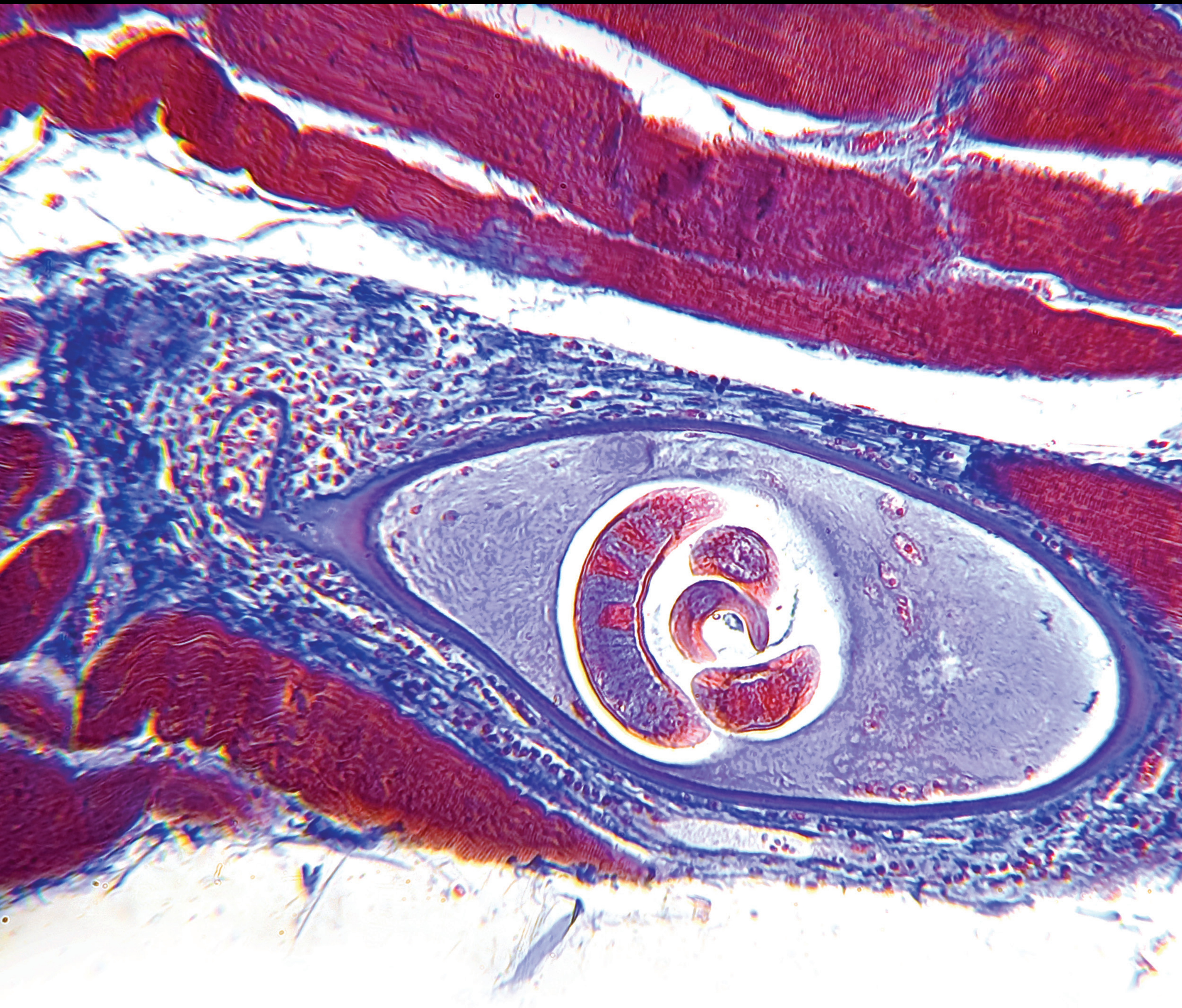
Gastroenterology Research and Practice

Evolving Techniques in Pancreatic Surgery

Guest Editors: Dejan Radenkovic, Michael B. Farnell, Claudio Bassi, and Marc Besselink



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Editorial Board

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Editorial

Evolving Techniques in Pancreatic Surgery

Dejan Radenkovic,[1] Michael B. Farnell,[2] Claudio Bassi,[3] and Marc Besselink[4]

[1] *Clinic for Digestive Surgery, Clinical Center of Serbia and School of Medicine, University of Belgrade, 11000 Belgrade, Serbia*
[2] *Department of Surgery, Division of Subspecialty General Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA*
[3] *Unit of General Surgery B, The Pancreas Institute, University of Verona Hospital Trust, Verona, Italy*
[4] *Department of Surgery, Academic Medical Center, Amsterdam, Netherlands*

Correspondence should be addressed to Dejan Radenkovic; dejanr@sbb.rs

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Diseases of the pancreas and periampullary region form an important clinical group of malignant and also benign diseases which still carry relatively high morbidity and mortality rates. Pancreatic ductal adenocarcinoma, in particular, is associated with very poor outcome as the number of new cases per year is just slightly higher than the number of deaths from this disease. Therefore, treatment of these conditions should always be based on both the highest level of evidence and technical expertise.

Surgery for diseases of the pancreas and periampullary region has evolved substantially during the last 15 years and several new surgical techniques have been described. According to recent randomized trials and advances in medical treatment, several surgical dogmas have been refuted.

The majority of patients with pancreatic and periampullary cancer at the time of diagnosis have advanced disease. However, in specialized centers, 10–15% of the patients with these malignances are suitable for resection. In these centers, the morbidity and mortality associated with major pancreatic resection have been reduced considerably in recent years. It is an undisputed fact that pancreatic resection ranks as one of the most, if not the most, complicated and technically challenging surgical procedures. It not only is a demanding technical exercise but also exerts a substantial logistical strain on healthcare resources.

The group from Heidelberg addressed the importance of vascular resections during pancreatic surgery. The limits of resection in patients with pancreatic and periampullary cancers have been extended. The recently published consensus paper by the International Study Group for Pancreatic Surgery (ISGPS) provided up-to-date definitions of borderline and extended resections. These definitions help clinicians worldwide to apply extended surgical approaches to an increasing number of surgical candidates. These procedures include vascular and multivisceral resections.

When dictated by tumor involvement, resection of portal and superior mesenteric and splenic veins should be performed routinely in patients if the patient's general condition allows and there are no major comorbidities. The decision for arterial resections should be strictly individualized. This type of surgery should be reserved for fit, younger patients, with preoperative careful examination of all aspects of this extended surgery. The majority of patients with infiltration of coeliac trunk or superior mesenteric artery should be considered for neoadjuvant therapy and then reevaluated for postponed surgical intervention and resection of infiltrated vessels.

D. Hartmann and H. Friess addressed the current status of the role of the surgery in the treatment of chronic pancreatitis. Surgical intervention in patients with chronic pancreatitis is mainly performed to resolve the complications of disease. In the majority of patients, intractable pain is the major indication for surgery, although jaundice, duodenal obstruction, and portal vein thrombosis are not rare. The goal of the surgery is pain reduction and management of complications, while preserving exocrine and endocrine pancreatic function and improving quality of life. Timing of surgery is an important feature during the prolonged natural history of the disease. New findings support early surgery for pain management in chronic pancreatitis patients, since early surgical intervention is associated with an improved postoperative pain relief, a reduced risk of pancreatic insufficiency, and decreased reintervention rates in comparison to conservative step-up approaches.

Duodenum-preserving pancreatic head resections (including Beger, Frey, and Berne procedures) seem to be superior in peri- and postoperative outcome parameters and quality of life compared to partial pancreatoduodenectomy (Whipple procedure) while being equally effective in postoperative pain relief, overall health, and postoperative endocrine sufficiency.

Organ-sparing operation at the right point of time carries a better outcome than performing an extended resection as a last resort once all therapeutic options are exhausted. An early timing of surgical therapy is crucial for the outcome of patients with painful CP and the indication of surgery should be considered early once symptoms are unambiguous.

The group from Verona evaluated technical aspects, indications, and results of the application of Radiofrequency Ablation (RFA) and Irreversible Electroporation (IRE) on locally advanced pancreatic cancer (LAPC).

RFA and IRE are the most frequently applied ablative techniques for the management of locally advanced pancreatic cancer. These techniques are versatile, since they can be performed at laparostomy, or via laparoscopic, endoscopic, or percutaneous routes. It has been demonstrated that their use is safe; however, since serious adverse events can occur, they are best performed at high volume centers and by high volume surgeons.

The application of RFA and IRE is recommended in a multidisciplinary decision-making setting and they should be used especially on locally advanced tumors that have not demonstrated a propensity to metastasize. That said, properly designed studies are still needed to assess their efficacy.

Finally, one of the most intriguing aspects of the application of RFA and IRE is their presumed stimulation of the immune system against the cancer. Once this aspect is further clarified and possibly confirmed, their use within the natural history of pancreatic cancer will become clearer. The group from Glasgow described the treatment of infected necrotizing pancreatitis. Treatment of acute pancreatitis is currently based on the definitions set forth in the 2012 Revised Atlanta Classification. Since the PANTER trial, there is now consensus that a "step-up approach" starting with catheter drainage and, if needed, followed by minimally invasive necrosectomy is the preferred treatment approach to infected necrotizing pancreatitis. The most commonly used minimally invasive strategies for necrosectomy are transgastric necrosectomy, percutaneous necrosectomy, and video-assisted retroperitoneal debridement (VARD). The recently completed TENSION trial compared transgastric necrosectomy with VARD within a "step-up approach," but the final results are awaited. The advantage of transgastric necrosectomy is that it minimizes the risk of a pancreatocutaneous fistula which can be very problematic in case of "central gland necrosis." The major disadvantage of transgastric necrosectomy is that multiple, often lengthy, procedures are required, whereas, with VARD via a 3–5 cm incision, only 1-2 procedures are sufficient in the majority of patients. Percutaneous necrosectomy probably holds the middle ground between these two options and several large series have described good outcomes.

The group from Belgrade overviewed the role of interventional treatment of abdominal compartment syndrome (ACS) during severe acute pancreatitis (SAP). Some unresolved questions persist which include the role of medical treatment and the indications for and the timing of interventional techniques. Currently, there is no unanimity of opinion regarding surgical or other interventional treatments for ACS during the course of SAP.

Critically ill patients with acute pancreatitis have a considerable risk for developing intra-abdominal hypertension. Routine measurement of intra-abdominal pressure is recommended, allowing the identification of patients at risk of abdominal compartment syndrome. First line therapy for this life-threatening complication is conservative treatment aiming to decrease IAP and to restore organ dysfunction. If nonoperative measures are not effective, early abdominal decompression is mandatory. Percutaneous catheter drainage should be the first step in interventional treatment which can relieve ACS. When ACS persists, surgery is indicated.

Timing of abdominal decompression also remains uncertain in the treatment of these patients. However, the Finnish group published their experience with 26 patients regarding early and late decompression. Results clearly showed that early decompression (first 4 days) was associated with a significantly lower mortality rate, compared with late decompression (after 4 days).

Midline laparostomy seems to be the method of choice, although full-thickness transverse subcostal bilateral laparostomy, subcutaneous linea alba fasciotomy, and fasciotomy of the anterior rectus abdominis sheath have been described as alternative options. Since laparostomy carries significant morbidity, randomized studies are needed to establish firm advantages over other techniques.

Better understanding of pathophysiology of diseases of the pancreas and periampullary region has led surgeons to change some traditional surgical approaches and develop new innovative techniques. Technological advances which have improved the safety and efficacy of pancreatic surgery have been performed mainly in selected high volume centers. In order to improve both quality of life and duration of survival for our patients, novel surgical techniques should become more widely available and accepted. Studies with sound design and statistical methodology are urgently needed.

In the present special issue, the authors have addressed new understanding of the pathophysiology of diseases of the periampullary region and pancreas. They have focused their interest in evidence-based, novel surgical techniques and approaches and challenging clinical settings have been emphasized.

Dejan Radenkovic
Michael B. Farnell
Claudio Bassi
Marc Besselink

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Review Article

Local Ablative Strategies for Ductal Pancreatic Cancer (Radiofrequency Ablation, Irreversible Electroporation): A Review

Salvatore Paiella,[1] Roberto Salvia,[1] Marco Ramera,[1] Roberto Girelli,[2] Isabella Frigerio,[2] Alessandro Giardino,[2] Valentina Allegrini,[1] and Claudio Bassi[1]

[1] *Unit of General Surgery B, The Pancreas Institute, G.B. Rossi Hospital, University of Verona Hospital Trust, Verona, Italy*
[2] *Pancreatic Surgical Unit, Casa di Cura Pederzoli, Peschiera del Garda, Verona, Italy*

Correspondence should be addressed to Salvatore Paiella; salvatore.paiella@univr.it

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Pancreatic ductal adenocarcinoma (PDAC) has still a dismal prognosis. Locally advanced pancreatic cancer (LAPC) accounts for the 40% of the new diagnoses. Current treatment options are based on chemo- and radiotherapy regimens. Local ablative techniques seem to be the future therapeutic option for stage-III patients with PDAC. Radiofrequency Ablation (RFA) and Irreversible Electroporation (IRE) are actually the most emerging local ablative techniques used on LAPC. Initial clinical studies on the use of these techniques have already demonstrated encouraging results in terms of safety and feasibility. Unfortunately, few studies on their efficacy are currently available. Even though some reports on the overall survival are encouraging, randomized studies are still required to corroborate these findings. This study provides an up-to-date overview and a thematic summary of the current available evidence on the application of RFA and IRE on PDAC, together with a comparison of the two procedures.

1. Introduction

PDAC is one of the deadliest cancer types. It accounts for about 7% of all cancer deaths and is actually the fourth cause of cancer death in the United States [1]. Only 20% of PDAC are resectable at time of diagnosis (with a 5-year survival of less than 20%), while the majority of patients are candidates only for chemotherapy or chemoradiotherapy according to various protocols [2–4]. 40% of patients are diagnosed with a locally advanced disease, with few chances to undergo surgery even after neoadjuvant treatments. Median overall survival (OS) reported for patients treated with upfront surgery and adjuvant therapy is about 20–22 months [5–7], while it is about 9.2–11.7 months for stage-III locally advanced pancreatic cancer (LAPC) treated with Gemcitabine alone [8–10] and 9–13 months for patients treated with chemo(radio)therapy [11]. Given that LAPC is nearly the most frequent diagnosis to face and that downstaging occurs only in 10–20% of patients [12], the novel local therapies, such as Radiofrequency Ablation (RFA) and Irreversible Electroporation (IRE), have been proposed as new treatment options in the multimodal treatment of the disease [13]. The aim of this paper is to evaluate and compare technical aspects, indications, and results of the application of both RFA and IRE on LAPC.

2. Physical Bases and Principles of Techniques

Local thermal or nonthermal techniques are applied to ultimately induce irreversible cellular damage leading to cell death *via* either apoptosis or coagulative necrosis. Physical bases and principles of technique of both RFA and IRE are briefly shown below.

2.1. RFA. RFA is an ablative therapy that, through the application of a high-frequency alternating current, conveyed by one or more needle electrodes, generates local high temperatures, leading to coagulative necrosis and protein denaturation inside neoplastic tissue. While at temperatures between 60

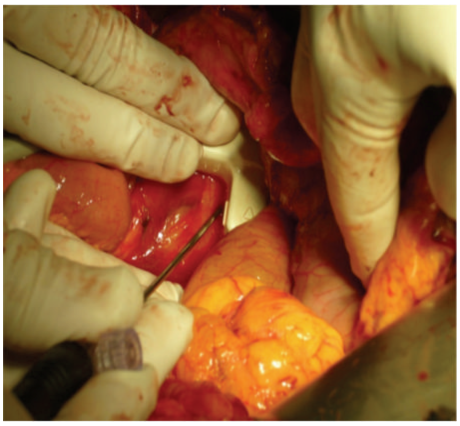


Figure 1: US-guided intraoperative application of RFA tip.

and 100°C immediate coagulation of tissue is induced, with irreversible damage to the inner structure of the cells, using 100–110°C, the tissue vaporizes and carbonizes [14]. At the beginning of the application of RFA on PDAC, high morbidity (0–40%) and mortality (0–25%) rates have been reported [15]. Later, *ex vivo* studies demonstrated that an adjustment of both temperature and length of the dispensed energy would conduce to better outcomes with fewer complications [16, 17]. Although several temperatures have been used, ranging from less than 30°C to 90°C according to the equipment used to perform RFA [18, 19], it seems that the ideal parameters to consider are actually represented by 90°C for 5 minutes, with a distance of 10 and 15 mm between probe and duodenum and portomesenteric axis, respectively [20]. The electrode must be introduced inside the tumor under ultrasound or CT-guidance and the procedure can be monitored in real time by ultrasound with a safe distance of the RFA probe from duodenum or portomesenteric vessels of 5–10 mm (Figure 1). The procedure can either be performed through laparotomy, percutaneously, or through an endoscopic approach [21, 22]. These mini-invasive techniques could be useful to avoid laparotomy, in patients unsuitable for surgery or in case of LAPC of the body-tail of the pancreas without symptoms.

2.2. IRE. IRE is a nonthermal technique that induces cell death. The ablative effect is based on the delivery of short high-voltage electric current fields that induce cell death. The application of short high-voltage electric pulses, conveyed by one or more monopolar electrodes, causes the irreversible permeabilization of the lipid bilayer, the disruption of intracellular homeostasis, and the activation of apoptotic pathways, ultimately resulting in cell death of neoplastic cells [30–36]. Interestingly, and differently from RFA, IRE is able to preserve surrounding structures, such as the underlying matrix that can work again as a scaffold for the healing tissue, or the vital structures like nerves or vessels [37–39]. Narayanan et al. in a retrospective review of 101 IRE procedures performed on different organs for tumors abutting or encasing major vessels reported a rate of vascular changes of only 4.4% (thrombosis or mild vascular narrowing phenomena) demonstrating a very high rate of patency of the major vessels in humans, after the application of IRE [40]. The proper ability of IRE to preserve the vessels could be a fundamental aspect when the tumor encases the major peripancreatic vessels, when the application of RFA could result as difficult, dangerous, and inefficacious (because of the heat-sink effect). However, it has been advocated that the cellular damage induced by IRE could be partially thermal. In fact, in some conditions of high intensity, current applied IRE can produce a coagulative necrosis similar to the one produced by thermal techniques [41]. Dunki-Jacobs et al. further investigated this aspect, concluding that IRE does not produce significant thermal energy, at least using the settings most commonly applied in clinical treatment. On the other side, they demonstrated that the presence of metallic stent could increase the risk of producing thermal injuries, because of the conductivity of the metal [42]. This aspect might be important in those patients carrying a biliary metallic stent for jaundice palliation. Hence, it should be kept in mind that IRE is not a "pure" nonthermal technique and that it remains connected in some way with thermal effects. Treatment planning of IRE is of utmost importance and several tools are available to properly manage the application of the technique [43–45]. Martin accurately described the procedure with the ideal settings on pancreas [46, 47].

3. Indications and Contraindications

Preoperative work-up should always include routine laboratory tests (including CA 19-9 levels) and a 3-phase CT-scan of the abdomen in order to assess exactly the location and the dimension of the tumor, the type of vascular infiltration, and the possible presence of abdominal metastases. Local ablative therapies, such as RFA and IRE, should be allotted to those tumors that show a local growth pattern without systemic involvement and should be considered as consolidative therapies in the multimodal therapeutic approach to LAPC. The decision to perform one or the other should be taken by a multidisciplinary group, considering the patients' comorbidities and quality of life, the natural history of the tumor, and, mostly, the response to medical oncological treatments. The assessment of resectability of LAPC after neoadjuvant therapy is still difficult [48]. In the FOLFIRINOX era, imaging seems to have no longer ability in determining the real response rate after neoadjuvant therapy [49]. In the future, RFA and IRE will be applied more often as "salvage" cytoreductive therapies or in the context of properly designed clinical trials, at least until randomized controlled trials will not demonstrate their oncological efficacy. Furthermore, it is of paramount importance that RFA and IRE should be performed selectively in high-volume HPB centers, and, for percutaneous-only approaches, by experienced interventional radiologists.

3.1. RFA. Indications are as follows. The most common worldwide application of RFA on PDAC is represented by the treatment of stage-III patients, either in case of no further response to standard systemic treatments or as an upfront option at the time of diagnosis [15, 16, 18, 28, 50–58]. However, some studies included also stage-IV metastatic patients

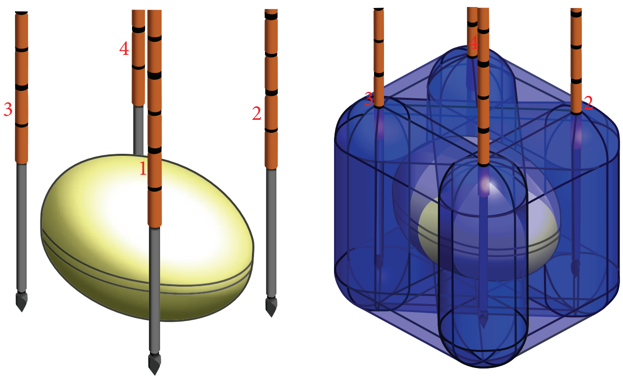


Figure 2: Example of a computerized model of the application of a 4-needle IRE technique. The yellow oval represents the tumor. Crossing blue beams represent the energy developed between each couple of probes.

[18, 19, 59, 60], probably to induce a positive modulation of the immune system [61]. Recently, the application of RFA upfront has been justified on the basis of a presumed immunological antitumoral stimulation aroused by RFA [50]; a randomized controlled study to prove or to disown it is currently running. However, RFA should be considered as a new tool in the surgeon's toolbox, in the context of a multidisciplinary approach to PDAC.

Tumor diameter is not a crucial parameter in the evaluation of the application of RFA as the technique itself allows ablating up to 5 cm or more [62]. Unfortunately, because of the proximity of vital structures surrounding PDAC (infiltrated by definition in LAPC), the whole ablation of the tumor would result in being too risky. Then, it is preferred to treat the biggest possible area, performing also pull-backs of the tip, leaving a "security ring" at the periphery of the tumor in order to avoid thermal injuries of the nearby structures [63]. This viable tissue at the periphery of the tumor will later be the target of the radiotherapy, to complete the ablation of the tumor [17].

Contraindications are as follows. RFA can interfere with implanted pacemakers and cardioverter defibrillators due to electromagnetic energy [64]. Hence, a cardiac evaluation is recommended in this special subset of patients, for a possible resynchronization of these devices.

3.2. IRE. Indications are as follows. Almost all the applications of IRE on PDAC are on stage-III LAPC [23, 24, 27, 47, 65–71]. Narayanan et al. reported three cases of application of IRE on stage-IV patients with centimetric liver metastases from PDAC and two cases of application of IRE as a "bridge" therapy in LAPC before submitting the patients successfully to a radical surgical resection [72]. Simultaneously, some papers report promising results on the use of IRE for margin accentuation, as a technique to reduce the rate of R1 resections in case of locally advanced/borderline resectable PDAC [24, 65, 68, 73]. In general, IRE works better on tumor sizes that are 3 to 3.5 cm and it is important to plan the ablation technique properly (Figure 2) in order to treat the whole tumor [74]. In addition, the application of IRE seems to be more appropriate than RFA when the tumor encapsulates the superior mesenteric artery. In fact, the application of multiple needles allows bracketing the artery and treating. Furthermore, the negligible amount of heat associated with IRE allows safe and efficacious ablations.

Contraindications are as follows. In general, electric fields applied to human body can cause arrhythmias; hence, it is of utmost importance to reduce this risk synchronizing pulsing with the heart rhythm, using a dedicated device [75]. For these reasons, IRE is contraindicated in patients with pacemakers or with cardiac arrhythmias. Moreover, a metallic biliary stent should be removed intraoperatively before IRE, because the presence of the metal could increase the risk of thermal injury [70].

4. Oncological Outcomes

All the results regarding the oncological outcomes of the application of RFA and IRE on PDAC are biased by the nature itself of the studies. The reports include very heterogeneous populations of patients, with either stage-III or stage-IV disease. There are no randomized controlled studies available. Most of them were created as phase-I studies in order to demonstrate the safety of the techniques; then, oncological outcomes were only secondary goals. Despite these intrinsic problems, some encouraging results can be extracted.

4.1. RFA. Given that all patients treated with RFA will relentlessly progress [16, 53, 57, 60], some papers report good oncological results obtained with the use of RFA on PDAC. Spiliotis et al. reported a reassuring mean survival of 30 months for patients suffering from PDAC treated with RFA, compared to the 13 months' survival for patients receiving a standard systemic treatment ($p = 0.0048$) [18]. Giardino et al. cited a median overall survival (OS) for their whole series ($n = 107$) of 25.6 months, 14.7 months in the group of patients receiving RFA plus several possible systemic treatments, and 25.6 months in the group treated with primary treatments plus RFA plus further systemic treatments ($p = 0.004$). Interestingly, those patients who received this latter therapy, the so-called "triple approach strategy," with RFA plus radiochemotherapy plus intra-arterial chemotherapy with further systemic treatments, had an OS of 34.0 months [17].

4.2. IRE. Despite the increasing number of papers reporting the application of IRE on PDAC, none of these studies is designed to demonstrate the oncological efficacy of the procedure. In fact, they mostly deal with safety and feasibility issues and for this reason the populations considered are not ideal models for the analysis of oncological outcomes. Table 1 shows the studies reporting data on the efficacy of IRE; however, all these results must be considered cautiously. Interestingly, two papers described five cases of downstaging with R0-resections of LAPC treated with percutaneous IRE [26, 27].

A recent paper from Martin et al. reports an outstanding median OS of 24.9 months (range 12.4–85 months;

Table 1: Efficacy of IRE on PDAC.

Author	Number of patients	Approach	Type of study	Survival (mo.)
Martin et al. [23]	54	Open (52) Percutaneously (2)	Propensity-matched comparison with standard chemo- or chemoradiation	20.2
Martin et al. [24]	200	Open	Data from multicenter registry	24.9
Trueba-Arguiñarena et al. [25]	1	Percutaneously	Case report	f-up 12 mo.
Narayanan et al. [26]	43	Percutaneously	Prospective	16.2
Belfiore et al. [27]	20	Percutaneously	Retrospective	12.9
Pai et al. [28]	5	Percutaneously	Phase-1 safety and feasibility	Range 1–6 mo.
Paiella et al. [29]	10	Open	Phase-1 safety and feasibility	Median 6.4, range 2.9–15.9

$n = 200$), for patients treated with IRE in situ or pancreatic resections with major vascular resections and IRE for the margin accentuation, after 6 months (median) of induction chemotherapy or chemo(radio)therapy [24]. As the authors state in the paper, the population considered is made of highly selected patients and this represents an important selection bias. However, these results are very surprising and encouraging, especially if compared with the historical populations of patients reported in literature suffering from LAPC.

Recently, Philips et al. reported an increased risk of accelerating the tumor growth after the application of incomplete sessions of IRE in a murine model. This worrisome finding should be further clarified and possibly verified in clinical scenarios [76].

5. Complications

The majority of the complications caused by local ablative techniques are consequence of an uncontrolled heating of the structures surrounding the tumor, rather than a direct lesion caused by the tip of the probe used. Therefore, obviously, it is of paramount importance to plan properly the procedure, setting the parameters according to location, dimensions, and morphology of the tumor.

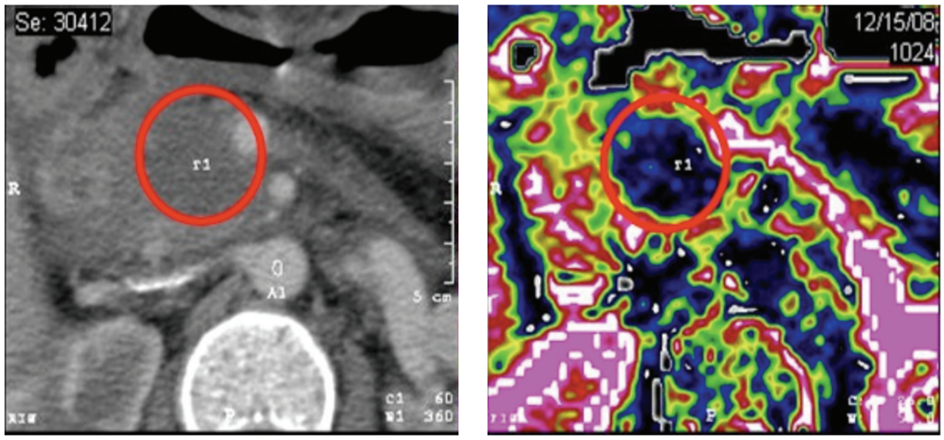
5.1. RFA. The first clinical applications of RFA were afflicted by a high rate of morbidity and mortality, ranging from 0 to 40% and from 0 to 25%, respectively [15]. Once the temperature was lowered from 105 to 90°C for 5 minutes' length, the reported number of complications reduced in parallel [16, 17]. The deaths related to RFA were most commonly caused by gastrointestinal hemorrhages. The most recent cohort of patients treated with RFA comes again from Girelli et al. They reported a reduction of the morbidity rate to 8%, with a mortality rate of 0% [50]. The overall reported rates of RFA-related complications and RFA-related mortality are 13.6 and 1.5%, respectively [13]. The most common complications reported in literature are gastrointestinal hemorrhages and minor local bleedings, acute pancreatitis (mild or severe), pancreatic and biliary fistulas, duodenal injury (thermal or direct), and portal vein thrombosis. It is suggested to cool the duodenum during the procedure with a cold saline solution administered using the nasogastric tube, to preserve it from the possible thermal injury [20].

5.2. IRE. A recent systematic review reported an IRE-related complication rate of 13%, with an IRE-related mortality of 2% [13]. The overall reported complications rate of the percutaneous approach is 29% [77]. Martin et al., in a recent study with a population of 200 patients suffering from LAPC treated with IRE, showed an overall rate of adverse events of 37% (74 patients with 149 overall complications) and a mortality rate of 2% [24]. The largest single-center percutaneous series of 50 IRE described an overall number of 27 complications [26]. The most common complications (including both percutaneous and open techniques) described after the use of IRE on pancreas are pancreatitis, pneumothorax, hematoma, abdominal pain, bile leakage, pancreatic leakage, duodenal leakage, duodenal ulcer, and deep vein thrombosis.

6. Ablative Techniques and Imaging

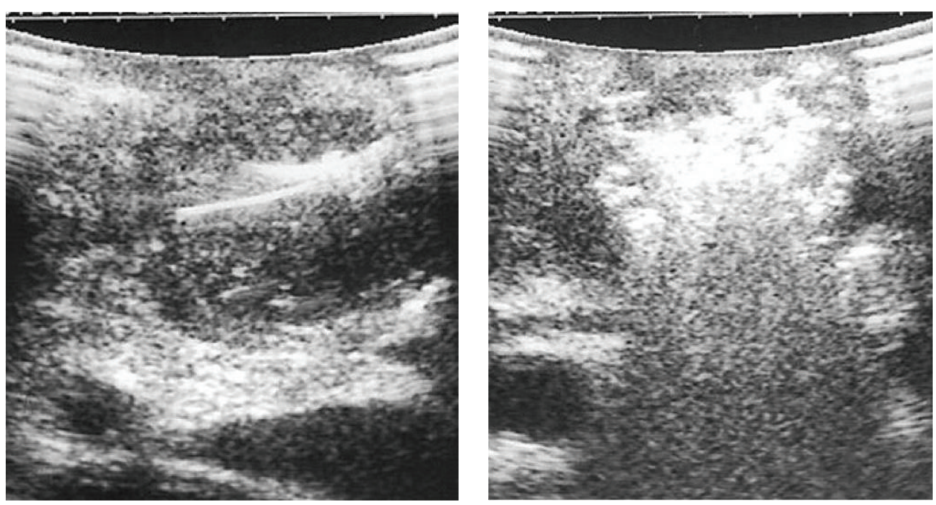
One of the most interesting and useful aspects of the application of the ablative techniques on PDAC is the possibility to appraise the amount of tissue ablated and the relationship between the treated area and tumor margins.

6.1. RFA. For RFA, and in general for "thermal techniques," the gold standard of imaging is represented by cross-sectional imaging *via* helical CT-scan, rather than ultrasonography [78]. A postablative hypointense area can be observed as result of the treatment (Figure 3). At our institution, we perform a three-phase contrast-enhanced CT-scan of the



(a) (b)

Figure 3: (a) Preoperative CT-scan of a locally advanced pancreatic cancer. (b) Post-RFA perfusion CT-scan, showing a postablative area of decreased perfusion within the head of the pancreas. Copyright Chirurgia del Pancreas Verona.



(a) (b)

Figure 4: (a) The tip for RFA is placed inside the tumor under US-guidance. (b) During RFA, the lesion becomes immediately hyperechoic.

abdomen at postoperative days 7 and 30. During the procedure, ultrasonography can both guide the tip and detect the immediate results of the thermal damage (Figure 4).

6.2. IRE. Because of the nonthermal noncoagulative action of IRE and because of the consequent preservation of the vessels, the application of contrast-enhanced CT-scan after IRE would not have the same results as for RFA. Several techniques have been used to evaluate the effect of the application of IRE. Magnetic resonance electrical impedance tomography (MREIT) seems to be able to identify the areas with insufficient electric field, in order to label potential untreated zones after IRE [79]. Either contrast-enhanced or diffusion weighted MRI seems to be able to depict the tissue zones ablated with IRE [80–82]. Even if using a swine model, a recent study stated that the best identification of tissue ablation after IRE is obtained with portal vein phase CT-scan. Anyway, differently from RFA, during CT-scan, a contrast enhancement can be appreciated on the more delayed venous phase, due to the congestion of blood in the tumor vessels [32, 83, 84]. Ultrasound findings during and after IRE could be useful to evaluate the approximate area of ablation. In the acute phase, a hypoechoic area can be registered, with a hyperechoic external rim that forms 90–120 minutes after the treatment [85, 86]. However, Martin et al. state that an early postoperative scanning after IRE should be performed only to rule out possible complications (deep vein thrombosis) and not to evaluate ablation efficacy [24]. It still has to be evaluated if a serum CA 19-9 level decrease could be used as predictor of efficacy.

7. Ablative Techniques and Immune System

The strongest factor supporting the clinical application of the ablative techniques, especially of RFA, is represented by their positive antitumoral effect on immune system. Nowadays, thanks to the several studies that have been published, RFA is called prudently "endogenous vaccine" for PDAC. How strong is this power and which are the best timing and proper methods to use it remain to be established.

7.1. RFA. All the processes involving the modulation of immune system have been exhaustively described by Chu and Dupuy [87]. While the direct effect of RFA is clearly represented by the necrotic area immediately identifiable after the procedure, on the other hand, the indirect effects are on the viable zone adjacent to this area (transition or peripheral zone). The cells populating the peripheral zone are affected by the RFA in terms of alteration of metabolic endocellular processes that makes them quite sensible to further cytolytic therapies, such as chemo- or chemoradiotherapy. These effects result, ultimately, in the almost total destruction of the tumor. In parallel to this "local" action, RFA can cause a "systemic" immune response involving proinflammatory cytokines [88–90], lymphocytes (T-, B-, and NK-types) [91–94], and antibodies [95] that are responsible for acquired antitumoral antigen-specific immunity [96, 97] that could confer better survival in some patients treated with RFA. It also seems promising to use the synergic use of RFA together with topic specific cytolytic agents or with immunotherapy with monoclonal antibodies or vaccine [98]. However, most of the findings described come from experimental models or from *in vivo* results from organs other than pancreas. Of course, there is need for more preclinical models, investigational studies, and large randomized controlled clinical trials to demonstrate the effects of RFA on PDAC selectively.

7.2. IRE. The immune system involvement after IRE has not been thoroughly investigated yet.

Some reports support the evidence that since the proteins are not denatured in IRE (differently from in RFA), in theory, this could result in a weak specific antigenic stimulation against the tumor. In fact, Al-Sakere et al., using murine models of sarcoma treated with IRE, showed that there is no local infiltration of tumor cells among the treated tissue. An early and prolonged decrease in both T lymphocytes (both CD4+ and CD8+) and antigen presenting cells can be detected within a couple of hours after IRE [99]. As they support, this is a demonstration that IRE does not need the involvement of the immune system to kill neoplastic cells and, for this reason, it could be applied on immunosuppressed patients too. On the other hand, other reports reached the evidence that both local and systemic immune antitumoral stimulation are enhanced after IRE [100, 101]. This aspect could be referred to the peculiar type of cellular death caused by IRE: the activation of the apoptotic processes leads to the release of intact and stimulating endogenous tumoral antigens able to induce a strong global antitumoral activity. Ultimately, according to Neal II et al., IRE would be able to generate the "three signals' sequence" that is mandatory for the production of a cytotoxic T-cell response [101].

These conflicting reports demonstrate how far we are from the understanding of the exact involvement of the immune system and how much we need further preclinical and clinical models.

8. Conclusions

RFA and IRE represent an innovation on the multimodal treatment of LAPC. The undeniable advantages connected with the use of these techniques are represented by low morbidity, reduced costs, possible percutaneous application, almost selective action with preservation of peritumoral tissues, possible application to patients at a high-risk for surgery, and suspected positive immune stimulation. Moreover, taking into account their positive effect on the immune system, they could be potentially very useful in those patients that, somehow, show an indolent disease, with a prevalent local growth and without a wide systemic involvement.

Nevertheless, as for any other technology introduced in medical practice, RFA and IRE have to be evaluated prospectively and systematically according to the IDEAL framework for evaluation of surgical innovation [102]. In the IDEAL paradigm for the introduction of new technologies in surgery, the application of RFA and IRE on LAPC is still stuck on the 2a phase where few people still adopt the technique, where the patients are selected, where the outcomes are mostly safety and feasibility, and where the clinical outcomes are timidly reported. Hence, the current available evidence is still not sufficient to permit conclusions about long-term benefits.

Nowadays, the patients suffering from LAPC are still waiting for answers that medical oncologists cannot give. Surgery and new ablative technologies can play an important role in giving hope, prolonging survival, and improving quality of life of the patients suffering from LAPC. However, we must move toward a rigorous evaluation of these new procedures through the creation of appropriate randomized controlled studies.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Interventional Treatment of Abdominal Compartment Syndrome during Severe Acute Pancreatitis: Current Status and Historical Perspective

Dejan V. Radenkovic,[1] Colin D. Johnson,[2] Natasa Milic,[3] Pavle Gregoric,[4] Nenad Ivancevic,[4] Mihailo Bezmarevic,[5] Dragoljub Bilanovic,[6] Vladimir Cijan,[7] Andrija Antic,[1] and Djordje Bajec[1]

[1]*Clinic for Digestive Surgery, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia*
[2]*Department of Surgery, University Hospital Southampton, Southampton, UK*
[3]*Institute for Biostatistics and Informatics, Faculty of Medicine, University of Belgrade, Belgrade, Serbia*
[4]*Clinic for Emergency Surgery, Emergency Center, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia*
[5]*Clinic for Surgery, Military Medical Academy, Belgrade, Serbia*
[6]*Clinic for Surgery, Clinical Center "Bezanijska Kosa", Faculty of Medicine, University of Belgrade, Belgrade, Serbia*
[7]*Clinic for Surgery, Clinical Center "Zvezdara", Belgrade, Serbia*

Correspondence should be addressed to Dejan V. Radenkovic; dejanr@sbb.rs

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Abdominal compartment syndrome (ACS) in patients with severe acute pancreatitis (SAP) is a marker of severe disease. It occurs as combination of inflammation of retroperitoneum, visceral edema, ascites, acute peripancreatic fluid collections, paralytic ileus, and aggressive fluid resuscitation. The frequency of ACS in SAP may be rising due to more aggressive fluid resuscitation, a trend towards conservative treatment, and attempts to use a minimally invasive approach. There remains uncertainty about the most appropriate surgical technique for the treatment of ACS in SAP. Some unresolved questions remain including medical treatment, indications, timing, and interventional techniques. This review will focus on interventional treatment of this serious condition. First line therapy is conservative treatment aiming to decrease IAP and to restore organ dysfunction. If nonoperative measures are not effective, early abdominal decompression is mandatory. Midline laparostomy seems to be method of choice. Since it carries significant morbidity we need randomized studies to establish firm advantages over other described techniques. After ACS resolves efforts should be made to achieve early primary fascia closure. Additional data are necessary to resolve uncertainties regarding ideal timing and indication for operative treatment.

1. Introduction

The morbidity and mortality of patients with severe acute pancreatitis (SAP) remain high despite significant improvement in treatment due to the better understanding of the pathophysiology of disease, early aggressive fluid resuscitation, timely surgical intervention, permanent monitoring, and organ supporting intensive care. It is widely accepted that major predictors of unfavorable outcome are development of persistent organ failure and presence of bacterial infection of necrosis [1].

Abdominal compartment syndrome (ACS) in patients with severe acute pancreatitis (SAP) is a sign of severe disease with high risk of adverse outcomes [2–5]. Abdominal compartment syndrome is defined as a state of serious organ dysfunction resulting from sustained increase in intra-abdominal pressure [6]. Very recently published systematic review on this topic showed that the mortality rate in patients who developed ACS during SAP was 49%, while it was 11% in patients without this complication [7]. The number of patients with ACS may have increased as a consequence of a move towards later intervention and minimally invasive rather than open surgery. Several studies demonstrated that development of organ failure in SAP is in correlation with presence of intra-abdominal hypertension (IAH) [3, 4, 8, 9]. Elevated intra-abdominal pressure (IAP) is well known predictor of mortality and serial measurements of IAP are recommended for all patients with severe acute pancreatitis in the intensive care units [6].

Currently there is no agreed surgical or other interventional treatment for ACS during the course of SAP. The World Society of Abdominal Compartment Syndrome (WSACS) has published definitions of IAH and ACS and recommendations for treatment [6], but it is not known if these can be applied to patients with SAP.

During recent years, several studies on ACS in patients with SAP have been published, but data of this problem still remains scarce [3, 10–13]. Some unresolved questions including medical treatment, indications, timing, and interventional techniques remain, and this review will focus on interventional treatment of this serious condition.

2. Pathophysiology

There are several reasons which may contribute to development of IAP during SAP. Inflammation of the pancreas is a crucial step, which starts a cascade of events including visceral edema, ascites, acute peripancreatic fluid collections, paralytic ileus, and duodenal obstruction causing gastric dilatations. Aggressive fluid resuscitation, a very important part of initial conservative treatment, is an additional factor leading to rapid fluid accumulation in the abdominal cavity which plays a role in elevation of IAP. Severe intra-abdominal inflammation together with capillary leakage further contributes to development of large quantity of ascites. The abdominal wall may also be edematous with decreased compliance, which in synergy with enlarged intra-abdominal volume leads to an increase of IAP. The presence of large peripancreatic fluid collections and paralytic ileus may also play a significant role in development of IAH.

Intra-abdominal hypertension leads to reduction of chest wall compliance and hypoperfusion of the gastrointestinal tract [14] which contribute significantly to the pathogenesis of organ dysfunction [15, 16]. Elevated IAP may reduce perfusion of abdominal organs, allowing hypoxic injury of the surrounding tissues which could exacerbate systemic inflammatory response. High IAP in patients with severe acute pancreatitis correlates with the degree of organ dysfunction and intensive care stay [9].

An IAP above 20 mmHg is associated with oliguria and significant reduction in cardiac output [17]. IAH appears to exacerbate organ failure, as it is associated with significantly higher APACHE II scores and MODS scores in patients with SAP [4, 5]. De Waele et al. [8] reported a higher incidence of respiratory, circulatory, and renal failure among the patients with IAH. Elevation of the diaphragm due to high IAP may lead to a decrease in lung and chest wall compliance and decline in functional residual capacity and residual volume and may cause respiratory insufficiency. High IAP may cause decrease in renal perfusion pressure, the filtration gradient, and renal blood flow, resulting in renal failure [9]. SAP is characterized by reduced pancreatic perfusion, and it is likely that IAH exacerbates this pancreatic hypoperfusion and consequently increases the extent of pancreatic necrosis. Splanchnic circulation may be decreased due to reduced cardiac output and increased mechanical pressure to splanchnic area [14].

3. Medical Treatments to Reduce IAP

Critically ill patients with acute pancreatitis have a considerable risk for developing IAH and routine measuring of IAP is recommended by WSACS guidelines, allowing identification of patients at risk of ACS [6]. If increased IAP is diagnosed, the first option in the management of the patients with IAH during SAP is always nonoperative treatment. This includes management in ICU and neuromuscular blockade with artificial respiration. In a study including 74 patients with SAP, 20 patients developed ACS during first 7 days of admission [3]. Seven patients responded to nonoperative therapy, but the remaining 13 patients had progressive deterioration of organ dysfunction and received interventional decompressive procedure.

Relief of pain and anxiety is an important part of treatment of patients with SAP, but it remains unclear whether this has any influence on IAH [6]. Neuromuscular blockers may reduce IAP by reduction of abdominal musculature tone and an increase in abdominal compliance.

Neuromuscular blockade is the major nonoperative measure in the management of IAH [18]. Since body positioning may alter IAP, the head of the patient's bed should be raised not more than 30 degrees. Nasogastric/colonic decompression via tubes should be established in presence of gastric or colon dilatation. In addition, some reports show a beneficial effect of neostigmine for the treatment of paralytic ileus associated with IAH [19]. Protocol to try to avoid positive cumulative balance is suggested by WSACS guidelines, but it remains uncertain whether use of diuretics and albumin and renal replacement therapy improve outcomes [6].

4. Interventional Treatment

When medical treatment fails to relieve IAH and ACS has developed, interventional measures seem to be necessary. First line therapy for those patients should be insertion of a percutaneous drainage catheter (PCD) under radiological guidance which can relieve ACS [20–22]. In a randomized study to compare the effects of indwelling catheter and conservative measures in the treatment of ACS in fulminant acute pancreatitis, Sun et al. [20] found that intra-abdominal pressure was positively correlated with drainage volume, duration of hospitalization time, and APACHE II score. Outcomes (relief of abdominal pain and hospitalization time) were significantly better in patients with abdominal catheter than in those treated conservatively. The observed reduction in mortality rate from 20.7% to 10% was not statistically significant.

In the previously mentioned systematic review including 103 patients with ACS, the authors found that PCD was performed as first line therapy in only 13% of patients [7]. In addition, surgical decompression was performed in 73% of patients in whom PCD was firstly inserted. Since these data come from observational retrospective and prospective studies with moderate to low methodological quality, it still remains uncertain why PCD was not performed in a bigger portion of patients. In addition, the time frames between diagnoses of SAP to ACS, as well as values of any organ scoring system in the moment of intervention, were not reported.

4.1. Indications and Timing of Interventional Treatment. Still there is no clear consensus on the optimal surgical management in patients with ACS during SAP. Data defining the optimal surgical procedure, indication, and timing of surgery in these patients are lacking. WSACS clinical practice guidelines "recommend decompresive [*sic*] laprotomy [*sic*] in cases of overt ACS compared to strategies that do not to use decompressive laparotomy..." [6]. There is no explanation on which approach should be used for laparotomy and what exactly means overt ACS (level of IAP, degree of systemic complications, and so forth).

Timing of abdominal decompression remains uncertain in the treatment of these patients. However the Finnish group published their experience regarding early and late decompression [10]. Results clearly showed that early decompression (first 4 days) was associated with significantly less deaths, compared with late decompression (after 4 days). Davis et al. [12] reported 25% mortality in surgically decompressed patients with ACS. Mean time from diagnosis to surgical intervention in their study was 3.1 h. It seems that early surgical decompression in patients with ACS during SAP may be associated with less mortality rate.

According to current literature, several surgical approaches have been described in order to improve outcome of patients who develop ACS during SAP. Some procedures have been reported that could be valuable and applicable in these patients. Decompressive laparotomy with subsequent laparostomy for the treatment of ACS has been used most frequently [2, 7, 10–13, 16]. The most commonly performed approach for full-thickness laparostomy is midline incision [23]. However, some authors suggested that bilateral subcostal incision has potential advantage such as easier and safer abdominal wall reconstruction [10, 24]. During both procedures, the abdominal wall is mainly reconstructed using some technique for temporary abdominal closure. For this purpose several types of abdominal zippers, plastic silo bag (Bogota bag), or vacuum assisted closed system were used. Temporary abdominal closure carries several advantages in comparison to leave abdomen open which comprises minimizing fluid and protein losses from the wound, prevention retraction of fascia edges, maintaining the abdominal domain, and avoiding the scenario of "hostile abdomen" [25].

When ACS is resolved using decompressive laparotomy, the most important goal is to obtain primary fascia closure. WSACS guidelines recommended protocolized efforts to achieve an early or at least same hospital stay fascial reconstruction [6]. However, this guideline did not make recommendation regarding use of an acute component separation technique to allow early abdominal fascial closure [6]. In addition, it did not suggest routine use of bioprosthetic mesh to facilitate early abdominal wall reconstruction. It seems that, without accumulative data regarding several techniques described, gradual fascial closure is an acceptable approach for early abdominal closure. When patient's condition does not allow primary fascia closure, skin coverage could be a good alternative. For this purpose, split-thickness skin graft or microvascular flaps for large defects could be used [25].

Several investigators also suggested skin incisions to perform a subcutaneous fasciotomy with the peritoneum left intact. Two techniques have been described: subcutaneous linea alba fasciotomy [26] and fasciotomy of the anterior rectus abdominis sheath [27]. The rationale for introducing these alternative methods was to avoid complications of open abdomen management. These approaches were reported in very limited group of patients and were associated with significant decrease in IAP levels. Risk of development of recurrent ACS is high and it should be monitored closely. Lower incidence of infection of pancreatic necrotic tissue and fistulas and no need for additional treatment connected to open abdomen are potential benefits, although a high proportion of these patients require additional surgery for ventral hernia repair. These approaches deserve attention, but we need more data to support implementation in daily practice.

5. Surgical Treatment

According to WSACS guidelines, in patients with persisting ACS despite PCD procedure performed, decompressive laparotomy is recommended [6].

First steps in surgical management for patients with ACS during SAP have been reported. Gecelter et al. [2] published 13 years ago their experience with 3 patients suffering from ACS during SAP who were surgically decompressed with mortality rate of 67%. In conclusion, the authors pointed out that this issue "has been ignored by current surgical literature." In the title of their paper they put question mark: "Abdominal compartment syndrome in severe acute pancreatitis: an indication for a decompressing laparotomy?". In 2005 Wong and Summerhays [28] presented case report and discussed the diagnosis and treatment of ACS as a new indication for operative intervention in SAP. In the same year, De Waele et al. [8] analyzed 44 patients with SAP of whom 4 received abdominal decompression due to ACS. In one patient necrosectomy was done during the decompressive laparotomy. Mortality rate in decompressed group was 75% and the authors concluded that it is not clear if surgical decompression in these patients is advantageous.

Among the 13 patients with ACS who did not respond to medical and PCD therapy, in 8 decompressive laparotomy was performed [3]. After laparotomy abdomen was temporarily reconstructed with silastic covering obtained from a sterilized inner surface of an intravenous bag sewn to the fascia, scheduled closure of abdominal wall was attempted as soon as acute episode resolved and edema and inflammatory collections reduced significantly. The authors did not report complications directly related to decompressive laparotomy. In this study, IAP decreased from 37 mmHg before decompression to 18 mmHg after procedure. In addition, the high peak airway pressure improved significantly, as well as other general physiologic parameters including serum pH, base excess, lactate, and mean arterial pressure.

Boone et al. [13] investigated the outcomes of 12 patients with SAP who underwent decompressive laparotomy for treatment of ACS during 9-year period. The laparotomy was performed within 4.5 days after disease onset and 4 patients were operated on in intensive care unit due to cardiopulmonary instability. Statistically significant improvements were noticed in several physiologic parameters. However, despite initial improvement almost in all patients, mortality rate of 50% was recorded. Authors concluded that patients with this highly lethal complication may have benefited from early surgical decompression.

There have been several case reports in the literature with high early mortality rate, ranging from 17 to 75% [3–6, 8, 9, 23]. A high proportion of patients in these reports, during surgical decompression, received retroperitoneal debridement and early mortality was mainly associated with uncontrolled retroperitoneal bleeding [8]. There is no evidence in the literature for early debridement of necrotic area during surgical decompression. Very limited experience supported the strategy of decompressive laparotomy in patients with ACS during SAP but without premature exploration of pancreatic region and retroperitoneum [23]. All these data have not provided enough clear evidence to support a treatment algorithm for ACS in patients with SAP, although two approaches deserve more attention than the others. These are decompressive laparotomy with temporary abdominal closure and percutaneous puncture with placement of abdominal catheter. Both of these procedures raise several unresolved issues for decompressive laparotomy: (a) the relation to potential necrosectomy, (b) difficulties in management of semiopen abdomen, (c) increased risk of enteric fistulas, (d) potentially higher number of patients with infected pancreatic necrosis than expected, and (e) incidence of postoperative hernias. The main unanswered question for percutaneous puncture with placement of abdominal catheter is whether it is possible to achieve sufficient decompression and relief of ACS using this procedure. In 2010, Belgrade group initiated multicenter, randomized, controlled study "Decompressive Laparotomy with Temporary Abdominal Closure versus Percutaneous Puncture with Placement of Abdominal Catheter in Patients with Abdominal Compartment Syndrome during Acute Pancreatitis" [29]. The rationale for this study was that during that time decompressive laparotomy for ACS associated with SAP has not been studied in large patients group. So far, 79 patients have been randomized and we expected that we will finish with patients recruitment until the end of this year.

6. Other Surgical Approaches

In a retrospective study Helsinki group showed results of surgical decompression in 26 consecutive patients with ACS during SAP [10]. In the biggest series published so far, different surgical decompressive methods were performed including full-thickness midline laparostomy, full-thickness transverse subcostal bilateral laparostomy, and subcutaneous linea alba fasciotomy. Bogota bag and vacuum assisted closure (VAC) were used for temporary abdominal closure. IAP decreased by 16 mmHg in patients who received full-thickness laparostomy and by 12 mmHg in those with line alba fasciotomy. Mean SOFA score before interventions was 12 but did not improve significantly during the first 5 postoperative days. The median number of reoperation was 4 and fistulas developed in 4 patients. All of these patients received either necrosectomy or bowel resection. The mortality rate in this study was 46%. More importantly, mortality rate in the group of patients who received decompressive surgery after day 5 after disease onset was 100%, in comparison with 18% in those who were operated on within first 4 days of disease. Results of this study clearly showed that early surgical decompression is more effective than late surgical decompression and that in patients with early MODS and ACS during SAP surgical intervention is indicated.

Subcutaneous linea alba fasciotomy (SLAF) as a minimally invasive treatment method for ACS was analyzed in a retrospective study including 10 patients with SAP [26]. The decrease of IAP after procedure was 10 mmHg. The value of SOFA score did not decrease in nonresponder patients, while in those with successful SLAF it decreased by five or more points. Four patients required a completion laparostomy within 24 hours. The mortality rate of 40% was noticed in this study. There were no complications related to SLAF. According to results it was concluded that SLAF is a safe decompressive technique and that in nonresponders a completion laparostomy is required.

The feasibility and effectiveness of subcutaneous fasciotomy of the anterior rectus abdominis sheath were assessed in 3 patients with ACS during SAP [27]. Surgical intervention was performed within 8 hours after admission to ICU and the diagnosis of ACS was confirmed. Decrease of IAP from 25 to 16 mmHg (mean values) was noticed, while MODS and APACHE II score were very slightly lower after intervention (from 6 to 5.3 points and from 12.3 to 10.6 points, resp.). Despite the effective control of IAH in all patients, systemic complications persisted, and two patients died. This report showed that subcutaneous fasciotomy of the anterior rectus abdominis sheath could decrease IAP, but effectiveness should be checked in carefully prepared prospective studies.

Deng et al. [11] reported experience of 8 patients with ACS during SAP which was surgically decompressed. During surgical intervention a catheter for antibiotic, octreotide, and protease inhibitor application was inserted into peripancreatic artery. APACHE II score decreased from 18 to 5.4 points, while IAP decreased from 29 mmHg to 7.7 mmHg. Mortality rate was amazingly low, 12.5%.

7. Complicating Factors for Surgical Decompression

A study dealing with the impact of obesity and decompressive laparotomy on mortality in SAP patients was published very recently [12]. Decompressive laparotomy was performed in 16 patients and the abdominal wall was reconstructed either with Bogota bag (11 patients) or with VAC system (5 patients). The mean BMI in this group was 30.3 kg/m^2, while 63% of patients were obese with BMI higher than 30 kg/m^2. Time interval between diagnosis of ACS and decompressive laparotomy was 3.1 h. Substantial morbidity was noticed including development of fistulas in 43% of patients, 18% of patients required the use of split-thickness skin graft for the closure of their incision, and 50% developed incisional hernias that required delayed repair. This approach was associated with mortality rate of 25%. Interestingly, according to results of this study, obesity was not predictive for development of ACS or mortality, nor was the presence of ACS a predictor of fatal outcome. Similar death rates were seen in patients who required decompressive laparotomy and those treated without surgery, indicating that in selected patients this procedure might be promising.

8. Conclusions

Abdominal compartment syndrome is a well-recognized clinical entity that significantly influences outcome of patients with SAP. It occurs as combination of inflammation of retroperitoneum, visceral edema, ascites, acute peripancreatic fluid collections, paralytic ileus, and aggressive fluid resuscitation. First line therapy for this life-threatening complication is conservative treatment aiming to decrease IAP and to restore organ dysfunction. If nonoperative measures are not effective, early abdominal decompression is mandatory. Midline laparostomy seems to be method of choice. Since it carries significant morbidity we need randomized studies to establish firm advantages over other described techniques. After ACS resolves, efforts should be made to achieve early primary fascia closure. Additional data are necessary to resolve uncertainties regarding ideal timing and indication for operative treatment.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Surgical Approaches to Chronic Pancreatitis

Daniel Hartmann and Helmut Friess

Department of Surgery, Klinikum Rechts der Isar, Technische Universität München, Ismaninger Straße 22, 81675 Munich, Germany

Correspondence should be addressed to Helmut Friess; helmut.friess@tum.de

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Chronic pancreatitis is a progressive inflammatory disease resulting in permanent structural damage of the pancreas. It is mainly characterized by recurring epigastric pain and pancreatic insufficiency. In addition, progression of the disease might lead to additional complications, such as pseudocyst formation or development of pancreatic cancer. The medical and surgical treatment of chronic pancreatitis has changed significantly in the past decades. With regard to surgical management, pancreatic head resection has been shown to be a mainstay in the treatment of severe chronic pancreatitis because the pancreatic head mass is known to trigger the chronic inflammatory process. Over the years, organ-preserving procedures, such as the duodenum-preserving pancreatic head resection and the pylorus-preserving Whipple, have become the surgical standard and have led to major improvements in pain relief, preservation of pancreatic function, and quality of life of patients.

1. Introduction

Chronic pancreatitis (CP) is an inflammatory condition characterized by a progressive loss of pancreatic parenchymal tissue that results in fibrosis, inflammation, and loss of exocrine and endocrine function [1]. It causes irreversible destruction of pancreatic parenchyma and leads to constant or recurring epigastric pain radiating to the back [2]. Alcohol abuse, pancreatic duct obstruction, systemic diseases, mutations of the cystic fibrosis gene, and hereditary or autoimmune pancreatitis have been found to be the main causes of CP. Progression of the disease can lead to complications such as pancreatic cancer development, duodenum and bile duct obstruction, or pseudocyst formation. Thus, medical and surgical treatment of CP aims to improve patients' quality of life by providing pain relief, improving pancreatic insufficiency, and reducing the number of complications [2].

With regard to pain in CP, several studies have shown a significant correlation between the severity of abdominal pain and the extent of intrapancreatic neural damage [3, 4]. Even though the pathophysiological mechanisms of neuropathic pain in CP have not yet been fully deciphered, recent studies point to a process of neural inflammatory cell infiltration leading to pancreatic neuritis and neural plasticity resulting in the formation of a dense intrapancreatic neural network [2, 5, 6]. Pain management strategies include the intake of pancreatic enzyme supplements, cessation of alcohol intake and smoking, and consequent analgesic therapy. In case of persistence of symptoms or suspicion of pancreatic cancer, surgical procedures come into play.

2. Surgical Techniques for Painful CP

Since the early 20th century, surgical treatment has been applied in CP patients who fail medical therapy, initially making use of pancreatic duct drainage by pancreatostomy [7]. In the ensuing decades, Puestow and Gillesby developed a technique that combined a longitudinal opening of the pancreatic duct and an anastomosis to the small intestine with a pancreatic left resection [8]. Shortly thereafter, Partington and Rochelle modified this procedure with an extended opening of the pancreatic duct and a preservation of the pancreatic tail, and their version is still being used nowadays for dilated pancreatic ducts of more than 7 mm in size [9]. As pointed out by these attempts of surgical treatment of CP, drainage operations were considered first; however, it has been shown that only a few procedures carry good

Table 1: Surgical techniques for the treatment of CP.

Authors	Publication	Surgical procedure
Link	Ann. Surg. 1911 [7]	Pancreaticojejunostomy
Kausch	Beitr. z. klin. Chir. 1912 [17]	Pancreaticoduodenectomy
Whipple et al.	Ann. Surg. 1935 [18]	Pancreaticoduodenectomy
Partington and Rochelle	Ann. Surg. 1960 [9]	Pancreaticojejunostomy
Puestow and Gillesby	AMA Arch. Surg. 1958 [8]	Pancreaticojejunostomy
Beger et al.	Acta Chir. Scand. 1990 [11]	Duodenum-preserving pancreatic head resection
Traverso and Longmire	Surg. Gynecol. Obstet. 1978 [19]	Pylorus-preserving pancreaticoduodenectomy
Frey and Smith	Pancreas 1987 [12]	Duodenum-preserving pancreatic head resection (Frey operation)
Büchler et al.	Am. J. Surg. 1995 [13]	Duodenum-preserving pancreatic head resection (Bern procedure)
Izbicki et al.	Ann. Surg. 1998 [20]	Pancreaticojejunostomy (V-shape)

long-term results [10]. Thus, several surgical procedures for painful CP that have been developed thereafter aimed at the resection of the pancreatic head carrying an inflammatory mass, such as (i) the standard Kausch-Whipple procedure with resection of the complete pancreatic head, gallbladder, duodenum, and gastric antrum, (ii) the pylorus-preserving pancreaticoduodenectomy (Traverso-Longmire procedure), or (iii) the total pancreatectomy in severe cases of CP with affection of the entire gland [2]. The Beger procedure, a resection of the pancreatic head that preserves the duodenum and intrapancreatic bile duct by subtotally excising the head and uncinate process, was developed in 1972 [11]. One decade later, the Frey procedure offered a less invasive organ-preserving variation of the Beger procedure that combined longitudinal pancreaticojejunostomy with a local pancreatic head excision without transection of the pancreas above the portal vein [12]. Further modifications of duodenum-preserving pancreatic resections exist, such as the Berne/Farkas technique developed independently by Büchler and colleagues and Farkas and colleagues, which consists of a partial resection of the pancreatic head without a lateral pancreaticojejunostomy [13]. This operation avoids the transection of the pancreas above the portal vein and combines the advantages of the Beger and Frey operations.

Additional surgical procedures have been subsequently developed to resolve CP-related complications but also to preserve pancreatic parenchyma as much as possible. Kutup and his team developed the longitudinal "V-shape excision" of the ventral pancreas in patients suffering from "small duct" pancreatitis (pancreatic duct diameter < 3 mm) [14]. In patients with a focal CP in the corpus of the pancreas, a middle segmental pancreatic resection has been developed as another organ-preserving operation [15]. Depending on pathology and location, other procedures include pancreatic left resection or total pancreatectomy [16].

Please see Table 1 for an overview of different surgical techniques for the treatment of CP.

3. Randomized Controlled Trials on the Endoscopic and Surgical Treatment of CP

One major controversial issue about the treatment of painful obstructive CP is whether surgical therapy is superior to endotherapy. The argument of interventional endoscopists is that surgery is too invasive and CP-related problems can be successfully treated by stenting. In order to analyze this issue, Díte et al. performed the first prospective, randomized controlled trial comparing surgery with endoscopy in a total of 72 patients with painful CP caused by ductal obstruction in 2003 [21]. Within the surgery arm, 20% of cases received a drainage procedure and 80% had a resection performed; within the endotherapy arm, 52% of patients underwent a sphincterotomy and stenting; 23% a sphincterotomy, stenting, and stone removal; and 23% solely a stone removal [21]. Initial pain relief success rates were above 90% in both groups at one year, but these results changed significantly after 3 and 5 years [21]. At the 5-year follow-up, surgery was found to be superior to endotherapy in both the whole group and the randomized subgroup for long-term pain reduction and increase in body weight [21].

A few years later, Cahen et al. performed a similar randomized trial on 39 symptomatic CP patients with a distal obstruction of the pancreatic duct in order to compare endoscopic and surgical ductal decompression either by endoscopic transampullary drainage (19 patients) or operative pancreaticojejunostomy (20 patients) [22]. After the first unscheduled interim analysis, the study had to be terminated because of ethical considerations (a decision of the safety committee based on a significant difference in outcome in favor of the surgical group). Compared with the stenting group, significantly better pain and physical health scores were found for CP patients undergoing surgical drainage of the pancreatic duct (p values < 0.001 and 0.003, resp.), while rates of complications, length of hospital stay, and changes in pancreatic function were similar within the two treatment groups [22]. In 2011, the authors published results on the long-term outcomes of these patients after another 5-year follow-up and were able to show that 47% of patients who underwent endoscopic transampullary drainage did need a surgical intervention in the end [23]. In addition, patients assigned to the surgical treatment arm needed significantly fewer procedures than endoscopically treated CP patients (4 versus 12; p value = 0.001) and had more relief from pain (80% versus 38%; p value = 0.042), while levels of quality of life and pancreatic function were similar [23]. The only drawback within this context is the fact that the

Table 2: Randomized controlled studies comparing endoscopic and surgical treatment of painful CP.

Authors	Publication	Number of patients	Results
Díte et al.	Endoscopy. 2003 [21]	72	Surgery better than endoscopy
Cahen et al.	N. Engl. J. Med. 2007 [22]	39	Surgery better than endoscopy
Cahen et al.	Gastroenterology. 2011 [23]	39	Surgery better than endoscopy

Table 3: Randomized controlled studies on the surgical treatment of painful CP.

Authors	Publication	Number of patients	Results
Izbicki et al.	Ann. Surg. 1995 [33]	42	Frey equal to Beger
Izbicki et al.	Chirurg 1997 [37]	74	Frey equal to Beger
Strate et al.	Ann. Surg. 2005 [34]	74	Frey equal to Beger
Klempa et al.	Chirurg 1995 [27]	43	Beger better than Whipple
Büchler et al.	Am. J. Surg. 1995 [13]	40	Beger better than Whipple
Köninger et al.	Surgery 2008 [35]	65	Berne/Farkas better than Beger
Izbicki et al.	Ann. Surg. 1998 [30]	61	Frey better than Whipple
Farkas et al.	Langenbecks Arch Surg. 2006 [29]	40	Frey better than Whipple
Bachmann et al.	Ann. Surg. 2013 [31]	64	Frey better than Whipple

study by Cahen et al. was not sufficiently powered for long-term follow-up analysis. Thus, the data from 2011 show lower significance levels compared to the original study from 2007 with a follow-up period of 24 months because there were fewer cases to consider over the long run. All in all, these randomized controlled trials give strong evidence that surgical therapy provides significantly better long-term results than endoscopic interventions.

Please see Table 2 for an overview of randomized controlled studies comparing endoscopic and surgical treatment of painful CP.

Since worldwide consensus and standard criteria on the choice of surgical procedure are lacking, the work of Cahen and colleagues has gained importance. Patients with a dilated pancreatic duct in the absence of an inflammatory mass in the pancreatic head can be effectively treated with an operative pancreaticojejunostomy [22, 24]. Different options exist with regard to the inflammatory pancreatic head mass, which is thought of as being the pacemaker of pain and progression of disease [24]. Thus, in patients with an enlarged pancreatic head, appropriate surgical options are pancreatoduodenectomy or duodenum-preserving pancreatic head resection, as mentioned above [24]. Radical pancreatic resectional procedures are also being carried out in the case of small duct CP with a nondilated main pancreatic duct and an associated head mass of uncertain etiology [25]. In particular, with regard to small duct CP with head dominant disease, several randomized trials have shown that duodenum-preserving pancreatic head resection and its modifications provide excellent long-term pain relief and can be considered the standard for this form of CP [25].

An important and oftentimes underestimated aspect is the timing of surgery in the management of patients with CP: early or late in the course of the disease. A recent systematic review and meta-analysis supports early surgery for pain management in CP patients because early surgical intervention is associated with improved postoperative pain relief, reduced risk of pancreatic insufficiency, and decreased reintervention rates in comparison with conservative step-up approaches [26]. A similar observation was made in the study by Cahen et al. that analyzed long-term follow-up data. Almost half of the patients who were initially treated endoscopically underwent salvage surgery. However, delayed surgery was not as effective as expected, indicating that postponing surgery in CP patients has a negative influence on the treatment outcome [23].

4. Randomized Controlled Studies on the Surgical Treatment of CP

Evidence-based data on the surgical treatment of CP favors tailored organ-sparing procedures, such as the Beger or Frey procedures, over the classic Whipple or the pylorus-preserving Whipple procedure. In two monocentric randomized controlled trials, Klempa et al. and Büchler et al. found duodenum-preserving pancreatic head resection to be superior to the classical Whipple procedure in regard to pain relief, weight gain, and endocrine pancreatic function [13, 27]. Comparing 21 patients treated with the classic Whipple and 22 patients treated with the Beger procedure, Klempa et al. also found the duodenum-preserving pancreatic head resection to lead to a significantly shorter hospital stay [27]. After long-term follow-up of the randomized clinical trial (14 years) from Heidelberg, these advantages were no longer significant [28]. However, it should be stated in this context that the original study had not been powered for long-term follow-up, and significance levels decreased because patients were lost to follow-up or passed away. There is a statistical limit in all studies listed in Table 3, because none of these studies was powered for long-term follow-up investigations. Therefore, there is a clear tendency for a better outcome following organ-preserving surgery compared to the Whipple operations.

In addition, two independent randomized trials by Farkas et al. and Izbicki et al. revealed that the Frey procedure provides a better quality of life, while the pylorus-preserving pancreaticoduodenectomy (pp Whipple) and the Frey procedure were found equally effective in pain relief [29, 30]. Long-term follow-up showed comparable pain control and pancreatic function between both procedures, while survival rates were superior after the Frey procedure [31, 32].

In a prospective, randomized trial on different techniques of duodenum-preserving pancreatic head resection, Izbicki et al. compared the Beger and the Frey procedures and found both equally safe and effective in pain relief, postoperative quality of life, control of complications affecting adjacent organs, and exocrine or endocrine pancreatic function [33]. About ten years later, Strate et al. published a long-term follow-up of these data showing no difference in mortality, quality of life, pain, or exocrine or endocrine insufficiency within the two groups [34]. In addition, a controlled, prospective, randomized study by Köninger et al. on the evaluation of the Beger and Berne/Farkas procedures for CP showed that the Berne/Farkas technique provided significantly shorter operation times and hospital stays, while the quality of life was found to be similar [35]. In a recent randomized trial on pylorus-preserving and duodenum-preserving pancreatic head resections, Keck et al. found both types of resections to be equally effective in pain relief and quality of life without differences in exocrine or endocrine pancreatic function [36].

Taken together, the duodenum-preserving pancreatic head resections (including Beger, Frey, and Berne/Farkas procedures) have been shown to be superior to the classic Whipple procedure, while Frey and Beger procedures have similar results when compared to each other.

Please see Table 3 for an overview of randomized controlled studies on the surgical treatment of painful CP.

A systematic review and meta-analysis of four randomized controlled trials on the surgical treatment of pancreatic head lesions in CP patients by Diener et al. showed duodenum-preserving pancreatic head resections (including Beger, Frey, and Berne/Farkas procedures) to be superior in peri- and postoperative outcome parameters and quality of life compared to partial pancreatoduodenectomy (Whipple procedure) while being equally effective in terms of postoperative pain relief, overall health, and postoperative endocrine sufficiency [38]. Another meta-analysis including 15 studies by Yin et al. revealed that pancreaticoduodenectomy offered significantly less postoperative pain relief than the Beger procedure and worse postoperative morbidity than the Frey procedure, while quality of life, pancreatic exocrine function, and delayed gastric emptying also favored duodenum-preserving strategies [39].

Another procedure that has been evaluated lately as a treatment option for a subset of CP patients is the method of total pancreatectomy and autologous islet transplantation (TP/IAT).

In a systematic review of the literature, TP/IAT has been shown to successfully reduce pain, while a significant proportion of patients are able to remain independent of insulin supplementation even in the long run [40]. Nevertheless, the impact of this surgical procedure on quality of life and its optimal timing in relation to the evolution of CP has not been studied sufficiently [40]. Therefore, it should only be considered as ultima ratio once all other surgical treatment options have been exhausted or are unlikely to improve the symptoms of these patients [40].

An additional example of problem-tailored surgery is portal hypertension. In most cases, surgery does provide good relief of portal hypertension [41]. Splenectomy and gastric devascularization are considered adequate treatment options for CP patients with bleeding gastric varices due to portal hypertension [41]. Several new developments have been made with respect to left-sided portal hypertension, which was considered a relative contraindication to laparoscopic splenectomy. In a recent case study, Patrono and colleagues reported on the management of a CP-related splenic vein thrombosis by laparoscopic splenectomy after splenic artery embolization [42].

5. Conclusion

With reference to postoperative functional outcome after surgical treatment of painful CP, a deterioration in pancreatic function can be seen in most cases, which is most likely inevitable after removal of pancreatic tissue [2]. In any case, surgery should be tailored to the needs of patients and should be as problem-oriented and organ-sparing as possible. Therefore, based on present evidence, patients suffering from CP and its associated complications (e.g., pain, duodenal or pancreatic duct obstruction, cholestatic jaundice, appearance of an inflammatory mass, and portal hypertension) should be evaluated for problem-tailored surgery in an interdisciplinary center with expertise in pancreatic surgery.

Unfortunately, many patients are sent for surgery at a prolonged disease stage, when even surgery cannot be an effective treatment anymore. Nowadays, surgical treatment of CP is associated with low morbidity and mortality, preservation of exocrine or endocrine pancreatic function, sustainable pain reduction, and major improvement in quality of life.

In particular against this background, one should bear in mind that an organ-sparing operation at the right point in time carries a better outcome than performing an extended resection, like a Whipple operation, as a last resort once all therapeutic options are exhausted. For this reason, early timing of surgical therapy is crucial for the outcome of patients with painful CP, and the indication of surgery should be considered early once symptoms are unambiguous.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Current State of Vascular Resections in Pancreatic Cancer Surgery

Thilo Hackert, Lutz Schneider, and Markus W. Büchler

Department of Surgery, University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany

Correspondence should be addressed to Thilo Hackert; thilo_hackert@med.uni-heidelberg.de

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Pancreatic cancer (PDAC) is the fourth leading cause of cancer-related mortality in the Western world and, even in 2014, a therapeutic challenge. The only chance for long-term survival is radical surgical resection followed by adjuvant chemotherapy which can be performed in about 20% of all PDAC patients by the time of diagnosis. As pancreatic surgery has significantly changed during the past years, extended operations, including vascular resections, have become more frequently performed in specialized centres and the border of resectability has been pushed forward to achieve a potentially curative approach in the respective patients in combination with neoadjuvant and adjuvant treatment strategies. In contrast to adjuvant treatment which has to be regarded as a cornerstone to achieve long-term survival after resection, neoadjuvant treatment strategies for locally advanced findings are currently under debate. This overview summarizes the possibilities and evidence of vascular, namely, venous and arterial, resections in PDAC surgery.

1. Introduction

Overall long-term survival rates of 1–5% are associated with pancreatic cancer (PDAC) underlining the poor prognosis of this tumor entity [1, 2]. The major obstacle to improve this situation is the fact that PDAC diagnosis is made late and in an advanced tumor stage in the majority of patients precluding them from surgical resection due to distant spread of the disease. Approximately 10–20% of PDAC patients can consequently undergo potentially curative surgery aiming at a radical R0 resection which results in long-term 5-year survival rates of 20–25% [3, 4]. As pancreatic surgery is challenging with regard to preoperative diagnostic, surgical procedures as well as postoperative care and complication management, the value of centralization of pancreatic surgery in centres of excellence and high volume institutions is unquestionable today and has been demonstrated in numerous studies the last 15 years [5, 6]. In this setting, implying experience of the individual surgeon who continuously performs pancreatic resections and the environment with an interdisciplinary team of specialists to optimize perioperative care including ICU treatment and complication management, mortality rates following major pancreatic resections below 5% are standard today [5, 6]. In this context, the borders of resectability have been pushed and extended surgical approaches in PDAC have become commonly performed, which include vascular as well as multivisceral resections [7, 8]. This has been accompanied by scientific work-up of the results of these operations in terms of surgical as well as oncological outcome resulting in an increasing number of publications and a meanwhile satisfying level of evidence with a relevant influence on recent national and international guidelines consensus statements [9, 10]. The present review gives an overview on the development and current state of venous and arterial resections in PDAC surgery.

2. Evaluation of Resectability and Borderline Resectability

Situations in which vascular resections are required are often described as "borderline resectable" findings. In 2014, the International Study Group for Pancreatic Surgery (ISGPS) has published a consensus statement to standardize the definition of borderline resectability in accordance with the guidelines of the National Comprehensive Cancer Network

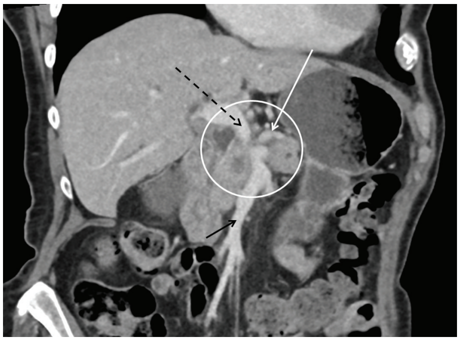

Figure 1: CT scan (coronary reconstruction) showing PDAC tumor infiltration of the portal vein confluence (white circle). Superior mesenteric vein (black arrow), portal vein (broken black arrow), and splenic vein (white arrow) without thrombosis, adequate diameter of the portal, and superior mesenteric vein to perform an end-to- end anastomosis.

(NCCN) as well as the definition of extended resections [11, 12]. Following these recommendations, preoperative evaluation of resectability should be based on a computed tomography (CT) scan with a pancreas-specific protocol, for example, a "hydropancreas" CT, as this offers best local resolution with regard to tumor extension and infiltration towards the vascular structures (Figure 1). Three grades of resectability can be defined for localized PDAC which are termed as "resectable," "borderline resectable," and "irresectable" [11]. While a resectable tumor has no vascular attachment (no distortion of the venous structures and clearly preserved fat planes towards the arteries), borderline resectability is defined as distortion/narrowing/occlusion of the mesentericoportal veins with a technical possibility of reconstruction on the proximal and distal margin of the veins. Furthermore, a semicircumferential abutment ($\leq 180^\circ$) of the superior mesenteric artery (SMA) or an attachment at the hepatic artery without the celiac axis is regarded as a borderline resectable finding. Consequently, irresectability is defined as a more extended involvement of the SMA, the celiac axis, aorta or inferior vena cava. Furthermore, involvement of the mesentericoportal venous system can fulfill the criteria of irresectability if there is no technical possibility for reconstruction, for example, in case of tumor-associated portal cavernous transformation.

Regarding the performance of resections, borderline findings in venous and arterial vessel involvement have to be differentiated. In venous borderline resectability, no neoadjuvant treatment is recommended, instead upfront surgery should be performed and, if the intraoperative finding matches the presumed borderline situation as defined above, completed as an en bloc tumor removal with venous replacement [11, 12]. In contrast, when suspected arterial borderline resectability is intraoperatively confirmed as a true arterial involvement, no general recommendation for resection is given, but palliative treatment should be regarded as the standard of care. In individual decision, however, these recommendations may be modified and neoadjuvant treatment with a consecutive reexploration and eventually resection is possible as well as direct arterial resection in exceptional cases or under study conditions.

Restaging after neoadjuvant treatment may be challenging, as the differentiation of vital tumor and fibrosis by conventional cross-sectional imaging is limited and even PET-CT scans do not offer 100% accuracy [27]. Therefore, in cases of clear tumor regression, a surgical exploration should be performed as well as in patients showing stable disease status after completion of the neoadjuvant treatment. The rationale for this is the fact that, despite still visible soft tissue, this is often found to be only fibrotic residual changes [28]. In these cases, after confirming absence of vital tumor, a sharp dissection without vascular resection is possible and eventually a ypT0 situation may be found. Patients with a clear tumor progression under neoadjuvant treatment should be excluded from secondary exploration. Due to the three scenarios described, the neoadjuvant treatment is helpful to stratify patients and recognize those with borderline findings who do not benefit from extended resections.

3. Venous Resections

En bloc vascular resections during pancreatoduodenectomy (PD) to achieve tumor clearance and improve survival in case of portomesenteric vein involvement were published more than 30 years ago [29]. From these anecdotal reports, the technical feasibility was concluded; however, it took another two decades until these approaches gained widespread acceptance in centres around the world. Besides venous resection in PD, this approach is also performed during distal (DP) or total pancreatectomy (TP) [30–32]. However, especially in TP, several aspects regarding venous drainage of the stomach have to be respected when the portal, and usually also the splenic vein, is resected, which is mentioned in detail below.

The site of tumor infiltration of the vein has to be carefully evaluated already in the preoperative cross-sectional imaging. Proximal tumor adherence or infiltration can usually be handled more easily, as the vessel diameter is large enough to create a sufficient anastomosis. In case of a more distally located tumor infiltration far below the mesenterico-splenic confluence, the decreasing vascular diameter of the superior mesenteric vein may limit the technical possibility to perform a venous resection [11].

Regarding surgical technique, venous resections can be performed differently depending on the location and length of tumor adherence. A latero-tangential resection of the portal vein is possible when tumor infiltration reaches the vein from the right circumference and can be excised with a small patch and direct closure of the defect directly without a hemodynamically relevant stenosis [30–32]. Adequate venous drainage of the small bowel needs to be ensured afterwards by direct flow measurement and the clinical evaluation of the perfusion aspect of the intestine during the remaining operation time, which is usually long enough to recognize venous congestion if present.

When a tangential vein resection is not possible, the mesenteric root should be mobilized completely by resolving the attachment of the right hemicolon to the retroperitoneal adhesions [33]. This gives a great flexibility of the mesenteric vein and almost always allows approximation of the distal and proximal resection margins of the vein without any critical tension. Following resection of the tumor-bearing venous segment, continuity of the vessel can be restored by a direct end-to-end anastomosis as the corresponding diameters of the distal and proximal lumen can usually be adapted without causing any obstruction to the free venous bowel drainage.

In case the resected venous length cannot be bridged by the direct anastomosis, a vascular graft needs to be inserted. For this purpose, autologous grafting (e.g., renal vein and saphenous vein) is possible but requires a venous harvesting before clamping and resection [34]. Alternatively, synthetic grafts, for example, a ringed goretex prosthesis, can be chosen to bridge the resected vein segment. The insertion of a synthetic graft always implies the possible problems artificial material may cause in case of infection or anastomotic leakage. A situation of a synthetic graft in combination with a pancreatic fistula must be regarded as a high risk constellation for postpancreatectomy hemorrhage or difficult to treat long-lasting graft infection. Yet, the clinical impact of this complication seems to be rather small; in a series of 110 patients undergoing venous resection with different reconstruction techniques no difference in surgical outcome was shown when different types of venous reconstruction (venorrhaphy, end-to-end anastomosis, and graft insertion) were observed [33].

When other surgical outcome parameters are considered, it has been demonstrated that both, resection with a direct anastomosis or the interposition of a graft, can be performed safely. Large series showed that surgical morbidity and mortality rates are comparable to standard pancreatic head resections [33–35]. This has been scientifically examined and confirmed in two recently published systematic reviews [36, 37]. In the review by Siriwardana and Siriwardena [36], 52 manuscripts with 6333 patients in whom pancreatic resection was performed for PDAC were included. 1646 of these patients (26%) underwent synchronous porto-superior mesenteric vein resection mainly together with partial pancreatoduodenectomy (71%) or total pancreatectomy (24%). Median operation time was 8.5 hours, median blood loss 1750 mL, overall morbidity 42% (9 to 78%), and perioperative mortality 5.9%. The more recent meta-analysis by Zhou et al. [37] included 19 studies and 661 patients with venous resections during PDAC resections that were compared to 2247 patients undergoing similar operation without vessel resection. Both groups were characterized by comparable surgical outcome. Furthermore, in terms of oncological results, no difference in overall survival between both patient collectives was found, resulting in a 5-year survival rate of 12.3%, certainly superior to palliative treatment. Table 1 gives an overview of the largest studies on venous resections in PDAC.

A special aspect in venous resections that has to be respected in certain situations is the patency of venous gastric drainage. In PD, the splenic vein can be closed during venous resection as the stomach is usually drained sufficiently via the coronary vein (if preserved) and collaterals via the short gastric veins.

In contrast, in TP for PDAC, which is usually combined with splenectomy, venous resections may cause severe disturbances of the gastric drainage, especially when the coronary vein is removed during resection. In this situation, two scenarios may occur. On one hand a venous congestion of the remaining stomach may require a classical distal or even subtotal stomach resection to avoid ischemic complications with either long-lasting delayed gastric emptying or even necrosis of the stomach with the need for a reintervention and consecutive stomach resection. On the other hand, if the resected coronary vein can technically be preserved, there is the possibility for reinsertion into the mesentericoportal axis to restore stomach drainage and avoid any type of gastrectomy [38].

In addition to PD and venous resection alone, also multivisceral approaches established procedures to achieve a radical tumor removal [24, 31, 32]. Although these are associated with an increased morbidity, perioperative mortality and long-term survival are not negatively influenced in these patients [31, 32]. In approximately 20% of the patients, multivisceral resection is performed together with portal or superior mesenteric vein resections. This additional procedure does not increase the risk for complications and should therefore be performed in patients qualifying for an extended approach of complete tumor removal [24].

In conclusion, venous resections during surgery for pancreatic cancer can therefore be regarded as a standard procedure in experienced hands and should be performed in a routine setting to achieve a complete removal of the tumor, which has meanwhile been generally accepted and is explicitly stated in national and international guidelines such as the German and the ISGPS consensus statements [9, 10].

4. Arterial Resections

The resection of the celiac axis or the superior mesenteric artery has occasionally been performed since the 1970s in selected patients but is still regarded as an extraordinary approach in PDAC surgery [31, 32, 39–42]. Arterial tumor infiltration of the hepatic artery, celiac axis, or the superior mesenteric artery can be regarded as a symptom of biologically aggressive tumor spread. Although in some patients this is considered as borderline resectable according to the ISGPS consensus statement, an upfront resection is rarely recommendable, even if it can technically be performed [10]. In general, in case of arterial tumor infiltration, a neoadjuvant treatment should be evaluated to achieve a better local tumor control. This treatment can be performed following different study protocols and is not standardized yet. In many protocols, gemcitabine is combined with a 50–60 Gy radiation over a 6-week period, followed by 4–6 week interval to await downsizing and development of fibrosis as a consequence of the therapy [43]. After restaging, patients should be subjected to surgical exploration as long as no signs of systemic tumor spread are visible. Using this approach, in 33–50% of all primarily irresectable patients, a radical resection is possible which achieves R0 resection rates comparable to standard resections [44–47]. To clarify arterial infiltration along the superior mesenteric artery intraoperatively, the "artery-first" approach is a useful procedure [48]. Preparation starts at the superior mesenteric artery as the initial step before

Table 1: Series with >50 patients comparing resection for pancreatic cancer with and without mesentericoportal vein resections 1995–2015.

Author, year	Patients PVR/no PVR	OP time (min)	R0 rate (%)	Morbidity (%)	Mortality (%)	Survival (months)
Harrison et al., 1996 [13]	58/274	444/348	74.1/76.3	nm	5.0/3.0	13.0/17.0 (median)
Hartel et al., 2002 [14]	68/203		61.8/73.4	27.0/22.0	4.0/3.0	
Riediger et al., 2006 [15]	53/169	500/440	69.0/79.0	23.0/35.0	3.8/4.1	15.0% (5 years)
Ouaissi et al., 2010 [16]	59/82	480/420	57.6/86.6	52.5/54.9	1.7/1.2	17.5/18.7 (median)
Banz et al., 2012 [17]	51/275	nm	49.0/63.3	27.5/28.4	13.7/5.1	14.5/14.8 (median)
Murakami et al., 2013 [18]	61/64	nm	50.8/71.9	36.1/21.9	0.0/0.0	14.7/26.7 (median)
Ravikumar et al., 2014 [19]	230/840	300/250	37.1/48.4	34.3/30.8	4.6/4.2	18.2/18.0 (median)
Kulemann et al., 2015 [20]	131/208	463/427	64.6/76.2	55.7/50.0	3.3/5.1	21.6/19.7 (median)

nm: not mentioned.

Table 2: Series of arterial resections for pancreatic cancer.

Author, year	Patients	OP time (min)	R0 rate (%)	Morbidity (%)	Mortality (%)	Survival (months)
Stitzenberg et al., 2008 [21]	12	660	50.0	100.0	17.0	17
Wang et al., 2008 [22]	19	nm	nm	36.8	0.0	16.0% (1 year)
Sugiura et al., 2009 [23]	26	nm	nm	nm	nm	10% (5 years)
Hartwig et al., 2009 [24]	14	450	57.4	37.6	6.9	nm
Ouaissi et al., 2010 [16]	8	570	50.0	75.0	12.5	11.0 (median)
Yamamoto et al., 2012 [25]	13	620	31.0	92.0	0.0	20.8 (median)
Yoshidome et al., 2014 [26]	7	522	nm	29.0	0.0	12.7 (median)

nm: not mentioned.

further mobilization of the pancreatic head. The preparation is carried out with the incision of the peritoneal layer at the ligament of Treitz from the left side and continued by clearing the tissue along the artery down to the origin from the aorta via this access. Tumor infiltration can be ruled out or confirmed by this preparation to determine the further procedure.

In a recent review, the role of arterial resection has been critically evaluated [49]. Besides this left-sided inframesocolic "artery-first" approach, various other techniques have been published starting from arterial preparation on the right side or from a supracolic approach [50–54]. Regarding resection of the superior mesenteric artery, only five studies were available, including a total number of less than 30 patients. All authors showed that the resection is technically possible; grafting with the saphenous vein was the most commonly used method for reconstruction. However, morbidity of this approach is high and the oncological outcome is not yet convincing from the limited evidence.

Celiac axis or hepatic artery resection is performed more often. The available literature on this topic includes approximately 200 patients [55, 56]. Surgical morbidity is up to 40%; mortality in pancreatoduodenectomy with arterial resection ranges from 0 to 35%, showing the inconsistent data basis of this approach. Outcome in terms of oncological results seems to justify the approach especially in distal pancreatectomy [57] as long-term survival seems to be nearly equal to the standard approaches. However, it must be clearly stated that arterial resection does not represent a standard procedure but has to be based on an individual decision of an experienced pancreatic surgeon. Table 2 summarizes selected studies on arterial resections.

From the technical point of view, when arterial resection is performed, resection without reconstruction has to be differentiated from resection with direct anastomosis or graft insertion to replace the resected vessel. The celiac axis might be resected down to its aortal orifice in PD as well as in DP or TP [55–57]. As long as the proper hepatic artery can be

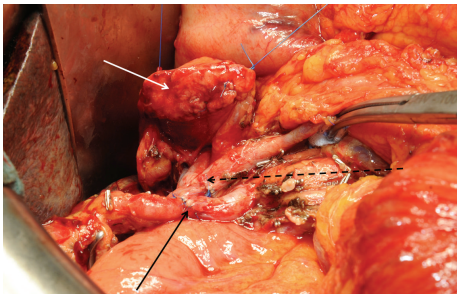

Figure 2: Intraoperative view in combined arterial and venous resection. Arterial anastomosis after resection of a replaced right liver artery (black arrow) infiltrated by the resected PDAC. Portal vein anastomosis (broken black arrow) and pancreatic remnant (white arrow) before completing the pancreatojejunostomy.

preserved, a reconstruction is possible. The left gastric and splenic artery can usually be cut without reconstruction; a consecutive splenectomy may be necessary in some patients. Restoration of the hepatic perfusion must be ensured by reconstruction of the proper or common hepatic artery. This reconstruction can be done with an interposition of any arterial vessel of the celiac axis or a venous interposition graft. The splenic artery especially is a suitable vessel for this reconstruction, either with a transposition if the base of celiac axis can be preserved or with an interposition which requires an additional anastomosis between graft and aorta [58].

However, the arterial perfusion of the liver should be controlled by regular duplex examinations and restored aggressively in case of a vessel occlusion. Arterial hepatic perfusion failure may otherwise cause acute problems postoperatively in terms of liver ischemia, necrosis, and infection and is a risk factor for bile-duct associated complications in the long-term follow-up [59, 60]. Using this approach, arterial resection can be carried out safely in experienced hands but has to be regarded as a highly individual decision in suitable patients.

5. Combined Vascular Resections

A combination of both venous and arterial vessel resections is technically possible in selected patients. Comparable to arterial resections alone, this approach is not recommended as a standard procedure but has to be based on individual decisions. As it has been performed in only small patient series to date, there is only very limited literature published on this topic; no conclusive evidence with regard to perioperative morbidity and oncological outcome is available. Combined vascular resections may be an individual option for patients that are considered suitable in terms of age and comorbidities (Figure 2). As this approach may be associated with a considerable surgical morbidity and even mortality as well as impaired postoperative quality of life compared to standard pancreatic operations, it must not only be evaluated with focus on technical feasibility but also on quality-adjusted lifetime that may be gained by its performance. As these extensive resections may be performed during total or even multivisceral pancreatectomies, side-effects of these approaches may be aggravated. Intestinal discomfort, diarrhoea, and food intolerance especially have to be taken into account as long-term consequences that may impair patients' performance status and especially suitability for adjuvant therapies. However, when a radical resection can be performed, present data support this concept in young and otherwise healthy patients as, once the postoperative course is completed, the prognosis from the oncological point of view seems to be superior to any palliative treatment option. Future studies in growing patient collectives will add evidence to these topics.

6. Conclusions

In conclusion, vascular resections in PDAC surgery are extended approaches and can be performed in many situations. The recent ISGPS consensus definitions of borderline resectability and extended resections will help to standardize these procedures in the scientific reporting in the future and make studies on this topic more comparable. Venous resections should routinely be performed when there are no other contraindications for surgery in the respective patients and can also be combined with multivisceral approaches with good surgical and oncological outcome which has also been clearly stated in national and international guidelines in the meantime. Arterial resections might be justified in selected cases after careful evaluation of the risk-benefit ratio for the individual patient. In the majority of patients, however, an evident arterial infiltration should primarily be treated by neoadjuvant therapy and reevaluated for a possibility of surgery afterwards. All surgical approaches must be part of interdisciplinary multimodal concepts as radical resection alone cannot achieve optimal patient outcome and always needs to be followed by adjuvant treatment.

Conflict of Interests

The authors declare no conflict of interests regarding the paper.

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Clinical Study

Mesenteric-Portal Vein Resection during Pancreatectomy for Pancreatic Cancer

Valentina Beltrame,[1] Mario Gruppo,[1] Sergio Pedrazzoli,[1] Stefano Merigliano,[1] Davide Pastorelli,[2] and Cosimo Sperti[1]

[1] *Department of Surgery, Oncology and Gastroenterology, 3rd Surgical Clinic, University of Padua, 35128 Padua, Italy*
[2] *Department of Oncology, Veneto Institute of Oncology, 35128 Padua, Italy*

Correspondence should be addressed to Cosimo Sperti; csperti@libero.it

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The aim of the present study was to determine the outcome of patients undergoing pancreatic resection with (VR+) or without (VR−) mesenteric-portal vein resection for pancreatic carcinoma. Between January 1998 and December 2012, 241 patients with pancreatic cancer underwent pancreatic resection: in 64 patients, surgery included venous resection for macroscopic invasion of mesenteric-portal vein axis. Morbidity and mortality did not differ between the two groups (VR+: 29% and 3%; VR−: 30% and 4.0%, resp.). Radical resection was achieved in 55/64 (78%) in the VR+ group and in 126/177 (71%) in the VR− group. Vascular invasion was histologically proven in 44 (69%) of the VR+ group. Survival curves were not statistically different between the two groups. Mean and median survival time were 26 and 15 months, respectively, in VR− versus 20 and 14 months, respectively, in VR+ group ($p = 0.52$). In the VR+ group, only histologically proven vascular invasion significantly impacted survival ($p = 0.02$), while, in the VR− group, R0 resection ($p = 0.001$) and tumor's grading ($p = 0.01$) significantly influenced long-term survival. Vascular resection during pancreatectomy can be performed safely, with acceptable morbidity and mortality. Long-term survival was the same, with or without venous resection. Survival was worse for patients with histologically confirmed vascular infiltration.

1. Introduction

Involvement of peripancreatic large blood vessels is detected in about half of pancreas cancers [1] and has been generally considered a contraindication to surgery, for many years. In fact, vascular resection was widely considered a difficult surgical procedure with high incidence of complications [2, 3] and without significant effectiveness in survival, compared to palliative operations [4, 5]. Nevertheless, surgical resection is still considered the only curative opportunity for patients affected by pancreatic cancer and, nowadays, it is considered an effective palliative procedure due to improvement of morbidity and mortality rates after surgery [6–9]. Moreover, in the last two decades, an increasing number of venous resections were reported in centers with high volume of pancreatic surgery, while arterial resection still remains an isolated exception [10].

Aim of this study is to present our single center experience of venous resections during pancreatectomy for pancreatic cancer.

2. Patients and Methods

Data were obtained from a retrospective analysis of a prospectively collected database of 241 patients who underwent pancreatectomy for pancreatic cancer from January 1998 to December 2012 at our institution. They were divided in two groups: patients who underwent associated venous (portal-mesenteric) resection (VR+) and those who underwent standard resection (VR−). The two groups were compared in terms of demographic features, surgical procedures, tumor pathologic findings, perioperative outcome, and survival. All surgical procedures were performed by the same surgical team. All patients underwent standardized preoperative assessment: routine blood tests and tumor markers CEA and CA 19-9 determination, abdominal ultrasound (US), computed assisted tomography (CT) scan, and, when needed, magnetic resonance imaging or positron emission tomography (PET). CT with angiographic reconstruction was the preferred imaging for tumor's staging. Limited involvement of superior mesenteric-portal axis (less than 2 cm), in absence of extrapancreatic disease and involvement of superior mesenteric artery and/or celiac trunk, was not considered as contraindication to surgery. No patient underwent neoadjuvant therapy.

Surgical technique included standardized lymph node dissection and para-aortic nodes sampling, pylorus-preserving pancreaticoduodenectomy (PD) for tumors of the head of the pancreas, and distal pancreatectomy with splenectomy for tumors of the body/tail. Total pancreatectomy was performed in selected patients, when resection margin of the pancreas was involved by the tumor or when pancreatic anastomosis was judged at high risk of leakage. In VR+ patients, surgical procedure was similar to standard resection in preparation and exposure of pancreas, with a wide Kocher maneuver. Complete evaluation of vascular invasion was determined after transection of the isthmus; in the last years, we performed translateral approach with dissection of uncinate process first and subsequent en bloc excision of pancreas head and infiltrated vein [11]. Vascular resection technique included tangential resection with linear nonstenosing suture when a focal invasion of superior mesenteric vein or portal vein occurred or excision of infiltrated venous tract and end-to-end anastomosis. In selected cases of longer involvement of vein, a vascular graft with internal jugular vein was performed. Curative resection was defined as tumor's resection with pathologically confirmed negative margins. R1 resection was defined as the presence of tumor ≤ 1 mm from the margin, according to Leeds criteria [12]. Perioperative morbidity and mortality were investigated in both groups: operative mortality was defined as death within 30 days from operation or during hospitalization. Pancreatic fistula was defined as the drainage of fluid with an elevated level of amylase and graded according to the International Study Group of Pancreatic Fistula recommendations [13]. All patients underwent regular follow-up that included physical examination, abdominal CT or US, and tumor markers determination every 3 months, for the first 2 years, and every 6 months, thereafter.

Survival curves were constructed with the Kaplan-Meier method and compared by the univariate log-rank test: significance was considered as $p < 0.05$. Tumor's stage, grading, lymph node status, radicality of resection, venous resection, true venous infiltration, and depth of venous involvement were considered as prognostic factors. Independent prognostic variables were evaluated with a Cox regression hazard model. Statistical analysis was performed using the SPSS statistical software package (version 18.0; SPSS Inc., Chicago, IL, USA).

Table 1: Clinicopathological features of patients subjected to pancreatic resection with (VR+) and without (VR−) vascular resection.

	VR+ ($n = 64$)	VR− ($n = 177$)
Age		
Median	60.7	63.7
Range	(37–82)	(37–84)
Gender		
M	23	95
F	30	82
pT1	0	3
T2	3	21
T3	22	149
T4	28	4
Lymph node		
Yes	39	117
No	14	60
Grading		
G1	14	29
G2	28	95
G3	11	53
Radicality		
R0	55	125
R1	9	46
R2	0	6
Type of resection		
PD	50	121
TP	10	6
DP	4	50

PD: pancreatoduodenectomy; TP: total pancreatectomy; DP: distal pancreatectomy.

3. Results

Clinicopathologic findings of patients included in the study are detailed in Table 1. During the study period, resection rate increased from 18% to 27% in the last 8 years together with the increasing number of vascular resection. A total of 64 patients (26%) underwent venous resection (27 males and 37 females with mean age of 62.5 yrs; range 37–82). We performed 50 pancreatoduodenectomy (PD) procedures, 10 total pancreatectomy (TP) procedures, and 4 distal pancreatectomy procedures with splenectomy (DP) (Table 1). Tangential resection with linear suture was performed in 13 patients and venous resection with end-to-end anastomosis in 50 patients; a prosthetic graft was used in 1 patient. According to the International Study Group of Pancreatic Surgery (ISGPS) classification, [14], 13 patients underwent type 1, 50 patients type 3, and 1 patient type 4 venous resection. All patients exhibited ductal adenocarcinoma at pathologic examination. Histological examination confirmed vascular invasion in 69% of cases; 55 patients (86%) had radical resection (R0), and 9 subjects (14%) had microscopic neoplastic residue (R1). Tumor involved superficial venous wall (up to tunica adventitia) in 8 cases, the tunica media in 24 cases, and the tunica

Table 2: Postoperative outcome of patients after pancreatic resection with (VR+) and without (VR−) vascular resection.

	VR+ (n = 64) n (%)	VR− (n = 177) n (%)
Complications		
Pancreatic fistula	7 (11)	23 (13)
Biliary fistula	3 (5)	5 (3)
Fluid collections	4 (6)	9 (5)
Peritoneal bleeding	3 (5)	9 (5)
Digestive bleeding	1 (2)	1 (0.5)
Ileal perforation	1 (2)	5 (3)
Pleural effusion	1 (2)	2 (1)
Others	1 (2)	6 (3)
Reoperation	**4 (6)**	**9 (5)**
Morbidity	**19 (29%)**	**53 (30%)**
Mortality	**2 (3%)**	**7 (4%)**

PD: pancreatoduodenectomy; TP: total pancreatectomy; DP: distal pancreatectomy.

Table 3: Univariate analysis of factors influencing overall survival.

Variables	Survival (mo) Mean	Median	Significance
Grading			
Well-moderate	26.7	17	$p = 0.009$
Poor	19.8	14	
Node status			
No	24.7	16	$p = 0.977$
Yes	23.6	15	
Radicality			
No	26.6	17	$p = 0.001$
Yes	19.5	10	
Vein resection			
No	25.8	15	$p = 0.301$
Yes	19.9	14	

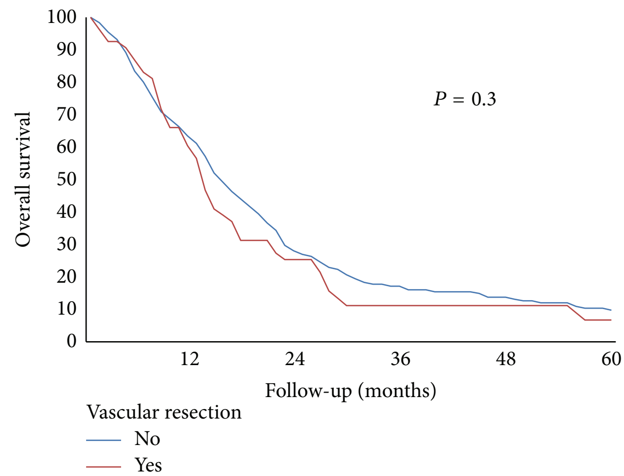

Figure 1: Overall survival in patients who underwent pancreatic resection with or without vascular resection.

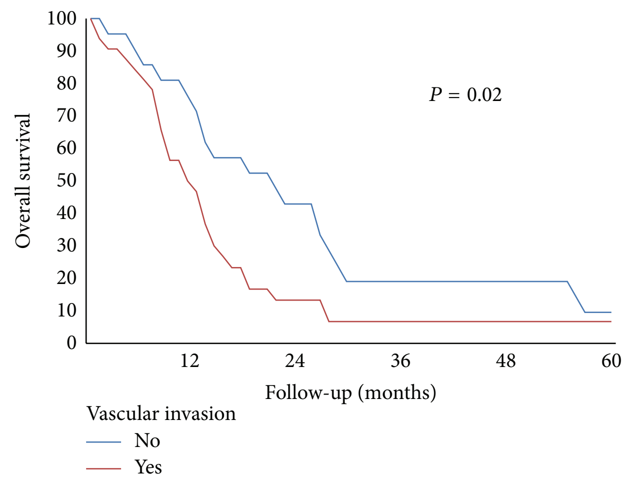

Figure 2: Overall survival in patients who underwent pancreatic resection with vascular resection and histological confirmation of vascular invasion.

intima in 12 cases. Postoperative outcome is reported in Table 2. Surgical complications occurred in 21 patients (33%): 7 pancreatic fistulas, 4 abdominal effusions, 3 peritoneal bleeding cases, 3 biliary fistulas, 1 bowel perforation, 1 bleeding of digestive tract, and 1 pleural effusion. Three patients underwent reoperation. Postoperative death occurred in 1 (3%) patient. Morbidity rate, types of complication, and reoperation's rate were not statistically different in the two groups of patients: mortality rate in VR− group was 3% versus 4% in the VR− group (Table 2). Two patients experienced portal vein thrombosis 11 and 13 months after operation, respectively. Both patients had endoscopic evidence of gastric varices without episodes of digestive bleeding. After operation, all patients underwent gemcitabine-based adjuvant therapy, associated with radiotherapy in cases of R1 resection.

Mean and median overall survival time were 24 and 15 months, respectively. Mean survival time was 26 months for patients without vascular resection versus 20 months for VR+ group, while median survival time was 15 and 14 months, respectively ($p = 0.31$) (Table 3). Mean and median survival time for VR+ group without or with histological confirmation of venous involvement were 26 and 22 months versus 17 and 12 months, respectively ($p = 0.02$). Median survival in R0 patients was 17 months versus 10 months in R1 group. Overall survival was 42% at 1 yr, 10% at 2 yrs, and 2% at 3, 4, and 5 yrs (Figure 1). In patients without evidence of vascular invasion, overall survival was 69% at 1 yr, 31% at 2 yrs, 6% at 3 yrs, and 6% at 5 yrs versus 30% at 1 yr and 0% at 2 yrs in subjects with confirmed vascular infiltration (Figure 2). There was a trend of worse prognosis for patients with deeper portal vein invasion without statistical significance ($p = 0.08$).

4. Discussion

In our study, we analyzed the outcome after pancreatectomy with or without portal vein resection in a group of 241 patients with pancreatic cancer. Patients with vascular resection had similar outcomes compared to patients who underwent standard resection, with no differences in morbidity, mortality, and long-term survival. Patients had also similar lengths of stay. These results compare favorably with that of other surgical series [15, 16].

The rate of vascular resection during pancreatic operation is strongly influenced by single centers strategies; in some series, associated en bloc vascular resection occurs in few cases [4], and it is depending on careful preoperative selection of patients or intraoperative findings. Other studies present high rates of vascular resections probably due to different behavior related to different persuasions [11]. Our department policy towards resection criteria was to perform venous resection in all cases of small vein involvement (≤2 cm in length), in absence of venous occlusion or thrombosis, in order to obtain an easier end-to-end anastomosis. This approach did not substantially change during the study period, although more operations were performed in the last 6 years. Moreover, we observed a trend of better survival in the last period even though the rate of recurrence after resection was not significantly modified. It is reasonable to believe that this fact could be explained by the introduction of more effective chemotherapeutic regimens (i.e., FOLFIRINOX) for the treatment of relapsing tumors.

Vascular resection and reconstruction could represent a theoretical additional risk in pancreatic-surgical procedures [3]. Nevertheless, morbidity and mortality rates, reported by many centers, are similar to those related to standard surgical technique [15, 16]. In our experience, postoperative complications and mortality rates are comparable with the most recent reports of other institutions, confirming that vascular resection does not increase operative risk. In 2012, Zhou et al. [17] performed a meta-analysis collecting 19 nonrandomized studies, for a total of 2,247 patients. There was no difference in perioperative morbidity and mortality between patients with VR and those without VR. More recently, a meta-analysis of Yu et al. [18] evaluating 22 retrospective studies including 2890 patients confirmed that there was no difference in perioperative morbidity and mortality rates between the two groups of patients, with VR or without VR. However, this study showed differences in median tumor size, R0 resection rate, lymph node metastases, and pancreatic fistula. Although randomized prospective studies are lacking, there are convincing evidences in the literature that pancreatectomy associated with vein resection is safe and feasible and does not increase postoperative morbidity. Thrombosis of the anastomosed vein may occur late after operation, as in our series and in another experience [19] but the risk of digestive bleeding remains only theoretical.

The potential oncological benefit, instead, is still unclear. In our experience, long-term survival was not statistically different between patients who underwent venous resection and those who did not.

Many series of pancreatectomies associated with venous resection show no difference in terms of survival compared to standard resections [20], while other centers report poorer outcome [21]. These differences could be explained by the possibility to obtain a R0 resection; this parameter is known to affect prognosis and is reported with a wide range in other studies (32–87%) [4, 5, 20–22]. In our experience, R0 resections rate was 86% with a median survival of 17 months versus 10 months for R1 patients. Furthermore, only patients with R0 resection were alive for 2 years, even in absence of statistical significance. Recently, in a prospective multicentric study, Delpero et al. [23] reported an increasing frequency of positive resection margins in patients who required portal-mesenteric vein resection: this finding was previously showed by other authors [24] and associated with tumor's size and biology, rather than with vascular resection.

Regarding histological confirmation of vascular infiltration, this parameter was not confirmed at histological analysis in 31% of our cases, with a median survival of 16.5 months versus 9.5 months in patients with histological report of vascular invasion ($p = 0.02$). These data suggest a satisfactory oncological benefit of vascular resection especially in selected patients with inflammatory vascular adherence [25]. However, better survival after pancreatectomy with venous resection compared to palliative surgical bypass has been reported [16]. Moreover, it is difficult to distinguish true neoplastic involvement from inflammatory adhesion both pre- and intraoperatively, so whenever possible, pancreatectomy with vascular resection is advisable to reach a radical resection together with the best tumor's staging. The depth of tumor invasion has been shown to be a negative prognostic factor. Fukuda et al. [26] showed that the deeper invasion (tunica media or intima) was an independent prognostic marker for poorer survival, with median survival similar to that of nonresected patients. In our experience, there was a trend to worse prognosis when deeper portal vein wall invasion occurred, but without statistical significance. Further studies are necessary to evaluate the depth of vein involvement as a possible contraindication to resection.

5. Conclusion

In conclusion, vascular resection seems to offer an oncological benefit when it increases tumor's resectability and R0 resection rates [27], in absence of other parameters affecting prognosis. Vascular resection presents acceptable perioperative morbidity and mortality rates, when performed in specialized centers; nevertheless, long-term survival rates are still conflicting and careful evaluation and selection of patients are recommended.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Minimally Invasive Necrosectomy Techniques in Severe Acute Pancreatitis: Role of Percutaneous Necrosectomy and Video-Assisted Retroperitoneal Debridement

Jennifer A. Logue and C. Ross Carter

West of Scotland Pancreatico-Biliary Unit, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK

Correspondence should be addressed to C. Ross Carter; rosscarterno1@gmail.com

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Consensus advocating a principle of early organ support, nutritional optimisation, followed ideally by delayed minimally invasive intervention within a "step-up" framework where possible has radically changed the surgical approach to complications of acute pancreatitis in the last 20 years. The 2012 revision of the Atlanta Classification incorporates these changes, and provides a background which underpins the complexities of individual patient management decisions. This paper discusses the place for delayed minimally invasive surgical intervention (percutaneous necrosectomy, video-assisted retroperitoneal debridement (VARD)), and the rationale for opting to adopt a percutaneous approach over endoscopic or laparoscopic approaches in different clinical situations.

1. Introduction

The incidence of acute pancreatitis (AP) varies between populations ranging from 150 and 420 patients per million population in the UK to 330–430 patients per million in the USA [1, 2]. One in five patients, however, will develop organ failure with or without local complications–a setting that defines severe acute pancreatitis. Half of the deaths attributable to AP occur within the first 7 days of admission [3], with the majority in the first 3 days. Patients with severe AP who survive this first phase of illness, particularly those with persistent SIRS or organ failure [4], are at risk of developing secondary infection of pancreatic necrosis. Mortality in patients with infected necrosis and organ failure may reach 20–30% and an increased mortality is seen with increasing age [5]. The aim of this paper is to discuss the role of minimally invasive surgical intervention in severe acute pancreatitis, provide a rationale for adopting either a single or multimodality approach based on the often variable clinical scenarios, and highlight potential complications.

2. Revised Atlanta Classification 2012

The 2012 Revised Atlanta Classification [6] divides acute pancreatitis into three categories: mild, moderate, and severe disease. These categories are based on the absence or presence of local and/or systemic complications. In addition to disease severity, early mortality is strongly associated with age and comorbidity. Furthermore, the classification further categorizes local complications on the basis of time from presentation (< or > 4 weeks) and on the presence of necrosis (Table 1). The vast majority of acute fluid collections without necrosis will resolve within 4 weeks and a persistent fluid collection with minimal or no necrotic component ("pseudocyst") is very rare. Collections may be sterile or infected. The majority of peripancreatic complications are therefore related to either acute necrotic collections (<4 weeks) or walled-off pancreatic necrosis (>4 weeks). This temporal separation is somewhat arbitrary, as the clinical management and surgical approach are determined by multifactorial individual patient factors. However, this does serve to provide a timeline beyond which, if appropriate, intervention should be delayed. A subsequent

Table 1: Local complications in acute pancreatitis (2012 Revised Atlanta Classification).

Time scale	Necrosis absent	Necrosis present
<4 weeks	Acute peripancreatic fluid collection (peripancreatic fluid associated with interstitial oedematous pancreatitis with no associated peripancreatic necrosis)	Acute necrotic collection (a collection containing variable amounts of both fluid and necrosis; the necrosis can involve the pancreatic parenchyma or the extrapancreatic tissues)
>4 weeks	Pancreatic pseudocyst (an encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis)	Walled-off necrosis (a mature, encapsulated collection of pancreatic or extrapancreatic necrosis that has developed a well-defined inflammatory wall)
Infection	Each collection type may be sterile or infected	

addendum added a category of "critical" recognizing those patients with sepsis and organ failure which was associated with the highest mortality [7].

3. "Step Up" Management of Postacute Peripancreatic Collections

Whilst the early management, rationale, timing, and technique of early percutaneous catheter drainage within a "step-up" framework have been discussed in previous sections, it is worth establishing the basis on which pancreatic necrosectomy may be considered within the minimally invasive era. Early debridement [8] has for many years been associated with and adverse outcome, in the absence of major (usually vascular) complications, being considered current standard practice. Freeny [9] and his colleagues in the 1990's showed that aggressive percutaneous sepsis control would promote recovery in the absence of formal necrosectomy, and this finding was confirmed within the PANTER trial [10] which demonstrated that 35% of patients with established necrotic collections did not require any further intervention over simple small diameter percutaneous catheter drainage.

Therefore, whilst a proportion of patients will recover without requirement for enhanced drainage, the majority will continue to exhibit signs of sepsis despite percutaneous catheter drainage alone. There is consensus that in those patients with persistent sepsis, a minimally invasive approach is preferred over open surgical necrosectomy, as described by Bradley, Warshaw, and Beger [11–13]. A number of "step-up" approaches have been described, including percutaneous necrosectomy (MIRP) [14], video-assisted retroperitoneal debridement (VARD) [15] and endoscopic [16] and laparoscopic [17] cystgastrostomy. Laparoscopic direct necrosectomy was described in the 1990's [18] but failed to gain popularity due to technical difficulty. There are 2 retrospective studies [19, 20] describing laparoscopic necrosectomy alone with a total of 29 patients. The patients were highly selected and no median follow-up was available for either study.

The choice of one approach over another is determined by the clinical condition of the patient, local experience and expertise, anatomical position/content of the collection, and the time from presentation/maturation of the wall of the collection. There is an acceptance that due to the complexity of presentation, no single technique is a panacea, and all options share a common concept of achieving minimally invasive sepsis control, whilst maintaining adequate nutritional competence. A detailed discussion surrounding nutritional support is beyond the scope of this paper but focuses on nasoenteric feeding [21] (NG or NJ), occasionally resorting to dual feeding (NJ/TPN) if nutritional targets are not being met enterically. Percutaneous gastrostomy or jejunostomy feeding tubes were commonplace in the open surgical era but are associated with procedure related complications which outweigh any advantage over the nasoenteric route and are not used in our unit.

The optimal approach is developing through evolution and the management concepts of the last decade, where solid predominant or infected necrotic collections were managed percutaneously by MIRP or VARD and well-organized predominantly fluid collections managed by endoscopic or laparoscopic transgastric drainage are now being challenged in randomized trials.

The choice of initial percutaneous or endoscopic drainage is now largely based on the position of the collection relative to the stomach, colon, liver, spleen, and kidney. Furthermore, the ability to perform EUS guided puncture within an ITU setting, without moving the patient to the radiology department for CT guided drainage, may be safer in a patient in extremis. In general, lateral collections and those extending behind the colon are usually better approached from the left or right flank whereas those medial collections where a percutaneous route is compromised by overlying bowel, spleen, or liver, may be better approached endoscopically. Initial percutaneous drainage is with an 8–12 FG single pigtail at the discretion of the radiologist, and catheter diameter or type does not seem to influence the requirement for secondary intervention. The route of percutaneous drainage should ideally take into account the probability of subsequent "step-up" escalation utilizing that drain tract, but the initial priority must be sepsis control, and if the initial drain placement is suboptimal, secondary alternative access can be obtained, sometimes involving a combination of percutaneous and endoscopic techniques.

Both MIRP and VARD retroperitoneal techniques are modifications of the open lateral approach initially described in the 1980's by Fagniez et al. [22] which utilised a loin/subcostal and retrocolic approach to allow debridement of pancreatic and peripancreatic necrosis. This open approach was associated with major morbidity (enteric fistula 45%, haemorrhage 40%, and colonic necrosis 15%) and failed to gain popularity. For both minimally invasive techniques,

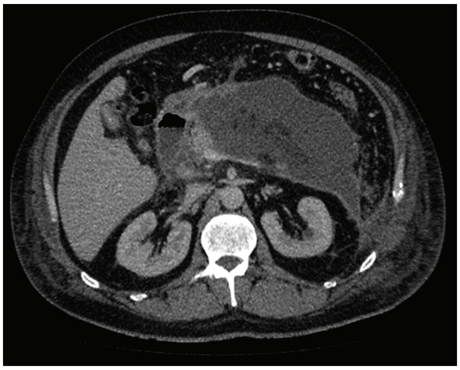

Figure 1: Acute walled-off pancreatic necrotic collection (W. O. P. N) at 6 weeks.

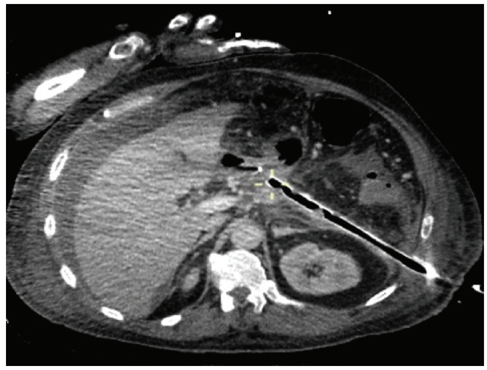

Figure 2: Retroperitoneal drain following enhanced "step-up" percutaneous necrosectomy in same patient as in Figure 1.

a left-sided small diameter percutaneous drain is ideally placed into the acute necrotic collection between the spleen, kidney, and colon (Figure 1). Right-sided or transperitoneal drainage is also possible. In those who fail to respond adequately to simple drainage this access drain is then used as a guide to gain enhanced drainage of the collection.

For percutaneous necrosectomy, the catheter is exchanged for a radiological guidewire and then a low compliance balloon dilator is inserted into the collection and dilated to 30 FG. Access to the cavity is achieved by passing the operating nephroscope through an Amplatz sheath, which allows debridement under direct vision. The nephroscope has an operating channel that permits standard (5 mm) laparoscopic graspers as well as an irrigation/suction channel. High flow lavage promotes initial evacuation of pus and liquefied necrotic material, exposing residual black or grey devascularised pancreatic necrosis and peripancreatic fat, which if loose is extracted in a piecemeal fashion until, after several procedures, a cavity lined by viable granulation tissue is created. At the end of the procedure an 8 FG catheter sutured to a 24 FG drain is passed into the cavity to allow continuous postoperative lavage of warm 0.9% normal saline initially at 250 mls an hour (Figure 2). The subsequent rate of lavage is determined by the return and can be reduced as the effluent clears and the clinical control of sepsis is achieved. Chemically assisted debridement with hydrogen peroxide has been reported during endoscopic drainage [23], but concerns regarding the risk of air embolism have been highlighted in previous studies [24] and should only be considered within a study format. Subsequent conversion of the lavage system to simple drainage may be all that is required prior to recovery or the procedure may be repeated until sepsis control is achieved and interval CT confirms resolution.

A video-assisted retroperitoneal debridement (VARD) procedure is performed with the patient placed in a supine position with the left side 30–40° elevated. A subcostal incision of 5 cm is placed in the left flank at the midaxillary line, close to the exit point of the percutaneous drain. Using the *in situ* percutaneous drain as a guide the retroperitoneal collection is entered. The cavity is cleared of purulent material using a standard suction device. Visible necrosis is carefully removed with the use of long grasping forceps, and deeper access is facilitated using a 0° laparoscope, and further debridement performed with laparoscopic forceps under videoscopic assistance. As with a percutaneous necrosectomy, complete necrosectomy is not the aim of this procedure and only loosely adherent pieces of necrosis are removed, minimizing the risk of haemorrhage. Two large bore single lumen drains are positioned in the cavity and the fascia closed to facilitate a closed continuous postoperative lavage system.

4. Early Procedure Related Complications

4.1. SIRS/Bacteraemia Requiring Critical Care Support. Occasionally intervention is associated with a significant SIRS or postprocedure bacteraemia, requiring critical care admission for organ support and often vasopressor therapy. This often resolves within 24–48 hours with appropriate supportive management. Therefore if possible, it is often beneficial for these patients to be observed in a critical care environment following intervention, particularly if they were not receiving level two care before procedure.

4.2. Acute or Delayed Haemorrhage. Probably the most frequent scenario is brisk haemorrhage complicating early or overenthusiastic necrosectomy. Attempts at open surgical haemostasis are associated with significant mortality, and in this setting control is usually achieved by packing, or balloon tamponade, but emergency angiography may occasionally have to be considered for arterial bleeding. Venous bleeding is common and should be suspected in patients with a nondiagnostic angiogram but usually settles with correction of any coagulopathy and with local pressure, by simple drain occlusion, a modified Sengstaken-Blakemore tube having amputated the gastric balloon (MIRP), or gauze packing if there is sufficient cutaneous access (VARD).

Secondary haemorrhage is occasionally sudden and massive, but there is usually a prelude with a "herald bleed," a self-terminating bleed presenting clinically with haemorrhage into a retroperitoneal drain or occasionally a gastrointestinal bleed. An arterial origin of haemorrhage is more common than venous when this occurs as a spontaneous secondary bleed. Overall, the mortality exceeds 30–40% and a high index of suspicion is essential in order to optimise proactive treatment. In our unit the patient is rapidly stabilized with controlled volume support of the circulation and a simultaneous emergency CT angiogram. Upper gastrointestinal endoscopy in this setting is usually nondiagnostic so should not delay radiological assessment which allows definitive management. Where arterial bleeding is identified on formal angiography embolisation offers the best chance of survival. The increased intracavity pressure, associated with haemorrhage into an infected cavity, may also often be followed by escalating organ dysfunction through bacteraemia and sepsis; therefore early introduction of targeted antimicrobials is essential.

4.3. Enteric Fistulation. Spontaneous discharge of a postacute collection into the gastrointestinal tract is also recognised which can decompress the collection and result in a clinical improvement without intervention, usually where the fistulous communication involved is the stomach or duodenum, mimicking an endoscopic drainage. It can also present with haematemesis or melaena and should be managed as described above. Whilst spontaneous resolution is possible, fistulation into the colon will often result in persistent sepsis and poorly controlled collections, and therefore, in this situation a defunctioning colostomy/ileostomy or resection may be necessary.

4.4. Late Complications

4.4.1. Pancreatic Fistulation. Parenchymal necrosis is commonly associated with disruption of the main pancreatic duct, and following resolution of associated sepsis residual duct leakage of amylase rich fluid is common, leading to a pancreatic fistula. Early endoscopic intervention should be discouraged whilst collections remain as this may introduce infection and usually prove detrimental. Following resolution of sepsis and any significant collection, transpapillary pancreatic duct stent insertion at ERCP may result in resolution of a persistent fistula, but persistent drainage is often associated with more extensive parenchymal loss or a disconnected tail (see below). Prolonged catheter drainage will lead to maturation of the fistula tract and interval drain removal may result in spontaneous resolution or development of a postacute pseudocyst, which can often be resolved by transmural endoscopic cystgastrostomy achieving enteric diversion.

4.4.2. Disconnected Tail. Where the necrosis extends across most of the transverse diameter of the body or tail, complete separation of the main pancreatic duct in the head of the pancreas and tail may occur leading to a persistent fistula and "disconnected duct syndrome." Ductal occlusion at the level of parenchymal loss often precludes transpapillary access but if this has not occurred, intracystic transpapillary stenting may result in resolution. If transpapillary access is not possible, options may be transmural EUS guided drainage. Surgical options are dependent on the anatomy and degree of anatomic distortion following resolution of the early phase of disease [25] and include a formal pancreaticojejunostomy, fistula-jejunostomy, or a "salvage" distal pancreatectomy to excise the residual disconnected functional pancreatic parenchyma, often in combination with a splenectomy, performing a limited pancreatico- (fistula-) jejunostomy.

5. Discussion

There is general agreement that intervention in the first two weeks of severe AP should be avoided if at all possible. During this period, many patients may require intensive care management, with escalating organ failure associated with a significant mortality [4], but intervention for the pancreatic or peripancreatic inflammatory mass has not been shown to enhance recovery and may be detrimental. Rare exceptions to the noninterventional approach include the presence of intra-abdominal haemorrhage or necrosis of bowel. In either case, it is better, if possible not to disturb the pancreatic inflammatory mass at this time. Thus, pancreatic intervention should be delayed until walled-off necrosis has developed, typically 3–5 weeks after onset of symptoms. Several observational studies have shown improved outcome for operation beyond 28 days from onset [26]. Some authors have expressed concern that delay beyond this risks the patient's general condition which will deteriorate, with resultant impaired nutritional and immune status, but where slow improvement continues, delay until established WOPN simplifies intervention.

The role of antibiotics has evolved in the last 20 years from a position supporting prophylaxis to one of selected targeted administrations to manage proven episodes of infection, with positive blood cultures or radiological evidence of infection [27]. Furthermore, attempts to confirm infection of necrosis by fine needle aspiration [28] of collections are no longer favored and treating positive drain culture in the absence of clinical sepsis results in emergence of fungal overgrowth or antibiotic resistance. Antibiotics may facilitate a delay in definitive intervention for infected necrosis presenting within the first 4 weeks, at which stage intervention is aimed at sepsis control.

Indications for intervention include strong suspicion or documented infection of necrosis or in the absence of infection, persistent organ failure for several weeks, with a walled-off collection and persistence of symptoms such as pain and ileus. Timing of intervention requires a judgment call by an experienced and specialist pancreatic team, involving a multifactorial decision algorithm based on radiological, clinical, and nutritional progress. Once the decision for intervention has been made, the options include open surgical necrosectomy, percutaneous or other forms of minimally invasive surgical necrosectomy, percutaneous catheter drainage, and endoscopic necrosectomy through the stomach as described above. No single treatment approach is ideal for use in all patients, and in practice a range of options may be required, often in combination, based on the position of the acute necrotic or walled-off collection taken in context with the patient's overall clinical condition.

There have been a number of studies attempting to compare types of intervention in acute pancreatitis. The complexity of presentation and evolution of the disease process, the relative position and content of collections, and relative rarity of these patients have made large scale trials with homogeneous characteristics impossible. Despite the challenges some small-scale studies have been completed which have informed the debate. The PANTER study [10], by the Dutch Pancreatitis study group, demonstrated an advantage to a minimally invasive approach (VARD) over open necrosectomy in early postprocedural organ dysfunction within a "step-up" management algorithm. The study was not powered to consider mortality, and perhaps the most significant finding was that 35% of patients resolved completely with small diameter catheter drainage alone. Other pilot studies by this group have explored the potential of endoscopic transmural drainage versus minimally invasive intervention (VARD), the PENGUIN trial [29] suggesting at least equivalence, if not benefit, from endoscopic drainage, but this has been criticized due to very small numbers and an excessive mortality, compared to the groups historical results, within the VARD arm. The results of the resultant TENSION trial [30] are awaited with interest.

Minimally invasive approaches have been criticized as they often require repeated intervention prior to resolution, with increased inpatient stay. In a clinically well patient with established walled-off necrosis, whose principal symptom is failure to thrive, a laparoscopic transgastric cystgastrostomy offers the potential of a single intervention with the possibility of simultaneous definitive management of cholelithiasis [17]. Worhunsky et al. recently reported a series of 21 patients [31] with retrogastric pancreatic necrosis who underwent debridement with a single intervention using laparoscopic transgastric necrosectomy suggesting that where feasible this allows primary definitive management. Cyst content (whether the acute necrotic collection/walled-off necrosis was predominantly fluid or solid) traditionally influenced decision-making; however limiting endoscopic transmural drainage to only fluid predominant collections has been challenged with increasing experience of endoscopic necrosectomy. We are currently engaged in a randomised trial of laparoscopic versus endoscopic cystgastrostomy in patients with walled-off necrosis and the results are awaited.

Complications following enhanced drainage are common and may be either disease or procedure related. Enteric fistulation is relatively common, and the requirement for secondary control is dependent on whether the fistula arises from the proximal or distal gut, colonic fistulae often requiring surgical enteric diversion to control persistent sepsis. Bleeding may occur intraoperatively and may be controlled by balloon tamponade, conversion to a VARD procedure with gauze packing, or occasionally angiography. Venous bleeding is more common intraoperatively. Secondary haemorrhage may arise on the background of poorly controlled sepsis and in the presence of an enteric fistula may result in GI bleeding or direct bleeding within a surgical drain. Angiographic control or again local pressure via the drain tract or VARD wound is preferred to open surgery, which historically was often an agonal intervention.

There is consensus that, within a "step-up" environment, some form of minimally invasive approach is superior to open intervention particularly in the critically ill patient. Operator experience is a key determinant of which minimally invasive approach to adopt. There is no evidence supporting the use of one approach over another. The VARD approach utilizes standard laparoscopic and surgical instruments whilst a minimally invasive necrosectomy utilizes standard urological equipment both of which are universally available. Many units may have experience in only one method, and this will influence the decision process. The differences between a VARD and MIRP are small, and in practice these procedures are interchangeable, whereas the addition of either an endoscopic or laparoscopic cystgastrostomy can increase management options particularly where collections are centrally placed and percutaneous access is difficult. A "gold standard" minimally invasive management algorithm would take into account the clinical condition of the patient, anatomical location of the collection and in an ideal world expertise in all 4 techniques which allows for adaptability and flexibility in the interventional approaches to an often extremely challenging clinical problem. An important point to note is that many patients may benefit from the use of a multimodal approach with the use of more than one technique during the course of their illness. For example a patient with escalating multiorgan failure can be stabilized within the ICU setting with EUS guided transgastric drainage and following a period of stabilisation more definitive intervention employed by either MIRP, VARD, or even laparoscopic cystgastrostomy. In reality, however, most units will not necessarily have access to all techniques which will obviously impact on management decisions.

In conclusion, in a patient with established criteria for intervention, simple percutaneous (or endoscopic) drainage of the dominant collection is indicated. Careful subsequent clinical observation with monitoring of biochemical and haematological indices will determine whether enhanced drainage is required, in which case where initial percutaneous catheter drainage was the initial procedure, a minimally invasive necrosectomy or VARD, establishing a postoperative continuous closed lavage system, will improve sepsis control and optimise outcome and the procedure may be repeated as required. The results of a number of randomised studies are awaited to inform the debate as to the optimal choice of enhanced surgical or endoscopic intervention within a step-up environment.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Jennifer A. Logue and C. Ross Carter were involved in preparation and critical revision of the paper.

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