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Invited Review Article

Endoscopic stent placement combined with tumor ablation therapy

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A B S T R A C T

Palliative therapy of advanced pancreatobiliary cancers is focused primarily on biliary stenting in most patients. However, biliary stent occlusion or dysfunction is a main concern. Several types of stents are bleed designed and studied to improve stent function, but with limited success. Local ablative therapy, such as photodynamic therapy (PDT) and radiofrequency ablation (RFA) in combination with biliary stenting is a paradigm shift in the management of advanced pancreatobiliary malignancies. The current review analyzes the data on the role of combining either PDT or RFA with biliary stenting in inoperable pancreatobiliary malignancies.

Keywords: endoscopic stenting, pancreatobiliary cancers, photodynamic therapy, radiofrequency ablation

Introduction

The management of pancreatobiliary cancers remains a formidable challenge.[1] Surgery, if feasible, is the mainstay of treatment. However, the majority of patients present in an advanced stage of the disease, when only palliative therapy is feasible.[2,3] In patients with unresectable disease, the main objective of palliative therapy is relief of biliary obstruction through endoscopic or radiological techniques, which include placement of plastic biliary stents, uncovered or covered self-expandable metallic stents (SEMS), or percutaneous transhepatic biliary drainage.[4,5] These techniques have limited success, primarily due to stent occlusion or dysfunction. Two endoscopic modalities, photodynamic therapy (PDT) and radiofrequency ablation (RFA), have been used recently as palliative therapy, especially to improve stent patency.[6] The main objective of this review is to discuss the role of PDT or RFA in combination with biliary stenting as palliative therapy for unresectable pancreatobiliary cancers.

Photodynamic therapy

PDT is a well-established therapeutic modality in oncology. It involves administration of a nontoxic photosensitizer that is preferentially retained by neoplastic tissue, which in turn, on activation by illuminating light of specific wavelength, causes ischemic necrosis of tumors.[7] In an animal study, PDT was shown to reduce xenografted human cholangiocarcinoma tumor volume by more than 50%.[8] These results generated further interest in PDT. Few uncontrolled human studies in unresectable cholangiocarcinoma were carried out in which PDT was combined with biliary stenting.[9–12] The results showed improvement in cholestasis and survival with few complications. Ortner et al[13] published a first randomized prospective study comparing PDT in addition to biliary stenting with stenting alone. The results of this study were so impressive in favor of PDT with stenting, the study was terminated prematurely. However, this study has a major limitation because it included the majority of those patients in whom technically successful biliary stenting did not result in successful biliary drainage. Subsequently, Kahaleh et al[14] compared efficacy of PDT with biliary stenting with biliary stenting alone in patients with unresectable cholangiocarcinoma. Their results were similar (median survival 16.2 months vs. 7.4 months, $P < 0.04$) to those of Ortner et al,[13] in which significant median survival was observed after PDT (16.4 months vs. 3.3 months, $P < 0.0001$). However, patients in this study were different from those in the study of Ortner et al,[13] because all patients who underwent both successful or unsuccessful biliary drainage were included.

PDT has also been used as ablative therapy in inoperable pancreatic ductal adenocarcinoma. In a previous study of 16 patients with inoperable pancreatic carcinoma, substantial tumor necrosis was shown in all patients.[15] Median survival after PDT was 9.5 months. Seven of 16 patients (44%) were alive 1 year after PDT. Significant gastrointestinal bleeding from the gastroduodenal artery developed in two patients and was managed endoscopically.

Tumors of the head of the pancreas commonly cause distal biliary obstruction, which is managed by endoscopic biliary stenting using either plastic or SEMS in most cases. The patency of SEMS is a major challenge. Local ablative techniques such as PDT have

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been used to prolong stent patency or to unblock SEMS *in situ* with promising results. However, the results are still conflicting.

Radiofrequency ablation

RFA is an effective local ablative therapy that has been used extensively in many solid organ malignancies, especially in hepatocellular carcinoma. It works by emitting heat energy via a bipolar probe by using high-frequency alternating current, which in turn causes localized tissue necrosis. Previous studies using percutaneous and intraoperative RFA in unresectable cholangiocarcinoma and pancreatic cancer have shown impressive results and significant survival advantage over both chemotherapy and supportive care.[16] Recently, there is a growing interest in the role of RFA in palliation of pancreatobiliary cancers with the advent of endoscopic RFA catheters. There are two types of endobiliary RFA probes currently available; Habib Endo HPB (EMcision, London, UK) and Endobilary RFA catheter (Starmed, Seoul, Korea). Both are wire–guided, bipolar probes that can be passed through the working channel of a therapeutic duodenoscope.

Steel et al[17] published their experience of treating endobiliary RFA in 22 patients with malignant biliary obstruction (16 pancreatic patients and 6 cholangiocarcinoma patients). Deployment of the RFA catheter was successful in 21 patients. Biliary SEMS were placed in all patients after RFA. One patient failed to demonstrate successful biliary drainage after SEMS placement. All other patients maintained stent patency at 30 days. At 90 days follow up, stent occlusion developed in three patients and one more patient died. Since then, few other series have demonstrated the safety and efficacy of endobiliary RFA. Our own experience of endobiliary RFA in inoperable pancreatobiliary tumors has been promising.[18] We performed cholangioscopic evaluation of bile ducts before and after endobiliary RFA in patients with inoperable cholangiocarcinoma (Figs. 1 and 2). Significant resolution of biliary stricture occured.

The first application of RFA in an animal pancreas was reported in 1999 and was found to be safe.[19] However, the results of early clinical applications of RFA in a human pancreas were disappointing and were associated with high morbidity (up to 40%) and mortality (up to 25%).[20–25] Most of the complications arose as a result of inadvertent injury to adjacent structures. Subsequently, based on the thermal kinetics of RFA, the temperature settings of RFA were changed and reduced from 105°C to 90°C. This change significantly decreased RFA-related complications.[26]

Deployment of SEMS is the standard of care for patients with inoperable malignant biliary obstruction if life expectancy is >3 months. However, stent occlusion remains a problem that requires further interventions in >50% of patients. To maintain patency of SEMS, several therapeutic options have been studied, such as placements of another SEMS or plastic stent, PTD and RFA. Endoscopically applied RFA combined with biliary SEMS has been found to be well tolerated, safe, and appears to improve stent patency.[16,21,22] We would further emphasize that endobiliary RFA has been applied in the management of inoperable cholangiocarcinoma and pancreatic cancer.

Although RFA is a user-friendly technique, it has some limitations. Because RFA causes coagulative necrosis of tissue by direct contact, there is a possibility of incomplete contact of the lesion with the probe, which may affect the efficacy of the procedure. As demonstrated earlier, there is a linear relationship between energy delivered and depth of ablation. However, there is no standardized optimal dose of thermal energy and duration. Most of the studies have used RFA generator settings as recommended by the beneficiary. One interesting observation in these studies is improvement in survival.[26,27]

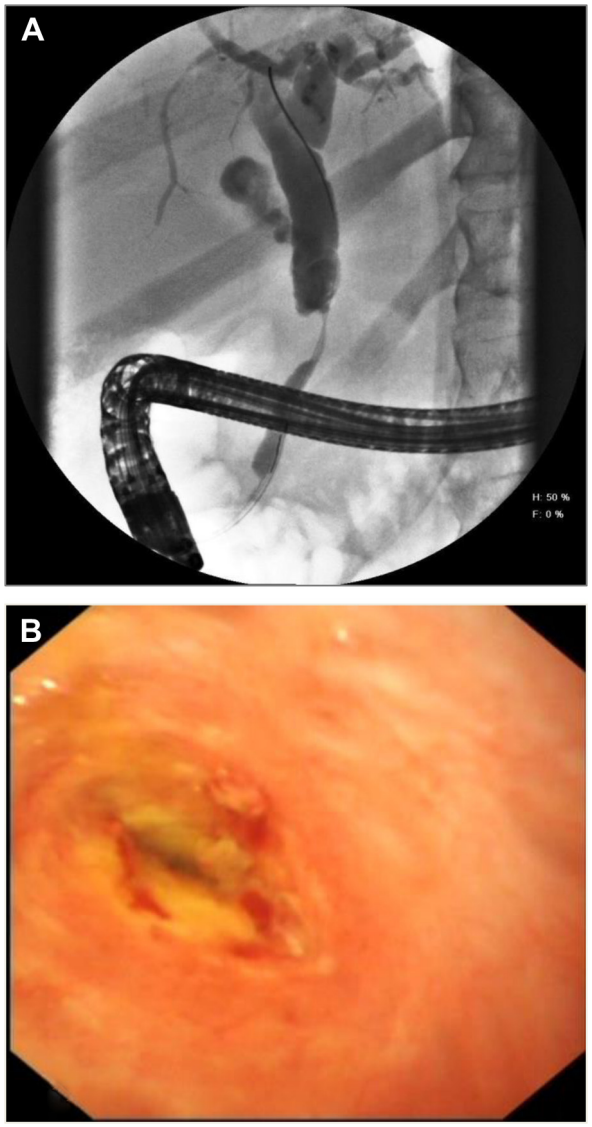

Fig. 1. Before radiofrequency ablation (A) Cholangiogram shows biliary stricture. (B) Cholangioscopic image also shows biliary stricture.

This observation needs further validation. To understand the mechanism and effect of RFA as ablative therapy, one must look beyond local thermal injury. In this regard, the role of proinflammatory cytokines and immune modulation needs to be studied further. We would also like to emphasize that there is a need to generate more data.

PDT versus RFA

Both PDT and RFA have been used as ablative therapy with and without stent placement. Both modalities have advantages and limitations. PDT has been used more extensively and showed significant improvement in survival and relief from cholestasis. However, the high cost and photosensitivity are major limitations of PDT. By contract endobiliary RFA is evolving and many studies are underway as the more data are needed. The major advantages of RFA are its relatively low cost and user-friendly technique. In a recent study, Strand et al[27] compared overall survival in 48 patients with unresectable cholangiocarcinoma who underwent palliative endoscopic retrograde cholangiopancreatography-directed RFA (16 patients) versus PDT (32 patients).[27] Overall, survival of patients who underwent RFA was similar to that of those who underwent