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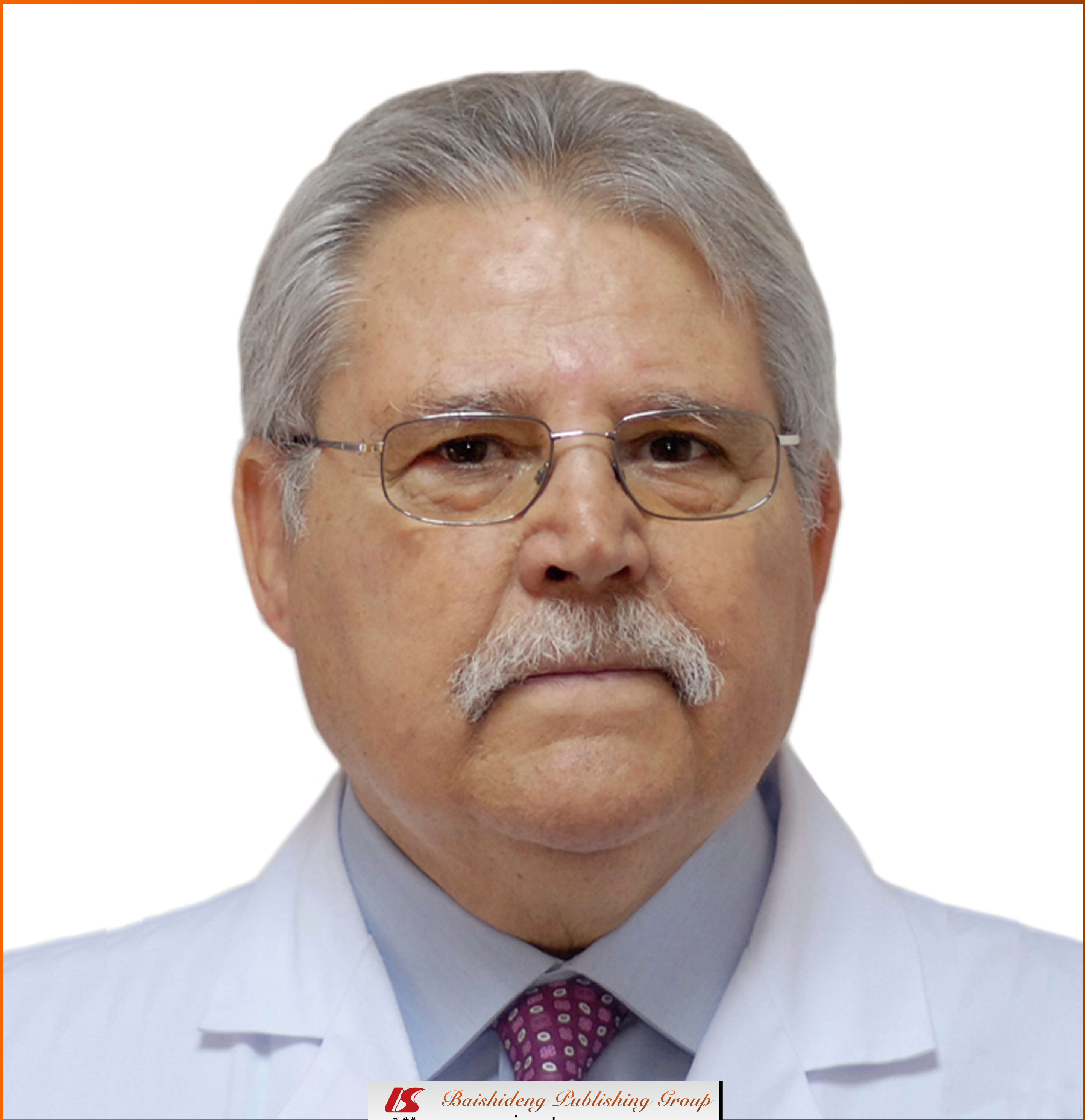

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EDITORIAL

Direct peroral cholangioscopy

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Abstract

Peroral cholangioscopy is an important tool for diagnosis and treatment of various biliary disorders. Peroral cholangioscopy can be performed by using a dedicated cholangioscope that is advanced through the accessory channel of a duodenoscope, or by direct insertion of a small-diameter endoscope into the bile duct. Direct peroral cholangioscopy refers to insertion of an ultraslim endoscope directly into the bile duct for visualization of the biliary mucosa and lumen. This approach provides a valuable and economic solution for diagnostic and therapeutic applications in the biliary tree. Compared to ductoscopy using a dedicated cholangioscope, the direct approach has several advantages and disadvantages. In this editorial, I discuss the advantages, disadvantages, and possible future developments pertaining to direct peroral cholangioscopy.

Key words: Cholangioscopy; Direct peroral cholangioscopy; Dedicated cholangioscopes

Core tip: Direct peroral cholangioscopy is a valuable and economic tool for diagnostic and therapeutic applications in the biliary tree. However, solutions are needed to make access to the biliary tree easier, and to improve the endoscope stability within the biliary tree for diagnostic and therapeutic maneuvers.

Parsi MA. Direct peroral cholangioscopy. *World J Gastrointest Endosc* 2014; 6(1): 1-5 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i1/1.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i1.1

METHODS OF PERORAL CHOLANGIOSCOPY

Peroral cholangioscopy has numerous applications in diagnosis and treatment of various biliary disorders[1]. Currently, peroral cholangioscopy can be performed by two different methods: (1) by using a dedicated cholangioscope and (2) by direct insertion of a small-diameter upper endoscope into the biliary tree (the direct method).

Peroral cholangioscopy using a dedicated cholangioscope

In this approach, a dedicated cholangioscope is advanced through the accessory channel of a duodenoscope and directed into the bile duct (Figure 1). A biliary sphincterotomy is usually necessary for advancement of the cholangioscope through the biliary sphincter. Although biliary cannulation can be achieved directly with the tip of the cholangioscope, most endoscopists prefer cannulation over a guidewire[2]. Once the scope is advanced to the target location, the guidewire is removed to enhance visualization and to permit use of the working channel. The duct is irrigated with sterile saline solution through the accessory channel of the cholangioscope for adequate visualization, followed by slow withdrawal of the scope, allowing systematic inspection of the ductal mucosa and lumen.

Direct peroral cholangioscopy

In direct peroral cholangioscopy, an ultraslim upper endoscope is inserted through the mouth and advanced to the duodenum. It is subsequently maneuvered across the biliary sphincter and into the bile duct for observation of the mucosa and the lumen of the bile duct (Figure 2). Maneuvering of the endoscope across the biliary sphincter requires presence of a sphincterotomy and in most cases performance of a balloon sphincteroplasty. Presence of a guidewire in the bile duct often allows a more proximal access, to the common hepatic duct. The guidewire is subsequently removed to better visualize the lumen and mucosa, to allow more freedom of movement at the tip of the endoscope and to make the accessory channel available for therapeutic measures if needed. The bile duct is irrigated with sterile saline solution through the accessory channel of the ultraslim endoscope followed by slow withdrawal of the endoscope allowing systematic inspection of the biliary tree. Sterile saline irrigation can be substituted with carbon dioxide (CO_2) insufflation. In a study involving 19 patients with suspected biliary disease, Ueki *et al*[3] reported superior image quality using CO_2 insufflation compared to saline irrigation. Another study involving 36 patients, however, reported that although the median time required to obtain a clear endoscopic image using CO_2 insufflation was significantly shorter than that required for saline irrigation, the quality of the endoscopic images obtained was similar in the majority of cases[4]. Air insufflation during direct cholangioscopy has been associated with serious adverse events and its use has been discouraged[5].

With the introduction of high-definition ultraslim upper endoscopes with narrow band imaging capability, direct peroral cholangioscopy has become more popular. The ultraslim upper endoscopes currently used for direct peroral cholangioscopy have an outer diameter of approximately 5 mm and an instrument channel with an inner diameter of approximately 2 mm[5].

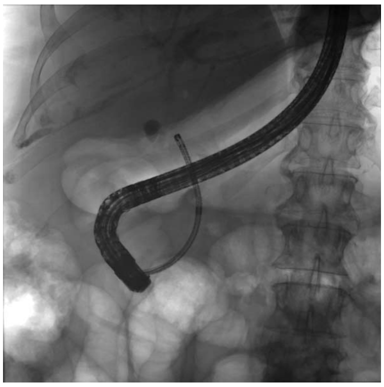

Figure 1 Cholangioscopy using a dedicated cholangioscope. In this approach, a dedicated cholangioscope is advanced through the accessory channel of a duodenoscope and directed into the bile duct.

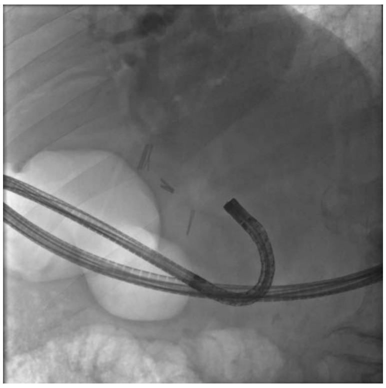

Figure 2 In direct peroral cholangioscopy, an ultraslim upper endoscope is inserted through the mouth and advanced to the duodenum. It is subsequently maneuvered across the biliary sphincter and into the bile duct for observation of the mucosa and the lumen of the bile duct.

ADVANTAGES OF DIRECT PERORAL CHOLANGIOSCOPY

Commercial availability

In cholangioscopy, whether direct or using a dedicated cholangioscope, the quality of the image is of utmost importance. Among dedicated cholangioscopes, only high-definition video cholangioscopes can offer the same image quality as the ultraslim upper endoscopes used in direct cholangioscopy. Dedicated high-definition video cholangioscopes are currently produced only as prototypes and thus not available for commercial use. Ultraslim upper endoscopes used for direct cholangioscopy, on the other hand, are widely available on a commercial basis.

Image quality

Currently, none of the commercially available dedicated cholangioscopes can offer high-definition images. High definition, refers to an increase in pixels (dots) received by the endoscope and displayed on the monitor to increase the detail of the surface being seen, enabling detection of smaller and more obscure lesions[6]. It also may allow for more detailed examination of lesions that may already have been seen in standard definition, although, with less detail. The new-generation of ultraslim upper endoscopes offer high-definition images allowing detailed examination of biliary mucosa and ductal lumen with subsequent increase in their diagnostic capability (Figure 3).

Operating expense

Currently-available dedicated cholangioscopes are expensive to use. The single-operator cholangioscopy systems have single-use components that have to be discarded after each case while the dual-operator systems are fragile, break easily and are in need of frequent repairs[1,2]. The expenses associated with direct cholangioscopy are far less compared to use of dedicated cholangioscopes.

Narrow band imaging capability

At present, commercially available dedicated cholangioscopes do not have narrow band imaging capability.

Figure 3 View of the bile duct lumen and mucosa by direct peroral cholangioscopy. Note the normal pit pattern.

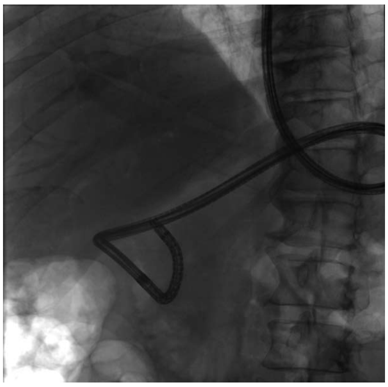

Figure 4 Fluoroscopic view of the ultraslim upper endoscope. Note looping of the endoscope in the stomach. Although the tip of the endoscope is well within the bile duct lumen, the endoscope cannot be further advanced to the more proximal ducts because of the looping.

Described by Gono and colleagues for the first time in 2004, narrow band imaging uses electronic processing of light in order to highlight particular components of an image[7,8]. The principle behind narrow band imaging technology is that the bandwidths of blue and green light are narrowed while the contribution of red light is negated out of the emitted light[8]. The narrowed bandwidths of green and blue light lead to superficial penetration of the mucosa accentuating the microvasculature pattern as hemoglobin has a peak absorption spectrum towards both these wave lengths[8]. Narrow band imaging can therefore improve visualization of the vascular pattern and aid in the diagnosis of various biliary disorders particularly indeterminate biliary strictures[2].

Size of accessory channel

The currently available ultraslim upper endoscopes have an accessory channel with an inner diameter of 2 mm, which is much larger than the accessory channel of the dedicated cholangioscopes measuring approximately 1.2 mm[2,5]. The larger size of the accessory channel allows easier passage of equipment such as biopsy forceps for tissue sampling or lithotripsy probes for fragmentation of difficult to remove biliary stones.

Operating a single endoscope

Compared to dedicated cholangioscopy which requires simultaneous operation of two endoscopes (the duodenoscope and the dedicated cholangioscope), direct cholangioscopy involves only a single endoscope that is manipulated into the lumen of the bile duct by a single endoscopist. Dealing with only one endoscope, avoids problems associated with simultaneous operation of multiple endoscopes such as coordination of movements.

Simultaneous irrigation, suction and therapeutic maneuvers

The ultraslim upper endoscope allows simultaneous irrigation, suction and therapeutic maneuvers. None of the currently available dedicated cholangioscopes have this capability.

DISADVANTAGES OF DIRECT PERORAL CHOLANGIOSCOPY

Larger outer diameter of the endoscope

The ultraslim upper endoscopes have an outer diameter of 5-6 mm, which is significantly larger than the diameter of most dedicated peroral cholangioscopes (3.0-3.5 mm). Direct cholangioscopy using the ultraslim upper endoscopes can therefore be performed only in patients with dilated bile ducts. In addition, the larger outer diameter requires generous sphincterotomy and sphincteroplasty for manipulation of the endoscope across the biliary sphincter.

Difficulty of insertion into the bile duct

The most profound disadvantage of direct peroral cholangioscopy is the difficulty associated with traversing the biliary sphincter to gain access to the bile duct. A high percentage of direct peroral cholangioscopy procedures, therefore, end up in failure. This difficulty of bile duct cannulation with an upper endoscope is mainly due to the looping of the ultraslim upper endoscope in the stomach or in the duodenum (Figure 4). There are therefore multiple published reports in the endoscopic literature with innovative suggestions on how to achieve this task. Introduction of the endoscope over a guidewire, through a regular overtube, or with the help of a double-balloon overtube are some of the suggestions[9-12]. However, despite use of these accessories, failure rate still remains high[13].

Lack of stability inside the bile duct

Another disadvantage of direct cholangioscopy is the instability of the ultraslim upper endoscope once it is inside the bile duct. This instability makes it difficult to perform diagnostic or therapeutic procedures such as

Table 1 Comparison of direct and dedicated cholangioscopy

	Direct cholangioscopy	Dedicated high-definition cholangioscopy
Commercial availability of the endoscope	Yes	No (prototypes)
Operating expense	Low	High
Image quality	Excellent	Excellent
Narrow band imaging capability	Yes	Yes
Required number of operators	One	Two
Irrigation capability	Yes	Limited
Suctioning capability	Yes	Limited
Fragility	No	Yes
Size of accessory channel	2 mm	1.2 mm
Insertion into the bile duct	Difficult	Easy
Stability inside the bile duct	Unstable	Stable
Access to proximal ducts	No	Yes

obtaining biopsies of lesions or lithotripsy of difficult to remove biliary stones. Endoscope instability can also lead to loss of access and prolongation of the procedure.

Lack of access to proximal ducts

In direct peroral cholangioscopy, access to the more proximal ducts is often not possible. Usually direct cholangioscopy can only visualize the ducts distal to the confluence of the right and left hepatic ducts. The right and left hepatic ducts and their branches are for the most part inaccessible for direct peroral cholangioscopy, limiting its use in only the most distal parts of the biliary tract[5].

FUTURE DIRECTIONS

Despite its many advantages, direct peroral cholangioscopy is rarely performed in nonacademic settings, mostly because of the difficult and time-consuming task of bile duct cannulation with an upper endoscope. Different variations of inflatable balloons used as an anchor within the biliary tree have been introduced for easier access[5,14]. Although these devices perform well for allowing access to the bile duct for assessment and therapy of disorders of the distal biliary system, it is often difficult to maneuver the endoscope and gain access to the ducts proximal to the bifurcation after deflation and removal of the anchoring balloon. Devices, such as overtubes, that can allow more proximal access while improving the stability of the endoscope are needed.

Currently, direct peroral cholangioscopy can only be performed in patients with dilated biliary tree. Ultraslim upper endoscopes with smaller outer diameter but preserved stiffness designed for direct peroral cholangioscopy will be a welcome addition to the existent array of endoscopes.

Finally, accessory equipment designed for use in direct peroral cholangioscopy can further improve the utility of this procedure.

CONCLUSION

Peroral cholangioscopy is an important tool for diagnosis and treatment of various biliary disorders. Peroral cholangioscopy can be performed by using a dedicated cholangioscope or by direct insertion of an ultraslim endoscope into the bile duct (direct peroral cholangioscopy). Compared to ductoscopy using a dedicated cholangioscope, the direct approach has several advantages and disadvantages (Table 1). The direct approach provides a valuable and economic solution for diagnostic and therapeutic applications in the biliary tree. However, solutions are needed to make access to the biliary tree easier, and to improve the endoscope stability within the biliary tree for diagnostic and therapeutic maneuvers.

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EDITORIAL

Virtual reality simulators for gastrointestinal endoscopy training

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Abstract

The use of simulators as educational tools for medical procedures is spreading rapidly and many efforts have been made for their implementation in gastrointestinal endoscopy training. Endoscopy simulation training has been suggested for ascertaining patient safety while positively influencing the trainees' learning curve. Virtual simulators are the most promising tool among all available types of simulators. These integrated modalities offer a human-like endoscopy experience by combining virtual images of the gastrointestinal tract and haptic realism with using a customized endoscope. From their first steps in the 1980s until today, research involving virtual endoscopic simulators can be divided in two categories: investigation of the impact of virtual simulator training in acquiring endoscopy skills and measuring competence. Emphasis should also be given to the financial impact of their implementation in endoscopy, including the cost of these state-of-the-art simulators and the potential economic benefits from their usage. Advances in technology will contribute to the upgrade of existing models and the development of new ones; while further research should be carried out to discover new fields of application.

Key words: Virtual endoscopic simulators; GI Mentor; Accutouch endoscopy simulator; Olympus Endo TS-1; Endoscopy training

Core tip: Virtual endoscopic simulators have a great potential in endoscopy training. There are currently two virtual simulators available to purchase as well as others available for non-commercial use. The use of virtual simulators in endoscopy boosts training procedure for upper and lower gastrointestinal endoscopy; the benefits being more prominent in novice trainees. More data are needed to document their position in endoscopic retrograde cholangiopancreatography and endoscopic ultrasound training. Available simulators should not be considered a tool for assessing the skills of endoscopists. The main disadvantage of virtual simulators is their high cost.

Triantafyllou K, Lazaridis LD, Dimitriadis GD. Virtual reality simulators for gastrointestinal endoscopy training. *World J Gastrointest Endosc* 2014; 6(1): 6-12 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i1/6.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i1.6

INTRODUCTION

The aim of endoscopy is to achieve the best diagnostic-therapeutic result while minimizing the risks of the patient. Acquiring skills to perform endoscopy needs experience and time and depends on the ability of the trainee, the feedback given by an experienced supervisor and the method of endoscopy training. Traditionally, novice residents commence their training by performing endoscopies on patients, which might result in prolonged procedure time[1] and abdominal pain and discomfort for the patient[2] due to lack of experience. In the era of higher endoscopy costs and increasing demand for advanced invasive procedures that minimize training opportunities[3], endoscopy simulation has been pointed out as a method of maintaining patient safety through reducing endoscopy errors[4-6] and achieving better and faster training results. Over the last decades, the use of endoscopy simulators has been spreading rapidly and an increasing number of medical centers in various countries worldwide have already incorporated them in endoscopy training.

ENDOSCOPY SIMULATORS

The first attempts of developing endoscopy simulators were found at the end of the 1960s with the creation of the first mechanical models[7]. Mechanical simulators have given their position to other more useful and realistic types of simulators, such as live animal models, *ex-vivo* simulators and virtual simulators. Although animal models are considered to offer the most human-like endoscopy experience, they are not widely used due to ethical concerns, the requirement for the presence of experienced staff, unavailability of necessary equipment and cost[8]. *Ex-vivo* simulators, which engage plastic materials with explanted animal organs are relatively cheap devices useful for scenario based training[9]. On the other hand, the need for tissue replacement increases preparation time, raises the cost and limits the trainee's access to training sessions[9]. Virtual (computerized) endoscopy simulators are presented as the most promising tool in endoscopy training. First developed in the 1980s[10,11], their use is spreading throughout the world and computer evolution aids the rapid improvement of these high-tech modalities. In this editorial, we will focus on virtual simulators, discussing their role in endoscopy training by reviewing the available literature.

VIRTUAL ENDOSCOPY SIMULATORS

Virtual endoscopy simulators are integrated systems that consist of mechanical parts and software. They run a computer program that simulates the procedure of endoscopy using endoscopic images of the gastrointestinal tract while the trainee handles an endoscope attached to a processor that gives a signal to a monitor. The moves of the endoscope interact with the monitor image, offering the user a virtual environment for practicing theoretical and practical knowledge under various conditions[12]. There are currently two virtual simulators in the market: GI Mentor (Simbionix, Cleveland, United States) and Accutouch Simulator, recently renamed as CAE EndoVR Simulator (CAE Healthcare, Montreal, Quebec, Canada)[13-15]. There are also simulators available for non-commercial use, such as the Endo TS-1 simulator (Olympus Keymed, Essex, United Kingdom), the construct validity of which has been tested in several trials.

Figure 1 The GI Mentor II simulator (Simbionix, Cleveland, United States), photo provided courtesy of Simbionix.

GI Mentor

Simbionix, a Cleveland, Ohio, United States headquartered company with an Israeli based research unit, produced the virtual simulator that offers the widest variety of tasks available. Suitable for upper and lower endoscopy training, GI Mentor provides a large library of modules from basic endoscopic skills and simple clinical procedures to complicated situations such as emergency gastric bleeding. There are also modules for endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) training. The simulation program includes features like a pain indicator and scope locator and trainees also have the opportunity to practice on virtual patient cases based on actual medical data[16] (Figure 1).

Accutouch endoscopy simulator

Although the company recently changed the name of the simulator, we will keep the old name throughout the manuscript because it appears as "Accutouch" in the available literature. The redesigned in 2012 simulator of CAE Healthcare (Canada) provides the user with a new, more realistic haptic sense of endoscopy. Modules of esophagogastroduodenoscopy (EGD), colonoscopy and endoscopic retrograde cholangiopancreatography (ERCP) are available and the trainee can also acquire skills in polypectomy, biopsy and hemostasis[17]. CAE's simulator offers a complete endoscopy experience by combining the endoscopy procedure with the background of a virtual patient. Endoscopy starts with the patient's history and various parameters change during endoscopy, such as vital signs and patient response to pain and discomfort. The trainee is also assigned to achieve the ideal virtual sedation without reducing the patient's oxygen saturation[18] (Figure 2).

Olympus colonoscopy simulator (Endo TS-1)

The Endo TS-1 (Olympus Keymed, United Kingdom) is

Figure 2 The CAE EndoVR (previously Accutouch) simulator (CAE Healthcare, Montreal, Canada), © 2013 CAE. Photo provided courtesy of CAE Healthcare.

a second generation virtual reality simulator that provides real-time movements of the colonoscope[19]. An Olympus CF180L endoscope is customized for the needs of the simulator and gives the user a realistic colonoscopy-like haptic sense by simulating the moves of the endoscope and the patient[20]. Olympus' Scope Guide that provides a 3-dimensional image of the position and shape of the endoscope within the colon was used as a pattern for Endo TS-1 and the luminal view is accompanied by a training tutorial[20]. The software is currently being updated and more complex procedures, like polypectomy, will be added[20].

USING VIRTUAL ENDOSCOPY SIMULATORS

From the first efforts of creating virtual endoscopy simulators to now, the positioning of these modalities regarding endoscopy training is still questioned. Numerous studies tried to investigate the improvement of endoscopy skills of trainees with various experience in endoscopy after receiving sessions of virtual endoscopy training. Other studies focused on using virtual simulators for the evaluation of acquired skills. Undoubtedly, use expansion of these high tech computer based machines depends on giving answers to these important issues.

Training

The significant acceleration of training procedure to the threshold that trainees are considered to have acquired sufficient skill is the most important condition for the positive validation of a simulator[21,22]. Although modern virtual endoscopy simulators offer a large variety of modules, trials reviewed herein examine only the effect of virtual endoscopic training in upper gastrointestinal endoscopy, colonoscopy and flexible sigmoidoscopy. The results of the major trials that examined the influence of virtual endoscopy simulators in gastrointestinal endoscopy training of novice trainees are shown in Table 1.

Regarding upper gastrointestinal endoscopy, training with the GI Mentor simulator in combination with a mechanical and an *ex-vivo* simulator seems to positively influence the learning curve of novice endoscopists when combined with clinical training, while independent simulator training appears to be insufficient[23]. Data reviewed from a Medical University of Vienna study indicate that trainees who underwent training sessions with a virtual endoscopy simulator before conventional training benefited in their first ten endoscopies on patients regarding procedure completion time and technical accuracy (as rated by experts) in comparison to their non-simulator trained fellows. A statistically significant difference in gastroscopy duration was still observable after 60 endoscopic examinations[24]. On the other hand, missed diagnosis of pathological findings, evaluated by blinded experts, was not significantly different between the two groups[24].

Three randomized, blinded, controlled trials have demonstrated the positive impact of three different virtual endoscopy simulators on the performance of novice colonoscopists. The first study, performed in Karolinska Hospital, Sweden, proved a significant increase of colonoscopy completion rate and reduction of both procedure time and patient discomfort in trainees who had already achieved a predetermined performance in the Accutouch simulator compared with controls[25]. In the second multicenter trial, the influence of GI Mentor simulator pre-training was investigated. The results showed that the pre-trained residents achieved higher competency scores than their control trainees during their first 100 cases; the difference in performance was even more prominent in their first 80 colonoscopies[26]. A third multinational European trial proved that novice trainees trained with the Olympus virtual simulator received similar rates by blinded experts in three live colonoscopy cases in comparison to others who underwent traditional training only. However, they achieved better results in simulator metrics in three virtual simulator cases than their fellows trained on patients[27].

Furthermore, one study demonstrated that skills acquired after sessions of colonoscopy training with virtual endoscopy simulators seem to be maintained for several months after the end of training[28]. The presence of a supervisor also boosts the training procedure as trainees complete the colonoscopy simulation and reach simulator proficiency levels faster than individual training[29]. Finally, intensive hands-on colonoscopy courses using computer simulator and live case teaching positively influence trainees' skills measured by a computer simulator and by a clinical index, while results are maintained during a 9 mo follow-up period[30].

The use of sigmoidoscopy virtual simulators was investigated in two trials. The results of a prospective randomized trial were not promising since trainees who were trained using virtual endoscopy simulators exclusively experienced more technical difficulties regarding initial endoscope insertion, negotiation of the rectosigmoid junction and ability to perform retroflexion, while their procedure completion rate was significantly lower than that of controls[3]. Another study demonstrated that a 3 h

Table 1 Evaluation of virtual simulators for the training of novice endoscopists

Ref.	Simulator	Procedure	Groups	Outcome measurement	Result
Ende *et al*[23]	GI Mentor (plus a mechanical and an *ex-vivo* simulator)	Gastroscopy	Clinical plus simulator training Clinical training only Simulator training only	Skills evaluation score Time (s) to pass pylorus	Median score: 7 *vs* 6 *vs* 5 (P = NS) 183 ± 65 *vs* 207 ± 61 *vs* 247 ± 66 (P = NS)
Ferlitsch *et al*[24]	GI Mentor	Gastroscopy	Simulator training before conventional training Conventional training	Time (s) to reach duodenum Percentage of unaided examinations (after 10 endoscopies)	239 *vs* 310 ($P < 0.000$) 85% *vs* 72% ($P < 0.01$)
Ahlberg *et al*[25]	Accutouch simulator	Colonoscopy	Simulator group Control group	Cecum reached during the first 10 colonoscopies Time (min) to reach cecum Patient discomfort (estimated probability in group 2)	52% *vs* 19% ($P = 0.0011$) 30 *vs* 40 ($P = 0.037$) 2.27 (95%CI: 1.14-4.76)
Cohen *et al*[26]	GI Mentor	Colonoscopy	Simulator group Control group	Competency after 100 cases Number of cases for reaching competency	Higher in group 1 ($P < 0.0001$) 160 in both groups (P = NS)
Haycock *et al*[27]	Olympus simulator	Colonoscopy	Simulator group On patient trained group	Live colonoscopy cases Completion rates Time taken Virtual simulator cases Cecum intubation Time (s) to cecum intubation	11% *vs* 7% (P = NS) 20 min *vs* 20 min (P = NS) 95% *vs* 70% ($P < 0.01$) 407 *vs* 743 ($P < 0.01$)
Gerson *et al*[3]	Accutouch simulator	Sigmoidoscopy	Virtual simulator training (without on-patient training) On patient training group	Time (min) to complete the live case Live cases that trainees completed independently	24 *vs* 24 (P = NS) 29% *vs* 72% ($P < 0.001$)
Sedlack *et al*[31]	Accutouch simulator	Sigmoidoscopy	Simulator group Control group	Patient discomfort score (1-10) Competence score to perform endoscopy independently (1-10)	1.3 *vs* 4 ($P < 0.01$) 2.8 *vs* 8 (P = NS)

NS: Not significant.

simulator pre-training course did not show a measurable effect in the graded skills of identification of pathology and safe scope insertion of novice trainees performing sigmoidoscopy. However, the patients experienced less discomfort[31].

There is limited information regarding the usefulness of virtual simulators in ERCP training. In two United States surveys in which ERCP virtual endoscopy simulators were evaluated compared to other modes (a mechanical simulator in the first study, an *ex-vivo* simulator and a live porcine model in the second), virtual simulators received lower scores in terms of realism and usefulness but they were ranked as more user friendly[32,33]. In another United States study, novice and expert endoscopists positively evaluated graphics and haptic realism of the ERCP module of GI Mentor and the vast majority of them claimed that it should be considered a useful ERCP training tool[34].

Finally, there are no data about GI Mentor's EUS mode contribution in trainees' learning curve. Kefalides *et al*[35] tested this EUS simulator mode and claimed that improvement is needed before being used as training tool. At the same time, eight EUS experts gave EUS Mentor mode the highest score among a mechanical simulator, an *ex-vivo* simulator and a live pig model in terms of usefulness and realism but expressed a negative view about the virtual simulator's EUS-FNA training mode[36].

Evaluation of endoscopic skills

The success of endoscopy depends on a number of factors, including among others, the endoscopist's technique, patient's condition and tolerance and the quality of equipment. As a result, it is difficult to assess endoscopic skills and there is no widely accepted scale for measuring competence. For a reliable evaluation of the training process, virtual endoscopy simulators must correlate simulator based benchmarks with clinical skills[37] and simulators' competitiveness scores with accepted clinical metrics[38].

The validation of the Olympus virtual simulator to evaluate colonoscopy skills has been tested in two different trials demonstrating promising results. In one trial that included participants with no endoscopy experience, trainees with median experience and experts showed a significant reduction of simulator procedure time and better scores in parameters measuring technique, like the number and size of passed sigmoid loops and use of variable stiffness function that depended on user's experience[20]. Another trial that included novices and experts demonstrated that experts achieved higher scores in colonoscopy competence measured by an Olympus simulator scale but the difference was not statistically significant[39].

Surveys involving GI Mentor as a skills assessment tool have shown contradictory results. Two studies, both dividing participants into novices, medium-experienced and expert endoscopists, have shown significant differences between novices and the other groups regarding virtual colonoscopy completion time and other parameters such as the percentage of lumen surface examined. Differences though were less prominent after the users had reached certain endoscopic experience[40,41]. A third trial demonstrated that GI Mentor colonoscopy simulator modules with a higher level of complexity were more suitable to distinguish endoscopists with different experience[42]. On the other hand two other surveys raised doubts about the reliability of GI Mentor to evaluate colonoscopy skills. A University of Pennsylvania, United States trial showed that the virtual simulator was unable to differentiate between novices and experts, not only in colonoscopy modules but also in upper gastrointestinal endoscopy modules[43], while a Cleveland, United States study displayed a wide range of scores in virtual colonoscopies performed by experts, claiming that an upgrade is needed for simulators to be considered accurate tools for measuring endoscopic skills[44].

The ability of the GI Mentor ERCP module to discriminate between novices and experts was tested in a US study. The combination of results in two simulated cases proved a statistically significant difference between the two groups but the study sample size was small and only one institution was involved[34].

The construct validity of the Accutouch sigmoidoscopy simulator has been tested in two trials. The simulator discriminated between groups with different sigmoidoscopy experience but results from the simulator metrics were not statistically significant in one of the two studies where experts and senior trainees were compared[45,46].

Finally, an attempt for creating a universal scale for measuring competence using virtual simulators was made in a multicenter Canadian trial. The researchers developed the "Global Assessment of Gastrointestinal Endoscopic Skills" for upper gastrointestinal endoscopy and colonoscopy, demonstrating a statistically significant difference between the scores of novices and experts[47].

FINANCIAL IMPACT

The two virtual endoscopy simulators currently available in the market are quite expensive. The cost of GI Mentor starts from $64500 (gastroscopy and colonoscopy modes) but the purchase of more complicated modules, such as those available for ERCP and EUS training, can raise the cost up to $114000[9]. As far as the Accutouch simulator is concerned, upper and lower gastrointestinal endoscopy packages can be purchased separately. The cost of the upper gastrointestinal endoscopy package is $46750 (bleeding mode upgrade adds $19000 to the cost), while the lower gastrointestinal endoscopy package is available at $74750. The addition of advanced modules, like the ERCP module and colonoscopy biopsy module, increases the cost from $7175-8650 for each separate purchase[9]. This high cost is the main reason that precludes the widespread of these modalities in countries where the total number of endoscopy trainees does not justify the cost or current fiscal austerity measures impose tremendous cut in state public health spending[48].

Their main financial advantage in comparison to other types of simulators, like *ex-vivo* and animal models, is that after installation, the expenses are minimized. The presence of a supervisor in a virtual endoscopy training procedure is not cost effective according to a University of Alabama study[49]. The concept of mobile virtual endoscopy simulators, being shared by more than one institutions, proved successful[50] and collaborative use may reduce the cost of their use in the future. Use of virtual endoscopy simulators though seems to also have a positive influence in health economics by reducing procedure time related to trainee involvement in endoscopy[1] and by limiting potential procedural complications and incorrect diagnosis[51]. Further research should be carried out in order to quantify the profit from their use.

CONCLUSION

Virtual endoscopy simulators use at the early stages of endoscopy training has considerable impact in the performance of novice endoscopists, not only in gastroscopy but also in colonoscopy. The benefit of their use for trainees who have acquired certain experience appears to be limited, while more data is needed to document their position in ERCP and EUS training. Despite the efforts for developing virtual simulators as tools for measuring endoscopic skills, the available modalities should not be considered as an objective means for validating the competitiveness of endoscopists. The main disadvantage of these computer-based simulators is their notably high price. The concept of mobile simulators and the purchase of basic modules of virtual simulators could be a solution for reducing cost. Rapid improvement in software and hardware technology promises even more realistic simulators and replacement of the first stages of conventional training with simulator training at a reasonable and affordable cost is the developers' challenge for the future.

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ORIGINAL ARTICLE

Intraductal endoscopic radiofrequency ablation for the treatment of hilar non-resectable malignant bile duct obstruction

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Abstract

AIM: To evaluate the safety and technical success of endoscopic radiofrequency ablation (RFA) for palliative treatment of malignant hilar bile duct obstruction.

METHODS: In this study, a recently CE and FDA-approved endoscopic RFA catheter was first tested in an *ex vivo* pig liver model to study the effect of electrosurgical variables on the extent of the area of induced necrosis. Subsequently, a retrospective analysis was conducted of all patients treated with endoscopic RFA for malignant biliary obstruction at our center between February 2012 and April 2013. All patients received an additional plastic stent implantation into the biliary tree following RFA.

RESULTS: In the pig model, ablation time of 60-90 seconds using the bipolar soft coagulation mode at 8-10 watts with an effect of 8 was found to be the most feasible setting. Twelve patients (5 females, 7 males; mean age, 70 years) underwent 19 endoscopic RFA (range, 1-5) sessions. Deployment of RFA was successful in all patients. Systemic chemotherapy was administered in four patients. We observed biliary bleeding 4-6 wk after the intervention in three cases and two of these patients died: in one patient, spontaneous hemobilia occurred, whereas bleeding started during stent extraction in the other. In the third patient, bleeding was stopped by insertion of a non-covered self-expanding metal stent. Another three patients developed cholangitis during follow-up. Seven patients died during follow-up and median survival was 6.4 mo (95%CI: 0.05-12.7) from the time of the first RFA.

CONCLUSION: Endoscopic RFA is an easy to perform and technically highly successful procedure. However, hemobilia possibly associated with RFA occurred in three of our patients. Therefore, larger prospective studies are needed to further evaluate the safety and efficacy of this promising new method.

Key words: Radiofrequency ablation; Endoscopic retrograde cholangiopancreatography; Endoscopy; Cholangiography; Bile duct cancer; Cholangiocarcinoma

Core tip: Radiofrequency ablation (RFA) is a promising tool for the treatment of patients with perihilar and intrahepatic bile duct cancer. While RFA is easy to perform and technical success rates are high, the outcome of patients remains unclear. Therefore, the long-term efficacy of this treatment approach needs to be studied in randomized trials.

Tal AO, Vermehren J, Friedrich-Rust M, Bojunga J, Sarrazin C, Zeuzem S, Trojan J, Albert JG. Intraductal endoscopic radiofrequency ablation for the treatment of hilar non-resectable malignant bile duct obstruction. *World J Gastrointest Endosc* 2014; 6(1): 13-19 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i1/13.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i1.13

INTRODUCTION

Hilar cholangiocarcinoma (CCA) accounts for about 70% of biliary tumors[1] and is not amenable to curative surgical resection in more than two thirds of cases at the time of diagnosis[1]. Palliative chemotherapy may increase median survival when a combination of chemotherapeutic agents is used[2]. In addition, endoscopic insertion of plastic endoprostheses or self-expanding metal stents (SEMS) plays an important role in the palliative treatment of biliary tract cancer[3,4].

Randomized controlled trials have indicated that endoscopic local ablation of intraductal CCAs by use of photodynamic therapy (PDT) significantly improves survival in non-resectable tumors[5,6] and these findings are also supported by non-randomized studies[7-10]. However, PDT is complex and expensive, requiring highly specialized equipment. Recently, ablation of intraductal tumors has been simplified by the introduction of a radiofrequency ablation (RFA) probe, the Habib EndoHBP probe (EMcision UK, London, United Kingdom) that is inserted through the working channel of a side-viewing endoscope during endoscopic retrograde cholangiopancreatography (ERCP) into the extra- and/or intra-hepatic biliary tract[11].

To date, few data exist on the clinical applicability of this new device. We therefore performed a retrospective analysis of all consecutive patients treated with endoscopic RFA for malignant biliary obstruction at our center, with a special emphasis on technical success rates, safety and patient survival.

MATERIALS AND METHODS

Pre-clinical study

Before the start of RFA treatments in patients, we performed an experimental pre-clinical study in an *ex-vivo* pig liver model to investigate the effect of electrosurgical variables on the extent of the area of RFA-induced necrosis. All procedures were performed using a RFA probe for bipolar cautery intended for use in endoscopic surgical procedures as described below (Habib EndoHPB; EMcision UK, London, United Kingdom; Figure 1).

In total, five consecutive freshly resected livers from adult pigs were obtained. All experiments were started within eight hours after the pigs had been euthanized and were performed at room temperature. The probe was advanced into the center of the liver over a guidewire and radiofrequency ablation was performed using different variations of power (watts), mode (effect) and ablation time. Ablations were performed with each technical setting three times in a row and the probe was inserted at least three centimeters apart from other ablation sites. Immediately after each application, the liver was cut along the guidewire with a scalpel to identify the ablation extent. The maximum diameter and length of the ablated area was measured separately for each application (Figure 2).

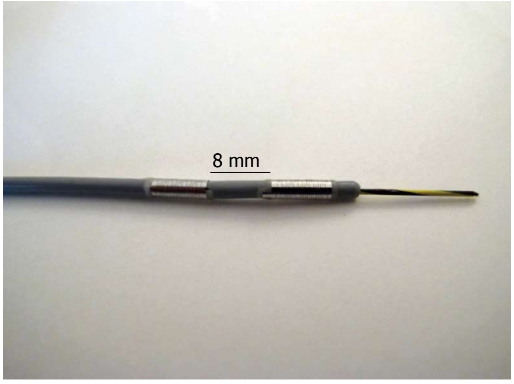

Figure 1 The radiofrequency ablation probe Habib EndoHPB (EMcision United Kingdom, London, United Kingdom) features two ring electrodes at the tip that are 8 mm apart. The probe is designed to perform bipolar cautery in endoscopic surgical procedures.

Clinical study

RFA was performed in patients with unresectable malignant biliary duct obstruction after the most feasible (8 to 10 watts, effect 8, 60-90 s) probe settings for optimal radiofrequency ablation had been identified in the pre-clinical study at our center starting in February 2012. All patients treated with endoscopic RFA for malignancy of an intrahepatic or perihilar bile duct were eligible for inclusion in this study and the study protocol was approved by the ethics committee of the Medical School of the University of Frankfurt, Germany. None of the patients had been eligible for curative surgery or had undergone a previous explorative laparotomy due to locally advanced disease or comorbidities. However, all patients reported symptoms such as painless jaundice or weight loss. Histological diagnoses were obtained by percutaneous needle biopsy or intraductal endoscopically operated biopsy during ERCP. All endoscopic RFA procedures were ascertained in an interdisciplinary conference of consultant physicians from the departments of surgery, gastroenterology and medical oncology and treatment recommendations were given in consent.

All endoscopic procedures (ERCP) were performed by an experienced pancreatobiliary endoscopist under standard operating conditions with a commercially available duodenoscope (TJF-160 VR or TJF Q180V, Olympus medical, Tokyo, Japan). Previously inserted plastic endoprostheses were removed before cholangiography, which were then used to confirm biliary length, diameter and localization of the tumor stenosis.

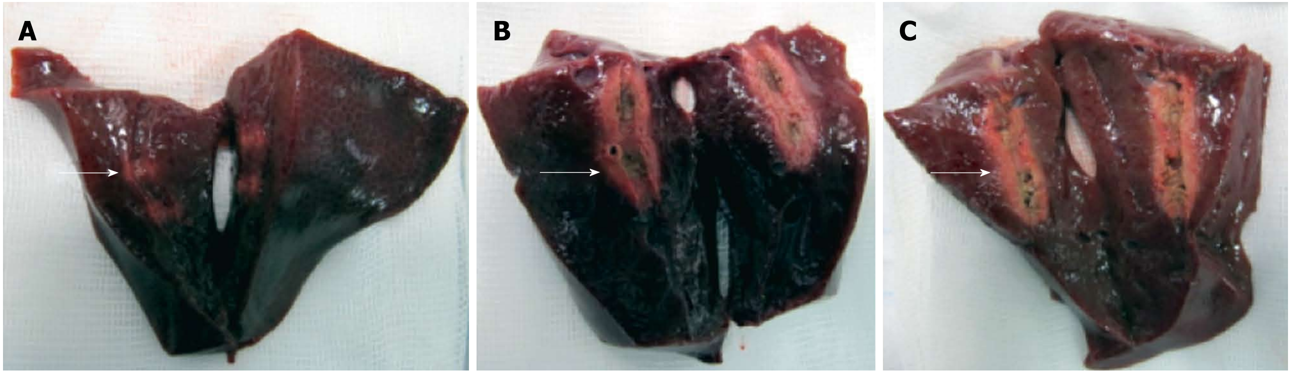

Figure 2 Exemplary results from the *ex vivo* pig liver model. From left to right, higher watt variables were used. Necrotic areas are marked by a arrow.

For endoscopic RFA, a recently FDA-approved and CE-certified[12] catheter was used. This probe (Habib EndoHPB; EMcision UK, London, United Kingdom) features two ring electrodes at the tip, lying 8 mm apart from each other (Figure 1). The catheter measures 8 French (2.6 mm) in diameter and 1.8 m in length. The RFA catheter can be connected to a bipolar electrosurgical generator to produce a cylindrical necrosis around the ring electrodes. The extent of the necrotic area depends on the mode of the electrosurgical generator, the power and ablation time. For the present study, the VIO 200D generator (Erbe Elektromedizin, Tübingen, Germany) with the "bipolar soft coagulation" mode, effect 8, 8 to 10 watts, for 90 s for treatment of the patients. Power was applied with 8 watts for the left or right intrahepatic biliary ducts and 10 watts for the subhilar section of the common hepatic or common bile duct, respectively. The RFA catheter was placed under fluoroscopic visualization of the biliary system after having visualized the tumor stenosis by injecting contrast medium (Iomeprol, Imeron® 300M, Bracco Imaging Deutschland, Konstanz, Germany) into the bile duct system *via* a standard ERCP probe. Positioning of the RFA catheter was performed exactly within the tumor stricture by using a guidewire. In cases of a stenosis more than 15 mm in length, repeated applications of RFA were carefully applied without overlapping the treated segments (1-4 applications per intervention). Thus, the RFA catheter was positioned into the right and/or the left intrahepatic bile ducts and we aimed to treat all segments involved in each specific tumor-dependent setting (Figure 1). After RFA treatment, plastic endoprostheses (Gastrosoft; Optimed, Ettlingen, Germany) were inserted according to standard protocols. The technical success of RFA was defined as positioning the RFA catheter at the region of interest and applying coagulation current as intended with consecutive successful insertion of an endoprosthesis.

Statistical analysis

The clinical part of this study is a retrospective cohort study. Data were analyzed from patients who underwent endoscopic RFA between February 2012 and April 2013 at our study center. The primary endpoint was the technical feasibility of endoscopic RFA. Secondary outcome measures included peri-interventional complications and overall survival.

Descriptive statistics are shown as mean ± SD or median and range, as appropriate. Survival was assessed using Kaplan-Meier statistics. All analyses were performed using the SPSS statistics software package for Mac (Version 20.0; IBM, Somers, NY, United States).

RESULTS

Pre-clinical study

In the *ex-vivo* pig liver model, significant differences in length and diameter of RFA-induced necrosis with variation of the electrosurgical parameters time, power and effect were observed. With an ablation time of 60-90 s using the bipolar soft coagulation mode, at 10 watts, effect 8 (equivalent to the recommendation of the manufacturer), a mean necrotic area of 22 mm × 9 mm (length × diameter) could be induced. Power seemed to have a more pronounced effect on tissue destruction when compared to time or mode. A power of 7 watts or less did not seem to produce a significant necrosis. Applying power in the range of 8-10 watts seemed to be most appropriate for intraductal biliary use and higher power was associated with deep tissue destruction (Figures 2 and 3).

Clinical study

In total, 19 RFA treatment cycles were performed in twelve patients (5 females, 7 males) with mean age of 70 years (median, 75; range, 33-85); Table 1, Figure 4.

All patients presented with malignant bile duct obstruction of the hepatic hilus (Klatskin like tumors). Final diagnosis included intrahepatic CCA in 2 patients, Bismuth stage IV in 8 patients, carcinoma of the gall bladder in two patients and metastases of gastric small cell carcinoma in one patient. Patients underwent either one (n = 9), two (n = 2) or five (n = 1) intraductal RFA applications that were considered technically successful during all applications. The ablations were applied to the left (n = 6), right (n = 9) or the main bile duct (n = 5) and RFA applications within one intervention ranged from 1 to 4 according to stricture length and/or bilateral *vs* uni-

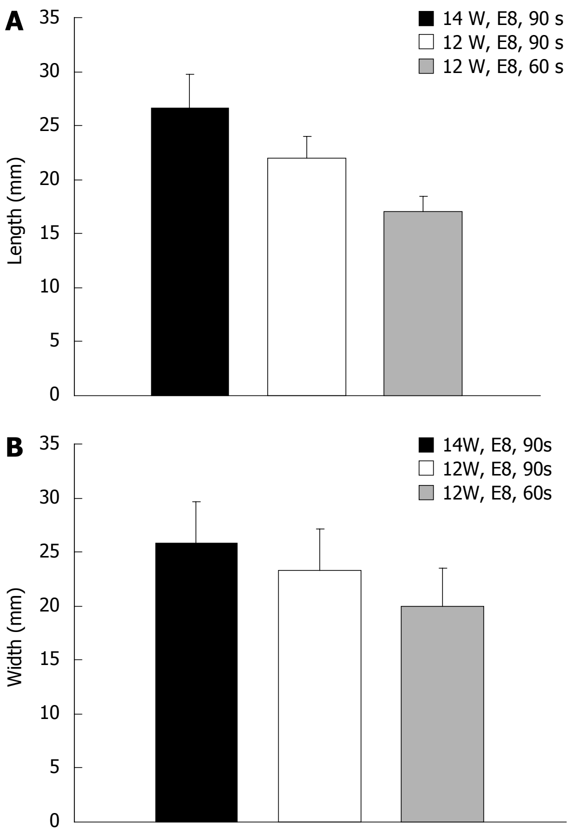

Figure 3 Results from the *ex-vivo* pig liver model. A: Length; B: Width. Varying electrosurgical variables revealed distinct differences in the extent of necrotic area. The used combinations are explained in the legend. *e.g.*, the blue column shows length and width of the necrosis caused by RFA with 14 watt, effect 8 with an ablation time of 90 s. RFA: Radiofrequency ablation.

lateral tumor stenosis. Four of the patients who had been diagnosed with CCA were also treated with systemic chemotherapy (cisplatin plus gemcitabine).

We observed biliary bleeding 4 to 6 wk after the intervention in three patients and two of these patients died of hemorrhagic shock. While one of these patients developed spontaneous hemobilia, bleeding started during stent extraction in the other patients that was successfully stopped in one patient by insertion of a non-covered self-expanding metal stent (SEMS). None of the three patients had undergone chemotherapy concomitantly to endoscopic treatment. Of the remaining patients, four patients developed recurrent cholangitis during follow-up that could be successfully managed with stent exchange and antibiotic therapy.

From the time of the first RFA in each patient, the 30 and 90 d mortality of the entire cohort was 8.3% and 50%, respectively; Figure 5. The extrapolated median survival from the first RFA and the time of diagnosis were 6.4 (95%CI: 0.05-12.7) mo and 8.5 (95%CI: 4.6-12.4) mo, respectively.

DISCUSSION

Successful stenting of the biliary tree with prior or additive photodynamic therapy has been demonstrated to show the longest overall survival and has been referred to as the "gold standard" for endoscopic treatment of malignant biliary obstruction[5,13]. However, the management of patients treated with PDT is expensive and time consuming and more feasible endoscopic options with equal survival benefit are warranted. Endoscopically applicable RFA represents a novel expansion of a method that is well known from its percutaneous applications and which has shown promising results in recently published case series. However, the safety of endoscopic RFA for biliary malignancy has not yet been clearly defined. Clinical data on intrahepatic treatment of CCA are scarce and many of the published studies included mostly extrahepatic tumors (Table 2). We here report our own experience on performing endoscopic RFA in 12 patients with malignant bile duct obstruction (mostly Klatskin Bismuth IV) due to hilar tumors of different etiologies. In our study, the technical applicability of RFA procedures was found to be excellent, successful in all patients, and this is in line with previously published studies. Indeed, in the largest study published so far, the technical success rate was reported to be 95%[12].

Despite this, we did observe three cases of hemobilia that occurred 4-6 wk after RFA application. Two out of these three patients died from the consequences of hemorrhagic shock, while bleeding was successfully stopped in one patient by immediate SEMS insertion into the bleeding bile duct.

Table 1 Overview of all patients treated with radiofrequency ablation for hilar malignancies included in our study

Patient	Patient gender/age	Tumor location	No. of RFA treatment cycles	Follow-up (mo)	Outcome
1	F/78	CCA Bismuth IV	2	6.4	Dead
2	F/73	Intrahepatic CCA	1	0.3	Dead
3	M/72	CCA Bismuth IV	5	19.8	Alive
4	M/85	CCA Bismuth IV	2	6.2	Dead
5	M/81	CCA Bismuth IV	1	1.1	Dead
6	M/33	Gastric carcinoma	1	Lost to follow up	-
7	F/77	Gallbladder cancer	1	6.6	Dead
8	F/78	CCA Bismuth IV	1	1.3	Dead
9	M/47	CCA Bismuth IV	1	14.1	Alive
10	F/78	CCA Bismuth IV	1	1.2	Dead
11	M/61	Gallbladder cancer	1	4.0	Alive
12	M/72	Intrahepatic CCA	1	2.9	Alive

The number of RFAs denotes the number of treatment cycles during follow-up. The number of follow-up months denotes the months from the first RFA in each patient. CCA: Cholangiocarcinoma; RFA: Radiofrequency ablation; F: Female; M: Male.

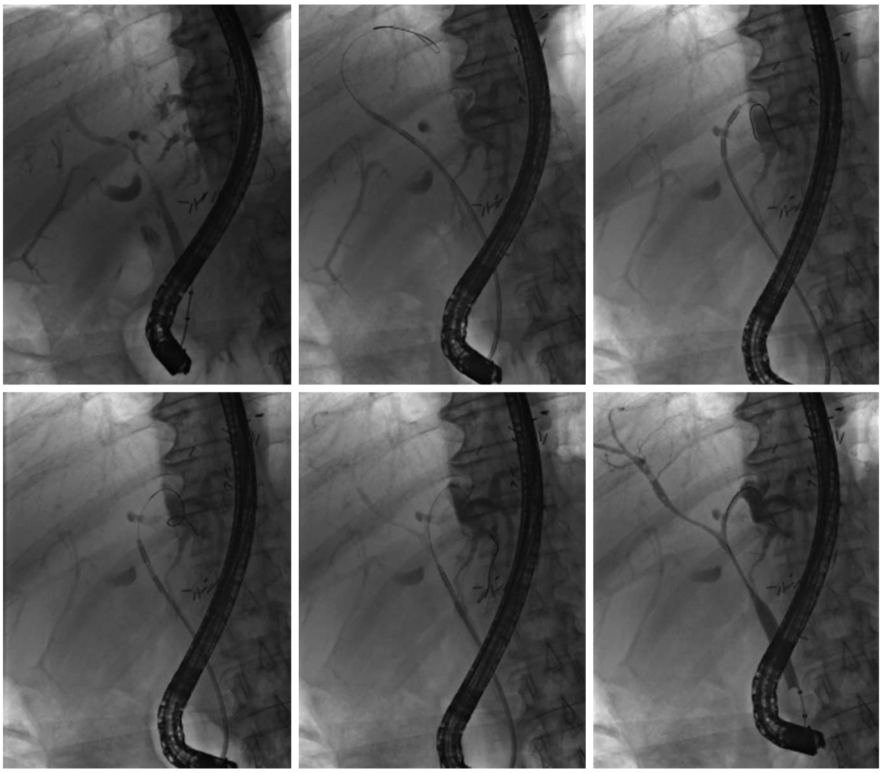

Figure 4 Application of endoscopically guided, intraductal radiofrequency ablation in a 72-year-old patient with an extended perihilar cholangiocarcinoma (Klatskin tumor, stage Bismuth IV, histologically proven) involving all subsegments. Multisegmental radiofrequency ablation (RFA) applications were performed (from left above to lower right). The patient experienced no treatment-associated complications and was doing well 15 mo after the initiation of endoscopic RFA treatment.

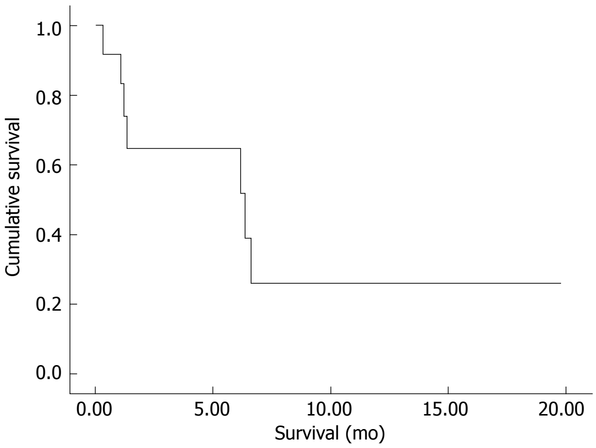

Figure 5 Kaplan-Meier survival curve of all study patients (n = 12). Calculation of survival started at the time of the first endoscopic radiofrequency ablation treatment in each patient.

Table 2 Literature overview of studies investigating the use of endoscopically-guided intraductal radiofrequency ablation in malignant biliary obstruction, localization of included tumors and complications are also listed for each study

Ref.	Year	*n*	Localization of the tumor	Complications
Figueroa-Barojas *et al*[15]	2011	8	Intra- and extra-hepatic	Pain: 4 Pancreatitis and Cholecystitis: 1
Steel *et al*[12]	2011	21	Extrahepatic	Empyema of the gallbladder: 1
Dolak *et al*[16]	2012	43	Intrahepatic	Hemobilia: 2 Liver infarction: 1 Empyema of the gallbladder: 1 Cholangitis: 1
Mizandari *et al*[17]	2012	39	Intra- and extrahepatic	Pain: 15
Own experience	2013	12	Intrahepatic	Hemobilia: 3 (2 deaths)

Although bleeding occurred several weeks after the RFA procedure in all three patients, a possible direct relationship to RFA may be assumed. In the two patients in whom bleeding occurred during stent extraction, deep necrosis induced by RFA may have been discarded from the perihilar tissue when necrotic material was removed while extracting the plastic endoprosthesis, thereby resulting in injury of a major blood vessel. Another possible explanation could be a strong necrotic effect induced by RFA that may have led to an increased angiogenic response within the tumor causing the recruitment of new vessel branches within the treated tissue. However, either of these hypotheses requires confirmation by analysis of immunohistochemical staining and biochemical processing of the treated tissues. Possible preemptive strategies to avoid biliary bleeding complications could include preinterventional investigation with intraductal ultrasound (IDUS) to rule out large blood vessels in the vicinity of the ablation site. For the prevention of late bleeding complications, insertion of a SEMS directly after the

RFA procedure seems to be feasible[12]. Severe complications associated with endoscopic RFA treatment have also been reported from most other published studies. For example, Dolak *et al*[14] reported that severe bleeding occurred in two of their patients and liver infarction in another patient, while Steel *et al*[12] reported that two of their patients required percutaneous gallbladder drainage for empyema.

Another secondary outcome measure of our study was overall survival following RFA therapy, which was shown to be 6.4 mo. In the above-mentioned Austrian multicenter study, the overall survival following RFA application was 10.6 mo. However, this was a multicenter cohort, involving 58 patients in total[14]. Other reported outcome measures included the increase of the diameter of tumor strictures[12] or stent patency at follow-up[12,14].

Taken together, our study shows that endoscopic RFA for malignant bile obstruction is a technically feasible and easy-to-apply procedure. However, based on the current experience, RFA should not be applied outside of study protocols given the risk of potentially fatal bleeding. Thus, randomized studies comparing PDT plus stenting *vs* RFA plus stenting, both with or without chemotherapy, are clearly desired.

COMMENTS

Background

Treatment with curative intent may be offered only for a minority of patients with cholangiocarcinoma. We evaluated the technical feasibility and safety of endoscopic radiofrequency ablation (RFA) for palliative treatment of malignant biliary obstruction.

Research frontiers

A new endoscopic RFA probe (Habib EndoHPB, EMcision United Kingdom, London, United Kingdom) has recently been CE and FDA-approved, thereby offering a new palliative treatment option for the therapy of malignant biliary strictures. The catheter can be positioned and applied during endoscopic retrograde cholangiopancreatography using a specific guidewire.

Innovations and breakthroughs

This study demonstrates that endoscopic RFA is easy to perform and a technically highly successful tool for the endoscopic treatment of biliary malignancies. However, severe bleeding occurred in three of our patients that may have been directly associated with RFA although it occurred several weeks after the respective RFA applications.

Applications

This study evaluates a new therapeutic approach in the palliative treatment of patients with malignant biliary obstruction.

Peer review

The authors showed in their retrospective study that endoscopic RFA is technically highly feasible for the treatment of malignant biliary strictures. However, severe complications such as biliary bleeding may occur and larger, prospective studies are warranted.

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BRIEF ARTICLE

A new peroral mother-baby endoscope system for biliary tract disorders

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Abstract

AIM: To investigate a new mother-baby system, consisting of a peroral cholangioscope and a duodenoscope in patients regarding its feasibility.

METHODS: In the study period from January 2007 to February 2010, 76 consecutive patients (33 men, 43 women; mean age 63 years old) were included in this pilot series. Endoluminal images and biopsies were obtained from 55 patients with indeterminate strictures, while 21 patients had fixed filling defects. The diagnostic accuracy of peroral cholangioscopy (POCS) in the visualization of strictures and tissue sampling was evaluated, and therapeutic success was monitored. Follow-up was performed over at least 9 mo.

RESULTS: A total of 55 patients had indeterminate strictures. Using the criteria "circular stenosis" and "irregular surface or margins", POCS correctly described 27 out of 28 malignant biliary strictures and 25 out of 27 benign lesions (sensitivity, 96.4%; specificity, 92.6%, diagnostic accuracy 94.5%). Visually targeted forceps biopsies were performed in 55 patients. Tissue sampling during POCS revealed malignancy in 18 of 28 cases (sensitivity: 64.3%). In 21 patients with fixed filling defects, 10 patients with bile duct stones were successfully treated with conventional stone removal. Nine patients with difficult stones (5 giant stones and 4 intrahepatic stones) were treated with visually guided laser lithotripsy. Two patients in the group with unclear fixed filling defects had bile duct adenoma or papillary tumors and were surgically treated.

CONCLUSION: The new 95 cm POCS allows for accurate discrimination of strictures and fixed filling defects in the biliary tree, provides improved sensitivity of endoscopically guided biopsies and permits therapeutic approaches for difficult intrahepatic stones.

Key words: Bile duct stenosis; Stones, Mother baby endoscopy; Peroral cholangioscopy; Cholangioscopy; Endoscopic retrograde cholangiopancreatography

Core tip: A new mother-baby system, consisting of a peroral baby cholangioscope and a maternal duodenoscope, was investigated in patients regarding its feasibility. Using the criteria "circular stenosis" and "irregular surface or margins", peroral cholangioscopy (POCS) correctly described 27 out of 28 malignant biliary strictures and 25 out of 27 benign lesions (sensitivity, 96.4%; specificity, 92.6%, diagnostic accuracy 94.5%). The new 95 cm POCS allows for accurate discrimination of strictures and fixed filling defects in the biliary tract, provides improved sensitivity of endoscopically guided biopsies and permits therapeutic approaches for difficult intrahepatic stones.

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INTRODUCTION

Strictures in the biliary system can lead to retention of bile, potentially resulting in jaundice, pain and fever, and are thus of great clinical importance. The differentiation between malignant and benign biliary strictures remains challenging, even with the use of transabdominal ultrasound (US), computed tomography (CT), and endoscopic retrograde cholangiography (ERC)[1]. Biliary strictures or filling defects can be caused by various inflammatory diseases, as well as by benign or malignant bile-duct tumors[2]. Malignant bile duct tumors, or so-called cholangiocarcinomas, are topographically categorized as intrahepatic or extrahepatic carcinomas[3]. Surgery is the only curative treatment for patients with cholangiocarcinoma, but the results have been more favorable for patients with early-stage disease. Therefore, a reliable diagnostic procedure is of great importance for these patients. Cholangiocarcinomas often grow longitudinally along the bile duct, rather than in a radial direction away from the bile duct. Consequently, imaging techniques, including ultrasound, CT, and magnetic resonance imaging are of limited sensitivity for the detection of cholangiocarcinoma. Therefore, biliary tissue collection during endoscopic procedures has been widely used to distinguish between benign and malignant strictures, thus providing the only definitive diagnosis that can be used to establish therapeutic strategies.

However, radiologically guided forceps biopsies, as well as brush cytology, has shown only limited sensitivity, usually approximately 40%-50%[4-6]. Furthermore, filling defects seen on ERC usually indicate the presence of bile duct stones, but these defects can also be caused by various benign or malignant tumors, including bile duct adenoma[7]. Intraductal tumors in the biliary tree can mimic large stones, and fixed filling defects that are thought to be intraductal polypoid lesions can also be stones.

Therefore, peroral cholangioscopy has been introduced to obtain visual images of the strictures, as well as visually guided biopsy[8]. Only direct endoscopic visualization of the bile duct enables a clear diagnosis of fixed filling defects and the undertaking of appropriate therapy. So far, conventional mother-baby endoscopes, such as the CHF-B20 or CHF-B30 long cholangio-pancreaticoscopes (usually longer than 160 cm), have been more demanding than the handling of short endoscopes, and thus, maneuverability inside the biliary system has been limited. In addition, the bioptic yield of the available very small biopsy forceps (outer diameter only 1 mm at the head) has been relatively poor. To overcome the aforementioned setbacks, a new, considerably shortened babyscope was developed, which allows for the insertion of a new, large-caliber biopsy forceps. The technical aspects have been presented in a separate manuscript.

The current study was designed to determine the feasibility of the new mother-baby system and to evaluate the diagnostic accuracy of a new peroral endoscope in patients with suspicious biliary strictures or fixed filling defects in the bile duct. The diagnostic accuracy of the new endoscope was consecutively evaluated in this pilot series over 2 years of continuous use in patients with unclear strictures and fixed filling defects, and patients were followed up over another 9 mo the verify their diagnoses.

MATERIALS AND METHODS

Patients

The study included 76 consecutive patients (33 men, 43 women, median age 63 years old) with obstructive jaundice, dilated ducts or fixed filling defects, who were treated by endoscopic sphincterotomy followed by intraluminal endoscopy from January 2007 until February 2010 in the Department of Gastroenterology at the Technical University Munich. The patients were followed up for at least 9 mo. The study was approved by the ethical committee (Ethical Committee TUM, decision from 08-14-2006). All of the patients included in this study agreed to be interviewed according to the study protocol. Written informed consent was obtained from all of the patients before ERC, cholangioscopy with a shortened peroral cholangioscope and endoscopically guided biopsy. All of the following inclusion criteria had to be confirmed: (1) clinical diagnosis of obstructive jaundice or other evidence of biliary stenosis; (2) unclear fixed filling defects or indeterminate strictures in the biliary tree suspected by transabdominal ultrasound; or (3) forceps biopsy during cholangioscopy in patients in whom strictures were observed, and stones could be excluded.

The exclusion criteria were as follows: (1) Previous surgery of the liver or bile duct, except for cholecystectomy (CHE); (2) a tumor in the main duodenal papilla; (3) histologically or cytologically confirmed carcinoma before cholangioscopy; or (4) previous photodynamic therapy for patients with cholangiocarcinoma. All 76 consecutive patients undergoing peroral cholangioscopy (POCS) to confirm a diagnosis of benign or malignant lesions and to evaluate the etiology of their lesions were included in this study. By the time of cholangioscopy, all of the patients had undergone ultrasound, but only 11 of 28 patients with malignant tumors had undergone additional CT scans and/or MRCP investigations before cholangioscopy. The reason for the divergent diagnostic procedures was that most of the patients were submitted for further clarification of an indeterminate stricture or fixed filling defect, and thus, the previous diagnostic procedure varied and could not be further investigated or compared.

Endoscopic equipment

The new mother-baby system was developed by one of the authors (Frimberger E). ERC and endoscopic drainage were performed with a videoduodenoscope manufactured by Storz Company, in Tuttlingen, Germany. The technical details of the new mother-baby system are described in an accompanying publication in the same issue. The new babyscope was shortened by more than 1/3 the length of conventional long babyscopes. The instrumentation channel was enlarged, allowing for the insertion of large-caliber biopsy forceps with an outer diameter of the cups of 1.3 mm, which is an increase of 30% compared to conventional forceps. Corresponding to the shortness of the babyscope, the length of the forceps was shortened, thereby reducing the biopsy time considerably. The newly developed endoscopes and the large-caliber biopsy forceps were provided at no cost by Karl Storz GmbH and Co. KG, in Tuttlingen, Germany. Repairs were performed by the company without charge. There was no further financial support from any study sponsors.

Endoscopic intervention

During endoscopic retrograde cholangiopancreatography (ERCP), sedation with propofol and midazolam was administered. Endoscopic sphincterotomy (EST) was conducted using an Olympus papillotome (Olympus, Hamburg, Germany), introduced over a Terumo guide wire. The bile duct was selectively cannulated with the peroral short cholangioscope, without using a guide wire. During cholangioscopy, the mucosal appearance of the biliary stricture was evaluated on the basis of the cholangioscopic findings; histological results were not available at this time. The procedure was performed by two physicians: one handling the mother duodenoscope, and the other handling the short peroral cholangioscope. The passage into the subsegments of the biliary system often required steering by two examiners, and therapeutic procedures particularly required the control of two examiners. The laser device was the SMART Lithognost Laser from StarMedtec, in Starnberg, Germany. The fibers were 300 μm in diameter, and the average applied intensity was 100 J. The laser distinguished stones from the bile duct and could not be activated when in contact with the bile duct wall.

Criteria for endoscopic visualization of the bile duct (POCS): forceps biopsies

The findings of malignant strictures included the following: (1) circular polypoid tissue with visible stenosis and (2) a non-homogeneous surface or irregular margins. Benign strictures included the following: (1) smooth surface mucosa, without polypoid or papillary tissue and (2) regular margins. At least two cholangioscopic images or video documentations were recorded in detail in the medical charts by the POCS operator. Endoluminal forceps biopsy was performed under endoscopic guidance. The tip of the open forceps was approximately 3 mm wide. All of the ERC, POCS and biopsy procedures were performed by experienced endoscopists, who were aware of the results of the prior ultrasound examinations, the blood parameters of cholestasis, and the previous ERC results. Forceps biopsy was performed by conventional methods *via* the operating channel of the POCS. Exactly 2 biopsies were obtained. The first biopsy was acquired under perfect visual control. In some cases, when post-biopsy bleeding occurred after the first biopsy, visually controlled acquisition of the biopsy was hampered due to blurred vision. In these cases, the bile duct was flushed with fluid until clear visibility was obtained, and the second biopsy was performed under visual control of the area of interest.

Pathologists received the biopsies of indeterminate bile duct strictures without knowledge of the clinical background or the endoscopic images.

For the purpose of analysis, suspicions of carcinoma and carcinoma found in biopsy specimens were considered malignant. The final diagnosis was confirmed by surgical resection, histological results, or clinical follow-up over at least 9 mo. Benign biliary lesions were confirmed by surgery (n = 2), by negative histopathologic results, and by clinical follow-up over more than 9 mo, without clinical or radiologic evidence of malignancy.

RESULTS

Endoscopic peroral cholangioscopy: indications, complications, diagnosis and clinical follow-up

A total of 76 patients, 36 men and 40 women with a mean age of 63 years old (range 30 to 86 years), were enrolled. On the basis of ERCP findings, 55 patients were examined due to biliary strictures and 21 because of fixed filling defects in the biliary system. A side port duodenoscope was used in all of the cases. Two prototypes of the duodenoscopes were used in all of the patients without major repairs, and two cholangioscope prototypes were also used without major problems or major repairs. The short babyscope could be inserted into the biliary system in all of the cases. In particular, access to the side branches of the biliary system was easy because of the direct transmission of rotation exerted on the rear portion of the scope to its tip. Excellent transmission of shaft rotation was observed with the cholangioscope, enabling controlled passage into the intrahepatic side branches. The insertion of the 1.3 mm biopsy forceps was unproblematic and rapid, due to its considerably reduced length.

In all of the attempts, cannulation of the bile duct and POCS (n = 76) were performed successfully, without complications. The cholangioscope was easily introduced into the bile duct without the use of guide wires. Among the 55 biliary strictures, 28 were malignant, and 27 were benign. In the group with malignant cholangiocellular carcinoma (n = 24), 6 patients were surgically treated, 9 received or were enrolled for PDT treatment, and 9 patients received supportive care. Two patients in the group with benign strictures were confirmed by surgical resection (n = 2), and all of the other patients with benign strictures were monitored over at least 9 mo. The final diagnoses of the 55 patients with indeterminate strictures

Table 1 Final diagnoses of the 76 patients with indeterminate strictures (n = 55) or unclear filling defects (n = 21)

Type of stricture	No.	Final diagnosis		
		OP	Biopsy	FU
Indeterminate stricture		55		
Malignant stricture	28	5	15	8
Cholangiocarcinoma				
Gallbladder cancer				
Metastasis				
Benign stricture	27	2	-	25
Inflammatory changes				
Postoperative stricture after cholecystectomy				
Biliary filling defects	21	2	-	19
Gallstones				
Bile duct adenoma (low-grade dysplasia)				
Bile duct adenoma (high-grade dysplasia)				

FU: Follow-up.

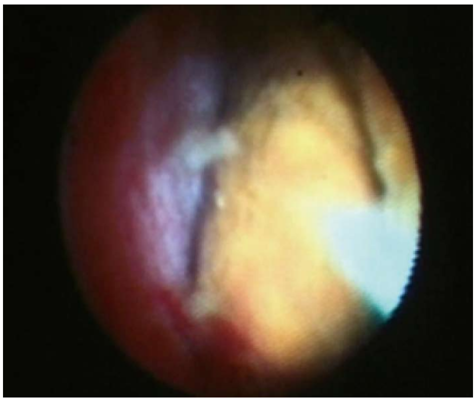

Figure 1 Peroral cholangioscopy aspect of a large bile duct stone. The stone was treated by visually guided laser lithotripsy and was completely removed. Overall, 4 giant stones and 5 intrahepatic stones with difficult access were completely removed.

and 21 patients with stones are listed in Table 1.

Endoscopic appearance of malignant and benign strictures: false negative and false positive endoscopic results during POCS and forceps biopsy

POCS alone identified 27 out of 28 malignant strictures (sensitivity, 96.4%). One patient with metastasis of an adenocarcinoma but an unknown primary tumor seemed to have benign pathology in the POCS investigation. All of the other patients fulfilled the criteria for having circular stenosis with irregular polypoid tissue. The diagnosis of malignancy was confirmed by histology, cytology, surgical resection or clinical course.

In the patients with benign strictures, there were 2 false-positive diagnoses among 27 benign strictures, according to the results of POCS observation. Twenty-five patients were correctly described as having benign strictures. Two patients with benign stricture had strictures that appeared malignant by POCS. These patients were operated on, but no cancer was identified. The biliary system was drained with a biliary anastomosis due to the long stricture. Overall, POCS alone identified 27 of 28 malignant strictures and 25 of 27 benign strictures from mucosal appearance, and the statistical values were thus calculated as follows: sensitivity: 96.4%; specificity: 92.6%; positive predictive value: 93.1%; and negative predictive value, 96.2%.

Endobiliary forceps biopsy during peroral cholangioscopy was performed in a total of 55 patients. Two subsequent biopsies were obtained in each patient, and biopsy acquisition was thus successful in all of the investigated patients. There were no complications related to tissue sampling. Tissue sampling correctly identified 18 of 28 malignant strictures in the bile duct and all 27 benign strictures (sensitivity, 64.3%; specificity, 100%; positive predictive value, 100%; negative predictive value, 73%).

Peroral cholangioscopy and fixed filling defects in bile duct

A total of 21 consecutive patients with suspected bile duct stones or unclear fixed filling defects were examined with the new cholangioscope. Detailed information regarding final diagnoses is provided in Table 1. In all 21 patients, initial ERCP with sphincterotomy was performed, and cholangioscopy was performed more than 4 d after the procedure. The cholangioscope was easily introduced into the biliary tract, including the right and left hepatic duct, in a time period shorter than 5 min. Typical features are shown in Figure 1, representing large intrahepatic stones. Nineteen patients had choledocholithiasis, and two patients had intrabiliary polyps. One patient with multiple fixed filling defects received a diagnosis of multiple bile duct adenoma with high-grade dysplasia, disseminated and continuously growing into the intrahepatic branches. One patient with a distal fixed filling defect was found to have adenoma of the bile duct, associated with a diagnosis of FAP.

Ten patients had bile duct stones, and all of the stones could be removed with a basket or balloon. In 9 patients, cholangioscopy revealed giant bile duct stones (n = 4) or intrahepatic bile duct stones not accessible by conventional methods (n = 5) (Figure 2). These stones were treated by visually guided laser lithotripsy and were subsequently successfully removed. Most of the stones were cleared in one session. Four patients had to undergo a second POCS to remove the remaining stones and to determine the absence of further stones.

In Figure 3A, the fluoroscopic ERC image of a patient with multiple fixed filling defects can be seen. The corresponding video of the POCS shows multiple bile duct polyps of papillary and polypoid shape, and the histological evaluation revealed adenoma with high-grade intraepithelial neoplasia. From the endoluminal aspects, a papillary neoplasm similar to intraductal mucinous neoplasia of the biliary system also appeared feasible. In this patient, liver transplantation was performed successfully. In Figure 3B, the ERC of a patient with intrahepatic gall stones in liver segment S7/8 is visualized, and the corresponding video showed detection of stones, which were treated by laser lithotripsy. In Figure 3C, a patient

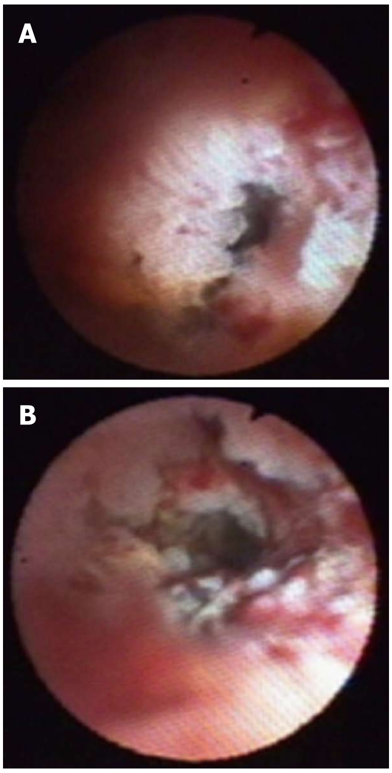

Figure 2 Cholangioscopic aspect of a malignant bile duct tumor. A circular stenosis can be seen, and irregular polypoid tissue with irregular margins indicates the cholangioscopic criteria for malignancy. A: Cholangoscopic aspect of a patient with hilar cholangiocarcinoma; B: Cholangioscopic picture of another patient with cholangiocarcinoma.

with hilar stenosis is presented. The corresponding video showed that when the scope was withdrawn from the right hepatic duct, no tumor could be seen. The left hepatic duct showed a high-grade stenosis. The stenosis of the left hepatic duct was passed, and withdrawal was performed from the left side. The patient was operated on with a hemihepatectomy and was cured of the tumor (R0 resection).

DISCUSSION

Peroral cholangioscopy has become an important additional tool for the investigation of biliary strictures and fixed filling defects. The practicability of the new mother-baby system was monitored in 76 patients with indeterminate strictures and filling defects, which are usually true challenges for diagnostic and therapeutic endoscopy. Intubation of the biliary system with the short babyscope was possible in all of the cases, without the use of a guide wire. The excellent direct transmission of shaft rotation to the tip of the babyscope, as a consequence of the shortened shaft (redesigned for optimal torque stability), facilitated intubation of the side branches of the biliary tree, thereby allowing passage into the deeper bile duct segments. The new large-caliber biopsy forceps could be easily inserted through the instrumentation channel of the babyscope, the diameter of which was larger than the channels of conventional babyscopes.

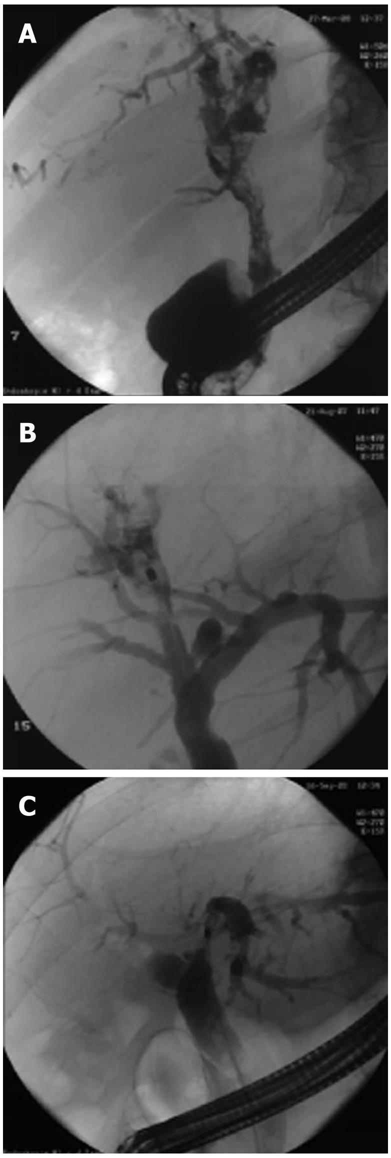

Figure 3 Endoscopic retrograde cholangiography fluoroscopic images and video illustrations of different cases. A: Patient with multiple papillary bile duct polyps; histology revealed adenoma with high-grade intraepithelial neoplasia, liver transplantation was successfully performed; B: Patient with intrahepatic stones (S7/8) treated by laser lithotripsy; C: Patient with stenosis of the left hepatic duct; histology revealed cholangiocellular carcinoma. Peroral cholangioscopy revealed that the right hepatic duct was without signs of infiltration, and left hemihepatectomy was successfully performed.

The new technical features of the shortened baby endoscope allowed for the determination of the true nature of undetermined bile duct strictures as diagnosed in an initial ERC, to obtain additional visual information about the shape and extent of a process and to obtain histological specimens with this process. Recent studies have suggested that the sensitivity of tissue sampling *via* fluoroscopically guided forceps biopsy was as low as 42%[4-6]. Thus, a more sensitive and accurate differentiation of malignant and benign bile-duct diseases is essential for the planning of appropriate therapy. Because the current study did not compare blinded forceps biopsy and brush cytology with POCS biopsy, a direct comparison between radiologically *vs* endoscopically guided techniques could not be performed. Therefore, the sensitivity of forceps biopsy of 64% appeared to be in a similar range[4-6].

Various techniques for POCS have been used, and many types of babyscopes were developed between 1976[8] and the late 1980s[9-12]. More recent studies have confirmed that POCS is especially advantageous in the diagnosis of small mucosal biliary lesions when combined with narrow band imaging[13]. Modern POCS techniques have been further helpful in diagnosing early malignant changes in laterally spreading biliary tumor patients and in patients with persistent primary sclerosing cholangitis[14-16]. However, most of these POCS investigators used long endoscopes, with lengths greater than 160 cm, and some of the investigators complained about reduced maneuverability in small bile ducts and across strictures[11,12].

At present, the CHF-B20 and CHF-B30 systems are widely used for the diagnosis of lesions in the intrahepatic duct and the common bile duct[9-11,14-16]. Fukuda *et al*[17] used a variety of cholangioscopes in a large series undertaken over more than 12 years. This study reported high sensitivity in discriminating strictures from filling defects. In that study, 21 fixed filling defects of uncertain etiology were seen on ERC, but 8 of these uncertain filling defects turned out to be malignant diseases, including bile-duct cancers and cystic duct cancers. This observation is entirely in agreement with our recommendation that such unclear filling defects require further diagnostic approaches, and peroral cholangioscopy is especially suitable for this purpose. Fukuda *et al*[17] also reported that ERCP/tissue sampling correctly identified only 22 of 38 malignant strictures. These results are in close accordance with the data presented here, but the accuracy, sensitivity, and specificity of our technique appeared to be superior.

Recently, a new wire-guided cholangioscope, SpyGlass (Boston Scientific, Boston, MA, United States), was introduced as a new tool for cholangioscopy[18]. The SpyGlass system is a single-use, single-operator, intraductal system that allows for optical viewing and optically guided biopsies. In a recent study, Chen *et al*[18] reported that the rate of procedural success was 91%. Twenty patients underwent SpyGlass-directed biopsy, and the specimens procured from 19 patients (95%) were found to be adequate for histologic evaluation. The preliminary sensitivity and specificity of SpyGlass-directed biopsy to diagnose malignancy were 71% and 100%, respectively. SpyGlass-directed electrohydraulic lithotripsy succeeded in 5 of 5 patients (100%).

Also, overtube-balloon-assisted enteroscopy was recently used to place a guide wire for the positioning of an ultraslim endoscope (diameter < 6 mm) into the bile duct[19], which was considerably thicker than the babyscopes used here. The authors reported excellent feasibility and technical success in 12 of 14 patients. The use of ultraslim gastroscopes to perform choledochoscopy is, in fact, gaining popularity, and it was again reported using an overtube-balloon-assisted method for destroying large stones[20]. Because neither of the above systems was available in our center, comparative studies could not be performed.

Using the new technique with the Storz mother-baby system, we found the new shortened cholangioscope especially suitable for the evaluation and treatment of indeterminate strictures, as well as unclear filling defects. Indeterminate strictures were visually evaluated by well-defined morphological criteria: (1) circular polypoid tissue with visible stenosis; and (2) a non-homogeneous or erosive surface, with irregular margins. These criteria were chosen because bile duct cancers have previously been shown to be polypoid or papillary growing tumors associated with the formation of a stenosis[16,17]. Previous studies have found that cholangioscopy performed using two peroral cholangioscopes, the CHF-B20 (4.5 mm outer diameter) and the CHF-BP30 (3.4 mm outer diameter), typically revealed that the criteria for polypoid masses with stenosis, as well as irregular surfaces with erosions and/or ulcerations with irregular margins, were suitable for the description of 22 malignant tumors of the bile duct in 22 patients with PSC[16,17]. Using these 2 independent criteria, we found that 27 of 28 true-positive malignant tumors appeared malignant, and thus, the use of peroral cholangioscopy was highly sensitive. However, 2 of 27 patients with benign strictures also appeared malignant, and thus, over-diagnosis can result. However, it must be emphasized that such over-diagnosis can further occur with regard to the histological results obtained and interpreted after obtaining feedback. Most importantly, malignant tumors might thus not be overlooked. Also, laser lithotripsy was performed in our study through the new cholangioscope, including in 5 patients with difficult intrahepatic stones. All of the patients, especially those with intrahepatic stones, could be successfully treated, indicating that the new technique is a very useful tool, not only for diagnosis but also for the treatment of such diseases in particular.

In summary, the new peroral mother-baby endoscope system provided for easy diagnostic and therapeutic access into the common bile duct and the periphery of the biliary tract. The endoscopically chosen criteria for malignancy were adapted to previous findings and showed true-positive values in all of the cases, indicating that growth of polypoid tissue with irregular surfaces and margins is a true criterion for tumors. Vessel density on top could be additional information that is further investigated. Diagnostic and therapeutic accessories, such as large-caliber forceps or laser probes, were easily and quickly inserted through the short babyscope. Thus, the new system could become an essential tool for clinical centers focusing on biliary diseases.

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COMMENTS

Background

Strictures in the biliary system can lead to retention of bile, potentially resulting in jaundice, pain and fever, and are thus of great clinical importance. The differentiation between malignant and benign biliary strictures remains challenging, even with the use of transabdominal ultrasound, computed tomography, and endoscopic retrograde cholangiography.

Research frontiers

Therefore, peroral cholangioscopy has been introduced to obtain visual images of strictures, as well as for visually guided biopsy. Only direct endoscopic visualization of the bile duct enables a clear diagnosis of fixed filling defects and the undertaking of appropriate therapy. So far, conventional mother-baby endoscopes, such as the CHF-B20 or CHF-B30 long cholangio-pancreaticoscopes (usually longer than 160 cm), are more demanding than the handling of short endoscopes, and thus, maneuverability inside the biliary system has been limited.

Innovations and breakthroughs

Peroral cholangioscopy has become an important additional tool for the investigation of biliary strictures and fixed filling defects. The practicability of the new mother-baby system was investigated in 76 patients with indeterminate strictures and filling defects, which are usually true challenges for diagnostic and therapeutic endoscopy.

Applications

Diagnostic and therapeutic accessories, such as large-caliber forceps or laser probes, were easily and quickly inserted through the short babyscope. Thus, the new system could become an essential tool for clinical centers focusing on biliary diseases.

Peer review

The new 95 cm peroral cholangioscopy allows for accurate discrimination of strictures and fixed filling defects in the biliary tract, provides improved sensitivity of endoscopically guided biopsies and permits therapeutic approaches for difficult intrahepatic stones.

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CASE REPORT

Confusing untypical intestinal Behcet's disease: Skip ulcers with severe lower gastrointestinal hemorrhage

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Abstract

Behcet's disease (BD) is a rare and life-long disorder characterized by inflammation of blood vessels throughout the body. BD was originally described in 1937 as a syndrome involving oral and genital ulceration in addition to ocular inflammation. Intestinal BD refers to colonic ulcerative lesions documented by objective measures in patients with BD. Many studies have shown that over 40% of BD patients have gastrointestinal complaints. Symptoms include abdominal pain, diarrhea, nausea, anorexia and abdominal distension. Although gastrointestinal symptoms are common, the demonstration of gastrointestinal ulcers is rare. This so-called intestinal BD accounts for approximately 1% of cases. There is no specific test for BD, and the diagnosis is based on clinical criteria. The manifestations of intestinal BD are similar to those of other colitis conditions such as Crohn's disease or intestinal tuberculosis, thus, it is challenging for gastroenterologists to accurately diagnose intestinal BD in patients with ileocolonic ulcers. However, giant ulcers distributed in the esophagus and ileocecal junction with gastrointestinal hemorrhage are rare in intestinal BD. Here, we present a case of untypical intestinal BD. The patient had recurrent aphthous ulceration of the oral mucosa, and esophageal and ileo-colonic ulceration, but no typical extra-intestinal symptoms. During examination, the patient had massive acute lower gastrointestinal bleeding. The patient underwent ileostomy after an emergency right hemicolectomy and partial ileectomy, and was subsequently diagnosed with incomplete-type intestinal BD by pathology. The literature on the evaluation and management of this condition is reviewed.

Key words: Intestinal Behcet's disease; Hemorrhage; Skip ulcers

Core tip: We present a patient with fever, abdominal pain and skip ulcers accompanied by lower gastrointestinal hemorrhage. Although the patient had undergone a number of examinations, no diagnosis was made. The patient underwent emergency surgery due to unmanageable lower gastrointestinal hemorrhage. Pathology of the resected bowel containing ulcer lesions indicated ectasia and blood vessel hyperplasia. The patient was diagnosed with incomplete-type intestinal Behcet's disease (BD). BD can influence any region of the gastrointestinal tract. It is more difficult to diagnose when intestinal BD is accompanied by multiple ulcers in various positions throughout the entire digestive tract.

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INTRODUCTION

Intestinal Behcet's disease (BD) refers to colonic ulcerative lesions documented by objective measures in patients with BD. Bechguard first described gastrointestinal involvement in 1940[1]. Oshima *et al*[2] reported that over 40% of BD patients had gastrointestinal complaints. Symptoms included abdominal pain, diarrhea, nausea, anorexia and abdominal distension[2]. Although gastrointestinal symptoms are common, the demonstration of gastrointestinal ulcers is rare. This so-called intestinal BD accounts for approximately 1% of cases[3,4].

The manifestations of intestinal BD are similar to other colitis conditions such as Crohn's disease or intestinal tuberculosis, therefore, it is challenging for gastroenterologists to accurately diagnose intestinal BD in patients with ileo-colonic ulcers. It is more difficult to diagnose when intestinal BD is accompanied by multiple ulcers in various positions throughout the entire digestive tract. Furthermore, giant skip ulcers and gastrointestinal hemorrhage are rare in intestinal BD. Here, we present a case of untypical intestinal BD. The patient had giant ulcers distributed in the esophagus and ileocecal junction accompanied by lower gastrointestinal hemorrhage, but no typical extra-intestinal symptoms.

CASE REPORT

A 47-year-old male presented to our hospital in October 2010 due to abdominal pain, fever and diarrhea. His abdominal pain was located in the epigastric region and lower right quadrant with no radiation. The pain was crampy and intermittent throughout the day. He could not recall what made the pain better or worse, but the symptoms had been present for approximately one year. In addition to fever and diarrhea the patient also experienced headache. His maximum temperature was 41 ℃. Endoscopy showed multiple giant ulcers in the esophagus and ileocolonic region. His clinical diagnosis was documented as Crohn's disease, and 5-aminosalicylate (mesalazine) 4.0 mg and prednisone 40 mg were administered orally. The above-mentioned symptoms gradually improved. However, his temperature rose when the dose of prednisone was tapered. The patient was referred to our hospital for further treatment.

The patient's past medical history consisted of recurrent oral aphthous ulcerations, folliculitis and facial acne-like lesions from 2009. He also had a history of chronic headaches. He denied ever using alcohol, tobacco products or illicit drugs. His family history was only significant for peptic ulcer disease and diabetes mellitus. On physical examination, his body temperature was 39.5 ℃, heart rate was 102 bpm and arterial blood pressure was 126/72 mmHg. There was some aphthous ulceration on the oral mucous membrane and multiple acne-like lesions on both cheeks and the neck. His abdominal pain was located in the epigastric region and lower right quadrant without rebound tenderness. On examination of the crissum, no ulceration was observed. The results of clinical laboratory tests and examinations are shown in Table 1. Based on these results it was hoped to discriminate intestinal BD from Crohn's disease. The patient was treated with oral prednisone 40 mg/d and a proton pump inhibitor. During further examination, the patient had massive acute lower gastrointestinal bleeding. Bleeding was located in the ileocecal region by emergent colonoscopy. A few oval ulcers were found around the crissum (Figure 1C). We were unable to achieve hemostasis by medical treatment. A surgical consult was obtained, and the patient underwent an emergency right hemicolectomy and partial ileectomy with ileostomy. During surgery, we observed that the wall of the cecum was thick and the lumen between the ileum and colon was filled with blood. Macroscopic examination of the resected material showed occasional discoloration in the serosa, mucosal edema, an ulcer (4 cm × 4 cm) and occasional necrosis in a segment 32 cm in length involving the ileocecal region (Figure 1D). On microscopic examination of the ulcer involving the serosa, there was mixed-type purulent cell infiltration rich in neutrophils, congestion and capillary proliferation. There was considerable thickening of some arterioles and venules, lymphocyte infiltration in and around the vessel wall, thrombus and recanalization in some vessels at the base of the ulcer (Figure 2). Treatment with oral prednisone 40 mg/d and thalidomide 300 mg/d was started after dermal sutures were removed. The abdominal symp-

Table 1 Results of clinical laboratory tests and examinations

Clinical examinations	Results
Routine blood examination	White blood cells 14400/μL, red blood cells 408 × 10^4/μL, hemoglobin 11.6 g/dL, hematocrit 35.7%, platelets 220 × 10^4/μL, C-reactive protein 38.9 mg/dL, blood sedimentation 58 mm/h
Routine stool examination	White blood cells, 20-30/HP; red blood cells, filled visual fields
Blood biochemistry	Total protein, 8.6 g/dL; AST, 36 IU/L; ALT, 32 IU/L; LDH, 171 IU/L; and total bilirubin, 0.2 mg/dL
Bacteriologic culture of blood, urine, and stool	Negative
Serum antinuclear antibody and antituberculosis antibody	Negative
PPD skin test and T-spot test	Negative
Pathergy test	Positive
Gastroscopy	Giant ulceration in the inferior extremity of the esophagus (Figure 1A)
Colonoscopy	A large ulcer in the ileo-cecal junction (Figure 1B)
Pathological examination of the endoscopic biopsy specimen	Nonspecific ulceration
Abdominal CT imaging	Thickening of the intestinal canal of the ascending colon and ileocecal region
Whole gastrointestinal barium meal examination	Inflammatory changes in the ascending colon and ileocecal region

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; CT: Computed tomography.

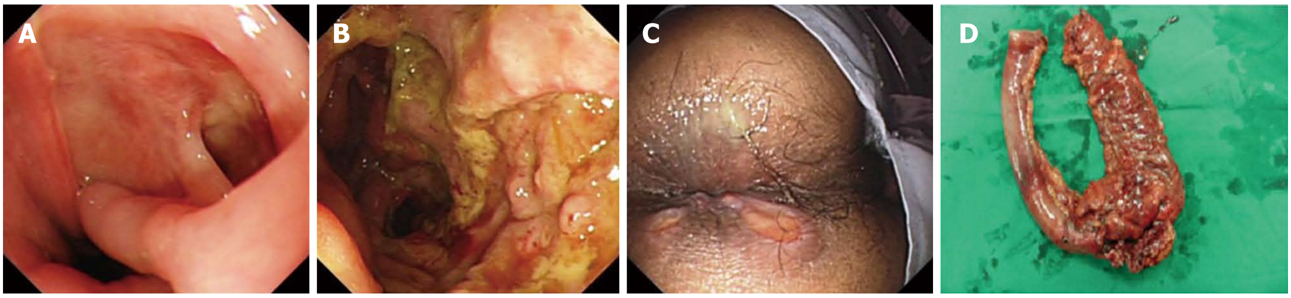

Figure 1 Positive manifestations in examination and in the surgically resected segment. A: A giant and ovoid ulceration in the inferior extremity of the esophagus; B: A typical oval-shaped large ulcer at the ileocecal junction; C: A few oval ulcers around the crissum; D: The resected material showed that the wall of the cecum was thick, occasional discoloration in the serosa, mucosal edema, an ulcer (4 cm × 4 cm) and occasional necrosis in a segment 32 cm in length involving the ileocecal region.

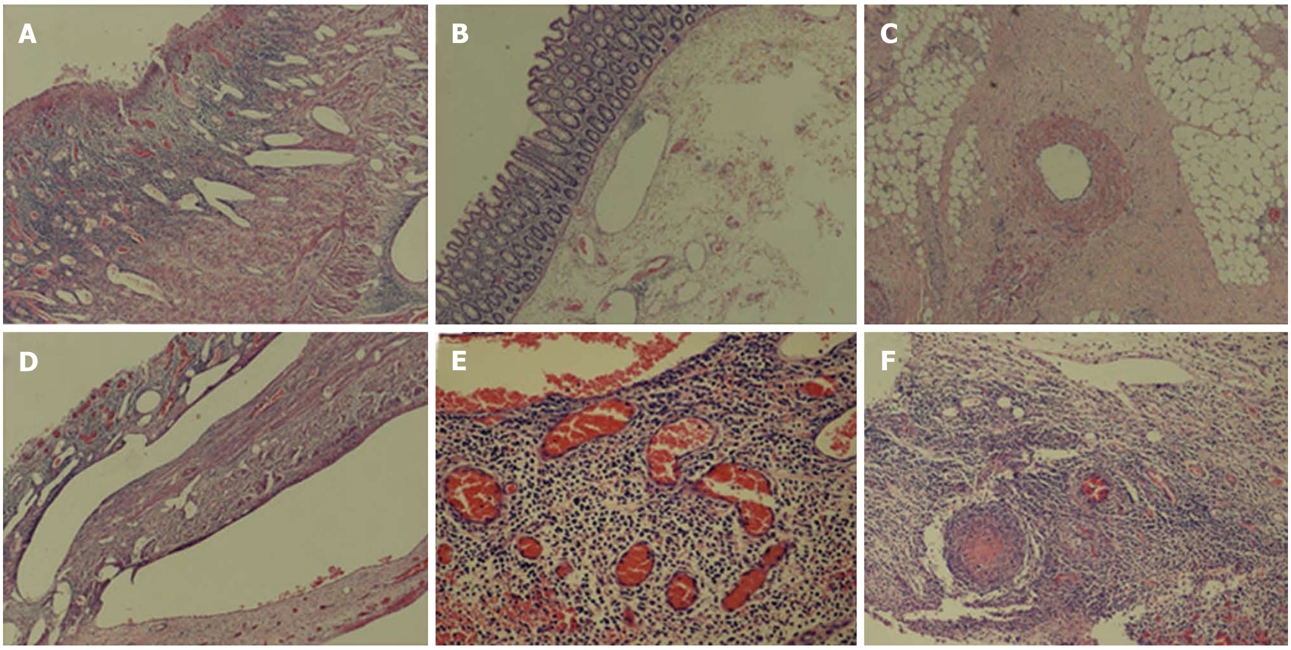

Figure 2 Positive pathological manifestations in the surgically resected segment. A: The ulcer in the ileocecal lesion encroached the whole segment with ectasia and blood vessel hyperplasia [hematoxylin and eosin (HE), × 40]; B: Ectasis in blood vessels was observed in normal tissues around the lesion (HE, × 40); C: The thickened vessel intima with lymphocyte and polymorphonuclear leukocyte infiltration (HE, × 40); D: Extreme ectasia in lesion blood vessels (HE, × 40); E: There was considerable lymphocyte infiltration in and around the vessel wall (HE, × 200); F: Thrombus and recanalization in some vessels at the base of the ulcer (HE, × 100).

toms and crissum ulcers gradually improved, and he was discharged 2 mo after admission.

DISCUSSION

BD is a rare and life-long disorder characterized by inflammation of blood vessels throughout the body[5]. BD was originally described in 1937 as a syndrome involving oral and genital ulceration in addition to ocular inflammation[6]. Since then, BD has been recognized and many other manifestations have been added to the original triad. The etiology of BD is unknown. To date, research has revealed that infectious, autoimmune and genetic mechanisms may cause this disease[7]. BD mostly affects children and young adults between the second and fourth decades of life[8]. Those affected before the age of 25 years (early onset) and males have been shown to have more severe disease symptoms[9].

Intestinal BD occurs most frequently along the ancient Silk Road which extends from the Far East to the Mediterranean basin. The prevalence varies widely among geographic locations. In Japan, the prevalence rate is 10 in 100000, in Saudi Arabia it is 20 in 100000, and in Northern Europe and in the United States it is only 0.3 per 100000. The male-to-female ratio also varies by geographic location. Men predominate in Egypt, Turkey, Israel, and Iran, whereas women predominate in Europe, the United States, and Japan. The age of onset can range from infancy to the 70s, although the highest frequency occurs in the third and fourth decades. Involvement of the gastrointestinal tract is variable in different populations, being more common in Japan (50%-60%) and less common in the Mediterranean basin, including Turkey (0%-5%)[1]. Although the reasons for this peculiar geographic distribution of intestinal BD are unknown, it may provide clues for the elucidation of putative etiological

Table 2 Diagnostic Criteria (Behcet's Disease Resarch Committee of Japan, 1987)

Maior
Recurrent aphthous ulceration of the oral mucous membrane
Skin lesion
Erythema nodosum
Subcutaneous thrombophlebitis
Folliculitis, acne-like lesion
Cutaneous hyperirritability
Eye lesion
Iridocyclitis
Chorioretinitis, retinouveitis
Definite history of chorioretinitis of retinouveitis
Genital ulcer
Minor
Arthritis without deformity and ankylosis
Gastrointestinal lesion characterized by ileocecal ulcers
Epididymitis
Vascular lesion
Central nervous system symptoms
Diagnosis
Complete type:4 major features
Incomplete type:
3 major features
Major + 2 minor features
Typical ocular symptom + 1 major or 2 minor features
Suspected type:
2 major features
1 major + 2 minor

Table 3 Guideline Statements for Diagnosis of Intestinal Behcet's Disease (Japan)

Diagnosis of intestinal Behcet's disease can be made if
There is a typical oval-shaped large ulcer in the terminal ileum or
There are ulcerations or inflammation in the small or large intestine;
And clinical findings meet the diagnostic criteria of Behcet's disease

agents or genetic factors that might be associated with intestinal BD.

BD can influence any region of the gastrointestinal tract. The mouth is the most common gastrointestinal site affected by BD followed by the ileocecal region[10]. Intestinal lesions are located on the antimesenteric side. Gastrointestinal symptoms related to BD include abdominal pain, nausea and vomiting. Some rare symptoms are present in emergency conditions, such as intestinal perforation or bleeding[11,12].

There is no specific test for BD, and the diagnosis is based on clinical criteria. In Japan, diagnostic criteria for BD have been established by the BD Research Committee (Tables 2, 3)[13,14]. Based on these criteria, the present case was a suspected type of BD. The patient was subsequently confirmed to have incomplete-type intestinal BD by pathology. It can be difficult to diagnose untypical intestinal BD. Moreover, intestinal BD manifests mainly in the terminal ileum, and esophageal lesions are rare. The patient had esophageal and terminal ileum ulcers accompanied by recurrent oral aphthous ulcerations, similar to Crohn's disease. Inflammatory bowel diseases should be kept in mind in the differential diagnosis of intestinal BD. Although International Study Group criteria for BD accurately distinguish between BD and Crohn's disease[15], there are some common features. Similar to Crohn's disease, BD manifests as discrete intestinal ulcers and discontinuous bowel involvement. Both of these diseases share extra-intestinal manifestations, such as arthritis and uveitis. Rectal sparing is common in both diseases. Intestinal lesions in Crohn's disease tend to be longitudinal ulcers with a cobblestone appearance, while those in BD are round and oval "punched-out" ulcers. Moreover, epithelioid granuloma is one of the pathological characteristics of Crohn's disease, whereas it is uncommon in intestinal BD. Another feature of Behcet's colitis is lymphocyte venulitis, which is a type of vasculitis. Despite these differences, it can be difficult to differentiate between these two diseases.

Ten percent of patients with BD accompanied by intestinal involvement require surgical treatment. The complications most frequently requiring surgery are perforation and bleeding. The recurrence rate after surgery has been reported to be 40%-87.5% and frequently appears at the anastomosis site. If suitable medical treatment is given after surgery, this condition can be improved. Thalidomide is a synthetic glutamic acid derivative first introduced in 1956 in Germany as an over-the-counter medication. The Food and Drug Administration approved its use in the treatment of erythema nodosum leprosum. Furthermore, it was shown to be effective in unresponsive dermatological conditions such as actinic prurigo, adult Langerhans cell histiocytosis, aphthous stomatitis, Behçet's syndrome and others. Zhang *et al*[16] reported a 29-year-old patient with a five-year history of BD who was administered prednisone and thalidomide. The patient was well with blood sedimentation and C-reactive protein in the normal range. Sayarlioglu *et al*[17] reported a patient with intestinal BD and recurrent perforating intestinal ulcers under immunosuppressive treatment with methylprednisolone and cyclophosphamide. The patient's symptoms did not disappear until she was treated with thalidomide[17]. These reports suggest the beneficial effects of thalidomide in BD. Direskeneli *et al*[18] revealed that thalidomide decreased TNF-alpha receptor levels, CD8/CD11b$^+$ T cells and natural killer cells during early treatment and increased CD4$^+$CD45RO$^+$ memory T and gammadelta$^+$ T cells during longer treatment in patients with BD. Therefore, thalidomide, in small doses, was thought to be safe and effective in the treatment of intestinal BD, was not addictive and did not have acute side-effects such as motor impairment.

In conclusion, practitioners should be aware of intestinal BD which accompanies intestinal ulcers and could lead to perforation or hemorrhage. Urgent surgical resection is mandatory in the case of hemorrhea without effective medical treatment, and medical treatment is required after surgery.

COMMENTS

Case characteristics

The patient had fever and abdominal pain, accompanied with skip ulcers with lower gastrointestinal severe hemorrhage.

Clinical diagnosis

The case should be diagnosed as untypical Intestinal behcet's disease (BD).

Differential diagnosis

The case should be difference from Crohn's disease and gastrointestinal tuberculosis.

Laboratory diagnosis

Serum antinuclear antibody, antituberculosis antibody, PPD cutantest and T-spot test were all negative, but pathergy test was positive.

Imaging diagnosis

Endoscopy displayed giant ulceration in the inferior extremity of esophagus and the ileocecal junction, abdominal computed tomography imaging indicated the intestinal canal of ascending colon and ileocecal region was thicken, and whole gastrointestinal barium meal examination presented the inflammatory change of ascending colon and ileocecal region.

Pathological diagnosis

Pathological examination of the endoscopic biopsy specimen indicated non-specific ulcer, but the ulcer of ileocecal lesion resected by surgical encroached whole range with ectasia and hyperplasia blood vessels.

Treatment

The patient underwent an emergency right hemicolectomy and partial ileectomy with ileostomy because of unmanageable lower gastrointestinal severe hemorrhage, and continued the treatment of prednisone and thalidomide.

Related reports

BD can influence any level of the gastrointestinal tract. The mouth is the most common gastrointestinal sites affected by BD. Next site is the ileocecal region. Intestinal lesions are located on the antimesenteric side. Gastrointestinal symptoms related to BD are abdominal pain, nausea and vomiting. Some rare symptoms present in emergency conditions, such as intestinal perforation or bleeding. The manifestations of intestinal BD similar to other colitis such as Crohn's disease or intestinal tuberculosis, therefore it is still challenging for gastroenterologist to accurately diagnose intestinal BD among the patients with ileo-colonic ulcers. Meanwhile it was more difficult to diagnose when intestinal BD accompanied with multiple ulcers in different positions of whole digestive tract. Furthermore skip giant ulcers and gastrointestinal hemorrhage are rare in intestinal BD.

Experiences and lessons

Clinical practitioners should be aware of intestinal BD which accompanies intestinal ulcers since the case probably could lead to perforation or hemorrhage. Urgent surgical resection is mandatory in case of hemorrhea without efficient medical treatment. And the medicinal treatments are still needed after surgery.

Peer review

The authors have presented a rare disorder of BD. The case reported here is interesting.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498.

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