(11)

膽胰腫瘤藥物治療與介入性內視鏡超音波新進展

Evolution of Interventional EUS and Pharmacal Treatment of Pancreaticobiliary Cancer

時　　間：114 年 6 月 28 日(星期六) 08:30~12:05
地　　點：臺北榮民總醫院 中正樓 12 樓會議室
協辦單位：台灣擬眞醫學教育學會

08:30-8:35	***Opening Remarks***	羅景全教授 Jiing-Chyuan Luo
	座長：李重賓 教授 (Chung-Pin Li)	
08:35-8:55	胰臟腺癌藥物治療之新進展 Advances in Pharmacological Therapy of Pancreatic Adenocarcinoma	許劭榮教授 Shao-Jung Hsu
	座長：黃怡翔 教授 (Yi-Hsiang Huang)	
08:55-9:15	膽管癌藥物治療新進展 Advances in Pharmacotherapy of Biliary Cancer	李懿宸醫師 I-Chen Lee
	座長：蘇穎文 主任 (Ying-Wen Su)	
09:15-9:35	次世代基因分析在膽胰癌症的角色 Role of NGS in Pancreaticobiliary Cancer	于洪元醫師 Hung-Yuan Yu
09:35-9:50	***Coffee Break***	
	座長：鄒永寬 主任 (Yung-Kuan Tsou)	
09:50-10:05	介入性內視鏡超音波簡介 Introduction of Interventional EUS	陳宥任醫師 Yu-Jen Chen
	座長：黃惠君 教授 (Hui-Chun Huang)	
10:05-10:20	內視鏡超音波導引組織抽取 EUS-Guided Tissue Acquisition	張天恩醫師 Tien-En Chang
	座長：黃文信 主任 (Wen-Hsin Huang)	
10:20-10:35	內視鏡超音波導引假性囊腫/壞死引流 Endoscopic Ultrasound-Guided Pseudocyst/Walled-off Necrosis (WON) Drainage (EUS-Guided Pseudocyst/WON Drainage)	林榮鈞醫師 Jung-Chun Lin

座長：孫灼基 主任 Cheuk-Kay Sun)

10:35-10:50	內視鏡超音波導引胃腸吻合術 EUS-Guided Gastroenterostomy	郭雨庭醫師 Yu-Ting Kuo

座長：李癸洲 教授 (Kuei-Chuan Lee)

10:50-11:25	**Keynote Speech (1):** LAMS 在膽胰腫瘤的應用 LAMS in Pancreaticobiliary Cancer	Prof. Dong-wook Oh (韓國)

座長：羅景全 教授 (Jiing-Chyuan Luo)

11:25-12:00	**Keynote Speech (2):** 內視鏡超音波膽汁引流的故障排除 Technical Tips and Troubleshooting of EUS-Guided Biliary Drainage	Prof. Ichiro Yasuda (日本)
12:00-12:05	***Closing Remarks***	侯明志副院長 Ming-Chih Hou

Advances in pharmacological therapy of pancreatic adenocarcinoma

胰臟腺癌藥物治療之新進展

Shao-Jung Hsu

許劭榮

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Pancreatic adenocarcinoma remains a leading cause of cancer-related mortality, with its incidence steadily rising. Over the past decades, advancements in pharmacotherapy have significantly improved patient prognosis. Gemcitabine-based regimens and FOLFIRINOX have demonstrated efficacy in prolonging survival across different disease stages. Recently, NALIRIFOX has emerged as a promising first-line treatment for metastatic pancreatic adenocarcinoma, offering superior survival benefits compared to gemcitabine plus nab-paclitaxel. Additionally, targeted therapies provide novel treatment avenues for select patient populations. Despite these advancements, surgical resection remains the only potentially curative approach. Therefore, the development of effective screening strategies for high-risk individuals remains a critical challenge. This section explores recent progress in pharmacological treatment and ongoing challenges in early diagnosis.

Advances in pharmacotherapy of biliary cancer

膽管癌藥物治療之新進展

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Biliary tract cancer (BTC), the second most common type of liver cancer, remains a therapeutic challenge due to its late diagnosis and poor prognosis. The current state of systemic therapy for advanced BTC has undergone significant changes. Despite significant advancements in understanding its biology over the past decade, the prognosis remains poor. Cisplatin and gemcitabine (GemCis) chemotherapy, followed by second-line FOLFOX, has been the standard treatment for advanced BTC. Recently, immunotherapy has emerged as a promising approach, with the TOPAZ-1 and KEYNOTE-966 trials demonstrating improved survival by adding durvalumab or pembrolizumab to GemCis chemotherapy. BTC is often associated with genetic alterations and is an excellent model for precision oncology. Advances in molecular profiling have led to targeted therapies for FGFR2 fusions, IDH1 mutations, HER2 amplification, and BRAF V600E. This review explores the evolution of systemic treatments and recent clinical trial findings.

Role of NGS in pancreaticobiliary cancer

次世代基因分析在膽胰癌症的角色

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Next generation sequencing (NGS) has emerged as a transformative diagnostic and research technology with profound implications for understanding and managing pancreatic and biliary tract cancers. These aggressive malignancies have historically presented significant challenges in early detection, prognostication, and personalized treatment strategies.

NGS enables comprehensive genomic profiling that reveals critical molecular alterations underlying these cancers. By facilitating high-throughput, comprehensive genetic analysis, this technology provides unprecedented insights into tumor heterogeneity, genetic mutations, and potential therapeutic targets. In pancreatic cancer, NGS has identified key driver mutations in genes such as KRAS (86.7% of cases), TP53 (73.3%), CDKN2A (66.7%), and SMAD4 (36.7%), which contribute to disease progression and treatment resistance. Targetable alterations were identified in 19.9% of patients, including DNA repair defects (e.g., BRCA1/2) and rare BRAF or NTRK fusions

For biliary tract cancers, NGS has uncovered complex genomic landscapes, including actionable mutations in IDH1/2, FGFR2 fusion genes, and HER2 amplifications. These discoveries have direct clinical implications, enabling more precise molecular classification and potentially guiding targeted therapeutic interventions.

The technology's potential extends beyond mutation identification. NGS supports liquid biopsy approaches, allowing minimally invasive monitoring of tumor evolution, treatment response, and potential recurrence. Moreover, it facilitates the development of personalized medicine strategies by identifying patients most likely to benefit from specific molecular targeted therapies.

Despite these advances, challenges remain in standardizing NGS protocols, interpreting complex genomic data, and translating molecular insights into effective clinical interventions. Continued research and interdisciplinary collaboration will be crucial in fully realizing the transformative potential of next generation sequencing in these challenging malignancies.

Introduction of interventional EUS

介入性內視鏡超音波簡介

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Interventional endoscopic ultrasound (EUS) has emerged as a revolutionary tool in modern medicine, bridging diagnostic and therapeutic capabilities with minimal invasiveness. This technique integrates endoscopy and ultrasonography, allowing clinicians to visualize and access internal structures with unparalleled precision. Its applications extend beyond traditional diagnostic imaging to include a broad spectrum of interventional procedures, such as fine-needle aspiration, fluid drainage, and tumor ablation. By enhancing procedural accuracy and patient outcomes, interventional EUS represents a critical advancement in the management of gastrointestinal, pancreatic, and biliary diseases. This introduction highlights the evolution, principles, and transformative impact of interventional EUS on contemporary clinical practice.

EUS-guided tissue acquisition

內視鏡超音波導引組織抽取

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Endoscopic ultrasound (EUS)-guided tissue acquisition has become a cornerstone in the diagnosis and management of gastrointestinal and pancreatic diseases, particularly pancreatic cancer. This minimally invasive technique allows real-time visualization and targeted sampling of deep-seated lesions that are often inaccessible by other imaging modalities. Using fine-needle aspiration (FNA) or fine-needle biopsy (FNB), clinicians can obtain high-quality cytological or histological specimens for diagnosis, staging, and even molecular profiling.

Advancements in needle design and technique—such as fanning, suction, and the slow-pull method—have significantly improved diagnostic yield while minimizing complications. Proper needle selection and technique adjustment based on lesion location, vascular proximity, and patient condition are critical to optimizing outcomes.

This presentation will briefly review current techniques in EUS-guided tissue acquisition, address key challenges such as sample adequacy and false negatives, and highlight its evolving role in precision oncology. As molecular testing becomes routine, EUS sampling is increasingly vital for personalized treatment planning.

Endoscopic ultrasound-guided pseudocyst/walled-off necrosis (WON) drainage (EUS-guided pseudocyst/WON drainage)

內視鏡超音波導引假性囊腫 / 壞死引流

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Pancreatic pseudocysts and walled-off necrosis (WON) resulting from necrotizing pancreatitis are common complications of acute pancreatitis. Endoscopic ultrasound (EUS) plays a crucial role in both the diagnosis and management of these conditions. EUS not only provides high-resolution imaging of the internal structure of the cyst or necrotic collection and its relationship with adjacent vasculature but also enables safe and effective drainage procedures.

This lecture will focus on EUS-guided drainage techniques for pancreatic pseudocysts and WON. The content will cover:

- Indications and Contraindications: Examining the applicability and limitations of EUS drainage in various clinical scenarios.
- Preoperative Assessment and Preparation: Emphasizing the importance of precise EUS evaluation of lesion characteristics and selection of appropriate drainage routes.
- Drainage Techniques: Providing a detailed overview of different EUS-guided drainage approaches, including cystogastrostomy, cystoduodenostomy, and direct drainage, while comparing the advantages and disadvantages of each method.
- Selection of Drainage Devices and Stents: Discussing the application of various types and sizes of drainage devices (such as pigtail catheters, metal stents, particularly lumen-apposing metal stents (LAMS)) in different lesions.
- Postoperative Management and Complication Management: Explaining the essential aspects of care following EUS drainage and providing management principles for potential complications (such as bleeding, infection, stent migration).
- Latest Advances and Future Directions: Introducing the latest techniques and research findings in the field of EUS-guided drainage for pancreatic pseudocysts and WON.

EUS-guided gastrojejunostomy

內視鏡超音波導引胃腸吻合術

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In recent years, endoscopic enteral stenting have provided an attractive alternative to surgery for palliation of malignant gastric outlet obstruction (GOO). Several studies have assessed the clinical and technical success rates of endoscopic enteral stenting for malignant gastroduodenal obstruction. Technical success rates of 90% to 100% and clinical success of 80% to 95% was achieved. The procedure was associated with quicker recovery and reduced morbidities as compared to surgical gastrojejunostomies. However, the long-term patency of uncovered stent is limited by the risk of tumor ingrowth that would lead to subsequent re-stenosis of the stents requiring re-intervention. Thus, to palliate malignant gastric outlet obstruction, surgical gastrojejunostomy is preferred in patients that are fit for surgery with prolonged life expectancy whilst insertion of enteral stent is preferred in patients that are associated with high-risk for surgery and short life expectancy.

A recent advancement, endoscopic ultrasonography-guided gastrojejunostomies (EUS-GJ), utilizing a lumen-apposing self-expandable metal stent (LAMS), offers a durable and minimally invasive solution for GOO. EUS-GJ was initially hypothesized and tested in animal models by Fritscher-Ravens in 2002. This technique has progressively evolved; it involves the creation of a bypass between the stomach and a small bowel limb placed distal to the obstruction, through the insertion of a lumen-apposing metal stent (LAMS) under EUS and fluoroscopic guidance. EUS-GJ creates a food pathway shortcut akin to surgical bypass, providing longer stent patency compared to standard duodenal stenting; furthermore, EUS-GJ is theoretically less invasive than surgical gastrojejunostomy (SGJ). The EUS-GJ technique's evolution from clinical trials and animal experiments, yielding three main techniques: (1) the direct technique; (2) device-assisted techniques; and (3) EUS-guided double balloon-occluded gastrojejunostomy bypass. In the general principle, the small intestinal tract intended for stent deployment should be adjacent to the stomach. A preprocedural computed tomography scan in both transverse and coronal view is helpful in deciding on the puncture site as a preoperative roadmap. It should be cautious to perform EUS-GJ in the presence of a large amount of ascites, which interferes with the adherence and fixation of the bowel loops. This procedure remains unoptimized, with some limitations that need to be overcome. All reports of EUS-GJ have been published only by experts of the procedure because the currently followed procedure is technically difficult and must be improved and simplified further to facilitate its use in clinical practice. LAMS design must also be improved because the currently available LAMSs have a maximum diameter that does not appear to be appropriate for EUS-GJ, which usually requires a bigger anastomosis and minimal risk of stent obstruction and migration.

LAMS in pancreaticobiliary cancer

LAMS 在膽胰腫瘤的應用

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Lumen-apposing metal stents (LAMS) are specialized stents initially designed for draining pancreatic fluid collections (PFCs). They feature a unique saddle-shaped design with dual flanges at both ends, enabling close apposition of two luminal structures. This design significantly reduces the risk of migration and facilitates direct endoscopic interventions, such as necrosectomy.

In recent years, the clinical applications of LAMS have expanded beyond PFCs to include various scenarios involving pancreatobiliary malignancies. Specifically, LAMS have become increasingly valuable for palliative management of complications like biliary obstruction and gastric outlet obstruction (GOO) associated with pancreatobiliary cancers.

One notable application is EUS-guided choledochoduodenostomy (EUS-CDS). Particularly, electrocautery-enhanced LAMS (EC-LAMS) are frequently utilized in patients with malignant distal biliary obstruction, especially when conventional ERCP is unsuccessful or challenging.

Additionally, LAMS have proven effective in EUS-guided gallbladder drainage, presenting a reliable alternative to percutaneous gallbladder drainage for high-risk surgical patients suffering from acute cholecystitis or malignant cystic duct obstruction. The advantages of using LAMS for gallbladder drainage include high technical and clinical success rates of approximately 95%, reduced risk of bile leakage and stent migration due to their excellent lumen apposition, and a larger lumen diameter which facilitates effective drainage and enables potential endoscopic interventions such as cholecystoscopy.

Another significant use of LAMS is EUS-guided gastroenterostomy (EUS-GE) for managing GOO. These stents have demonstrated high technical success rates ranging from 87% to 100%, and similarly high clinical success rates of 84% to 100%. Benefits of using LAMS in gastroenterostomy include improved quality of life and symptom relief by restoring luminal patency, fewer early adverse events compared to surgical gastrojejunostomy, and superior long-term patency compared to traditional enteral stenting methods.

Furthermore, LAMS have demonstrated efficacy in managing post-surgical fluid collections, although they were not initially designed for this purpose. They have shown notable success in draining peri-pancreatic abscesses or fluid collections that arise following surgical interventions like Whipple's procedure or distal pancreatectomy performed for pancreatic malignancies. Compared to traditional plastic stents, LAMS offer benefits such as easier deployment, shorter procedural times, lower risks of leakage, and improved technical success rates.

In summary, LAMSs represent a significant advancement in interventional EUS, particularly for pancreatobiliary cancers. Their versatility facilitates effective palliation in complex clinical scenarios, addressing complications such as biliary obstruction, GOO, and post-surgical fluid collections.

Technical tips and troubleshooting of EUS-guided biliary drainage

內視鏡超音波膽汁引流的故障排除

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EUS-guided biliary drainage (EUS-BD) has been rapidly gaining popularity in recent years. It may be performed in patients in whom conventional endoscopic transpapillary biliary drainage is not feasible or has failed. This technique includes various procedures such as EUS-guided choledochoduodenostomy (EUS-CDS), EUS-guided hepaticogastrostomy (EUS-HGS), EUS-guided antegrade stenting (EUS-AS), and EUS-guided rendezvous technique (EUS-RV). Among them, EUS-HGS is mostly performed in Japan because it can be performed even in patients with inaccessible papillae due to duodenal invasion of pancreatic cancer and surgically altered anatomy. The most recent meta-analysis showed a high technical success rate of 98% and a clinical success rate of 88% in this procedure. However, adverse events also occurred relatively frequently in the early stage of development. EUS-HGS is performed ordinally in the following steps: puncture site selection, biliary puncture, contrast injection, guidewire insertion and manipulation, dilation of the puncture tract, and stent placement.

Puncture site selection: Needle puncture can be made to B2 or B3. Before the puncture, the estimated puncture line should be checked using a color Doppler and interposed vessels should be avoided. It should be also confirmed on the fluoroscopic image that the ultrasound probe surface is facing the hepatic hilum so that the guidewire can easily advance downward. **Biliary puncture:** In cases of B2 puncture, the location of the EG junction should be checked in advance to avoid trans mediastinal puncture. Usually, a 19G needle is used for puncture, but if the intrahepatic bile ducts are only mildly dilated, consider using a 22G needle. However, in this case, a 0.018G guide wire is used, so subsequent guide wire manipulation becomes difficult. It has been reported that the risk of bile leakage can be reduced if the intervening liver parenchyma along the puncture route is at least 25mm. **Contrast injection:** The contrast medium is used to confirm the appropriate puncture into the bile duct and obtain the cholangiogram. **Guidewire insertion and manipulation:** A guidewire with good torque transmission and seeking performance should be used. Also, if it was possible, two guidewire placements would increase the stability of the subsequent procedure. **Dilation of the puncture tract:** This is the most troublesome step of the whole process, but in recent years, specialized devices such as dedicated dilation balloons and dilators have been developed, making the procedure easier. **Stent placement:** In recent years, we have preferably used plastic stents rather than metal stents. This is because they are easier to insert and avoid the risk of cholangitis by not occluding the side branches of the intrahepatic bile ducts.

Establishing techniques and developing dedicated devices have made the procedures easier and safer, and the frequency of procedure-related adverse events appears to have decreased.