

Direct therapeutic intervention for advanced pancreatic cancer

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Abstract

Currently, chemotherapy is an accredited, standard treatment for unresectable, advanced pancreatic cancer (PC). However, it has been still showed treatment-resistance and followed dismal prognosis in many cases.

Therefore, some sort of new, additional treatments are needed for the better therapeutic results for advanced PC. According to the previous reports, it is obvious that interventional endoscopic ultrasonography (EUS) is a well-established, helpful and low-risky procedure in general. As the additional treatments of the conventional therapy for advanced PC, many therapeutic strategies, such as immunotherapies, molecular biological therapies, physiochemical therapies, radioactive therapies, using siRNA, using autophagy have been developing in recent years. Moreover, the efficacy of the other potential therapeutic targets for PC using EUS-fine needle injection, for example, intra-tumoral chemotherapeutic agents (paclitaxel, irinotecan), several ablative energies (radiofrequency ablation and cryothermal treatment, neodymium-doped yttrium aluminum garnet laser, high-intensity focused ultrasound), *etc.*, has already been showed in animal models. Delivering these promising treatments reliably inside tumor, interventional EUS may probably be indispensable existence for the treatment of locally advanced PC in near future.

Key words: Interventional endoscopic ultrasonography; Advanced pancreatic cancer; Radiofrequency ablation; Gemcitabine; Endoscopic ultrasonography guided-fine needle injection; Dendritic cells

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Core tip: Unresectable, advanced pancreatic cancer (PC) has been still showed treatment-resistance and followed dismal prognosis in many cases with conventional therapies. Therefore, some sort of new, additional treatments are needed for the better therapeutic results for advanced PC. In recent years, interventional endoscopic ultrasonography (EUS) has been developed, disseminated and used efficiently all over the world as indispensable therapeutic strategies for PC. Therapeutic trials by interventional EUS for advanced PC until now, and describe the possibilities and expectations of anti-

tumor therapy for advanced PC by interventional EUS to the future through this epoch-making deployment are summarized in this Editorial.

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TEXT

In recent years, interventional endoscopic ultrasonography (EUS) has been developed, disseminated and used efficiently all over the world as indispensable therapeutic strategies for various diseases of digestive area, such as malignant tumors, drainage, pain relief and recurrent lesions. Besides, unresectable, advanced pancreatic cancer (PC) has been still showed treatment-resistance and followed dismal prognosis in many cases. Some sort of new, additional treatments are needed for the better therapeutic results. Because of the merit which approaches inside the pancreas directly through stomach or duodenum, interventional EUS may be a potential target of crucial treatment strategy. Different strategies of interventional EUS for advanced PC have been conducted, and will also be carried out in the future. We hope to summarize the therapeutic trials by interventional EUS for advanced PC until now, and describe the possibilities and expectations of anti-tumor therapy for advanced PC by interventional EUS to the future through this epoch-making deployment in this Editorial.

Since EUS techniques allow access to pancreas in a comparatively minimally invasive fashion, it is a feasible procedure for the potential of a targeted delivery of therapeutic agents for PC by fine needle injection (FNI) through gastric or duodenal wall. Hence, many therapeutic trials for advanced PC by EUS guided-FNI (EUS-FNI) with a curative intent have been conducted so far. EUS-FNI involves direct intra-tumoral delivery of anti-tumor agents under EUS guidance for local control of tumor growth in patients with unresectable PC. As opposed to systemic administration, direct treatment is able to effect the targeted lesion of cancer without many normal lesions. Therefore, the EUS-FNI technique offers theoretic potential to deliver high dose concentration while minimizing systemic side effects. In addition, immune-modulating cells such as mixed lymphocyte and dendritic cells (DCs) can also be injected into PC as a potential anti-tumor therapy. However these results were not fulfilled the expected level as well as conventional treatments for advanced PC.

Chang *et al.*^[1] RFA conducted a phase I trial in which 8 patients with advanced PC were given intra-tumoral injections of activated allogenic mixed lymphocyte culture (cytoimplant) guided by EUS. In this report, no patient had treatment-related pancreatitis in the

procedures. However, the trial was suspended and final results have not been published. Irisawa *et al.*^[2] reported a pilot study about EUS-FNI of immature DCs into advanced PC. In 7 patients with unresectable PC who previously failed a chemotherapeutic agent, gemcitabine. DCs are potent antigen-presenting cells which have ability to initiate CD4⁺ helper and CD8⁺ cytotoxic T lymphocytes (CTLs)-mediated anti-tumor immune responses^[3]. In the report, injected immature DCs may intake apoptotic/necrotic pancreatic tumor cells and present tumor-associated antigenic peptides into MHC class I and II molecules on DCs, resulted in induction of antigen-specific CTLs. There were 3 partial responses (PR), 2 patients with stable disease (SD). Median survival was 9.9 mo without complication associated with EUS-FNI procedure. The results have not been achieved satisfactory level, however it is hopeful to publish the final results about the project. Apart from that, a combination therapy of chemotherapy (gemcitabine) with immunotherapy (OK-432-stimulated mature DCs) using EUS-FNI, followed by intravenous infusion of lymphokine-activated killer cells stimulated with anti-CD3 monoclonal antibody has reported^[4]. In this report, 5 patients with inoperable locally advanced PC had been treated. No serious treatment-related adverse events were observed during the study period. One patient had PR and 2 had long-SD more than 6 mo in this regimen. Demonstrating in many more number of patients with locally advanced PC will be desired.

In locally tumors, induction of tumor necrosis factor- α (TNF- α), which is a pro-inflammatory cytokine can induce tumor necrosis and shrinkage. A phase I clinical trial using TNFerade *via* EUS-FNI in combination with radiation for patients with advanced PC therapy has been reported^[5]. TNFerade is a replication-deficient adenovirus vector carrying the human TNF- α gene regulated by a radiation-inducible promoter (Egr-1). Intra-tumoral TNFerade with radiation has been shown to be safe in a phase I clinical trial of 30 patients with PC^[5]. In addition, a phase I / II trial was conducted for 50 patients with advanced PC, using TNFerade in combination with chemoradiation therapy. In the study, TNFerade was delivered by EUS guidance for 27 patients without severe procedure-related complications^[6]. Over a 5-wk treatment period, 1 patient had complete response, 3 had PR, and 12 patients had SD. The results showed a trend toward improved overall survival, however, it was not statistically significant. Moreover, the strategy is only suitable for patients with locally advanced PC. Although the clinical results suggest that TNF- α may be a useful candidate for locally advanced PC therapy, clinical benefits remain unknown. Subsequently, ONYX-015, an oncolytic attenuated adenovirus that preferentially replicates in malignant cells, leading to cell death had been introduced into PC^[7]. Hecht *et al.*^[8] completed a phase I / II trial of EUS FNI-guided intra-tumoral delivery of ONYX-015 combined with gemcitabine in 21 patients with advanced PC. Four patients developed comparatively severe complications, such as sepsis

and duodenal perforations which were attributed to the EUS procedures, in spite of no convincing efficacy of ONYX-015 was found. The median survival was 7.5 mo that has no significant difference with the conventional therapies.

Otherwise, EUS injectable anti-tumor agents, there are EUS-guided coagulative therapies. Radiofrequency ablation (RFA) therapy guided by EUS for advanced PC has not been actually clinical trial, because of the poorly accessible PC, in spite of the feasibility and effectiveness was confirmed in a porcine model^[9]. Indeed, RFA provides localized tissue ablation within 1 cm zone from the FNI needle catheter. Another ablative technique is photodynamic therapy (PDT), which is more selective than RFA. The safety and efficacy of PDT guided by EUS for advanced PC was also demonstrated in a porcine model^[10]. EUS-guided low-dose PDT may be safe and feasible for advanced PC, without no significant procedure-related complications. Moreover, brachytherapy using iodine-125 or palladium-103 has been successfully placed directly into tumors for the treatment of patients with PC. Pilot studies by Sun *et al.*^[11] in 15 patients and by Jin *et al.*^[12] in 25 patients with unresectable PC showed the safety and feasibility of EUS-guided brachytherapy. However, it may be needed to solve the mechanical difficulties of inserting solid seeds for contributing and disseminating worldwide.

Conceivable causes of the limited therapeutic effects by EUS-FNI for advanced PC are wide varieties. Primarily, advanced PC has extremely aggressive nature originally and increases momentarily. As the other conventional treatments, it is uneasy to overwhelm the progression of advanced PC. Secondly, many factors, such as genetic alterations, cellular dynamics and influences of intracellular or microenvironmental stress are intricately entangled in the development of PC. In existing state, it has never demonstrated the clinical effect by one kind of drug or tool alone for advanced PC. Thirdly, advanced PC has a feature of stubborn object because of the high density of fibrosis due to intense parenchymal inflammation. So that, it is incapable of piercing into PC without difficulty and penetrating injected solution adequately inside tumor in many cases. Lastly, even if the efficacy of injected solution is crucial, it is briefly uncontrollable the metastasis, invasion and angiogenesis of the PC, because EUS-FNI is only regional treatment. It may probably be needed to combine with some other systematic treatments for advanced PC in actual clinical application.

Currently, chemotherapy is an accredited, standard treatment for unresectable, advanced PC. According to the previous reports, it is obvious that interventional EUS is a well-established, helpful and low-risky procedure in general. The problems of interventional EUS as the decisive treatments for advanced PC that we must overcome are not the endoscopic procedures but how the therapeutic agents are delivered accurately and what are inserted directly inside the tumor. As the additional treatments of the conventional therapy

for advanced PC, many therapeutic strategies, such as immunotherapies, molecular biological therapies, physiochemical therapies, radioactive therapies, using siRNA, using autophagy have been developing in recent years. Moreover, the efficacy of the other potential therapeutic targets for PC using EUS-FNI, for example, intra-tumoral chemotherapeutic agents (paclitaxel, irinotecan), several ablative energies (RFA and cryothermal treatment, neodymium-doped yttrium aluminum garnet laser, high-intensity focused ultrasound), *etc.*, has already been showed in animal models^[13-17].

In conclusion, delivering these promising treatments reliably inside tumor, interventional EUS may probably be indispensable existence for the treatment of locally advanced PC in near future.

REFERENCES

- 1 **Chang KJ**, Nguyen PT, Thompson JA, Kurosaki TT, Casey LR, Leung EC, Granger GA. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. *Cancer* 2000; **88**: 1325-1335 [PMID: 10717613]
- 2 **Irisawa A**, Takagi T, Kanazawa M, Ogata T, Sato Y, Takenoshita S, Ohto H, Ohira H. Endoscopic ultrasound-guided fine-needle injection of immature dendritic cells into advanced pancreatic cancer refractory to gemcitabine: a pilot study. *Pancreas* 2007; **35**: 189-190 [PMID: 17632329 DOI: 10.1055/s-2007-995476]
- 3 **Steinman RM**. The dendritic cell system and its role in immunogenicity. *Annu Rev Immunol* 1991; **9**: 271-296 [PMID: 1910679 DOI: 10.1146/annurev.iy.09.040191.001415]
- 4 **Hirooka Y**, Itoh A, Kawashima H, Hara K, Nonogaki K, Kasugai T, Ohno E, Ishikawa T, Matsubara H, Ishigami M, Katano Y, Ohmiya N, Niwa Y, Yamamoto K, Kaneko T, Nieda M, Yokokawa K, Goto H. A combination therapy of gemcitabine with immunotherapy for patients with inoperable locally advanced pancreatic cancer. *Pancreas* 2009; **38**: e69-e74 [PMID: 19276867 DOI: 10.1097/mpa.0b013e318197a9e3]
- 5 **Senzer N**, Mani S, Rosemurgy A, Nemunaitis J, Cunningham C, Guha C, Bayol N, Gillen M, Chu K, Rasmussen C, Rasmussen H, Kufe D, Weichselbaum R, Hanna N. TNFerade biologic, an adenovector with a radiation-inducible promoter, carrying the human tumor necrosis factor alpha gene: a phase I study in patients with solid tumors. *J Clin Oncol* 2004; **22**: 592-601 [PMID: 14726502 DOI: 10.1200/JCO.2004.01.227]
- 6 **Hecht JR**, Farrell JJ, Senzer N, Nemunaitis J, Rosemurgy A, Chung T, Hanna N, Chang KJ, Javle M, Posner M, Waxman I, Reid A, Erickson R, Canto M, Chak A, Blatner G, Kovacevic M, Thornton M. EUS or percutaneously guided intratumoral TNFerade biologic with 5-fluorouracil and radiotherapy for first-line treatment of locally advanced pancreatic cancer: a phase I/II study. *Gastrointest Endosc* 2012; **75**: 332-338 [PMID: 22248601 DOI: 10.1016/j.gie.2011.10.007]
- 7 **Ries SJ**. Elucidation of the molecular mechanism underlying tumor-selective replication of the oncolytic adenovirus mutant ONYX-015. *Future Oncol* 2005; **1**: 763-766 [PMID: 16556054 DOI: 10.2217/14796694.1.6.763]
- 8 **Hecht JR**, Bedford R, Abbruzzese JL, Lahoti S, Reid TR, Soetikno RM, Kirn DH, Freeman SM. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. *Clin Cancer Res* 2003; **9**: 555-561 [PMID: 12576418]
- 9 **Goldberg SN**, Mallery S, Gazelle GS, Brugge WR. EUS-guided radiofrequency ablation in the pancreas: results in a porcine model.

- Gastrointest Endosc* 1999; **50**: 392-401 [PMID: 10462663]
- 10 **Chan HH**, Nishioka NS, Mino M, Lauwers GY, Puricelli WP, Collier KN, Brugge WR. EUS-guided photodynamic therapy of the pancreas: a pilot study. *Gastrointest Endosc* 2004; **59**: 95-99 [PMID: 14722560 DOI: 10.1016/S0016-5107(03)02361-7]
 - 11 **Sun S**, Xu H, Xin J, Liu J, Guo Q, Li S. Endoscopic ultrasound-guided interstitial brachytherapy of unresectable pancreatic cancer: results of a pilot trial. *Endoscopy* 2006; **38**: 399-403 [PMID: 16680642 DOI: 10.1055/s-2006-925253]
 - 12 **Jin Z**, Du Y, Li Z, Jiang Y, Chen J, Liu Y. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. *Endoscopy* 2008; **40**: 314-320 [PMID: 18283622]
 - 13 **Matthes K**, Mino-Kenudson M, Sahani DV, Holalkere N, Fowers KD, Rathi R, Brugge WR. EUS-guided injection of paclitaxel (OncoGel) provides therapeutic drug concentrations in the porcine pancreas (with video). *Gastrointest Endosc* 2007; **65**: 448-453 [PMID: 17173909 DOI: 10.1016/j.gie.2006.06.030]
 - 14 **Karaca C**, Cizginer S, Konuk Y, Kambadakone A, Turner BG, Mino-Kenudson M, Sahani DV, Macfarlane C, Brugge W. Feasibility of EUS-guided injection of irinotecan-loaded microspheres into the swine pancreas. *Gastrointest Endosc* 2011; **73**: 603-606 [PMID: 21238959 DOI: 10.1016/j.gie.2010.11.003]
 - 15 **Carrara S**, Arcidiacono PG, Albarello L, Addis A, Enderle MD, Boemo C, Campagnol M, Ambrosi A, Doglioni C, Testoni PA. Endoscopic ultrasound-guided application of a new hybrid cryotherm probe in porcine pancreas: a preliminary study. *Endoscopy* 2008; **40**: 321-326 [PMID: 18389449 DOI: 10.1055/s-2007-995595]
 - 16 **Di Matteo F**, Martino M, Rea R, Pandolfi M, Rabitti C, Masselli GM, Silvestri S, Pacella CM, Papini E, Panzera F, Valeri S, Coppola R, Costamagna G. EUS-guided Nd: YAG laser ablation of normal pancreatic tissue: a pilot study in a pig model. *Gastrointest Endosc* 2010; **72**: 358-363 [PMID: 20541187 DOI: 10.1016/j.gie.2010.02.027]
 - 17 **Hwang JH**, Wang YN, Warren C, Upton MP, Starr F, Zhou Y, Mitchell SB. Preclinical in vivo evaluation of an extracorporeal HIFU device for ablation of pancreatic tumors. *Ultrasound Med Biol* 2009; **35**: 967-975 [PMID: 19201519 DOI: 10.1016/j.ultrasmedbio.2008.12.006]

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