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OPERATIVE ENDOSCOPY
FOR BENIGN GASTRO-INTESTINAL LESIONS

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A mio padre
Grande esempio di serietà ed onestà

Nel lavoro come nella vita

To my father

Whose integrity and honesty

In his work and in his life

Is a beacon to me

Confidentially note

This thesis, including all its chapters and sections, should be intended only as an internal communication destined exclusively to the authorized members of the doctoral committee and it is not, in any way, a publication. It is solely for the use of the addressee, since it contains strictly privileged, confidential and proprietary information, and should not be redistributed in any way without the author's consent.

Introduzione

L'Endoscopia Operativa ha conosciuto negli ultimi anni un grande sviluppo. Le indicazioni al trattamento con l'endoscopio flessibile delle lesioni gastro-intestinali sono infatti sempre maggiori ed ora, tramite la cosiddetta NOTES (Natural Orificial Trans-Endoluminal Surgery) o, sfruttando la visione in profondità degli ecoendoscopi con canale operatore, tale disciplina si affaccia addirittura al di là delle pareti del lume, per accedere alle cavità peritoneale, pelvica e mediastinica.

Il motivo di tale sviluppo è da ascriversi innanzitutto ad un miglioramento della tecnologia di supporto all'endoscopia, ma anche alle richieste da parte del paziente di un trattamento sempre meno aggressivo ed invalidante. Anche la diagnosi precoce delle malattie tumorali e delle forme pre-neoplastiche, grazie ai protocolli di screening, ha portato parallelamente ad un incremento della terapia locale endoluminale. Si rivalutano di conseguenza i costi ed i benefici in termini di qualità di vita e di rischio di complicanze da un lato, di efficacia del trattamento dall'altro.

In questo periodo di sviluppo della disciplina è dunque essenziale pesare di volta in volta i vantaggi e gli svantaggi che essa offre nei confronti della chirurgia tradizionale o della terapia farmacologica, che rappresentano per molte patologie un trattamento di efficacia già nota e consolidata. Ma in maniera ancora più complessa essa si deve embricare con la terapia chirurgica tradizionale, secondo valutazioni precise di timing, stadiazione e prognosi delle malattie. Vale a dire che l'endoscopia operativa si rapporta alla chirurgia tradizionale anticipandola in alcuni casi, collaborando anche in rendez vous in altri casi ed infine, asservendola nel trattamento delle complicanze post-operatorie.

E' sulla base di queste considerazioni che è stato intrapreso il presente studio, che affronta le tematiche di alcune patologie benigne del tratto gastro-enterico trattate per via endoscopica, valutando l'efficacia di nuove metodiche operative endoscopiche allo scopo di definirne vantaggi, svantaggi e limiti in rapporto ad altre più consolidate metodiche terapeutiche.

Il primo argomento presentato (capitolo 1) riguarda il trattamento laser endoscopico e chirurgico delle teleangiectasie del tratto gastroenterico superiore. Da tale studio sono emerse le indicazioni ed i limiti della metodica endoscopica, che resta comunque la terapia principale nella gestione della malattia. Questo studio ha fornito inoltre lo spunto per approfondire le conoscenze sulla patologia dal punto di vista prognostico e di staging, rivalutando l'utilità della videocapsula nella gestione del paziente. Ne è risultato che la malattia può frequentemente interessare tutto il tratto gastroenterico, potendo rendere in questo caso insufficiente un trattamento troppo localizzato.

Il secondo argomento, sempre nel campo della prevenzione del sanguinamento, è rappresentato dalla terapia profilattica delle varici esofagee nei pazienti candidati a trapianto di fegato. (capitolo 2) Si tratta di un trial clinico randomizzato di confronto tra legatura endoscopica ed uso di

betabloccanti (propranololo) in pazienti con cirrosi di grado Child B o C, con varici esofagee ad alto rischio ma che non hanno mai sanguinato. In questo caso la procedura endoscopica non ha dimostrato maggiori vantaggi rispetto alla terapia farmacologica, mentre è risultata più costosa e gravata da complicanze mortali. Si è quindi discusso di come la profilassi del sanguinamento nei pazienti cirrotici in attesa di trapianto di fegato, richieda un trattamento provvisorio e non definitivo, di questa complicanza, nell'attesa della disponibilità di un organo da donatore.

Vengono poi presentati due studi sull'efficacia della terapia laser endoscopica nel trattamento di forme pre-cancerose gastro-intestinali, quali l'esofago di Barrett e gli adenomi colo-rettali. In entrambi gli studi l'indicazione al trattamento endoscopico è stata posta perchè i pazienti risultvano inoperabili o rifiutavano l'intervento chirurgico. (capitolo 3 e 4). Anche se critiche possono essere mosse sui limiti di radicalità e sullo scarso campionamento istologico di tale metodica rispetto alla chirurgia resettiva od alla stessa mucosectomia endoscopica, i buoni risultati ottenuti in termini di sicurezza e di efficacia a lungo termine suggeriscono comunque un'ulteriore riflessione sull'argomento.

Ancora l'endoscopia operativa si dimostra un supporto valido alla chirurgia nel trattamento delle complicanze anastomotiche, sia in ambito di chirurgia esofagea che trapiantologica epatica, come dimostrato nei capitoli 5 e 6.

Infine con l'apporto dell'ecoendoscopia, l'endoscopia flessibile permette, prima ancora della nascita della NOTES, il trattamento di lesioni esterne al lume intestinale, come ad esempio nel caso del drenaggio di ascessi intra-addominali e di necrosi pancreatiche, come descritto nel Capitolo 7.

Introduction

Operative endoscopy has progressed enormously in recent years. The number of referrals to treat gastrointestinal lesions using flexible endoscopes continues to grow and thanks to natural orifice transluminal endoscopic surgery (NOTES) and the in depth view provided by operative channel ecoendoscopes this procedure has recently gone beyond luminal walls reaching out to the peritoneal, pelvic and mediastinic cavities. This development can be attributed to technological progress as well as to patients' growing demand for less invalidating, aggressive treatment procedures. Thanks to screening protocols, early diagnosis of malignant and pre malignant diseases is another reason for the increase in the use of local endoluminal treatment. The costs and benefits in terms of quality of life and risk of complications, on the one hand, and treatment efficacy, on the other, are as a consequence under close scrutiny by endoscopists

At a time of great progress health care professionals are weighing the advantages and disadvantages that this procedure offers with respect to traditional surgery or pharmacological therapy. But even in a more complex way this procedure must be given the opportunity to play its part together with traditional surgical treatments that have already proven themselves following precise guidelines with regards to identifying and staging the disease prognosis. In other words, operative endoscopy is connected to traditional surgical procedures, at times preceding it, at other times working hand in hand with it, and, finally, sometimes supporting its efforts in treating post operative complications. The present study, which addresses the efficacy of new endoscopic methods in the treatment of some benign gastrointestinal lesions, was undertaken with the intent of defining its vantages and disadvantages in relation to other, more established, conventional methods.

The first part (Chapter 1) concerns endoscopic laser and surgical treatments of telangiectasia of the higher intestinal tract. Indications and limits of this methodology, which remains in any case the principal therapy in the disease's management, were evaluated in the attempt to provide new data to facilitate staging of a pathology also evaluated from the point of view of capsule endoscopy. Thanks to this new endoscopic tool, the study was able to report that the disease is frequently active throughout the entire digestive tract and to explain why localized treatment sessions in these patients is, to some degree, ineffective.

The second part, likewise related to bleeding prevention, concerns prophylaxis of esophageal varices in candidates for liver transplants (Chapter 2). This randomized clinical trial compared endoscopic banding with the use of betablockers (propranol) in high risk patients with Child B or C cirrhosis and esophageal varices without previous bleeding. The endoscopic procedure utilized here did not seem to present any advantages with respect to pharmacological treatment but was found

instead to be costly and associated to fatal complications. It was concluded that prophylaxis of bleeding in cirrhotic patients awaiting liver transplant requires provisional and not definitive treatment strategies

Two studies on the efficacy of endoscopic laser therapy in the treatment of pre malignant gastrointestinal forms such as Barrett's Esophagus and colorectal adenomas are then presented. Both showed that endoscopic laser therapy is useful in patients who prove to be inoperable or who reject surgery (Chapter 3 and 4). Despite criticism concerning the risk of incomplete extirpation and the minimal histological sampling that is collected respect to resective surgery or to endoscopic mucosectomy, the positive results obtained in terms of long term safety and efficacy all suggest that further studies along these lines are warranted.

Operative endoscopy has also proven to be a valid support to surgery in the treatment of anastomic complications both with regards to esophageal surgery and well as to liver transplantation, as demonstrated in chapters 5 and 6.

Finally, thanks to the ecoendoscopy a flexible endoscope has made it possible, even before NOTES became feasible, to treat lesions external to the intestinal lumen, for example to perform drainage of intraabdominal abscesses and toilette of pancreatic necrosis, as described in Chapter 7.

Chapter 1:

Endoscopic treatment of gastrointestinal vascular ectasia

Laser therapy and surgical treatment in transfusion-dependent patients with upper-gastrointestinal vascular ectasia.

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Abstract

We report the results of endoscopic laser therapy on 59 patients with upper gastrointestinal vascular ectasia. After 300 sessions complications were 2 non-bleeding and 3 bleeding ulcers, treated successfully with endoscopic therapy. Following treatment blood transfusions were abolished in 61% and reduced in 22% patients, whereas 17% of patients were no-responders and 5% died for bleeding. Treatment outcome correlated with endoscopic healing, number of yearly transfusions and lesions' localization. Patients who did not respond to laser therapy by the sixth session, showed no improvement afterwards. Four patients with persistence of bleeding despite laser therapy underwent surgery and in 3 of them a long-term control of bleeding was obtained. In conclusion laser therapy was safe and effective, nonetheless surgical treatment should be considered, following adequate staging, for those patients receiving more than 10 blood units per year or who have undergone more than 6 laser sessions without improvement.

INTRODUCTION

Upper GI vascular ectasia, including angiodysplasia and watermelon stomach, may present clinically chronic and acute gastrointestinal (GI) bleeding. In the former case it can at times be life threatening in patients in poor condition and often requires hospital admission. In the latter case significant iron deficiency anaemia can develop and patients frequently become transfusion dependent, requiring up to 100 blood units per year, with risk of viral infection.

GI vascular ectasia can be the expression of a multisystem vascular disease such as hereditary hemorrhagic telangiectasia (HHT), in which lungs, liver, brain and skin can also be involved [1]. It is moreover often associated with autoimmune disorders, such as Raynaud's disease or Systemic Lupus Erithematosus, or with liver cirrhosis, renal failure and aortic stenosis. Except for HHT, in which some genetic alterations of the receptors for the angiogenic transforming growth

factor-beta have been identified [2,3], the aetiology of these vascular alterations is unknown and is probably diverse according to the underlying disease.

Several treatment modalities have been employed to minimize or eliminate transfusion requirements in these patients and the risk of acute bleeding [4]. Pharmacological therapy, endoscopic ablation and surgical treatment are the primary approaches that have been utilized. Medical therapy with corticosteroids [5-7], tranexamic acid [8], octreotide [9] or oestrogen and progesterone [10,11]have been used to control GI bleeding from vascular ectasia but contrasting results have been reported [12,13]. Endoscopic treatment consists in sclerotherapy [14,15], monopolar and bipolar electrocoagulation [16], heater probe coagulation [17,18], or laser therapy and Argon Plasma Coagulation [19,20]. Neodymium-yttrium-aluminium garnet (Nd:YAG) laser coagulation has been demonstrated to be effective and associated to few complications [21-24]. Surgical treatment, consisting in antrectomy or gastrectomy, seems to be the most reliable method for controlling bleeding, but co-morbid illnesses increase the mortality risk. Surgery is thus usually considered a last resort measure when medical and endoscopic therapy have failed. The first choice treatment for upper GI vascular ectasia should be chosen on the basis of the severity of the lesions, the patient's general condition, and the quantity of blood transfusions required. Although many initially attempt an endoscopic approach, at what point should it be abandoned in favour of surgical treatment has not been well defined. In the present study we analysed the effect of Nd:YAG and Diode laser therapy on 59 patients with gastric vascular ectasia, treated in our Surgical Unit during a 12 year period. We were particularly interested in evaluating its effect on transfusion requirement. The incidence and results of surgery and its possible indications in this group have also been evaluated.

PATIENTS AND METHODS

Fifty nine patients were treated for bleeding upper GI telangiectasia from November 1993 to June 2005 in our Surgical Endoscopy Unit. Diagnosis was made on the basis of esophagogastroduodenoscopy (EGD) findings and the endoscopic appearance of bright red mucosal lesions. We were able to distinguish watermelon stomach from portal hypertensive gastropathy in cirrhotic patients when diffuse or linear red spots were located in the antrum [25]. Colonoscopy was generally performed to exclude colonic bleeding lesions, while video-enteroscopy and, more recently, capsule endoscopy were carried out when endoscopic therapy was ineffective or when the lesions already extended to the 2nd portion of duodenum at EGD. The upper GI sites affected were: 19 in the gastric antrum, 16 in the whole stomach, 9 in the duodenum, 4 in the antrum and duodenum, 11 in the whole stomach and duodenum. The macroscopic patterns were characterized as follows: watermelon stomach in 25, few lesions (<5) in 22, multiple lesions (>5) in 12. Some of

these patients also presented lesions in other sites: 6 in the colon, 2 in the jejunum, 2 in the jejunum and in the ileum and 1 in the esophagus. Associated diseases were: liver cirrhosis in 30, cardiovascular diseases in 13, neoplasia in 5, HHT in 2, chronic renal failure in 2, mielodysplasia and rheumatologic disease respectively in one. Out of 59 patients, 40 presented with macroscopic bleeding, while in the other 19 diagnosis was made when anaemia was detected. Fifty of these patients had undergone at least one blood transfusion. The decision to attempt laser therapy in the other nine was based upon their anaemic condition despite iron therapy. Patients who had other bleeding sources, such as non-eradicated varices or severe portal hypertensive gastropathy, were excluded. In 18 patients with liver cirrhosis esophageal varices were eradicated by endoscopic treatment before laser therapy was begun. At that point upper-GI telangiectasia was then considered the sole cause of bleeding and of the need for blood transfusion.

Laser method

Laser sessions were conducted during a one-day hospital stay in our surgical ward, after informed consent was obtained from the patients. After intravenous sedation with propofol, laser treatment was carried out using MBB Medilas 2 Nd:YAG laser (MBB, Germering, Germany) (wave length 1064 nm, maximum power 100 watts) from 1993 to 1999. Beginning in January 2000 a Dornier Medilas D Diode laser (Dornier, Germering, Germany) (wave length 940 nm, maximum power 60 watts) was utilized [26,27]. The Olympus fibre EGD (Olympus, Tokyo, Japan) with a photo-resistant distal end (white head) and the Olympus or Pentax (Pentax, Tokyo, Japan) photo shielded video EGD were the endoscopes used. Coagulation of vascular lesions was carried out utilizing non contact fibres and applying sufficient energy to thermally treat them. The aim was to induce superficial scarring only. Lesions and the surrounding mucosa were treated just enough to become of white colour without causing a deep tissue necrosis. The total applied energy and the endoscopic appearance of the lesions were recorded at each session, which were scheduled from one month to another in order to ensure that complete healing of the gastric mucosa had taken place. Maintenance sessions were performed every 3 to 6 months, depending upon the patients' transfusion requirement and the lesions' endoscopic appearance. Throughout the time period in which patients underwent laser therapy all were given prophylactic treatment with acid suppressors (proton pump inhibitors). Out of entire patient group in 4 laser therapy was also carried out in the jejunum and in 6 in the colon, by means of enteroscopy or colonoscopy respectively.

Follow-up

Endoscopically healed patients underwent repeated blood tests (after 1 and 3 months, thereafter every 6 months) and received follow-up EGD only if anaemia recurred. The number and date of

blood transfusions before and after laser treatment were obtained from 2 provincial Transfusional Centres. All the other data were obtained by interviewing patients during endoscopic sessions and, when they did not require an EGD control, by telephone.

Statistical analysis

Results are expressed as mean ± SE. Statistical analysis was performed using the Student T test for paired samples. Correlations were assessed using Spearman's rank correlation test and frequencies were compared with the Fisher Exact Test. Statistical significance was set at $p<0.05$.

RESULTS

Morbidity and mortality

The mean energy used per laser session was 2667 J (range 267-9445 J). After a total number of 301 laser sessions, a mean of 5 per patient (range 1-27), we recorded 5 complications (8.5%): 3 bleeding and 2 non-bleeding ulcers. All of the complications were treated successfully by medical (non-bleeding ulcers) and endoscopic therapy (bleeding ulcers).

At the end of a mean follow-up period of 29 months (range 2-140), 15 of the patients were dead (25%). Causes of death were bleeding from upper-GI vascular ectasia in three (5%), and associated diseases in the others (4 for neoplastic disease, 5 liver failure, 2 heart disease, 1 gangrene and sepsis). There was no treatment-related mortality. All the deaths for bleeding happened more than two weeks after the last laser session, so were not considered a complication of laser treatment.

Effect of laser therapy on bleeding and blood transfusions

On the basis of endoscopic findings, complete and partial remission was obtained in 31 (53%) and 19 (32%) respectively, while no improvement was seen in 9 (15%). Long term control of macroscopic bleeding (haematemesis, melaena) was achieved in 80% of the patients. The total number of blood units transfused during the observation period was a mean of 18±4.1 per patient (range 1-130). Following laser treatment the mean number of blood transfusions per month was reduced from 3.62±0.76 to 1.7±1 ($p<0.01$). Transfusion independence following laser therapy was obtained (28) or maintained (8) in 36 patients (61%) and a reduction in the number of blood transfusions per month was achieved in 13 (22%). In 10 patients (17%), instead, there was no improvement in blood transfusion dependence. Out of the 9 patients not requiring blood transfusions before laser treatment, one subsequently did (11%) when haemoglobin levels worsened. Transfusion requirements were significantly reduced compared to pre-treatment after one to 6 laser sessions, while this reduction in patients who underwent 7 or more sessions was not statistically significant [**figure 1**]. The efficacy of laser therapy, in terms of blood transfusion reduction, correlated with the endoscopic healing appearance ($p<0.01$). [**Table 1**] Nevertheless recurrence of severe anaemia requiring blood transfusions was found in 6 out of 31 patients (19%)

who showed a complete endoscopic regression of upper-GI telangiectasia. The causes were: colonic angiodysplasia in 2, jejunal-ileal angiodysplasia in 2, small-bowel cancer in 1 and gastric telangiectasia recurrence in 1. In these patients Jejunal and small bowel lesions were discovered by means of enteroscopy and capsule endoscopy. Laser efficacy was likewise related to the number of blood transfusions required the year before treatment was begun. It was found to be significantly worse in those patients who needed more than 10 blood transfusion units per year with respect to those who required fewer ($p<0.05$). Another important factor related to treatment success was the telangiectasia localization: gastric lesions showed more improvement than did duodenal or jejunal ones ($p<0.01$). The number of vascular ectasias was not found to be an important factor. Finally no difference was found between the cirrhotic patients and the other subjects and, in the cirrhotic group, between those with signs of portal hypertension (those who had previously been treated for esophageal varices) and those without.

Surgical treatment

Four patients with persistent bleeding were treated by surgical measures:

1) A patient who had undergone 2 laser sessions for gastric telangiectasia was subsequently admitted for acute intestinal bleeding. Following an EGD that excluded gastro-duodenal acute bleeding and for the persistence of a severe haemorrhage, the patient underwent exploratory laparotomy. An intraoperative enteroscopy found multiple bleeding telangiectasia in the terminal ileum and an ileocaecal resection was then carried out, resolving the acute bleeding. Following surgery the patient remained transfusion-dependent and capsule endoscopy demonstrated diffuse jejunal and ileal vascular lesions, so the patient underwent laser therapy once again through enteroscopy.

2) A patient affected with multiple antrum telangiectasia and caecal angiodysplasia, who remained transfusion dependent despite 11 sessions of laser therapy, underwent antrectomy with Billroth II anastomosis and ileocaecal resection. The histological report confirmed the diagnosis of submucosal angiodysplasia in both the antrum and caecum. Following surgery the patient became transfusion independent during the 3 year follow-up.

3) Two patients with watermelon stomach who still necessitated blood transfusions despite 2 and 7 laser sessions respectively, underwent liver transplantation for cirrhosis. Both became transfusion independent following liver transplantation.

Complete remission of bleeding was then obtained in 75% (3/4) patients after surgery.

Prognostic factors	Patients without transfusions / total			P
Endoscopic aspect: complete vs incomplete healing	25/31 (81%)	vs	11/28 (39%)	<0.01
<10 vs ≥ 10 Blood Units/year before laser	32/47 (68%)	vs	4/12 (33%)	<0.05
Gastric vs duodenal or jejunal telangiectasias	26/35 (74%)	vs	10/24 (42%)	<0.05
<5 vs ≥ 5 telangiectasias	16/22 (73%)	vs	20/37 (54%)	n.s.
Cirrhotics vs others	20/30 (67%)	vs	16/29 (55%)	n.s.
Portal hypertension vs non hypertension in cirrhotics	7/10 (70%)	vs	13/20 (65%)	n.s.

Table 1: evaluation of prognostic factors in obtaining a complete transfusion independence after endoscopic laser treatment of upper GI vascular ectasia. Patients are each time categorized according to the different risk factors.

DISCUSSION

As already demonstrated by other authors, laser therapy for upper gastro-intestinal vascular ectasia is a safe method, associated to few complications and minimal mortality. This was confirmed in the patient group studied by us in whom treatment related mortality was absent and morbidity low. Only 5 of our patients suffered from complications and all were successfully treated by medical and endoscopic therapy. Nevertheless, two cases of mortality after gastric perforation have been described in literature [21,22] but it must be emphasized that in both the energy applied had been excessive (28000 and 14000 J in a single session). We applied a mean of 2667 J per session and care was taken to avoid tissue necrosis. Nevertheless 8.5% of our patients developed an ulcer, and that is why we always prescribe high dosage proton pump inhibitors during treatment and wait a month between sessions. In fact some necrosis in the treated area is unavoidable, thus causing erosions or ulcers that are detectable in the first 2 weeks after treatment.

The risk of developing hyperplastic polyps after laser therapy was evaluated by Geller et al [28] who observed 7 in a total of 60 cases receiving laser therapy. Another case was described by Mathou [22] and 3 others by Gostout [24]. We found hyperplastic polyps in 8 out of our 59 patients, but only two of them after laser treatment. The fact that these lesions were already present in 6 cases before treatment was begun, seems to indicate that there is a possible association between the two diseases rather than that laser therapy is responsible for their development. Antrum narrowing and pyloric stenosis are other generally asymptomatic reported complications that can be treated by balloon dilatation [21,22].

On the basis of our experience laser therapy was effective in controlling macroscopic bleeding in 80% of the patients and in achieving or maintaining blood transfusion independence in 61%. In another 22% a reduction in blood transfusion requirement was obtained, while in 17% there was no improvement and 3 patients (5%) died as a result of GI bleeding. These findings are less enthusiastic than those reported by Gostout [24] (no transfusion requirement in 24/28, 86%), and by Mathou [22] (20/24, 83%) concerning laser treatment in patients with exclusively watermelon stomach, but they are similar to those reported by Sargeant [21] regarding laser ablation of all kinds of upper GI vascular ectasia (minimal or no transfusion requirement in 25/41, 61%; number of transfusions kept under control by laser in 22%, laser failure in 17%).

Surgical treatment for gastric vascular ectasia consists in gastric resection or gastrectomy and, in cirrhotic patients, in liver transplantation. Removing the diseased tissue or organ would seem, when possible, the most effective therapeutic option to cure watermelon stomach.

As only case reports dealing with this subject can be found in the literature, it is difficult to draw conclusions. In a review by Novitsky et al [29], only 2/45 (4.4%) patients required transfusions during the 1-48 month follow-up period following gastrectomy or antrectomy for watermelon stomach, while post-operative mortality in this group was 3/45 (6.6%). Patients with upper GI vascular ectasia, in fact, often present associated diseases that increase the risk of surgery. Analysis of our data showed that surgery was successful in 75% of the patients studied and mortality was absent. It was unsuccessful in only one emergency operation in which the origin of bleeding was difficult to detect even using intraoperative enteroscopy. Moreover as the disease was extended to the entire GI tract, complete healing was impossible.

Emergency surgery for GI vascular ectasia should in any case be avoided and patients who might benefit from a surgical treatment should be selected ahead of time and studied carefully.

Which are then the characteristics of the patient who would probably benefit from surgery? Traditionally surgery has been considered the last resort following the failure of medical and endoscopic therapy [24]. Thus indication for surgery should be limited to those patients in good general health and whose response to laser therapy is expected to be inadequate [**Figure 2**]. In our study poor response to laser therapy was found in patients requiring more than 10 blood units during the year before treatment was begun and in those with extra-gastric (duodenal or jejunal) disease. The latter unfortunately tend to be poor surgical candidates.

It was found that the mean number of laser sessions to obtain complete healing was 2, but significant improvement was possible up to 6 sessions. After that cut off point laser therapy does not seem to be beneficial. Then from our experience it would seem that surgery should be considered only after 6 unsuccessful laser sessions. This is in contrast with reports by Novitsky et al

[29], who considered a trial of one or two endoscopic sessions sufficient to identify patients for endoscopic treatment. Analysing the results of Nd:YAG laser therapy on 36 patients with upper GI vascular ectasia, Sargeant et al [21] found that it was significantly effective in reducing transfusion dependence up until 24 months. After that time the difference was not statistically significant. In our opinion two years is in any case a long period to wait before deciding if the patient is responding to therapy and consequently if surgery should be considered.

Before any medical, endoscopic or surgical treatment is initiated, colonoscopy needs to be performed to exclude other sources of bleeding. If there is a non satisfactory response to endoscopic therapy or to complete staging before surgery, enteroscopy and capsule endoscopy should be performed and another colonoscopy should be carried out. These are necessary as it is possible that the disease is extended to the colon (10%), jejunum and ileum (here detected in 7%, but probably much more frequent), and to exclude other causes of bleeding along the entire intestinal tract (we found by capsule endoscopy that one no-responder patient had a small bowel cancer). Enteroscopy and capsule endoscopy moreover should always be performed in symptomatic patients with HHT. Proctor et al, in fact, found telangiectasia in the first 60 cm of ileum of 89% of GI bleeding HHT patients [30] and Ingrosso et al observed small-bowel telangiectases by capsule endoscopy in 10/13 patients with HHT and gastric involvement [31].

Special mention should now be made to the watermelon stomach in cirrhotic patients. Antrectomy is in fact associated to high perioperative morbidity and mortality in this group of patients [29]. Some authors have reported that this subpopulation does not respond well to endoscopic ablation therapies [29, 32] and advocate the use of portal decompression as a bridge to surgery [29] or as conclusive treatment if portal hypertension is involved [33]. While single case reports have described successful treatment of watermelon stomach in cirrhosis using radiological or surgical porto-caval shunt [33,34], Spahr et al [35] and Kamath et al [36], have on the other hand reported that transjugular intra-hepatic portosystemic shunt was ineffective in a large group of patients with GI vascular ectasia.

In our patients with cirrhosis outcome of laser treatment was not worse with respect to results in other diseases and complete transfusion independence was achieved in 20/30 (67%). Moreover we did not find a significant difference between cirrhotic patients with signs of portal hypertension and those without. In two patients who did not respond to laser therapy, despite 2-7 laser sessions, liver transplantation was effective in healing watermelon stomach. Vincent et al likewise reported that antral lesions were healed in two patients following transplantation for cirrhosis [37] despite persistence of portal hypertension. Of course telangiectasia in cirrhotic patients is not per se an indication for liver transplantation.

In conclusion endoscopic laser treatment is safe and effective in controlling bleeding and in reducing the blood transfusions in about 80% patients. Surgical treatment, after adequate staging, should be considered in those patients requiring more than 10 blood units per year or who have undergone more than 6 laser sessions without improvement.

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Gastrointestinal telangiectasia: a study by EGD, colonoscopy, and capsule endoscopy in 75 patients.

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Abstract

Background: The distribution of lesions in the gastrointestinal tract in patients with sporadic telangiectasia is at present unknown.

Patients and methods: Seventy-five patients with sporadic telangiectasia underwent esophagogastroduodenoscopy (EGD), capsule endoscopy, and colonoscopy. Endoscopic diagnosis of telangiectasia and gastrointestinal bleeding were required for enrollment in the study. Hemorrhagic diathesis, co-morbidity, number of blood transfusions, and subsequent management were also noted.

Results: Thirty-five of the patients presented gastroduodenal vascular lesions, 51 small-bowel lesions, and 28 colonic lesions. Sixty-seven percent of patients in whom EGD found telangiectasia also presented small-bowel vascular lesions at capsule endoscopy and 43% colonic lesions at colonoscopy. Fifty-four percent of the patients with positive colonoscopy also presented gastroduodenal lesions and 48% small-bowel lesions. Patients with known duodenal lesions were more likely to have small-bowel lesions at capsule endoscopy (odds ratio [OR] 10.19, 95% CI 2.1–49.33, $P = 0.003$). Patients with associated diseases, such as liver cirrhosis, chronic renal failure, or heart valvulopathy, presented more severe disease requiring blood transfusions (OR 6.366, 95% CI 1.39–29.2, $P = 0.015$). The number of blood transfusions correlated with the number of sites affected ($R = 0.35$, $P = 0.0023$). The detection of new lesions at capsule endoscopy allowed new treatment in 46% of patients. Mean follow-up was 18 months.

Conclusions: Sporadic telangiectasia is a multifocal disease potentially involving the whole digestive tract. Patients with duodenal telangiectasia show a higher risk of jejunal or ileal lesions. Capsule endoscopy is a useful diagnostic tool for the detection of such small-bowel vascular lesions, indicating a more specific prognosis and treatment strategy.

Introduction

Gastrointestinal telangiectasia is an important cause of gastrointestinal bleeding. Occasionally, presentation with acute bleeding can be life-threatening in patients in poor clinical condition. Generally, patients with this disease present with chronic bleeding and significant anemia requiring blood transfusions.

In hereditary hemorrhagic telangiectasia (HHT), genetic alterations of the receptors for the angiogenic transforming growth factor-β have been identified [1,2]; by contrast the pathogenesis of the sporadic form of intestinal hemorrhagic telangiectasia is unknown. Most cases are sporadic, and association with autoimmune disorders [3], liver cirrhosis [4], renal failure [5], aortic stenosis [6], and ischemic heart disease [7] has been reported. Bleeding vascular ectasias can be difficult to diagnose and to treat. The diagnosis is generally made on the basis of esophagogastroduodenoscopy (EGD) or colonoscopy, but lesions located in the small bowel are inaccessible to conventional endoscopy and can be detected only by push enteroscopy, double-balloon enteroscopy, or capsule endoscopy.

Patients experiencing bleeding or who are dependent on transfusions despite iron therapy should be treated. Treatment modalities are medical therapy, endoscopic ablation, or hemostasis and surgical resection.

Surgical resection is the most radical treatment, but associated illnesses increase the mortality risk. Moreover, as the disease is multifocal, surgical resection can sometimes be ineffective. Pharmacological therapy with corticosteroids [8], tranexamic acid [9], octreotide [10], or estrogen and progesterone [11,12] has been proposed to control gastrointestinal bleeding due to vascular ectasia, but contradictory results have been reported [13]. Endoscopic treatment consists of sclerotherapy [14,15], electrocoagulation [16], heater probe coagulation [17], argon plasma coagulation [18,19], and laser therapy [6,20]. In a previous study [21], laser therapy with Nd:YAG resulted in cessation of blood transfusions in 61% of the patients with upper gastrointestinal vascular ectasia and reduced the demand in another 22%. Unfortunately, 17% of the patients did not respond to the treatment, and 5% died because of bleeding. The failure of endoscopic therapy can in some cases be explained by small-bowel lesions. What happens in these cases is that only those lesions detected by EGD or colonoscopy are treated, while the disease is still active in the rest of the gut. Investigators studying HHT have reported that push endoscopy [22] or capsule endoscopy [23] identified small-bowel lesions in 56–89% of the patients. Tang et al. [24] described two patients

with gastric antral vascular ectasia (GAVE) who presented small-bowel lesions at capsule endoscopy, and that is why they proposed the name "gastric intestinal vascular ectasia" (GIVE).

The aim of the present study was to examine the whole gastrointestinal distribution of non-hereditary hemorrhagic telangiectasia from the perspective of EGD, capsule endoscopy, and colonoscopy. Risk factors predicting small-bowel lesions and the development of a more severe transfusion-dependent stage were also evaluated. The role of capsule endoscopy in the therapeutic management of the patients was examined.

Study design

All the patients who underwent EGD, colonoscopy, or capsule endoscopy in our department (a tertiary referral center) from July 2002 to November 2006 and in whom evidence of angiectasia was revealed were considered for enrollment in the study. Inclusion criteria were: (i) the presence of gastrointestinal vascular ectasia found at any of the following endoscopic examinations: EGD, colonoscopy, or capsule endoscopy; and (ii) any of the following: sideropenic anemia, or occult or overt gastrointestinal bleeding. Exclusion criteria were: diagnosis of HHT [25], other causes of bleeding (such as varices, ulcers, tumors), cardiac pacemaker or other electromedical device, clinically suspected or documented intestinal strictures, pregnancy, age below 18 years, and refusal to give signed informed consent.

All enrolled patients underwent a clinical examination and exploration of the whole gastrointestinal tract: all bleeding patients with telangiectasia on EGD underwent colonoscopy and capsule endoscopy; all patients with telangiectasia found on colonoscopy underwent EGD and capsule endoscopy; all bleeding patients with negative conventional upper and lower gastrointestinal endoscopy who had telangiectasia on capsule endoscopy were also enrolled. A follow-up examination was then performed at 6-monthly intervals, to record which therapy the patients were following after endoscopic staging and the clinical outcome.

This study was performed in accordance with the principles of the Declaration of Helsinki. All the patients who participated gave their informed written consent, and the use of capsule endoscopy was approved by the Ethics Committee of the University Hospital of Padova.

Methods

Clinical examination

During the clinical examination the patients were asked about their medical history. Clinical information was requested regarding bleeding symptoms, bleeding lesions, associated diseases, use

of anticoagulant or antiplatelet drugs, hemoglobin and iron levels, platelet count, prothrombin time, and activated partial thromboplastin time.

Push endoscopy

EGD, colonoscopy, and enteroscopy were performed utilizing video endoscopes (Olympus Co., Ltd., Tokyo, Japan and Pentax Corp., Tokyo, Japan). Patients were sedated with propofol for colonoscopy or enteroscopy, while those undergoing EGD received local anesthesia (lidocaine).

The diagnosis of telangiectasia was made when bright red mucosal lesions at least 2 mm wide were detected. Differentiation of watermelon stomach from portal hypertensive gastropathy in cirrhotic patients was made when diffuse or linear red spots were located in the antrum [26]. The number, size, and position of all vascular lesions were recorded.

Capsule endoscopy

Bowel cleansing was achieved using PEG 4000 (Norgine Italia SrL, Milan, Italy) in all patients [27]. A 4-L solution was administered the day before capsule endoscopy. Metoclopramide 10 mg (Gruppo Lepetit SpA, Rome, Italy) was administered intramuscularly 10 minutes before an M2A Given Capsule (Given Imaging Ltd., Yoqneam, Israel) was swallowed by the patients with a sip of water after overnight fasting. Patients were allowed to drink water or take medication 2 hours later and to eat a light snack 4 hours later while continuing to carry out their usual activities. Eight hours after ingestion of the capsule, the equipment was removed. If the device was not expelled within 4 days, a plain film of the abdomen was obtained and the patient closely observed until expulsion of the capsule. The capsule video films were reviewed by two gastroenterologists (RD and GCS), who were unaware of the clinical picture, at 15–20 frames per second. Vascular ectasia was taken to be a circumscribed, patchy, flat, sharply demarcated area of redness [28]. Medium to large vascular lesions (>2 mm [23]) recognized by both endoscopists were considered significant. The number, size, and position of all vascular lesions were recorded.

Follow-up

All the patients were contacted by telephone every 6 months and offered an appointment for a clinical examination. During the follow-up examinations the patients were questioned about the treatment they had been4 following since their capsule endoscopy exam. They were also asked if they had experienced gastrointestinal bleeding or had undergone transfusions. Data concerning those patients who were available for at least 6 months' follow-up were included in our results.

Information concerning the number of blood units needed before the study and during follow-up was provided by two provincial transfusional services (Padova and Treviso, Italy). These data were utilized for staging of the disease, which was considered severe when the patients required blood

transfusions, and to assess whether any improvement had taken place after treatment (absence of blood transfusions during follow-up).

Treatment protocol

The management protocol was as follows. Patients taking anticoagulants or nonsteroidal anti-inflammatory drugs were evaluated for treatment suspension or replacement with other less risky drugs. Anemia was managed with iron therapy and blood transfusions according to hemoglobin and ferritin levels. Lesions which could be reached with EGD, colonoscopy, or enteroscopy were treated with diode laser, injection therapy, or argon plasma coagulation. The number of sessions depended on the clinical results. Persistent bleeding was managed by surgery where indicated [21].

Study aims, sample-size calculation, and statistical analysis

The aim of the study was to evaluate the prevalence of small-bowel vascular lesions in patients with gastrointestinal telangiectasia and to obtain evidence of how often the disease has multiple locations. Ingrosso et al. [23] found small-bowel telangiectasias with capsule endoscopy in 10 out of 13 patients with gastric lesions, with a prevalence of 77%. We therefore considered it necessary to enroll at least 64 patients to obtain a 95% confidence level and a 5% confidence interval.

As secondary endpoint, the utility of staging the disease with capsule endoscopy was assessed. We recorded the detection of new lesions on capsule endoscopy, and noted when this finding defined a new treatment strategy (endoscopic treatment of previously unknown intestinal lesions, medical or surgical therapy as indicated) in the patient management. Treatment efficacy was judged on the number of blood transfusions needed during follow-up.

Statistical analysis was carried out using the Statistica 5.0 package software. Fisher's exact test or Yates' corrected X^2 test were used, when appropriate, to compare the frequency of predictors in the different groups. Multinomial logistic regression was used to identify possible predictors of the presence of telangiectasia in jejunum and ileum, of severe bleeding requiring transfusions, and of macroscopic bleeding. Spearman's test was used to analyze the correlation between the number of blood units needed and the number of affected sites. Statistical significance was set at $P < 0.05$.

Results

Patients enrolled after EGD or colonoscopy

From July 2002 to November 2006, 5546 EGDs and 4541 colonoscopies were performed in our endoscopy unit. Seventy-four patients were diagnosed with gastrointestinal telangiectasia and were considered for inclusion. Twenty-one patients who had no anemia or evidence of gastrointestinal bleeding, nine who refused to undergo capsule endoscopy, and eight presenting other causes of bleeding (esophageal varices, polyps) were excluded from this study. In conclusion, 36 patients were enrolled to complete the endoscopic exploration after EGD or colonoscopy.

Patients enrolled after capsule endoscopy

Over the same time period, 372 patients underwent capsule endoscopy in our department for obscure bleeding (negative colonoscopy and gastroscopy). Capsule endoscopy detected significant vascular ectasia in 39 patients: 33 had lesions in the small bowel (in five cases also associated with colonic or duodenal vascular lesions), five in the cecum, and one in the duodenum.

Clinical data

The total number of patients with telangiectasia who underwent complete exploration of the gut with EGD, colonoscopy, and capsule endoscopy was 75 (42 male and 33 female, median age 74 years, age range 24–87 years). Bleeding was overt in 31 patients and occult in 44. A mean of 30 blood units (range 2–187) were required in 42 patients, while 33 received iron therapy only. Twenty-four patients presented hemorrhagic diathesis at the time of endoscopy (six of these were using antiplatelet drugs, four nonsteroidal anti-inflammatory drugs, eight anticoagulants, five had liver cirrhosis, and one von Willebrand disease). Other associated diseases were chronic renal failure in five patients, heart valvular disease in 10, ischemic heart disease in three, vasculopathy in three, autoimmune disease in one, and neoplastic disease in two.

Capsule endoscopy examination

Average recording time was 7 ± 1 hours. The procedure was well tolerated in all patients. Visualization of the small bowel was defined as "sufficient and adequate" in all except 10 exams (12%). In two of these the capsule was not able to explore the small bowel (in one case it lodged excessively in the stomach and in the other the battery ran out). In eight exams there was residual luminal content that did not permit good visualization of the small-bowel mucosa (blood in five patients, bile/food in three). No case of capsule retention occurred. Capsule endoscopy was repeated successfully in seven cases. At the end of the study capsule endoscopy had produced clean and recognizable small-bowel images in 72 patients.

The average time for interpretation of capsule endoscopy videos was 70 ± 30 minutes.

Distribution of the lesions

Lesions were sporadic (fewer than 10 [23]) in 37 and multiple (more than 10) in 38 patients. The lesions were located in the stomach in 22/75 (29%), in the duodenum in 23/75 (31%), in the jejunum in 37/72 (51%), in the ileum in 34/72 (47%), and in the colon in 28/75 (37%). Sixty-seven percent of patients with positive EGD showed small-bowel lesions on capsule endoscopy and 43% colon lesions on colonoscopy. Fifty-four percent of patients with positive colonoscopy presented gastroduodenal lesions on EGD and 48% small-bowel lesions on capsule endoscopy. Associations between the different sites involved are outlined in Tables 1 and 2.

Risk of presence of small-bowel lesions

The risk factors for small-bowel lesions when telangiectasia was detected at EGD or colonoscopy were analyzed. Sex, age, the site of the vascular lesions at EGD or colonoscopy, macroscopic bleeding or blood transfusion requirement, hemorrhagic diathesis, and associated diseases were analyzed in univariate analysis (Table 3). A significant association with transfusion requirement, duodenal lesions, and associated diseases was found. Multivariate analysis showed that only the presence of duodenal lesions significantly predicted the presence of small-bowel lesions (OR 10.19, 95% CI 2.10–49.33, $P = 0.003$).

Risk of severe bleeding

Risk of severe bleeding (defined by blood transfusion requirement and the occurrence of macroscopic bleeding) was assessed in all 75 patients studied. In the univariate analysis, multiple lesions, hemorrhagic diathesis, associated diseases, duodenal lesions, ileal lesions, and the number of sites affected (≥2 tracts versus a single tract) (Table 4) seemed to be associated with blood transfusion requirement. Associated diseases were the major predictor of transfusion requirement on multivariate analysis (OR 6.37, 95% CI 1.39–29.20, $P = 0.015$). The number of blood transfusions correlated with the number of sites affected ($R = 0.35$, $P = 0.0023$). According to univariate analysis, macroscopic bleeding was more frequent in women and in the presence of gastric involvement, and the latter was confirmed by multivariate analysis (OR 4.66, 95% CI 1.53–14.20, $P = 0.006$) (Table 4).

Follow-up data

Fifty patients were followed for a mean of 18 months (range 6–42 months). Thirty patients received endoscopic treatment, which successfully removed all detected lesions in 14 of them. Additional vascular lesions, not seen on conventional endoscopy, were detected by capsule endoscopy in the duodenum, the small bowel, or the colon of 35/50 patients (Figure 1). On the basis of capsule endoscopy findings, surgical resection was carried out in four, endoscopic treatment of new sites was performed in 14 (by laser probe or sclerosis), and antiplatelet or anticoagulant therapy was suspended in five patients. Capsule endoscopy therefore influenced the treatment management in 23/50 patients (46%). Independence from blood transfusions during follow-up was achieved in 21/23 patients (91%) following treatment.

Discussion

To our knowledge this is the largest study ever conducted on patients with sporadic intestinal telangiectasia undergoing complete exploration by means of EGD, capsule endoscopy, and colonoscopy.

Capsule endoscopy was utilized in patients with HHT by Ingrosso et al. [23], who reported small-bowel lesions in 10 out of 18 patients (56%). All those with small-bowel involvement also had gastric lesions on EGD. HHT (or Rendu–Osler–Weber disease) is a multisystem vascular disease that can also involve the lung, liver, brain, and skin. It is thus not surprising that lesions were found along the whole intestinal tract. Proctor et al. [22] found jejunal lesions in 89% of 27 patients with HHT and gastrointestinal bleeding who underwent push endoscopy. They also demonstrated a correlation between the number of lesions found in the stomach or duodenum and those in the jejunum. Tang et al. [24] found small-bowel vascular lesions with capsule endoscopy in two cases of gastric antral vascular ectasia.

The findings of the present study demonstrate that even patients with sporadic telangiectasia are at high risk of multifocal disease. In fact, 67% of the patients in whom EGD detected vascular lesions also presented small-bowel lesions on capsule endoscopy, and 43% colonic lesions on colonoscopy. The frequency of small-bowel lesions was also high (48%) in patients with colonic angiectasia. This finding underlines the importance of small-bowel exploration in staging telangiectasia. Patients with duodenal disease, who are more at risk of small-bowel vascular lesions (OR 10.19), should be monitored in particular.

Small-bowel exploration is also helpful in managing the disease in patients who respond poorly to conventional endoscopic treatment. In fact, the recognition of new vascular lesions by capsule endoscopy permitted new treatment strategy in 46% of the patients, 91% of whom achieved transfusion independence. In a previous study we reported that endoscopic laser treatment of upper gastrointestinal lesions was unable to halt transfusion dependence in 39% of patients [21] with telangiectasia, who can require up to 4–6 blood units a month. Even more important than the high toll that this has on the community, it should be remembered that 5% of these patients eventually bleed to death [21]. Persistence in bleeding can be due to the presence of a large number of lesions in a restricted area, as in the watermelon stomach, or to a distribution of lesions along the whole gut. In the first case, when endoscopy fails, surgery should be considered; in the latter it may not be enough, or may even be useless.

Since the recent introduction of capsule endoscopy, this new diagnostic modality is being utilized to obtain images of the entire small-bowel mucosa, which was previously inaccessible to noninvasive procedures. Even push endoscopy has been found to miss a third of the vascular lesions detected by capsule endoscopy. In their meta-analysis Leighton et al. [29] included 14 studies carried out in patients with obscure gastrointestinal bleeding in whom capsule endoscopy and push endoscopy were compared. According to that analysis, capsule endoscopy offered a 35% incremental yield for all findings and a 30% advantage for clinically significant findings (P <0.01). In our experience, we utilized push endoscopy usually for treatment purposes in those patients shown to have small-bowel lesions on capsule endoscopy. Double-balloon enteroscopy (DBE) is a new endoscopic tool that can explore the entire small bowel and treat lesions, including vascular ectasia [28]. It is, however, a time-consuming, invasive procedure that should be limited to patients with treatable lesions detected by capsule endoscopy [30,31]. We did not have the opportunity to treat patients with DBE, but we expect a significant impact of this procedure on the outcome of patients with bleeding lesions in the small bowel.

Although the pathogenesis of gastrointestinal vascular ectasia is unknown, several disorders, such as chronic renal failure, liver cirrhosis, and heart valvulopathy, have been found in association with this disease, and in the present study 40% of the patients presented associated disease. Detection by capsule endoscopy of small-bowel telangiectasia in chronic renal failure and liver cirrhosis has already been reported in the literature. Using capsule endoscopy, Karagiannis et al. [32] detected small-bowel angiectasia in 8/17 (47%) patients with chronic renal failure and De Palma et al. [33] in 9/37 (24.3%) patients with cirrhosis. Both these authors demonstrated a higher prevalence of the lesions in these patients than in controls. Moreover, we found that associated diseases are significant predictors (OR 6.37) of the development of a more severe stage of the disease requiring blood transfusions.

Identifying patients with multifocal disease is in any case an important prognostic factor, as they will require a large number of blood transfusions (R = 0.35, P = 0.0023).

In conclusion, sporadic hemorrhagic telangiectasia often spreads to the whole digestive tract, including the small bowel. Patients with duodenal disease are more at risk of lesions in the jejunum or ileum. Capsule endoscopy is preferable to push endoscopy for detecting small-bowel vascular lesions and can help to identify treatment strategy and the prognosis of the disease.

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Chapter 2:

Primary prophylaxis of variceal bleeding in candidates for liver transplantation

A randomized study comparing ligation with propranolol for primary prophylaxis of variceal bleeding in candidates for liver transplantation.

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Abstract

Aim: Whether beta-blockers or banding is the best therapy for primary prophylaxis of variceal bleeding is subject to debate. A randomized comparison between the two treatments was performed in candidates for liver transplantation.

Patients and methods: Sixty-two patients with Child B-C cirrhosis and high risk varices received propranolol (31) or variceal banding (31). Primary end point was variceal bleeding.

Results: Variceal hemorrhages were 2 (6.5%) in the banding, related to post-banding ulcers, and 3 (9.7%) in the propranolol group (p=n.s.). Deaths and bleeding related deaths were respectively 3 and 1 for banding and 3 and 2 for beta-blockers (p=n.s.). Fourteen patients underwent liver transplantation in the banding and 10 in the propranolol group (p=n.s.). Adverse events were 2 post-banding ulcer bleedings in ligated patients (one fatal) and 5 were intolerant to propranolol (p=n.s.). Mean costs per patient were higher with banding than with propranolol treatment (4289±285 versus 1425±460 Dollars, p<0.001). **Conclusions:** Propranolol and banding are similarly effective in reducing the incidence of variceal bleeding in candidates for liver transplantation, but ligation can be complicated by fatal bleeding and is more expensive. Our results suggest that banding should not be utilized as primary prophylaxis in transplant candidates who can be treated with beta-blockers.

Introduction

Non-selective β-adrenergic antagonists are widely used in the prevention of first hemorrhage from esophageal varices in patients with cirrhosis and portal hypertension.(1) These drugs reduce the risk of bleeding by about 45% and the mortality rate by 20% at 2 years. (2) Unfortunately, many patients have contraindications or severe side effects making it necessary to suspend therapy. (3,4) This is why other treatments have been used to prevent the first episode of variceal bleeding in high risk patients, in particular two endoscopic techniques: sclerotherapy and endoscopic variceal ligation (EVL). Sclerotherapy has been abandoned because several trials have reported increased mortality, as well as morbidity due to complications. (5,6) EVL, that results in fewer complications than sclerotherapy in the prevention of rebleeding, (7-10) is the currently used endoscopic therapy for primary prophylaxis of esophageal variceal bleeding. Several trials comparing EVL with beta-blockers (BB) in primary prophylaxis have been performed, (11-16) but whether BB or endoscopic banding is the best therapy is still unclear and still subject to debate. (17,18)

The aim of the present study was to compare, by means of a randomized controlled trial, the safety and the results of EVL versus BB, in the prevention of the first variceal bleeding in patients who are candidates for liver transplantation (LT).

Methods

Study design

A prospective randomized trial was conducted in the Department of Surgical and Gastroenterological Sciences of Padova University, where LT is performed. Study subjects were selected from those patients referred for LT evaluation. The patients enrolled met the inclusion and exclusion criteria summarized in **table 1.** The study was performed according to the 1975 Declaration of Helsinki and the study protocol was approved by the ethics committee of the University of Padova, Italy.

Randomization, Treatments and follow-up schedule

After the patients were enrolled, treatment assignment was made by opening a sealed opaque envelope that designated one of the two treatments: EVL or BB. Numbers of randomization were assigned by a statistical software. After starting treatment all patients had an EGD and a clinical examination every 6 months and were provided with the emergency numbers of investigators so that they could report all new events about treatment complications or bleeding. During the screening and follow-up endoscopies, varices were graded according to Beppu's classification (19). Their extension in length was also recorded. Moreover gastric varices and hypertensive portal gastropathy were detected and their severity described.

Endoscopic variceal ligation

At the first session a diagnostic EGD without the ligation device was performed before banding to confirm the presence of high risk esophageal varices and the absence of gastric varices. Banding placement was then performed using multiband ligator with 6 or 7 bands (Sixshooter, Wilson-Cook, Winston-Salem, NC; SpeedBand SuperView Super7, Boston Scientific, Inc., Natick, MA). The endoscopist entered the esophagus only once and banded the varices starting from the cardias and progressing proximally every one cm, in an upward spiral fashion attempting to avoid placing the bands too close together. Patients were treated during a one-day hospital stay, followed by a liquid diet for 24-hours and semi liquid one for 1 week. Subsequent sessions were performed every two weeks until the varices were completely eradicated avoiding to place the bands near to the scars left by the previous treatment. During the period of eradication patients were also prescribed proton-pump inhibitors. Recurrent varices detected during the follow-up EGD were banded again using the same method as above.

Beta-blocker therapy

Patients were treated with propranolol, starting with a low dosage of 10 mg twice a day and increasing by 20 mg/day until a 25% reduction of the baseline heart rate was obtained. One hundred

and sixty mg twice daily was considered the maximal dosage. Patients recorded their systolic and diastolic blood pressure and their pulse rate twice a day. After the first week time these recordings were sent by fax to the study investigator, who decided if the propranolol dosage needed to be modified. The process was repeated weekly until the maximum tolerated dose was achieved.

Treatment was interrupted when the systolic blood pressure fell to below 90 mmHg or the heart rate was under 50 beats/min or when patients developed severe disabling side effects. At every six month check up, pulse rate and blood pressure were taken and all home recordings, that the patients brought, were reviewed by the study investigators.

Treatment end-points and treatment failure

These were defined as the following:

1) Death from esophageal variceal bleeding.
2) Esophageal variceal bleeding confirmed by an EGD
3) Major complications due to endoscopic treatment.
4) Severe adverse effects caused by propranolol making it necessary to discontinue treatment.

All of the patients who developed upper gastrointestinal bleeding were hospitalized and underwent endoscopy for diagnosis. Patients with variceal haemorrhage were treated by sclerosant injection or, when possible, by banding. Treatment was suspended in patients who did not tolerate BB and EVL was then used. All bleeding events were recorded for the analysis of results on an intention-to-treat basis. The suspension of BB treatment was decided by a collegial discussion of 3 investigators and the consultation of a specialist was obtained (for example a cardiologist) when deemed appropriate. Patients who received liver transplantation were censored at this point for analysis.

All the treatment costs were calculated using Italian Health Ministry cost assignments current at the time, for both the groups of patients. They include treatment medications, endoscopic treatment, follow-up endoscopies and visits, hospitalization due to treatment-related complications, bleed-related hospitalization and readmission for rebleeding as well. In particular for the costs of propranolol therapy we considered the dosage and time of assumption of this drug, while costs of ligation sessions, endoscopies, visits and admission for bleeding were calculated according to the Diagnosis Related Groups (DRG).

Data management

Patients' data were collected prospectively by a study investigator, entered into data files and checked for completeness and accuracy by a second data manager.

Sample-size determination and statistical analysis

This study was carried out to verify the superiority of EVL with respect to BB in prevention of first variceal bleeding which was the primary end-point.

When this study was set up Sarin et al. (12) had published the first paper comparing BB with EVL in primary prophylaxis of variceal bleeding. On the basis of their results reporting a 28% reduction of bleeding incidence in EVL (15%) versus BB (43%) treated patients at 18 months, we hypothesized a smaller 23% difference of bleeding incidence between the two treatment groups. With this treatment difference a sample size of 51 patients per group was calculated to provide 80% power with a 2-sided α of 0.05 by log-rank test. A drop out rate of 15% was assumed, so that 60 patients needed to be included in each treatment group to provide 120 study patients. An interim analysis was planned when 50% of the patients had been enrolled. For continuous variables, comparison of the baseline characteristics of the two groups of patients was made using t test or the Mann Whitney test if a Gaussian model was not appropriate. When the variables were categorical, we used the chi-square or the Fisher's exact test. Discrete time-to-event outcomes (time to haemorrhage and death) were compared in the 2 groups by the Kaplan Meier method and significance testing by log-rank test. Statistical difference was set at $p<0.05$. Statistical calculations were made by using SAS software for Windows.

Results

Between September 2001 and December 2005, 99 patients who met the inclusion criteria were considered for this trial. Of these, 37 were excluded because they presented one or more exclusion criteria, while 62 patients were enrolled and randomly assigned to one of the two treatment groups: 31 EVL and 31 BB. At randomization the two groups were well matched with respect to baseline characteristics. **(Table 2)** All of the banding group patients, except for two who had severe complications, completed the treatment and came to the scheduled follow-up sessions. According to our follow-up, of the patients under BB, at least 95% maintained their maximally tolerated dose. Their mean compliance in reporting their pulse rate after the first week of treatment was 94%. The compliance rate of attending the six monthly EGD controls for both the treatments was 92%.

EVL

Out of 31 patients treated with EVL, two (6.5%, 95% C.I. 0-15.2%) presented with a dramatic hemorrhage due to post-banding ulcer that required emergency treatment with sclerosant injection. In both patients its developed few days after the first banding session. **(figure 1)** One of the 2 patients survived and underwent liver transplantation 3 months later, the other died despite treatment. Three sessions were sufficient in the other 29 patients for a complete eradication of varices. During banding and after variceal eradication, none bled from varices, while three patients presented with melaena due to portal hypertension gastropathy, in two cases requiring hospital admission. Variceal recurrence was reported by two patients at follow-up and underwent another banding session. Two patients died because of liver failure after 1 and 7 months respectively.

Fourteen patients underwent liver transplantation after a mean follow-up of 14.64 months (range 2-29 months).Mean costs for patient and mean standard error (including treatment, follow-up and bleeding-related costs) were 3383±225 Euros (4289±285 Dollars).

Propranolol

Patients were treated with a mean dose of 30 mg per day of propranolol (range 20-80 mg). During treatment the mean heart rate decreased from 79.7±13.0 to 62.3±6.9 beats/min (mean reduction percentage 22%). Treatment was suspended in 2 patients for persistent, symptomatic bradycardia (<55 bpm) despite the low dosage (10 mg twice a day), in 2 for symptomatic persistent hypotension (systolic pressure <90 bpm), and in one for vertigo. Of these 5 patients, one underwent a transplant one month later without complications, 3 were banded prophylactically: one subsequently had a liver transplantation without prior bleeding, another had no bleeding throughout the 16 month follow-up and the third developed a dramatic bleeding episode 6 months after endoscopic treatment from a recurrent cardial varix and subsequently died. The fifth patient who did not tolerate beta-blockers experienced a bleeding episode one month later, before prophylactic treatment banding was initiated. He received in emergency sclerosant injection and subsequently underwent banding. He died two months later of liver failure. Of the 26 patients who were able to continue propranolol treatment, one had variceal bleeding after 11 months follow-up and was treated with EVL and another was hospitalized for upper GI bleeding from portal hypertensive gastropathy. In both the reduction of the pulse rate was sub-optimal (<25%). One other patient died due to liver failure one month later. Globally, on an intention-to-treat basis, 3 patients from the propranolol group bled from esophageal varices (9.7%, 95% C.I. 0-20.1%) and 2 patients died of esophageal bleeding (6.5%, 95% C.I. 0-15.2%). Ten patients underwent liver transplantation after a mean follow-up of 7.6 months (range 1-19 months). Mean costs for BB patients and mean standard error (including treatment with propranolol, follow-up and bleeding-related costs) were 1124±363 Euros (1425±460 Dollars).

Study outcomes according to treatment allocation

The planned interim analysis was performed on an intention–to-treat basis. As summarized in **Table 3,** the difference between the rates of first esophageal variceal haemorrhage, the overall mortality and the bleeding-related mortality were not significantly different. Also the bleedings from portal hypertensive gastropathy were not significantly different.

The cumulative incidence of bleeding at one and two years were respectively 6.5% and 6.5% for the banding and 9.6% and 27.7% for the propranolol group **(figure 2)**. The cumulative global mortality at one and two years was 10% and 10% for banding and 6% and 25% for propranolol group **(figure 3)**. The bleeding related mortality at one and two years was respectively 3.2% and 3.2% for banding

and 3.5% and 22.9% for propranolol. The rates of liver transplantation were also not significantly different (14/31 in the banding and 10/31 in the propranolol group).

Both groups had adverse events requiring interruption of treatment (2 in the banding and 5 in the propranolol group, p=n.s.), but only variceal ligation was associated with fatal complications. According to an intention-to-treat analysis treatment failure (variceal bleeding or treatment interruption) was not significantly different between the two treatment groups (2/31 in the banding and 6/31 in the propranolol group, p=n.s.).

Recalculation of the sample size showed that more than 1000 patients per group would need to be enrolled to achieve a statistical significance for the small difference observed with 62 patients. For this reason and because of two iatrogenic bleedings that occurred after banding, one of which was fatal, we decided, after a collegial meeting, to bring the trial to an end.

Costs resulted significantly higher for EVL than for BB treatment ($p<0.001$) **(Table 4).**

	Inclusion criteria
1	Diagnosis of liver cirrhosis on the basis of clinical, biochemical or histological analysis.
2	Child-Pugh ≥ B7
3	Studied for liver transplantation.
4	Age between 18 and 65 years.
5	No previous bleeding from esophageal varices.
6	Signed informed consent.
7	Esophageal varices F3 or F2 blue with red signs, according to Beppu.[19]
	Exclusion criteria
1	Esophageal varices less than F3 or F2 blue with red signs.
2	Presence of gastric varices**.**
3	Previous endoscopic, radiological or surgical treatment of esophageal varices.
4	Hepatocarcinoma.
5	Portal vein thrombosis.
6	Severe heart, respiratory or renal failure.
7	Contraindications to beta-blockers (severe chronic obstructive pulmonary disease, sever asthma, severe insulin-dependent diabetes mellitus, brady-arrhythmia).
8	Treatment with nitrates, calcium antagonists or other anti-arrhythmic drugs, including beta-blockers, that can not be suspended.
9	Pregnancy.
10	Neoplasias.
11	An uncooperative attitude or the suspect that the candidate could or would not return for routine follow-up examinations.

Table 1: inclusion and exclusion criteria for the patients' enrollment.

Discussion

From the results of this study both propranolol and endoscopic banding reduced the expected incidence of bleeding in the presence of high risk varices of more than 30% after one year (20) to a lower percentage (6.5%-9.6% at one year).

The two treatments were not significantly different at the interim analysis and when the sample size was recalculated, it would have been impractical to continue randomization.

Other authors likewise interrupted their studies for similar reasons: Thuluvath et al, (13), reporting only 3 bleeding episodes (1 BB and 2 EVL) in 31 patients (15BB and 16 EVL), calculated that 424 patients would have been required in each group to show a statistically significant difference. Schepke et al, (14) who treated 152 cirrhotic patients (75 EVL and 77 BB), observed no significant difference between the two groups in terms of bleeding or mortality. This interim analysis of the planned randomization of 400 patients showed the impossibility of demonstrating a significant difference with completion of the study. Importantly Schepke et al (14) also reported two fatal bleedings due to ligation but no life-threatening complications in the propranolol group. Two other studies (11,15) found no significant difference in terms of first esophageal bleeding between EVL and BB.

The meta-analysis by Khuroo et al (21) included 596 patients and showed that prophylactic EVL significantly reduces bleeding episodes and adverse severe events in comparison to BB, but without any effect on mortality. However, although adverse severe events were found more frequently in the BB group, fatal complications were described only after EVL. The authors' conclusion was that endoscopic banding should be used only in those patients who cannot be treated with beta-blockers.

Jutabha et al (16) subsequently published a comparison of the two treatments on 62 patients who were transplant candidates with high risk varices. This study was also halted following the interim analysis because a significant increase in both variceal bleeding and cumulative mortality, was found in the propranolol group, even if there was no difference in bleeding-related deaths. This result could have been influenced by the two non-bleeding related deaths in the propranolol group versus no deaths in the banding group and thus this trial appears to be an outlier (18). According to Jutabha et al the two treatments had the same costs (16). In contrast, in a similar group of patients, we found significantly higher costs for banding compared to propranolol.

No bleeding event due to banding was reported in Jutabha's trial, (16) which may have been fortuitous as bleeding from dropped bands and esophageal ulcers are well described complications after variceal banding (22). During prophylactic treatment, at least 11 episodes of bleeding complications due to endoscopic banding have been described by some authors, 3 of which were

fatal. (14,22) We too observed two cases of esophageal bleeding caused by endoscopic treatment that required emergency treatment, one of which lethal. In the propranolol group we suspended therapy for intolerance or side effects in 16% of the patients, none of whom died. To reduce the frequency of side effects, we started with the lowest dosage of 20 mg/day, increasing it gradually to obtain a reduction of 25% in the heart rate. Although the mean dosage of propranolol utilized in our study was low: about half of that utilized by other authors, (11,12,14,16) we obtained nonetheless a mean reduction of 22% in the pulse rate. Moreover the low incidence of bleeding would seem to confirm that the drug was effective particularly considering that we enrolled only patients with Child-Pugh B or C, while in other studies also patients with Child A cirrhosis were enrolled. (11,13-16). We believe the lower dose of propranolol tolerated by our cohort of patients, reflects their severity of liver disease.

All our patients were liver transplant candidates, similar to the cohort randomized by Jutabha et al (16), but not by other trials. This meant that at the time 24 patients underwent a liver transplantation (after a mean of one year) they were censored for follow-up. Although this made the overall mean follow-up time shorter (15 months), this was similar to that of Jutabha (16) and longer than that of Sarin (12). We believe that the low incidence of bleeding we observed with both therapies, despite having a more severely ill population in comparison to other studies, was related to the effectiveness of treatment and not to the shorter follow-up.

Bleeding after suspension of BB is considered by some authors as an indirect complication of the pharmacologic treatment. (14,16) Thus, for ethical reasons, endoscopic ligation was offered to all the patients intolerant to beta-blockers, as banding compared to no therapy has been shown to be effective (23). However a recent randomized study in patients intolerant to beta-blockers, reported iatrogenic bleeding complications with banding (24). The authors concluded that ligation may be harmful as a primary form of prophylaxis, just as sclerotherapy (18,24).

In our study, the finding of low incidence of variceal bleeding following ligation (6.45% at 15 months) in patients in whom the expected incidence if untreated was superior to 30%, supports the use of banding when beta-blockers are contraindicated in high-risk patients. However physicians and patients should be aware that there is risk of iatrogenic death during endoscopic treatment. This must be placed in the balance of risk-benefit, considering on one hand the variceal risk of bleeding and on the other hand the fact that in patients intolerant to propranolol fatal bleeding may still occur despite banding, as happened in 1 of 3 patients in our study. Thus beta-blockers should remain the first choice of prophylactic therapy in candidates for liver transplantation.

In conclusion both propranolol and endoscopic banding are similarly effective in reducing the incidence of variceal bleeding in cirrhotic patients with high risk varices, candidates for liver

transplantation, but ligation can be complicated by severe and fatal bleeding and is significantly more expensive. Our results suggest that banding should not be utilized as the primary prophylaxis in candidates for liver transplantation who can be treated with beta-blockers.

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Reply letter to the Editor
Submitted on request to Liver Transplantation, in print.
"Prophylactic variceal ligation is not recommended for patients awaiting live donor liver transplant"

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We thank Wai and colleagues for their comment to our article [1]. Their experience is consistent with ours and different from that reported by Jutabha et al. [2] In all the three studies the patients were liver transplant candidates, thus a particular subgroup of cirrhotic patients, as underlined also by Boyer [3]. In our opinion, this favours the use of beta-blockers instead of banding for primary prophylaxis for at least two reasons. The first, as underlined by Wai et al, is the short follow-up before liver transplantation. In fact, as shown in figure 2 of our study, patients treated by ligation can bleed during treatment, but not after variceal eradication unless for varices recur. By contrast patients taking beta-blockers present the same risk of bleeding over the same time period. As a consequence, a possible advantage of banding can only be seen after a long follow-up, which is unlikely in patients awaiting liver transplant as usually this occurs within 1 year. The other reason is that this group of patients is followed up intensively and this may increase compliance to therapy. The use of beta-blockers does require dose adjustment and trying to maximise the dose tolerated by the patient.

The two bleeding episodes from post-banding ulcers reported by Wai et al are added to several others taken place during prophylactic treatment, including two events described in our study. Globally the reported cases are at least 15, some of which fatal. By contrast, beta-blockers for primary prophylaxis of variceal bleeding have not caused, thus far, fatalities [4].

It is difficult to predict which patients are at risk for post-banding ulcer bleeding. Our patients bled 9 and 11 days after the first banding session respectively. One was Child B7, the other Child C14. The patients treated by Wai et al bled 8 and 9 days after the second prophylactic ligation. Shepke et al [5] reported 5 (7%) bleeding episodes from post-banding ulcers, two of them fatal. The latter happened 3 and 12 days after the first banding session respectively. Triantos et al, [6] treating patients unable to take beta-blockers, reported three cases of variceal bleeding, all between the first and the second prophylactic banding session. As most of bleeding occurs after the first banding

session, we think that longer intervals between sessions, advocated by some authors to overcome this problem [4], do not reduce this risk. In addition and not to be discounted, we found that the costs are reduced to a third when using beta-blockers with respect to banding for primary prophylaxis in these patients. Thus non-selective beta-blockers remain the therapy of first choice for primary prophylaxis in liver transplant candidates.

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Chapter 3:

Laser treatment of Barrett’s esophagus

High-energy laser therapy of Barrett's esophagus: preliminary results.

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Abstract. We present the preliminary results obtained by our research group utilizing Nd:YAG and diode lasers to treat Barrett's esophagus (BE). A total of 15 patients with BE (mean age 58 years) underwent endoscopic laser therapy: 11 with intestinal metaplasia, 2 with low-grade dysplasia, and 2 with high-grade dysplasia. The mean length of BE was 4 cm (range 1–12 cm). Six of these patients also underwent antireflux surgery, and nine were prescribed acid-suppressive medication. Endoscopic Nd:YAG laser treatment was carried out from 1997 to 1999; thereafter, diode laser was employed. The mean follow-up of these patients after the first laser session was 28 months. Patients underwent a mean of 6.5 laser sessions (range 3–17 sessions), with no apparent complications. The mean energy per session was 1705 JJ. Only six of these patients (40%) showed complete endoscopic and histologic remission, but a mean of 77% (SD 23.8%) of the total metaplastic tissue in all these patients was ablated. The percentage of healed mucosa was higher in patients with short-segment BE (92%) ($p < 0.05$) and in subjects treated by two or more laser sessions per centimeter of BE length (89%) ($p < 0.05$). All four patients with dysplasia showed histologic regression to nondysplastic BE or to squamous epithelium, without recurrence during a mean follow-up of 30 months. The patients who underwent antireflux surgery and those prescribed pharmacologic treatment had similar results. Nd:YAG and diode laser treatment of BE is a safe, effective procedure; it required two sessions per centimeter of metaplasia; and it achieved complete regression of the dysplasia. Further studies are necessary to quantify its effect on cancer incidence.

Introduction

Barrett's esophagus (BE), defined as the presence of intestinalized metaplastic columnar epithelium within the tubular esophagus [1], is a complication of gastroesophageal reflux disease (GERD). The prevalence of BE has been found to be 1% among patients undergoing endoscopy for any clinical indication [2], 3% to 5% in subjects with reflux symptoms, and about 10% in patients with endoscopically diagnosed reflux esophagitis [3]. The risk of developing adenocarcinoma is 30 to 125 times higher in individuals with BE than in the normal population, emerging at a rate of 1 cancer per 150 patient-years [2, 4, 5].The carcinogenesis of BE follows the sequence from intestinal metaplasia, through low-grade and highgrade dysplasia, to invasive adenocarcinoma [6, 7]. Treatment of BE, indicated to cure the symptoms of GERD and to prevent the development of

adenocarcinoma, consists of acid-suppression medication, antireflux surgery, esophagectomy (limited to patients with high-grade dysplasia or invasive adenocarcinoma), and endoscopic ablation. Acid-suppression medication is effective in reducing GERD symptoms but does not seem to influence the incidence of cancer in BE patients [8–10]. Antireflux surgery, which prevents esophageal exposure to the acid as well as to the nonacid gastroduodenal contents, does not prompt regression of the intestinal metaplasia but seems to delay its malignant progression [11, 12]. Endoscopic ablation therapies have been shown to reverse highgrade dysplasia and the early esophageal adenocarcinoma that develops in BE. These procedures, moreover, are characterized by low morbidity and mortality rates. They thus seem to be a valid alternative to more invasive surgical treatment, but results from long-term studies are not yet available. Endoscopic ablation of noncomplicated intestinal metaplasia is performed only in the context of research trials. Data on large numbers of patients are needed if their utility in the long-term prevention of malignancy is to be evaluated. The endoscopic techniques that can be considered for BE ablation should present a low risk of complications and minimal risk of recurrences. Many endoscopic ablation procedures, such as argon plasma coagulation (APC), photodynamic therapy (PDT), and laser therapy (argon, KTP, Nd:YAG), have been shown to reduce intestinal metaplasia, inducing regeneration of the squamous epithelium in patients with pharmacologic or surgical antireflux treatment. Major complications, such as strictures, perforation, and hemorrhage, which have been reported by some authors, seem to depend on the technique utilized and the technical expertise of the endoscopic center where they are carried out. Hidden subsquamous intestinal metaplasia [13, 14] and subsquamous adenocarcinoma growth [15] have been described under the healed tissue after endoscopic ablation. The hazard is related to the depth of the ablation procedure utilized. The depth of the ablation depends on tissue optical properties and laser parameters. Absorption of optical radiation is highly wavelength-dependent [6]. Nd:YAG and diode lasers, with wavelengths of 1064 and 819 nm, respectively, have a penetration depth of about 5 to 6 mm in the tissue, whereas argon and KTP lasers, with wavelengths of 458 to 515 and 632 nm, respectively, have a penetration of 2 to 3 mm [16– 18]. Similarly, APC and PDT have a penetration depth of 2 to 3mm [19–21].Alower risk of residual metaplastic tissue is to be expected following high-energy laser treatment. Results of treatment procedures utilizing Nd:YAG laser have been evaluated by few research groups, who have not always reported encouraging results [22–25]. This paper presents a preliminary analysis of the effects and complications of Nd:YAG and diode laser therapy on 15 patients with BE who were studied for a mean of 28 months.

Methods

Patients

Altogether, 15 patients (13 men, 2 women), all affected by BE, were included in this study. BE was diagnosed when intestinal metaplasia was found in esophageal bioptic material obtained following chromoendoscopy with toluidine blue (1%) [26, 27]. Multiple esophageal biopsies were carried out with jumbo forceps, taking samples from the four quadrants every 2 cm starting from the gastroesophageal junction. Four-quadrant biopsy specimens were taken every centimeter in patients with known high-grade dysplasia. Among the 15 patients, 11 had intestinal metaplasia, and 4 patients also had dysplasia (2 low grade, 2 high grade). Deeper tumor invasion was excluded by endoscopic ultrasonography and computed tomography (CT) scans in the two patients with high-grade dysplasia. BE metaplasia was circumferential in seven patients, with isles in five, and in the shape of tongues in three. The mean BE length was 4 cm (range 1–12 cm). Its length was ≥ 3 cm in nine patients (long Barrett) and < 3 cm in six (short BE). Patients' ages ranged from 32 to 73 years (mean 56 years). Before laser and surgical therapy were available, these patients would have been studied by 24-hour pH monitoring to confirm esophageal reflux and by manometry to exclude motility disorders. Six had undergone antireflux surgery before the laser therapy was initiated: An antireflux Nissen-Rossetti fundoplication was performed in all cases. The efficacy of antireflux surgery was then tested with a 24-hour pH study and manometry, demonstrating remission of the acid reflux and the absence of motility disorders in all six cases. Two other patients had been subjected to gastroesophageal operations: a Billroth II gastric resection for gastric ulcer and a gastroesophageal resection for intramucosal carcinoma in BE, with esophagogastric anastomosis performed 38 cm from the incisors. The other patients did not undergo surgery (fundoplication for BE or esophagectomy for high-grade dysplasia) because of advanced age or poor health or because they refused to grant consent. Informed consent was obtained for all patients participating in the study.

Laser Therapy

Laser therapy was performed from August 1997 to July 2003. For endoscopic laser ablation the patients received local hypopharyngeal anesthesia with lidocaine (Xylocaine), and intravenous propofol was used for sedation. The patients were admitted for 1-day surgery. The Olympus fiber esophagogastroduodenoscope (EGD) (Olympus, Tokyo, Japan) with a photo-resistant distal end (white head) and the Olympus or Pentax (Pentax, Tokyo, Japan) photoshielded video EGD were the endoscopes used. The MBB Medilas 2 Nd:YAG laser (MBB, Germering, Germany) (wavelength 1064 nm, maximum power 100 watts) was used from 1997 to 1999. The Dornier Medilas D diode

laser (Dornier, Germering, Germany) (wavelength 940 nm, maximum power 60 watts) was utilized beginning in January 2000. The laser utilized noncontact fibers. The mean energy used was 1705 J for each session. Laser therapy sessions were generally performed monthly during the first 3 months, then every 3 months in the patients with highgrade dysplasia. For the others, laser sessions took place every 3 months, during the first year of treatment, and then every 6 months until the BE was completely eradicated. Endoscopy was performed yearly during the follow-up period. All the patients who did not undergo antireflux surgery also received acid suppression treatment consisting in proton pump inhibitors such as omeprazole (40 mg daily). Patients who had undergone fundoplication and those receiving medical treatment were all negative for reflux symptoms. A 24-hour pH study was therefore not carried out during the laser treatment. Savary's and pneumatic dilatations were associated in three patients, with cardial, pyloric, or both peptic strictures, respectively. All the strictures developed before the laser treatment was initiated. Laser was applied to metaplastic tissue during the sessions until the surface became white. A deeper injury was provoked in the presence of dysplasia, in which case two opposite quadrants were treated, saving some tissue between them, to avoid stricture development. The two saved quadrants were then treated during the successive session. The effects of laser therapy were analyzed by histology from multiple jumbo biopsy specimens obtained after chromoendoscopy during follow-up and by brush cytology. The endoscopic appearance of BE regression, expressed in the percentage of healed mucosa area, was also reported. Particular attention was given during endoscopy to describing the length of the BE mucosa extension (expressed in centimeters) and circumferentially (expressed in fourths). The percentage of Barrett's ablation was then calculated from the metaplasia extension reported during follow-up. The mean follow-up, from the first laser session, was 28 months (range 7–61 months).Statistical analysis was performed using the Mann Whitney U-test.

Results

The characteristics of the 15 patients studied, the treatment program, and the results are outlined in Table 1. A total of 97 laser sessions were carried out during the study, with a mean of 6.5 sessions per patient (range 2–19 sessions). The cost of laser treatments was 613 Euros ($723) per session, hence 3980 Euros ($4692), on average, per person. The mean ratio of the number of sessions and the length of BE was two sessions per centimeter. The patients received a mean of 11,000 J during the entire treatment period and 1705 J (range 270–6135 J) for each session. The total energy used per centimeter of BE was 2970 J/cm (range 320-8344 J/cm), or 457 J/cm per session. None of the patients had complications during the treatment period, although some of them reported mild retrosternal burning that lasted about 1 week. The mean percent healed metaplastic area, according to the endoscopic report, was 77.0% (SD 23.8%). Patients with short-segment BE (92% of ablation,

SD 13%) presented better results than those with long-segment BE (67% of ablation, SD 25%) ($p < 0.05$). If the ratio between the number of laser sessions and the length of BE is compared, the percent of healed metaplastic area was 89% (SD 14%) for patients treated by two or more sessions per centimeter versus 58% (SD 24%) for patients treated by fewer than two sessions per centimeter ($p < 0.05$). All four patients with dysplasia displayed histologic regression: two to nondysplastic BE (one with high-grade dysplasia, one with low-grade dysplasia) and the other two to squamous epithelium (one with high-grade dysplasia, one with low-grade dysplasia). The follow-up periods after eradication were 38 and 61 months, respectively, for the two patients with high-grade dysplasia and 7 and 14 months, respectively, for the patients with low-grade dysplasia. Another four patients, with intestinal metaplasia, showed complete histologic regression to squamous epithelium. Complete regression, confirmed by endoscopic and histologic findings, was achieved in only 6 of the 15 (40%) patients studied, and all 6 had lesions ≤ 3 cm in length and underwent almost two laser sessions per centimeter. Patients who had undergone antireflux surgery and those prescribed pharmacologic treatment had the same results: The mean percentages of metaplastic area reduction were, respectively, 73% (SD 23%) and 79% (SD 25%), a nonsignificant difference.

Discussion

Endoscopic ablation of BE is the object of much interest as it is a risk factor for esophageal adenocarcinoma. Quantifying the efficacy of these procedures to reduce the incidence of cancer is extremely difficult because adenocarcinoma develops in BE patients in only 0.7% per year [2, 4, 5]: hence the need for further studies. In effect, which techniques are more indicated for these studies? The endoscopic procedures that are candidates should present a minimum of complications, a low risk of retaining intestinal metaplasia underneath the restored squamous epithelium, and good ablative capacity. Argon plasma coagulation is a noncontact thermoregulation procedure with the advantage of limited depth of penetration, thereby minimizing the risk of perforation. Nevertheless Byrne et al. [28] reported two perforations and one death following treatment with APC on 27 patients. In the same study, the presence of retained intestinal metaplasia was found in 30% of the patients. In another group of 31 patients treated with APC, Van Laethem et al. [14, 29] reported two cases of stenosis, one of esophagitis, and recurrence in 62% after 36 months of follow-up. Morino et al. [30] reported much better results. These authors obtained complete squamous reepithelialization using APC in 20 of 23 patients, without significant complications during a mean follow-up of 31.9 months. However, retention of intestinal metaplasia underneath the neosquamous epithelium (9%) was also described. Photodynamic therapy (PDT) is a local endoscopically guided treatment approach based on the selective sensitization of precancerous or malignant lesions and light-induced tissue destruction. The growth of subsquamous intestinal metaplasia has been reported

after this procedure. Overholt et al. [31], who treated 100 patients affected by dysplasia or early carcinoma using PDT, documented the growth of metaplastic tissue with high-grade dysplasia and even adenocarcinoma underneath areas completely covered with squamous epithelium. Moreover, after treatment 34 patients developed an esophageal stricture. The incidence of strictures reported in other studies was 12% to 35% [32, 33], whereas that of photosensitivity reactions was 13% [32]. Atrial fibrillation, pleural effusions, and esophageal perforations have also been outlined [31–34]. Photodynamic therapy seems a more appropriate procedure when dysplasia and cancer are present, in contrast to uncomplicated BE. In fact, complete remission of early cancer was achieved in 52% to 89% [31, 32, 35] and of high-grade dysplasia in 72% to 100% [31, 36, 37], whereas complete ablation of BE was obtained in only 36% to 43% [31, 38]. Nd:YAG laser therapy has been used in some studies in association with PDT or alone. No data on diode laser treatment of BE has been reported in the literature. Salo et al. [23], using antireflux surgery and Nd:YAG laser with a contact tip in 11 patients, obtained ablation of all the BE with no complications. Discussing the results, Salo et al. emphasized the importance of antireflux surgery in maintaining the condition for squamous epithelium growth. The difference between the group treated by antireflux surgery and that receiving pharmacologic treatment was not significant. Less optimistic results were reported by Bonavina et al. [24], who treated 18 patients using Nd:YAG laser with noncontact fibers. Macroscopic and histologic eradication of BE was documented in 11 of 18 patients (61%). Only partial ablation was achieved in five other patients, whereas two patients were defined as "nonresponders." During follow-up they reported two recurrences after 8 and 12 months, respectively. There were no nonresponders or recurrences among our patients, but it must be remembered that we used double the number of laser sessions (6.5 vs. 3.0), treating our patients with two sessions per centimeter of BE. Six months after eradication of the intestinal metaplasia, Bonavina et al. reported an undermining adenocarcinoma in one patient, but it is possible that it was already present before treatment was begun. The efficacy of Nd:YAG laser therapy on high-grade dysplasia and early adenocarcinoma was studied by Weston and Sharma [25], who treated 14 patients using contact probes, obtaining complete elimination of dysplasia and cancer in all the subjects. In addition, complete endoscopic and histologic ablation of BE metaplasia was achieved in 11 patients (78%). These authors reported some major complications: two esophageal strictures (11.8%) and one mild upper gastrointestinal bleed (5.9%). Unfortunately, there was a follow-up of only 12.8 months carried out in only seven patients, so we do not know the long-term results of this treatment on high-grade dysplasia and early cancer. The two patients with high-grade dysplasia treated by us did not have a recurrence after 38 and 61 months of follow-up, respectively. Complete ablation was attained in only 40% of our patients, but 77% of the BE was ablated. Moreover, 90%

of the ablation was obtained in the patients with short-segment BE and in those treated by almost two laser sessions per centimeter of BE length. During the 28-month follow-up, there was no recurrence or the presence of subsquamous metaplastic tissue in the esophageal biopsy specimens, nor were any complication reported after 97 sessions of laser therapy. Obviously, the follow-up is too short to achieve definitive conclusions with regard to the risk of recurrence. The results we obtained from the treatment of dysplastic lesions are promising, but the benefit of laser ablation of noncomplicated intestinal metaplasia requires further long-term studies. If the low risk of recurrence is confirmed, we can speculate that those patients who were completely healed by laser therapy, when gastroduodenal reflux is excluded, could avoid undergoing multibioptic esophagoscopic screening, which is usually performed every 2 years. The others, in whom a reduction of the metaplastic area is obtained, may require less extensive bioptic analysis and may have a lower risk of cancer growth, as this is proportional to the disease's extension [39].

Conclusions

Further studies are necessary to evaluate the impact of BE endoscopic ablation on cancer risk and on the cost of endoscopic surveillance. The low risk of complications associated with their use make Nd:YAG and diode lasers eligible for such studies on the efficacy of endoscopic ablation in BE patients, especially in the presence of short lesions, when performed in specialized endoscopic centers. Presently, these techniques are recommended only in patients with inoperable high-grade dysplasia or cancer.

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Letter to the Editor
Submitted

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Dear Editor,

in 2004 we published the preliminary results of our studies on high energy laser therapy (Nd:YAG and Diode lasers) utilizing non-contact fibers to treat Barrett's esophagus (BE) [1]. Fifteen patients with intestinal metaplasia (IM), including two with high grade dysplasia (HGD) and two with low-grade dysplasia (LGD), underwent a mean of 6.5 laser sessions with a mean follow-up after the first session of 28 months. Histologic regression to IM or to squamous epithelium was obtained in all four cases of dysplasia, but only 40% of the patients with IM were completely healed. A mean of 77% of the total metaplasic tissue was ablated and no complications were observed.

With the present letter we report the results of laser therapy in patients who were studied for a longer follow-up period. After giving informed consent, 22 patients (19 males, 3 females, mean age 56 years) with short (9) or long (13) segment BE, underwent laser therapy. The patients presented: 2 HGD, 4 LGD and 16 IM. The mean follow up after the first session was 52 months (range 7-115). The methods were the same as those previously reported, both with regards to the laser sessions and the endoscopic follow-up. The 15 patients who did not undergo anti-reflux surgery were treated with full dosage proton pump inhibitors. After 174 laser sessions (in mean 8 per patient), just as in our precedent work, no complications, with the exception of retrosternal burning in 4 patients, were reported. The mean length of metaplasic tissue was reduced from 3.6 cm (SD 2.68cm) to 0.8 cm (SD 1.38 cm, $p<0.0001$). Histologically proven, complete IM healing was achieved in 14/22 (64%) patients: 8/9 (89%) with short BE and 6/13 (46%) with long BE ($p=0.07$). All 6 cases of dysplasia healed to squamous (4) or to metaplasic (2) epithelium. A mean of 83% (SD 25%) of the BE surface was ablated. IM recurrence was observed in one patient (7%), after 6 years of follow-up, but

dysplasia recurrence and histological/endoscopical disease progression were not reported. As in our previous work, patients with short-segment BE presented better results (mean of BE ablation 97%, SD 10%) than did those with long-segment BE (73% of ablation, SD 28%, $p<0.05$). The number of laser sessions per cm of IM length was also significant: the patients treated with 3 or more sessions per cm of BE length had better results (97%, SD 9%) with respect to those who underwent fewer sessions (69%, SD 28%, $p=0.005$). No significant difference was found between patients who underwent antireflux surgery (mean BE ablation 89%, SD 20%) and those treated with proton pump inhibitors (mean BE ablation 80%, SD 27%, p: n.s.).

In conclusion, according to our experience, ablation of BE with laser therapy is a safe method, effective in most cases of short BE, thought its efficacy is minor in the long form. The number of sessions required is in fact proportional to the length of metaplasic tissue. As some authors have reported infrequent, but severe complications (strictures [2,3,4], bleedings [3,4] and even perforation [3]), in particular when contact fibers were used, and others have described cancer development under the healed squamous tissue [2,3], laser treatment of uncomplicated BE should continue to be monitored in experimental trials in specialized Endoscopic Centers.

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Chapter 4:

Laser treatment of colorectal adenomas

Laser photoablation of colorectal adenomas: a 12-year experience.

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Abstract:

Background: Here we analyse laser photoablation as an alternative treatment of large sessile polyps in inoperable patients.

Methods: Ninety-four colorectal polyps (mean diameter 3.09 ± 2.7 cm, range 1-15 cm) were treated using high energy lasers (Nd:YAG and Diode). Grade of dysplasia was low in 51, high in 35, with focally invasive cancer in 8.

Results: After 405 laser-sessions (4.3 per polyp) 5 procedure-related complications were observed: 2 strictures, 2 bleedings and 1 perforation. The latter needed a surgical resection, the others were successfully treated by endoscopic therapy. Fifty seven polyps (61%) were completely eradicated and the growth was controlled in all but 2 (98%). No degeneration was found after 28 months follow-up of treated adenomas with low or high grade dysplasia. Outcome of treatment was dependent on the dimension and grade of the dysplasia ($p<0.05$), but not on the polyps' position (rectum or colon). Relief of rectal bleeding was obtained in 90%, of mucus discharge in 77%, and of tenesmus in 100% of cases.

Conclusions: Laser photoablation of colonic adenomas can be considered a valid procedure not only to relieve symptoms, but also to control the risk of degeneration in patients unfit for surgery or when surgical treatment is considered excessively invalidating.

Introduction

Endoscopic polypectomy is considered an essential step in the surveillance and prevention of colorectal cancer [4, 24]. Not all colorectal adenomas can be completely ablated by forceps or snare diatermic resection due to their size or conformation (sessile polyps). In these cases or when there is malignant stalk invasion, surgery is necessary. The procedures to eliminate colorectal polyps are: colonic resection or colotomy during laparotomic or laparoscopic surgery, transanal endoscopic microsurgery (TEM) and trans-sphincteric or trans-sacral posterior resection. Endoscopic laser

terapy can be used to ablate the polyp or to relief symptoms, as bleeding, mucus discharge and tenesmus in the elderly, in inoperable patients or in subjects who refuse surgery.

This study presents 12 years of experience results of laser photoablation of colorectal adenomas in our surgical department.

Patients and methods

Patients

Endoscopic laser therapy was carried out in 59 patients (35 males and 24 females) with colorectal adenomas from 1992 to 2004. Mean age was 69 years (range between 26 and 93).

Twenty-two of these patients had undergone surgery for colon adenomas or cancer: 2 trans-anal polypectomy, 1 transcoccigeal polypectomy, 2 polypectomy through colotomy, 3 anterior rectal resection, 4 sigmoid resection, 2 right hemicolectomy, 4 left hemicolectomy and 4 subtotal colectomy with ileo-rectal anastomosis (2 for familial adenomatous polyposis, 2 for ulcerative colitis).

The total number of polyps treated was 94 (1,6 in mean per patient): 63 in the rectum, 17 in the sigmoid colon, 8 in the right colon (3 of them in the cecum) and 6 at colo-rectal anastomosis. The mean diameter of the polyps was 3.09 ± 2.7 cm (range 1-15 cm). The histology in all was adenoma: 22 tubular, 38 tubulo-villous and 34 villous. The dysplasia was low grade (LGD) in 51, high grade (HGD) in 35, with focally invasive cancer in 8. Polyps with HGD or with focal adenocarcinoma, were studied by endoscopic ultrasound and CT to exclude a deeper cancer invasion or lymph nodes metastases.

Nd:YAG or Diode lasers were used in the presence of large sessile polyps, when a snare or forceps polypectomy was incomplete and the patients were inoperable for age or unfit to surgery or refused operation. Informed consent was obtained for all treated patients.

Laser Therapy

Treatment sessions were conducted during one-day admission to our surgical department. No sedatives were used during tratment of rectal polyps. Patients were sedated with propofol for more proximal polyps and during colonoscopies. A Nd:YAG laser (MBB Medilas 2, wave length 1064 nm, maximum power 100 watts) was used from 1992 to 2000. From January 2000 a Dornier Medilas D Diode laser (wave length 940 nm, maximum power 60 watts) was utilized. The laser utilized non-contact fibres and was performed through flexible endoscopy. The Olympus fibre colonoscope with photo-resistant distal end (white head) and the Olympus or Pentax photo-shielded video colonoscopes were the endoscopes used.

Pulses were applied to large polyps until substantial amounts of the lesion were vaporized and heat conduction was avoided by changing laser direction often to maximally reduce the risk of perforation.

The treatment was generally associated with diatermic snare or forceps polypectomy, to reduce dimension of the polyp and with submucosal water injection, before polypectomy , for flat adenomas.

Laser sessions were generally performed monthly until the polyp was healed. Monthly piecemeal debulking sessions were carried out on massive lesions for 3-4 months, thereafter they were performed every 3 months. The adenomas dimensions were measured during every session: the length and the width for the smaller ones and the length and the circumpherence for the larger ones. First, second and successive follow-up endoscopies were carried out respectively after 6 months, 1 year and thereafter every 2 years. During the examinations, biopsies were carried out and, in the case of recurrence, polyps were scheduled for laser therapy. In presence of polyps with HGD or focal adenocarcinoma, endoscopic ultrasound and CT were performed during follow-up, to exclude deeper cancer invasion and lymph nodes involvement.

Polyps were considered completely eradicated on the basis of endoscopic healing, confirmed by scar biopsies. The percentage of debulking was calculated from the dimensions described before laser treatment and during the last endoscopy, for the polyps that were not completely ablated.

The mean follow-up was 28 months (range 8-116).

Statistical analysis was performed with Student T test, Mann-Whitney U test, Ancova, Log-ratio.

Results

A total 405 laser-sessions, with a mean of 6 sessions for every patients and in mean 4.3 sessions per polyp were performed. The mean energy applied in every session was 4600 joules (J), 2875 J for every polyp, 930 J/ cm of polyp/ session.

There was no laser related mortality and 5 complications (8.5% of treated patients): 2 strictures, 2 bleedings and 1 perforation for a ciecal polyp. The latter required a surgical resection, without stoma, while, the others were successfully treated with endoscopic therapy. In the 2 patients with rectal bleeding, effective laser hemosthasis was carried out. In the 2 patients with stricture, dilatation was carried out, in one with Savary bougies and in the other with endoscopic balloons, obtaining a complete clinical and endoscopical remission.

A complete ablation was obtained in 57 polyps (61%), a partial ablation in 20 (21%), while the dimension and histology of the polyp was stabilized in 15 (16%). In 2 other cases (2%) the lesion was found to be larger (1 case with LGD), or the cancer invasion deeper (1 case with previous diagnosis of microinvasive adenocarcinoma). During the follow-up, 5 recurrences (5/57, 8.7%), which were successfully treated with laser therapy, were found.

Taking into consideration the dimensions of the adenoma before and after the laser treatment we obtained in mean the reduction of the 71% of the polyp mass, in particular 89±25% for polyps ≤ 3

cm of diameter, versus 38±44% for bigger polyps ($p<0.01$) **(Table 1, Figure 1)**. The Percentage of ablation was also higher (85±32%) in the case of tubular adenomas with respect to tubulo-villous or villous adenomas (67±50%, $p<0.05$).

The grading of displasia was also determinant for the result of laser treatment: in polyps with LGD, the mean percentage of ablation was 82±34%, significant higher with respect to the ablation in the polyps with high grade displasia (60±40%, $p<0.05$) or with focal cancer (59±50%), being this result independent from the polyp dimension **(Figure 2)**.

The site of the polyp was not relevant for the ablation efficacy. The mean diameter of rectal adenomas was 3.16±2.7 cm, whereas of colonic adenomas was 2.79±2.97 cm. The colonic polyps were 18 with LGD, 6 with HGD and 2 with focal adenocarcinoma. The rectal polyps were instead 30 with LGD , 26 with HGD and 6 with microinvasive cancer. Thus rectal polyps were in mean of higher dimensions and higher grade of dysplasia. The mean percentage of ablation resulted 64±42% for rectal polyps and 85±29% for colonic polyps, the difference was not statistically significant if we take *also* into consideration the difference of dysplasia grade (multivariate analysis).

Adenomas with microinvasive adenocarcinoma presented a cancer progression in one case (12.5%), subsequently treated by trans-anal resection and radio-chemiotherapy (histologic and radiologic diagnosis T3N1M0). No degeneration was found in the polyps with LGD or HGD.

Finally, with regards to symptoms, relief of rectal bleeding was obtained in 90% (10/11), of mucus discharge in 77% (10/13), and of tenesmus in 100% (2/2) patients.

Polyp parameters	**Percentage of ablation**	**Significativity**
≤3 vs >3 cm	89±25% vs 38±44%	$p<0.01$
Tubular vs villous	85±32% vs 67±50%	$p<0.05$
LGD vs HGD	82±34% vs 60±40%	$p<0.05$
Rectum vs colon	64±42% vs 85±29%	n.s.

Vs= versus, n.s= non significant, LGD= low grade dysplasia, HGD= high grade dysplasia

Table 1 : Outcome of laser treatment is dependent on the dimension and grade of the dysplasia but not on the polyps' position.

Discussion

Several procedures can be utilized in the treatment of large sessile polyps, including snare polypectomy, surgical resection, transanal endoscopic microsurgery (for the rectum) and finally laser therapy.

In presence of large sessile polyps, piecemeal diatermic snare polypectomy, when feasible, presents an increased risk of bleeding (4-12%) [1, 9, 12, 23] and perforation (up to 3%) [6]. Its advantage is that all the tissue can be analysed histologically to exclude the presence of invasive cancer.

Even when the polyp is completely resected, 3 months follow-up is necessary because of the high risk of the surrounding tissue (22-28%) [9, 23].

Transanal endoscopic microsurgery for sessile polyps can be utilized in presence of invasive adenocarcinoma (T1), but it is practical only in lesions within 18 cm of the anal verge [7]. General anaesthesia is often required and hospitalisation lasts for a mean of 5-6 days. Some risk of morbidity (4-5%) [2, 15, 22] and of mortality (up to 0.5%) [3] has been reported.

Surgical colorectal resection, by laparotomy or laparoscopy, which presents a mean mortality risk of 1-2% [13] (0.2-5% depending on the patients' conditions [8, 21]), is recommended in presence of invasive cancer, as it permits the surgeon to leave clean margins and to perform a lymphadenectomy. When patients are inoperable or when a benign sessile polyp is located in the lower rectum, less invasive treatments should be considered.

Of these, laser treatment has been demonstrated to be a well tolerated technique, without mortality and with low morbidity (only 1.7% patients required a surgical operation for complications). It has been seen that complete eradication can be obtained in only 61%, but the polyp growth can be controlled in 98% of the cases. Finally no degeneration was found after 28 months of follow-up when the adenoma (with LGD or HGD) was treated with laser application, a procedure which is nearly always feasible and requiring only light sedation.

The efficacy of laser-therapy for colo-rectal adenomas has also been evaluated by others [5,10-11, 14, 16-19]. Mathus-Vliegen and Tytgat [20] investigated the effect of laser photoablation of colorectal adenomas in 196 adenomas. They reported that complete ablation was obtained in 82% of the polyps, but they also observed high frequency of recurrences (23%), and of subsequently cancer diagnosis (12%). This result underlines the importance of taking enough tissue for histological examination to exclude the presence of invasive cancer.

Like those authors, we found that better results are obtained when small or medium-size polyps are being treated, with respect to larger ones, in which laser treatment is utilized to relieve symptoms, like bleeding, mucus discharge or tenesmus. Another important finding was that laser therapy plays an important role in controlling the risk of tumour degeneration. In fact no cases of degeneration to

invasive carcinoma were observed in the 86 benign polyps with LGD or HGD treated by laser therapy after 28 months follow-up. A 12.5% risk of deeper cancer invasion was found instead when polyps presented microinvasive adenocarcinoma.

In presence of HGD and microinvasive adenocarcinoma it is necessary to perform an adequate follow-up including CT and transrectal ultrasound to detect deeper invasion, lymph-node status or tumour spread.

Moreover in all the patients in which the complete ablation of a polyp with microinvasive adenocarcinoma is not obtained, radiotherapy should be considered as an option to avoid the risk of cancer spread, if not fit for surgery.

In our study no difference was found between rectal or colonic polyps in terms of response to laser treatment, whereas there could be a higher risk of perforation in colonic polyps, especially in the cecum.

Finally the response to the laser therapy depended on the grade of dysplasia, regardless of the polyp dimension, probably because polyps with HGD present a higher replicating activity.

In conclusion laser photoablation of colonic adenomas can be safely utilized to relieve symptoms and control the risk of degeneration in inoperable patients or when surgical treatment is considered excessively invalidating.

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Chapter 5:

Endoscopic dilation of esophageal strictures

Endoscopic Dilation of Benign Esophageal Strictures in a Surgical Unit: A Report on 95 Cases

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Abstract:

Ninety-five patients were treated by endoscopic dilation without fluoroscopic guidance between 1997 and 2005 for benign esophageal strictures. The aetiologies were: anastomotic (38), post-fundoplication (13), caustic (14), peptic (11), radiation-induced (10) and others (9). The strictures were classified at every session on a 0 to 4 scale on the basis of the diet and the luminal diameter. Savary-Gillard or TTS balloon dilators were utilized depending on the type and the location of the stenosis.

A total of 472 dilation sessions were carried out without serious complications. A normal and a semi-solid diet were respectively achieved in 75% and 91%. Recurrence of dysphagia was found in 33% and 51% of the patients respectively after two months and one year. Improvement of dysphagia, the number of sessions and recurrence were significantly better in the patients with post-surgical stenosis as compared to those affected by caustic, peptic and radiation induced strictures.

Introduction

Benign esophageal strictures have different aetiologies: the most frequent are peptic, caustical, radiation induced, post-surgical or congenital stenosis[1]. Regardless of the aetiology, dysphagia is the principal symptom and endoscopic dilation is the treatment of choice. [2,3] Savary or pneumatic endoscopic dilation is a generally feasible, well known technique, with a low risk of complications achieving remission of dysphagia in most stenotic patients.[4-8]

The defect of this treatment modality is the high rate of recurrence, but repeating dilation sessions has been found to be effective. In this study, conducted in a Surgical Endoscopic Unit, our attention was focalized on the results of endoscopic dilation for post-surgical esophageal strictures, in comparison with other types of benign strictures.

Patients and methods

Patients

A total of 110 patients with benign esophageal and cardial stenosis consecutively treated between January 1997 and December 2005 in our Endoscopic Unit were considered for this retrospective

comparative study. All patients, whose strictures were confirmed by means of endoscopy and esophagogram, presented with dysphagia of varying degrees.

As previously described by Wang et al., [9] all of the strictures were prospectively classified both according to the endoscopical estimation of the diameter and to the tolerated diet on a 0 to 4 scale during dilation sessions.The post-dilation scores were derived in the same way during the endoscopic follow-up.

- Score 0 indicated that the patient was able to manage a normal solid diet, that a 12 mm video-esofagogastroduodenoscope (EGD) GIF-2T160 (Olympus Corp, Tokyo, Japan) could be passed, and the luminal diameter was > 12 mm;
- Score 1 indicated that the patient was able to swallow some solid foods, the video-EGD GIF-Q145 (Olympus) can pass, and the luminal diameter was between 9 and 12 mm;
- Score 2 indicated that the patient was able to swallow only a semi liquid diet, the video-paediatric EGD GIF-XP160 (Olympus) could pass, the luminal diameter was between 6 and 9 mm;
- Score 3: the patient was able to swallow only a liquid diet, a fibreoptic paediatric EGD GIF-N30 (Olympus) could be passed, the luminal diameter was between 5 and 6 mm;
- Score 4 indicated that the patient was on a water diet or with complete dysphagia, only the guide wire could pass, and the luminal diameter was < 5 mm

All the dilation sessions and the dysphagia grade were prospectively recorded. The stricture length was likewise endoscopically misured and reported. The technical feasibility, the treatment related complications, the symptom relief, the improvement of the stricture scale, the number of dilation sessions required and the length of time until a recurrence of dysphagia occurred were recorded and analyzed.

Dilation methods

Strictures were treated as soon they caused dysphagia.

Dilation of the strictures was carried out utilizing Savary-Gillard polyvinyl dilators (Wilson Cook Medical Inc, Winston, Salem, USA) or Through-the Scope (TTS) balloon dilators (Rigiflex and CRE, Boston Scientific Corporation, USA).

The Savary-Gillard dilators were passed after a marked guide wire had been positioned, if possible assisted by endoscopic guidance, with the tip distal to the stricture. Dilation was then carried out gently without fluoroscopic aid utilizing 3 dilators of ascending sizes and care was taken to avoid

shifting the guide wire during the procedure. An endoscopic control was performed at the end of each session.

Use of fluoroscopic guidance was considered only when it was difficult to pass the marked guide-wire. In this case we try to position a Terumo wire deeply under radiologic control.

It was found that TTS balloon dilators are better suited for short strictures. The catheter can be passed through the working channel of a standard endoscope under endoscopic guidance keeping the middle balloon at the narrowest part of the stenosis. Inflation duration was in mean 30 to 60 seconds and the maximal achieved pressure was 20 psi. Treatment sessions were conducted during one-day admission to our surgical unit and patients were sedated during endoscopic dilation sessions with propofol. When lesions under the mucosa were suspected during the endoscopic examination a chest x-ray and an esophagogram with water soluble contrast medium were immediately performed to exclude perforation. Dilation sessions were initially performed weekly until symptom relief was obtained and patients were able to manage a semi-liquid diet. The sessions were then performed monthly or every three months depending on the severity of the stricture until there was a complete remission of dysphagia. The patients were then asked to contact us at the first sign of symptom recurrence. When the data were analyzed for this study, patients who had not returned for dilation over the preceding six months, were contacted to verify that they were indeed symptom free. Patients with peptic stenoses were also advised to use proton pump inhibitors (PPI) such as omeprazole.

Statistical analysis

Statistical analysis was performed with Fisher's Exact Test and Chi-square. Correlation was analysed with the Spearman Correlation Test. Times of recurrence were compared with the Log-Rank Test.

Results

Out of 110 patients originally considered, 15 patients who were lost at the follow-up stage were excluded. Hence the actual number of patients with ≥6 months follow-up (mean 22 months) studied by us was 95.

On the whole these patients underwent 472 dilation sessions, a mean of 5 per patient without any complication such as perforation or bleeding.

The aetiology of the strictures was classified as follows **(fig.1)**:

- 38 anastomotic stenosis: 1 pharyngogastroplasty, 7 cervical esophagogastroplasty, 18 thoracic esophagogastroplasty, 1 pharyngocoloplasty, 4 esophagocoloplasty, 7 esophagus-jejunum anastomosis.
- 13 post gastric fundoplication: 7 Nissen-Rossetti, 3 Nissen, 2 Toupet, 1 Heller + Dor
- 14 caustic esophageal strictures (8 had previously undergone surgery: 2 esophageal-gastroplasty, 2 esophagocoloplasty, 2 gastric resections, 2 total gastrectomies, one with esophagostomy)
- 11 peptic esophageal strictures, 6 located at the distal esophagus and 5 at the cardias.
- 10 radiation induced strictures (2 treated for lymphatic diseases, 3 for laryngeal carcinoma, 1 for head-neck tumor, 1 for pharyngeal carcinoma, 1 for early carcinoma of cervical esophagus, 2 with radiation strictures at the esophagus after neo-adjuvant radiotherapy and esophageal-gastroplasty for esophageal cancer)
- 9 strictures due to other benign diseases (post-sclerotherapy of esophageal varices in 1, Crohn's disease in 2, congenital stenosis in 3, micotic strictures in 3).

The length of the stricture was significantly shorter ($p<0.05$) in the anastomotic type (1.2 cm, range 1-5) as compared to the caustic (4.4 cm, range 1-17), peptic (2.5, range 1-5) and the radiation induced stenoses (3.3 cm, range 1-7 cm).

Dilation was possible in all of the strictures except in 2 patients with respectively radiation-induced and anastomotic stenoses, in whom even the endoscopic retrograde cholagiopancreatography guide wire was unable to pass. These patients were treated surgically. In two other patients who presented with anastomotic stenosis and fistula, dilation was carried out with stent positioning under endoscopic guidance. The stents were later successfully removed.

A normal diet was achieved in 75% of all of the treated patients and a semi-solid one in 91%. A mean improvement of 1.38 degrees was obtained according to the stricture score (from 1.78 to 0.4). A semi-solid diet was achieved in 97% of the patients treated for anastomotic strictures, in 79% of those treated for caustic strictures, in 91% of those with peptic strictures and in 80% of those treated for radiation-induced stenoses (**table 1**). A complete remission was obtained in all the stenoses after fundoplication (normal diet in 100%) (**fig.2**).

The mean stricture score went from a grade 1.8 ± 0.74 to 0.28 ± 0.72 in subjects with an anastomotic stricture ($p<0.05$), from 1.1 ± 0.3 to 0 ± 0 in patients with fundoplication ($p<0.05$), from 2.0 ± 0.8 to 0.78 ± 0.97 in caustic injured patients ($p<0.05$), from 1.7 ± 0.46 to 0.45 ± 0.7 in peptic disease ($p<0.05$) and from 2.1 ± 1.0 to 0.9 ± 1.29 following radiotherapy ($p<0.05$).

The results of endoscopic dilation were different in the various kinds of strictures treated. It was found that dilation was more successful in achieving a normal diet ($p<0.05$) and in improving the stricture grade ($p<0.05$) in the anastomotic stenoses than in the non-surgical lesions (caustic, peptic or radiation induced strictures, considered together here).

A mean of one and half sessions were required to obtain complete regression of the dysphagia in the patients with fundoplication and 3.5 sessions in those with anastomotic strictures, hence fewer than in the patients with peptic (6.4, p=n.s.), radiation induced (5.4, p=n.s.) and caustic strictures (13, $p<0.05$).

Recurrence of dysphagia was found in a mean of 33% of the patients after two months and of 51% after one year and was more frequent in the peptic, radiation-induced and caustic strictures (together 42.5% after two months and 76% after one year), than in the post-surgical anastomotic or post-fundoplication stenosis (24% after two months, 32% after one year $p<0.05$) (**fig.3**). The stricture length correlated inversely with the stricture score improvement ($R=-0.5$, $p<0.05$).

Aetiology of the strictures	N° of patients treated	Savary/ Balloon/ both	Score before	Score after	Patients who achieved semi-solid diet	Patients with recurrence after 1 year
Anastomotic	38	33/4/1	1.8±0.74	0.28±0.72	37 (97%)	14 (38%)
Post-fundoplication	13	2/10/1	1.1±0.3	0±0	13 (100%)	2 (15%)
Peptic	11	11/0/0	1.7±0.46	0.45±0.7	10 (91%)	7 (70%)
Caustic	14	14/0/0	2.0±0.8	0.78±0.97	11 (79%)	7 (64%)
Post-radiotherapic	10	10/0/0	2.1±1.0	0.9±1.29	8 (80%)	8 (100%)
Others	9	8/1/0	2.1±0.93	0.55±0.73	8 (89%)	6 (75%)
Total	95	78/15/2	1.78±0.75	0.4±0.63	87 (91%)	44 (51%)

Table 1: The results of endoscopic dilation of strictures of varying aetiologies.

Discussion

Endoscopic dilation of benign esophageal lesions without fluoroscopic guidance has been found to be an effective, safe procedure characterized by a low risk of complications. It is the first choice therapy, when feasible, even though several sessions are generally needed to achieve complete

regression. Different methods are utilized but there are principally two: the pneumatic with radial action and the bouginage with associated radial and longitudinal actions. [10] Savary-Gillard dilators were generally used in our unit for more proximal, longer stenoses and Balloon dilators for distal, shorter strictures. Moreover when the stenosis was very narrow with a luminal diameter between 5 mm and 1 cm, Savary-Gillard dilators were preferred because they are not compressible and guarantee the luminal diameter achieved. When the strictures measured between 1 and 1.5 cm either dilator could be used depending upon the length and the contour of the stricture and the skill of the endoscopist. When the luminal diameter was more than 15 mm (for example in post-fundoplication dysphagia) pneumatic dilators were preferred. A possible disadvantage of balloon dilation is that it does not furnish the endoscopist any tactile "feeling" of resistance to dilation. [4]

As already demonstrated by others [9,11] fluoroscopic guidance is not necessary. In our unit if a paediatric endoscope was able to pass, the guidance wire was placed under endoscopic guidance. When this was not feasible a marked guide wire was inserted beyond the stenosis and we gently dilated. All of the strictures included in this study, except two (1.43%), could be treated in this way. Wang et al [9], were able to pass a guide wire without fluoroscopic guidance in all of their 55 patients while Fleisher [12] and Kadakia [13] utilized fluoroscopy, respectively, in 5% and 29,4% of their cases. When guide wire passage is not possible, surgical treatment must be considered unless a combined anterograde and retrograde dilation procedure can be attempted. [14]

In our patients post-surgical strictures responded better and had less recurrences with respect to radiation induced, peptic or caustic strictures. This may be due to the fact that the stenotic segment is generally longer and the grade of dysphagia higher in non-surgical with respect to post-surgical strictures, and also because the inflammatory processes may continue to damage tissues in the former.

The recurrent damage could be due to acid or basic reflux in the case of peptic strictures and to persistent inflammatory activity in the case of caustic incident or radiation injuries. Likewise anastomotic stenoses in presence of a persistent fistula may be associated to inflammatory processes. Endoscopic dilation of this type of stricture seems to be less effective and stent placement could improve the results, as we were able to observe in 2 of our patients. Repici et al obtained long term resolution of dysphagia in 13 out of 15 patients using temporary stent placement for refractory benign esophageal strictures. [15]

The role of inflammation on the outcome of dilation therapy was also evaluated by Said et al [16] who found that the persistence of heartburn and of hiatal hernia were significant predictors of recurrence of dysphagia in patients with peptic strictures. Reflux in these cases could contribute to persistence of stenosis by damaging the esophagus. PPI therapy might be advisable in these patients. [17]

Other authors, instead, found no differences in response to therapy between anastomotic, peptic and caustic strictures.[11] Said et al [16] reported that non-peptic strictures were significant predictors for early recurrence. It must be pointed out that the few cases of post-surgical stenoses included in their study were considered together with the radiation induced and congenital strictures in the results' analysis. Our study, which was carried out in a surgical department, provided us the opportunity to observe a large number of post-surgical strictures and to evaluate them with particular attention.

On the basis of our results we confirmed that the length of the stricture is an important factor influencing treatment results. [18] Some authors argue that caustic lesions longer than 5 cm are an indication for surgical treatment, nevertheless in our patient group caustic strictures were medially 4.4 cm long and strictures as long as 17 cm have been successfully treated. In cases of caustic injuries endoscopic dilation can avoid the risks of a major operation in patients who have unfit for or have already undergone surgery. On the other hand surgery can be prescribed for young patients who are fit enough when dilation is unsuccessful. Many authors have suggested that intralesional corticosteroid therapy be utilized when strictures are refractory. Kochar [19] achieved good results utilizing intralesional corticosteroid therapy associated with dilation for long caustic lesions, while others have reported poor results in long lesions. [20] We have had no experience to offer in this regard.

Post-fundoplication dysphagia is a particular kind of post-surgical stenosis. It has been reported more frequently after a Nissen-Rossetti operation (4%) than after the Nissen or Toupet (1%). [21] The explanation could lie in the fact that there is a high tension of the fundoplication that twists the esophagus counterclockwise, obstructing the bolus. Another mechanism explaining post operative dysphagia could be slipping of the fundoplication showing up in the esophagogram exam by the gastric pouch proximal to the fundoplication. [22] In both these cases dilation is unsuccessful in the absence of a real stricture, while it is indicated in presence of a narrow fundoplication. Better results (normal diet in all the patients treated) were obtained in our case records as a result of dilation of post-fundoplication stenosis as opposed to those reported by Wo et al. [22] We hypothesize that remission of only 52% of the dysphagia, can be attributed to the fact that they utilized Savary dilators instead of TTS balloons. Consistent radial dilation seems the best choice of treatment to us for this kind of stenosis.

Recurrence is an important aspect of dilation treatment. The incidence rate was high in our case study: 33% after 2 months and 50% after one year, but new sessions carried out following recurrence proved successful in most of the patients. A normal diet in 75% and a semi-solid diet in 91% was in fact achieved in our patients. Surgery should be anyway taken into consideration for fit patients who present with poor results after repeated dilation sessions. No major complications

were found by us in this study, but perforations have been described by several investigators at a rate of 0.1% to 0.4%. [23-26] This complication was instead found by us during the first years of our activity between 1980 and 1987 [27] and it is probable that endoscopic experience is important in reducing this risk. Bleeding is another major complication that has been reported by some authors,[19] but never observed in our patients.

In conclusion endoscopic dilation of benign esophageal and cardial strictures without fluoroscopic guide is feasible and effectively achieves symptom relief in most cases. Although several sessions are necessary and the recurrence rate is high, new dilation sessions have proven to be successful in relieving dysphagia. Better long term results were obtained in anastomotic or post-fundoplication strictures as opposed to peptic, caustic, or radiation-induced stenoses.

Acknowledgments

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Chapter 6:

Endoscopic treatment of bile duct complications after OLTX

Endoscopic treatment of bile duct complications after orthotopic liver Transplantation

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Abstract:

Aim: to assess indications and results of endoscopic retrograde cholangio-pancreatography (ERCP) in patients who underwent ortotopic liver transplantation (OLT) in our Institution.

Methods: We reviewed all the data of 42 consecutive patients that underwent ERCP for biliary complications after OLT in an 8 year period, in particular recording indications and success of the treatment after a mean of 17 month follow-up.

Results: Cholangiogram (performed in 33/42 patients,79%) found anastomotic strictures in 17 patients (52%),bile duct stones in 8 (24%), both bile duct stones and anastomotic stricture in 2 (6%), papillary stenosis in one (3%) and anastomotic biliary leakage in one (3%), while in 4 patients the contrastogram was normal (12%). Stones' extraction was complete in 9/10 patients (90%) with a mean of 1.2 sessions, while stricture dilation was achieved in 12/19 patients (63%) after a mean of 1.7 sessions, by stent positioning (7 patients), balloon dilation (4 patiens) or with Soehendra dilator (1 patient). Both, the biliary leakage and the papillary stenosis were cured by ERCP. Procedure-related complications were represented by 1 severe pancreatitis (2.4%) and mortality was absent.

Conclusion: ERCP is safe and effective in the management of bile duct complications after OLT and should be attempted before a surgical approach. Better results are obtained for treatment of biliary stones than of anastomotic strictures.

Introduction

Complications of biliary tract after liver transplantation are a frequent event, with an incidence, according to different studies, between 7% and 51% of the patients [1], [2], [3], [4]

They are represented by anastomotic leakage, biliary strictures, ampullary disfunction, sludge and stone formation. Biliary complications are more frequent after living donor liver transplantation, due to surgical technical difficulties, but also ischemia time prior to transplantation, ABO incompatible grafts and the type of donor aortic preservation solution are considered as determinant risk factors[5]. Such a complication need to be recognized and treated appropriately, as a delay in the proper diagnostic and therapeutic approach may result in the death of the patient[6].

Surgical treatment, in particular in presence of extraepatic strictures, is represented by reconstruction of the biliary tract through an hepaticojejunostomy (HJ) on a Roux-en-Y loop. Recently a nonoperative approach, with endoscopic or radiologic percutaneous techniques, is

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becoming more common, but between authors there is not yet accordance on which should be the first choice treatment.

Endoscopic retrograde cholangio-pancreatography (ERCP) is a valid tool both for diagnosis and therapy of such complications. Aim of this study is to assess indications and results of this technique in patients who underwent liver transplantation in our Institution.

Patients and methods

Patients

In this retrospective study we reviewed the data of all consecutive patients who underwent endoscopic treatment of biliary duct lesions after liver transplantation in the Surgical Endoscopy Unit of the 1st Surgical Clinic of Padova University (Italy) in the period between 1998 and 2006.

Ortotopic Liver Transplantation (OLT) recipients who underwent at least one ERCP were identified through an endoscopic computerized data-base. Indications, findings and interventions performed during the exam were noted for each patient from the ERCP report. All the other data, including outcome of endoscopic treatment, complications, cholangiograms, blood tests, other treatment modalities (surgical or radiological) and follow-up were obtained from outpatient and inpatient medical records.

In this period 42 transplanted patients underwent 58 ERCP procedures. Indications to ERCP was the suspect of bile duct complications on the basis of blood text with cholestatic pattern in absence of rejection, abdominal ultrasound demonstrating bile duct dilation or biloma, trans-Kehr T-tube cholangiography or Cholangio-Magnetic Resonance demonstrating bile duct lesions.

Were considered bile duct lesions anastomotic leakage, biliary strictures, ampullary disfunction, sludge and stone formation.

Methods

ERCP was performed under sedation with propofol and since 2001 all patients received also 6-hour infusion of gabesate mesilate 0.5g, starting 60 minutes before the procedure, to reduce the risk of post-ERCP pancreatitis[7]. Routinely antibiotics were administered before the procedure. Amilase and lipase were controlled after procedure and patients were kept in parenteral nutrition until the pancreatic enzymes returned normal.

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Analysis of results and Statistical Analysis

For result analysis we considered:

1) The ability to obtain an adequate diagnosis of the bile duct lesions
2) The cure of the bile duct lesions, represented by complete stone removal, stricture dilation and healing of a bile leakage, all confirmed by improvement of patient symptoms, radiological images and cholestatic patern from laboratory data.
3) Recurrence of the lesion and its treatment.
4) Complications due to ERCP.

Data are expressed as mean ±standard deviation. Statistical analysis was performed using T Student test. Statistical significance was set at $p<0.05$.

Results

Forty-two patients (mean age 50 years, range 13-65 years) underwent 58 ERCP (in mean 1.38 sessions per patient) for biliary duct complications a mean of 29 months after liver transplantation (range 0-133 months). Indications to ERCP were suspect of bile duct stricture in 31, suspect of bile duct stones in 9, suspect of bile leakage in 2.

Papilla cannulation was possible in all but 2 patients who presented a spastic papilla (5%). After entering the papilla, choledochus was contrasted in 33 patients, while in 7 patients was not possible to deeply cannulate the bile duct. Precut was performed in 9 patients and permitted in 7 of them full access to choledochus. The Wirsung duct was cannulated in 23 from 58 procedures (40%).

Cholangiogram was then performed in 33/42 patients (79%) and demonstrated: in 17 patients (52%) an anastomotic stricture, in 8 patients only bile duct stones (24%), in 2 patients (6%) both bile duct stones and anastomotic stricture, in 1 patient (3%) papillary stenosis and in 1 (3%) anastomotic biliary leakage, while in 4 patients the contrastographic exam resulted negative (12%).

Stones' extraction was complete in 9/10 patients (90%) and in one patient a good toilette of the coledocus was obtained, but persisted a hard calcified concretion at liver hilum, that was subsequently treated by performing a surgical HJ. Mean number of sessions for biliary stones' extraction was 1.2.

ERCP achieved a satisfying dilation of anastomotic strictures in 12/19 patients (63%).

In 7 patients the stricture was treated by stent positioning, in 4 only through pneumatic dilation, in one with the Soehendra dilator. In 7 patients was not possible to pass the stricture to perform dilation because it was very narrow or with an angulated shape. Two of these patients had anyway an improvement after papillotomy and did not require other treatments. Four other patients underwent an HJ, two of them after an unsatisfactory attempt of treatment with percutaneous

transhepatic balloon cholangioplasty (PTC) and one after a severe pancreatitis post-ERCP (see below). One other patient was successfully treated with PTC. Mean number of sessions for stricture endoscopic treatment was 1.7 (significantly more then for treatment of biliary stones, $p<0.05$).

Bile leakage was found in one patient and treated with success by positioning a nasobiliary catheter. Finally one patient with papillary stenosis was successfully treated by papillotomy.

Overall ERCP, after access to the choledochus, was successful for diagnosis and treatment of biliary duct lesions in 27/33 patients (82%), while in 18% surgical (5) or radiological treatment (1) was required.

We observed only one serious complication (2.4%), represented by severe pancreatitis, treated successful, together with the biliary stricture, by a surgical operation.

After a mean of 17 month follow-up, disease recurrence was observed in one patient with anastomotic stricture, treated successfully by HJ.

Lesions at cholangiogram	**Patients**	**Treatment success**	**Mean n. sessions**
Anastomotic stricture	19[#]	14 (74%)*	1.7
Stones	10[#]	9 (90%)	1.2
Biliary leakage	1	1 (100%)	1
Papillary stenosis	1	1 (100%)	1
No lesions	4		
Total (patients)	33	27 (82%)	1.38

Table 1: Result of ERCP treatment according to the lesions found at cholangiogram.

*including 2 patients in whom improvement was obtained after papillotomy, without stricture dilation. [#] Two patients were found with both anastomotic stricture and stones.

Discussion

Biliary duct lesions are the leading cause of surgical complications after liver transplantation, whichever biliary reconstruction is performed, choledocho-choledocostomy or HJ.[2] Diagnosis and treatment of these complications is performed more frequently respect to past by a nonoperative approach, through percutaneous transhepatic cholangiography and ERCP. According to the results of this study, ERCP is a safe treatment modality, with low risk of complications (2.4%) and absence of mortality. Cholangiography is feasible in about 80% patients and, after access to bile duct,

treatment of the lesions is possible in 82% of the cases. Overall success of ERCP (including those resulting with a normal cholangiogram) was 64%, while in 36% of cases was not possible to obtain an appropriate diagnosis or to treat the lesion. The only 80% rate of choledochus cannulation could be justified by the scarce use of pre-cut, as we were careful to reduce as much as possible the incidence of complications like pancreatitis, in immune-suppressed patients.

The two lesions that we found more frequently were anastomotic strictures (58%) and biliary duct stones (30%). Better results were obtained with the latter than with the former and less sessions were required ($p<0.05$).

In his study Thuluvath described a response rate of strictures to endoscopic management of 68%[8], while filling defects, represented by bile duct stones, were all successfully treated by extraction after sphyncterotomy and after dilating the strictures, when required. Stent positioning seems to be the best and durable treatment of anastomotic biliary strictures, as demonstrated by Morelli et al. with long-term stricture resolution in 80% of patients.[9]

Schwartz et al taking together their and other authors' experience, concluded that dilation is successful for stricture treatment in 41% cases, while stent placement is successful in 74%[10].

Anastomotic strictures that are identified within 1 year show an excellent response to short-term stenting (3-6 months), while late-appearing anastomotic strictures (after 12 monhs) require long-term stenting (12-24 months)[11].

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Even if the overall success of ERCP varies according to different studies (ranging between 50% and 80%)[9],[12] anyway, in view of the minimal morbidity, it should be considered the first choice treatment before performing a surgical intervention.

In fact, after surgical choledochojejunostomy, Davidson et al[13] described a rate of 6% perioperative deaths, 26% early complications and 22% of late complications. They also demonstrated that prior nonsurgical intervention (endoscopic or percutaneous management) did not adversely influence the outcome of subsequent surgical reconstruction and concluded recommending surgery in the treatment of biliary complications after OLT in patients in whom an endoscopic or percutaneous approach fails.

PTBC can be considered a valid alternative to ERCP for the first choice treatment of biliary strictures and is even preferable in patients with choledocho-jejunal anastomosis.

In a series of Sung et al.[14] PTBC treated successfully 51.3% cases of biliary strictures after OLT and complications, represented by cholangitis or bleeding, occurred in 2-5% of patients.

Also with a percutaneous approach, dilation presents a good initial success, but a low 1-year patency rate. Thus, like endoscopic biliary stenting, transepatic stent placement is preferable to give a better long-term patency rate.

While we consider ERCP the best option for the treatment of bile duct stones after OLT, which is preferable between endoscopy and PTBC for the first treatment of bile duct strictures is still debatable. Randomized trials comparing these two techniques could give an answer to this question.

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Role of the cold ischemia time in the development of biliary strictures after liver transplantation.

Subnormothermic mechanical perfusion versus traditional hypothermia at 4°C in hepatic presevation for transplantation.

In liver transplantation, the development of biliary strictures (BSs) remains a significant problem. BSs affect 10% to 30% of liver transplant recipients, sometimes several months post-LT, and are a source of morbidity, graft loss, and even mortality.[1-4] The cause of BSs is multifactorial, and ischemic, immune, and technical factors may have a role.[1-6] In particular, prolonged cold ischemia time (CIT) has been associated with a greater rate of BSs.[5] Many centers try to keep CIT at less than 10 hours for this reason. When preservation is conducted by continuous perfusion and added with oxygen, hypothermia is not necessary and normothermic or subnormothermic perfusion may become the ideal way of preservation for long intervals added with oxygen and energetic substrates. We tried to create a Machine Perfusion model in a big animal to sample, at different temperatures, which is the best condition of perfusion and graft preservation. Fifteen Landrace pigs, of 22 Kg weigh were utilized for this purpose. They were divided in three groups: in Group C (5 pigs) the collected liver was preserved in cold storage for 8 hours at 4°C, in Group N (5 pigs) the collected liver was preserved in the Machine Perfusion at 37°C for 8 hours, in Group I (5 animals) the liver was preserved in the Machine Perfusion at 20°C, for 8 hours. All the 15 grafts underwent 2 hours re-warming at 37°C to evaluate the effect of reperfusion. Biochemical, histological and functional evaluations followed. According to biochemical (GOT, GPT, LDH), functional (biliary production and indocyanine green clearance) and histological (necrosis and congestion) parameters, the 20°C Machine Perfusion gave better results, with respect to the other two groups. According to these results, the preservation at 20°C with the Machine Perfusion seems promising to reduce the damages due to the cold ischemia, including the development of biliary strictures following liver transplantation.

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Chapter 7:

EUS guided drainage of abdominal abscesses

EUS Guided Drainage of Abdominal Abscesses

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Abstract

Traditionally abdominal abscesses have been treated with either surgical or radiologically guided percutaneous drainage. However, surgical drainage procedures may be associated with considerable morbidity and mortality. Percutaneous drainage has limitations, especially when there is a need to traverse other organs. EUS-guided drainage of well demarcated abdominal abscesses, with adjunctive endoscopic debridement in the presence of significant debris and associated necrosis, has been shown to be feasible and safe. This review summarizes the current status of EUS-guided drainage of abdominal abscesses and describes the available and emerging techniques, and also highlights the indications, limitations and safety issues.

Here inserted with the kind permission of Prof. Soehendra and collegues,
submitted

BACKGROUND

Treatment of abdominal abscesses is a therapeutic challenge, which includes the expertise of interventional endoscopists, surgeons and radiologists. Traditionally
Abdominal abscesses have been treated with surgical drainage. However, surgical drainage procedures may be associated with considerable morbidity and mortality (13 – 53% and 6.2 – 25% respectively)[1 – 8] Radiologically guided percutaneous drainage is less invasive, however its use is often limited by the need to transverse abdominal organs andineffective for removal of necrotic material and debris.

Endoscopic ultrasound (EUS) provides previously inaccessible routes and enables a minimally invasive yet effective treatment of abdominal abscesses. Areas which are well accessible by EUS are subphrenic space, left lobe and central segments of the liver and the parapancreatic area. Pelvic abscesses can also be effectively drained under EUS guidance. EUS guided drainage has the advantages of an excellent visualization of the abscess cavity even in the absence of endoscopic bulging, close approximation of the transducer to the cavity wall, direct passage of the needle into the cavity through the gastric or duodenal walls, the ability to avoid inadvertent puncture of interposed vessels through the use of color Doppler and the avoidance of transcutaneous infection and formation of external fistulas. EUS guided drainage should be attempted as the first line therapy in any cases. There are two different ways of utilizing EUS for abdominal abscess drainage: EUS-assisted and EUS-guided drainage.

The therapeutic use of EUS-guided drainage was first reported by Grimm et al in 1992 in the context of a pancreatic pseudocyst [9]. The initial EUS-guided transmural puncture and guidewire placement was performed using a linear echoendoscope with a 2 mm working channel. However the echoendoscope had to be changed for a 3.7 mm working channel duodenoscope so that a 10 Fr pigtail stent could be inserted. With the development of therapeutic linear echoendoscopes with larger working channels, the technique of one-step EUS-guided pseudocyst drainage had been developed. [10-12] These techniques were soon extended to the drainage of pancreatic [13-15], hepatic [16], subphrenic [17], pelvic [18,19] and mediastinal abscesses [20-22]. For abscesses with solid necrotic material aggressive endoscopic debridement is mandatory to ensure a successful drainage [23]

OBJECTIVES

The objectives of performing EUS-guided drainage of abdominal abscesses are to evacuate all purulent material, remove all devitalized tissue, and to provide continuous irrigation to facilitate resolution of the infection. This review summarizes the current status of EUS guided drainage of abdominal abscesses and describes the available and emerging techniques, and also highlights the indications, limitations and safety issues.

BASIC PRINCIPLES

The abdominal abscess must have been encapsulated with a mature wall which is adjacent to the gastrointestinal (GI) wall. The abscess cavity is first visualized by EUS and interposed vessels are excluded by color Doppler. The abscess cavity is then punctured with a needle under EUS and fluoroscopic guidance, followed by insertion of a guidewire through the needle and subsequent placement of stents and catheters for drainage and continuous irrigation. In addition, in the presence of significant necrosis and debris, gradual dilatation of the puncture site should be performed to allow endoscopic debridement. Furthermore concomitant predisposing conditions must be treated, such as pancreatic duct strictures [24]and fistulas [25].

EQUIPMENT USED

The endoscope

EUS-guided transmural puncture of an abdominal abscess is performed using a linear array echoendoscope with color Doppler function. Currently 2 models are available from Olympus Optical Co Ltd (Olympus Optical Co, Ltd, Tokyo, Japan). These are the GF-UC160P model, which has a 2.8 mm working channel, and the GF-UCT160 model, which has a 3.7 mm working channel. These echoendoscopes utilize either the EU-C60 processor from Olympus or ultrasound processors (SSD 4000 US system and later models, Alpha 5 and 10) from Aloka Co Ltd, Tokyo, Japan. Linear echoendoscopes available from Pentax-Hitachi include the EG-3830UT and EG-3870 UTK, which are therapeutic echoendoscopes with a working channel of 3.8 mm, as well as others with smaller working channels (FG-38UX: 3.2 mm; EG-3630U and FG-36UX: 2.4 mm; FG-34UX: 2 mm). These echoendoscopes utilize the Hitachi (Hitachi, Tokyo, Japan) ultrasound processors (EUB 525, 5500, 6000, 6500).

Fujinon (Tokyo, Japan) has recently produced a new linear echoendoscope, the EG-530UT, which utilizes the SU-7000 processor and has a 3.8mm large working channel.

The use of an echoendoscope with a large working channel is important when considering drainage procedures which require catheter and stent placement. A working channel of 3.7 mm (GF-UCT160) or 3.8 mm (EG-3830UT, EG-3830UTK or 530UT) will theoretically permit the insertion of a size 10 Fr stent, whereas a smaller working channel such as 3.2 mm (FG-38UX) and 2.8 mm (GF-UC160P) will only permit the insertion of a size 8.5 Fr stent and 7 Fr stent respectively. However, due to the friction between the inner lining of the working channel and the stents, stent placement is usually difficult when performed with an echoendoscope. When echoendoscopes with smaller working channels (eg 2 – 2.4 mm) are used, after the initial EUS-guided puncture and passage of guidewire into the abscess cavity, the echoendoscope will have to be exchanged for a therapeutic duodenoscope with a larger working channel (3.7 – 4.2 mm) in order to allow stent and/or nasoabscess catheter placement.

Puncture needle

Several punctures sets are available.

1. We use a 22 gauge needle (GIP; Medi-Globe, Achenmuehle, Germany) with a 6 Fr Teflon outer sheath (H.C. Grosse GmbH and Co KG Medizintechnik, Daldorf, Germany).

2. Giovannini Needle Wire Oasis" (Cook Endoscopy, Winston-Salem, NC) set can also be used. [11] This set consists of a pushing catheter (8.5 or 9 Fr),a guiding catheter (5.5 Fr)a dual function electrocautery needle-wire (0.035 inch) and a 5 cm stent (8.5 or 10Fr). The dual function electrocautery needle-wire first punctures the pancreatic pseudocyst wall under EUS guidance ad then facilitates stent placement, all in a single-step procedure without need for wire-guide exchanges.

3. Another punture set is the "Cystotome" (Cook Endoscopy) first used by Cremer [26] which consists of a needle knife inside a 5 Fr sheath and 10 Fr outer sheath with a coaxial conic-tip cutting device. This can be utilized with 3.8 mm Pentax or Fuji EUS scope [27], while the tip of the outer sheath can not pass in the Olympus GF-UCT160. In fact this set was initially conceived for its use with 4.2 mm operating channel duodenoscopes [26].

4. The 19 gauge EUS-FNA needle (EUSN-19-T ; Cook Endoscopy) was used either to aspirate the abscess [18] or to introduce the guide wire for subsequent dilation and stent placement [21]

5. Seifert utilized [28] a particular set that permits one-step puncture-drainage procedure. This set consists of a stainless steel needle, of 1 mm outer diameter, equipped with blunted mandrel (Grosse,

Daldorf, Germany). The needle is loaded with a 7-F Teflon pusher and a modified 6 cm long 7-F Teflon stent with two-sides holes that can be released as the puncture needle is retracted.

Other accessories and equipment for the cannulation, ballon dilation and necrosectomy of the abscess cavity

1 Endoscopes: therapeutic video-duodenoscope with 4.2 mm working channel (e.g. TJF 160; Olympus); diagnostic and therapeutic gastroscopes (e.g. GIF 1T 140, GIF-Q140/160, GIF-1T100, GIF XT 30;Olympus), pediatric gastroscopes (e.g. GIF XP 160 and 240; Olympus), trans-nasal gastroscope (e.g. GIF Q180, Olympus).

2 0.035 inch Terumo wire (Terumo Medical Corporation, Tokyo, Japan).

3. Standard 0.035-inches guidewire (Dispo-Medica, Hamburg, Germany

4. 7F Soehendra dilator (Cook Endoscopy)

5. Contrast medium (Telebrix 180, Guerbet GmbH, Sulzbach, Germany)

6. TTS-Balloon 8-20 mm diameter *(*Boston Scientific Corporation, Natick, MA).

7. 7 Fr Teflon nasocystic drainage catheter (H.C. Grosse GmbH & Co KG Medizintechnik, Daldorf, Germay), 8.5 and 10 Fr double pigtail or straight plastic (we use double pigtail Teflon stents to reduce the risk of stent migration)

8. Dormia baskets (FG 18Q-1, FG-22 Q-1, Olympus)

9. Roth Net (US Endoscopy, Mentor, OH)

10. Braided snare

11. Eppendorf flushing catheter (Grosse GmbH & Co. KG, Daldorf, Germany)

12. Endo water jet. (EJ-2, endo-je 2000, Pauldrach Medical GmbH, Garbsen, Germany)

13. CO_2 Efficient endoscopic insufflator (E-Z-EM, INC, Lake Success, NY, USA) for endoscopic debridement.

DESCRIPTION OF PROCEDURE

Established Technique of Abscess Drainage

1. The abdominal abscess is visualized using linear array echoendoscope, and interposed vessels are excluded using color Doppler US.

2. Under EUS guidance, the abscess cavity is then punctured with the puncture set. We Use a 22-gauge needle (GIP; Medi-Globe, Achenmuehle, Germany) with a 6 Fr Teflon outer sheath (H.C. Grosse GmbH and Co KG Medizintechnik, Daldorf, Germany) to puncture the cavity, assisted by

short bursts of cutting current, after which the needle is withdrawn, leaving the Teflon outer sheath within the cavity.

3. Successful puncture is confirmed by EUS, injection of contrast medium under fluoroscopy and further documented by the aspiration of pus. Culture of the aspirated fluid with antibiogram should be done. A small unilocular abscess may be potentially treated by complete aspiration, but a larger abscess would need additional drainage procedures.

4. A 400 – 480 cm long, 0.035-inch diameter guidewire is then inserted through the Teflon sheath (or through the 19 gauge EUSN-19-T needle if it is used), into the abscess cavity, and advanced to form 2 loops within the abscess cavity to facilitate safe catheter exchange.

5. The Teflon outer sheath (or EUSN-19-T needle) is then removed leaving the guide wire in place.

6. A dilation balloon (diameter of 8 mm up to 16 mm in the following sessions) is then inserted over the guide wire and the tract dilated.

7. Depending on the working channel of the linear echoendoscope used, a 10 Fr (working channel 3.7 – 3.8 mm), 8.5 Fr (working channel 3.2 mm) or 7 Fr (working channel 2.8 mm) double pigtail Teflon stent is inserted over the guide wire to drain the abscess.

8. The abscess cavity is recannulated with a universal catheter (Cook Endoscopy) and a 260-cm-long, 0.032-inch-diameter angulated-tip guide wire catheter (Terumo Corporation, Tokyo, Japan). Once the catheter has been forwarded into the abscess cavity the Terumo wire is exchanged with a 0.035-inch guide wire. A 7Fr nasoabscess Teflon catheter is then inserted over the guidewire. The catheter is advanced to form at least one loop inside the cavity to prevent it from being dislodged when the echoendoscope is withdrawn.

9. The abscess cavity is irrigated with 1500 ml saline/per day via the nasoabscess catheter until absence of purulent discharge. This process of irrigation is necessary to prevent accumulation of pus and debris.

10. Follow up: Once sepsis has settled clinically, and there is no longer any purulent discharge from the nasoabscess catheter, the catheter may be removed. Once resolution of the abscess has been documented, either by transabdominal imaging or EUS, the internal stent may also be removed.

Adjunctive endoscopic debridement

In the presence of significant thick purulent material, necrosis and debris, adjunctive endoscopic debridement would be needed. In this situation, additional steps would be necessary:

1. Step-wise balloon dilation of the puncture site from 8 mm up to 20 mm using a transendoscopic balloon dilator (eg CRE balloon; Microvasive Endoscopy, Boston Scientific Corp, Natick, Mass).

Dilation is performed with a direct endoscopic view of the inside of the abscess cavity by maintaining the proximal end of the transparent balloon directly in front of the viewing lens.

2. Performance of endoscopic necrosectomy and lavage in a stepwise manner as the cystgastrostoma or cystduodenostoma is dilated:

a. Initial insertion of a Dormia basket (eg FG-22Q-1; Olympus) into the abscess cavity under fluoroscopic guidance by using a therapeutic gastroscope to remove the debris.

b. Insertion of a trans-nasal or pediatric gastroscope directly into the abscess cavity, with the removal of necrotic material using a smaller Dormia basket (FG-18Q-1; Olympus) after dilation of the cystgastrostoma or cystduodenostoma.

c. After adequate dilation of the cystgastrostoma or cystduodenostoma, a standard gastroscope, or even a therapeutic gastroscope, can be introduced into the cavity to inspect the abscess cavity under direct endoscopic vision and to suction out the debris and necrotic material.

Precaution must be taken to avoid too much air insufflation for the risk of embolism. CO2 insufflator can be used to reduce this risk. The necrosis should not be removed aggressively.

d. Generous endoscopic lavage is performed daily with 500 to 1000 ml saline solution by using a spray catheter connected to an Endo Water Jet system (Pauldrach Medical GmbH, Garbsen, Germany) under direct endoscopc view.

3. The transendoscopic lavage and debridement is repeated until the abscess cavity looks clean and no further pus or debris is present.

Sometimes the debris can stick in the working channel or damage the baskets. In this case a snare can be used very carefully to remove the necrotic material.

Newer techniques

As re-entry into the abscess cavity after stent placement to position the nasoabscess catheter can be cumbersome, some new techniques have been proposed to permit the simultaneous placement of multiple guidewires.

1. Double wire technique

For EUS-guided abscess drainage, insertion of a transgastric or transduodenal stent & nasoabscess catheter in the 1st session is essential for continuous irrigation. Sequential stent & nasoabscess catheter insertion maybe time consuming due to difficulty in abscess cavity recannulation after the initial stent placement because the direction of the puncture tract may be tangential. To solve this problem of recannulating the abscess cavity to reinsert a second guidewire, we have developed a

prototype puncture kit which allows the simultaneous insertion of 2 guidewires at the initial puncture. This puncture kit consists of a 6Fr inner Teflon catheter, an 8.5Fr outer Teflon catheter and a 22 gauge GIP puncture needle. Using the assembled kit with the needle protruding out at the distal end of the catheter, the abscess cavity is punctured under EUS-guidance using a cutting current as described earlier. The assembled inner and outer catheters are then pushed into the abscess cavity, with the inner catheter protruding out distally, and thus serving as a tapered tip to facilitate the entry of the larger outer catheter. Once entry into the abscess cavity is confirmed by EUS and by aspiration of pus, the needle and the inner catheter are withdrawn, leaving the 8.5Fr outer catheter within the abscess cavity. The size of this 8.5Fr outer catheter permits the simultaneous insertion of two 0.035-inch guidewires, and the sequential insertion of a stent and nasoabscess catheter can be performed without a need for recannulation of the abscess cavity. It must be noted that using a therapeutic linear echoendoscope with a working channel of 3.7 mm or 3.8 mm, the largest stent that can be inserted would be size 8.5Fr, because of the additional space taken up by the second 0.035-inch guidewire within the working channel. With this novel technique establishing an irrigation system for the treatment of abscesses becomes easier and safer.

2. Fusion™ IDE system

The Fusion™ system with its intra-ductal exchange (IDE) technology allows the guidewire to disengage from the accessory device within the ductal system, and remain securely fixed in place through a wire-locking device attached to the opening of the working channel during ERCP. The key feature of this system is the presence of an IDE port at the distal end of various accessories such as ERCP catheters, sphincterotomes and stent introducer sets. The guidewire is inserted through this IDE port into the lumen of the accessory device, traveling a short distance before exiting at the distal end of the device. In addition, there is also a conventional proximal wire port through which guidewires can be inserted conventionally. Since only the distal end of the guidewire is located within the catheter, with the rest of the guidewire lying parallel to it, upon selective ductal cannulation, the guidewire can be disengaged from the catheter within the ductal system simply by either pushing the catheter further inward until the IDE port goes beyond the distal end of the guidewire, or by pulling back the guidewire, if the catheter is deep enough, such that the distal end of the guidewire slips out of the IDE port. With this ability to disengage the guidewire from a catheter intraductally, it is possible to place multiple stents over one guidewire placement, without a need for further recannulation. In addition, after disengagement of the guidewire, a second guidewire can also be placed by insertion through the proximal wire port in the conventional manner. These concepts, as demonstrated by Hanrath et al. [29] may be applied to EUS-guided

pseudocysts drainage, and thus also for abscess drainage when there is a need to insert more than one stent.

It must be emphasized that for this technique, a therapeutic linear echoendoscope with a working channel of either 3.7 mm or 3.8 mm would be necessary, and that the largest stent that can be inserted would be size 8.5Fr, because of the additional space taken up by the 0.035-inch guidewire within the accessory channel. In fact, passage of the stent using the 3.7 mm accessory channel echoendoscope would already be somewhat difficult.

3. Simultanous positioning of 2 guide wires with the 10F cystotome.

The 10F cystotome permits also the positioning of 2 guide wires: after the pseudocyst has been accessed with the tip, the needle is removed. The first wire is then placed through the sheath of the needle. After the 10F outer sheath of the cystotome has been advanced into the cyst, the inner catheter is removed and a second wire can be placed. Now the outer sheath is also removed and two wires are in place inside the pseudocyst. [29]

4. Forward viewing echoendoscope

A new prototype linear echoendoscope with forward viewing optics and a field view of 120° has been produced by Olympus (Olympus GF-UCT140-AL5). The ultrasonic scanning range is 90° and is parallel to the insertion direction and the working channel is large 3.7 mm. The forward viewing optics of this echoendoscope allows the initial puncture to be directed perpendicularly. The perpendicular puncture makes easier the subsequent procedures, such as balloon-dilations and necrosectomy, as we observed in 5 patients (data not published).

SUCCESS RATE AND LIMITATIONS

Current published data on EUS-guided drainage of abdominal abscesses are either case reports or large case series. No randomized controlled data are available, especially in terms of comparison with current traditional methods of drainage such as surgery and radiologically guided percutaneous drainage. Nonetheless, the results, in terms of both high efficacy and a low complication rate, are very promising, especially when seen in the light of the known morbidity and mortality of the traditional drainage procedures. (Different areas are accessible by EUS for abscess drainage, including subphrenic space, left epatic lobe, peripancreatic area, pelvis and mediastinum. Several authors reported about drainage of pancreatic abscesses. Giovannini et al [13] treated 20 cases of pancreatic abscesses with EUS-guided drainage, and was successful in 18, with 2 needing surgery; on long-term follow up, 2 more patients underwent surgery because of abscess recurrence. No

major complications occurred, except one pneumoperitoneum. Krüger at al [30] reported on their experience in 35 patients with pancreatic abscesses or pseudocysts and reported initial success rate of 33/35, and overall resolution rate of 88%, with 12% recurrence, again with no complications. After the success of pancreatic abscess drainage under EUS guidance, other areas have been approached with this technique.

Seewald et al reported on successful drainage of a case of hepatic abscess [16] and 2 cases of subphrenic abscesses [17] again without any complications. In terms of pelvic abscesses, Attwell et al [19] successful drained a sigmoid diverticular abscess as an adjunct to subsequent surgery, such that sigmoid colectomy with primary anastomosis could be carried out later. Giovannini et al [18] attempted EUS-guided drainage in 12 cases of perirectal or pelvic abscesses and was able to insert a stent successfully in 9, of which surgery was required only in 1 because of incomplete drainage; 3 patients were treated by simple aspiration as the distance of the abscess cavity from the transducer of the echoendoscope was greater than 20 mm and of these 3 patients, 2 needed subsequent surgery. In the treatment of paraesophageal mediastinal abscesses, Fritscher-Ravens et al [20] successfully treated 2 cases by simple aspiration in the intensive care setting, while Kahaleh et al [21] used an internal stent for treatment.In the presence of thick purulent material, debris and infected necrosis, such drainage procedures alone would not suffice. Seifert et al [14] first reported on their experience in endoscopic debridement in 3 patients with infected pancreatic necrosis and was successful in all 3 cases without any complications. Seewald et al [15] further treated 13 patients with infected pancreatic necrosis and abscess with an aggressive endoscopic approach which included synchronous EUS-guided multiple transmural and/or transpapillary drainage procedures followed by balloon dilatation of the cystgastrostoma or cystduodenostoma, daily endoscopic necrosectomy and saline lavage and sealing of pancreatic duct fistula with N-butyl-2-cyanoacrylate. Initial drainage was successful in all 13 patients, thus avoiding the need for emergency surgery. In addition, 9 patients avoided surgery completely, while one needed adjunctive surgery to drain the extension of abscess into the right paracolic gutter, and 2 patients later underwent surgery because of total pancreatic duct disruption which led to pseudocyst recurrence. Wehrmann et al [22] adopted this concept of endoscopic debridement of pancreatic necrosis and abscess and applied it to the treatment of large paraesophageal abscesses after esophageal perforation. Out of 20 patients, simple EUS-guided drainage procedure sufficed in 4 patients while one case could not be performed due to technical reasons; of the remaining 15 patients, endoscopic debridement was successful in all cases.

Although shown to be very effective, limitations exist. The abscess cavity must be well-defined, with a well-formed wall; EUS-guided drainage is not suitable for poorly defined fluid collections.

Stenting is not possible when the distance of the abscess cavity is more than 20 mm from the transducer. The usefulness of drainage procedures is also limited when very thick fluid or multiple cavities are present. Certain areas such as the paracolic gutters are not accessible endoscopically and so adjunctive surgery would be necessary. In addition, solid debris will not be evacuated by placement of endoscopic drains and stents alone, and irrigation of the abscess cavity via a nasocystic catheter placed alongside a stent will result in slow resolution of solid necrosis and debris. Hence a more aggressive approach with endoscopic debridement would be necessary in these situations but this approach is technically demanding and the required expertise may not be readily available.

COMPLICATIONS AND SAFETY

No major complications have been reported thus far in the context of EUS-guided drainage without endoscopic necrosectomy and debridement. In the series on endoscopic debridement of paraesophageal mediastinal abscesses by Wehrmann et al [22], 1 fatality (7%) occurred due to pulmonary embolism one day after successful treatment in a patient with iliac vein thrombosis.In the case series on endoscopic debridement of pancreatic necrosis and abscess by Seewald et al [15], minor bleeding occurred in 4 out of 13 patients after balloon dilation and necrosectomy, but these cases were either self-limiting or controlled endoscopically. Seifert et al [31] recently reported the results of endoscopic necrosectomy after EUS-guided drainage on 50 patients. Some procedure-related complications were observed, including 6 sepsis (5 letal), 2 bleedings, 2 air embolisms (1 letal), 2 pneumoperitoneum. These authors concluded that retroperitoneal interventions should use CO_2 instead of air. Also recognition of possible collections not amenable by endoscopy should be always done to avoid death for severe sepsis. Again from the German Multicenter Study on Endoscopic Pancreatic Retroperitoneal Debridement (GEPARD) [23], 8 out of 60 patients treated by endoscopic necrosectomy (not all under EUS guidance) experienced complications: 2 perforations, 5 bleedings and 1 pneumoperitoneum.

CONCLUSIONS

EUS-guided drainage of well demarcated abdominal abscesses, with adjunctive endoscopic debridement in the presence of significant debris and associated necrosis, is feasible and safe. It is a viable alternative to the traditional methods of surgical and percutaneous drainage methods when the required technical expertise is available.

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Sintesi dei risultati

1) Trattamento e stadiazione delle teleangiectasie intestinali

Lo studio effettuato sulla teleangectasia intestinale sporadica fornisce alcune utili informazioni per il management di questa patologia, che risulta essere a volte invalidante, richiedendo anche la trasfusione di più di 100 unità di emazie concentrate in un anno e può risultare mortale, nonostante il trattamento, nel 5% dei casi.

La laser-terapia endoscopica delle lesioni teleangiectasiche delle prime vie digestive è risultata in grado di abolire la necessità di trasfusioni nel 61% dei casi e di ridurne il numero in un altro 22%. Il 17% dei pazienti è invece risultato non-responsivo alla terapia. Dopo aver analizzato quali siano i fattori predittivi di una mancata risposta alla laser-terapia endoscopica, si è giunti a proporre una flow-chart, che invita a prendere in considerazione per un trattamento resettivo chirurgico i pazienti che ricevono più di 10 unità di emazie all'anno e coloro che sono stati sottoposti ad almeno 6 sedute di laser terapia senza beneficio. E' comunque primariamente necessario sottoporre i pazienti che presentano una scarsa risposta alla terapia endoscopica ad una stadiazione accurata della malattia.

Infatti il trattamento di un'area isolata del tratto digestivo, trascurando le altre, risulta spesso insufficiente ad ottenere un controllo del sanguinamento.

Dallo studio effettuato mediante gastroscopia, videocapsula e colonscopia è emerso infatti che la teleangiectasia sporadica, come quella ereditaria, presenta un elevato rischio di multifocalità. I pazienti con teleangiectasie riscontrate alla gastroscopia hanno presentato nel 67% dei casi anche lesioni del piccolo intestino evidenziabili con l'endoscopia capsulare e nel 43% lesioni coliche riscontrabili mediante colonscopia. I pazienti con lesioni coliche hanno presentato nel 54% lesioni gastro-duodenali e nel 48% lesioni del piccolo intestino. Permettendo il riconoscimento di nuove lesioni la videocapsula ha condizionato favorevolmente il management terapeutico nel 46% dei casi. Un sottogruppo a parte tra i pazienti portatori di teleangiectasia è rappresentato dai cirrotici candidati a trapianto di fegato, i quali, dopo il trattamento sostitutivo d'organo presentano una risoluzione anche del cosiddetto "stomaco a melone".

2) Profilassi primaria del sanguinamento da varici esofagee nel paziente cirrotico candidato a trapianto di fegato

Dal trial clinico di confronto tra betabloccanti (propranololo) e legatura endoscopica per la prevenzione del sanguinamento nei pazienti con varici ad alto rischio (F2 blu con segni rossi o F3), è emersa un'indicazione terapeutica importante per quanto riguarda questo sottogruppo di pazienti.

I due trattamenti si sono dimostrati entrambi efficaci nel ridurre il tasso di sanguinamento rispetto a quello atteso in assenza di terapia, che, visto il grado di cirrosi e lo stadio delle varici, doveva essere intorno al 30% ad un anno. La percentuale di sanguinamento registrata è stata rispettivamente nel gruppo della legatura ed in quello del betabloccante di 6,5% e 9,6% ad un anno.
La legatura presenta forse un modesto vantaggio rispetto ai betabloccanti nel prevenire il rischio di sanguinamento, ma tale differenza è evidenziabile solo con un lungo follow-up, che appare improbabile nei pazienti in attesa di trapianto, i quali infatti vanno incontro a sostituzione d'organo entro tempi ragionevolmente brevi. La legatura endoscopica ha presentato due svantaggi rilevanti rispetto al propranololo. Uno di essi è rappresentato dal sanguinamento iatrogeno in sede di ulcera post-legatura, che, nella nostra esperienza e in quella di altri autori, può avere esito fatale. I betabloccanti invece non hanno mai causato complicanze mortali durante il trattamento profilattico del sanguinamento da varici, secondo quanto riportato in letteratura.
L'altro svantaggio della legatura endoscopica è rappresentato dal costo del trattamento, risultato tre volte superiore rispetto alla terapia con propranololo. In conclusione nei pazienti cirrotici candidati a trapianto di fegato, l'uso dei betabloccanti è da considerarsi preferibile rispetto alla legatura endoscopica, per la profilassi primaria del sanguinamento da varici esofagee.

3) Laser terapia dell'esofago di Barrett

L'esofago di Barrett rappresenta un fattore di rischio per lo sviluppo di adenocarcinoma. Tale rischio è calcolato intorno allo 0,5%-2% per anno a seconda delle casistiche. Dai dati finora riportati in letteratura, non è ancora emerso quale sia l'atteggiamento terapeutico da tenere in presenza dell'esofago di Barrett non complicato da displasia grave, oltre al follow-up endoscopico con biopsie. La terapia farmacologica a tutt'oggi è risultata efficace nel trattamento dei sintomi da reflusso e dell'esofagite, ma non sulla progressione della metaplasia. La plastica chirurgica antireflusso sembra ridurre la progressione di malattia, pur senza portare alla guarigione dell'esofago di Barrett. Sono stati quindi proposti alcuni trattamenti endoscopici ablativi per la metaplasia, tra cui l'argon plasma coagulation (APC), la PDT, la radiofrequenza ed i laser di potenza, ma non è ancora chiaro se essi offrano un vantaggio rispetto al semplice follow-up nelle forme non degenerate.
Abbiamo voluto con questo studio verificare l'efficacia e la sicurezza della terapia laser endoscopica per l'esofago di Barrett, dapprima su una casistica più limitata ed un follow-up più breve, per verificare la sicurezza della metodica, poi su una casistica di poco più ampia, ma con un follow-up più lungo, per valutare i risultati a lungo termine ed il rischio di recidiva della malattia. Secondo la nostra esperienza la laser-terapia dell'esofago di Barrett è risultata scevra da

complicanze ed efficace nell'ottenere la regressione della displasia, essendo però quest'ultimo dato verificato in un numero di casi limitato (6/6). La metodica è stata inoltre efficace nel portare a guarigione completa la metaplasia intestinale in quasi tutti i casi di short Barrett (8/9). Nei pazienti portatori di long Barrett tale terapia si è dimostrata meno efficace (remissione completa in 6/13 casi). A lungo termine si è registrato un tasso di recidiva di metaplasia piuttosto basso (7%) e nessun caso di recidiva di displasia o degenerazione. Da quanto emerso da questo studio la laser-terapia con laser di potenza è poco consigliabile per i casi di long-Barrett, mentre può essere utilizzata con successo nei portatori di short Barrett, sempre all'interno di trial clinici. Ulteriori studi su una più ampia casistica sono infatti necessari per poter verificare l'utilità di tale metodica nel ridurre il rischio di sviluppare l'adenocarcinoma. Per quanto riguarda la displasia di alto grado inoltre bisogna sottolineare che un limite importante di questa terapia, se confrontato con la mucosectomia endoscopica, è rappresentato dalla scarsità di materiale fornito per un accurato esame istologico.

4) Laser terapia degli adenomi colorettali

Con questo studio ci siamo posti l'obiettivo di verificare l'efficacia della fotoablazione laser endoscopica per il trattamento degli adenomi sessili di grandi dimensioni del colon-retto in pazienti inoperabili o che avevano rifiutato l'intervento chirurgico.

Il trattamento dei polipi colo-rettali di grandi dimensioni può essere infatti effettuato mediante resezione chirurgica, polipectomia diatermica endoscopica con piece meal resection, mediante transanal endoscopic microsurgery o mediante terapia laser.

Quest'ultima, da quanto emerso dal nostro studio, risulta gravata da scarse complicanze ed efficace non solo nella palliazione dei sintomi, quali sanguinamento, mucorrea e tenesmo, ma anche nel controllare il rischio di degenerazione. Infatti in un follow-up medio di 28 mesi non si è osservato alcun caso di degenerazione a carico di 86 polipi con displasia lieve o severa trattati mediante laser-terapia. Il limite di questo tipo di trattamento è comunque rappresentato dalla mancata raccolta di materiale per esame istologico, per cui è essenziale associare un accurato sampling bioptico ed una stadiazione eco-endoscopica nei casi con displasia di alto grado, per evitare di trascurare le forme di carcinoma invasivo.

5) Dilatazione endoscopica delle stenosi esofagee post-chirurgiche

Da questo studio è emerso che la terapia dilatativa delle stenosi esofagee post-anastomotiche e post-fundoplicazio è effettuabile in quasi tutti i casi anche in assenza di guida fluoroscopica, permette di ottenere una dieta semisolida nel 97-100% dei pazienti trattati, e, pur se gravata da un

alto tasso di recidiva (32% ad un anno), è facilmente ripetibile. Sia per la brevità della lesione, che per l'assenza di una persistente noxa patogena, la dilatazione delle stenosi anastomotiche offre migliori risultati rispetto a quella delle stenosi da caustici, attiniche o peptiche.

6) La terapia dilatativa delle complicanze della via biliare dopo trapianto di fegato

Se il trattamento endoscopico delle complicanze anastomotiche in chirurgia dell'esofago presenta risultati eccellenti, meno efficace è il trattamento endoscopico delle stenosi della via biliare dopo trapianto di fegato, che risulta efficace solo nel 63% dei casi dopo incannulazione della via biliare. A rendere più difficile questo tipo di trattamento è il danno ischemico, cui spesso la via biliare è sottoposta durante o in seguito al trapianto di fegato. Il posizionamento di stent, laddove possibile, riduce il rischio di recidiva stenotica. L'endoscopia operativa, come il trattamento radiologico transepatico, rappresenta comunque il trattamento di prima linea di tale complicanza rispetto a quello chirurgico.

7) Drenaggio eco-endoscopico degli ascessi addominali

Da questo studio, effettuato in collaborazione con il gruppo di Amburgo diretto dal Prof. Soehendra, emerge una nuova frontiera dell'endoscopia operativa, che permette, con l'ausilio dell'ultrasonografia endoluminale, di accedere per via trans-gastrica e colo-rettale alla cavità addominale e di effettuare il drenaggio di ascessi addominali anche associato a debridement e necrosectomie. Questo campo di applicazione rappresenta un primo step, già di fatto utilizzato nella pratica clinica, verso quella nuova disciplina chirurgica miniinvasiva definita con l'acronimo NOTES (Natural Orificial Trans-Endoluminal Surgery), al momento ancora in fase di sperimentazione, ma che sta raccogliendo particolare interesse sia nel campo endoscopico che chirurgico.

Summary of the Results

1)Treatment and staging of intestinal telangiectasia

The study carried out on sporadic intestinal teleangiectasia furnishes useful information on the management of an at times invalidating disease requiring as many as 100 blood units a year and which proves to be fatal in 5%.

Endoscopic laser therapy of teleangiectasic lesions of the digestive tract was successful in abolishing transfusions in 61% and in reducing their number in 22%. Seventeen percent of the

patients, however, did not respond to therapy. The flow chart that was drawn once the predictive factors of no response to laser therapy were analyzed indicates that surgical resection should be considered for those patients receiving more than ten blood units a year and for those who have undergone at least six sessions of laser therapy without benefit. Patients who are unresponsive to endoscopic therapy must in any case undergo staging of the disease. In fact, treating an isolated area of the digestive tract and neglecting others often results in inadequate bleeding control.

The study carried out utilizing EGD, capsule endoscopy and colonscopy showed, in fact, that in sporadic, just as in hereditary, telangiectasia there is a high risk of multifocal disease. Sixty-seven percent of the patients in whom telangiectasia was found at the EGD exam also presented small lesions in the small bowel and the colonscopu uncovered colic lesions in 43%. Fifty-four percent of patients with colic lesions presented gastroduodenal lesions and 48% in the small bowel. Capsule endoscopy facilitated therapeutic management of the disease in 46% of the patients by uncovering undiagnosed lesions. A separate group within the larger heading of subjects affected with telangiectasia was made up of cirrhotic patients awaiting liver transplantation. Their watermelon stomach regressed after transplantation.

2) Primary bleeding prophylaxis for esophageal varices in cirrhotic patients awaiting liver transplant

The clinical trial comparing betablockers (propranolol) to ligation to prevent bleeding in patients with high risk varices showed that both treatments were efficacious in reducing bleeding with respect to that expected in the absence of therapy which, considering the degree of cirrhosis and the stage of the varices, should have been 30% a year. The percent of bleeding registered in the group undergoing ligation and in that taking propranolol was 6.5 and 9.6%, respectively, a year.

Ligation has perhaps a slight advantage over betablockers in preventing risk of bleeding but the difference is evident only after a long follow up period which is improbable in patients awaiting transplantation who face surgery within a reasonably short period of time. Endoscopic ligation has presented two important disadvantages with respect to propranolol. The first is iatrogenic bleeding from the post ligation ulcer which on the basis of our data and that of other investigators can at times prove to be fatal. According to literature reports, betablockers have never caused fatal complications during prophylactic treatment of variceal bleeding.

The second disadvantage is the high cost of treatment, three times higher than that of propranolol therapy. Treatment with betablockers is, therefore, to be considered preferable to endoscopic ligation for the primary prophylaxis of bleeding esophageal varices in cirrhotic patients awaiting liver transplant.

3) Laser Therapy in Barrett's Esophagus

Barrett's Esophagus is a risk factor for adenocarcinoma. On the basis of case reports its risk is calculated at 0.5-2% a year. What therapy should be utilized, besides endoscopic follow-up with biopsy, in forms not complicated by severe severe dysplasia has not been clarified in the literature. Pharmacological therapy has proven to be efficient in the treatment of reflux symptoms and esophagitis but not against metaplasic progression. Anti reflux plastic surgery seems to reduce the disease's progression but there is no disease remission. Some endoscopic ablation procedures such as argon plasma coagulation (APC), photodynamic therapy (PDT), radiofrequency, and high energy laser therapy have been proposed but their advantages over simple follow-up has not been verified in non degenerative forms.

The study carried out in our institute aimed to verify the efficacy and safety of laser therapy in Barrett's Esophagus first using a limited number of patients and a brief follow up period and then going on to a larger number and a longer period to evaluate long term results and the risk of recurrence. There were no complications associated to laser therapy which was found to be efficacious in causing regression of dysplasia in the limited number of patients (6) studied. Complete healing of the intestinal metaplasic area was, moreover, obtained in almost all of the patients with the short segment form (8/9) but it was found to be less efficacious in the patients with the long segment form causing a complete remission in 6/13 cases. Long term recurrence was found to be low (7%). On the basis of these results, high energy laser therapy could be recommended in short segment BE patients but is not advisable in those with the long segment form. Further studies are anyway warranted to verify its utility in reducing the risk of adenocarcinoma in these patients. With regards to high grade dysplasia, it should be underlined that laser therapy is limited with respect to endoscopic mucosectomy in these patients as it provides scanty material for histological examination.

4) Laser therapy of colorectal adenomas

This study was carried out with the aim of verifying the efficacy of endoscopic laser photoablation in the treatment of large sessile adenomas in inoperable patients or in those who reject surgical treatment.

Treatment of large colorectal polyps can be carried out by means of surgical resection, endoscopic diathermic polypectomy with piece meal resection, transanal endoscopic microsurgery or laser therapy.

Our data revealed that the latter had few complications and was efficacious not only in relieving symptoms such as rectal bleeding, mucous discharge and tenesmus but also in controlling the risk

of degeneration. No degeneration in the 86 polyps treated was, in fact, found during the 28 month follow-up of patients with low or high grade dysplasia. The treatment's only limitation is the fact that it is not possible to collect material for the histological exam. That is why it is important to associate it with an accurate bioptic sampling and ecoendoscopic staging in cases of high grade dysplasia to avoid overlooking invasive cancer forms

5) Endoscopic dilation of post surgical esophageal stenoses

It was seen from this study that dilation therapy of benign esophageal strictures that were for the most part anastomotic and postfundoplication can be carried out in almost all cases even in the absence of fluoroscopic guidance. A semisolid diet was obtained in 97-100% of the patients treated and, though there is a high degree of recurrence (32% in a year's time), new dilation sessions are easily repeated. Thanks to shorter lesions and the absence of a persistent damage, better long term results were obtained in anastomotic or postfundoplication strictures as opposed to peptic, caustic, or radiation-induced stenoses.

6) Dilation therapy for complications of the biliary tract following liver transplant

While the results of endoscopic treatment of anastomic strictures of the esophagus are excellent, its use in the treatment of stenoses of the bile duct following liver transplant has proven to be efficacious in only 63% of cases following bile duct cannulation. What complicates the modality in this pathology is the ischemic damage which the biliary tree often undergoes during or following liver transplant. Placing a stent, when possible, reduces the risk of stenotic recurrence. Operative endoscopy just as transhepatic radiologic treatment is the first choice treatment of that complication with respect to surgery.

7) Echoendoscopic drainage of abdominal abscesses

Carried out in collaboration with Prof. Sohendra's group in Hamburg this study heralds a new frontier making it possible, with the help of trasluminal ultrasound, to enter into the abdominal cavity through the transgastric or colorectal via and to drain abdominal abscesses, with debridment and necrosectomy, if necessary. The technique is a first step, already utlized in clinical practice, towards the new mini-invasive surgical discipline called NOTES, still at an experimental stage, whose developments are being watched with great interest by both endoscopic and surgical communities.

Riassunto conclusivo

L'endoscopia operativa flessibile è una disciplina in continuo sviluppo. Le indicazioni all'uso dell'endoscopio flessibile per patologie del tratto gastro-enterico sono infatti crescenti. A ciò contribuisce da un lato la diagnosi sempre più precoce delle malattie ed il riconoscimento delle lesioni pre-cancerose, che possono essere trattate localmente, dall'altro lo sviluppo tecnologico delle strumentazioni endoscopiche, che permette ora anche di accedere alla cavità addominale oltre le pareti del lume intestinale, per effettuare interventi chirurgici mininvasivi.

Ovviamente l'endoscopia operativa deve confrontarsi e collaborare con le altre discipline di uso più consolidato, quali la farmacoterapia, la radiologia interventistica, ma soprattutto la chirurgia tradizionale. Con quest'ultima deve in particolar modo embricarsi, anticipandola in presenza di lesioni pre-neoplastiche, asservendola nel trattamento delle complicanze anastomotiche e mirando ad essa nello sviluppo della chirurgia miniinvasiva per-endoluminale. In questo studio sono stati affrontati alcuni campi di applicazione dell'endoscopia operativa effettuata per lesioni benigne del tratto gastroenterico, tra cui: la terapia endoscopica delle teleangiectasie, di cui rappresenta il trattamento principale, previa stadiazione e bilancio adeguato della malattia; la legatura profilattica delle varici esofagee nei candidati a trapianto di fegato, che, dato il follow-up ridotto per la sostituzione d'organo, presenta più svantaggi che vantaggi rispetto alla farmacoterapia con propranololo; la laser terapia dell'esofago di Barrett, che si propone di ridurre il rischio di sviluppo dell'adenocarcinoma dell'esofago, mediante ablazione della mucosa metaplasica, ma che richiede ulteriori studi per quantificarne l'effetto; la laser terapia dei grossi adenomi colo-rettali, che si dimostra un'efficace alternativa alla chirurgia nei pazienti inoperabili o che rifiutano l'intervento, evitando comunque il rischio di degenerazione; il trattamento delle complicanze anastomotiche nella chirurgia esofagea e del trapianto di fegato, in cui quello endoscopico rappresenta il trattamento di prima scelta; infine il drenaggio degli ascessi addominali e la necrosectomia effettuati per via endoscopica con l'ausilio dell'eco-endoscopia, che rappresentano una estensione della disciplina al di là delle pareti del lume intestinale. Anche in questo caso è essenziale effettuare un adeguato bilancio e stadiazione di tale complicanza infettiva, tenendo presente anche i limiti della metodica.

Questo ultimo campo di applicazione rappresenta un primo step, già di fatto utilizzato nella pratica clinica, verso quella nuova disciplina chirurgica mini-invasiva definita con l'acronimo NOTES (Natural Orificial Trans-Endoluminal Surgery), al momento ancora in fase di sperimentazione, ma che sta raccogliendo particolare interesse sia nel campo endoscopico che chirurgico.

Concluding abstract

Operative endoscopy has proven to be a discipline that continually renews itself. Referrals for treatment using flexible endoscopes in the gastroenteric tract are in fact on the rise. Diagnoses made at earlier phases of the disease uncover pre cancerous lesions that can be treated locally. The technological development of endoscopic instruments, on the other, make it possible to enter into the abdominal cavity and to go beyond the intestinal lumen and to carry out mini-invasive surgical procedures.

Operative endoscopy must, of course, confront and collaborate with other traditional disciplines such as pharmacological therapy, interventistic radiology, and, above all, traditional surgery. It must, in particular, join hands with the latter placing itself at its service in the treatment of anastomic complications and imitating it in the development of miniinvasive endoluminal surgery.

Some fields of application of operative endoscopy used in the treatment of benign lesions of the gastroenteric tract have been considered here. These include: endoscopic therapy of telangiectasia which represents its principal therapy once the disease has been staged and controlled; prophylactic ligation of esophageal varices in trasplant candidates who, due to their limited follow up, present more disadvantages than advantages with regards to propranolol therapy, laser therapy of Barrettt's esophagus which aims to reduce the risk of adenomacarcinoma of the esophagus by ablating metaplasic tissue – further studies are warranted here to quantify its effect; laser therapy of large colorectal adenomas found to be an efficacious alternative to surgery in inoperable patients or those who reject surgery, avoiding the risk of degeneration; treatment of anastomic complications in esophageal surgery and in liver transplant patients in whom endoscopic therapy is the first choice therapy, and finally drainage of abdominal abscesses and necrosectomy carried out endoscopically with the aid of ecoendoscopy, which has taken operative endoscopy beyond the intestinal lumen.

The latter field of application is a first step, already in fact utilized in clinical practice, towards the development of NOTES, the new miniinvasvie surgical discipline, still in an experimental stage but already being watched with great interest by the endoscopic and surgical worlds.

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