chemotherapy

A greater body of evidence exists for the use of chemotherapy combinations for pancreatic endocrine tumors. Of all the gastroenteropancreatic tumors, those of the pancreas are probably most sensitive to chemotherapy and certainly more so than the classical small intestinal carcinoids. Agents that have been investigated previously include streptozocin (Schein et al. 1974; Murray-Lyon et al. 1968; Broder and Carter 1973; Moertel et al. 1980, 1992; Frame et al. 1988; Bukowski et al. 1992; Rivera and Ajani 1998; Cheng and Saltz 1999; Gonzalez et al. 2003; Delaunoit et al. 2004; Sarker et al. 2004; Kouvaraki et al. 2004; Kulke et al. 2004), adriamycin and epirubicin (Frame et al. 1988; Bajetta et al. 1998; Di Bartolomeo et al. 1995), dimethyltriazenoimidazole carboxamide (DTIC) (Bajetta et al. 1998; Di Bartolomeo et al. 1995; Altimari et al. 1987; Bukowski et al. 1994; Ramanathan et al. 2001), 5-fluorouracil (Moertel et al. 1980, 1992; Bukowski et al. 1992; Rivera and Ajani 1998; Gonzalez et al. 2003; Sarker et al. 2004; Kouvaraki et al. 2004; Bajetta et al. 1998; Di Bartolomeo et al. 1995; Rougier et al. 1991; Fjallskog et al. 2001; Kaltsas et al. 2002; Andreyev et al. 1995), and cisplatin (Sarker et al. 2004; Rougier et al. 1991; Fjallskog et al. 2001; Moertel et al. 1986, 1991; Kulke et al. 2006a). Newer drugs include paclitaxel, docetaxel, irinotecan (Kulke et al. 2006a), gemcitabine (Kulke et al. 2004) and, most recently, temozolomide (Kulke et al. 2006b) and capecitabine.

In the 1960s to the 1980s, most regimens were based on streptozotocin alone or in combination with 5-fluorouracil, doxorubicin, cisplatin, and DTIC. In the 1990s, focus switched to schedules combining 5-fluorouracil/doxorubicin/cisplatin (Rougier et al. 1991), cisplatin/etoposide (Fjallskog et al. 2001), chlorozotocin (Moertel et al. 1980; Bukowski et al. 1992), DTIC alone (Ramanathan et al. 2001), DTIC/5-fluorouracil/epirubicin (Bajetta et al. 1998; Di Bartolomeo et al. 1995), as well as streptozocin/doxorubicin with (Rivera and Ajani 1998) or without 5-fluorouracil (Cheng and Saltz 1999). Since 2000, some of the studies have repeated the previous combinations but CCNU and infusional 5-fluorouracil (Kaltsas et al. 2002) and infusional 5-fluorouracil/interferon (Andreyev et al. 1995) have been investigated.

Most studies have reported response rates of around 30–40%, with a few exceptional studies quoting response rates in excess of 60%, and curiously the paper by Cheng and Saltz (1999) which attempted to repeat the Moertel study (Moertel et al. 1980) which showed less than 10% response rate using objective criteria. Responses may last for an average of 18–24 months. When patients relapse, choice of treatment is difficult. If the treatment-free interval is greater than 18 months, it may be reasonable to consider re-treating the patient with the same regime. There is, however, considerable interest in newer combinations and new treatments. The results of the

UK-NET 01 study (randomized phase II, 80 patients, opened 2006), comparing cisplatin combined with streptozotocin versus cisplatin combined with streptozocin and capecitabine, are keenly awaited.

Newer cytotoxic drugs such as temozolomide may show promise, but many experts would feel that the way forward is probably looking at novel agents such as the targeted anticancer agents. These act by modifying complex overlapping cell-signaling processes. Epidermal growth factor receptor, vascular endothelial growth factor, platelet-derived growth factor receptor, and mammalian target of rapamycin (mTOR/PTEN) are extremely interesting. Early data from phase II studies show that temsirolimus (CCI 779) (an mTOR pathway inhibitor) shows some activity against these tumors (Duran et al. 2006), but a whole variety of targeted agents including the EGFR receptor inhibitors, the VEGF receptor inhibitors, and the anti-angiogenesis drugs need to be evaluated. Novartis has a phase III randomized clinical trial opening in early 2007 (RAD 2324), in which patients with pancreatic endocrine islet-cell tumors will be randomized between everolimus (RAD 001) and best supportive care. Other agents including sorafenib are being investigated, and the future indicates more drugs will be developed. Whether these agents should be used singly or in combination remains unclear; however, given the complexity of cell-signaling, multitargeted therapy may fare better.

## 10.7 Proposed Study

A greater understanding of the molecular changes in pancreatic endocrine tumors as they become capable of spreading to the liver will be key to the success of designing treatment strategies, especially for those patients who have undergone noncurative surgery. Resected primary pancreatic endocrine tumors (and their pair-matched liver metastases) provide a powerful opportunity to conduct translational research exploring the molecular mechanisms associated with metastasis. In addition, nationally collated archived material would constitute a unique and valuable resource which will aid in the development of panels of immunohistochemical markers (for adoption in everyday clinical practice) to help navigate the algorithm of adjuvant therapy. One potentially productive area of study would be to ascertain whether combinatorial expression of certain key oncoproteins and related molecular markers associates with the natural history of pancreatic endocrine cancers.

The evidence presented earlier (histopathology) consolidates the position of Ki-67 as the most logical candidate marker for proliferative activity measurement, but in recent years, multiple other molecular markers, e.g., cytokeratin 19, CD10, CD99, p27, tumor suppressor gene hypermethylation, microsatellite instability, and MAGE1, have been examined for their use as prognostic predictors in pancreatic endocrine tumors (Canavese et al. 2001; Deschamps et al. 2006; Deshpande et al. 2004; Goto et al. 2004; Hansel et al. 2003; House et al. 2003a, b). Immunohistochemical expression of hormone receptors, for example, those for somatostatin, cholecystokinin, vasoactive intestinal peptide, pituitary adenylate cyclase-activating peptide,

tachykinin, serotonin, and dopamine are postulated to associate with clinical course, although only those for somatostatin are currently accepted to be highly relevant (Modlin et al. 2008). From a mechanistic perspective, the neuronal developmental transcription factors mASH1 and NeuroD have been identified as potentially influencing to the development of PET and subsequent survival (Shida et al. 2008). Circulating serum markers, for example, chromogranin-A, chromogranin-B, pancreatic polypeptide, and neuron-specific enolase have diagnostic utility; their clinical application has recently been comprehensively reviewed by Ardill (2008) The proposed study tests the hypothesis:

- Expression of different combinations of key oncoproteins and molecular markers in primary pancreatic endocrine tumors associates with the interval to the first occurrence of liver metastasis (if not already present), with clinical course (in instances of noncurative primary tumor resection), and with overall survival.

The specific aims of the proposed study are:

1. To investigate the prognostic significance of the key oncoproteins and molecular markers, in addition to key transcription factors associated with tumor invasion in primary pancreatic endocrine tumors and in relation to the presence and biological behavior of extrapancreatic metastases.
2. To ascertain the stability of expression of these molecular markers between the primary and daughter liver metastases.

This study may shed light on certain molecular mechanisms of pancreatic endocrine cancer dissemination and lay scientific foundations for novel therapy.

## 10.8 Research Plan

### *10.8.1 Overview of Strategy*

The proposed study will investigate the association between tumor metastasis and expression of key oncoproteins and molecular markers, including those in the non-exhaustive list above. It is important to acknowledge that the identity of the most influential molecular candidates is constantly changing and the list of targets would need to be adapted appropriately at the commencement of the study, not only to take into account the most up-to-date panel of markers, but also to allow scope for an open, forward-looking approach to identify novel markers, using applied genomics, proteomics, and other systems biological tools. Furthermore, the list of specific candidate markers should probably be allowed to evolve during the course of the project. In the proposed study, protein expression would be quantified in resected primary pancreatic endocrine tumors and their pair-matched, and resected liver metastases would be taken from a cohort of 50 patients followed up for 1–15

years from the date of pancreatic tumor excision, both selected from the UK-NET database on the basis of availability of archived tumor material. Ethical approval would be obtained through the National Research Ethics Service through the Integrated Research Application System.

Immunohistochemistry, and potentially in situ hybridization to quantify mRNA expression of target genes, would be performed according to established methods, as previously described and validated (Rudland et al. 2002; El-Tanani et al. 2004). The intensity of staining would be compared with coded, anonymized clinical data pertaining to WHO classification, tumor appearance, stage, grade, adjuvant, and neo-adjuvant therapy, time lapse between primary and secondary resection, and overall survival. Expression levels of the key molecular determinants would be assessed. The prognostic significance of different combinations of expression would then be assessed.

### *10.8.2 Statistical Overview*

Following extensive consultation with two expert medical statisticians, statistical power for a study such as that proposed above may only be usefully analyzed retrospectively. A practical starting point would be to therefore collect the largest number of sample pairs for which specimen data, histology, and clinical data are robust, aiming to achieve 50 matched pairs in the first instance. Previous similar research into the role of the osteopontin transcription activation complex in breast cancer has used a smaller number of unmatched samples with meaningful statistical interpretation (Rudland et al. 2002). Analysis would be by matched pair testing (adapted Sign test for graded scoring), and Cox's proportional hazards modeling for association of protein expression with clinical course and survival

## 10.9 Conclusions

Pancreatic endocrine tumors are fascinating and challenging to treat. Optimal management is probably through a small number of regional or supraregional multidisciplinary teams including surgeons, oncologists, pathologists, and radiologists familiar with this patient group. Locally agreed protocols which interface with regional networks should allow the development of national protocols. We need to strengthen national and European databases to reinforce our evidence base. As a first step, a minimum core data set should be agreed and collected prospectively. Further workshops to achieve consensus on these issues will be of use. Clinical trials are essential to successfully progress in this area in addition to a coordinated approach to translational research. Through these actions, we aim to improve the outlook for patients with pancreatic endocrine tumors.

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# Chapter 11
# The Role of the Systemic Inflammatory Response in Predicting Outcome in Patients with Pancreatic Cancer

**Donald C. McMillan**

## 11.1 Introduction

Although pancreatic cancer is only the tenth most common cancer, it is the sixth most common cause of cancer death in the United States (Jemal et al. 2007). In the UK, each year there are approximately 7,000 cases of pancreatic cancer and a similar number of deaths from the disease. The outlook of these patients remains poor having the lowest, 5-year survival rate of any cancer, being approximately 5% (Cancerstats, www.cancerresearchuk.org).

Pancreatic adenocarcinoma accounts for approximately 80% of all pancreatic cancers. At the time of initial presentation, less than 20% of the patients presenting with pancreatic adenocarcinoma will have operable disease due to local invasion of the adjacent blood vessels, lymphatics, and nerves, or metastatic spread to liver or peritoneum. Although surgery remains the only proven approach for improving survival in patients with pancreatic cancer, it is complicated and is associated with appreciable morbidity and mortality. As a consequence, potentially curative surgery is carried out relatively infrequently and usually in a specialist center. Nevertheless, 5-year survival rates in these patients are commonly less than 25%, and therefore the benefit of radical resection in some patients is not clear.

The majority of the patients with inoperable pancreatic cancer may be offered palliative chemotherapy/radiotherapy regimens. However, selection of patients for palliative chemotherapy/radiotherapy remains problematical, since there is little clear survival advantage (Sultana et al. 2007). This may result in patients undergoing assessment and, perhaps, active treatment in the later stages of their illness, when they may be better served by early referral to palliative care services.

Therefore, the decision on how aggressively to treat these patients is often difficult and depends on a number of factors, including age, medical comorbidity, cancer staging, patient preference, and local expertise. Unfortunately, in many cases,

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individual prognosis is unclear, and decision making, even within the multidisciplinary team, can be subjective. Moreover, detailed pathological findings are only available following a major operation with significant morbidity and mortality.

Therefore, there is an important clinical need to accurately identify patients with biologically aggressive pancreatic cancer, prior to treatment, and to tailor both nonsurgical and surgical therapies accordingly.

## 11.2 Systemic Inflammatory Response

It is now recognized that in addition to tumor stage and proliferative activity, disease progression is dependent on a complex interaction of the tumor and the host inflammatory response (Coussens and Werb 2002; Vakkila and Lotze 2004; DeNardo et al. 2008). There is now good evidence in humans that the presence of a chronic systemic inflammatory response results in the cardinal features of cancer cachexia, principally the progressive loss of weight (in particular lean tissue) and poor survival (Morley et al. 2006; Fearon et al. 2006; McMillan 2008). The most common measures of the systemic inflammatory response in cancer patients have been elevated C-reactive protein concentration or white cell, neutrophil, and platelet counts. Hypoalbuminemia or a low lymphocyte count is also recognized to be part of the systemic inflammatory response (Gabay and Kushner 1999). Indeed, an elevated C-reactive protein concentration and hypoalbuminemia have been included in recent definitions of cancer cachexia (Morley et al. 2006; Fearon et al. 2006).

This concept has led to the development of systemic inflammation-based scores where two or more systemic inflammatory response markers are combined such as the Glasgow Prognostic Score (C-reactive protein and albumin), Neutrophil Lymphocyte Ratio, and the Platelet Lymphocyte Ratio (McMillan 2009). In particular, there is evidence that such scores are useful in esophogastric and colorectal cancer (Crumley et al. 2006a; Crumley et al. 2008; Yamanaka et al. 2007) (McMillan et al. 2007; Ishizuka et al. 2007; Malik et al. 2007; Halazun et al. 2008).

## 11.3 Prognostic Role of the Systemic Inflammatory Response in Advanced/Inoperable Pancreatic Cancer

In advanced inoperable pancreatic cancer it has been recognized since 1995 that the systemic inflammatory response a tumor stage and performance status is independent prognostic factor (Tables 11.1 and 11.2). In particular, an elevated C-reactive protein has been consistently reported to independently predict poor survival in these patients.

For example, Falconer et al. (1995) reported that, in 102 patients with advanced pancreatic cancer, both an elevated C-reactive protein (>10 mg/l) and hypoalbuminemia

**Table 11.1** Systemic inflammatory response as a prognostic factor in patients with advanced inoperable pancreatic cancer

| Author | Patients (n) | Comments |
|---|---|---|
| Falconer et al. 1995 | 102 | CRP and albumin prognostic independent of tumor stage |
| Ueno et al. 2000 | 103 | CRP prognostic independent of tumor stage and treatment |
| Engelken et al. 2003 | 51 | CRP prognostic independent of tumor stage |
| Glen et al. 2006 | 187 | Combination of CRP and albumin (GPS) prognostic independent of tumor stage |
| Fearon et al. 2006 | 170 | CRP prognostic independent of weight loss and reduced food intake |
| Fogar et al. 2006 | 115 | Total lymphocyte count prognostic independent of tumor stage |
| Siddiqui et al. 2007 | 69 | Albumin and white cell count independently predicted survival of less than 6 months |
| Nakachi et al. 2007 | 74 | CRP prognostic independent of performance status and peritoneal dissemination on gemcitabine |
| Tingstedt et al. 2007 | 119 | CRP prognostic independent tumor size and treatment |
| Papadoniou et al. 2008 | 215 | CRP prognostic independent tumor stage and treatment |
| Sawaki et al. 2008 | 66 | CRP component of validated prognostic score for gemcitabine treatment |
| Tanaka et al. 2008 | 264 | CRP prognostic independent of performance status and stage in gemcitabine treatment |
| Pine et al. 2009 | 141 | CRP prognostic independent of age |

**Table 11.2** Systemic inflammatory response as a prognostic factor in patients undergoing resection for pancreatic cancer

| Author | Patients (*n*) | Comments |
|---|---|---|
| Jamieson et al. 2005 | 65 | Preoperative and postoperative CRP prognostic independent of tumor stage |
| Smith et al. 2008 | 110 | Preoperative platelet lymphocyte ratio prognostic independent of tumor size and lymph node ratio |

(<35 g/l) were associated with poorer survival independent of tumor stage. Also, Ueno et al. (2000) assessed the prognostic value of 20 factors in 103 patients with metastatic pancreatic cancer receiving chemotherapy and reported that C-reactive protein was the most significant prognostic factor. More recently, in a large cohort study ($n$ = 187) and with mature follow-up (181 deaths), the combination of an elevated C-reactive protein and hypoalbuminemia (Glasgow Prognostic Score, GPS) was shown to be independent of age and TNM stage (Glen et al. 2006).

To date few studies have examined the prognostic value of white cell counts in patients with advanced inoperable pancreatic cancer. Fogar et al. (2006) reported that, in 115 patients, a low circulating lymphocyte count was associated with poorer survival independent of tumor stage. Also, in 69 patients of varying tumor stage,

low serum albumin and an increased white cell count independently predicted survival of less than 6 months (Siddiqui et al. 2007).

Most recently, a number of studies have examined the value of C-reactive protein as a prognostic factor in patients receiving gemcitabine treatment. Nakachi et al. (2007) reported in 74 patients that C-reactive protein predicted response to treatment. This observation has been confirmed in two other studies containing a total of 330 patients (Sawaki et al. 2008; Tanaka et al. 2008). In the light of the response rate being less than 20%, toxicity and the cost of gemcitabine treatment this is of considerable interest and may enable targeted use of gemcitabine in patients with locally advanced or metastatic pancreatic cancer.

Therefore, it can be concluded that the systemic inflammatory response, in particular an elevated C-reactive protein, improves the prediction of survival in patients with advanced inoperable pancreatic cancer and may be useful in predicting response to gemcitabine treatment.

## 11.4 Prognostic Role of the Systemic Inflammatory Response in Resectable Pancreatic Cancer

The value of the preoperative systemic inflammatory response, as evidenced by an elevated C-reactive protein concentration, in predicting cancer-specific survival, following potentially curative resection, has been most extensively examined in patients with colorectal cancer (McMillan 2008). There are also a number studies which have shown that an elevated C-reactive protein independently predicts cancer-specific survival, following potentially curative resection of gastroesophageal cancer (Ikeda et al. 2003; Crumley et al. 2006b; Gockel et al. 2006). In contrast, there appears to be only a single study which has examined the prognostic value of a preoperative elevated C-reactive protein in pancreatic cancer. Jamieson et al. (2005) reported that, in 65 patients who underwent potentially curative resection for ductal adenocarcinoma of the head of the pancreas and with mature follow-up (60 deaths), an elevated C-reactive protein concentration prior to, and approximately 1 month following, surgery had prognostic value, independent of age and TNM stage. Recently, Smith et al. (2008) reported that, in a similar group of patients ($n = 110$), the preoperative platelet lymphocyte ratio had prognostic value independent of tumor size and lymph node ratio. Further work is required to validate the prognostic role of the systemic inflammatory response in patients undergoing resection for pancreatic cancer.

Therefore, in resectable pancreatic cancer, the host systemic inflammatory response may also be useful in identifying those patients whose disease will progress rapidly and who are less likely to benefit from surgery and chemotherapy. If this does prove to be the case then an elevated C-reactive protein concentration, platelet lymphocyte ratio, or other marker of the systemic inflammatory response, prior to surgery, might be taken into account as to whether an operation will offer sufficient benefit to the pancreatic cancer patient. For example, the median survival of patients who underwent resection for pancreatic cancer with an elevated C-reactive protein, prior to surgery, was only 8.3 (95% CI 6.6–10.0) months (Jamieson et al. 2005).

In summary, further work is required to establish the value of measures of the systemic inflammatory response as stratification factors and selection criteria in randomized trials and as therapeutic targets in patients with pancreatic cancer. Nevertheless, the presence of a systemic inflammatory response appears to be a reliable tumor-stage-independent prognostic factor in patients with pancreatic cancer. Therefore, a measure of the systemic inflammatory response such as C-reactive protein, albumin, or differential white cell count should be included with tumor staging as part of the routine assessment of all pancreatic cancer patients. As a consequence, this will highlight the need not only to treat the tumor but also the systemic inflammatory response.

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# Part IV
# Topic Reviews

# Chapter 12
# Botulinum Toxin and the Sphincter of Oddi

**William R. Murray**

Sphincter of Oddi (SO) dysfunction can be physical or functional. Physical dysfunction is referred to as SO stenosis, papillary stenosis, or ampullary stenosis and is most commonly due to post-inflammatory fibrosis thought to be secondary to the passage of small gallstones. Symptoms may be biliary and/or pancreatic, and diagnosis is based on the demonstration of a localized SO stricture or its back pressure effects. Endoscopic sphincterotomy is associated with a >90% cure rate (Bistritz and Bain 2006). Physiological dysfunction of the SO is referred to as SO dysfunction or, more accurately, SO hypertension (SOH). In the resting phase, the SO contracts and relaxes up to seven times per minute. SOH is defined by SO manometry, and the critical measurement has been shown to be the relaxation (basal) pressure exhibited by the resting SO. An abnormal SO pressure profile is said to exist when the SO relaxation pressure is >40 mm Hg. SOH has been associated clinically with acalculus biliary pain, postcholecystectomy right upper quadrant abdominal pain, postprandial pancreatic pain and idiopathic recurrent acute pancreatitis (Sherman and Lehman 2001). Updated (Rome III) diagnostic criteria, investigative algorithms and suggestions regarding management were published in 2006 (Behar et al. 2006).

The gold standard diagnostic test for SOH is SO manometry (SOM). Unfortunately, even in experienced hands, SOM is not without risk. It is well recognized that the incidence of acute pancreatitis following SOM performed on patients suspected of having SOH is high (10–30%). This is now thought to be patient determined rather than procedure determined (Freeman and Guda 2004). In a study of 1963 consecutive ERCP procedures, non-jaundiced women with SOH were found to have a 12-fold increase in risk of developing postprocedure pancreatitis when compared to patients without documented risk factors (Freeman et al. 2001). Freeman et al. report an incidence of acute pancreatitis of 19% in 272 patients suspected of having SOH who underwent endoscopic biliary sphincterotomy

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(Freeman et al. 1996). The Rome III group advise that, because of the high incidence of complications, patients requiring SOM should be referred to a specialist unit for assessment (Behar et al. 2006). Unfortunately, these are few and far between.

The second major problem with SO manometry is that the technique can quantify the relaxation pressure of the SO at that moment, but cannot provide any evidence to support the fact that SOH has anything to do with the patient's current symptoms. The author's experience of over 20 years of investigating and treating patients with functional disorders of the gallbladder and SO has led to the conclusion that the majority of these patients have a global gastrointestinal smooth muscle dysfunction syndrome which, at various times, can present with symptoms arising from different parts of the gastrointestinal tract. Other smooth muscle organs are also often affected (e.g., uterus and bladder) and, on the whole, pharmacological treatment is poorly tolerated due to a low threshold for drug side effects. It is therefore quite possible that manometric documentation of SOH is simply a surrogate marker for a global smooth muscle dysfunction in a patient whose symptoms arise from somewhere else. Endoscopic sphincterotomy based on misleading SOM can be detrimental in such a patient, since duodeno-gastric bile reflux with symptomatic bile gastritis may follow. What is needed is a simple, safe "cause and effect" diagnostic test to select patients with SOH which is responsible for their symptoms.

Resting smooth muscle tone in the gut is under the influence of both excitatory (acetylcholine, substance P) and inhibitory (VIP, nitric oxide) neurotransmitters and this balance is disrupted in favor of the former in patients with SOH. Botulinum toxin inhibits the release of acetylcholine at the neuromuscular junction (Zhao and Pasricha 2003). Intrasphincteric injection of botulinum toxin into the SO has been shown to reduce the mean basal sphincter pressure by around 50% (Pasricha et al. 1994; Sand et al. 1998). In a small clinical study 11 of 12 patients with postcholecystectomy right upper quadrant pain, whose symptom settled following botulinum toxin injection into the SO, gained pain relief following endoscopic biliary sphincterotomy (Wehrmann et al. 1998).

The author's experience with botulinum toxin injection into the SO musculature spans around 4 years and currently totals 195 injection procedures in 125 patients. There have been no complications related to the injection of botulinum toxin. Initially patients were observed for 24 h in the hospital, but the author now carries out this procedure as a day case. Duodenoscopy is performed under sedation using a diagnostic duodenoscope. Four 0.5 ml aliquots of 25 units each of botulinum toxin (Botox, Allergan Ltd., UK) are injected into the SO muscle using a 23 gauge variceal injection needle. Botox is made up to a volume of 2 ml with normal saline. If symptoms are related to SOH then the median onset of significant symptom relief is 7 days after injection. Symptom relief lasts from 2–4 months and in the author's experience, if Botox in the SO muscle does relieve pain, patients have no doubt about a positive response which is usually dramatic. Endoscopic sphincterotomy should be discussed with patients who have a positive Botox response, while patients with 2 negative Botox responses can be reassured that SOH is not the cause of their symptoms.

A prospective audit has been carried out and preliminary results have been presented (Kong et al. 2007). Information is available for the most easily defined group of patients, i.e., patients presenting with postcholecystectomy biliary pain without evidence of biliary pathology. To date 64 such patients have been studied, 57 of them female. Forty-one of these patients underwent manometry and 68% were found to have SO relaxation pressures >40 mm Hg, the definition of SOH. As the results with Botox became apparent fewer patients were submitted to SOM. Forty-six of the 64 patients (72%) had temporary right upper quadrant (RUQ) pain relief following Botox injection into their SO musculature. These 46 patients underwent endoscopic biliary sphincterotomy with RUQ pain relief in 44 (96%). The accuracy of prediction of RUQ pain relief following biliary endoscopic sphincterotomy for postcholecystectomy patients was 81% for SOM alone, 94% for a positive Botox test alone and 100% for positive SOM plus a positive Botox test. It is currently the author's opinion that the small gain achieved by adding SOM to a Botox test does not justify the risk of acute pancreatitis incurred by SOM.

Botox injection into the SO appears to be a simple and safe technique to determine clinically whether or not SOH is contributing to symptoms thought to be arising from functional spasm of the SO. Botox only acts where it is injected and has no systemic side effects. The sphincter relaxation induced by one session of Botox injections lasts long enough for most patients with genuine symptomatic SOH to experience a significant clinical difference. The exception to this is idiopathic recurrent acute pancreatitis where the interval between attacks is usually too long for Botox to be useful. The neuromuscular blockade induced by Botox wears off and no long-term detriment has been demonstrated following one injection session. It is the author's experience that Botox relaxation of the SO can unmask patients susceptible to duodeno-gastric reflux and symptomatic bile gastritis. This should be taken into account when discussing biliary endoscopic sphincterotomy with Botox-positive patients and should warn against sphincterotomy for Botox-negative patients.

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# Chapter 13
# The European Study Group for Pancreatic Cancer (ESPAC) Trials

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## 13.1 Introduction

Pancreatic cancer is one of the most lethal malignancies with recent data quoting a worldwide annual incidence of 232,306 cases, resulting in 227,023 deaths (http://www-dep.iarc.fr/). In spite of the recent advances in the understanding of the biology, refined imaging systems, and improving surgical outcomes of pancreatic cancer, the overall 5-year survival for pancreatic cancer remains poor at less than 5% (Cress et al. 2006; Bramhall et al. 1995).

Surgical resection remains the only potentially curative intervention. Due to late presentation, however, curative resections can be offered to only 10–15% of patients with pancreatic cancer (Alexakis et al. 2004) and confer only a median survival of 12–15 months (Shaib et al. 2007; Wagner et al. 2004). The aggressive biology of pancreatic cancer dictates that even following resection, the majority of patients experience tumor recurrence either locally or through distant metastases.

In an effort to improve survival, more radical approaches to surgical resections including extended lymphadenectomy and total pancreatectomy have been attempted; however, these have failed to prove any demonstrable survival benefit (Fortner et al. 1996; Muller et al. 2007; Pedrazzoli et al. 1998; Yeo et al. 2002; Farnell et al. 2005), and hence, their use has largely been abandoned. The logical approach to improving survival is to investigate the role of adjuvant therapy in pancreatic cancer.

The European Study Group for Pancreatic Cancer (ESPAC) was set up in order to conduct the largest prospective randomized trial of adjuvant chemotherapy and chemoradiotherapy in resected pancreatic cancer, the ESPAC-1 trial. This provided clear evidence of the benefit from adjuvant chemotherapy (5-Flourouracil (5-FU) and folinic acid) in resected pancreatic cancer. The ESPAC group has continued to investigate adjuvant therapy in pancreatic cancer; the ESPAC-3 trial, which has

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closed to recruitment and the results of which are awaited, compared adjuvant 5-FU with adjuvant gemcitabine, and the ESPAC-4 trial is now recruiting patients into a two-arm, open-label, phase III, multicenter randomized control trial of adjuvant gemcitabine and capecitabine versus adjuvant gemcitabine alone.

## 13.2 Rationale Behind the ESPAC Trials

Trials of adjuvant therapy in pancreatic cancer were initiated as a result of studies published in the late 1960s and early 1970s demonstrating good tumor response following treatment with radiation alone or with a combination of chemoradiation in locally unresectable pancreatic cancer (Haslam et al. 1973; Moertel et al. 1969). These studies served as the basis for one of the first prospective, randomized trials to evaluate the role of adjuvant chemoradiation in the treatment of resected pancreatic adenocarcinoma, which was published by the Gastrointestinal Tumor Study Group (GITSG) in 1985.

### *13.2.1 GITSG Trial*

This trial randomized 43 patients to either 40 Gy radiotherapy with 5-fluorouracil followed by weekly 5-fluorouracil for up to 2 years (21 patients) or no adjuvant treatment (22 patients) (Kalser and Ellenberg 1985). Median survival was 20 months in the treatment group compared with only 11 months in the no treatment group and, therefore, the trial was stopped early. The trial was initially designed to enroll 150 patients in order to have a 90% power to detect a doubling of survival time; however, recruitment was slow and limited to 43 patients over 8 years. Other problems with the trial included poor compliance and quality assurance, only 9% of the patients completed the intended 2 years chemotherapy and 32% had violations of the radiation therapy (Twombly 2008). Given these arguments against GITSG, the authors conducted a confirmatory treatment trial; here, a further 30 patients were entered into the treatment group without randomization with an overall median survival of 18 months and 2-year survival of 46% (Douglass 1987). Unfortunately, even with the extra patients, this trial was too small to demonstrate a statistically significant difference in survival curves.

### *13.2.2 Norwegian Study*

Following this, Bakkevold et al. (1993) conducted a prospective randomized controlled trial of adjuvant chemotherapy in resected pancreatic cancer. The trial evaluated the efficacy of adjuvant combination chemotherapy: 5-FU (500 mg/m$^2$),

doxorubicin (40 mg/m$^2$), and mitomycin C (6 mg/m$^2$), once every 3 weeks for six cycles compared to control. Sixty-one patients were randomized to the adjuvant regimen of combination chemotherapy (30 patients) versus no adjuvant treatment (31 patients). Postoperative radiation was not used (Haslam et al. 1973; Bakkevold et al. 1993). Chemotherapy was associated with an increased median survival (23 months versus 11 months; $p = 0.04$), but there was no difference in 2-year survival ($p = 0.10$). The study pooled both pancreatic and ampullary cancers, and the chemotherapeutic regimen used was associated with an unacceptably high level of treatment-related toxicity, making patient compliance a major issue as only 56% of the treatment group completed the six courses of chemotherapy.

### *13.2.3 EORTC 40891*

In an attempt to confirm or refute the positive findings of the GITSG trial the European Organization for Research and Treatment of Cancer (EORTC) conducted a multicenter prospective randomized phase III trial of adjuvant chemoradiotherapy in 1987, the results of which were published in 1999. Klinkenbijl et al. (1999) recruited 218 patients with pancreatic and ampullary cancer. Randomization was to either observation or radiotherapy with split course radiotherapy (40 Gy) and concurrent 5-FU as continuous infusion. Median survival was 19 months in the observation group and 24.5 months for the treatment group (log rank $P = 0.208$). In patients with pancreatic ductal adenocarcinoma, the trend was in favor of chemoradiation, with the overall survival being 12.6 months in the observation group and 17.1 months in the treatment group ($p = 0.099$). A recent report (Smeenk et al. 2007) on the long-term survival of patients from this trial, after a median follow-up of 11.7 years, reaffirmed that there was no difference in overall survival between the two arms (death rate ratio 0.91, 95% CI 0.68–1.23; $p = 0.54$). The overall 10-year survival was 18% in the entire population, and 8% in the subgroup of pancreas head cancers. The patterns of recurrent disease observed in both arms of the trial were very similar and in each case over 70% of the patients had distant metastases. These findings, again, highlight the need for a systemic component when considering adjuvant therapy for pancreatic cancer. The limitations of this study can be identified as a lack of maintenance chemotherapy and a questionable statistical design that limited its ability to detect a benefit for adjuvant chemoradiation.

### *13.2.4 Johns Hopkins Data*

Two years prior to the publication of the EORTC 40891 trial results, the Johns Hopkins hospital group retrospectively reviewed their experience on adjuvant chemoradiotherapy in 174 patients (Yeo et al. 1997). All the patients had potentially curative resections of pancreatic cancer and received either adjuvant chemoradiotherapy

(modified from the GITSG trial – external beam radiotherapy to the pancreatic bed with prophylactic irradiation of the hepatic bed followed by 5-FU plus leucovorin) or no adjuvant therapy. The median survival in the treatment group was significantly improved compared to the no treatment group (19.5 versus 13.5 months $p = 0.003$). By virtue of this being a retrospective analysis it is prone to selection bias and its results should be viewed with caution.

It should now become evident that reliable data on adjuvant therapy in pancreatic cancer were lacking, and the trials discussed above were inadequately powered. Nevertheless, the GITSG trial especially has tended to influence treatment protocols in the United States where adjuvant chemoradiotherapy is a common practice. For this reason, the European Study Group for Pancreas Cancer (ESPAC) set out to answer the two key questions of adjuvant therapy:

- Is there a role for adjuvant chemotherapy?
- And is there a role for adjuvant chemoradiotherapy?

## 13.3 ESPAC-1

The ESPAC-1 study was designed as a simple, pragmatic trial in order to encourage maximum recruitment. Patients were recruited if they had histologically proven ductal adenocarcinoma of the pancreas which had been macroscopically resected, with no evidence of local spread or distant metastases. The design was as a 2 × 2 factorial trial such that patients were randomized twice; to either chemotherapy (bolus 5-FU 425 mg/m$^2$ plus folinic acid 20 mg/m$^2$ days 1–5, monthly for six cycles) or no chemotherapy and to chemoradiation (20-Gy dose to the tumor given in ten daily fractions over a 2-week period plus an intravenous bolus of 5-FU 500 mg/m$^2$ on each of the first 3 days of radiotherapy and again after a planned break of 2 weeks) or no chemoradiation. Randomization was by phone call or fax to one of the four randomization centers (UK, Switzerland, Germany, and France), where eligibility was checked before treatment was allocated. Randomization was stratified according to center and resection margin status (R0 or R1). Adjuvant therapy was started as soon as possible after recovery from the surgery, and patients were followed up at 3-month intervals until death.

The aim was to recruit a total of 280 patients; 140 into each of the two randomizations. It was powered to detect an excess of 20% deaths at 2 years between each main comparison, at the 5% significance level with 90% power. This calculation assumed that approximately 80% of the patients would have negative resection margins (R0) and a 2-year survival of 20–40% and that the remaining 20% of the patients with positive resection margins (R1) would have a 2-year survival of 1–20%.

Clinicians were encouraged to randomize into the factorial design, to answer the two main questions. Because this approach restricted randomization, the trial was expanded to include randomization options of chemoradiotherapy or chemotherapy only. Clinicians were allowed to randomize to either one or both of the research questions.

Recruitment started in 1994 and finished at the beginning of 2000 having randomized a total of 549 patients from 83 clinicians in 61 cancer centers in 11 countries, thus making it, at the time, the largest adjuvant therapy trial in pancreatic cancer ever completed. A total of 289 patients were randomized into the 2 × 2 factorial design, a further 261 patients were randomized to either chemotherapy or chemoradiation versus observation outside the original design (ESPAC-1 plus).

The results of the ESPAC-1 trial have been the subject of some controversy due largely to confusion over the 2 × 2 trial design, but the results of both the 289 patients entered into both randomizations and the full cohort of patients have been published separately (Neoptolemos et al. 2001, 2004).

In the final analysis, the median survival was 15.9 months in the chemoradiotherapy arm and 17.9 months in the group who were not assigned to receive chemoradiotherapy ($P = 0.05$) (Table 13.1). The estimated 5-year survival was 10% in the chemoradiotherapy arm compared to 20% in those who did not receive chemoradiotherapy ($p = 0.05$).

The lack of a survival advantage following chemoradiotherapy could be due to delays in administering radiation in patients who suffered postoperative complications. This reduces the potential benefit of chemotherapy that is derived by administering it as soon as possible after resection. The arguments that the radiation given during the ESPAC-1 trial was substandard or not exposed to rigorous quality control do not stand up, given that the survival in the individual groups are the same or superior to that observed in North American randomized studies.

As for adjuvant chemotherapy, after a median of 47 months follow-up of patients in the 2 × 2 factorial design, the median survival was 20.1 months (95% CI, 16.5–22.7) among the 147 patients who received chemotherapy and 15.5 months (95% CI, 13.0–17.7) among the 142 patients who did not receive chemotherapy (hazard ratio for death, 0.71; 95% CI, 0.55–0.92; $p = 0.009$) (Table 13.2). The 2-year and 5-year survival estimates were 40% and 21%, respectively, among patients who received chemotherapy and 30% and 8%, respectively, among patients who received no chemotherapy.

Survival results for the individual treatment arms showed a benefit for adjuvant chemotherapy, but not for adjuvant chemoradiotherapy (Tables 13.3). The survival

**Table 13.1** The effect of chemoradiotherapy in the ESPAC-1 trial

| | | No | Median | 2 years | 5 years |
|---|---|---|---|---|---|
| ESPAC1 All patients (interim analysis 2001) | Chemoradiotherapy | 175 | 15.5 | 24.6 | |
| | No chemoradiotherapy | 178 | 16.1 | 23.5 | |
| ESPAC1 2 × 2 (final analysis 2004) | Chemoradiotherapy | 145 | 15.9 | 29 | 10 |
| | No chemoradiotherapy | 144 | 17.9 ($p = 0.05$) | 41 | 20 |
| ESPAC1 individual groups | Chemoradiotherapy | 73 | 13.9 | 21.7 | 7.3 |
| | Observation | 69 | 16.9 | 38.7 | 10.7 |

**Table 13.2** Effect of chemotherapy in ESPAC-1

| | | No | Median | 2 years | 5 years |
|---|---|---|---|---|---|
| ESPAC1 2 × 2 (final analysis 2004) | Chemotherapy | 147 | 20.1 | 40 | 21 |
| | No chemotherapy | 142 | 15.5 ($p = 0.009$) | 30 | 8 |
| ESPAC1 individual groups | Chemotherapy | 75 | 21.6 | 44 | 29 |
| | Observation | 69 | 16.9 | 38.7 | 10.7 |

**Table 13.3** Survival in individual treatment arms of 2 × 2 randomization

| | Median | 2 years | 5 years |
|---|---|---|---|
| Observation | 16.9 | 38.7 | 10.7 |
| Chemoradiotherapy | 13.9 | 21.7 | 7.3 |
| Chemotherapy | 21.6 | 44.0 | 29.0 |
| Chemoradiotherapy + chemotherapy | 19.9 | 35.5 | 13.2 |

benefit was evident in resection margin positive (R1) as well as resection margin negative (R0) patients.

Unfortunately, because of the relatively small numbers entered into the individual treatment groups in the ESPAC-1 trial, the differences between the four groups do not reach statistical significance; however, the advantage of adjuvant chemotherapy is maintained in a meta-analysis pooling the ESPAC data with data from smaller trials from Norway and Japan. This meta-analysis was aimed at investigating the roles of adjuvant chemoradiation and chemotherapy following resection of pancreas ductal adenocarcinoma on survival. The meta-analysis included five randomized trials of adjuvant therapy (Bakkevold et al. 1993; Takada et al. 2002; Stocken et al. 2005). Individual patient data were available in four (875 patients) out of the five selected randomized controlled trials (total number of patients with pancreatic adenocarcinoma = 939). Assessment of adjuvant chemotherapy trials indicated a 25% significant reduction in the risk of death with chemotherapy (hazard ratio (HR = 0.75, 95% CI: 0.64, 0.90, $P = 0.001$) with median survival estimated at 19.0 months (95% CI: 16.4, 21.1) with chemotherapy and 13.5 months (95% CI: 12.2, 15.8) without. The 2- and 5-year survival rates were estimated at 38% and 19%, respectively, with chemotherapy, and 28% and 12%, without. On the other hand, there was no significant difference between chemoradiation versus no chemoradiation in the risk of death (hazards ratio (HR) = 1.09, 95% CI: 0.89, 1.32, $P = 0.43$) with median survivals estimated at 15.8 months (95% CI: 13.9, 18.1) with chemoradiation and 15.2 months (95% CI: 13.1, 18.2) without. The 2- and 5-year survival rates were estimated at 30% and 12%, respectively, with chemoradiation and 34% and 17%, without.

A further meta-analysis looked at the influence of resection margin status in the same patient population and concluded that resection margin involvement was not a significant factor for survival (Hazard ratio = 1.10, 95% CI: 0.94, 1.29) (Butturini

et al. 2008). The 2-year and 5-year survival rate were 33% and 16% respectively for R0 patients and 29% and 15% for R1 patients. Adjuvant chemotherapy had a greater influence on survival in patients following an R0 resection than after R1, conferring a 7-month median survival benefit; median survival 20.8 months (95% CI: 17.7, 23.2) after R0 compared with 13.8 months (95% CI: 12.2, 16.4) after R1 resection, and 13.5 months (95% CI: 12.2, 15.8) after R0 but without chemotherapy. Chemoradiotherapy, however, had the opposite effect, with a median survival after R1 resection of 14.7 months (95% CI: 11.5, 20.5) compared with 15.9 months (95% CI: 14.0, 18.5) after R0, and 11.2 months (95% CI: 9.4, 16.7) after R1 without adjuvant chemoradiotherapy. Thus, the meta-analysis revealed a possible beneficial effect of chemoradiotherapy in the subgroup of patients with positive resection margins (Butturini et al. 2008).

It is apparent from ESPAC-1 that chemoradiotherapy not only had no advantage, but in fact may also have had a detrimental effect by delaying the onset of chemotherapy after surgical resection, and thus may have had a confounding negative effect on the chemotherapy versus no chemotherapy randomization. This finding remains controversial, however, with many US centers especially, continuing to support adjuvant chemoradiotherapy as standard treatment (Twombly 2008).

In a subset analysis of 316 patients who had completed 1,201 quality-of-life questionnaires (EORTC QLQ C-30), quality of life was measured over a 24-month period after surgery (Carter et al. 2009). For those patients receiving adjuvant chemotherapy, the mean Quality Adjusted Life Months over a 24-month measure (QALM-24) was 9.6 months (95% CI: 8.7, 11.2), compared with 8.6 months (95% CI: 7.6, 10.5) for those without adjuvant chemotherapy. Similarly, mean QALM-24 for those receiving chemoradiotherapy was 7.1 months (95% CI: 6.0, 9.0) versus 8.1 months (95% CI: 7.0, 10.0) in the no chemoradiotherapy group. Thus, the previously reported survival advantage for adjuvant chemotherapy was maintained when adjusted for quality of life over the 24-month period following resection.

## 13.4 ESPAC-3

Following the success of the ESPAC-1 trial in providing evidence for the use of adjuvant chemotherapy to improve survival in resected pancreatic cancer, the ESPAC group embarked upon the ESPAC-3 trial. This was an international multicenter phase III adjuvant trial in pancreatic cancer comparing 5-FU and D-L-Folinic acid versus gemcitabine. The aim was to answer two questions: first, whether adjuvant treatment with gemcitabine, or 5-Fluorouracil and Folinic Acid (5-FU/FA), improved survival compared to no adjuvant treatment; second, to determine the optimum chemotherapeutic agent by direct comparison of survival differences between patients receiving adjuvant gemcitabine and 5-FU/FA chemotherapy.

### 13.4.1 Rationale Behind the ESPAC-3 Trial

In 1997, Burris et al. published the results of a randomized trial of gemcitabine as first-line therapy for patients with advanced pancreas cancer. He recruited 126 patients with advanced symptomatic pancreatic cancer and randomized these to receive either gemcitabine (1,000 mg/m$^2$ weekly × 7 followed by 1 week of rest, then weekly × 3 every 4 weeks thereafter) (63 patients), or to fluorouracil (5-FU) 600 mg/m$^2$ once weekly (63 patients). He described a significant clinical benefit response in the gemcitabine-treated patients compared with the 5-FU-treated patients (23.8 % and 4.8%, respectively, $p = 0.0022$). He also described significant improvements in the median and 12-month survival for the patients treated with gemcitabine compared to 5-FU (5.65 versus 4.41 months and 18% versus 2%, respectively, $p = 0.0025$) (Burris et al. 1997).

Between 1998 and 2004, Oettle et al. conducted a large multicenter phase III randomized trial to determine the influence of adjuvant gemcitabine chemotherapy following resection of pancreatic cancer on disease-free survival (CONKO-001). Three hundred and eighty-six patients were randomized to receive adjuvant chemotherapy with six cycles of gemcitabine (1,000 mg/m$^2$ by intravenous infusion during a 30 min period on days 1, 8, and 15 every 4 weeks) ($n = 179$), or to observation following surgery only ($n = 175$). An early analysis (Oettle et al. 2007) identified a significant increase in median disease-free survival with gemcitabine (13.4 months 95% CI: 11.4–15.3) compared with control (6.9 months 95% CI: 6.1–7.8) but just failed to demonstrate a significant advantage in median overall survival ($p = 0.06$) with gemcitabine compared with control. More recently the final analysis (Riess et al. 2008) has been completed and the results presented. Median disease-free survival for the gemcitabine group was 13.4 months compared to 6.9 months for the observation arm ($p < 0.001$). The estimated disease-free survival at 3 and 5 years was 23.5% and 16.0% in the gemcitabine group versus 8.5% and 6.5% in the observation group, respectively. There was a significant improvement in median overall survival with gemcitabine, 22.8 months, compared to observation alone 20.2 months ($p = 0.005$). Estimated overall survival at 3 and 5 years was 36.5% and 21.0% for gemcitabine patients versus 19.5% and 9.0% for observation patients, respectively. These results offer a good chance for prolonged disease-free survival in patients undergoing R0 or R1 resection for pancreatic cancer. The question of whether 5-FU/FA or gemcitabine should be used as adjuvant therapy in patients with pancreatic cancer remained unanswered; the ESPAC-3 trial was designed to clarify this situation.

### 13.4.2 ESPAC-3 Design

The initial study design involved three arms:

- 5-Fluorouracil/folinic acid as used in ESPAC-1 (folinic acid (D-L 20 mg/m$^2$ iv bolus), 5-fluorouracil (425 mg/m$^2$ iv bolus) 5 days every 28 days × six cycles)

- Gemcitabine (gemcitabine (1,000 mg/m$^2$ i.v. infusion) once weekly × 3 weeks, 1 week rest × six cycles)
- Observation

The aim was to recruit 330 patients into each arm of the trial, and recruitment began in June 2000. On publication of the ESPAC-1 results, however, it became apparent that there was a definite survival advantage for adjuvant chemotherapy after resection of pancreatic ductal adenocarcinoma over observation alone, and therefore the trial design was amended and the observation arm was dropped. The recruitment targets for the remaining two arms were increased to 515 patients each (a total of 1,030 patients with pancreatic ductal adenocarcinoma) and the trial renamed as the ESPAC-3 (v2).

ESPAC-1 had been underpowered to determine the role of adjuvant therapy in less common malignancies such as bile duct cancers and ampullary tumors, and therefore the observation arm of ESPAC-3 was continued for these patients. The aim of the ESPAC-3(v2) for the ductal adenocarcinoma group had become focused on identifying overall survival difference by direct comparison of gemcitabine and bolus 5-FU/FA when used as adjuvant therapy following resection. However, for the ampullary and other pancreatic cancer groups, randomization was still into the original three arms and the aims remained unchanged.

The trial closed having recruited a total of 1,583 patients; 1,088 of these with ductal adenocarcinoma. The target of 1,030 patients with ductal adenocarcinoma was reached in December 2006 and the target of 300 patients with ampullary tumors was reached in April 2008 (Table 13.4).

The first results of the ESPAC-3 trial have been published, reporting on the patients recruited prior to closure of the observation arm (ESPAC-3(v1)) (Neoptolemos et al. 2009a). This paper pools the data from ESPAC-1 (2 × 2) with ESPAC-1 plus and ESPAC-3(v1). The inclusion criteria for all three groups of patients were identical, and postoperative restaging or Ca19.9 results were not used to determine patient inclusion. A comparison is made between those patients undergoing adjuvant chemotherapy with 5-FU/FA versus those receiving observation alone. A total of 225 patients were randomized to surgery alone, and 233 to adjuvant chemotherapy alone (no chemoradiotherapy). Median survival was 16.8 months (95% CI: 14.3, 19.2) for observation and 23.2 months (95% CI: 20.1, 26.5) for adjuvant 5-FU/FA. The 2-year and 5-year survival rates were 37% and 14% for observation alone and 49% and 24% for adjuvant chemotherapy (Table 13.5). The overall survival was superior in patients randomized to adjuvant chemotherapy compared with no adjuvant treatment (pooled hazard ration = 0.70 (95% CI: 0.55, 0.88) $p = 0.003$).

**Table 13.4** Recruitment to ESPAC-3, final figures

| | 5FU | GEM | OBS | Total treated | Overall total |
|---|---|---|---|---|---|
| Ductal Adenocarcinoma | 551 | 537 | 61 | 1,088 | 1,149 |
| Ampullary | 101 | 96 | 103 | 197 | 300 |
| Other | 42 | 48 | 41 | 90 | 131 |
| | | | | | 1,580 |

**Table 13.5** Pooled survival data from ESPAC-1, ESPAC-1 plus, and ESPAC-3(v1)

| | No of pts. | Median | 2 years | 5 years |
|---|---|---|---|---|
| ESPAC-1 | | | | |
| Observation | 69 | 16.9 | 39% | 10% |
| 5FU/FA | 75 | 21.7 | 44% | 27% |
| ESPAC-1 plus | | | | |
| Observation | 95 | 12.8 | 28% | 14% |
| 5FU/FA | 97 | 24.0 | 49% | 24% |
| ESPAC-3(v1) | 61 | 20.3 | 48% | 20% |
| Observation | 61 | | 54% | 20% |
| 5FU/FA | | 25.9 | | |
| Overall | | 16.8 | 37% | 14% |
| Observation | 225 | | | |
| 5FU/FA | 233 | 23.2 | 49% | 24% |

Early results, after 2-years follow-up, show no difference in survival between the two treatment arms (Neoptolemos et al. 2009b). Median survival from resection of patients treated with 5-FU/FA was 23.0 months (95% CI: 21.1, 25.0) and for patients treated with gemcitabine this was 23.6 months (95% CI: 21.4, 26.4). Log-rank analysis revealed no statistically significant difference in survival estimates between the treatment groups ($c^2_{LR} = 0.7$, $p = 0.39$, $HR_{GEM} = 0.94$ (95% CI: 0.81, 1.08)). There was no significant difference in the effect of treatment across subgroups according to R status (test of heterogeneity $c^2_1 = 0.3$, $p = 0.56$).

## 13.5 ESPAC-4

ESPAC-4 is a phase III, two arm, open-label, multicenter randomized clinical trial comparing combination gemcitabine and capecitabine therapy with gemcitabine alone when used as adjuvant therapy following resection for pancreatic adenocarcinoma. The main objective is to investigate whether combination chemotherapy (gemcitabine and capecitabine) when used in the adjuvant setting following resection of pancreatic adenocarcinoma improves survival over adjuvant therapy using gemcitabine alone.

Patients will start treatment within 8–10 weeks of undergoing curative surgery and will receive 24 weeks of chemotherapy. All patients will be followed up from randomization every 3 months for a minimum of 2 years and ideally until death. Patients will be randomized equally between two arms:

- Arm 1: gemcitabine (1,000 mg/m$^2$ is given as an i.v. infusion) will be administered once a week for 3 weeks out of every four (one cycle) for six cycles i.e., 24 weeks.
- Arm 2: gemcitabine (1,000 mg/m$^2$ is given as an i.v. infusion) will be administered on day 1, 8, and 15. Capecitabine (1,660 mg/m$^2$/day in two divided doses) will be administered orally for 21 days followed by 7 days' rest. Treatment will be repeated every 4 weeks for a total of 24 weeks.

The trial is now open to recruitment and aims to recruit 1,080 patients (540 in each arm), it is anticipated that trial will be completed in 2014.

## 13.6 Conclusions

Much controversy surrounds the use of adjuvant therapy in pancreatic cancer. The ESPAC-1 trial was instrumental in providing clear evidence for the role of adjuvant chemotherapy (5-FU and folinic acid), and the lack of benefit from chemoradiation in improving survival following resections of pancreatic cancer. These results have not only shaped the delivery of adjuvant therapy, but affected the design of future European clinical trials such that they no longer include a chemoradiotherapy arm.

It appears that a trend towards using systemic chemotherapy in the adjuvant setting following resection of pancreatic cancer is developing. The results of CONKO-001 trial added more weight to this argument; however, they left an important question unanswered; which agent is most effective when used in the adjuvant setting – gemcitabine or 5-FU? The ESPAC-3(v2) is aimed at assessing this, and these results will be available soon.

These have been exciting and encouraging times for pancreatic cancer; small steps toward improving survival from this devastating disease are taken with every trial. The European Study Group for Pancreatic Cancer continues to produce trials that will shape and improve our understanding of adjuvant therapies in pancreatic cancer. The next step is the ESPAC-4 trial; this will address the use of adjuvant combination chemotherapy, gemcitabine, and capecitabine versus gemcitabine alone.

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