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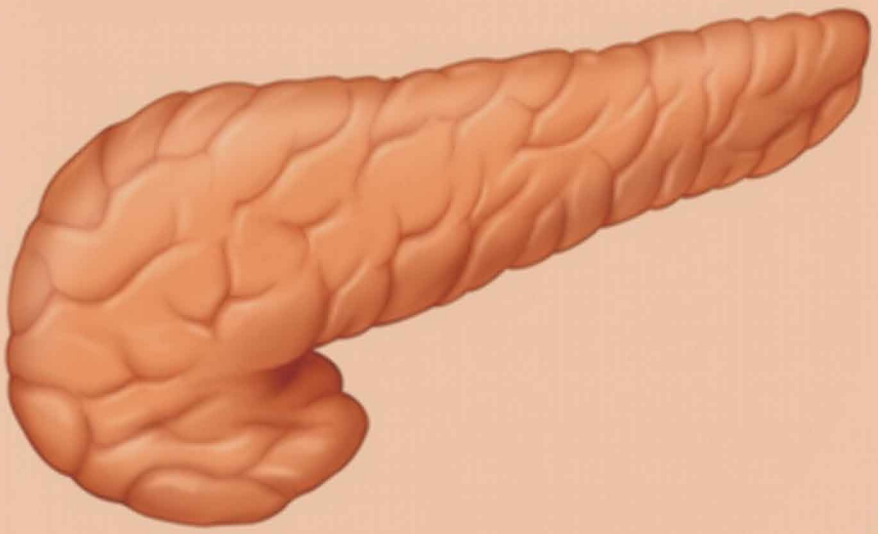

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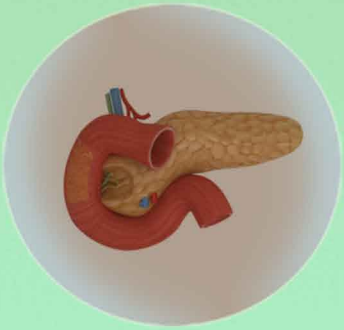

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Editorial

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Epithelial-To-Mesenchymal Transition in Pancreatic Ductal Adenocarcinoma: Fiction or Fact?

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Pancreatic Ductal Adenocarcinoma (PDAC) is one of the most aggressive and lethal tumors, representing the fourth most common cause of cancer death in the Western world, with an estimated incidence of more than 40,000 cases per year in the United States. Despite continuous progress in imaging, surgical techniques, intensive care, and chemotherapeutic approaches, the current overall 5-year survival is less than 6%.[1,2]

In carcinoma progression, including PDAC, cancer cells acquire their metastatic phenotype undergoing a complex step-wise process defined as Epithelial-To-Mesenchymal Transition (EMT), leading to a "phenotypic switch" of epithelial cells to mesenchymal cells.[3]

The epithelial phenotype is characterized by distinct, well demarcated intercellular adhesive structures, and apical-basal polarity, all mediated by the expression of E-cadherin on the plasma membrane of the cell. The EMT-related phenotype of carcinoma cells is characterized by the loss of epithelial features, including loss of cell adhesion and polarity, down-regulation of E-cadherin, cytoskeleton reorganization by expressing vimentin and α-Smooth Muscle Actin (αSMA). Moreover, the acquisition of motile properties and secretion of Matrix Metalloproteinases (MMPs) leads to the disruption of basement membranes.[3]

The key event of EMT is considered the loss of E-cadherin, a transmembrane glycoprotein with its intracellular domain linked to β-catenin to form the E-cadherin/β-catenin complex, mediating cell-cell adhesion and playing a major role in the control of epithelial cell architecture, differentiation and phenotype.

Interestingly, the EMT process can exhibit different characteristics in different carcinoma cells, therefore sometimes is difficult to recognize the typical EMT-related phenotype and the events responsible of carcinoma progression. This is evident in PDAC, since it was shown that 6 out of 7 PDAC cell lines maintain E-cadherin expression on the cell membrane, and that the expression of some EMT markers in PDAC are similar than in benign pancreatic ducts.[4] The point is: how is it possible that PDAC cells exhibiting highly invasive and malignant behavior retain a differentiated epithelial phenotype? Do these cells undergo EMT? Moreover, what is the role of E-cadherin in these cells?

To understand this apparent inconsistency, we have to consider that some invasive and metastatic carcinoma cells possess morphological and molecular characteristics typical of well-differentiated epithelia, including high levels of E-cadherin and the presence of cell junctions and cell polarity, possibly due to an incomplete EMT.[5] Carcinoma cells exhibiting an epithelial morphology were described also in prostate[6] and breast cancer.[7,8]

Moreover, EMT is not an "all or nothing" event, but rather a multistep process that manifests in a broad range of phenotypic changes, not occurring consecutively and not all necessarily present in a given sample.[6] According to this suggestion, epithelial-related phenotype and mesenchymal markers can be concomitantly expressed in the same cell.

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Finally, a relevant point is the modality adopted by carcinoma cells for invasiveness. The mode of cell migration and invasion was originally classified based on the morphology of migration patterns. As main categories, cell move either individually (amoeboid or mesenchymal) or collectively (the migration of cohesive multicellular units). Collective cell migration is pivotal in remodeling complex tissues and tissue compartments, and also contributes to cancer progression by local invasion.[9,10]

As opposed to individually migrating cells, during collective migration, the rear of the front cell retains intact cell-cell junctions, thereby mechanically holding the cells together and increasing the efficiency of multicellular coordination. According to this model, invasive carcinoma cells may adopt a collective migration characterized by invasive multicellular aggregates containing well-differentiated cells retaining epithelial morphology and cohesiveness, that collectively invade within the adjacent tissues. In this situation, collectively migrating cells maintain their cell-cell junctions, and migrate in clusters forming invadopodia where the release of MMPs leads to the proteolytic breakdown of ECM in the tumor microenvironment.[11] This was described for significant number of cancers, including certain breast, prostate, large cell lung and ovarian cancers: they do not lose E-cadherin expression and use collective migration and invasion.[11,12]

In the last years we focused our attention to better understand the role of EMT in PDAC, with particular attention to E-cadherin expression. We analyzed the phenotype of three PDAC cell lines (HPAF-II, HPAC and PL45) in relation to the expression of the main EMT markers, and we found that these cells, although highly invasive, maintained E-cadherin and the E-cadherin/β-catenin complexes at cell boundaries, suggesting that adherens junctions are preserved and functional.[13,14]

Interestingly, the analysis of the same PDAC cells grown in 3D-spheroids revealed that the phenotype of PDAC cells cultured in 2D-monolayers or in 3D-spheroids is different relatively to expression of some EMT markers. In particular, some "Mesenchymal" markers such as collagen type I, became evident only in PDAC cells grown in 3D-spheroids, and were concomitantly expressed together with E-cadherin.

These experimental findings strongly support the previously suggested role of 3D cell cultures as a useful experimental tool, allowing to mimic the functions of living tissues and providing some keys to the information encoded in the tissue architecture.[15]

Many of these studies have demonstrated the particular power of 3D-spheroids to gain insight into metabolic and proliferative gradients in cancer cells, and the importance of 3D cell-cell and cell-matrix interactions.[16-19]

Gene expression in 3D is much closer to clinical expression profiles than those seen in 2D, therefore *in vitro* 3D culture systems offer the possibility to investigate aspects of cancer tumor biology and pathophysiology maintaining a 3D cell arrangement reflecting the *in vivo* situation in relation to cell-cell interaction and differentiation patterns.[20]

Previous studies demonstrated that cancer cells grown in 3D exhibit different gene expression levels, compared with the same cells cultured in 2D. In particular, in melanoma cells it was described that cell cultures in a 3D system, allowing structural modifications of the architecture of tumor cell cultures in monolayer and the maintenance of cell-cell interactions, exhibited a significant up-regulation of the expression of a number of genes previously shown to play a role in melanoma progression and metastatic process.[21]

Our experimental findings in 3D-spheroids can contribute to describe the phenotype of PDAC cells in relation to EMT, suggesting a concomitant expression of "epithelial" and "mesenchymal" markers in these cells. This suggests an EMT-related phenotype for PDAC cells and strengthens the general assumption that an inverse correlation between E-cadherin expression and invasive potential of carcinoma cells is not absolute. According to these observations, we can also hypothesize that PDAC cells adopt a collective migration mechanism, but further experiments will be necessary to definitively clarify the role of EMT in PDAC progression.

We are convinced that the study of EMT markers in PDAC 3D culture systems, such as spheroids, could provide a better understanding of the complexities of the tumor context and allow to more clearly understand the biology, development and progression of PDAC, and possibly to develop new therapeutic strategies to finally improve the treatment effectiveness of patients with PDAC.

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Short Communication

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Pancreas: Do All Roads Lead to Mitochondria?

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Over several millions of years of evolution, mitochondria have transformed into specialized organelles. Today, they cannot live outside the cell nor can the host cell live without them, resulting in a symbiotic relationship. Richard Altmann, in 1894, documented them as cell organelles and called them "bioblasts". Later, the term "mitochondria" itself was coined by Carl Benda in 1898. Ever since these findings, we in the field of medicine have learned a lot about this tiny organelle, but numerous aspects continue to be discovered. In this article, we will review the significance of this organelle in terms of pancreatic dysfunctions.

Mitochondria are a double membrane organelle and are often considered to be "the powerhouse of the cell." This organelle is extremely important to the maintenance of vital biological processes such as the Krebs cycle, Tricarboxylic acid (TCA) cycle, the generation of Adenosine Triphosphate (ATP) (the body's main energy source), signal transduction, cell growth, cell death and much more. Due to the many roles that the mitochondrion plays in these biological processes, it is evident that any type of mitochondrial dysfunction would result in a myriad of diseases. Over the past decade, we have become aware of several clinical syndromes that might be associated with mitochondrial DNA (mt-DNA) mutations. The increasing recognition of mt-DNA involvement in disease is partially due to the relative ease of sequencing the mitochondrial genome.[1] Mitochondrial DNA (mt-DNA) carries only 37 genes that encode 13 polypeptides, 22 transfer RNAs (tRNAs) and 2 ribosomal RNAs (rRNAs).[2] A number of the common diseases that have shown to have possible mt-DNA variations are Alzheimer's disease, Parkinson's disease and diabetes. The associations of these diseases with mt-DNA mutations have encouraged a large number of studies.[1] The mitochondrial electron transport chain is an important site of Reactive Oxygen Species (ROS) production within the cell. Despite intracellular protective mechanisms, including superoxide dismutase, catalase and reduced glutathione, excess ROS is detrimental to cellular physiology.[3] Aging, defined as an irreversible decline in physiologic function overtime, is also characterized by mitochondrial dysfunctions. Neurons are also known to be vulnerable to mitochondrial dysfunction, synaptic regions of axons are known to contain abundant mitochondria, thus suggesting that mitochondrial dysfunction may play a key role in many neurological diseases such as Parkinson's and Alzheimer's disease.[4] Current research is starting to highlight the relationship of mitochondrial dysfunction with a multitude of diseases. The pancreas is one such organ where more research is necessary to identify possible treatments for mitochondrial related ailments. Already, pancreatitis, diabetes, and pancreatic cancer have shown a connection with mitochondrial dysfunction to certain subgroups of these diseases.

Diabetes may be one of the most studied diseases when it comes to mitochondrial dysfunction related to pancreatic issues. Diabetes includes a wide group of conditions that overall cause hyperglycemia.[5] Recent research has shown mutations in mt-DNA can be related to diabetes. Wang, et al. suggested that the mitochondrial gene $tRNA^{(Leu\ (UUR))}$ 3243 A to G mutation is a potential risk factor in developing diabetes.[6] Along with mitochondrial dysfunction leading to diabetes, problems in the mitochondria have also been shown to lead to pathologic changes caused by diabetes. For example, diabetic retinopathy is one of the hallmarks of progressive diabetes. It is known that apoptosis of capillary cells precedes the development of retinopathy.

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Mitochondrial ROS is increased in the retina, which impairs mt-DNA.[7] Also, Transcription Factor A Mitochondrial (TFAM) is a key regulator of the transcription of mt-DNA.[7] Santos, et al. have shown that ubiquitination of TFAM in diabetes prevents its transport to the mitochondria, which disrupts mitochondrial homeostasis indicating the strong relation with diabetes and mitochondrial dysfunction.[7]

Kearns-Sayre Syndrome (KSS) is a rare cause of diabetes in children. KSS has a group of diseases, known as the classic triad, which includes retinitis pigmentosa, progressive external ophthalmoplegia, and cardiac conduction problems.[8] Mitochondria Deoxyribonucleic acid (DNA) deletions have been shown to be abnormal in pancreatic islet cells in patients with KSS. Surprisingly, insulin receptor abnormalities do not appear to contribute to the development of diabetes in KSS, further highlighting the role of mitochondrial dysfunction.[8] Another rare mitochondria disorder that can cause diabetes is Pearson Marrow Pancreas Syndrome (PMPS). This disorder is caused by impaired mitochondrial respiratory chain complexes, although the specific mutations may differ among individuals with PMPS.[9]

Unfortunately, compared to diabetes, research on mitochondria related dysfunction to pancreatitis has been thus far extremely limited. However, from what has been published, it has been demonstrated that mitochondrial irregularities can be linked to pancreatitis. Pancreatitis is often described as an inflammation of the pancreas and can represent as an acute or chronic form.[10] Recent studies have shown mitochondrial damage leading to ATP depletion as a common factor related to acute pancreatitis. Also, the generation of ROS is another major cause of acute pancreatitis.[11]

Similar to pancreatitis, there has not been enough research on the relation between mitochondrial dysfunction and pancreatic cancer. However, there has been an increase in understanding the possible involvements of mitochondria in pancreatic cancers.[12] It has been shown that pancreatic cancer cells have a greater density of mitochondria, which could be used as a potential diagnostic marker.[13] Mathematic modeling has shown that perhaps a random mutation in the mt-DNA can cause homoplasmy among mitochondria in pancreatic cancer cells, which in turn can lead to an increase in dysfunctional mitochondria in the cancer cells.[13]

In conclusion, this review supports that many human ailments including diabetes, pancreatitis and pancreatic cancers are in part, due to faulty mitochondrial function. Hence, it is necessary to understand the nature of mitochondrial involvement in pancreatic dysfunction for proper treatment regimens. It has been over 100 years since Richard Altmann's discovery of mitochondria and we continue to learn new things today. With this, we wish the *Pancreas - Open Journal* all the success in their endeavor; and we hope that future researches related to mitochondrial dysfunction and pancreatic ailments will be discussed in this Journal dedicated to the pancreas.

CONFLICTS OF INTEREST

The authors whose names are listed in the manuscript certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Case Report

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Eus-Pancreaticogastrostomy in a Patient with Subtotal Gastrectomy and Roux-En-Y Reconstruction

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KEYWORDS: Endoscopic pancreatic drainage; Endoscopic ultrasound-guided drainage; Pancreatitis; Gastric surgery.

BACKGROUND

Chronic Pancreatitis (CP) is often associated with pain due to pancreatic duct obstruction. In these patients, surgical drainage was more effective than endoscopic treatment, achieving a faster, effective, and sustained pain relief.[1] However, when surgery is not suitable, different endoscopic procedures could be performed. Endoscopic drainage usually requires transpapillary access to the pancreatic duct during Endoscopic Retrograde Cholangio-Pancreatography (ERCP). The main limitation of endoscopic procedure is that the pancreatic duct could not be accessible at ERCP because of Roux-en-Y reconstruction after gastric-pancreatic surgery. Interventional Endoscopic Ultrasound (EUS) may allow a successful drainage of a dilated pancreatic duct, by using an endoscopic cysto-enterostomy followed by stent placement. We described the EUS-pancreaticogastrostomy performed in a patient who underwent a subtotal gastrectomy complaining with chronic pancreatitis.

CASE REPORT

A 60 year-old man with previous diagnosis of chronic pancreatitis presented with upper abdominal pain due to pancreatic duct dilation after sub-total gastrectomy with Roux-en-Y reconstruction for gastric cancer performed 15 year before. According to postsurgical anatomy, a first endoscopic attempt with colonscope (EC38-i10M, 160 cm, 3.8 mm, Pentax Medical) to the site of pancreatico-jejunal anastomosis failed because of afferent loop length. Therefore, we performed a transgastric EUS approach using a linear echo endoscope (EG-3870 UTK, 3.8 mm, Pentax Medical) showing a pancreatic duct ectasia of 9 mm and multiple stones into the lumen (Figure 1). After EUS-guided transgastric puncture of the pancreatic duct using a 19 G needle (EUS-19-T; Wilson Cook Medical Inc.), the guide wire was inserted into the pancreatic duct (pancreatic fluid was aspirated to confirm location) and a dilation was performed with a 10 Fr cystoenterostome (Cystatin-10 (CST-10); Wilson Cook Medical Inc.). At the end of the procedure, a metallic stent (Niti-S Biliary Covered Stent, Toewoog Medical, 12 mm diameter, 20 mm length) was placed using the fluoroscopy guide (Figure 2). The following pancreatography showed the correct position of the stent. The patient was discharged 2 days after the procedure, and the postoperative course was uneventful. He remained symptoms free for 24 months. Thereafter, an inflammatory stenosis of the main pancreatic duct was found. A pneumatic dilation of the stricture was performed, and a second stent (Wallflex, Boston Scientific, fully-covered, metal stent, 10 mm diameter, 40 mm length) was successfully placed.

DISCUSSION

In the international literature, there are many articles about EUS-guided PG. The

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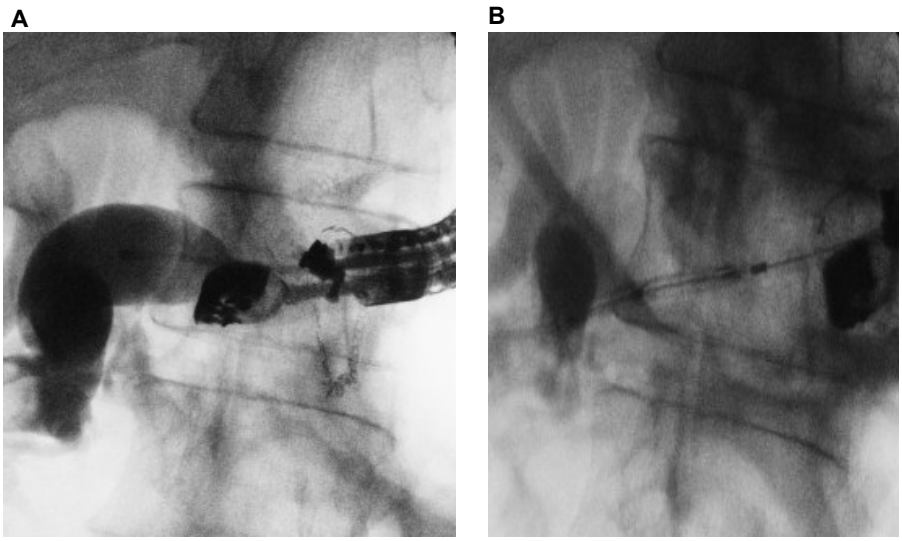

Figure 1: Fluoroscopic view of EUS-guided transmural drainage: A. The echoendoscope is at the bottom of the gastric remnant and the contrast medium flows in the afferent loop; B. Performing dilation with cystoenterostome.

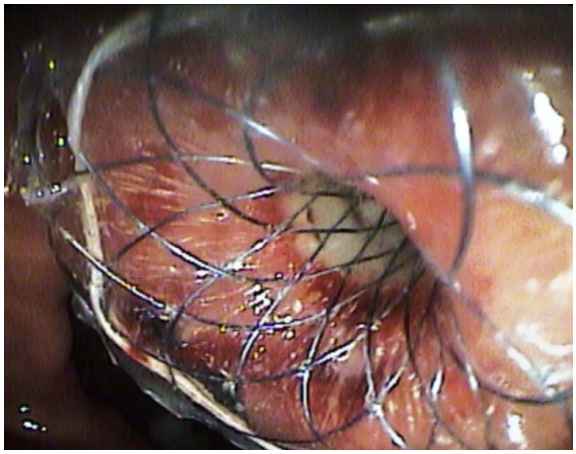

Figure 2: Endoscopic view of the fully covered stent placed in site.

safety of the procedure is well-known in patients with chronic pancreatitis without previous surgery already more than 10 years ago.[2] However, the use in surgical patients is newer and it has been described in the last years.[3-5] The only paper with a "pure" small surgical casistic[4] confirmed feasibility of this technique with a success rate of 67%.[4] Other papers contain surgical patients[3,5] in bigger series with higher success rates. However, the authors did not consider a specific success rate and morbidity for the operated class of patients. Another limitation is about the type of reconstruction: all the papers consider patients who have undergone Whipple intervention, but none of the authors specify the type of reconstruction. After the demolitive phase, in fact, two types of reconstructions are allowed: Billroth II and Roux-en-Y. This is a crucial point for subsequent endoscopic procedures: in case of Billroth II reconstruction, the endoscopist finds an afferent and an efferent loop at the bottom of the gastric remnant, and the afferent loop is generally shorter but it could be more angulated than in the other type of reconstruction; in case of Roux-en-Y reconstruction, instead, the endoscopist finds only one intestinal loop anastomized with the gastric remnant and the afferent loop is more distal and sometimes longer than in Billroth II, and so, more challenging to reach.

In patients with severe chronic pancreatitis who previously underwent upper gastrointestinal surgery, endoscopic treatment could be an alternative to a surgical re-intervention.[2] Because of technical difficulties in performing the papillary approach in these patients, the use of EUS may easy allow a correct identification of the dilated pancreatic duct. We do not agree with the use of enteroscope because it does not allow the endoscopist to use large diameter stents. Technical success of EUS-guided pancreatic drainage was reported to range from 25% to 100%, with complications developing in 15% to 50% of patients.[2,6,7] Most of technical failures were related to unsuccessful manipulation of the guidewire, whereas complications – mainly pancreatic leaks – depend on management of the transmural fistula.[4] An initial insertion of a plastic stent in order to stabilize the created fistula is widely described in the literature.[2-11] However, we found that a direct metallic stent positioning is possible, with less risk of pancreatic leak after the procedure. In addition, we

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believe that metal stents can drain longer and better than plastic stents, due to a greater diameter.[6,10,11] Since pancreatic duct obstruction may occur in chronic pancreatitis, we would also suggest to leave the metallic stent in site.[6] Such a stent may be easily identified when a re-stenting in needed. Indeed, we found that EUS guided puncturing of the main pancreatic duct from the gastric remnant is feasible, and it seems to be safe. Further studies are needed to confirm our encouraging data and we are organizing a monocentric case series. In conclusion, EUS-pancreaticogastrostomy is safe also in surgical patients whenever endoscopic reaching of the peri-ampullary area is dangerous and does not guarantee technical success.

CONFLICTS OF INTEREST

All the authors declare no conflicts of interest regarding the paper "Eus-Pancreaticogastrostomy in a Patient with Sub-total Gastrectomy and Roux-En-Y Reconstruction".

CONSENT

The patient has provided written permission for publication of the case details.

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Opinion

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Ultrasound Ablation in Advanced Pancreatic Cancer Patients – What should be the Next Step?

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To the Editor,

In the last decades the treatment for many diseases has changed dramatically. Open surgery procedures with high morbidity and complication rates, suboptimal clinical results based on large impairment for the patients were replaced by drug treatment or minimally invasive techniques. Examples such as interventional cardiology procedures in acute myocardial infarction, interventional endoscopies in the treatment of hepato-biliary tract diseases, eradication of *Helicobacter pylori* for gastric ulcer using drugs are good evidence that the words of William Osler "Diseases that harm require therapies that harm less" are valid now-a-days.[1]

Pancreatic Cancer (PC) is one of the most aggressive malignant diseases which survival rate, clinical results and treatment has not improved substantially in the past 40 years. Radical surgery is still the only curative method for pancreatic cancer in early stage. Estimated, only 20% of all cases with PC in early stage are suitable for surgical resection at the time of diagnosis, still the expected 5-year survival rate remains 5-20%. The other 80% of cases with advanced PC (including locally and systemically advanced pancreatic cancer) have an expected median survival time of only a few months and almost 0% of 5 year-survival rate when effective alternative treatment methods are missing.[2,3] In those patients with unresectable advanced pancreatic cancer, there is still an urgent need for effective therapies that should not only achieve sufficient local tumor control but also improve local symptoms and quality of life as well as alleviate tumor-associated pain.

During the last decade, High Intensity Focused Ultrasound (HIFU) has been introduced as an innovative non-invasive method for thermal ablation of benign and malignant solid tumors. For the last 15 years clinically approved medical devices using MRI- or US (ultrasound) – guidance have been introduced.[4] From 2003 to 2014, series of studies have been published regarding Asian patients with advanced PC who were treated by US-guided HIFU (USgHIFU) with good clinical results.[4-6] Despite the great number of Asian studies, there are only a few cases with Caucasian patients.[7,8] All of these studies showed that USgHIFU ablation is a feasible, safe and effective treatment for pancreatic cancer with a crucial clinical benefit for the patients in terms of reduction of tumor volume and pain intensity.

All studies described in the literature include selected patients. Similar inclusion and exclusion criteria are followed. All of the articles showed a single institution experience based on case series. According to the levels of evidence developed by the Oxford Centre for Evidence-based Medicine for treatment, this represents level 4 and the grade of recommendation for the physicians should be grade C (optional).[9]

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In our centers, we have used USgHIFU device for non-invasive ablation of advanced PC. In our daily practice, we have seen that the patients treated with USgHIFU and simultaneous chemotherapy experienced significant and lasting reduction of pain intensity and tumor volume regression over time. Hence, patients' quality of life was improved which emphasizes the clinical benefit of USgHIFU. But we still don't have results from prospective or retrospective multi-center studies. Case-control or cohort large-scale studies are also missing. Hereby, we would like to emphasize on the acute necessity for large-scale prospective randomized and multi-center clinical trials to evaluate the safety, clinical and long-term efficacy of USgHIFU treatment especially regarding overall survival with or without simultaneous chemotherapy in the patients with advanced PC. After this step up on the evidence based medicine stairs, more physicians and patients should be involved and the position of HIFU in future algorithms for the management of locally advanced pancreatic cancer can be defined.

CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest.

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Research

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Evaluation of the Best Power Setting of Laser Waves in Pancreatic Surgery: ECHO ND-YAG Laser Ablation on Bovine Pancreatic Tissue

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ABSTRACT

Background: Pancreatic surgery is one of the most difficult and life-threatening surgical therapy especially during necrotizing pancreatitis and advanced solid neoplasms.
Aim of the study: To evaluate the possibility to use ECHO Neodymium-Doped Yttrium Aluminium Garnet (ND-YAG) laser in pancreatic surgery and to establish the best power setting for the application on pancreatic tissue.
Methods: An ECHO Laser ND-YAG 1064 nm, at the constant fluence of 1800 J/cm^2 was used. The laser waves were inserted inside of the samples with optical fibers of 500 micron diameter for a pre-established timing (11 min, 6 min, 4 min) in order to reach the constant fluence. Samples were, then, prepared for hystological examination.
Results: At 3W power setting, the pancreatic tissue was not macroscopically modified except for an increased cutting consistency. Histological examination showed no substantial microscopical differences in pancreatic cells that appeared only partially burnt (in fact, nuclei and membranes are still recognizable). The vessels in the surrounding area have the normal morphological aspects.
At 5W, macroscopically the presence of a completely burnt area, corresponding to the site of direct interaction of laser and tissue, was found and the surrounding tissue did not appear substantially modified.
Histological examination showed the complete absence of cells in the burnt area and an important heat damage of the surrounding cells till the 2th centimeter from the site of laser application. The vessels in the heat damage area appeared completely coagulated.
At the power of 7 W, the burnt area was about twice than in the previous setting and histological examination showed the complete absence of cells in the burnt area and a larger heat damage of the nearest cells (till the 4th centimeter from the application site). The vessels in heat damage area were found completely coagulated.
Conclusions: A power setting between 4 and 6 W have been found as the best one for laser application on pancreatic tissue because a complete destruction of the cells in the site of application but a limited heat damage in the surrounding healthy cells have been obtained.

KEYWORDS: Vessels; Surgery; Laser; Pancreatic cells.

ABBREVIATIONS: ND-YAG: Neodymium-Doped Yttrium Aluminium Garnet; ANP: Acute Necrotizing Pancreatitis; CT: Computed Tomography; H&E: Haematoxylin and Eosin.

BACKGROUND

Acute Necrotizing Pancreatitis (ANP) surgery is one of the hardest challenges in gen-

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eral surgery.[1-8] Tissue is loose, friable and much vascularized; so, pancreatitis and major bleedings are well-described during surgery.[1]

Approximately 20% of patients with acute pancreatitis develop pancreatic necrosis, and mortality rates up to 39% have been reported.[1-8] Surgical debridement (so-called necrosectomy) is the traditional management of necrotizing pancreatitis with specific indications.[1-9]

In severe AP, current indications for surgery include the presence of infected pancreatic necrosis, extensive sterile necrosis in patients in whom symptoms have failed to resolve despite maximal conservative treatment or in patients who develop catastrophic complications related to pancreatic necrosis such as bleeding, visceral perforation or infarction.[1-8]

The Computed Tomography (CT) evaluation of necrotic pancreatitis often show a superficial necrosis of the gland that contains vital tissue, this has led to gradually abandoning the performance of demolitive resection in favor of a treatment that combines the debridement of necrotic tissue associated with different draining techniques and postoperative cleaning procedures with open or closed packing.

These procedures are associated with a lower mortality and a lower rate of impairment of the functions of the endocrine and exocrine pancreatic gland compared to the demolitive ones (100% of diabetes in the surgical resection *versus* 52% post-necrosectomy).[8,9]

Today the treatment of infected necrosis can be performed in both open and laparoscopic procedure even if it is preferred the classic technique followed by open-abdomen techniques in order to facilitate possible re-operations.

Pancreatic adenocarcinoma, commonly known as pancreatic cancer, represents the 12th most common type of cancer in the United States.[1] With a national age-adjusted incidence rate of 12.3 per 100,000, approximately 46,420 individuals were diagnosed with pancreatic cancer in 2014. Although the disease is relatively rare, pancreatic cancer is one of the most fatal cancers among adults in the United States. Pancreatic cancer has the lowest 5-year survival rate of any cancer, is the fourth leading cause of cancer death in the nation, and approximates breast cancer's death toll.

No major professional group recommends routine screening for pancreatic cancer; the natural history of the disease is not fully understood and current screening tools, including imaging modalities and serum biomarkers, are limited in diagnostic accuracy. Because screening is not recommended and the cancer typically develops with few symptoms, the majority of patients are diagnosed at an advanced stage. As an aggressive disease, the 5-year survival rate is <5%, and despite occasional cases of early disease detection, nearly all patients die from pancreatic cancer within 1-2 years.[2]

The main risk factors of pancreatic cancer include smoking, obesity, long-standing diabetes, and family history of disease. Cigarette smoking is the most well-established risk factor for pancreatic cancer. Smoking cigarettes causes a 75% increase in the risk of pancreatic cancer compared to non-smokers. Accordingly, 20% of pancreatic tumors may be attributed to cigarette smoking. Epidemiological investigations have also reported a 20-50% increased risk of disease among obese relative to no obese individuals. Although the relationship between diabetes and pancreatic cancer is complex, long-term type 2 diabetes has been associated with a significant increase in the risk of pancreatic cancer as well. Lastly, up to 10% of patients have a family history of pancreatic cancer, and the risk of disease is considerably greater (80%) among persons with affected family members compared to those without.[1]

Promising data about the application of Neodymium Doped Yttrium Aluminium Garnet (ND-YAG) and CO_2 laser in clinical fields are available.[10,11]

The use of ND-YAG laser in this kind of surgery could prove useful due to its ablative, antiseptic and hemostatic properties at the same time that would enable us to perform necrosectomies with a minimum invasiveness and without touching the inflamed tissue. Only few studies are disponsable in the international literature.[10-13]

AIM OF THE STUDY

The authors have focused the study on two main points:

1. To assess the viability of ND: YAG 1064 nm laser employment in the pancreatic surgery, particularly with regard to its possible application in necrosectomies for severe acute necrotizing pancreatitis.
2. To evaluate which are the best settings to achieve efficient ablation of the necrotic or tumoral areas intended as a thermal coagulation of the tissue and at the same time saving the surrounding healthy tissue.

Secondary endpoints are: To evaluate vessel damage due to laser application on pancreatic tissue (considering any interruption of the endothelial line).

MATERIALS AND METHODS

For this purpose, the authors used bovine pancreas on which different experimental settings were tested and subsequently evaluated both macroscopically and microscopically in order to show if the laser waves have performed a complete destruction of pancreatic cells in the site of application and how far the heat damage has arrived.

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We have used the ECHO LASER 1064 ND-YAG with fluence of 1800 J and at increasing power settings: 3 W, 5 W and 7 W.

The laser waves were collected in the tissue with an optical fiber of 500 µ diameter inserted inside of the pancreatic tissue.

The timing of application was 11 minutes at the power of 3 W, 6 minutes at 5 W, 4 minutes at 7 W (that are the time needed to reach the fluence of 1800J).

Immediately after the laser application, all specimens were fixed in 10% neutral buffered formalin, dehydrated through a crescent ethanol series, embedded in paraffin, sectioned (3 micron thickness) and stained with Haematoxylin and Eosin (H&E) for examination with light microscope. All the specimens were analyzed by the same pathologist. H&E) for examination with a light microscope

RESULTS

We have analyzed 100 pancreatic bovine tissue samples without any pathological findings before laser application (Table 1).

Power (W)	N. samples	Time (min)	Area of burnt in mm^3 (+/-)	Area of heat damage in mm^3 (+/-)
3	33	11	0	1500(100)
5	34	6	70(20)	2000(130)
7	33	4	90(45)	4000(205)

Table 1: Mean value of area of burnt and area of heat damage at different power settings.

Direct observation of tissue samples after treatment with ECHO ND-YAG laser at the power setting of 3 W on 33 samples shows that the pancreatic tissues is not macroscopically modified except for the increased cutting consistency.

Histological examination shows no substantial microscopical differences in pancreatic cells that appear only partially burnt (in fact, nuclei and membranes are still recognizable). The vessels around the point of application do not show microscopically any sign of damage.

Increasing the power of laser waves to 5 W on 34 samples, macroscopically the presence of an area, corresponding to the site of direct interaction of laser and tissue, completely burnt was found and the surrounding tissue did not appear substantially modified.

Histological examination shows the complete absence of cells in the burnt area (with a complete destruction of the lissome containing amylases) and an important heat damage of the surrounding cells (the authors think that this cells have been definitively compromised and are supposed to undergo apoptosis) till the 2th centimeter from the site of laser application. (Figure 1) The vessels around the point of application are all coagulated.

At the power of 7 W on 33 samples, the burnt area is obviously higher, about twice than in the previous setting.

Histological examination shows the complete absence of cells or any cell's components (including lissome) in the burnt area and a larger heat damage of the nearest cells (till the 4th centimeter from the application site). The vessels around the point of application are, again, all coagulated. (Figure 2)

DISCUSSION

The results obtained in this study show how increasing laser power setting increases its effectiveness in coagulation and thermoablation of pancreatic tissue both *de visu* and microscopically: we have found that a power setting between 4 and 6 W could be acceptable for applications on pancreatic tissue.

Our data confirm the few ones already available in the international literature[12,13] as we agree that the best power setting is between 4 W and 6 W. Moreover, we were able to find out why in the previous studies,[12] the authors found no hemorrhage: the laser waves, in fact, allow a complete coagulation of the vessels in the area of application.

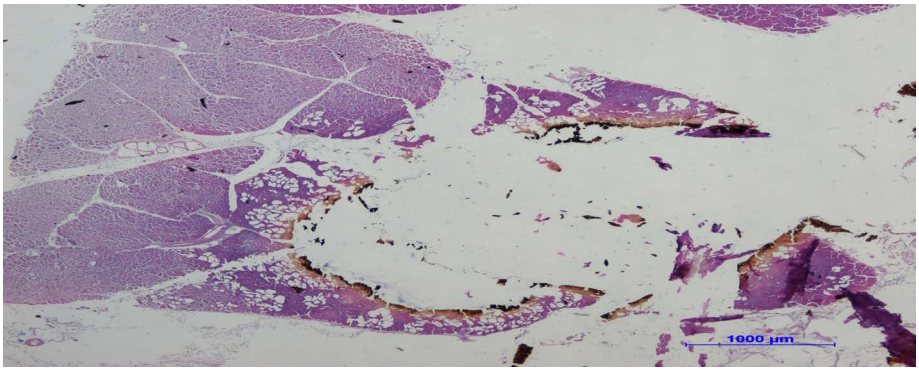

Figure 1: Site of application at the 5W setting. The burnt area (without colored cells, with black margins) and the surrounding area of heat damage (in which vacuolization is present) can be seen. In the distal part of the samples, a normal pancreatic tissue can be seen.

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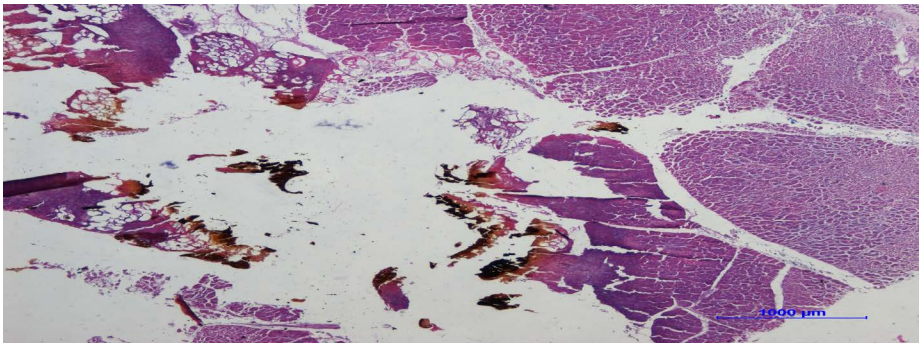

Figure 2: Site of application at 7W setting. The burnt area is in the central part (with some black group of necrotic material). The heat damage area is around with the typical vacuolization and it is wider than in the previous setting. Once again, in the marginal areas (upper part of the figure), normal tissue can be seen.

The main limitations of the present study are that this is an *ex vivo* study and not on human tissue. Despite the early stage of our research, we can assume that this new technique ,once developed and optimized, can be used in many different ways and with interesting surgical applications (necrosectomy, thermoablation of solid not resecable neoplasm, biopsies of pancreatic tissues).

The main advantages in fact in this type of treatment are the possibility of an operating treatment without touching the parenchyma (*touch-sparing technique*) and the capability to ablation, coagulation and disinfection at the same time of the treated tissue (*aseptic thermoablative technique*). Moreover, the laser ablation is more defined than other types of thermoablation (i.e. radiofrequency) and this is important in order to save as much tissue as possible without damaging the healthy part of the organ. Further studies are needed to continue analyzing the interaction of laser waves on pancreatic tissue.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONSENT

No consent is required to our article publication regarding the paper “Evaluation of the best power setting of laser waves in pancreatic surgery: ECHO ND-YAG laser ablation on pancreatic tissue samples and its potential applications in necrosectomy and other pancreatic pathologies”.

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Short Communication

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Nutritional Support of Patients with the Abdominal Compartment Syndrome during Severe Acute Pancreatitis

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There is growing evidence in the literature that development of Abdominal Compartment Syndrome (ACS) in patients with Severe Acute Pancreatitis (SAP) has a strong impact on the course of disease. Incidence of ACS in patients with SAP is around 20%. The mortality rate in patients who developed ACS during SAP is 49%, while it is 11% in patients without this complication. The development of organ failure in SAP is in correlation with the presence of intra-abdominal hypertension which can deteriorate already compromised pancreatic perfusion and perfusion of gut in early stages of SAP. The latter leads to the alteration of gut functioning with consequent reduced possibility for enteral feeding. Enteral Nutrition (EN) facilitates gut motility and alleviates bacterial translocation, but in patients suffering from ACS during course of SAP could aggravate bowel ischemia. Parenteral nutrition is required as nutritional support in ACS, but it may increase bacterial translocation and deteriorate gut functioning. Since in the literature data there still have not had recommendations regarding nutritional support of patients with ACS during course of SAP, including optimal time for initiation, duration and amount of specific nutritional regiment, in this short review we have tried to give insight into problems in nutritional support in those patients. This should fortify the interest of physicians to make additional research in order to support further strategies for the more optimal nutritional support of patients with this lethal complication.

The abdominal compartment syndrome (ACS) is well described entity which importance in various clinical conditions has been recognized in the last two decades. It is defined as a state of serious organ dysfunction resulting from sustained increase in Intra-Abdominal Pressure (IAP).[1] There is growing evidence in the literature data that the development of ACS in patients with severe form of acute pancreatitis (SAP) has strong influence on the course of disease.[2-5] The incidence of Intra-Abdominal Hypertension (IAH) in patients suffering from SAP is approximately 70%, while ACS can be found in up to 27% of patients with this form of AP.[3,4,6,7] When we add to this a mortality rate of 49% in patients with SAP and ACS,[5] it is clear that IAH and ACS have become an issue of concern in patients with AP. In addition, it was recently mentioned that the number of patients with AP and this complication has increased, but still there have not had standard recommendations for interventional treatment of patients who develop ACS during SAP.[8] The step-up approach for conservative treatment of ACS was proposed several years ago.[9] However, the appropriate interventional procedure, including surgical technique, and optimal time for reacting in the treatment of AP patients suffering from this serious condition is still debated.

From a metabolic point of view, SAP is characterized by nitrogen waste and protein catabolism with negative nitrogen balance and secondary malnutrition.[10] Similarly with septic patients, the AP patients have an impaired capacity for net protein synthesis and are less sensitive to protein sparing of glucose infusion.[11] Also, in patients suffering from AP energy expenditure is increased 1.49 (1.08 to 1.78) of the predicting resting energy expenditure, 58% of patients with SAP have increase in energy expenditure, approximate net nitrogen loses are 20-40 grams per day, and proteolysis can be increased by 80%.[12] Therefore, the nutrition therapy is necessary in patients with SAP.

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Hypovolemia is common in AP, especially in the severe form of the disease, and is a result of a massive fluid loss into the retroperitoneal space and interstitial space overall. However, an early substantial fluid loss in patients with SAP occurs in retroperitoneal space and interstitial space of gut. Cytokines activation in the early phase of AP results in increased capillary permeability, vasoconstriction and transendothelial migration of leukocytes. This event is associated with significant increase of leukocytes infiltration with histological changes and decreasing in intestinal and pancreatic perfusion and mucosal ischemia of the gut.[13-16] In early stages of SAP the profound fluid losses in a "third space" associated with inflammation of the pancreas may induce splanchnic vasoconstriction. Hypovolemia also leads in decreasing in splanchnic perfusion with consequent cellular hypoxia especially in intestinal mucosa.[17,18]

It is certain that the gastrointestinal system and liver functions are the most vulnerable to the high Intra-Abdominal Pressure (IAP). Mainly two functions are altered: (1) the mucosal barrier function (influencing both intermucosal nutrient flow and bacterial translocation) and (2) the gastrointestinal motility. The reduction of splanchnic blood perfusion occurs at the level of IAP of 10 mmHg, with the exception of the adrenal glands.[19,20] The metabolic changes in the gut, such as acidosis and decreased intestinal oxygenation, are evident at the IAP level of 15 mmHg.[21] It was shown that IAP from 20-25 mmHg in the duration of 60 minutes leads to the bacterial translocation from gut.[22] In our recent study we found a highly significant correlation between IAP and procalcitonin (PCT) in patients with AP suggesting bacterial translocation.[7] The impact of elevated IAP on the gut is essential due to circumstantial evidences of relationship between bacterial translocation and multi-organ dysfunction syndrome.[23-25]

Present recommendations regarding nutritional support in patients with SAP favour enteral nutrition (EN) over parenteral nutrition (PN) due to several reasons. Firstly, nasoenteric tube feeding as compared with total PN reduced the rate of infection and mortality among patients with SAP throughout stimulating intestinal motility – thus reducing bacterial overgrowth, and increasing splanchnic blood flow which helps to preserve the integrity of the gut mucosa. Second, total PN lacks the trophic effect of EN and is associated with central venous catheter related infections as well as metabolic complications. Also, in all patients in whom the clinician decides that some form of nutritional support is indicated, should provide it by enteral route. Only in patients whose gut has failed or administration of EN is impossible for other reasons (prolonged ileus, complex pancreatic fistulae and ACS), total PN is indicated.[26-30]

However, in the literature data there still have not had recommendations regarding nutritional support in patients with ACS. This includes an optimal time for initiation and duration of specific nutritional regiment. Also, there has not had randomized control trials regarding nutritional support of patients suffering from AP and IAH. In a pilot study by Sun et al,[31] which compared the incidence of IAH in 60 patients with early or delayed administration of EN, IAH was more prevalent in patients with delayed EN administration. They were also argued that higher IAP may correlate with intolerance to enteral feeding.

Indeed, there are several papers, case reports and retrospective studies, in which were reported non-occlusive bowel ischemia and bowel necrosis after EN.[32-35] In most reports were suggested that EN may play a central role in bowel ischemia (Table 1).[32-40] The pathogenesis of ischemic changes of gut secondary to EN is multifactorial including intraluminal factors, such as increased energy demands in metabolically stressed enterocytes, intestinal bacterial overgrowth and increased bowel's intraluminal pressure with the subsequent reduction in gut perfusion. In AP patients who have hypovolemia, increased capillary permeability, splanchnic hypo perfusion and possible reperfusion injury after initial treatment, they surly may have additional mucosal damage after enteral feeding. In addition to this, patients with IAH and ACS already have significant decreased in splanchnic perfusion associated with mucosal ischemia, thus could have more pronounced mucosal damage of gut and serious gut dysfunction. It has been reported a gut barrier dysfunction in patients with ACS during AP by higher serum concentrations of antiendotoxin core antibodies and PCT in those patients, suggesting increased bacterial translocation from gut.[23]

Early results of our prospective observational study conducted among patients with SAP and ACS showed that majority of patients suffering from ACS during course of SAP had better tolerance for total PN than for EN, suggesting gut dysfunction. Regarding certain nutritional support in patients with ACS during course of SAP, we found that combined usage of EN and total PN was better tolerated than EN or total PN alone. Moreover, in patients who received total PN serum values of PCT were higher than in those who received EN or combined total PN and EN. However, in patients who received EN alone it was found a higher serum values of PCT noted at the time of IAH/ACS occurrence than in those who received combined EN and total PN. This fact point to the favorable effects of EN on gut functioning in patients with SAP, but without effects, even deterioration in gut functioning, in patients suffering from ACS during course of the SAP.[41]

It is certain that EN should be the first line of nutritional support in almost all patients with AP, but in those with IAH/ACS this route of feeding should be carefully monitored. The occurrence of further abdominal distension, elevation of IAP and high nasogastric output should result in immediate discontinuation of tube feeding rather than repeated attempts to alter the formula. In all patients with this serious condition the balanced usage of EN and total PN should be considered, even in those with intractable IAH. What should be the critical value of IAP which may indicate the adverse effects of EN remains to be examined. However, because of the complexity of intensive care together with the heterogeneity of patients with AP as unpredictable disease, optimal nutrition support remains a difficult topic to study. As a result, nutrition support practices among providers

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	Article type	Number of patients	Route	EN only	Part of changed bowel	Pathological changes	Outcome
De Brabandere K, et al[32]	Case report	1	ileum	Yes	Ileum and left colon	Congestion in ileum / colon necrosis	Survived
Melis M, et al[33]	Case report	1	Jejunum	Yes	Small bowel	Necrosis	Died
Gwon JG, et al[34]	Case report	2	Jejunum	Yes	Part of small bowel and colon / colon	Necrosis	Died / Survived
Marvin R, et al[35]	Retrospective study	13	11 in jejunum / 2 in duodenum	Yes in 12 patients	Small bowel and colon in 1 / jejunum and or ileum in 7 / ileum and right colon in 3 / right colon in 2 patients	From bowel inflammation to bowel necrosis with multiple perforations	6 died
Schunn CG, Daly JM[36]	Retrospective study	4	Jejunum	Yes	Small bowel in 4 and colon in 1	Necrosis	2 died
Brenner DW, Schellhammer PF[37]	Case report	1	Jejunum	Yes	Small bowel	Inflammation and ulcerations with necrosis	died
Munshi IA, et al[38]	Case report	1	Jejunum	Yes	Jejunum	Necrosis	died
Jorba R, et al[39]	Case report	1	Jejunum	Yes	Jejunum	Necrosis	died
Lawlor DK, et al[40]	Retrospective study	3	Jejunum	Yes	Jejunum and ileum	Necrosis	survived

Table 1: Non-occlusive bowel ischemia after enteral nutriotion.

are extremely variable. Well designed experimental and randomized clinical studies should be expected to shed more light of the most appropriate nutritional support in patients with this lethal condition.

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