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Endoscopic intraductal radiofrequency ablation for extrahepatic cholangiocarcinoma: An update (2023)

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Abstract

Recently, endoscopic intraductal radiofrequency ablation (ID-RFA) has attracted attention as a local treatment method for malignant biliary obstruction (MBO). ID-RFA causes coagulative necrosis of the tumor tissue in the stricture and induces exfoliation. Its effects are expected to extend the patency period of biliary stents and prolong the survival period. Evidence for extrahepatic cholangiocarcinoma (eCCA) is gradually accumulating, and some reports show significant therapeutic effects in eCCA patients without distant metastasis. However, it is still far from an established treatment technique, and many unsolved problems remain. Therefore, when performing ID-RFA in clinical practice, it is necessary to understand and grasp the current evidence well and to operate appropriately for the true benefit of the patients. This paper reviews the current status, issues, and prospects of endoscopic ID-RFA for MBO, especially for eCCA.

INTRODUCTION

Biliary drainage is an indispensable therapeutic technique for treating obstructive jaundice and cholangitis associated with malignant biliary obstruction (MBO). The endoscopic placement of a biliary stent was introduced in the 1980s[1]; owing to its minimal invasiveness and usefulness, it is now the procedure of choice in most cases of

MBO. Although there are various types of stents, metal stents (MS) are recommended for unresectable cases because they have a longer patency period than plastic stents (PS)[2]. However, progress in antitumor therapy has resulted in extended survival period of malignant disease with MBO[3,4], and stent occlusion occurs in a relatively large number of cases even when MS is indwelled. Therefore, extending the stent's patency period is required, including changing the drainage strategy.

Against this background, intraductal radiofrequency ablation (ID-RFA) has emerged as a novel local treatment for MBO[5,6]. ID-RFA was introduced to prolong the patency of the stents. Besides, it has been suggested that it is effective in prolonging survival for extrahepatic cholangiocarcinoma (eCCA). Since the prognosis of eCCA is poor and numerous patients are unresectable at the time of diagnosis, ID-RFA has attracted huge attention and has high expectations as a feasible alternative. However, it is difficult to say that ID-RFA has been established because many unsolved problems remain. To effectively benefit patients, ID-RFA in clinical practice requires a thorough understanding of the available evidence and proper operation.

In this paper, we review the current status, issues, and prospects of endoscopic ID-RFA for MBO, particularly for eCCA.

EFFECT OF ID-RFA ON PROLONGING SURVIVAL FOR eCCA

It is considered that ID-RFA can extend the survival period by reducing the tumor burden, a secondary effect by prolonging the patency of the stent, and antitumor immunity[7,8]. Presently, five randomized controlled trials (RCTs)[9-13] of endoscopic ID-RFA have been reported (Table 1). Yang *et al*[9] and Gao *et al*[11] focus on only eCCA patients, while others involve patients with various diseases. The three RCTs with various etiology did not show a survival benefit of ID-RFA, while Yang *et al*[9] showed that the overall mean survival time was significantly longer in the ID-RFA with stent group (13.2 ± 0.6 *vs* 8.3 ± 0.5 mo; $P < 0.001$) and Gao *et al*[11] reported that the median overall survival was significantly higher in the patients receiving ID-RFA (14.3 *vs* 9.2 mo; hazard ratio, 0.488; 95% confidence interval, 0.351–0.678; $P < 0.001$). However,

caution in interpreting these results is that both studies by Yang *et al*[9] and Gao *et al*[11] included a mixture of locally advanced and distant metastatic diseases, which were not investigated separately. Although there is hope for the abscopal effect, it is questionable whether ID-RFA, which only ablate the bile duct and its surroundings, has the same effect in patients with a distant metastatic lesion that are directly related to life prognosis and those with only locally advanced disease. Xia *et al*[14] reported a retrospective study with many cases of MBO because of various primary diseases and underwent ID-RFA, and stated that the effect of prolonged survival was shown only in eCCA without distant metastasis.

In summarizing the results of the study above, it is said that the effect of ID-RFA on prolonging the survival period for eCCA can be expected; however, that effect may be limited to locally advanced cases. Therefore, in the future, it will be necessary to further examine the relationship between each disease stage and the effectiveness of ID-RFA, especially focusing on the presence or absence of distant metastasis.

COMBINATION OF ID-RFA AND CHEMOTHERAPY FOR eCCA

Chemotherapy is the current standard treatment for unresectable eCCA[15]. However, the previous RCT by Yang *et al*[9] excluded patients who underwent chemotherapy, and the study by Gao *et al*[11] included only a minimal number of patients who underwent chemotherapy. Therefore, when performing ID-RFA in clinical practice, it is necessary to grasp another evidence of ID-RFA when combined with chemotherapy.

There are three reports regarding the combination of chemotherapy and ID-RFA for eCCA[16-18] (Table 2). First, Yang *et al*[16] reported that the median overall survival was longer in patients who underwent ID-RFA and S-1 chemotherapy than in those who underwent only ID-RFA (16.0 *vs* 11.0 mo; $P < 0.001$), showing the additional effect of S-1 chemotherapy in patients who underwent ID-RFA. However, it noted that distant metastatic cases were excluded from this study. Second, Gonzalez-Carmona *et al*[17] conducted a retrospective study on the additional effect of ID-RFA on patients undergoing gemcitabine-based chemotherapy. They showed significantly longer

median overall survival in patients with combined ID-RFA and chemotherapy compared to those with only chemotherapy (17.3 *vs* 8.6 mo, P = 0.004). On subgroup analysis of this study, longer median overall survival with the combination of ID-RFA and chemotherapy was maintained in patients with the non-metastatic disease (20.9 *vs* 12.4 mo, P = 0.043), whereas it disappeared in patients with metastatic disease (15.0 *vs* 8.6 mo, P = 0.116). Finally, Inoue *et al*[18] compared patients who underwent ID-RFA with gemcitabine and cisplatin chemotherapy and those with only gemcitabine and cisplatin chemotherapy. The median overall survival was significantly higher in the patients with ID-RFA and chemotherapy (17.1 *vs* 11.3 mo, P = 0.017), indicating an additional effect of ID-RFA in patients treated with gemcitabine and cisplatin. However, like the results of the study by Gonzalez-Carmona *et al*[17], subgroup analysis showed a significant difference in median overall survival in patients without distant metastases (23.1 *vs* 16.6 mo, P = 0.032), while no significant difference in patients with distant metastases (11.4 *vs* 8.5 mo, P = 0.180).

These results are similar to those reported by Xia *et al*[14]. The effect of ID-RFA, a local treatment, may be limited to locally advanced cases (no distant metastases). Systemic effects, including induction of antitumor immunity, need to be investigated in more detail, the including the mechanism and evidence from basic research.

EFFECT OF ID-RFA ON PROLONGING STENT PATENCY IN eCCA

In the two currently available RCT for eCCA, PS was used. Yang *et al*[9] showed that the mean stent patency was significantly longer in patients combined with ID-RFA (6.8 *vs* 3.4 mo, P = 0.02). In contrast, Gao *et al*[11] found that the median stent patency was insignificant with or without ID-RFA (3.7 *vs* 4.1, P = 0.674). However, in Yang *et al*'s study, stent replacement was performed every 3 mo, and interpretation is difficult because it was not a pure evaluation of stent patency[9]. The other RCTs, in which patients were not limited to eCCA, used uncovered MS[10,12,13]. They all showed no significant differences in stent patency with or without ID-RFA.

These results suggest that there is currently no strong evidence to support the effectiveness of endoscopic ID-RFA in prolonging stent patency. However, numerous studies, including prospective, retrospective, and percutaneous approaches, have shown that ID-RFA prolongs stent patency, especially when combined with uncovered MS[5,6,19-24]. Therefore, it may be considered promising that ID-RFA prolongs stent patency, but it is not easy to judge its usefulness because there is not enough evidence. In the future, it will be necessary to determine the usefulness of ID-RFA in further studies by strictly standardizing the target disease, the site of stricture, the type of stent to be used, the placement method, and the approach method.

FUTURE PROSPECTS OF ENDOSCOPIC ID-RFA

As previously indicated, a number of reports of ID-RFA in recent years and evidence has accumulated regarding its therapeutic efficacy, especially for eCCA without distant metastasis. However, while robust evidence is lacking, there are still many unresolved issues, such as differences in tumor localization between the hepatic hilum and distal bile duct, the number of ablation applications performed, and so on. Therefore, it is necessary to conduct well-designed clinical studies and further clarify the indications and situations in which ID-RFA is useful. Additionally, in treating hepatocellular carcinoma, it has been suggested that ablation induce systemic immune effects, so combined use with immunotherapy is expected to prolong further survival[25]. Since recent significant advances were made with immunotherapy in the first-line treatment of advanced CCA with the addition of durvalumab to cisplatin-gemcitabine chemotherapy showing a survival benefit[26,27], it is also expected to investigate the additional effect of combining with ID-RFA.

Another problem is that, sometimes, the currently available ID-RFA catheters cannot ablate sufficiently due to their structure[5,28], and it has been pointed out that the portion in contact with the electrode is ablated strongly, resulting in uneven and unstable ablation depth and area[29]. Additionally, it has been suggested that the entire lesion must appropriately ablate to improve stent patency and survival[12,28]. Therefore,

to firmly determine the effect of the use of ID-RFA and for the spread of ID-RFA, improvement of the device is essential; the development of a device that can obtain a stable ablation effect in any stricture lesion and appropriately control the ablation range is needed. Although it is still in the animal experiment stage, attempts have also been made to develop a balloon-based ID-RFA catheter that enables regular contact all around[30,31]. This balloon ID-RFA catheter provides a significantly more stable and appropriate ablation range than the conventional ID-RFA catheter[29]. In addition, a system that can perform ablation under real-time observation with cholangioscopy has also appeared[32]. Next-generation ID-RFA devices are expected to enter clinical trials soon, resulting in enhanced treatment outcomes and broader ID-RFA indications.

CONCLUSIONS

The current issues and prospects of endoscopic ID-RFA were reviewed, focusing on eCCA. ID-RFA can be a useful option as an intrabiliary local therapy, but there are still many unclear points. Although increasing reports suggest its usefulness, mainly for eCCA without distant metastasis, it is still far from being a standard treatment. Additionally, it should be recognized that the existing catheter could not always provide sufficient ablation in all cases. Therefore, in addition to accumulating further evidence, it is necessary to establish its usefulness, clarify its indication, and develop an innovative device that can perform appropriate ablation for all lesions.

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