REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Gallbladder Cryoablation: A Novel Option for High-Risk Patients with Gallbladder Disease

David McNiel, MD PhD, Charles Hennemeyer, MD, Greg Woodhead, MD PhD, Hugh McGregor, MD

Department of Medical Imaging, University of Arizona, Tucson.

ABSTRACT

Management of high-risk surgical patients with cholecystitis poses a significant clinical problem. These patients are often left with the options of permanent cholecystostomy tube drainage or high-risk surgery. Numerous attempts have been made over the past 4 decades to fulfill the need for a minimally invasive, definitive treatment option for such gallbladder disease. These attempts have largely focused on endoluminal ablation with a variety of sclerosants and have been unable to reliably achieve permanent gallbladder devitalization. The advent of modern percutaneous devices and techniques have provided further opportunity to develop minimally invasive treatment options for high-risk patients. Cryoablation, a thermal ablation modality that induces cell death through tissue freezing, has recently emerged as a promising potential option to treat gallbladder disease. Early studies have demonstrated good technical and clinical success, and a prospective trial is ongoing. This manuscript explains the clinical need for gallbladder cryoablation, briefly revisits historical minimally invasive treatments, describes cryoablation technology and why it is well suited for the gallbladder, and reviews the preclinical and clinical studies evaluating the safety and efficacy of gallbladder cryoablation.

 • *The American Journal of Medicine (2021) 134:326–331*

KEYWORDS: Cholecystitis; Cryoablation; Gallbladder; High-risk

INTRODUCTION

Twenty million patients in the United States suffer from gallbladder disease, with over 200,000 cholecystectomies performed annually.[1] The gold-standard treatment for cholecystitis is laparoscopic cholecystectomy. A subset of high-risk patients who are not surgical candidates may require gallbladder drainage.[2] Percutaneous cholecystostomy is the most common method of gallbladder drainage, with over 7000 performed in the United States annually.[3] While effective in treating acute cholecystitis, cholecystostomy tube placement does not provide definitive management. Recurrent cholecystitis rates following cholecystostomy tube removal are as high as 46% in patients with gallstones.[4,5] Repeat episodes of acute cholecystitis result in significant morbidity and mortality in this high-risk population. Recently, advances in minimally invasive percutaneous interventions have provided a potential treatment option for high-risk patients. Gallbladder cryoablation has demonstrated promise in providing definitive management for these patients who would otherwise require long-term cholecystostomy tube drainage or high-risk surgery.[6,7] This review describes historical attempts at minimally invasive gallbladder treatment, the development of gallbladder cryoablation, and the most up-to-date clinical experience in patients.

HISTORICAL ATTEMPTS AT MINIMALLY INVASIVE TREATMENT FOR GALLBLADDER DISEASE

Multiple attempts have been made in the past to fulfill the need for a minimally invasive, definitive treatment option for high-risk patients with cholecystitis. Salomonowitz et al[8] first attempted luminal ablation of the gallbladder through a cholecystostomy tube in 1984, using a variety of

Funding: None.

Conflict of Interest: HM has a patent pending for a cryoablation devices and related methods. None of the other authors have identified a conflict of interest.

Authorship: All of the authors had access to and contributed to the writing of this manuscript.

Requests for reprints should be addressed to Hugh McGregor, MD, Department of Medical Imaging, University of Arizona, 1501 N. Campbell Avenue, Tucson, AZ 85724.

E-mail address: hughmcgregor@radiology.arizona.edu

0002-9343/
https://doi.org/10.1016/j.amjmed.2020.10.007

sclerosing agents in 36 rabbits. Histology at 2 weeks demonstrated promising transmural fibrosis with ethanol sclerosant. In 1988, Iaccarino et al[9] reported 2 cases of luminal ablation in humans with ethanol and cystic duct occlusion with bucrylate. One patient was followed for 14 months and had an uncomplicated course. The other died of unrelated causes. Becker et al[10] attempted luminal ablation with ethanol and sodium tetradecyl-sulfate and cystic duct occlusion with radiofrequency electrocoagulation, achieving complete mucosal ablation in 13 of 16 pigs. A follow-up human trial, published in 1990, demonstrated less promising results, with multiple ablation sessions required and persistent gallbladder lumens (likely indicating residual mucosa) in a high percentage of patients.[11] Aagaard et al[12] attempted luminal thermal ablation in 1994, with mixed results secondary to difficulties achieving even heat distribution. More recently, Lee et al[13] used n-butyl cyanoacrylate and coils to occlude the cystic duct and acetic acid for mucosal ablation in 4 canines. Complete mucosal ablation was not achieved, with remnant or regenerated mucosa identified in the gallbladder neck.

CLINICAL SIGNIFICANCE

- High-risk patients with cholecystitis may require percutaneous gallbladder drainage.
- Cholecystostomy tube drainage is not a definitive solution, with high recurrence rates after tube removal.
- Gallbladder cryoablation is a minimally invasive option for permanent gallbladder devitalization.
- Early studies demonstrated a technical success rate of 86% and 100% clinical success.

While endoluminal ablation through an existing cholecystostomy tube is an elegant solution and has demonstrated some promise in animal models, complete mucosal ablation in humans has not been reliably achieved. It has been postulated that mucosal regeneration occurs from mucosal deposits within Rokitansky-Aschoff sinuses, into which the ablative solution does not pass. Metaplasia from the underlying muscularis layer may also account for incomplete ablation.[14] Residual mucosa in communication with the biliary system puts the patient at risk for recurrent cholecystitis and, if the cystic duct is occluded, mucocele formation. In 1985, Bornman et al[14] described the subtotal cholecystectomy, a technique for partial surgical removal of the gallbladder in which safe dissection of the cystic duct was obviated by severe cholecystitis. This technique entails devitalizing the posterior wall of the gallbladder attached to the liver with electrocautery and ligating the cystic duct distally from within the gallbladder. The subtotal cholecystectomy has been applied in modern laparoscopic practice and demonstrates good results. Hubert et al described no postoperative biliary or intra-abdominal infectious complications in 39 patients followed for an average of 4.3 months.[15]

CRYOABLATION

Cryoablation is a thermal ablation technique that induces cell death by exposing tissue to low temperatures. Several underlying mechanisms for cryoablation injury have been described, including direct cell injury, vascular injury and ischemia, apoptosis, and immunomodulation. Direct cell injury occurs when intracellular water freezes and expands, resulting in disruption of the cell membrane. Vascular injury occurs via endothelial damage with subsequent microvascular occlusion and ischemic necrosis. Apoptosis has been observed at the outer edges of the ablation zone where cells are exposed to less extreme cold. Immunomodulation has been described in the setting of cancer, with several reports describing distant metastatic regression following cryoablation of a primary tumor (abscopal effect). An immunological etiology is likely, as numerous pro-inflammatory cytokines are released in high quantities following cryoablation.[16]

Modern cryoablation systems utilize the Joule-Thomson effect, which dictates that pressurized Argon gas cools on expansion. Pressurized Argon is passed through a metallic probe and allowed to expand in the tip of the probe, cooling the probe and any adjacent tissue (Figure 1A). Ice forms within tissue at a predictable rate and geometry and can be clearly visualized with computed tomography (CT), ultrasound, or magnetic resonance imaging (MRI) in real time during a procedure (Figure 1B). Ice within frozen tissue has several physical properties allowing for visualization on different imaging modalities, including lower density than surrounding tissue, aiding visualization on CT, increased echogenicity on ultrasound, and signal modulation with many MRI sequences. Visualization of the ice ball is achieved through intermittent intraprocedural imaging examination and can direct cryoprobe position and freezing times. This visualization allows for highly controllable ablation zones that are well suited for precise ablation in anatomic areas with adjacent sensitive structures. Additionally, tissue cooling has an anesthetic effect and cryoablation can be performed under conscious sedation rather than general anesthesia.[17] The performance of cryoablation requires the precise placement of probes within the target tissue under imaging guidance. Once the appropriate position of the probes is confirmed, a number of serially performed cycles of freezing and thawing are performed, each under periodic imaging evaluation to ensure that appropriate anatomic boundaries are maintained as the iceball expands. Following successful cryoablation, the body forms an "ablation cavity" within the space occupied by previously frozen tissue, which is resorbed by the body in a well-described sequence with eventual fibrosis of ablated tissue.[16]

Cryoablation has been successfully applied in oncologic settings, with reliable, complete tissue ablation achieved in several organs. For example, Georgiades and Rodriguez[18]

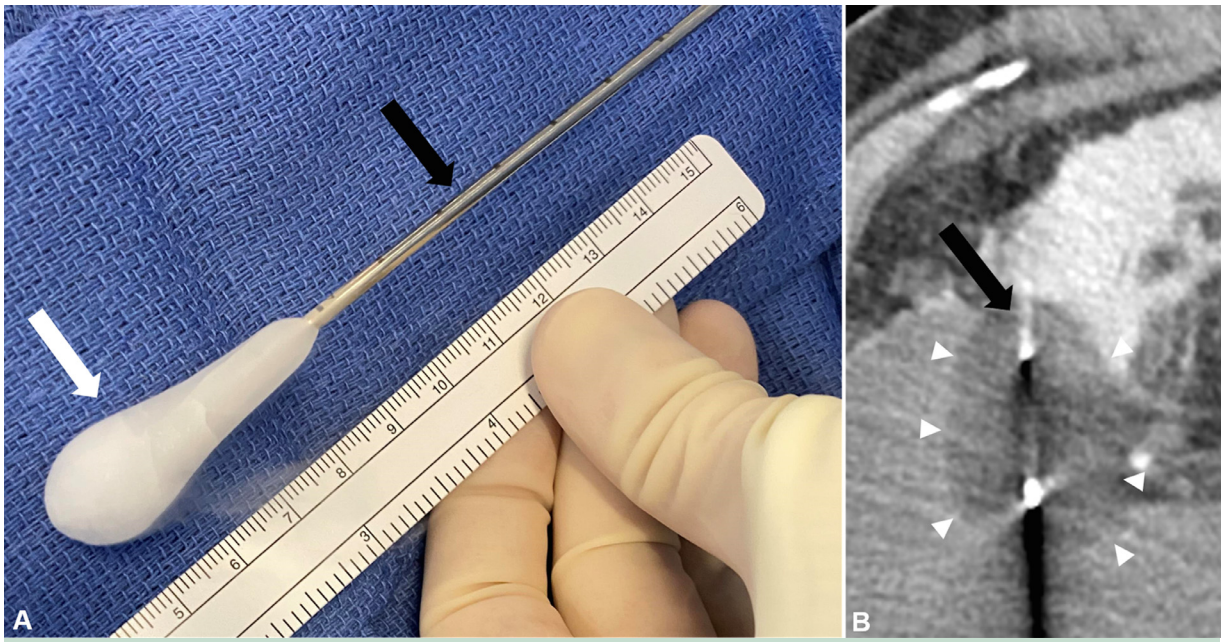

Figure 1 Photograph demonstrating **(A)** the metallic cryoprobe (black arrow) with an iceball (white arrow) forming around the tip. **(B)** Axial computed tomography image demonstrating the hyperattenuating cryoprobe (black arrow) with a hypoattenuating iceball (white arrowheads) forming during a liver ablation. Note the differential attenuation of the iceball and the adjacent liver, enabling intraprocedural monitoring of the ablation zone.

achieved a 5-year survival of 97.8% following cryoablation of biopsy-proven renal cell carcinomas with a median tumor size of 2.8 cm. Additional studies have demonstrated its efficacy in treating hepatocellular carcinoma and prostate adenocarcinoma.[19,20] Cryoablation is a reliable and robust method for inducing controlled tissue necrosis, and its characteristics are well suited for applications outside of oncology.

PRECLINICAL STUDIES

In 2016, McGregor et al published a series of pilot studies investigating gallbladder cryoablation in a porcine model utilizing standard techniques and off-the-shelf cryoprobes.[21,22] These studies demonstrated clinical, radiological, and histological evidence of permanent gallbladder devitalization following cryoablation. The technique employed in these experiments involved extensive hydrodissection around the gallbladder, a commonly used method to thermally isolate tissues and minimize damage to nontarget tissues by injection of fluid between tissue planes. During gallbladder ablation in these animal studies, the transverse colon and duodenum were at greatest risk due to their close anatomical apposition to the gallbladder. Three probes were advanced percutaneously into the gallbladder lumen and neck under CT and ultrasound guidance. Two cycles of freezing and thawing were performed, with periodic re-imaging during the procedure to ensure ablation of the entirety of the gallbladder with sufficient margins. In a series of survival experiments, the animals were sacrificed after 30-45 days, allowing for histologic and imaging follow-up.[22] Postablation imaging of these animals demonstrated findings consistent with gallbladder devitalization and cystic duct occlusion. Histologic analysis of the gallbladders demonstrated transmural gallbladder wall fibrosis without repopulation of normal gallbladder epithelial lining and involution of the gallbladder lumen.

CLINICAL STUDIES

Gallbladder cryoablation was first performed in a human in 2018.[6] A 71-year-old man with chronic obstructive pulmonary disease, obesity, ischemic cardiomyopathy, and cholecystitis underwent gallbladder cryoablation 24 days after cholecystostomy tube placement. The cholecystostomy tube was removed immediately after the procedure and the patient was discharged on postprocedure day 1. The patient is now over 2 years post procedure and has been asymptomatic since the cryoablation. MRI demonstrated complete involution of the gallbladder at 1 year (Figure 2). Recently, McGregor et al[7] expanded on this initial case and described their 1-year experience with gallbladder cryoablation in patients with chronic cholecystitis. An 86% technical success rate was achieved and symptoms resolved in all cryoablated patients after cholecystostomy tube removal. Gallbladder involution on imaging was noted in 5 of 6 patients, and cholescintigraphy demonstrated occlusion of the cystic duct in all patients. Two adverse events were reported. Of note, both adverse events occurred in patients with large gallstones. One patient was deemed technically

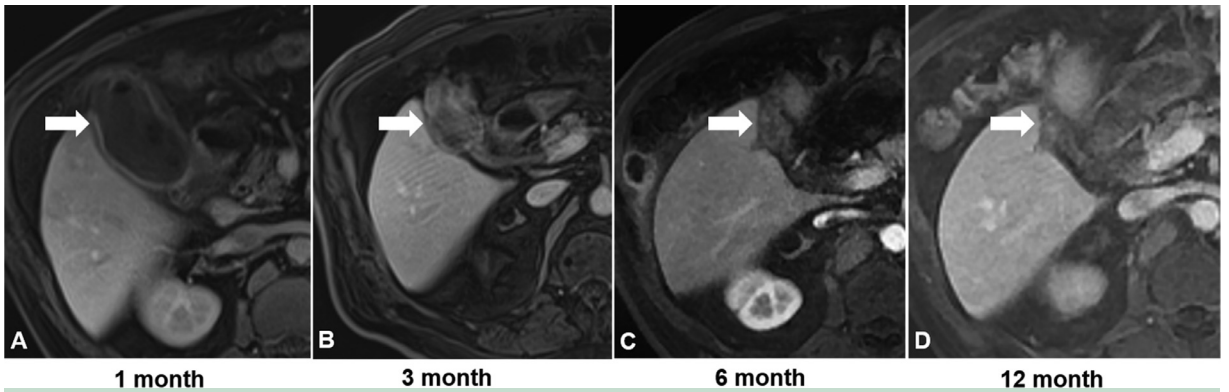

Figure 2 Axial, contrast-enhanced magnetic resonance images 1-12 months after gallbladder cryoablation demonstrating involution of the gallbladder (white arrow) over time.

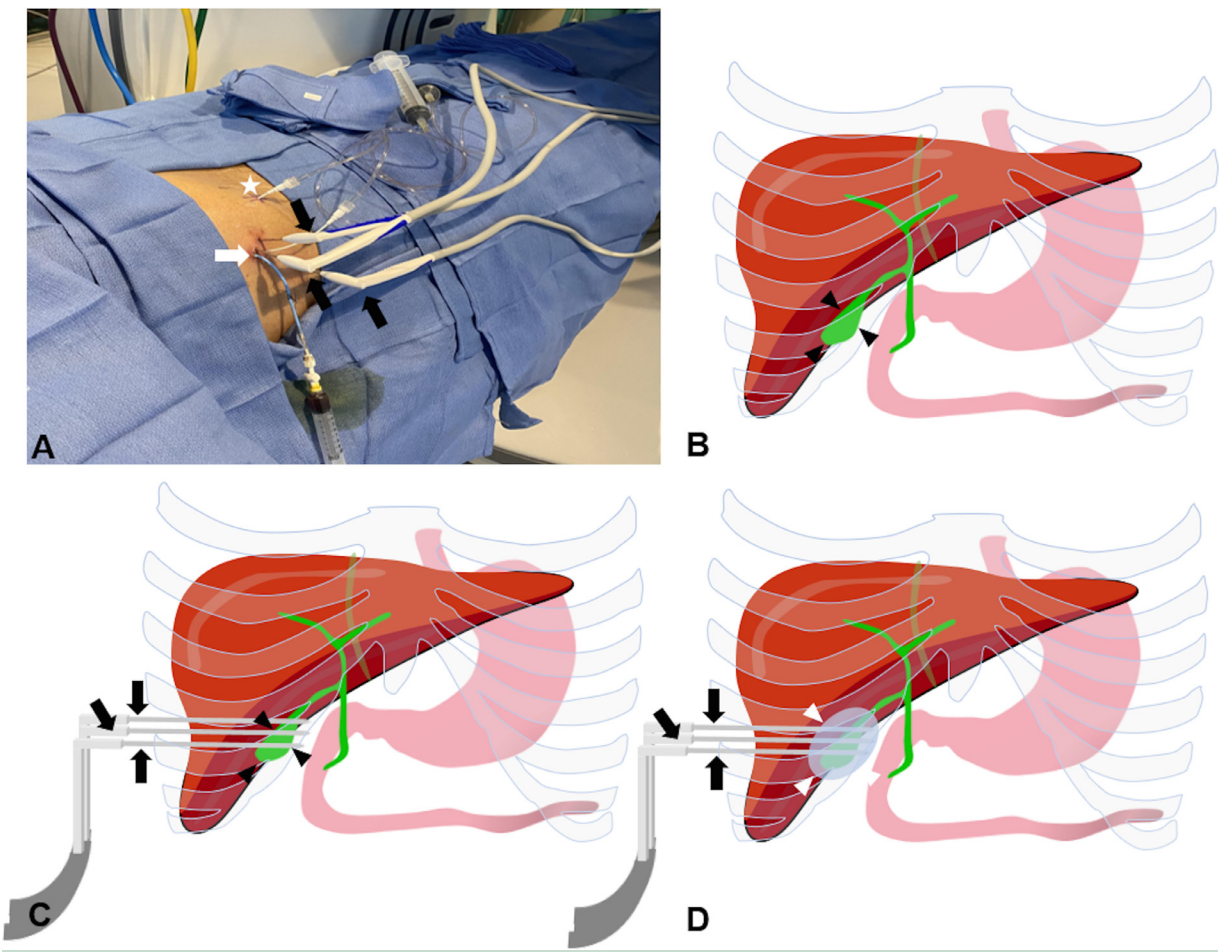

Figure 3 **(A)** Photograph and **(B-D)** illustrations depicting a gallbladder cryoablation. **(A)** Note the 3 cryoprobes (black arrows), the cholecystostomy tube (white arrow), and the catheter inserted for hydrodissection (star). The procedure is performed in the computed tomography (CT) suite. **(B)** The gallbladder (black arrowheads) is located on the underside of the liver and often has ribs directly overlying it. **(C)** Cryoprobes (black arrows) are inserted percutaneously in or surrounding the gallbladder. **(D)** After confirmation of probe positioning with CT, the freeze cycles commence, creating an iceball (white arrowheads) that surrounds the gallbladder. Intermittent intraprocedural CT scanning monitors the size of the iceball and helps avoid ablation of nearby structures.

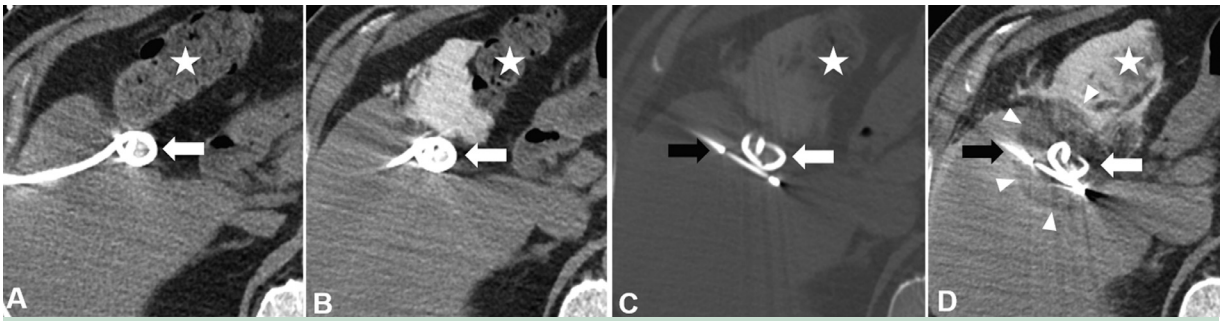

Figure 4 Axial computed tomography (CT) images demonstrating the procedural steps involved in a gallbladder cryoablation. **(A)** A cholecystostomy tube (white arrow) is placed. Note the proximity of the gallbladder (as demarcated by the cholecystostomy tube) to the colon (white star). **(B)** Saline mixed with iodinated contrast (black star) has been instilled through a catheter into the tissue plane separating the gallbladder (white arrow) and colon (white star). This hydrodissection provides adequate space around the gallbladder for safe cryoablation. **(C)** A cryoprobe (black arrow) is advanced percutaneously immediately adjacent to the gallbladder (white arrow) under CT guidance. **(D)** An image during a freeze cycle demonstrates the hypoattenuating iceball (white arrowheads) adjacent to the cryoprobe (black arrow) clearly encompassing the gallbladder (white arrow) and avoiding the colon (white star).

not feasible due to adhesions between the gallbladder fundus and transverse colon, which prevented sufficient hydrodissection and thermal isolation of the colon.

Performance of the procedure in human subjects involves 4 major steps: insertion of a cholecystostomy tube if not already present, hydrodissection, image-guided probe placement, and multiple freeze/thaw cycles (Figures 3 and 4). Preprocedural insertion of a cholecystostomy tube allows decompression of the gallbladder in the periprocedural period and is useful in reducing the volume of the gallbladder, thus decreasing the size of the iceball required to fully encompass the target. Subsequent hydrodissection is performed in order to physically distance and thermally isolate tissues that lie immediately adjacent to the gallbladder serosal surface (Figure 4). Following precise CT- and ultrasound-guided placement of multiple ablation probes into and in close proximity to the gallbladder and cystic duct, ablation is performed using sequential 10-minute freeze cycles (Figure 4). Freezing is continued until a 5-mm margin of frozen tissue is visualized beyond the gallbladder margin as confirmed by intraprocedural CT examination.

Toward further adoption of this technique in human subjects, a prospective clinical trial was initiated in 2019, with more than a dozen subjects having undergone the procedure at the time of this writing, with encouraging results.

CHALLENGES

Technical concerns remain about patients with dense adhesions between the gallbladder and a hollow viscus that may render thermal isolation of these structures impossible using current techniques. Additionally, patients with large gallstones may be at greater risk of complications based on the current clinical experience. Although all patients in the current published cohort who underwent gallbladder cryoablation had known cholelithiasis, both complications occurred in patients who had large-sized gallstones. While the reason for this remains unclear, 2 factors may be implicated: large gallstones serving as a bacterial nidus, and inflammatory cytokine release following bacteriolysis. The iceball created during cryoablation may not penetrate deep microscopic fissures within large gallstones, and surviving bacteria may potentially infect the ablated tissue bed. Additionally, large gallstones may harbor a larger burden of bacteria, producing a significant systemic inflammatory reaction after cryoablation due to the sudden lysis and systemic redistribution of bacterial components upon thawing.

FUTURE

Definitive management of cholecystitis in patients who are not surgical candidates remains a significant clinical need. While currently employed methods of treating gallbladder inflammation are effective in the short term, definitive management in the form of percutaneous gallbladder cryoablation may provide a viable solution in certain patient populations.

Toward broader applicability, investigating adjunct therapies to reduce gallstone burden is a logical next step. The utilization of gallstone retrieval or lithotripsy under cholecystoscopic guidance offers promise in this regard.[23] Regardless of the method's final incarnation in clinical use, gallbladder cryoablation has the possibility to provide a significant improvement in the quality and quantity of life for high-risk patients who are unable to tolerate cholecystectomy.

References

1. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. *Gastroenterology* 1999;117(3):632–9.
2. Yokoe M, Hata J, Takada T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). *J Hepatobiliary Pancreat Sci* 2018;25(1):41–54.

3. Duszak R Jr, Behrman SW. National trends in percutaneous cholecystostomy between 1994 and 2009: perspectives from Medicare provider claims. *J Am Coll Radiol.* 2012;9(7):474–9.
4. Ha JP, Tsui KK, Tang CN, Siu WT, Fung KH, Li MK. Cholecystectomy or not after percutaneous cholecystostomy for acute calculous cholecystitis in high-risk patients. *Hepatogastroenterology* 2008;55 (86-87):1497–502.
5. McKay A, Abulfaraj M, Lipschitz J. Short- and long-term outcomes following percutaneous cholecystostomy for acute cholecystitis in high-risk patients. *Surg Endosc* 2012;26(5):1343–51.
6. McGregor H, Woodhead G, Conrad M, et al. First in-human gallbladder cryoablation in a patient with acute calculous cholecystitis initially treated with a cholecystostomy tube. *J Vasc Interv Radiol* 2019;30 (8):1229–32.
7. McGregor H, Woodhead G, Patel M, et al. Gallbladder cryoablation for chronic cholecystitis in high-risk surgical patients: 1-year clinical experience with imaging follow-up. *J Vasc Interv Radiol* 2020;31 (5):801–7.
8. Salomonowitz E, Frick MP, Simmons RL, et al. Obliteration of the gallbladder without formal cholecystectomy. A feasibility study. *Arch Surg.* 1984;119(6):725–9.
9. Iaccarino V, Niola R, Porta E. Percutaneous cholecystectomy in the human: a technical note. *Cardiovasc Intervent Radiol* 1988;11(6):357–9.
10. Becker CD, Quenville NF, Burhenne HJ. Gallbladder ablation through radiologic intervention: an experimental alternative to cholecystectomy. *Radiology* 1989;171(1):235–40.
11. Becker CD, Fache JS, Malone DE, Stoller JL, Burhenne HJ. Ablation of the cystic duct and gallbladder: clinical observations. *Radiology* 1990;176(3):687–90.
12. Aagaard BD, Wetter LA, Montgomery CK, Gordon RL. Heat ablation of the normal gallbladder in pigs. *J Vasc Interv Radiol* 1994;5(2):331–9.
13. Lee JH, Won JH, Bae JI, Kim JH, Lee HS, Jung SM. Chemical ablation of the gallbladder with acetic acid. *J Vasc Interv Radiol* 2009;20 (11):1471–6.
14. Bornman PC, Terblanche J. Subtotal cholecystectomy: for the difficult gallbladder in portal hypertension and cholecystitis. *Surgery* 1985;98 (1):1–6.
15. Hubert C, Annet L, van Beers BE, Gigot JF. The "inside approach of the gallbladder" is an alternative to the classic Calot's triangle dissection for a safe operation in severe cholecystitis. *Surg Endosc* 2010;24 (10):2626–32.
16. Chu KF, Dupuy DE. Thermal ablation of tumours: biological mechanisms and advances in therapy. *Nat Rev Cancer* 2014;14 (3):199–208.
17. Erinjeri JP, Clark TW. Cryoablation: mechanism of action and devices. *J Vasc Interv Radiol* 2010;21(8 suppl):S187–91.
18. Georgiades CS, Rodriguez R. Efficacy and safety of percutaneous cryoablation for stage 1A/B renal cell carcinoma: results of a prospective, single-arm, 5-year study. *Cardiovasc Intervent Radiol* 2014;37(6): 1494–9.
19. Lee SM, Won JY, Lee DY, et al. Percutaneous cryoablation of small hepatocellular carcinomas using a 17-gauge ultrathin probe. *Clin Radiol* 2011;66(8):752–9.
20. Rodríguez SA, Arias Fúnez F, Bueno Bravo C, et al. Cryotherapy for primary treatment of prostate cancer: intermediate term results of a prospective study from a single institution. *Prostate Cancer* 2014; 2014:571576.
21. McGregor HC, Saeed M, Surman A, et al. Gallbladder cryoablation: proof of concept in a swine model for a percutaneous alternative to cholecystectomy. *Cardiovasc Intervent Radiol* 2016;39 (7):1031–5.
22. McGregor HCJ, Surman A, Fernandez A, et al. Pilot study of the safety and efficacy of gallbladder cryoablation in a porcine model: midterm results. *J Vasc Interv Radiol* 2018;29(3):340–4.
23. Stirrat J, Patel NR, Stella SF, Mafeld S, Ho CS, Shlomovitz E. Safety and efficacy of percutaneous gallstone extraction in high-risk patients: an alternative to operation or long-term drainage? *J Am Coll Surg.* 2020;7515(20) [S1072-7515(20)32379-6.