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SLOVENSKO ZDRUŽENJE
ZA GASTROENTEROLOGIJO
IN HEPATOLOGIJO

4th SLOVENIAN CONGRESS OF GASTROENTEROLOGY AND HEPATOLOGY WITH INTERNATIONAL PARTICIPATION

Ljubljana, June 7th – 10th 2017

Dear colleagues,

Slovenian Assotiation for Gastroenterology and Hepatology was founded in the year 1967 in Rogaška Slatina. We organize regular biannual professional meetings, as well as many one day special symposias. Every four years we organize Alpe Adria Danube Symposia, which is a regional meeting. From the year 2001 we also organize every four years an International Congress of Gastroenterology and Hepatology. At the 4th Slovenian Association for Gastroenterology and Hepatology (SAGH) Congress that will be held in Ljubljana, Slovenia, from June 8th to 10th 2017 we will host more than 300 paticipants from 17 European countries.

The scientific programme will cover many challenging and changing aspects of gastrointestinal and hepatological diseases from the point of view of diagnosis and treatment. Along with state of the art lectures, many research projects will be presented, too.

On the first day we will organize Postgraduate course fom gastroenterology and hepatology for specialist of Family medicine. On the second day, a Postgraduate Course will be organized in collaboration between EAGEN (European Society for Gastroenterology, Endoscopy and Nutrition), EHMSG (European Helicobacter Microbiota Study Group) and SAGH which will bring you highlights in recent developments on some important gastrointestinal and hepatological diseases.

Endoscopic training on simulators will be made possible with the support of Olympus company, especially for fellows and young clinicians. Annual meetting of Slovenian Society of Gastroenterology and Endoscopy Nurses and Associates will also be a part of our Congress.

The internationally renowned speakers from 15 EU member countries and other European countries testify to the high scientific level of the Congress. The Congress and the Course are organised under the auspices of SAGH, EAGEN and EHMSG.

I'm sure that 4th Congress of SAGH will be not only a high level scientific meetting , but also a place were old friends can come together and a place where many new friendships will be made.

I would like to thank all the lecturers, guests, colleagues and sponsors that contributed to the organization of the 4th SAGH Congress.

SAGH President
Prof Bojan Tepeš MD PhD FEBGH

Ljubljana May 20th 2017

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4th Slovenian Congress of Gastroenterology and Hepatology

Program

Friday, June 9th 2017

8.30 am OPENING

9.00 – 11.20 am Esophagus, Stomach

Panel: Tepeš, Potrč, Malfertheiner, Tack (lectures 15 min, QA)

1. J. Tack: Upper GI functional diseases
2. L. Lundel: What is important in antireflux surgery
3. B. Tepeš, et al.: European registry on Helicobacter pylori management - Slovenian data and National recomendations
4. B Tepeš, et al.: Incidence of premalignant gastric lesions in SVIT population and National recomendations on gastric cancer preventions
5. P. Malfertheiner: H. pylori and gastric cancer
6. Potrč, Velenik, Ocvirk: Resectable gastric cancer treatment with perioperative chemotherapy – preliminary results
7. T. Jagrič: Possibilities for minimally invasive approaches to treating resectable gastric cancer

11.20 – 11.40 am BREAK

11.40 – 2.00 pm Pancreas

Panel: Tomažič, Štabuc, Lundel, Štimac (lectures 15 min, QA)

1. J. Brecelj: Cystic fibrosis of the pancreas and esophagus
2. M. Vujasinovič, B. Tepeš, S. Rudolf: Exocrine pancreas insufficiency in different diseases, our results
3. S. Rudolf, S. Potrč, T. Jagrič: What should a CT/MR report provide prior to a foreseen pancreas operation
4. L. Lundel: Surgery in locally advanced pancreatic cancer
5. A. Tomažič, M. Petrič: Laparoscopic distal pancreatectomy
6. J. Weitz: Pancreatic cancer – Vascular reconstructions in pancreatic surgery
7. S. Potrc, A. Ivanecz, M. Horvat, V. Pivec, U. Marolt, S. Rudolf, B. Iljevec, T. Jagric: Impact factors for perioperative morbidity and mortality and repercussion of perioperative morbidity on long term survival in pancreatic head resection

2.00 – 3.00 pm LUNCH

3.00 – 5.20 pm Liver

Panel: Ivanecz, Popovič, Milič, Papp (lectures 15 min, QA)

1. D. Majc, B. Tepeš: The impact of outpatients clinical care on the survival and hospitalisation rate in patients with alcoholic liver cirrhosis
2. P. Popovič, B. Štabuc, P. Skok: Programed TIPS and endoscopic treatment for prevention of recurring bleeding from esophageal and gastric varices in patients with portal hypertension
3. A. Ivanecz: Patient selection for laparoscopic liver surgery
4. B. Edwin: Laparoscopic liver resection for colorectal liver metastases
5. J. Weitz: Surgical strategies for treatment of bilobar liver metastases
6. B. Trotovšek, D. Stanisavljević, A. Tomažič: Liver transplantation and HCC
7. M. Ribnikar: Twenty years of experience in liver transplantation in Slovenia

5.20 – 5.40 pm BREAK

5.40 – 7.40 pm Small intestine

Panel: Stefanovič, Orel, Dumitrascu, Banič (lectures 15 min, QA)

1. Volfand: Functional gastrointestinal disorder and food intolerance
2. N. Thapar: Small Intestinal Bacterial Overgrowth
3. N. Rotovnik Kozjek: Nutritional challenges of short bowel syndrome
4. A. Orel: Diet for patients with major neurological disorders
5. L. Strniša: Capsule endoscopy – Slovenian experience
6. T. Pintar, G. Kunst: Metabolic effects of by-pass surgery in morbid obesity treatment

8.30 pm DINNER

Saturday, June 10th 2017

8.20 – 11.20 am Colon / Rectum

Panel: Tepeš, Bordin, Bevanda, Di Mario (lectures 15 min, QA)

1. Stefanovič, B. Tepeš, B. Štabuc: Effects of quality control on the efficiency of CRC SVIT prevention programme
2. J. Jeruc: Microsatellite instability and colorectal carcinoma
3. A. Frudinger: Anal incontinence – treatment with stem cells
4. J. N. Mensah: Management of recurrent anal fissure and fistula
5. V. Velenik: Novelties in oncological treatment of locoregionally advanced rectum cancer
6. G. Norčič: Liquid biopsies in patients with colorectal cancer
7. M. Omejc: Prognostic significance of tumor regression in locally advanced rectal tumor
8. N. de Manzini: Transanal surgical techniques: TAMIS and TATME
9. Krebs: Protective stoma: yes or no with laparoscopic low rectum resection

11.20 – 11.40 am BREAK

11.40 – 2.05 pm Inflamatory bowel disease

Panel: Drobne, Smrekar, D'Haens, Krznarič

1. I. Ferkolj: IBD in Slovenia (10 min)
2. G. D'Haens: Choosing the right treatment for the right patient in IBD (20 min)
3. F. Magro: Azathioprine fine-tuning in IBD: genotype, metabolites and beyond (20 min)
4. B. Vucelič: Aminosalicylates: old and effective drugs for IBD (20 min)
5. D. Drobne: Optimisation of TNF inhibitors in IBD (15 min)
6. NEW HORIZONS IN IBD TREATMENT
   G. D'Haens: Complexity of Crohn's disease – implications of biologics (20 min)
   D. Drobne: Gut selective biologic therapy: Translating clinical data in real world clinical practice (20 min)
7. A. Tomažič, N. Smrekar: Pro et contra: complicated Crohn's disease: surgery first, then drugs or vice versa (20 min)

2.05 – 3.00 pm LUNCH

3.00 – 5.00 pm Gastrointestinal oncology

Panel: Štabuc, Velenik, Joksimovič, Krstić (lectures 15 min, QA)

1. S. Potrč: Current trends in treatment of GE junction cancer Siewert II and III
2. V. Velenik: Esophagus cancer - recommendations
3. B. Trotovšek: Gallbladder cancer – surgical treatment results after laparoscopic cholecystectomy
4. M. Horvat: Single Nucleotide Polymorphisms as Prognostic and Predictive Factors of Adjuvant Chemotherapy in Colorectal Cancer of Stages I and II
5. J. But Hadžić: Shortening of overall treatment time using intensity-modulated radiotherapy with simultaneous integrated boost in preoperative chemoradiotherapy for locally advanced rectal cancer
6. P. Popovič, M. Garbajs, R, Dežman, M. Štabuc, D. Nuredini, R. Janša, B. Štabuc: Survival of patients with intermediate stage hepatocellular carcinoma treated with super-selective transarterial chemoembolization using doxorubicin-loaded DC Bead under cone-beam computed tomography control

5.00 – 5.20 pm BREAK

5.20 – 7.25 pm Free topics

Panel: Skok, Forte, Jelenc, Plut (lectures 15 min, QA)

1. P. Skok: Foreign bodies in the upper gastrointestinal tract – overview of the period 1994–2016
2. A. Stožer: Pancreas physiology and pathophysiology in tissue slices
3. U. Marolt, S. Potrč, T. Jagrič: Patients with celiac axis stenosis discovered in pancreas head resection
4. M. Džokić: Electrochemotherapy in HCC – alternative or definitve solution
5. M. Rupnik: Gut microbiota in chronic inflammatory bowel disease (IBD) and association with Clostridium difficile infection
6. U. Potočnik: Genetics and pharmacogenomics of chronic inflammatory bowel disease
7. Best poster presentation

Kazalo / Contents

Does the Asian style of laparoscopic lymphadenectomy hold the key to laparoscopy in locally advanced gastric cancer patients?

Tomaž Jagrič*[1], Stojan Potrč[1]
[1]*Abdominal and General Surgery, University Clinical Center Maribor, Slovenia*
Gastroenterolog 2017; suplement 3: 9–14

***Keywords**: Laparoscopic gastrectomy, lymphadenectomy*

ABSTRACT

Background: In patients with advanced gastric cancer only a meticulous D2 lymphadenectomy can bring the cure. To increase the quality of our laparoscopic lymphadenectomy, we adopted a technique modified after Huang et al. We evaluated the results of this new technique by comparing the results of open and laparoscopic gastrectomy in a case-matched study.

Methods: Thirty patients were included in this case matched study. The results of open gastrectomy were compared to the results of laparoscopic gastrectomy before and after the adoption of the modified lymphadenectomy technique.

Results: Patients were equally balanced the open and laparoscopic group according to age, gender, BMI, ASA score. The laparoscopic operations were insignificantly longer, but the patients recovered significantly better compared to open surgery. Laparoscopically operated patients passed stool faster and required less postoperative analgesia compared to open surgery. The hospitalization was insignificantly shorter in laparoscopically operated patients. Morbidity was similar in both groups; there was no mortality in the included patients group. Laparoscopically operated patients had insignificantly lower LN yield per operation compared to open surgery. After the induction of the modified lymphadenectomy technique, the LN yield rose significantly in the second period compared to the first period ($p = 0.05$). In the second period, the number of harvested LN was 24.1±8 LNs compared to 17±3LNs in the first. With the better quality of the lymphadenectomy, we were able to include similar TNM stages in the laparoscopic group that would be operated with open surgery.

Conclusion: Our results confirm that the new lymphadenectomy technique allows a more meticulous lymphadenectomy necessary for treatment of patients with locally advanced gastric cancer.

*Tomaž Jagrič, MD, PhD
Abdominal and General Surgery, University Clinical Center Maribor; Ljubljanska 5, 2000 Maribor, Slovenia
E-mail: tomaz.jagric@gmail.com

INTRODUCTION

At first, the laparoscopic gastrectomy was proposed only for early gastric cancer because the extent of the lymphadenectomy was significantly smaller compared to open approach. With growing experience surgeons began to perform more extensive lymphadenectomies, allowing a safe resection for advanced distal cancers according to oncological principles [1–6]. Complex reconstruction after total gastrectomy and the lymphadenectomy in the distal pancreatic region, splenic hilum, however, still presented a significant challenge. Because Western patients present in more advanced stages compared to Asian patients and have proximal tumor location, a more radical resection is indicated to implement laparoscopic resections in these patients.

In the University Clinical Center Maribor in Slovenia, we have begun with laparoscopic gastric resection for adenocarcinoma in the year 2015. At first, these resections were performed only in distal gastric cancer patients with early carcinoma. As we felt that the extent of laparoscopic lymphadenectomy was inferior to the open approach, we were reluctant to extend indications to locally advanced gastric cancer patients. In 2016, however, we adopted the lymphadenectomy technique proposed by Huang et al. [8]. This technique takes advantage of unique properties of laparoscopy making the lymph node yield more efficient. Because we were able to improve the lymphadenectomy quality and mastered the totally laparoscopic oesophagal-jejunal reconstruction, we have extended the indications for laparoscopy to node negative serosa-negative patients and serosa-negative patients with perigastric lymph nodes. To determine whether laparoscopic gastrectomy can be safely performed for advanced gastric cancer in our center we compared the results of open and laparoscopic gastrectomy in a case-matched study.

METHODS

Patients

We have begun with laparoscopic gastrectomies in 2015. Since then 15 laparoscopic gastrectomies have been performed. These patients were case matched to 15 patients operated in the same period with an open approach. The clinicopathological characteristics of the patients were prospectively collected and stored in our department database. We compared age, gender, ASA score, BMI, TNM stage between open and laparoscopically operated patients.

The lymphadenectomy technique proposed by Huang et al. was adopted in our center in 2016. By that time we started to include also patients with locally advanced gastric cancer. To determine the quality of lymphadenectomy technique, we divided patients operated with laparoscopic approach in two groups. In the first group (LG1) seven patients were included. The second group (LG2) consisted of eight patients in whom extensive lymphadenectomy was performed. In the subgroup analysis, we compared groups LG1, LG2, and patients with open approach (OG) to determine the quality of the lymphadenectomy.

Surgery

Our initial approach to laparoscopic lymphadenectomy was similar to open surgery. After the opening of the gastrocolic ligament, we began to dissect the lymph nodes around right gastroepiploic artery and vein. Then we retracted the stomach caudally and dissected the hepatoduodenal ligament and the right gastric artery. After the duodenal transection, we continued with the dissection of lymph nodes along the anterior surface of the common hepatic artery towards the coeliac trunk. We recently begun with a lymphadenectomy modified after Huang et al. After the entry into the bursa, the right gastroepiploic artery and vein are skeletonised up to the gastroduodenal artery. The

gastroduodenal artery is dissected intraduodenally toward the confluence with the common hepatic artery. Here we dissect the distal portion of the common hepatic artery, the proper hepatic artery, and the proper hepatic artery. Next, we transect the duodenum. The duodenal transection and the retraction of the stomach toward left allows a better approach to perivascular plane in the hepatoduodenal ligament. The dissection is carried toward the portal vein posteriorly and toward the left gastric artery and vein on the left.

Table 1. Clinico-pathological characteristics of patients operated with laparoscopic and open gastrectomy

	Type of the operation		*p*
	Laparoscopic	**Open**	
Age	67±11 years	69±11 years	NS
Gender **Male** **Female**	 8 (53.3%) 7 (46.7%)	 9 (64.3%) 5 (35.7%)	NS
T stage **Bng** **T1** **T2** **T3** **T4**	 3 (20%) 5 (33.3%) 2 (13.3%) 4 (26.7%) 1 (6.7%)	 1 (6.7%) 4 (26.7%) 0 (0%) 7 (46.7%) 3 (20%)	NS
N stage **N0** **N1** **N2** **N3a** **N3b**	 10 (66.7%) 2 (13.3%) 2 (13.3%) 1 (6.7%) 0 (0%)	 6 (42.9%) 2 (14.3%) 2 (14.3%) 2 (14.3%) 2 (14.3%)	NS
BMI	24.5±4 kg	28.6±8 kg	NS
ASA **I** **II** **III**	 3 (20%) 9 (60%) 3 (20%)	 1 (6.7%) 10 (66.7%) 4 (26.7%)	NS
Complications **Yes** **No**	 3 (20%) 12 (80%)	 1 (6.7%) 15 (93.3%)	NS
Dindo-Claviene **0** **II** **IIIa** **IIIb**	 12 (80%) 1 (6.7%) 0 (0%) 2 (13.3%)	 14 (93.3%) 0 (0%) 1 (6.7%) 0 (0%)	NS
Operation time	269.5±67 min	229.3±64 min	NS
Days until passage of first stool	3±1 days	5±1 days	p = 0.012,
Days of iv analgesia	4±0.8 days	7±1 days	p < 0.0001
Hospital stay	9±5 days	10±6 days	NS
No. of harvested LNs	16±11 LNs	23±16 LNS	NS
No. of harvested LN in adenocarcinoma patients	21±14 LNs	23±13 LNs	NS

Statistical analysis

Continuous data are expressed as means ±SD, while categorical variables are given as percentages. Comparisons of continuous variables were carried out with Student's t-tests for parametric data and Mann–Whitney U tests for nonparametric data. Chi-square tests were used for comparisons of discrete variables. All of the predictors that were significant on univariate analysis were included in the multivariate analysis. In the multivariate analysis, a backward stepwise binary logistic model was used. P values <0.05 were defined as the limit of significance. SPSS version 20 for Windows 10 was used for the statistical analysis. For the analysis, SPSS version 20 for Windows was used.

RESULTS

Patients

Thirty patients were included in the study. Patients in both groups were balanced according to their age, gender, TNM stage, BMI and ASA score (Table 1). Even though the laparoscopic operations were somewhat longer, this difference was not statistically different (269.5±67 min in the laparoscopic group and 229.3±64min for open procedure; p = 0.117). Both groups had a similar complication rate (p = 0.283). Laparoscopically operated patients had a significantly faster return of bowel function as measured with the number of days until first passage of stool (p = 0.012). On average laparoscopically operated patients passed stool on the day three, while patients operated with an open approach first passed stool on the day 5. Also, the patients operated laparoscopically experienced less pain in the postoperative period as evidenced by the smaller number of days of intravenous analgesic use (p < 0.0001). Patients operated laparoscopically needed four days of intravenous analgesia compared to seven days in the open group. The hospital stay was on average nine days in laparoscopically operated patients and ten days in the open group, but this difference was insignificant (p = 0.708).

Lymphadenectomy

The average number of harvested nodes was 21±14 LNs for all patients and 23±13 for patients with adenocarcinoma in the whole study group. Laparoscopically operated patients had a similar number of harvested LN per operation than patients operated with open gastrectomy (p =0.359). In the subgroup of patients operated for adenocarcinoma the LN yield in laparoscopic operations was 21.5±7 LNs per operation and 23.3±16 LNs per operation for the open approach.

The number of harvested LNs per operation rose significantly in the second period (p = 0.05) (Figure 1). This marked rise in the number of LNs was noted starting with the implementation of the modified lymphadenectomy technique (figure 1). The number of LN in period 2 was 24.14±8 (17±3LNs in the first period), which is comparable to open gastrectomy.

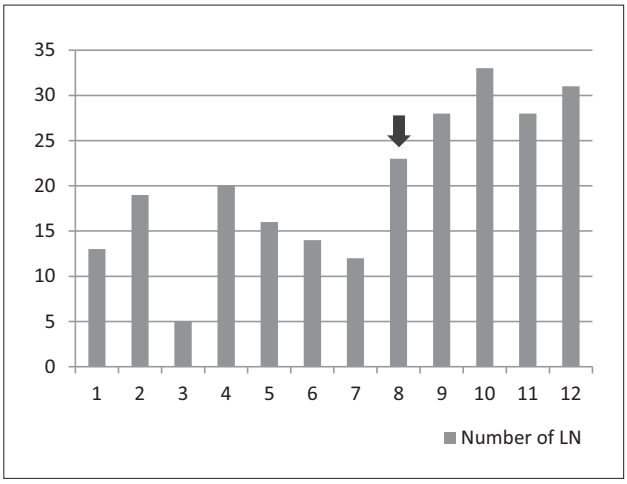

Figure 1. Number of harvested lymph nodes during laparoscopic operations for addenocarcinoma.
The arrow represents the first operation using the modified lymphadenectomy technique as proposed by Huang et al.

Also, the structure of T stages changed significantly with the modification of lymphadenectomy (p = 0.038) (Figure 2). In the first period, 28.6% of patients were operated for a benign disease, and 57.2% of patients had either pT1 or pT2 stage adenocarcinoma. In the second period, 50% of patients alone had a pT3 stage adenocarcinoma.

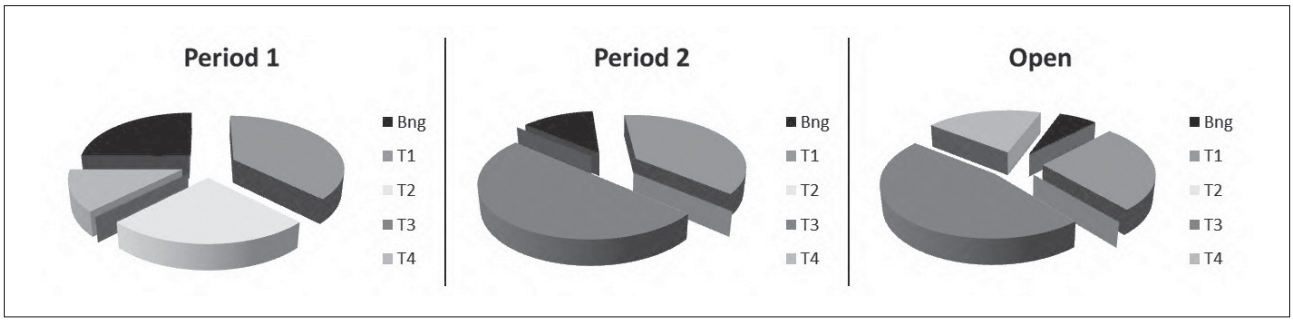

Figure 2. The distribution of pT stages in Period 1 and 2 of the laparoscopically operated patients and in patients with an open approach

This was comparable to open gastrectomies (p = 0.569) where 46.7% of the operated patients had pT3 stage adenocarcinoma.

DISCUSSION

Even after more than 20 years after the first laparoscopic gastrectomy, this operation is still a challenge to any laparoscopic surgeon. Leading the front of laparoscopic development are the Asian surgeons, who proved in randomized studies the effectiveness of the laparoscopic distal subtotal gastrectomy for early gastric cancer and are now set to determine its usefulness for advanced gastric cancer. Specialist centers in the East have successfully developed laparoscopic D2 lymphadenectomies that have enabled the use of laparoscopy in advance gastric cancer patients. We have adopted these techniques and analyzed our results to determine whether it is safe to use laparoscopy in locally advanced gastric cancer patients on our center. A prerequisite for a successful implementation of laparoscopy in gastric cancer patients is its noninferiority compared to open surgery. Many authors have shown that for early gastric cancer, the laparoscopic approach is comparable to open gastrectomy [3, 4, 6, 7]. Moreover, the perioperative course in laparoscopically operated patients seems to have its merits when compared to open surgery [1–7]. In our study, we have also found that both procedures had similar perioperative morbidity and no mortality, but patients operated laparoscopically had a significantly faster return of bowel function as evidenced by the shorter time to the first passage of stool. They also experienced significantly less pain and required significantly less intravenous analgesics. These results coincided with other authors [1–7]. Unfortunately, the faster return of digestive functions and lesser perioperative pain did not transcend to shorter hospital stay in our analysis. Even so, these results confirm that there are indeed benefits that can be drawn from laparoscopic surgery. In patients with advanced gastric cancer, however, improved perioperative course is not enough to advice laparoscopy as a substitute for open surgery. To implement this operation, a similar extent of lymphadenectomy has to be achieved than in open surgery. Dissatisfied with our first lymphadenectomies, we modified our approach to laparoscopy based on the success of Eastern surgeons [8]. With the implementation of the technique suggested by Huang et al. [8], we produced a marked increase in the LN yield per operation. The lymphadenectomy in the second period was comparable to open surgery. Therefore we extended the indications to locally advanced gastric cancer patients. Indeed, laparoscopic surgery is now being be offered to almost all gastric cancer patients. The contraindications for laparoscopy now are large tumors infiltrating other organs, large and fixed retroperitoneal lymphadenopathy, patients with large amount of intraabdominal fat, inability to safely step in the *bursa omentalis* and intraabdominal adhesions. Similar contraindications for laparoscopic surgery are recommended by other authors [1]. Even though more advanced stages have been operated starting with the second period, there has

not been an increase in the number of incomplete resections or extent of the lymphadenectomy. Our results show an immense improvement of the lymphadenectomy technique. Together with evolving experience in the complete laparoscopic oesophagal-jejunal reconstruction, the indications for laparoscopic surgery have expanded. As we are witnesses of the increase of proximal tumor incidence and the advanced stages are still the most prevalent in the western hemisphere, radical surgery comparable to open surgery is essential for the use of laparoscopic surgery in the future. Our results have shown that with increasing experience and excellent technique this goal can be achieved with minimally invasive surgery on our center.

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What should a CT/MR report provide before a foreseen pancreas operation

Saša Rudolf*[1], [1] Stojan Potrč[2], Tomaž Jagrič[2]
[1]*University Clinical Center Maribor, Department of Radiology, Maribor, Slovenia*
[2]*University Clinical Center Maribor, Department of Abdominal and General Surgery, Maribor, Slovenia*
Gastroenterolog 2017; suplement 3: 15–16

REWIEV

Pancreatic head tumors are the most common cause for pancreatic surgery. The most common primary malignancy of the pancreas is ductal adenocarcinoma (PDA). 60–70 % of all PDA are located in the pancreatic head. It is highly aggressive tumor, found mostly in advanced stage disease. Prognosis and treatment depend whether tumor is resectable or nonresectable. Imaging evaluation plays a central role in the initial decision-making process and must provide information that can be translated into established clinical staging system. Staging is based on the termination of tumor size, location within the pancreas, local extent and involvement of surrounding vessels and the presence of metastatic disease. In the absence of metastatic disease for surgical planning, additional imaging findings not directly relevant for staging should be described. The presence of tumor or bland venous thrombosis, tumor relation to surrounding vessels, presence of increased hazy attenuation or fat stranding, any arterial variants of celiac axis, SMA or CHA, relevant arterial disease as median arcuate ligament compression or significant SMA stenosis need to be reported.

Multi-detector computed tomography (MDCT) is the standard imaging method for initial evaluation in patients in whom PDA is suspected. MR imaging is for its cost and availability predominantly utilized as problem-solving tool. However, with excellent soft-tissue contrast, it can provide additional information on morphologic features of pancreatic parenchyma. MRI has been used to evaluate the texture of the pancreas.

Strong association between pancreatic texture and post-operative pancreatic leaking has been found. The texture of pancreas is usually related to the underlying disease process. It is widely accepted that fibrotic pancreatic remnant in chronic pancreatitis holds the pancreatic anastomosis well, while a soft, friable pancreatic parenchyma is found to be complicated with formation of postoperative pancreatic fistula (POPF).

In our institution preoperative imaging is mostly performed with MDCT with high-quality reformatted images. Our protocol includes pre-contrast images for the purpose of additional evaluation of fatty infiltration of pancreas. For quantification, densitometric values of pancreatic tissue are compared to densitometric values of spleen. The same

*Saša Rudolf, MD
Radiology Department, University Clinical Center Maribor; Ljubljanska 5, 2000 Maribor, Slovenia
E-mail: sasa.rudolf@ukc-mb.si

is performed on contrast-enhanced images for validation of structural parenchymal changes. Those, together with measurement of pancreatic duct width, could potentially represent signs of parenchymal fibrotic changes and be related to a more firm pancreatic tissue. An important additional data before surgery that could potentially modify peri-operative clinical course and management.

Liver transplantation and hepatocellular carcinoma

Blaž Trtotovšek*[1]
[1]*Department for the hepatobiliary and liver transplantation surgery, Department for abdominal surgery, University Medical Centre Ljubljana, Slovenia*
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***Keywords**: liver transplantation, hepatocellular carcinoma, Milan criteria, survival*

ABSTRACT

Hepatocellular carcinoma (HCC) is a major cause of cancer mortality worldwide, and liver transplantation (LT) has potentials to improve survival for patients with HCC. For patients with hepatic insufficiency and HCC within Milan criteria (MC), LT provides the best long-term recurrence-free survival. However, there is controversy about the role of LT in subgroups of patients with compensated cirrhosis or tumours < 2cm and of course in those HCC exceeding MC. Expansion of indications beyond MC and use of bridging/downstaging procedures to convert advanced intermediate stages of HCC to those within MC criteria are countered by graft shortage. Graft shortage also resulted in increased utilisation of marginal donors. Benefit of LT for patients with HCC should be determined through composite scores that can capture both efficiency and equity endpoints. Patients exceeding MC have higher post-LT recurrence rates and worse survival than those within MC, and any potential benefit of LT to these patients must be weighed against harms to others on the waiting list, particularly where donor availability is limited.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and accounts for more than 6 x 10^5 deaths annually (1). The major risk factor for developing HCC is chronic liver disease and cirrhosis, which is present in 70–90% of patients, with a cumulative 5-year incidence ranging between 15% and 20% (2). The major causes of cirrhosis in patients with HCC include hepatitis B (HBV) and hepatitis C infections (HCV), followed by alcoholic liver disease and non-alcoholic steatohepatitis (3).

Surgical treatment has always been considered as the major curative option for HCC, although eligibility and outcome of patients undergoing resection depend on two variables: the tumour itself and the underlying liver disease at the time of treatment.

*Blaž Trotovšek, MD, PhD
Department for the hepatobiliary and liver transplantation surgery, Department for abdominal surgery
University Medical Centre Ljubljana, Zaloška Cesta 7, 1525 Ljubljana, Slovenia
E-mail: blaz.trotovsek@kclj.si

Over the last two decades, the role of surgery has been challenged by less invasive therapeutic modalities. Currently, liver resection remains curative treatment for HCC in patients without cirrhosis. In patients with cirrhosis, careful selection should be performed before resection to diminish the risks of postoperative liver failure and death (4).

Different from resection, liver transplantation (LT) offers cure to the advanced underlying disease (cirrhosis Child Pough B, C) and the HCC at the same time. There are many grey zones in decision making.

SINGLE TUMOR AND CHILD A CIRRHOSIS

There is also intermediate group of patients with Child Pough A cirrhosis and unifocal HCC. Resection, local ablative therapies, and LT are all viable options (5). Surgical resection is reserved for those without portal hypertension, but local ablative techniques can be used for all patients even with it. Although LT offers lower recurrence rates than resection or ablative techniques, immunosuppression in patients after LT carries specific and important risks. Organ shortage creates prolonged waiting time with increased risk of tumour progression and consequently increased drop-off the waiting list. In a meta-analysis, LT offers similar 1-year survival when compared with but significantly better 3 and 5-year survival rates (6). Despite the limitations of the studies in this group of patients, because the inclusion criteria are not equal for LT and resection, the results of analysis may be conclusive. Most of studies, unfortunately, reports survival only for patients who underwent LT and not for all patients placed on waiting list. Overestimation op post-LT survival could be corrected by taking in account also the survival of those dropped off the waiting list. Those are mainly patients with biologically aggressive HCC with higher probability for drop off from waiting lists.

Model for End-Stage Liver Disease (MELD) score is a strong predictor of survival for patients on waiting list for LT but also after liver resection. Post-resectional 5-year survival rates of 67% in patients with MELD < 10 compared with 47% in those with MELD ≥10 were observed (7). Better survival in patients with MELD > 10 and microvascular invasion is expected after LT than after resection. From economic point of view, LT is costly. Only 5-year survival of more than 87.6% makes LT cost-effective in those patients.

Today, in case of organ shortage, resection or other modalities with curative intent when tumours are inside MC, followed by salvage LT in case of recurrence is recommended. Salvage LT has good long-term survival rate, with 3 and 5-year survival rates of 80 and 62%, respectively (8).

Recurrence of HCC occurs in majority of cases (> 80%) in liver. Those patients with extrahepatic recurrence have less favourable tumour biology and would have higher risk for waiting list drop-off or recurrence after LT. This strategy allows reallocation of liver grafts to the remaining on waiting list. In case of shortage of grafts, LT should be reserved for patients whose outcomes are superior to those achieved with resection. Those are patients with HCC with MELD more than 10 and hepatic insufficiency. Today surgical resection or local ablative therapy should be regarded as first-line therapy and the most cost-effective for these patients, with salvage transplant as a rescue option for those with recurrent disease.

MILAN CRITERIA – WILL THEY HOLD

Patients in the Eurotransplant region receive additional points on waiting list to their MELD score when inside MC (one tumour < 5cm or 3 tumours smaller than 3cm, without vascular invasion or extrahepatic spread). It is similar situation in USA, where patients with T2 tumours receive priority on waiting list for LT (9). When these criteria are

Table 1. Expanded criteria for liver transplantation

Expanded criteria	Description
University of California San Francisco (UCSF)	1 tumour < 6,5 cm ***or*** 2–3 tumours < 4,5 cm with total diameter ≤ 8 cm
Hangzhou	Total diameter ≤ 8 cm, α-fetoprotein ≤ 400 ng/ml
Up to seven	Total diameter + number of lesions ≤ 7

applied, recurrence rates are less than 15%, and 5-year survival rates approach 68% (10). However, there are many who believe that limits are too restrictive and decline chance of LT to some patients who may benefit from it. Tumours exceeding Milan criteria are typically not eligible for LT.

But several selection criteria have been proposed with expanded limits (Table 1). Outcomes between expanded criteria and Milan criteria were in most studies compared instead by radiological findings with pathology reports. But radiological findings are concordant with histology in less than 50% (11). Studies mostly had small cohorts of patients and had limited statistical power. In one of the studies (12) patients within UCSF criteria had lower but not statistically significant survival than patients within MC, with 5-year recurrence-free survival rates of 65 vs. 74%. UCSF and Hangzhou criteria were able to expand access to LT by 16.3 and 51.5%, respectively. Although patients exceeding MC inside UCSF or Hangzhou criteria had lower recurrence-free survival, the difference was not statistically significant (13). Other studies could not confirm these findings (14). In a meta-analysis including 19 studies, patients exceeding MC had lower survival than those within MC (15). Potential benefit for patients with tumours exceeding MC must be weighed against the harm from delaying or preventing LT for other on-HCC patients on the waiting list. This is even truer when donor shortage is severe. The harms of expanding criteria for LT in HCC outweigh the benefits when 5-year survival rates fall below 60% (16). The living donor liver transplantation (LDLT) offers an alternate approach, which does not adversely affect other on-HCC patients on the waiting list. But on the other hand, LDLT exposes donor to invasive procedure, and risk of donor complications should be balanced with recipient survival benefit. Patients after LDLT have higher recurrence rate than deceased donor LT even when adjusted for tumour characteristics (17). Despite this fact has LDLT acceptable risk-benefit ratio for HCC patients within MC. In tumours exceeding MC, it is a matter of debate because of poorer results but offers to each patient opportunity for decision. Although conflicting data exist for patients exceeding Milan criteria, they appear to have higher recurrence rates and lower overall survival after LT.

BRIDGING AND DOWNSTAGING – A WAY TO LT?

For patients with tumours inside MC with advanced stage of liver cirrhosis (Child-Pough B or C) is LT standard treatment. However, when on a waiting list up to 10% of the patients with T1 HCC (tumour < 2 cm) can progress directly beyond MC and are therefore lost for curative treatment. Patients especially exposed to such risk are those with α-fetoprotein ≤ 500 ng/ml and with rapid growth (> 1 cm in diameter/3months). Treatment of patients with advanced stage of liver cirrhosis and HCC traditionally involved palliative therapies, including transarterial chemoembolization (TACE) and sorafenib. For those inside MC TACE is used for bridging the time to LT. Although associated with improvement in survival, these therapies rarely result in long-term cure, but can prolong the interval to progression and therefore allow patients on waiting list to receive LT.

Downstaging is an approach where locoregional therapies are used to reduce tumour from outside to within MC, to facilitate LT. It was proposed as a way to expand transplant access and improve long-term survival.

Some studies (18, 19) have proven that downstaging is successful in decreasing tumour burden to within MC. Downstaging was observed in 65% of patients outside MC, with 54% undergoing LT. Recurrence of disease occurred in 8% of patients. A systematic review of downstaging success rates has shown that these are below 50%, and recurrence rates after LT were higher (17%) than in patients within MC (20). There was substantial variability (70–90%) in 5-year survival among studies and differences in downstaging protocols, and patient population were attributed for. Better outcomes can be expected with stricter patient selection, better quality of downstaging modalities, with limited tumour burden and with mandatory observation period before LT. Last but not least important is required observation period which may reflect tumour aggressiveness indirectly. Patients with unfavourable tumour biology will have higher drop-out rates from the waiting list because of tumour progression.

Lack of consistent data in literature is a reason why downstaging before LT can't be recommended at present. Further studies of this approach with defined protocols should be done in prospective manner before widespread adoption can be recommended.

CONCLUSION

LT today is one of the cornerstones in the management of patients with HCC and is providing the best chance for long-term survival. MC are the most widely used, but some believe that they are too restrictive. Although may offer chance for survival to some patients with larger tumours, benefits to these patients must be weighed against harms to others on the waiting list, due to organ shortage. Until sufficient benefit in patients with expanded criteria is proven, LT should be reserved for those within MC.

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Twenty Years of Experience in Liver Transplantation in Slovenia

Marija Ribnikar*[1], Marjana Turk - Jerovšek[1]
[1]*Department of Gastroenterology, University Medical Centre Ljubljana, Slovenia*
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***Keywords**: liver transplantation, single center experience*

ABSTRACT

Liver transplantation is a successful way of treatment for patients with liver cirrhosis with complications, acute (fulminant) hepatic failure, liver tumors, and liver-based metabolic disorders. 283 patients underwent liver transplantation in the University Clinical Center (UKC) Ljubljana, Slovenia, between 20. 6. 1995 and 31. 12. 2016. One-year survival of our patients is 84,2%, and five-year survival is 76,6%. Our results are comparable with results of other centers included in Eurotransplant.

INTRODUCTION

The first successful liver transplantation in the world was performed in 1963 by Starzl in the United States (1). On 20. 6. 1995 the first liver transplantation by a Slovenian surgical team, led by French surgeon J. Belghiti, was performed in UKC Ljubljana, Slovenia. The patient is still alive today. In 1998 the national program for liver transplantation started and in 2000 we became a member of Eurotransplant. Slovenia has one transplant center, UKC Ljubljana. In the last years, we performed 20 to 30 liver transplantations per year. Our liver transplant team discusses patients before and after liver transplantation at weekly liver transplant meetings. The transplant team includes hepatologists, liver surgeons, intensivists and other specialists contributing in liver transplantation. Patients who are candidates for liver transplantation are admitted to the Clinical Department of Gastroenterology UKC Ljubljana to be prepared for the procedure and for contraindications for liver transplantation to be excluded. These include advanced cardiopulmonary disease, uncontrolled sepsis, extrahepatic malignancy, untreated alcohol and drug addiction, body mass index (BMI) above 40, Acquired Immune Deficiency Syndrome (AIDS) and anatomical abnormalities that preclude liver transplantation. Patients who fulfilled liver transplant criteria are listed to the waiting list. After the transplantation procedure patients are hospitalized at the Surgical Intensive Therapy unit first and then at the Department of Abdominal Surgery. After hospital discharge patients are followed by hepatologists of the Department of Gastroenterology. Indications for liver transplantations are divided into four groups: chronic liver diseases, liver tumors, acute (fulminant) liver fail-

*Marija Ribnikar, dr. med.
Department of Gastroenterology, University Medical Centre Ljubljana, Japljeva 2, 1000 Ljubljana, Slovenia
E-mail: mojca.ribnikar@kclj.si

ure and metabolic liver diseases (2) (3). **Chronic liver diseases** include: cholestatic liver diseases (primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and secondary biliary cirrhosis), hepatocellular liver diseases (alcoholic liver disease, autoimmune hepatitis (AIH), cryptogenic liver cirrhosis, chronic hepatitis B and C) and vascular liver diseases such as Budd-Chiari syndrome. The decision for liver transplantation in chronic liver diseases is made according to Child-Pugh classification, Model of End-stage Liver Disease (MELD) score and presence of complications of liver cirrhosis such as: variceal bleeding, refractory ascites, spontaneous bacterial peritonitis (SBP) and other infections, hepatic encephalopathy, hepatic- pulmonary syndrome (HPS), hepatorenal syndrome (HRS) and hepatocellular carcinoma (HCC) (4).

Liver tumors

HCC is one of the most frequent indications for liver transplantation in the western world. Liver transplantation is a successful way of treatment of HCC in patients within Milan criteria (one nodule up to 5 cm in diameter, up to 3 nodules smaller than 3 cm in diameter, without vascular and lymph nodes invasion and extrahepatic metastases) (5). Other tumors in which liver transplantation is indicated include hepatic epithelioid hemangioendothelioma, isolated neuroendocrine tumor (NET) liver metastases after primary tumor removal and liver hemangiomatosis.

Acute (fulminant) liver failure

Acute liver failure (ALF) is a sudden onset of hepatic encephalopathy with concomitant jaundice, coagulopathy and multiorgan failure in a patient without history of liver disease. Predominant causes of ALF are viral infections (hepatitis A, B, and E) in the eastern world and drug-induced liver injury (most often caused by paracetamol) in the western world. Other causes: acute ischemic liver injury due to systemic hypotension in sepsis or cardiac failure, acute Budd-Chiari syndrome, neoplastic infiltration, heat-stroke, mushroom ingestion, autoimmune hepatitis, acute liver failure of pregnancy and acute Wilson's disease. The decision for emergency liver transplantation in ALF is made according to King´s College Criteria. The presence of hepatic encephalopathy is a key indicator, with further consideration given to patient´s age, etiology of liver disease and severity of liver dysfunction assessed by extent of coagulopathy and jaundice (6).

Metabolic liver diseases

Metabolic liver diseases that may occur with chronic liver disease and require liver transplantation due to liver cirrhosis and its complications include genetic hemochromatosis, alpha one antitrypsin deficiency and Wilson´s disease. Indications for liver transplantation also include some metabolic disorders originating in liver, affecting other organs but not involving liver: type 1 hyperoxaluria, familiar homozygous hypercholesterolemia and familiar amyloidosis (7). The most common complications after liver transplantation include: infections, biliary complications (most commonly stenosis of biliary anastomosis and leakage) that occurred in up to 32% (8), vascular complications (mostly hepatic artery and portal vein thrombosis) in 7% (9), acute rejection in 25%, chronic rejection in 5% and malignancy. HCC recurrence rate after liver transplantation is up to 20% (10). De novo cancers ranging up to 19% and 34% at 10 and 15 years, respectively, following liver transplantation (11) (12).

PATIENTS AND METHODS

283 patients underwent liver transplantation in UKC Ljubljana, Slovenia, between 20. 6. 1995 and 31. 12. 2016. Of those 186 (65,7%) were men and 97 (34,3%) women. The average age at transplantation was 50,2 years. (Indications for liver transplantation are shown in Figure 1.) 208 (73,5%) patients, of which 139 (66,8%) men and 69 (33,2%) women, were transplanted due to chronic liver diseases: 59 because of cholestatic liver diseases (26: 4 men and

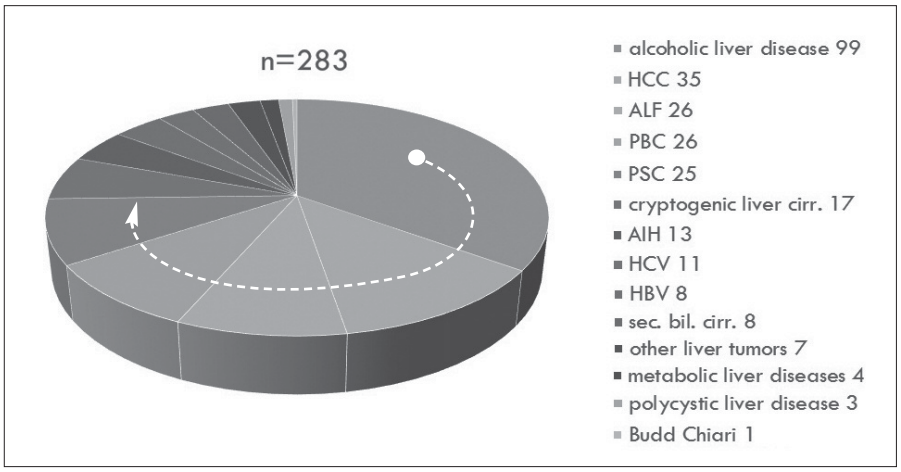

Figure 1: Indications for liver transplantation in Slovenia 20. 6. 1995 – 31. 12. 2016.

22 women, because of PBC, 25: 19 men and 6 women, because of PSC and 8: 4 men and 4 women, because of secondary biliary cirrhosis), 148 due to hepatocellular liver diseases (99: 80 men and 19 women because of alcoholic liver disease, 13: 3 men and 10 women, because of AIH, 17: 12 men and 5 women, because of cryptogenic liver cirrhosis, 8: 7 men and 1 woman, because of chronic B hepatitis and 11: 10 men and 1 woman, because of chronic hepatitis C). 1 woman was transplanted because of Budd-Chiari syndrome. 42 (14,8%) patients, of which 35 (83,3%) men and 7 (16,7%) women, were transplanted due to liver tumors: 35: 30 men and 5 women, because of HCC, 4: 3 men and 1 woman, because of hepatic epithelioid hemangioendothelioma, 2 men because of isolated neuroendocrine tumor (NET) liver metastases after primary tumor of terminal ileum removal and 1 woman because of liver hemangiomatosis. 26 (9,2%) patients, of which 7 (26,9%) men and 19 (73,1%) women, were transplanted due to ALF: 4: 2 men and two women, because of acute Budd-Chiari syndrome, four women because of acute Mb. Wilson, 4: 2 men and two women, because of drug-induced ALF, four women because of acute AIH, two women because of fulminant hepatitis B, one woman because of mushroom poisoning and one woman because of ALF in pregnancy. In 6 transplanted patients, three men and three women, the cause of ALF remained unknown. 4 (1,4%) patients: 3 men (75%) and one woman (25%), were transplanted due to metabolic liver diseases: 2: 1 man and one woman, because of Mb. Wilson, one man because of familiar homozygous hypercholesterolemia and one man because of familiar amyloidosis.

3 (1%) patients, two men, and one woman were transplanted because of polycystic liver disease. 29 (10,2%) patients, of which 16 (55,2%) men and 13 (44,8%) women were re-transplanted, 13: 5 men and 8 women, underwent urgent and 16: 11 men and 5 women, underwent elective re-transplantation. One man had two elective re-transplantations.

RESULTS

On the date 31. 12. 2016 out of 283 transplanted patients 207 were alive.

76 (26,8%) patients: 51 men and 25 women, died. Causes of death are shown in Table 1.

Table 1. Causes of death in liver transplant patients in Slovenia 20. 6. 1995 – 31. 12. 2016

Cause of death	Number of patients	%
infection	26	34,2%
cancer	15	19,7%
graft failure	9	11,8%
cardiovascular	7	9,2%
intraabdominal hemorrhage	4	5,3%
intracranial hemorrhage	4	5,3%
trauma	1	1,3%
complication of tx	1	1,3%
unknown	9	11,8%
SUM	76	99,9%

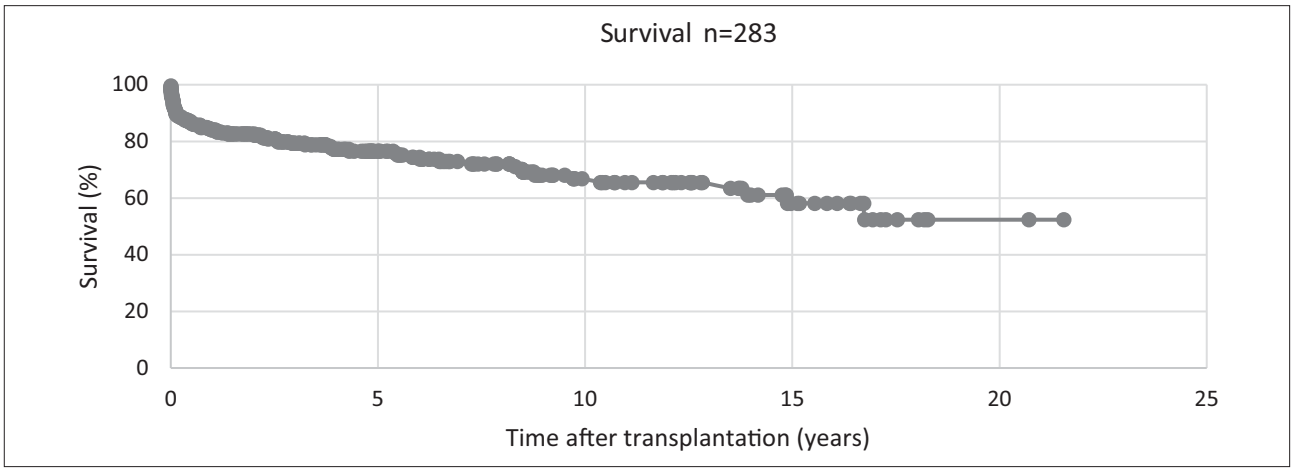

Figure 2: Survival curve after liver transplantation in Slovenia 20. 6. 1995 – 31. 12. 2016

1-year survival of our liver transplanted patients is 84,2%, and 5-year survival is 76,6% (Figure 2). In the same period 1- and 5-year survivals after liver transplantation in Eurotransplant are 82 and 70%, respectively.

1-year survival of our patients transplanted due to chronic liver disease is 87,7%, and 5-year survival is 81,3%.

1-year survival of patients transplanted because of liver tumors is 76%, and 5-year survival is 57%.

1- and 5-year survival of patients transplanted due to ALF is 72,1%.

1-year survival of only four patients transplanted due to metabolic liver diseases is 75%, and 5-year survival is 50%.

In 83 (29,3%) patients after liver transplantation biliary tract complications occurred, most frequently stenosis of biliary anastomosis; the majority were treated endoscopically. In 51 (18%) of transplanted patients, vascular complications occurred that were mostly solved surgically. In 95 (33,6%) of patients acute and 24 (8,5%), chronic rejection occurred, both proven by liver histology.

Cancer is one of the leading causes of morbidity and mortality after liver transplantation. In 41 (14,5%) patients, 32 men and nine women, transplanted in our center, 44 occurrences of cancer were found (Figure 3). HCC recurs in 3 of 35 (8,6%) patients transplanted because of HCC and NET reappears in 1 of 2 patients transplanted due to NET liver metastases. Three patients had two cancers: 1 skin and lung cancer, one skin cancer and hypernephroma and one osteosarcoma and bladder carcinoma. 15 (5,3%) patients: 12 men and three women, died because of cancer, which makes it with 19,7% the second leading cause of death in liver transplant recipients, following infections. (Figure 4) Analysis of infections after liver

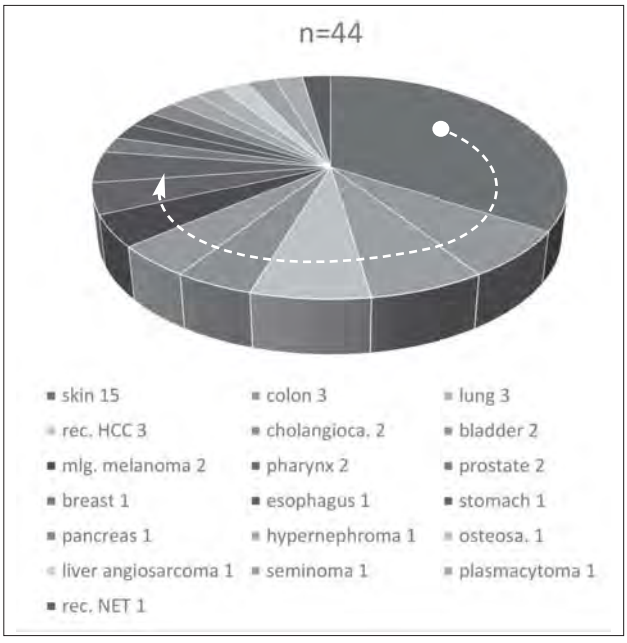

Figure 3: Cancer after liver transplantation

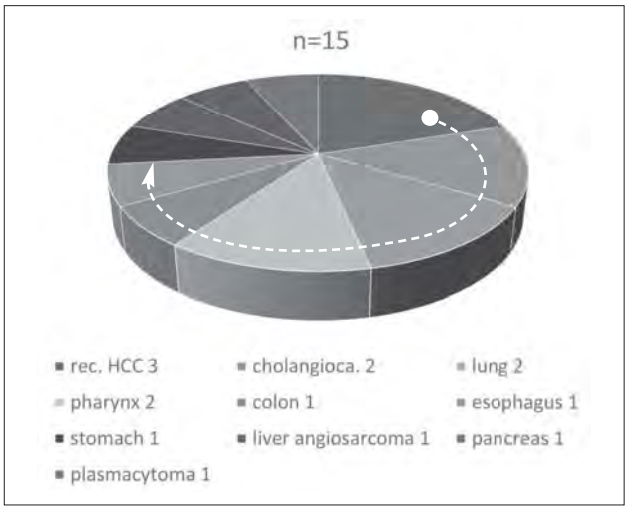

Figure 4: Mortality due to cancer after liver transplantation

transplantation in our cohort was impossible to make because of shortage of data.

CONCLUSION

Liver transplantation is a successful way of treatment for patients with advanced chronic liver disease and its complications as well as for patients with acute liver failure. 1- and 5-year survival of our patients after liver transplantation is comparable to survival rates of other centers included in Eurotransplant. According to published data, our complication rate is quite high, which is mostly due to procedures performed in first years of our program. Our goal for the future is to improve our results using better patient selection and optimization of patient care using multidisciplinary approach, aiming to detect and treat complications following liver transplantation as soon as possible.

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Review article

Functional gastrointestinal diseases and food hypersensitivity

Jasna Volfand*[1]
[1]*Diagnostični center Bled*
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ABSTRACT

Many patients with functional gastrointestinal diseases (FGID) link food intake with development of symptoms. Ingestion of food indeed can affect gastrointestinal tract function on many different levels. Recently the role of food in FGID achieved a renewed interest, and several dietary approaches have been studied in more detail, providing evidence for satisfactory symptom improvement in certain groups of patients. The basics of diet, low in fermentable carbohydrates, and the role of gluten restriction will be addressed in this review, along with the evidence for possible involvement of allergic mechanisms in pathogenesis of FGID.

FUNCTIONAL GASTROINTESTINAL DISEASE

Functional gastrointestinal diseases (FGID) are considered to be a disorder of gut-brain interaction (1). It is a group of disorders classified by gastrointestinal (GI) symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing. The relative contribution of these physiological features may differ in various FGIDs and across individuals over time. Altogether, 33 adult and 20 pediatric FGID have been defined in the latest edition of ROME IV (1); irritable bowel syndrome (IBS) and functional dyspepsia (FD) are the most studied as far as the impact of food is concerned and will be referred to in this review. The role of food in FGID. Traditionally, the research on the pathophysiology of FGID has been focused primarily on enteric neuromuscular apparatus and its central connections through the brain-gut axis. However, recently the recognition of dietary factors in pathogenesis of symptoms has been recognized. Food is a major factor able to modify all above physiological functions implicated in the development of FGID. Diet, e.g. ingestion of lipids, can influence GI motility (2). CNS functioning is dependent on and also modulates food intake and circumstances related to meal. Visceral hypersensitivity can also be modified by ingesting several specific nutrients. Nutritional factors can also influence mucosal function, e.g. intestinal barrier disruption by ingesting gluten and thus set the stage for an inappropriate immune response.

*Jasna Volfand, MD
Diagnostični center Bled d.o.o., Pod skalo 4, 4260 Bled
E-mail: jasna.volfand@dc-bled.si

Altered immune function has also been implicated in development of FGID, based on the findings of low-grade inflammation in several disorders.

In recent years, many developments have been achieved in analyzing gut microbiota and their interrelationship with diet. Diet can shape microbiota composition, and microbiota can differentially impact gut fermentation of ingested substrates, thus raising possibility of interindividual differences in enterotypes and also in ester metabolites. Various fermentation products can have a major role in pathogenesis of FGID, especially IBS (3). There has been a discrepancy between patients' and physicians' attributions to the effect of food on FGID symptoms, with patients believing the effect of food is more important (4, 5, 6). This probably reflects the complex interplay of all factors involved in symptom generation which makes it extremely difficult to study and confirm the impact of specific food, even more so given the Intra- and interindividual variability in adverse reactions to food.

ADVERSE REACTIONS TO FOOD

Adverse reactions to food can be broadly grouped in toxic reactions and hypersensitivities. The term food hypersensitivity is used to describe objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons. It is divided in immune-mediated and non-immune mediated, the latter sometimes also called intolerance (7, 8). Immune-mediated reactions can be further described as IgE-mediated (food allergy), mixed/eosinophilic (eosinophilic esophagitis, gastroenteritis, colitis) and non-IgE-mediated (celiac disease). Non-immune mediated food hypersensitivities may be due to pharmacological effects of food components (e.g. histamine or methylxanthines) or enzyme and transport protein defects, e.g. lactose intolerance.

POSSIBLE ROLE OF ALLERGY IN FGID

Patients with IBS or FD often refer to their symptoms as »food allergy.« The direct contribution of immunological factors in pathogenesis of symptoms is difficult to prove and has not been universally accepted yet. However, many epidemiological clues implicate co-occurrence of atopy and FGID. Functional GI symptoms have been found to be much more common in patients with atopy and allergic diseases like asthma (9–14), and atopic conditions were found in excess among all FGID groups (15). Various cells that are traditionally part of allergic processes seem to be also involved in patients with FD and IBS (mast cells (MC), eosinophils...). Histological studies of patients with IBS demonstrate signs of low-grade inflammation, along with increased numbers and increased activation of mast cells in the mucosa. A substantial increase in the number of degranulating MCs releasing histamine has been found in proximity of the nerves that are correlated with abdominal pain in IBS (16–23). Recently, the researchers have proven by confocal endomicroscopy that significant changes occur after application of food on duodenal mucosa in patients with FGID (24). So far, the diagnostics of food allergy in the gut relies on elimination diets and open or Blind food challenges; studies of IBS patients and controls found no significant differences in results of skin prick testing or serum specific IgE antibodies to food antigens. However, colonoscopic allergen provocation test (COLAP) has disclosed many positive results, implicating possible role of local IgE production (25, 26). Of course, the clarification of the role of allergy in FGID needs further studies, and perhaps later we can also expect therapeutic benefit; first observations point towards a possible therapeutic role of IgE blockade in IBS (27, 28). Therapeutic effect has already been noticed with ketotifen, and several new mast cell stabilizers are in development (29).

NON-CELIAC GLUTEN SENSITIVITY (NCGS)

Although cases of adverse reaction to gluten in absence of celiac disease or allergy were already described in the 70s, only in the last decade this condition has been acknowledged and has received more scientific interest. NCGS is a syndrome characterized by intestinal and extraintestinal symptoms related to the ingestion of gluten containing food, in subjects in whom either celiac disease or wheat allergy previously has been ruled out (30, 31). It seems to be a melting pot of different patients groups lumped together under a common label (32). While reliable biomarkers for this condition are still lacking, the golden (although imperfect) standard for diagnosis is double-blind, placebo-controlled, cross-over gluten challenge. However, only 16% of patients who had claimed to feel better after gluten free diet were eventually positive in the blind test. This does not reflect only potential methodology flaws in the protocol of gluten challenge, but it also casts doubt on gluten as the culprit food component in most patients. The considerable FODMAP content of wheat could play a major role. Thus proper characterization of FODMAP intolerance in patients with NCGS is important. Also, non-gluten proteins in wheat deserve further attention; wheat germ agglutinin has epithelial damaging properties, and ATI (amylase trypsin inhibitors) have been proven to activate innate immune responses (33). A subgroup of NCGS patients may also have subclinical celiac disease, while other studies (34) point out that some patients have non-IgE wheat allergy-like profile. Many opened questions will have to be answered by future studies.

FODMAP

The acronym FODMAP stands for Fermentable Oligo-, Di- and Mono-saccharides and Polyols. They comprise fructose, lactose, fructose- and galactooligosaccharides (fructans, and Galatians), and polyols (such as sorbitol, mannitol, xylitol, and maltitol). They have three common functional properties:

- Poorly absorbed in the small intestine, either because of slow /inexistent transport mechanisms across the epithelium (fructose, polyols), or reduced activity of degrading enzymes (lactose) and physiological absence of hydrolases (fructans, Galatians).
- Small osmotically active molecules: This effect has been demonstrated with, for example, a synthetic FODMAP, lactulose, which exerts a laxative effect when given in sufficient dose by increasing the liquidity of luminal contents and subsequently affecting gut motility.
- Rapidly fermented by bacteria: The rapidity of fermentation by bacteria is dictated by the chain length of the carbohydrate and of microbiota composition and function.

The concept of FODMAPS in a way extends and broadens the simple concept of lactose and fructose malabsorption and intolerance. The reason the symptoms are triggered by the ingestion of lactose or fructose in the individual is the response of the enteric nervous system to luminal distension (due to visceral hypersensitivity, excessive gas production due to the nature of the resident microbiota, or motility problems with clearance of the fluid/gas) not because the malabsorption of the sugar is abnormal or a 'condition'. After all, delivery of dietary FODMAP to the distal small and proximal large intestine is a normal phenomenon, one that will generate symptoms if the underlying bowel response is exaggerated or abnormal. Therefore, the reduction of intake of all poorly absorbed short-chain carbohydrates is more effective in reducing luminal distension than merely concentrating on one of these (35). Studies have confirmed the positive impact of FODMAP diet; in two blinded studies, FODMAP diet reduced symptoms of IBS at least as good as traditional dietary advice (36, 37). Whether alteration of FODMAP intake affects visceral sensitivity has not been directly assessed. However, SCFAs as a product of fermentation can alter such sensation, Because

alteration of FODMAP intake changes the gut microbiome, other pathogenic mechanisms for modulating symptoms might also play a role (38). The FODMAP diet is restrictive and reduces consumption of many common food items, including various fruits, several vegetables, and cereals. Fructans and galactooligosaccharides have prebiotic actions. Several studies have shown that a diet very low in FODMAPs is associated with a reduction in the relative abundance of Bifidobacteria in feces (39). The FODMAP diet is not meant to be lifelong; it is usually recommended only for several weeks and is then followed by gradual reintroduction of excluded items. So far, studies have not examined the microbiome of patients with IBS following the reintroduction of high-FODMAP foods to tolerated levels.

CONCLUSIONS

Although the pathogenesis of FGID is multifactorial, in recent years a lot of progress has been made in researching the role of food components in symptom generation. In the future, this will enable us to actually improve patients' well-being by influencing the diet.

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Review article

Metabolic effects of bypass surgery for morbid obesity

Tadeja Pintar*[1], Kunst Gregor[2]
[1]*UMC Ljubljana, Abdominal Surgery and Medical Faculty Ljubljana,* [2]*UMC Ljubljana*
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ABSTRACT

Morbid obesity is associated with a high risk for cardiovascular complications, the high incidence of diabetes type II, arterial hypertension, dislipidemias of the mixed type, osteoarthritis, and increased mortality (approx. 2.8 million death/year due to obesity related cardio vascular diseases). The global problems associated with the pandemic morbid obesity dimensions are the metabolic syndrome and increased incidence with obesity related cancers. Studies confirm the positive long-term effects of surgical interventions for obesity correlated to weight loss, and thus highly important clinical improvement obesity-related associated diseases. Effects of bariatric and metabolic surgical interventions have a favorable effect on components of metabolic syndrome (hyperglycemia, hiperlipidemija, arterrial hypertension); OSA is an independent risk factor for cardio vascular complications, non-alchoholic steatohepatitis associated with morbid obesity, reproductive health in both sexes, locomotor skills, psichosomatic health and social life of the patients. Resolution of morbid metabolic components is related to the type of surgical intervention. All over effects are in direct correlation of the impact of surgical techniques, diet, and adjustments to life style.Surgical technics associated to perioperative surgical and non-surgical complications and long-term metabolic complications. Appropriate preoperative individual patient preparation and continuous postoperative short and longterm follow up significantly reduce surgical and metabolic complications, both short and long term. A range of different bariatric procedures are in common use and the mechanisms underlying the efficacy of metabolic surgery are based to interfere with the important role of gastrointestinal and pancreatic peptides. including ghrelin, gastrin, cholecystokinin (CCK), glucose-dependent insulinotropic hormone (GIP), glucagon-like peptide 1 (GLP-1), peptide YY (PYY), oxyntomodulin, insulin, glucagon and somatostatin.

METHODS

Bariatric and metabolic surgical technic are a) restrictive, b) combination of restriction and malabsorbtion and c) primary malabsorbtive procedures (biliopancreatic diversion. Duodenal switch, Sadi's operation represents single anastomosis duodenal switch, ileal interposition and derived technics). Primary malabsorbtive procedures are mostly two step surgical interventions; stage one is gastric po-

*asist. prof. Tadeja Pintar, MD.
UMC Ljubljana, Abdominal Surgery and Medical Faculty Ljubljana
E-mail: tadeja.pintar@kclj.si

uch formation that allows moderate EWL% to reduce risk factors and stabilize patologic metabolic situation and stage two, in the time period of 3–6 mounths after primary stage, representing malapsorbtive part of the procedure. Primary malabsorbtive procedures are reserved for patients suffering of metabolic syndrome resistent to treatment modalities. Baseline intervention of combined restriction and malabsorbtion and primary malabsorbtive procedures is small pouch formation from native stomach and malabsorbtive part responsable for malapsorbtive component of the procedure. The first step of the malabsorbtive part of the intervention is small intestinal lenght measurement and common trunck definition to prevent life treathening metabolic complications. Common trunc lower than 2 m trigger life treathening malabsorbtive situation. Schematic situation is presented in Figure 1.

Malabsorbtive part of the procedure is correlated to different surgical and functional anatomical situation responsable to reduced nutritient resorbtion, importantly vitamins, minerals and trace elements; major nutritional complications are typically associated with the malabsorptive effect of bariatric procedures and are usually seen after BPD, RYGB, OAGB and, less commonly in restrictive procedures. Effects of metabolic surgeries to gut peptides are summarised in Table 1.

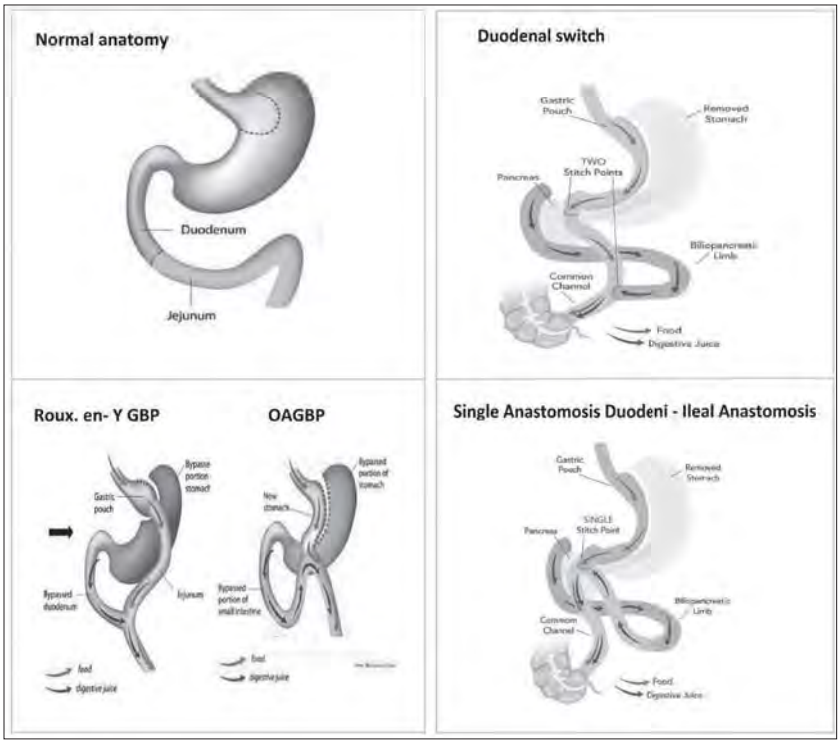

Figure 1. Restrictive and malabsorbtive procedures commonly performed and altered anatomy.

Hormone	Obesity (without surgery)	Roux-en-Y gastric bypass
Gastrin (7, 10–12)		↓ postprandial
Ghrelin (total) (6, 7, 14, 16–19, 22, 100, 101)	↔ or ↓ fasting ↔ or ↓ postprandial	↓ fasting ↓ postprandial
Cholecystokinin (CCK) (6, 19, 26, 101)	↔ fasting ↔ or ↓ postprandial	↔ fasting ↑postprandial
Gastric inhibitory peptide (GIP) (10, 31, 38, 84)	↔	↔ or ↓ fasting ↔ or ↓ postprandial
Glucagon-like peptide -1 (GLP-1) (6, 19, 22, 40)	↔ or ↓	↔ or slight ↑ fasting ↑postprandial
Glucagon-like peptide -2 (GLP-2)(67, 69)		↔ or ↑ postprandial
Peptide YY (PYY) (6, 73, 74, 76, 77)	↓	↔ or slight ↑ fasting ↑postprandial
Oxyntomodulin(78)		↔ fasting ↑postprandial
Insulin (86, 102)	↔, ↑ or ↓ depending on diabetes status	↓ fasting ↔ or ↓ postprandial
Glucagon (85, 95, 96)	↔ or ↑	↑or ↓ fasting ↔ or ↓ postprandial
Somatostatin (6)		↑ fasting ↑ postprandial

Table 1. Effects of metabolic surgeries to gut peptides.

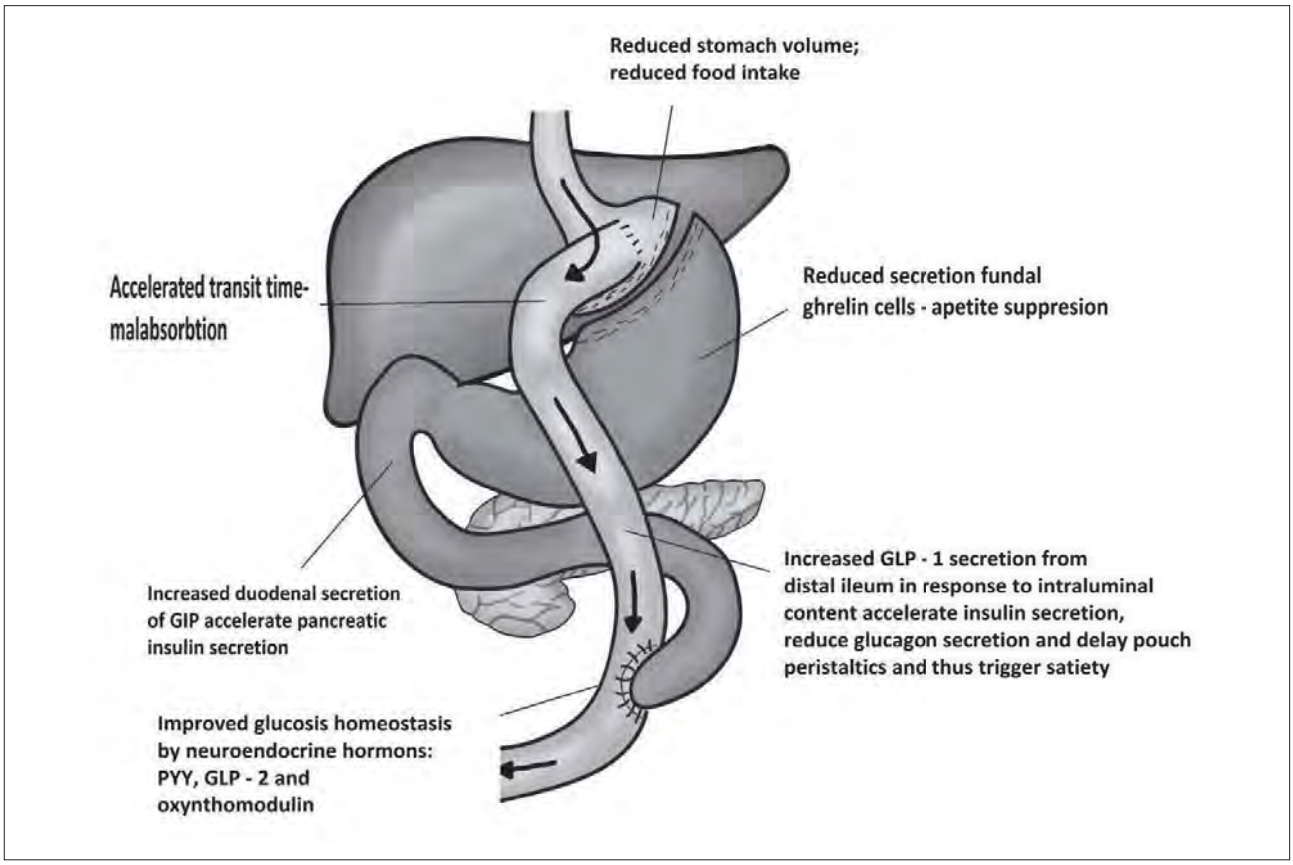

Figure 2. Effects of malabsortive surgery to improved metabolic parameters, physiologic effects.

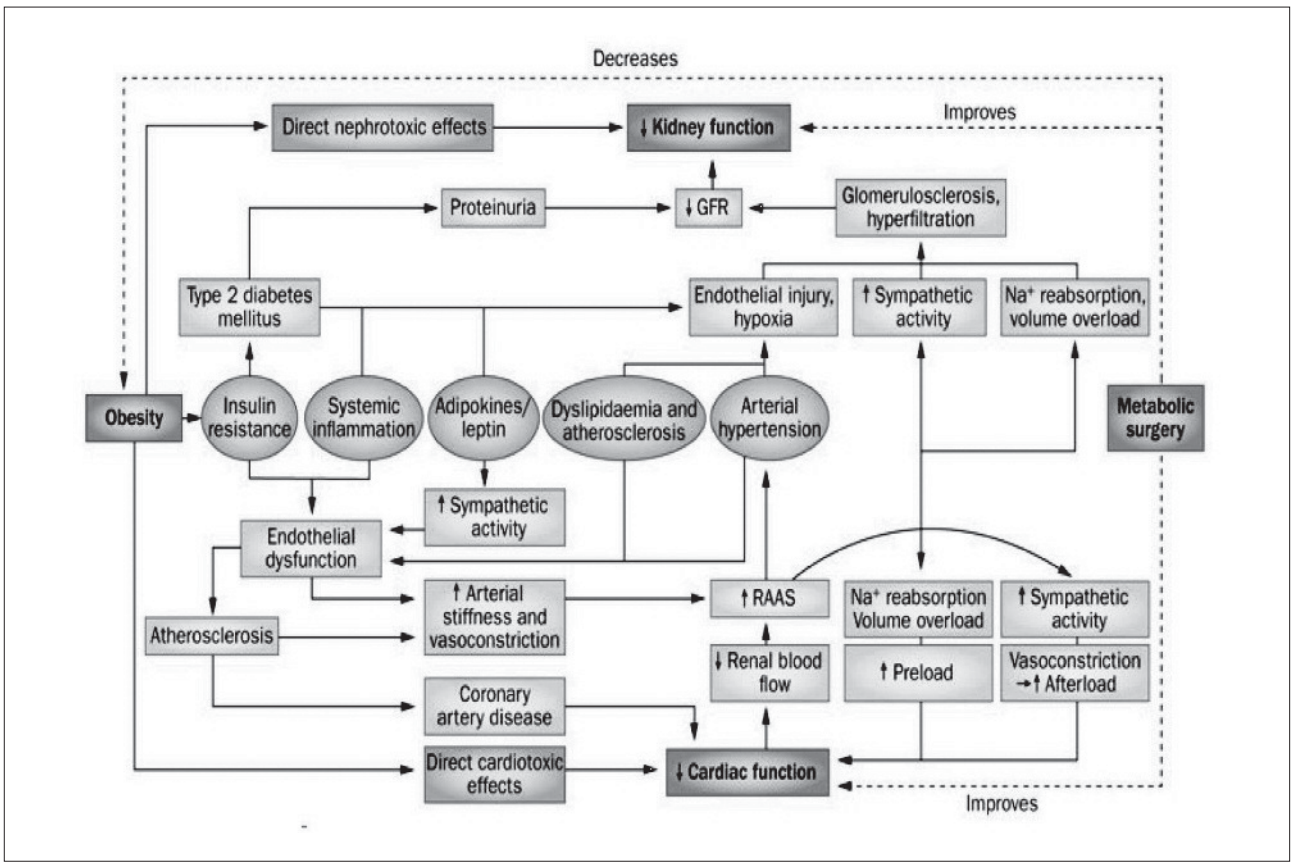

Figure 3. Overal risk reduction and physiological mechanisms triggered with metabolic surgery procedures.

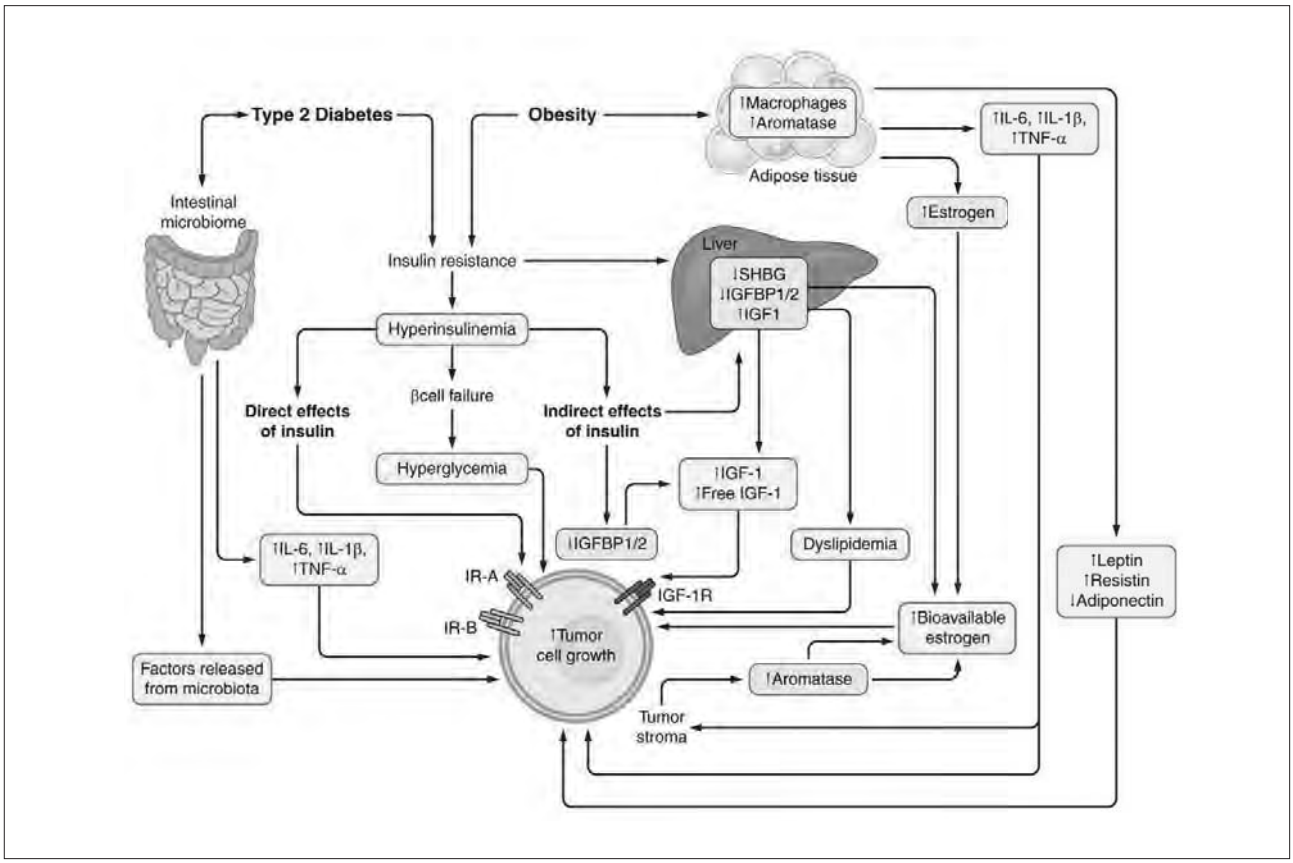

Figure 4. Glucose homeostasis and obesity; risk factors and inflammation.

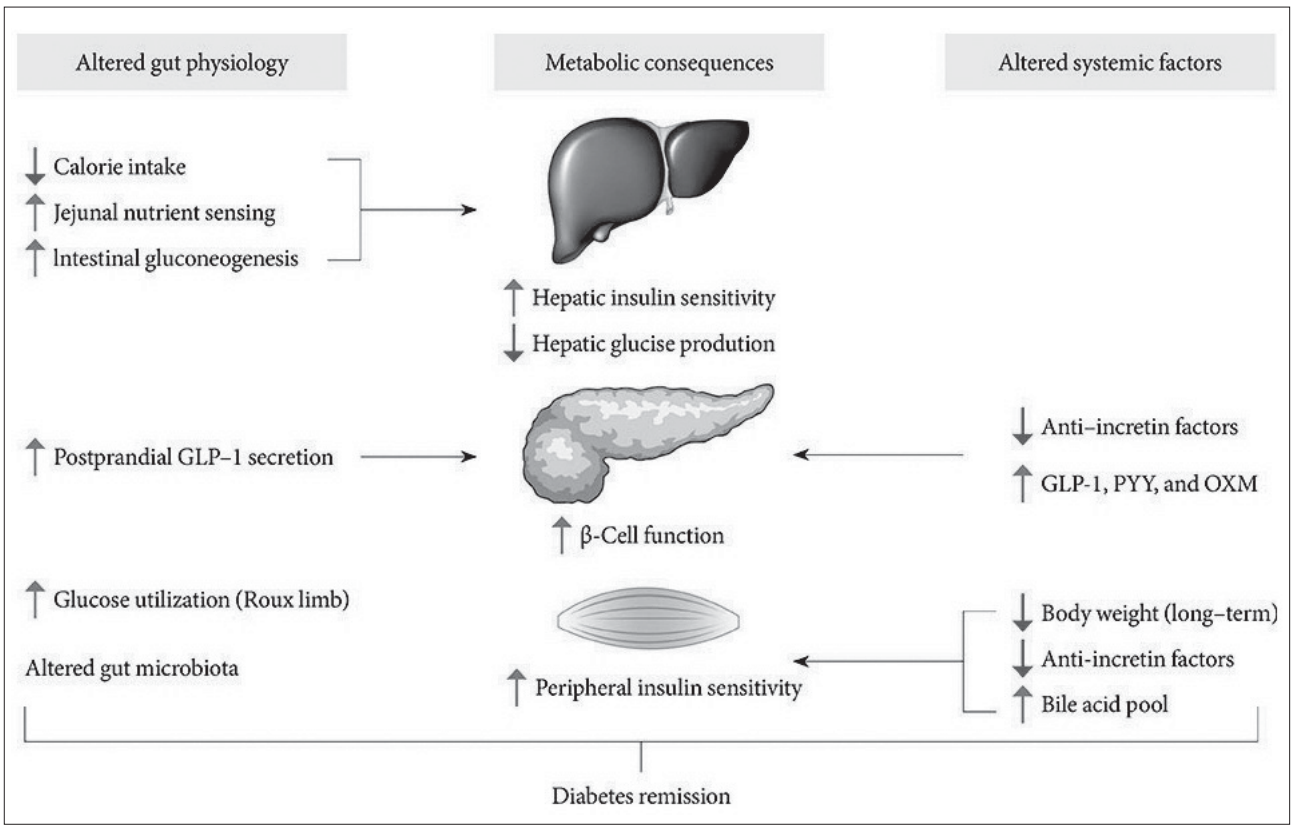

Figure 5. Potential mechanisms involved in diabetes remission after metabolic surgery. Altered gut physiology, sistemic and circulating factors improve glucosis homeostasis.

Metabolic complications are mostly related to malabsorbtive part of the procedure. The detailed schema to supplementation is needed to all bariatric surgery procedures.

Complication	Clinical Features	Management
Acid-base disorder	Metabolic acidosis, ketosis	Bicarbonate orally or intravenously; adjust acetate content in PN
	Metabolic alkalosis	Salt and volume loading (enteral or parenteral)
Bacterial overgrowth (primarily with BPD-DS)	Abdominal distention Pseudo-obstruction Nocturnal diarrhea Proctitis Acute arthralgia	Antibiotics (metronidazole) Probiotics
Fat-soluble vitamin deficiency	Vitamin A—night vision Vitamin D—osteomalacia Vitamin E—rash, neurologic Vitamin K—coagulopathy	Vitamin A, 5,000-10,000 U/d Vitamin D, 400-50,000 U/d Vitamin E, 400 U/d Vitamin K, 1 mg/d ADEK, 2 tablets twice a day (http://www.scandipharm.com)
Folic acid deficiency	Hyperhomocysteinemia Anemia Fetal neural tube defects	Folic acid supplementation

Complication	Clinical Features	Management
Iron deficiency	Anemia	Ferrous fumarate, sulfate, or gluconate Up to 150-300 mg elemental iron daily Add vitamin C and folic acid
Osteoporosis	Fractures	DXA, calcium, vitamin D, and consider bisphosphonates
Oxalosis	Kidney stones	Low oxalate diet Potassium citrate Probiotics
Secondary hyperparathyroidism	Vitamin D deficiency Negative calcium balance Osteoporosis	DXA Serum intact PTH level 25-Hydroxyvitamin D levels Calcium and vitamin D supplements
Thiamine deficiency (vitamin B_1)	Wernicke-Korsakoff encephalopathy Peripheral neuropathy Beriberi	Thiamine intravenously followed by large-dose thiamine orally
Vitamin B_{12} deficiency	Anemia Neuropathy	Parenteral vitamin B_{12} Methylmalonic acid

DXA = dual-energy x-ray absorptiometry; PN = parenteral nutrition; PTH = parathyroid hormone.
Mechanick JI, et al. *Endocr Pract*. 2008;14(suppl 1):1-83.

Figure 6. Metabolic complications after bariatric and metabolic surgery procedures.

CONCLUSIONS

1. The most effective and durable treatment for morbid obesity is obtained with bariatric and metabolic surgery procedures.
2. Surgery results in significant weight loss and helps prevent, improve or resolve more than 40 obesity-related diseases or conditions including type 2 diabetes, heart disease, obstructive sleep apnea and certain cancers.
3. Individuals with morbid obesity or BMI ≥ 30 kg/m^2 have a 50–100% increased risk of premature death compared to individuals of healthy weight.
4. Surgery reduces a person's risk of premature death by 30–40%.
5. Clinical studies have demonstrated significant improvements in safety, showing that the risk of death is 0.1%, and the overall likelihood of major complications is about 4%. Center of excellence program offers better results, short and long term.
6. Postoperative metabolic screening is mandatory to prevent life treathening complications and morbidyty related.
7. Metabolic screening is based to the type of metabolic/bariatric surgery type.
8. Long term postoperative controls significantly reduce weight recidivism and morbidity and importantly lifestyle intervention is needed fort he purpose to support all type of surgery interventions.

Liquid biopsy in patients with colorectal cancer

Gregor Norčič*[1], Srdjan Novaković[2]
[1]*University Medical Centre Ljubljana, Clinical Department of Abdominal Surgery, Ljubljana, Slovenia*
[2]*Institute of Oncology Ljubljana, Department of Molecular Diagnostics, Ljubljana, Slovenia*
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***Keywords**: liquid biopsy, colorectal cancer, peripheral blood, KRAS, BRAF*

ABSTRACT

Background: Management of colorectal cancer patients mainly relies on the assessment of disease by radiological imaging, clinical and pathohistological investigations, which all provide little direct information about the systemic spread of the disease. There is growing evidence that the assessment of the disease in patient's peripheral blood by liquid biopsy might have clinical importance.

Methods: The aim of our prospective study of 31 colorectal cancer patients with specific DNA mutations (KRAS/BRAF) found in their primary tumor was to test the possible clinical use of liquid biopsy in assessing the stage of the disease before treatment, residual disease after treatment and patients' prognosis.

Results*:* The same mutations as in primary tumor were also detected in peripheral blood ("positive liquid biopsy") of 10 and five patients before and after surgery, respectively. We have not found any significant correlation between the incidence of positive liquid biopsy before surgery and the stage of the disease. However, we have found a significant association between positive liquid biopsy after surgery and radicality of surgery expressed in R category (p=0.02). We have also observed a statistically insignificant relationship of positive liquid biopsy and the disease recurrence (p=0.09). In Kaplan-Meier survival plots we noticed an apparent trend towards poorer overall survival of patients with positive liquid biopsy as compared to patients with negative liquid biopsy (p=0.152).

Conclusions*:* Despite the encouraging results of our study and growing evidence for the potential clinical benefits of liquid biopsies found in the literature, the concept of liquid biopsy remains a challenging field for further research.

INTRODUCTION

The crucial steps in the management of colorectal patients after diagnosis of the disease are staging of the disease, treatment, assessment of treatment effect and follow-up of patients (1, 2).

Staging of the disease is assessment of its spread in local lymph nodes or via hematogenous route to

*Gregor Norčič, MD, Ph.D
University Medical Centre Ljubljana, Clinical Department of Abdominal Surgery, Ljubljana, Slovenia
E-mail: gregor.norcic@kclj.si

distant organs and is expressed in TNM categories and stages (3). Stage of the disease serves as a basis for decisions regarding the treatment strategy. After the treatment, either by surgery or after systemic therapy, the treatment effect should be assessed. In surgery, for example, the treatment effect is reported by using the R classification of residual disease (4). The treatment effect is the most important determinant of patient's prognosis, which is clinically expressed as probability of disease recurrence and patient's survival. After the end of apparent successful treatment, the follow-up of patients is necessary for many years to detect the possible disease recurrence (5).

In colorectal cancer patients, the staging of the disease, the assessment of the treatment effect and the follow-up are all performed clinically by the combination of physical examination, radiological imaging, endoscopic investigations and laboratory tests (1, 2). These clinical methods, however, are unable to detect small amounts of tumor tissue in the patient's body and give no direct information about the spread of the tumor in the patient's blood stream. Therefore a more sensitive method of tumor detection would be of great clinical value. Since it is known that tumor cells spread into the blood stream very early in the course of tumor progression, every tumor (primary, residual or recurrent), no matter how small, should therefore theoretically be assessable by examining the patient's peripheral blood (6). For that reason, numerous studies have been performed on the subject of tumor detection from peripheral blood in the past. At the beginning, the research focused on the detection of cancer cells in patient's blood (»circulating tumor cells«; CTC), and it has been shown in many studies, that their presence in patient's blood has negative impact on patient's prognosis (7, 8, 9). Later it turned out, that the detection of circulating tumor DNA (»ctDNA«) in patient's peripheral blood alone has negative prognostic effect too (10, 11). Implicating the potential clinical use of these blood tests and because of their close resemblance to the conventional tissue biopsy, the term »liquid biopsy« has been coined for the assessment of tumor presence in patient's peripheral blood (12, 13).

The aim of our study was to test the potential clinical use of the ctDNA based concept of liquid biopsy in colorectal cancer patients.

PATIENTS AND METHODS

Patients

Sixty-one patients scheduled for elective surgery between July 2011 and January 2012 at the University Medical Centre Ljubljana due to colorectal cancer were enrolled into the study. All patients have given informed consent to take part in the study. The study was approved by the Republic of Slovenia National Medical Ethics Committee (Nr. 136/06/11).

The patients were staged according to the preoperative staging results, intraoperative findings and pathohistological results of the resected specimens into Union for International Cancer Control (UICC) TNM categories and stages. The decisions regarding the surgical approach and technique were left to the discretion of the attending surgeon. After surgery, the pathohistological analysis of the resected specimens was performed in standard manner. The clearance of tumor tissue by surgery was expressed by R category based on surgery reports and pathohistological analysis of the resected tumor specimen. Patients received adjuvant treatment based on the recommendations of the multidisciplinary tumor board. After the end of treatment, all patients received regular follow-up by attending surgeon and oncologist. The observation terminated on the 31st of December 2016. The data on survival of patients by the end of observation period were obtained from the National Cancer Registry of Slovenia.

Samples

A sample of tumor tissue, normal bowel tissue, and two blood samples were collected from each patient. First blood sample was collected just before the start

of the surgical procedure and second blood sample was collected 5–7 days after surgery (Figure 1). Only in cases with positive tumor-specific DNA mutations in tumor tissue (and negative in healthy bowel) the collected blood samples were analyzed on the presence of the same mutation. KRAS and BRAF mutations were regarded as tumor-specific DNA mutations in this study because of their known association with colorectal cancer and their well-standardized detection protocol.

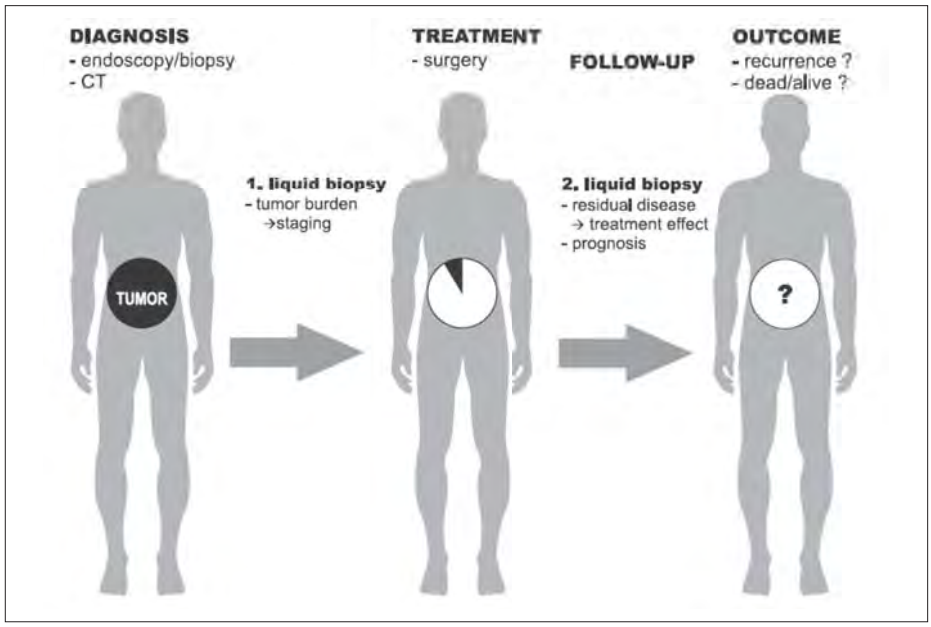

Figure 1. Potential clinical use of liquid biopsy in course of management of colorectal cancer patients. First liquid biopsy is taken before start of the treatment (surgery) for assessment of the tumor burden (staging). Second liquid biopsy is taken after the treatment for the assessment of the residual disease (treatment effect and prognosis).

After tumor resection, the appropriate FFPE tumor and normal tissue block was selected by the pathologist, who also evaluated the percentage of tumor cells in the paraffin slides from the first and last HE-stained cut. The whole blood samples were collected in 10 ml EDTA tubes and stored at –80°C. Prior DNA extraction the samples were centrifuged at 4000 rpm for 25 min to obtain pellets (cells and cellular debris). The pellets were used for DNA extraction.

For the DNA extraction from FFPE tumor tissue, a QIAamp DNA FFPE Kit (Qiagen, Hilden, D) was used according to the manufacturer's protocol. The DNA from blood samples was extracted using an Arrow Blood DNA Kit (NorDiag, Dublin, IE) according to the manufacturer's protocol. After the isolation, the DNA concentration was measured spectrophotometrically at 280/260 nm using a NanoDrop 1000 spectrophotometer (Thermo Scientific, Waltham, MA, USA).

Determination of KRAS and BRAF mutation status was performed using the KRAS/BRAF Mutation Analysis Kit (EntroGen, Tarzana, CA, USA), a real-time PCR assay based on allele-specific PCR. The assay is designed to preferentially amplify mutant DNA even in samples that have mostly wild-type DNA. In the assay, an endogenous control gene is included to ensure that a sufficient amount of DNA is available for amplification. The detection of the amplification product is done by using fluorescent hydrolysis probes. The assay was performed according to the manufacturer's protocol, with a 25 ng of DNA per reaction and ABI7900 set up (Applied Biosystems). For data analysis, the manufacturer's instructions were followed (EntroGen). The KRAS/BRAF Mutation Analysis Kit detects the 18 most common *KRAS* mutations in codons 12, 13, 61, 117, and 146 and a single *BRAF* mutation in codon 600.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics Version 20 (IBM Corp. Armonk, USA, 2011). Chi-Square test was used for comparing the presence of specific tumor mutations in peripheral blood and TNM stages. Fisher's exact test was used for testing the correlation between the presence of tumor-specific DNA mutations in blood of patients and treatment effect (described in R category) or disease recurrence at the end of the observation period.

Log-rank test was used for comparing the difference in disease-specific survival curves. P values of < 0.05 were considered statistically significant.

RESULTS

Sixty-one patients (40 male, 21 female) with average age of 66 years (range 39–91 years) operated for colorectal cancer with curative intent were included in our study. Operations were performed in open and laparoscopic technique in 52 (85.2%) and 9 (14.8%) cases, respectively. Tumor localizations were right colon or hepatic flexure in 16 (26.3%) cases, transverse colon in 1 case (1.6%), splenic flexure or left colon in 4 (6.6%), sigmoid colon and rectum in 16 (26.3%) and 24 (39.3%) cases, respectively. Stage distribution of the tumors was 12 (19.7%), 27 (44.3%), 14 (23.0%) and 8 (13.1%) for stages I, II, III and IV respectively. Nine (14.7%) patients received neoadjuvant therapy (3 short course radiotherapy, six radiochemotherapy) and 21 (34.4%) patients received adjuvant therapy (18 chemotherapy, one radiochemotherapy, two radiotherapy). Median follow-up of patients after surgery was 61 months.

In 31 of 61 patients (50.8%) we found a specific *KRAS* or *BRAF* mutation in tumor tissue. In 27 patients we detected *KRAS* mutation and in 4 patients *BRAF* mutation.

The same mutation as detected in primary tumor was found in peripheral blood of 10 patients before surgery and in 5 patients after surgery. In 6 patients the tumor specific mutation has been detected in blood before surgery, but not after surgery. In 4 patients the same mutation has been detected in blood before and after surgery. In one patient the tumor specific mutation has been detected in blood after surgery only. All mutations found in blood were *KRAS* mutations.

Only 31 patients with proven tumor-specific DNA mutation in primary tumor were respected in further analysis. The detection of the same specific DNA mutation in peripheral blood of patients was considered as a positive liquid biopsy.

Staging (disease burden)

Stage distribution of 31 tumors with specific DNA mutation was 4 (12.9%), 14 (45.2%), 8 (25.8%) and 5 (16.1%) for stages I, II, III and IV respectively.

Before surgery the liquid biopsy of patients was positive in 2, 3, 2 and 3 cases in tumor stages I, II, III and IV respectively. The results are shown in Table 1.

Table 1. Correlation between the first liquid biopsy and the tumor TNM stage (Chi-Square test) in 31 colorectal cancer patients with specific DNA mutation in primary tumor

		1st liquid biopsy		*p*
		positive	negative	
TNM stage	I	2	2	0.350
	II	3	11	
	III	2	6	
	IV	3	2	

Treatment effect (residual disease)

In 26 of 31 (83.9%) patients radical tumor resection (R0 resection) has been performed, and in 5 (16.1%) patients the resection was not radical due to unresectable distant metastases (R2 resection).

After the surgery, the liquid biopsy was positive in 2 patients with R0 resections and three patients with R2 resections. The results are shown in Table 2.

Table 2. Correlation between the second liquid biopsy and radicality of surgery expressed in R category (Fisher exact test) or disease recurrence (Fisher exact test) in 31 colorectal cancer patients with specific DNA mutation in primary tumor

		2nd liquid biopsy		*p*
		positive	**negative**	
Radicality of surgery	R0	2	24	0.02
	R2	3	2	
Recurrence	yes	3	5	0.09
	no	2	21	

Prognosis (recurrence, survival)

By the end of observation period 11 (35.5%) of 31 patients with mutation-positive primary tumor have died, and in 8 of these 31 patients (25.8%), the disease recurred. Eight of deceased patients were diagnosed with disease recurrence at the time of death. Cancer-specific survival of patients at the end of observation period was 74.2%.

The correlation of positive liquid biopsy after surgery and disease recurrence is shown in Table 2. The correlation of positive liquid biopsy after surgery and overall survival of patients is shown in Figure 2.

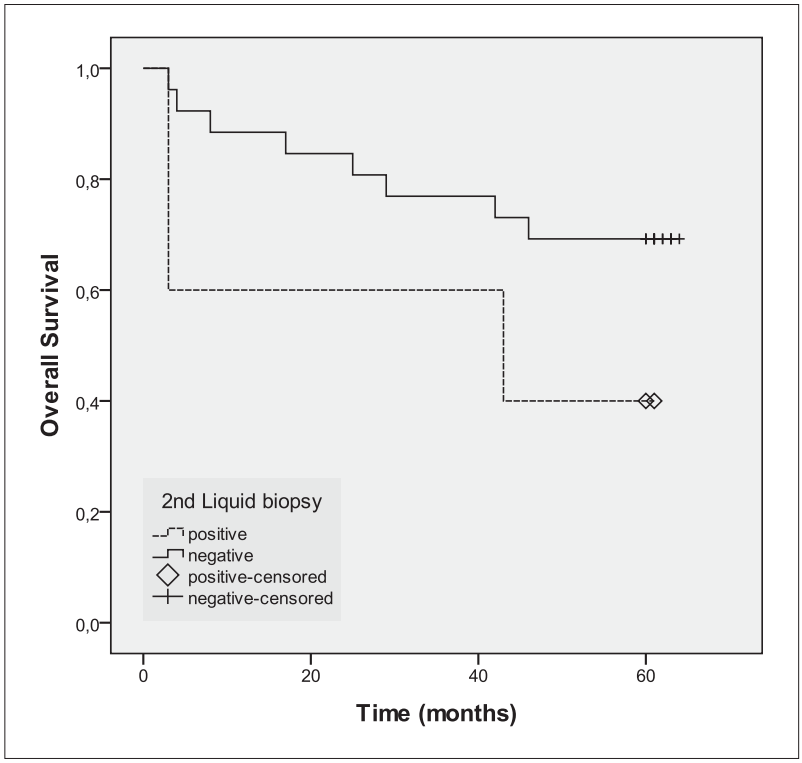

Figure 2. Kaplan-Meier overall survival plot of 31 colorectal cancer patients with specific DNA mutation in primary tumor in relation to the result of the second liquid biopsy (p=0.152; log rank test).

DISCUSSION

We have tested the potential clinical use of liquid biopsy in our study of 31 colorectal cancer patients with specific DNA mutations (KRAS, BRAF) detected in their primary tumors. We focused on the crucial steps in the course of management of patients where the standard means of tumor assessment to our opinion are lacking on sensitivity. These essential steps are the assessment of the disease stage before the start of treatment, assessment of treatment effect and prediction of prognosis.

In assessing the stage of the disease we were not able to find significant differences in incidence of positive liquid biopsies between TNM stages. Deriving from the conclusion that bigger primary tumor and spread of the disease to local lymph nodes or distant organs mean a greater tumor burden, one would expect proportionate increase of the tumor traits also in the patient's blood stream. We thus expected a higher proportion of positive liquid biopsies in higher tumor stages. Some researchers indeed have found the correlation of mutations in peripheral blood and stage of disease (14). Others, however, similar to our results, have found no correlation (15, 16).

In assessing the treatment effect, we were able to demonstrate a significant difference between R0 and R2 resections. As expected, the patients with incomplete tumor clearance due to unradical surgical procedure (R2 resections) had higher percentage of positive liquid biopsies after the surgery as compared to patients with radical surgery (R0 resections). Surprisingly only few und indirect data exist in the literature on the comparison of surgical radicality and presence of tumor mutations in peripheral blood. As expected, researchers mostly report on a negative correlation of radical surgery and presence of tumor in peripheral blood (16–18).

Regarding the prognostic significance of positive liquid biopsy after the end of treatment, our results are also very promising. We have observed a high, yet insignificant association of positive liq-

uid biopsy and the disease recurrence. Similar trend is evident from the patient's survival curves. As we expected, patients with positive liquid biopsy after surgery show worse overall survival as compared to patients with negative liquid biopsies, although the difference is not statistically significant. Our results are in concordance with majority of the reports from the literature which also report on the negative impact of mutations or tumor cells in peripheral blood and patients prognosis expressed either as higher incidence of recurrences and poorer patients survival (19–22).

Our study clearly suffers from a small number of patients and from the fact that the liquid biopsy was practically based on one single tumor DNA mutation. The later hardly takes account of the fact, that each tumor is genetically different from the other, and that each tumor itself is genetically highly heterogeneous (23, 24). The sensitivity of the method could, therefore, be increased by adding additional mutations that are known to be associated with colorectal cancer as some other researchers have done. Furthermore, in the sense of personalized medicine, one could improve sensitivity by identifying a different set of personal mutations for each patient. The statistical power of study itself could apparently be increased with the higher number of included patients.

We, therefore, regard our study as a demonstration of a new concept since there are some significant theoretical advantages in the concept of liquid biopsy over the standard means of management as shown from now on.

Liquid biopsy could offer information on the stage of the disease before the start of treatment in contrast to the current clinical staging, where the certain stage cannot be determined until the end of the surgical treatment (and pathohistological report). Maybe the concept of liquid biopsy could even render the division of patient in numerous stages and sub-stages unnecessary some day because the later hardly serves any clinical use. For the decisions in clinical medicine are mostly binary, the disease is either systemic or local, a certain treatment modality is offered or not, the disease recurs or not, and patients either survive or die. Based on the liquid biopsy after surgery, more objective indications for the adjuvant systemic therapies could be made (currently based on the removed tissue and targeting only presumed residual disease) (22). Closer to the clinical use is the concept of monitoring treatment effect depending on the results of liquid biopsy (25). This is especially useful in the form of guiding the systemic treatment (26). Liquid biopsy could also improve the estimates of patients prognosis and significantly improve the follow-up of patients after the end of therapy. All these theoretical advantages, however, remain to be sufficiently proven in clinical trials to enter clinical routine.

We, therefore, have to conclude, that neither results of our study, nor the evidence from the literature, are robust enough to prove the concept of liquid biopsy superior to the standard means of disease assessment for now. Clinical staging and pathohistological analysis of specimens remain the gold standards and pillars of management of patients with colorectal cancer.

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Review article

Protective stoma: yes or no after laparoscopic low rectum resection for cancer

Bojan Krebs*[1], Arpad Ivanecz[1], Stojan Potrč[1]
[1]*Abdominal and General Surgery, University Clinical Center Maribor Slovenia*
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***Keywords**: Rectal cancer, low anterior resection, stoma, anastomotic leakage*

ABSTRACT

Background: Rectal cancer is an important health problem in the developed world. Surgery plays a central role in the treatment of rectal cancer. Low anterior resection in combination with oncological therapy is the standard management. Anastomotic leakage is one the most serious complications that may occur after surgery. The diverting stoma may prevent the occurrence of anastomotic leak, but its use is still controversial in open and laparoscopic surgery.

Patients and Methods: We searched medical databases from 2000 to 2015 for following keywords in various combinations: »low anterior resection,« »stoma,« »protective stoma,« »diverting stoma,« »anastomotic leakage.« We also performed retrospective evaluation of all patients operated on rectal cancer in our institution in 15 year period between 2001 and 2015 and searched for anastomotic leakage.

Results: The results of internet search suggest that the absence of protective stoma is associated with a higher incidence of anastomosis leakage and reoperation.

The anastomotic leakage rate in our study was nearly three times higher in group of patients without protective stoma so we may say that protective stoma is a suitable procedure to diminish the danger of anastomotic leakage.

Conclusions: Recent literature review and our data confirm that protective stoma is recommended in open and laparoscopic surgery for rectal cancer as the procedure effectively reduces the risk of anastomotic leakage.

INTRODUCTION

Rectal cancer is an important health problem in the developed world. In the European Union, the incidence of rectal cancer is about one-third of all colorectal cancers and accounts for around 15–25 per 100 000 inhabitants per year (1). Age is one of the most important risk factors as more than 90 % of patients are older than 50 years. Unfortunately, at diagnosis, only one-fifth of patients has limited disease, and in more than 80 % the cancer already has local or distant metastases (2).

Bojan Krebs, MD, PhD
Abdominal and General Surgery, University Clinical Center Maribor; Ljubljanska 5, 2000 Maribor, Slovenia
E-mail: bojan.krebs@guest.arnes.si

Surgery plays a central role in the treatment of rectal cancer (3). Low anterior resection is the standard operation, especially for cancers of the middle and lower thirds of the rectum. The technique allows us to make very low anastomosis, practically just above the anal sphincter muscle, which in this way can be preserved (4). Low anterior resection can be performed open or laparoscopically. Most studies have shown that laparoscopic approach is not inferior to open and that this approach has all of advantages of minimally invasive surgery: reduced postoperative wound pain, decreased length of hospital stay, earlier return of bowel function, and improved cosmetic (5–7). There are also randomized prospective studies, where the non-inferiority of laparoscopic low anterior resection could not has been confirmed. According to their findings, laparoscopic rectal cancer surgery is inferior to open technique (8, 9). The general opinion is that the laparoscopic approach is more difficult and demanding than open, but this technique in hard cases still has better visibility and allows us to see better some sensitive, gentle vascular and neural structures which has to be preserved during rectum resection. In general, we can say that the laparoscopic rectal cancer surgery is a reliable method comparable with the open technique, but only in the hands of an experienced and well-trained surgeon who annually make a sufficient number of operations. Anastomotic leakage is one the most severe complications that occur after surgical treatment for rectal cancer. Leakage is defined as a communication between the Intra- and extraluminal space because of defect of the intestinal wall at the anastomosis between colon and rectum. The leak may increase morbidity, mortality and the duration of hospital stay. The problem of leak has been widely addressed in multiple studies over the last years (10). Use of a diverting stoma may prevent the occurrence of anastomotic leak but remains unclear whether the stoma is useful for patient after low anterior resection.

METHODS

We searched three databases (Cochrane Library, Medical Literature Analysis and Retrieval System Online (MEDLINE), and PubMed Health) from 2000 to 2015 for following keywords in various combinations: »low anterior resection,« »stoma,« »protective stoma,« »diverting stoma,« »anastomotic leakage.« Internet search engines were also used to perform a manual search for those keywords. We were mainly interested in prospective randomized studies, meta-analysis, and reviews published in English language.

At our department, all data from operated colorectal cancer patients are systematically collected and processed since year 1996. We performed retrospective evaluation of all patients operated on rectal cancer in our institution in 15 year period between 2001 and 2015 and searched for anastomotic leakage. We were interested in the overall rate of anastomotic leakage, the association between diverting stoma formation and anastomotic leakage rate and differences between open and laparoscopic approach regarding anastomotic leakage. Anastomotic leakage was defined as peritonitis caused by leakage, pelvic abscess, or discharge of feces from the pelvic drain at any postoperative stage.

RESULTS

We found 13 prospective studies and two meta-analysis. All studies have investigated the impact of protective stoma to clinical expression of anastomosis leakage. The results suggested that the absence of protective stoma is associated with a higher incidence of anastomosis leakage and reoperation.

In 15 year interval, we operated on 1085 patients with rectal cancer. There was 618 low anterior resections, 566 performed open and 52 laparoscopically. 68 patient have had cancer in lower third, 385 in middle third and 165 in higher third

of the rectum. There was 371 men and 245 women. Average age was 66 years, between 29 and 88 years. Overall anastomotic leakage rate was 5.5 %, 5.47 % at open and 5.75 % at laparoscopic operation. The difference was not statistically significant (p= 0.456). In patients with diverting stoma the leakage rate was 2.88 % and in patient without diverting stoma 8.06 %.

DISCUSSION

Anastomotic leaks are among the most dreaded complications after intestinal surgery and especially after rectal surgery because it can lead to permanent stoma, which strongly affect patient's quality of life (11). Some studies have reported that a leaking anastomosis may also lead to an increase in local recurrence rate along with a decreased tumor-free survival time (12). Its incidence rate varies from 2 up to 39 percent and may depend on the height of the anastomosis, the type of the intervention and the experience of the surgeon (3). Risk factors contributing to anastomosis leakage include male gender, malnutrition, preoperative weight loss, cardiovascular disease, steroid use, advanced age, obesity, neoadjuvant therapy, and a low level of anastomosis (13). To avoid the severe complications of anastomotic failure, it is crucial to take all possible measures to prevent symptomatic anastomotic leakage (14).

A so-called diverting or protective stoma for proximal fecal diversion has been suggested for low anterior resection. The creation of a stoma should effectively divert the fecal stream from a healing anastomosis, thereby mitigating the consequences of anastomotic failure (14). But evidence of benefit of such a procedure has been con icting. Some authors have recommended routine fecal diversion, and others have found similar leakage and mortality rates despite the presence of a stoma. They recommend a selective approach, with stoma formation only when there is concern about the anastomosis. It should not be forgotten that a stoma may itself cause significant morbidity and even mortality (15). However, literature search shows that diverting stoma is justified in low anterior resection. The conclusion of recent meta-analysis is that the presence of a protective stoma effectively decreases the incidence of anastomotic leakage and reoperation and is recommended in patients undergoing low rectal anterior resections for rectal cancer (16).

In our study anastomotic leakage rate was acceptable. There was no differences in anastomotic leakage rate between open or laparoscopic technique which proves that laparoscopic technique is as good as open with all the benefits of minimally invasive surgery. The rate of AL in group of patients without protective stoma was nearly three times higher than in patients with protective stoma so we may say that protective stoma is a suitable procedure to diminish the danger of anastomotic leakage.

CONCLUSION

Recent literature review and our data confirm that protective stoma is recommended in open and laparoscopic surgery for rectal cancer as the procedure effectively reduces the risk of anastomotic leakage.

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Review article

Complicated Crohn's disease; timing of surgical treatment

Aleš Tomažič*[1]
[1]*Department for the hepatobiliary and liver transplantation surgery, Department for abdominal surgery, University Medical Centre Ljubljana*
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***Keywords**: Crohn's disease, ileocolic resection, surgical treatment, medical treatment, timing*

ABSTRACT

Introduction: Crohn's disease is a chronic disease characterized by the presence of inflammation in different segments of the digestive tract which is accompanied by areas of ulceration and wall damage. Traditionally, the first line of treatment is medical. Over time, the target of gastroenterologists shifted from symptom control over steroid free remission to mucosal healing. All the time surgery is reserved for those who failed medical therapy and was considered the last resort treatment. Considerable progress have also been made in the surgical treatment over the past years, and fairly straightforward minimally invasive operation can be seen as an alternative for maintenance therapy with biologicals and immunosuppressants. However, little research has been undertaken on the issue concerning timing of surgery regarding efficacy, costs, and quality of life.

Timing of surgery*:* Surgery should be theoretically performed to achieve maximal relief of symptoms with minimal surgical disadvantage. The timing is strongly influenced by patient's medical advisers. Early surgery may offer several advantages: reoperation rate is not increased, quality of life improves considerably compared to prolonged disease activity, and long-term medical treatment and early resection reduces postoperative morbidity and the extent of resected specimen. Despite widespread use of immunosuppressants, the natural history of the disease regarding reduction of complications and need for surgery remains unchanged. Major drawbacks of medical therapy are long-term use of medication with constraints for the patients, associated impairment of quality of life, morbidity and high costs. Nevertheless, substantial part of patients with Crohn's disease should be operated earlier in the course of their disease. Surgical resection as a treatment option is often overlooked, and consecutive courses of immunosuppressants are given with significant burden on quality of life.

Conclusions*:* Currently, there is poor evidence available pointing to a particular strategy, although more long-term evidence can be found on surgical treatment. At present, benefits and risks must be

*Aleš Tomažič, MD, Ph.D
Department for the hepatobiliary and liver transplantation surgery, Department for abdominal surgery
University Medical Centre Ljubljana, Zaloška Cesta 7, 1525 Ljubljana, Slovenia
E-mail: ales.tomazic@kclj.si

weighed carefully and discussed with the patient to decide which therapy path should be chosen. Participation of gastroenterologist and surgeon in the decision making is of paramount importance. Further trials are needed to be able to answer the question medical or surgical treatment?

INTRODUCTION

Crohn's disease is a chronic disease characterized by the presence of inflammation in different segments of the digestive tract which is accompanied by areas of ulceration and wall damage. Inflammatory lesions start in the mucosa and extend to the deeper layers, including entire bowel wall. This eventually may result in complications e.g. fibrotic strictures and perforations causing enteral and perineal fistula. Unfortunately, there is quite often a considerable patient's and doctor's delay before the diagnosis of Crohn's disease is established. The inflammation might have caused irreversible damage to the bowel before treatment is initiated. At diagnosis of Crohn's disease, around 20% of patients have already developed a penetrating complication or/and stricture. (1)

Traditionally, the first line of treatment is medical. Over time, the target of gastroenterologists shifted from symptom control over steroid free remission to mucosal healing. All the time surgery is reserved for those who failed medical therapy and was considered the last resort therapy. In the beginning of nineties, anti-TNFα was introduced as the most powerful drug against Crohn's disease. Over the past years, clinicians adapted dosage and used combination therapy with immunosuppressants (thiopurines, methotrexate) to prevent immunogenicity (antibody formation against anti-TNFα agents) (2). Considerable progress have also been made in the surgical treatment over the past years. Surgeons became more specialized from general surgeon to colorectal surgeon; minimal invasive surgery was introduced with beneficial effect especially in young Crohn's disease patients, and evidence-based decision making is done in multidisciplinary teams in tertiary referral hospitals. More specialized surgery, well indicated and minimally invasive can be considered as an alternative to long-term medical therapy for certain indications (3). Ileocolic resection is relatively safe operation with extremely rare complications requiring reoperation (Table 1) (4).

Table 1. Complications after ileocolic resection requiring reoperation within 30 days.

Type of complication	**Number of cases (N=596)**
Intraabdominal abscess	2
Anastomotic leakage	5
Necrotizing wound infection	1
Small bowel obstruction	1
Total	**9 (1,5%)**

Surgical treatment can be subdivided into surgery where symptoms warrants operations at the expense of bowel loss and ostomies, and surgery where a relatively simple minimally invasive operation can be seen as an alternative for maintenance therapy with biologicals and immunosuppressants. The first type can be considered as the end line of treatment that we want to avoid (e.g. total proctocolectomy, extensive small bowel resections, etc.). In this paper, we will try to advocate the second type of surgery (limited segmental resections, surgical closure of perianal fistula), which can be an alternative for maintenance therapy with expensive and potentially harmful drugs. Nonetheless, the decision for early surgery depends also on the strategy for postoperative treatment. For example, patient with short ileal involvement and perianal lesions will not be proposed resection of the terminal ileum since maintenance therapy will be given because of perianal lesions (3). However, little research has been undertaken on the issue concerning timing of surgery regarding efficacy, costs, and quality of life.

Timing of surgery

Surgery should be theoretically performed to achieve maximal relief of symptoms with minimal surgical disadvantage. The timing is strongly influenced by patient's medical advisers. The patient after resection, with personal experience of both disease symptoms and surgery, is in the best position to judge whether or not the timing of surgery was ideal. Scott and Hughes reported results of a questionnaire sent to 80 consecutive patients after elective ileocolonic resection. Response rate was 88%, and none of them would have wanted their ileocolonic resection performed later than it was done. By contrast, 74% of patients thought that the resection should have been carried out earlier and remaining 26% were satisfied with the timing of surgery. Among patients who would like to have an earlier operation, the median preferred operation time was 12 months earlier. One patient would have an operation 15 years earlier. Severity of symptoms and inability to eat normally were main reasons for this, but in some these symptoms had a significant deleterious effect on marriage, education, and employment. The rate of recurrence was higher if patients preferred earlier resection (41% vs. 29%). In this retrospective study delay could not be quantified. However, three elements were recognized; delay at general practitioner level, delay at gastroenterologists resistant to surgery and delay by surgeons without a specific interest in inflammatory bowel disease (5). The probability of surgery is 20–40% during the first year of the disease, 30–70% ten years after the diagnosis and after 15 years it is as high as 70–90% (6). Surgery is not curative, after 5 years 20–60% of patients will develop symptoms and 15–50% will need further intestinal resection (7). Early surgery may offer several advantages: reoperation rate is not increased (8), quality of life improves greatly compared to prolonged disease activity, and long-term medical treatment (9) and early resection reduces postoperative morbidity and the extent of resected specimen. (10) Despite widespread use of immunosuppressants, the natural history of the disease regarding reduction of complications and need for surgery remains unchanged (11). Major drawbacks of medical therapy are long-term use of medication with constraints for the patients, associated impairment of quality of life, morbidity and high costs (Table 2) (3).

Table 2. Pros and cons of early surgery and extensive medical therapy.

	Pro	Con
Early surgery	Rapid remission Early return to daily activity Early restoration of quality of life	Short & long-term morbidity Surgical recurrence
Extensive medical therapy	No surgery Less morbidity	Adverse effects of medication Long-term efficiency unknown More extensive surgery later on

Aratari analyzed long-term postoperative course in the group of patients who have undergone early surgery (acute or subacute presentation) and compared it with late surgery group (established diagnosis of Crohn's disease with complications or refractoriness to medical therapy). Follow-up of 207 patients lasted for ten years, the cumulative probability of clinical recurrence was significantly lower in the early surgery group, there was a trend for reduced need for immunosuppressants, but no difference was observed regarding surgical recurrence. At multivariate analysis, early surgery was the only independent variable associated with reduced risk of clinical recurrence, but not with need for immunosuppressants and surgical recurrence (12).

Important trial evaluating effectiveness of laparoscopic ileocecal resection was LIR!C trial was finished in 2015 (13). Results were not published yet, but were presented at UEG week in 2016. They included patients with Crohn's disease of the

terminal ileum who failed >3 months of thiopurine treatment or steroids, patients were randomly allocated to either infliximab or laparoscopic ileocecal resection. A significant difference for resection group was observed in quality of life, on mental and physical scale. Mean total direct costs per patient at one year were 19.655 EUR in the infliximab group and 10.724 EUR in the resection group.

DISCUSSION AND CONCLUSION

Nowadays, when ileocolonic resection has become minimally invasive, with low morbidity and long-term low surgical recurrence rate it has become very competitive with long-term maintenance biological therapy. Limited small bowel resections, strictureplasties and segmental colectomies for Crohn's disease might likewise be considered for early surgery. Very few data are available on the comparison of medical and surgical treatment (3). Over time, patients were treated more intensively with different types of drug combinations. As a result, the time interval from initial diagnosis to surgery increased, however, did not lead to more limited resections. In a recent study by Fu, they observed a significant difference in time from diagnosis to surgery in patients treated with anti-TNF compared to patients without anti-TNF between 2005 and 2010 (90 months vs. 48 months) (14). This was also confirmed in study by de Groof (10). Both studies found no effect on the length of resected bowel.

Trade off between limited surgery and maintenance therapy with expensive and potentially harmful drugs remain unclear. Results of LIRC trial bring strong evidence for early surgery, but longer follow-up is necessary for final evaluation (13). Patients are afraid of early surgery, probably with significant influence of gastroenterologist's opinion.

Aratari published retrospective analysis with a lot of bias (12). However, it would be interesting to randomize patients with established diagnosis of Crohn's disease to immediate surgery or medical treatment and observe long-term results and cost effectiveness. In the era of extensive medical treatment this would be very challenging and doubtful from ethical point of view. Nevertheless, substantial part of patients with Crohn's disease should be operated earlier in the course of their disease. Surgical resection as a treatment option is often overlooked, and consecutive courses of immunosuppressants are given with significant burden on quality of life.

Guidelines differ in their recommendations. The ECCO guidelines state that for severely active localized ileocecal disease not responding to conventional therapy infliximab should be considered, although surgical options should also be considered and discussed (15). The AGA practice guidelines states that surgery is advocated for neoplastic/preneoplastic lesions, obstructing stenoses, suppurative complications or medically intractable disease, suggesting that all medical options should have been tried before turning to surgery (16). Patients with obstructive symptoms due to fibrotic terminal ileum are best treated surgically since medication will have no effect. However, in clinical practice distinction between a fibrotic stricture and inflammatory stenosis may be difficult (17).

In conclusion, no evidence is available pointing to a specific strategy, although more long-term evidence is available on surgical treatment. At present, benefits and risks must be weighed carefully and discussed with the patient to decide which therapy path should be chosen. Participation of gastroenterologist and surgeon in the decision making is of paramount importance. Further trials are needed to be able to definitely answer the question which care modality is the better option?

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Gallbladder cancer – surgical treatment results after laparoscopic cholecystectomy

Blaž Trtotovšek*[1], Urban Stupan[2]
[1]*Department for the hepatobiliary and liver transplantation surgery, Department for abdominal surgery, University Medical Centre Ljubljana,*
[2]*Medical faculty, Korytkova 2, University of Ljubljana*
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ABSTRACT

Background: Better appreciation of the course and factors that influence incidental gallbladder cancer (iGBC) is needed to develop treatment strategies aimed at improved outcomes. The purpose of this study was to determine the impact of re-resection of iGBC on survival.

Methods: Patients undergoing radical re-resection for iGBC from January 2012 to December 2016 were analysed. Influence of variables (lymph node ratio, ASA grade, gender, adjuvant treatment, time interval between cholecystectomy and radical re-resection (in days), TNM stage and survival was assessed.

Results: Of 43 patients, 34 (31 female and three male patients; median age 73,5 years) underwent re-resection. Median duration between two surgeries was 52 days (range 12 –180). Primary procedure – cholecystectomy was performed laparoscopically in 29 patients with conversion rate of 20%. Among those with radical re-resection were 80% patients with pT2 tumour, all 3 with pT1b and 15% with pT3. Where only exploration was done more than half of the patients (5/9) had pT3 and others pT2 tumours at first procedure. During resection of segment 4b–5 and lymphadenectomy with or without resection of bile ducts average of harvested LN was 6,5 LN per procedure, but nine patients had less than 6 LN harvested. Lymph node metastasis was the single variable significantly influencing survival.

Conclusion: The most important predictor of survival is lymph node metastases. Not the delay in re-resection but the TNM stage is what that influences outcomes in IGBC.

*Blaž Trotovšek, MD, PhD
Department for the hepatobiliary and liver transplantation surgery, Department for abdominal surgery
University Medical Centre Ljubljana, Zaloška Cesta 7, 1525 Ljubljana, Slovenia
E-mail: blaz.trotovsek@kclj.si

INTRODUCTION

Gallbladder cancer (GBC) is a relatively uncommon aggressive malignancy with poor prognosis. Only 25% of patients will undergo potentially curative surgery, and just 16% will survive for more than five years. Surgical treatment has proven to be curative in some patients. Postoperative survival is so closely associated with pathologic tumour stage that resectional surgery has as much of a role as a staging modality as it does as a therapeutic endeavour. Current evidence shows that surgical approaches, margin-free resection rates and long-term survival differ completely between GBC and other bile duct malignancies, such as Intra- or extrahepatic cholangiocarcinoma. Therefore, GBC must be considered and treated as a separate entity (1).

Patients with symptoms of indigestion, pain, weight loss and jaundice or without them may be discovered to have a gallbladder mass with US or cross-sectional imaging. The majority of GBC patients who present with jaundice will have disseminated disease even if it is not detectable during preoperative workup.

Once identified, gallbladder masses are best evaluated by contrast-enhanced abdominal computed tomography (CT). CT it the most accurate modality to determine resectability because of its capacity to interrogate portal nodes, peritoneal implants and vascular invasion (2). Staging accuracy of CT may be augmented by contrast-enhanced magnetic resonance imaging (MRI, MRCP), which can provide more detailed evaluation of the hepatic ducts.

The presence of lymph node (LN) metastases in GBC is hard to determine preoperatively; and cross-sectional imaging (CT, MRI) is successful in 24% (3). If there is suspicion of advanced disease, endoscopic, percutaneous or laparoscopic biopsy should be performed before resection.

In patients with suspected or known GBC, 18-FDG positron emission tomography (PET)-CT has demonstrated the ability to detect occult metastases with sensitivity of 56% (4). Detection of clinically occult metastasis in patients with GBC is a contraindication for radical surgical approach (5). Following adequate staging to rule out distant metastases, unresectable regional nodal disease or local advancement to main hepatic vascular/biliary structures, medically fit patients should undergo surgical exploration.

In the absence of a preoperative diagnosis, needle biopsy with immediate frozen-section analysis is recommended before committing to radical resection. Staging laparoscopy, laparoscopic US and aortocaval LN frozen-section evaluation can prevent unnecessary surgical exploration in more than 60% of patients (6). Based on the high incidence of positive findings, staging laparoscopy is recommended before laparotomy for all instances of suspected or proven GBC.

GBC most commonly spreads from the gallbladder to the periportal and then to the aortocaval and coeliac LN stations. Long-term survival after resection has been reported in patients with involvement of the pancreaticoduodenal and hepatic artery LNs (N1), but there was no survival benefit in those with aortocaval and coeliac LN metastases (N2). Aortocaval LN sampling should be performed routinely at the initiation of the procedure (7,8). Although periportal regional LN (N1) involvement is not contraindication for radical resection, it is a very poor prognostic indicator (6). According to the recent perspective, minimally invasive surgery in oncologic GBC resection is not the standard of care. Oncological principles of adequate portal and aortocaval lymphadenectomy, R0 liver and common bile duct (CBD) margins are of utmost importance.

Patients with GBC limited to the wall of the gallbladder (T1b–2) are recommended to undergo radical cholecystectomy with en bloc resection of adjacent liver parenchyma. CBD resection is reserved for those cases where cystic duct margin is intraoperatively involved (9). Bile duct involvement has poor prognosis and is often associated with regional LN

involvement (10). In locally advanced GBC and with adjacent organ involvement (T3 or T4), the extent of the primary resection is debatable. When direct invasion of adjacent organs (duodenum or colon) without nodal involvement (T3) occurs, en bloc resection is advocated although it is not associated with improved long-term survival (9). Radical resections that included hepatectomy, CBD and vascular resection have been reported (9,11), but without prolongation of overall survival. Increased morbidity and mortality associated with extended surgical procedures are important factor in survival, and extended procedures should be reserved for medically fit patients after multidisciplinary discussion. Although R0 resection for GBC is associated with longer survival, stage and tumour biology are the most significant predictors of survival (10). Extensive lymphadenectomy (min 6 LN) and LN ratio has been shown to be an important predictor of survival after surgery (12). Positive regional LNs have negative influence on survival in GBC.

INCIDENTAL GALLBLADDER CARCINOMA

Incidentally discovered GBC after cholecystectomy presents a diagnostic and therapeutic challenge. Incidental GBC (iGBC) is reported in approximately 0.7% of patients undergoing cholecystectomy. The rationale for re-resection is based on the incidence of residual disease. Ability to gather additional staging information during workup is beneficial but the extent of disease and spread after first procedure are often not detectable. Overall incidence of residual disease varies according to T-stage of the primary tumour. In T1 tumours can be as high as 37.5%, 56.7% in T2 tumours, and 77.3% in T3 tumours. Incidence of residual disease in the liver bed and LNs is lower, ranging from 12% in patients with T1 tumours to 46% in those with T3 tumours (13). Current results of mainly observational studies indicate that complete resection of residual disease is associated with improved survival (14). A 5-year survival rate of 41% was reported in patients who underwent re-resection compared with only 15% in those who did not (15). The improved survival after R0 resection at re-exploration was not dependent regarding to the presence of residual disease (16). Re-resection has been associated with improved survival in both T2 and T3 tumours (15). In T1 stage there are two different groups of patients. Most authors agree that T1a tumours are adequately treated with laparoscopic or open cholecystectomy alone (survival 90–100%) (17). Re-resection of T1b tumours is today a standard of care although still debatable. Re-resection of T1b tumours is associated with improved 5-year survival of 87.5% against 61.3% in resected cases. The number of years gained was greatest in younger patients (18). Re-resection is therefore indicated for T1b, T2 and T3 incidentally discovered GBC. In preoperative workup CT or MRI are necessary, but the role of PET-CT is unknown since there is always inflammation which can lead to misconclusions. Thus, the role of PET-CT before re-resection surgery remains undetermined but is additional diagnostic tool with small impact on decision making (13% of patients), probably useful only when questionable or concerning features are apparent on CT or MRI (13).

Operative strategy in re-resection consists of staging laparoscopy, resection of port sites or previous incision, liver, bile ducts and lymphadenectomy. Before performing laparotomy at the time of re-resection, a staging laparoscopy may be performed. Up to 20% of patients with previously treated incidental GBC can be determined as unresectable due to distant disease during staging laparoscopy. Predictors of positive findings are T3 disease, a poorly differentiated tumour and positive margin at the time of original cholecystectomy. In these patients, laparoscopy should always be performed before exploration (19).

Port site resection is not supported by the literature. It is not associated with improved survival and was associated with higher complication rate such as incisional hernia (15%). Positive histology of port sites is associated with the peritoneal dissemination of primary tumour and has poor prognosis. Therefore routine port site resection is not indicated.

The incidence of LN involvement varies by T-stage, approximating 12%, 31% and 45% in patients with T1b, T2 and T3 tumours, respectively (13). Lymphadenectomy and radical resection was associated with improved survival in comparison with radical resection alone in patients with T1b and T2 tumours (20). It is recommended that at least six LNs should be removed for accurate staging (21). Biopsy of N2 LN may be used to tailor surgical approaches. LN dissection can be limited to the hepatoduodenal ligament, as extended LN excision (i.e. coeliac or aortocaval) is not associated with improved outcomes. Involvement of distant LN represents distant metastatic disease (22). The goal of the liver resection is to obtain an R0 resection (13). Major hepatectomy compared with a non-anatomic resection of the gallbladder bed or a formal segment 4b-5 resection has not been associated with improved survival but had higher complication rate (9). Resection with negative margins should be achieved.

Routine bile duct resection has repeatedly been shown to have no impact on survival but increases morbidity (9, 13). Therefore it should not be routinely performed. It is indicated in patients with positive cystic duct margin after cholecystectomy or when it is necessary during re-resection for achievement of negative margins. Allowing sufficient time for the resolution of portal inflammation following previous procedure often aids in the identification and preservation of common bile duct.

Timing of re-resection is still controversial issue. When GBC is discovered during primary procedure immediate resection should follow. If it is discovered after final pathologic examination, intensive workup for staging and re-resection should follow in T1b-T3 tumours. The optimal time interval for re-resection for incidentally discovered gallbladder cancer appears to be between 4 and eight weeks after the initial cholecystectomy (23). Time to re-resection was not confirmed as a predictor of survival in study of Fuchs et al. (15). Therefore re-resection should be performed early after primary procedure but after thorough diagnostic workup to exclude the patients who would not benefit from radical surgery.

PATIENTS AND METHODS

A retrospective analysis was performed of patients who were referred to the Department of Abdominal Surgery of the University Medical Centre Ljubljana with incidentally detected gallbladder cancer from January 2012 to December 2016. All operations were performed by or under the supervision of the consultant surgeons in the unit. Preoperatively, all patients were investigated with routine blood investigations, and tumour marker serum carbohydrate antigen 19–9 (CA 19–9). Preoperative evaluation also included contrast-enhanced computed tomography (CT scan) of the abdomen and pelvis and a review of the histopathology of the gallbladder specimen excised during the primary surgery (laparoscopic or open cholecystectomy) to determine the histological type. All patients (pT1b and above) with non-metastatic, locally resectable disease were offered surgical exploration with an intent to perform a radical re-resection. All patients had their pathology re-staged by the 7th Edition of the American Joint Cancer Committee TNM staging system for purpose of uniformity (24). Data, such as age, sex, duration between the primary cholecystectomy and the radical re-resection were recorded. The patients in this study span a period of 5 years. Postoperatively, patients were followed up at 3-monthly intervals for the first two years, then every six months for another year and then yearly. Statistical analysis was performed SPSS for Windows, 20th Edition.

RESULTS

Of 43 patients, 34 (31 female and three male patients) median age 73.5 years (range 47–84 years) underwent radical re-resection. Exploration without resection was performed in 21% of the patients.

Primary procedure

Cholecystectomy was performed laparoscopically in 29 patients with conversion rate of 20%. Open approach was chosen in 14 patients (33%). Patients had tumour stage T1b, T2 and T3 in 9%, 63% and 28% respectively. At least one LN was harvested in 70% and was positive in 10% of patients. 2 patients had pT3 tumour and one patient had pT2 tumour and positive LN on histological examination after primary procedure.

Preoperative workup

All 43 patients had CT scan performed preoperatively. In 10/43 (24%) patients residual disease was found on CT scan. Residual tumour in liver was found in 4 patients and regional LN in hepatoduodenal ligament larger than 10 mm in cross-section in 7. In 4 patients CT scan was not conclusive because pathological findings could be attributed to postoperative fibrosis or inflammation after previous procedure. When comparing CT staging and final histology of the specimen, CT staging was correct in 74%, overestimated the extent of residual disease in 6% and underestimated it in 20% of re-resected patients.

Re-resection

In 34 out of 43 patients who underwent exploratory laparotomy, re-resection was performed. 31 patients (72%) had successful R0 resection. In 3 patients R1 resection was performed, in 2 cases because of infiltration in the major vessel wall and in 1 in duodenum, where additional cephalic pancreatoduodenectomy was not performed because of advanced age. Median duration between two surgeries was 52 days (range 12 –184). Exploratory laparotomy was performed in 9 patients with median duration 49 days (range 12 –184). Reasons for abandoning of radical approach were distant metastases in 7 and local unresectability in 2 cases.

17 out of 34 patients underwent resection of segment 4b–5 and lymphadenectomy and another 13 patients had additionally resected common bile duct beside resection of segment 4b–5 and lymphadenectomy. In 4 cases, right Hemi hepatectomy in 2, right tri sectionectomy in 2 patients and one of them with additional cephalic pancreatoduodenectomy was performed.

Lymph node dissection of the hepatoduodenal ligament was performed in all 34 patients. Lymphadenectomy of celiac trunk and aortocaval LN was not performed routinely at the time of study and was extended to N2 nodes in only 45%. In average 9 LN (range 2-35) was harvested during re-resection. During resection of segment 4b–5 and lymphadenectomy with or without resection of bile ducts average of harvested LN was 6,5 LN per procedure, but in 9 patients less than 6 LN was collected.

Resection achieved complete tumour removal in 71,1% of all patients who underwent "intention to treat" procedure. After final pathology patients were classified according to TNM 7th ed. classification system. In stage, I were two patients, in stage II 17, in stage III 15 and stage IV 9 patients.

SURVIVAL

Out of 43 patients, only one has died (2.3%) on the 59th day due to the liver failure and sepsis after ALPPS procedure. Another seven patients had postoperative complications, mostly level 2 by Clavien-Dindo scale (CD), with majority requiring application of intravenous antibiotics. One of them had pulmonary embolism and was treated by heparin. We also had 1 level 4b CD complication due to haemorrhage, which needed surgical haemostasis. Overall, the morbidity rate was 20.9%, median hospitalisation time was seven days with an average time of 11.5 days.

Survival analysis till the 1st of April 2017 showed, that out of 34 patients who underwent re-resection 20 are alive (58.8%), 12 have died, and we lost track of 2. On one hand, 19 patients who were re-

operated less than 60 days following primary operation, 12 survived (63.2%) and on the other hand 6 out of 11 patients survived if being re-operated after 60 days (54.5%) but the difference was not statistically significant. We had 17 patients with stage I or II and 15 patients with stage III disease. In first group 15 patients survived (88.2%) and only five patients in second group (33.3%). When focusing on LN involvement on primary or secondary operation, 16 out of 21 patients with negative LN survived (76.2%) compared to 4 survivors out of 11 patients (36.4%) with positive LN.

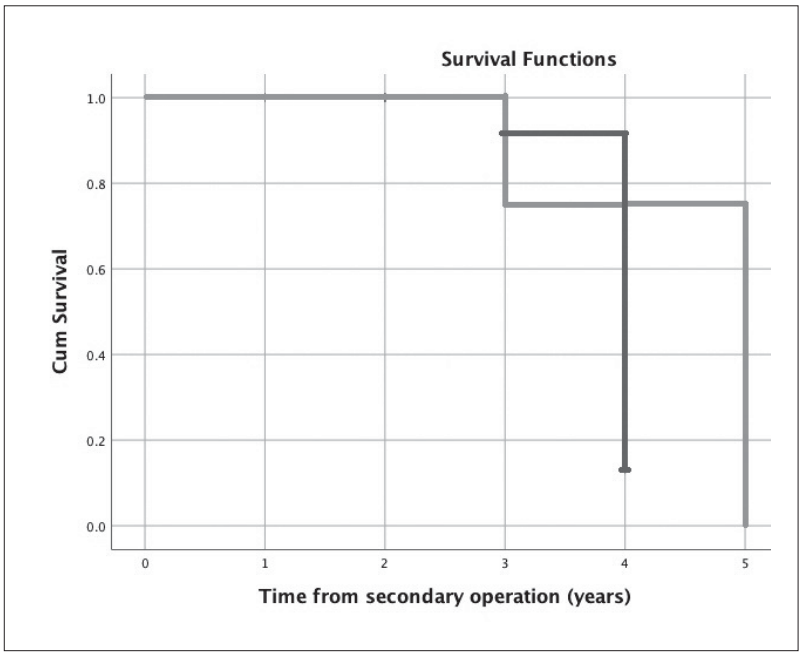

Figure 1. Patients who underwent re-resection within 60 days (n = 19) (blue) versus patients who had re-resection over 60 days (n = 11) (red) showed no benefits in survival rate (p = 0,193)

DISCUSSION

Cholecystectomy for gallstones is the second most frequent procedure in digestive surgery. Incidental GBC (iGBC) is going to become an increasingly common medical entity since it can be found in one of every 150 cholecystectomies performed (13). Cholecystectomy is a treatment of choice and oncologically adequate in Tis and T1a GBC. In case of iGBC radical re-resection has been advocated for other stages of disease. The aim of re-resection in incidental iGBC is definitive staging and when feasible, resection of the entire tumour. Mortality and morbidity of re-resection for iGBC should be as low as possible. GBC is more common in females (15) but the results of our study with female to mail ratio 9:1 were surprising. GBC is a disease of elderly. With median age of 73,5 years, we confirmed those findings. In the era of laparoscopy, it is interesting that one-third of primary procedures - cholecystectomies, were performed through open approach. We can speculate that there were probably some changes of gallbladder wall on US that convinced surgeon to use open approach. In these cases, additional workup, with tumour markers and CT, could change the diagnosis and would alter the course of treatment. High proportion of pericystic LN harvested during primary procedure is also consequence of frequent open approach in our study.

CT is the most accurate modality to determine resectability because of its capacity to interrogate portal nodes, peritoneal implants and vascular invasion (2). In preoperative workup CT or MRI are necessary. Since there are always sequel of previous procedure, in form of inflammation and fibrosis, imaging techniques may be misleading (13). Sensitivity of CT in our study was 74% which is comparable with the data from the literature (13).

Re-resection rate of 80% in our study is comparable with other published data (15,19), where 20% of patients considered being resectable after preoperative workup is nonresectable during staging laparoscopy or exploratory laparotomy. R0 resection was achieved in 91% of re-resected patients and 71% in whole group. All three patients with R1 resection had stage IIIb disease according to TNM 7th ed. classification. Re-resection consisted of resection of liver segments 4b, 5 and lymphadenectomy of various extents in 88% of

patients and additional resection of bile ducts was performed in 43% of them. More extensive re-resections were performed in 4 patients. Average of 9 LN procured at resection, was satisfying but in 25% of patients, lymphadenectomy did not reach the proposed threshold of 6 LN during re-resection. We found residual tumour in liver in 25% of patients, and LN invasion in 26.5% of the patients. Review of re-resection specimen increased stage of the disease in 32% of our patients. The presence of residual tumour was found to be a significant predictor of survival. Although many surgeons advocate routine resection of the common bile duct (CBD) at the time of curative resection (13,15), we confirmed the absence of improvement in the R0 resection rate. CBD resection was performed in 38%, and only two patients of 13 had histologically proven infiltration of CBD. Therefore routine resection of CBD is not recommended and should be done only when there is strong suspicion of infiltration on previous histology (positive margin at cystic duct) or CT. In Japanese study (25), the resected and unresected bile duct groups did not substantially differ regarding the 5-year cumulative survival and local recurrence along the hepatoduodenal ligament. We found that resection of CBD was important risk factor for postoperative morbidity as did other authors (25). Overall, we confirmed that radical re-resection in T2 patients offers a significant survival benefit over those who do not undergo radical re-resection. Survival in of patients in TNM stage I and II was better than in reviewed literature. Survival in stage III was poor (33,3%), and patients had often LN involved. Underestimation of TNM stage before resection is common finding. The present study confirmed the benefit of re-resection in the subgroup of T3 patients (5-year survival: 19% vs. 0%) with nine real survivors at three years. In the German registry, there was no benefit of re-resection in T3 patients, and none of the patients who underwent 4b-5 segmentectomy or wedge resection survived more than three years.

CONCLUSION

High rate of residual disease in liver bed and regional lymph nodes (LN) justifies re-resection, and it appears to have a beneficial effect in T1b, T2 and T3 patients. Modification in the surgical management of incidental GBC occurred. Bisegmentectomy 4b,five is recommended, but CBD resection is indicated only in selected cases. Regional lymphadenectomy with harvesting of at least 6 LN is recommended. Aortocaval and celiac LN are harvested for staging at the beginning of the procedure and should be used for tailoring of it. Although LN status and the presence of residual disease are associated with outcome, long-term survival can be achieved in a subset of these patients. Therefore, re-resection, which is still the only curative treatment, should be considered whenever possible, having in mind, that it is essential to achieve R0 surgical margins.

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Endoscopic treatment of patients with foreign bodies in the upper gastrointestinal tract - a retrospective study of the period 1994–2016

Pavel Skok*[1]
[1]*Department of Gastroenterology, Clinic for Internal Medicine, University Medical Centre Maribor*
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***Keywords**: foreign bodies, upper gastrointestinal tract, endoscopy, extraction, complications.*

ABSTRACT

Background: Foreign bodies in the upper gastrointestinal tract are rarely the cause of an urgent condition. The aim of the study was to determine the frequency of patients in which immediate endoscopic investigation revealed foreign bodies in the upper gastrointestinal tract and to evaluate the success of endoscopic extraction.

Patients and Methods: The retrospective study includes patients in which urgent endoscopic investigations of the upper digestive tract were performed in a 22-year period, 1st January 1994 – 31st December 2016.

Results: Altogether 12720 patients were investigated, 4970 (39,1 %) females and 7750 (60,9 %) males, mean age 62,5 years, SD±18,2 years, range 1–106 years. In 164 patients, 1,3 % of all subjects, females 48 (41,3 %), males 116 (70,7 %), true foreign bodies were detected (in range from 1–8) in the esophagus or stomach. In these patients a total of 230 endoscopic procedures were performed, in 95.7 % the foreign bodies were removed endoscopically (157/164 patients), in seven cases (7/164, 4,3 %) the endoscopic procedures were not successful. Among the foreign bodies removed were various metal or plastic objects: coins, keys, screws, hooks, batteries, razor blades, needles, parts of kitchen, toilet or writing utensils, lighters, buttons, toys, three toothbrushes as well as impacted safety pin. In patients with successful endoscopic removal of the objects, no significant complications were noted. In 11 patients (11/157, 7 %), hemorrhages from the region of the esophagogastric junction or stomach were observed, endoscopic hemostasis was performed in 9/11 patients.

Conclusions: In the analyzed period interventional endoscopy has proved successful in removing true foreign bodies from the upper gastrointestinal tract.

*Prof. Pavel Skok, MD, PhD
Clinic for Internal Medicine, University Clinical Centre Maribor, Ljubljanska 5, 2000 Maribor,
Medical Faculty, University of Maribor, Taborska 8, 2000 Maribor
E-mail: pavel.skok@ukc-mb.si

INTRODUCTION

Foreign bodies in the upper gastrointestinal tract are rarely the cause of an urgent condition (1). They can be »true foreign bodies,« different objects that accidentally enter the gastrointestinal tract, bezoars, commonly composed of hair, vegetable matter and food or medical prostheses (2,3). Foreign bodies are also classified as blunt and sharp-pointed objects, long objects, food bolus and others, like packets of illegal drugs (4). Unfortunately, we do not have epidemiological data on this problem for Slovenia, but an estimated 1500 deaths occur each year in the United States as a result of foreign body ingestion (5). In a Swedish study, the annual incidence of foreign body ingestion was confirmed to be 122 per million persons (5). About 80–90% of ingested foreign bodies pass the gastrointestinal tract spontaneously, in 10–20% impaction occurs and endoscopic or surgical removal is necessary. They usually enter the digestive tract during nutrition or by mistake. Certain groups, prisoners, and psychiatric patients tend to swallow them intentionally, alcoholics accidentally during acute intoxication, and young children who out of curiosity swallow smaller toys (6). Foreign objects most often lodge in the esophagus, the narrowest part of the digestive tube. Due to gastrointestinal obstruction, a typical clinical picture develops with acute dysphagia, odynophagia, sialorrhea and chest pain. Urgent removal of the foreign object impacted in the esophagus is indicated since serious; even life-threatening complications may occur as stated in the literature (3). The development of endoscopic instruments, video endoscopy and devices for endoscopic procedures in the last 20 years widened the scope of minimally invasive operative procedures in the gastrointestinal tract. Endoscopic retrieval is an important advancement in the management of foreign body impaction and has become the mainstay of treatment.

In the article, the author presents the analysis of effectiveness of emergency endoscopy in the removal of true foreign bodies from the upper gastrointestinal tract from a tertiary institution.

PATIENTS AND METHODS

In the retrospective study were included patients in which urgent endoscopic investigations of the upper gastrointestinal tract were performed in a 22-year period, from January 1st, 1994 till December 31st, 2016, at the Department of Gastroenterology and Endoscopy of University Clinical Centre Maribor. In 1993, a 24-hour endoscopic service was organized at our institution, with an endoscopic team consisting of a doctor and a nurse at all times. Patients data were obtained from the database MEDIS (Medical Information System) of the institution. All included patients had urgent endoscopic investigations of the upper gastrointestinal tract performed. Patients or their representatives signed the informed consent before the procedure. Most endoscopic procedures were performed in an outpatient setting. Prior to the procedure patients received butylscopolamine 20 mg/ml (Buscopan, Boehringer Ingelheim) intravenously and a local anesthetic lidocaine as a 10% aerosol (Xylocaine, Astra), usually 1–2 sprays orally, some also received an individually titrated dosage of midazolam intravenously (Dormicum, Hoffmann-La Roche) and an antidote flumazenil (Anexate, Hoffmann-La Roche) at the end of endoscopy. In the period 2002–2004 the use of the local anesthetic, lidocaine was suspended, due to reports of adverse effects in the literature. During endoscopy, all patients had their vital signs monitored with an electrocardiography (ECG), noninvasive measurements of blood pressure and pulse oximetry. In cases of endoscopic procedures in children, a pediatrician or an anesthesiologist were also present, for premedication, sedation or anesthesia. Since 2010, pediatricians themselves perform these endoscopic procedures. After foreign-body extraction, we endoscopically evaluated possible mucosal damage. Adult patients were observed for 6–8 hours at endoscopy unit, but children were hospitalized for observation on the pediatric ward. In the first period 1994 – 2001, all investigations were performed with flexible endoscopic instruments Olympus, in the period 2001 – 2014 with endoscopic TV system EVIS (Endoscopic Video Information

System, CLV U20, Olympus Optical, Hamburg GmbH) and since 2015 with HD (High Definition) video endoscopy system Olympus. For foreign body extractions, original instruments of the equipment manufacturer were used: different types of snares, retrieval nets, baskets, retrieval graspers and grasping forceps. In case of hemorrhage epinephrine solution (1:10000) was used for endoscopic hemostasis, since 2010 also hemostatic clips.

STATISTICAL ANALYSIS

For statistical analysis, the statistical program SPSS (Statistical Package for Social Sciences, version 21.0) was used.

RESULTS

In the analyzed period, 12720 patients were investigated, 4970 (39.1 %) females and 7750 (60.9 %) males, mean age 62.5 years, SD±18.2 years, range 1–106 years. In 164 patients, 1.3 % of all subjects, females 48, males 116, true foreign bodies were detected (in range from 1–8) in the esophagus or stomach. In these patients a total of 230 endoscopic investigations were performed, in 95.7 % the foreign bodies were removed endoscopically (157/164 patients), in seven cases (7/164, 4,3 %) the endoscopic procedures were not successful.

More often, in 98 patients (98/164, 59,8 %), foreign bodies were found in the esophagus, and in 66 patients (40,2 %) they were lodged in the stomach. In these patients, 230 endoscopic procedures were performed all together. Foreign bodies were endoscopically removed in 157 patients (157/164, 95,7%), in 7 cases (7/164), 4,3 % we were not successful. Four patients had to be treated surgically, one prisoner twice, two patient were lost from follow-up. In one patient the ingested foreign body passed the gastrointestinal tract spontaneously.

The highest number of foreign bodies found in stomach was 8; they were metal and plastic objects intentionally ingested by a convict. The longest foreign body was an 19-cm long toothbrush swallo-

*Figure 1. Part of the true foreign bodies found and extracted from the upper gastrointestinal tract during emergency endoscopy. (*The ruler only illustrates the dimensions of the objects.)*

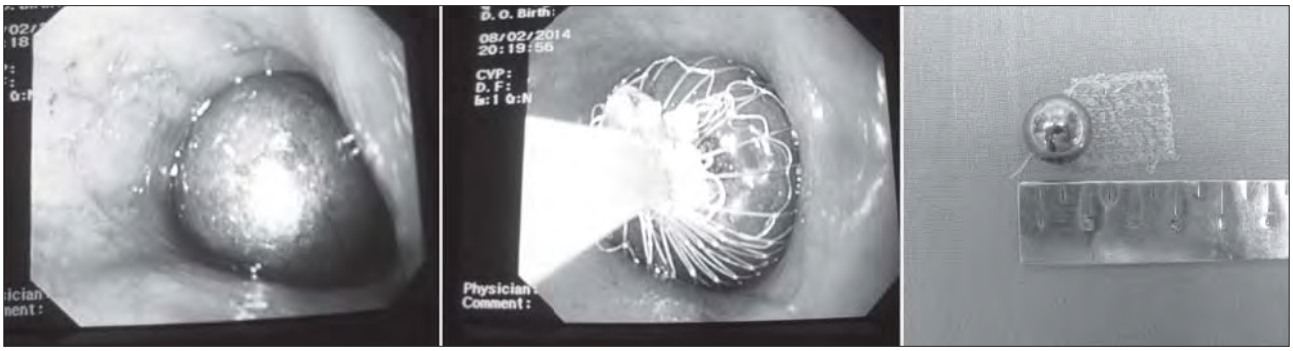

Figure 2. a, b, c. A 10 mm large metal marble impacted in the esophagus and the removal with a retrieval net in a 8-year-old child by the author.

wed by a drunk young woman trying to induce vomiting. The youngest patient was a 1-year-old boy who swallowed a safety pin. We retrieved all kinds of metal and plastic foreign objects: coins, keys, screws, batteries, razor blades, parts of kitchen, toilet and writing utensils, lighters, buttons, toys and three toothbrushes (Fig 1. and. Fig. 2 a, b, c). In patients with successful endoscopic removal of the objects, no significant complications were noted. In 11 patients (11/157, 7 %) mild hemorrhages from the region of the esophagogastric junction and stomach were observed. In 5 patients hemostasis with epinephrine solution (1:10000) was needed in 4 patients hemostatic clips were placed, in 2 patients bleeding stopped spontaneously. The most important results of this analysis are shown in Table 1.

DISCUSSION

Foreign bodies in the upper gastrointestinal tract are rarely the cause of an urgent condition. They can be found anywhere throughout the gastrointestinal tract, most often in the esophagus and the stomach, seldom in the small and large intestine or the anus (3, 7–10). Esophagus is the proximal and the narrowest part of the digestive tract. The most common sites of foreign body impaction are at the physiological narrowings and the pathological strictures. First such area is at and just distal to cricopharyngeus, second is at the level of the aortic arch, third is at the level of tracheal bifurcation, and last is at the esophagogastric junction or the lower esophageal

Table 1. Foreign bodies extracted during emergency endoscopy in the period (1994–2016)

Patients with foreign bodies in the upper gastrointestinal tract: number (%)	**164 (1,3 %)**
Av. age of patients (in years, ± SD)	**48,3 (± 25,5)**
Sex: male/female	**116/48**
Location of the foreign bodies esophagus: number (%) - upper esophagus - mid esophagus - distal esophagus stomach: number (%)	**98 (59,8)** **17/98 (17,3)** **28/98 (28,6)** **53/98 (54,1)** **66 (40,2)**
Longest foreign body (toothbrush) - cm	**19,5**
Largest number of foreign bodies - stomach	**8**
Sedation/anesthesia used during endoscopy: number (%)	**58/164 (35,3)**
Efficacy of endoscopic removal: number (%)	**157/164 (95,7)**
Average number of endoscopic procedures (per patient)	**1.4** [1]
Complications (bleeding) following endoscopic procedures: number (%)	**11/157 (7)**
Surgery: number (%)	**5/164 (3)**

[1]*This number does not include control endoscopy performed to evaluate possible mucosal injuries immediately after foreign body extraction.*

sphincter (10). In patients, pathological stenosis are most often the result of progressive gastroesophageal reflux disease (reflux esophagitis stage C or D), embryonal developmental anomalies or other organ changes as fibrotic rings (Schatzky ring), mucosal foldings or diverticula. The most frequent diverticula are Zenker's diverticulum in the proximal part of esophagus and parabronchial and epinephrine diverticula (5,10). Other areas of foreign body impaction in the digestive tract are duodenum, ileocecal valve, Meckel's diverticulum and anus (4–6).

Foreign bodies enter the digestive tract during nutrition, by mistake or due to curiosity in children. Certain groups like convicts ingest them intentionally, we often find them in the digestive tube of psychiatric patients or alcoholics (11). They usually swallow them during acute alcoholic intoxication. A rare form of eating disorder in psychiatric patients is »pica« (Latin for magpie), characteristically they swallow bizarre materials like parts of plastic, fabric, plaster or coal (7). A unique problem of "foreign bodies" represent packets of drugs transported by people for smuggling, the so-called "mule." This is often done using a mule's gastrointestinal tract or other body cavities (rectum, vagina) as containers. Swallowing has been used for the transportation of heroin, cocaine, and MDMA (3,4-methylenedioxymethamphetamine), ecstasy (11). Children ingest foreign bodies, smaller parts of toys, like marbles, while playing (3, 5). Most ingestions occur in children younger than five years of age, who out of curiosity swallow colorful smaller toys or parts of toys. A variety of articles may be ingested: parts of kitchen utensils, spoons, forks, needles, thimbles, pieces of wire, razor blades - usually broken in half, coins, batteries, buttons, toothbrushes, nail clippers, hairpins, rings, safety pins, screws, nuts and many others (2, 5, 10). In elderly loose or broken dentures, poorly chewed or undigested food can present »foreign bodies.« Complications, as perforation of gastrointestinal wall, regularly occur with impacted chicken or fish bones, and complications after ingestion of toothpicks or sharp, metal objects have also been described in the literature (11). According to the latest ESGE (European Society of Gastrointestinal Endoscopy) recommendations emergent, preferably within 2 hours, but at the latest within 6 hours, therapeutic upper endoscopy for foreign bodies inducing complete esophageal obstruction, and for sharp-pointed objects or batteries in the esophagus is mandatory. Especially in the Far East (Japan, China, Korea, Hong Kong) impacted fish bones may cause complications due to dietary habits (10). During different medical procedures or interventions ruptured tubes, dental instruments, drills, endoprostheses and surgical instruments may lodge in the digestive tract. Some authors include in this group of foreign objects surgical sutures that do not reabsorb as they can cause inflammation or even ulcerations of the gastrointestinal mucosa (11).

Foreign bodies we rarely encounter in our population of patients are trichobezoars, phytobezoars and phytol trichobezoars, conglomerates composed of different substances in the stomach (7). The name bezoar from Arabic »bad her« and Persian »pad air« means antidote. Trichobezoars, or hairballs, consist of ingested hair or nails and are commonly found in younger women. Fruits like peaches, apricots or cherries, also oranges, figs, dates, coconuts, peanuts, and cabbage may predispose to formation of phytobezoars. They occur especially in individuals with hypomotility of the stomach and impaired gastric emptying, after vagotomy or partial gastrectomy. Patients who have undergone a Billroth type I gastrectomy seem particularly prone to bezoar formation (3, 7). In the literature lately recognized types of bezoars are lactol bezoars derived from milk products, and concretions composed of medicines, sand, cement or even chewing gum (8). Lactobezoars are primarily found in low-birthweight infants fed a concentrated formula partly consisting of milk products. In the neonates, gastric emptying and motility may also be impaired. Numerous medications, primarily antacids, aluminum hydroxide, cholestyramine, sucralfate, slow-release theophylline, long-acting nifedipine, enteric-coated aspirin and others, have been implicated in the formation of bezoars (3, 10).

Endoscopy is the most effective method for foreign-body removal from the upper gastrointestinal tract (5, 8–10). Technological advancements of flexible endoscopes, video endoscopy and instrumental accessories for manipulation have facilitated wider use and high success rate of the method. Those accessories include magnets, different retrieval forceps, Dormia-type baskets, specially designed nets and polypectomy snares. During preparations for endoscopic removal of a foreign body, we must take into consideration the form and type of the object, number, and size, anatomical circumstances of the digestive tract, where the foreign body is lodged and experience and skills of the endoscopic team (4, 5, 9, 11). Some foreign bodies, like button batteries, are potentially dangerous because of corrosive and toxic actions due to disintegration through stomach acid, others sharp-pointed objects (like pieces of wire, screws, nails) can cause severe, life-threatening complications while passing through the alimentary tract. They mostly cause mucosal edema, bleeding, pressure necrosis and ulcers, perforations, fistula formation, abscesses or inflammation, mediastinitis or peritonitis (6). These complications may occur during endoscopic extraction, or the foreign body may slip and cause obstruction of the airway. Complication rate can be significantly reduced by using appropriate safety measures as overtures, transparent cap or latex rubber hood while retrieving sharp objects (6, 9, 11). The author has in the past described the use of Sengstaken tube in the removal of sharp bone from the esophagus. The inflated tube expanded the lumen of the esophagus and released the impacted bone (9).

As our data show, we achieved a 95% success rate at urgent foreign body extraction from esophagus and stomach. Included were only "true foreign bodies," not food boluses, retained sutures or bezoars. Our results are comparable with data from the literature, although certain specialized endoscopic units have a success rate of up to 99 % with a complication rate of 0.2–0.4% (5, 10, 11). The effectiveness of procedures depends on skills of the endoscopic team, modern equipment, number of all endoscopic procedures and the percentage of successful extractions. Meticulous preparation, patient and competent execution of the procedures resulted in a low complication rate in our study. Relevant literature describes serious, even life-threatening complications of endoscopic manipulations, perforation of the gastrointestinal wall being the commonest (11).

Extraction of impacted foreign objects requires not only prudence but often imagination. For sedation, authors recommend different drugs, mostly from benzodiazepine group like midazolam or diazepam, and as analgesics pethidine or pentazocine; after the procedure antagonists flumazenil and naloxone are used respectively (12–15). In recent years some endoscopic centers prefer propofol and ketamine (from the group of hypnotics and sedatives), piritramide, fentanyl, remifentanil and alfentanil (opioid analgesics) and nonsteroidal anti-inflammatory drug (NSAID) metamizole. The choice of sedatives and analgesics is influenced by the duration and type of endoscopic procedure and whether the procedure is done in a hospital or an outpatient setting (16–18). Particularly in children with a foreign body impacted in the middle or lower third of the esophagus some investigators recommend glucagon intravenously to induce relaxation of the esophageal smooth muscles. It facilitates the extraction of the lodged object (19). Unfortunately, glucagon has side effects, nausea, and vomiting in particular. When the impacted object is in place longer than 24 hours in young children endotracheal intubation and endoscopic removal under general anesthesia is advised (20–22).

The author has already pointed in the past to a major problem: prisoners who repeatedly ingest foreign bodies or ingest many at once (19). Some of them refuse endoscopic extraction and demand surgical treatment because they can stay longer in hospital. One patient from this study was a prisoner who had ingested six metal objects at the same time and has repeatedly been returning to our endoscopic unit. He

had two surgical interventions with foreign bodies extraction from stomach in the span of few weeks. Thus a choice of the most appropriate treatment no longer remains only a medical debate but more and more an ethical and legal dilemma (23,24).

CONCLUSION

Interventional endoscopy is the most effective method for foreign body extraction from upper gastrointestinal tract. Various factors affect the success of the procedure, the more important being adequate endoscopic equipment and the experience and skills of the endoscopic team. The introduction of video endoscopy and technological development of different devices for endoscopic procedures enabled the effective cooperation of the whole team for complex interventions in emergency settings.

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Review article

Pancreas Physiology and Pathophysiology in Tissue Slices

Andraž Stožer*[1]
[1]*Institute of Physiology, Faculty of Medicine, University of Maribor*
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***Keywords**: Pancreas, tissue slice, exocrine, endocrine, acinus, islet of Langerhans, acinar, beta cell, physiology, pathophysiology, pancreatitis, diabetes mellitus.*

ABSTRACT

Pancreas is a bifunctional gland, with the exocrine part playing an essential role in absorption of energy-rich nutrients and the endocrine part coordinating their assimilation and use. During the last half century, many aspects of normal pancreas physiology, as well as pathophysiological mechanisms, have been described into some detail. The advances in understanding have been catalyzed by development of experimental approaches to studying exocrine and endocrine cells in their normal tissue context. In this paper, the role of the pancreas tissue slice technique in studying normal and pathological pancreas function is described into some detail, together with its translational relevance in understanding human diseases of the pancreas, such as pancreatitis and diabetes mellitus.

FUNCTIONAL ANATOMY OF THE PANCREAS

Both structurally and functionally, pancreas consists of two tightly interrelated compartments, the exocrine acinar and ductal cells that make up roughly 95–99 % of parenchyma, and the endocrine islets of Langerhans that make up the remaining 1–5 % [1, 2]. Islets of Langerhans are spheroid microorganism (50–500 μm in diameter), composed of glucagon-secreting α cells (30–40 % in humans, 10–20 % in mice), insulin-secreting beta cells (50–60 % in people, 60–80 % in mice), somatostatin secreting δ cells (<10 % in humans and mice), pancreatic polypeptide-secreting PP or γ cells (<5 % in humans and mice), and of a few ghrelin-secreting cells [3]. Insulin regulates proper distribution of energy-rich nutrients between tissues and extracellular space including blood plasma in all possible nutrition regimes [4, 5]. The higher three-dimensional organization of beta cells with a range of homo- and heterotypic contacts between cells seems crucial for the proper functioning of beta cells since dispersed beta cells display a decreased capacity to produce and secrete insulin [6]. The exocrine pancreas consists of lobes, each of which contains several smaller lobules (1–10 mm in diameter in humans). Each lobule is a single glandular unit draining into a single duct lined by ductal cells. Finally, each lobule is composed of acini that drain into intercalate ducts, several of

*Andraž Stožer, MD, PhD
Institute of Physiology, Faculty of Medicine, University of Maribor, Taborska ulica 8, 2000 Maribor, Slovenia
E-mail: andraz.stozer@um.si

which join to form an intralobular duct [1, 2]. In contrast to islet cells which secrete their protein products into the portal blood to regulate energy homeostasis, acinar and ductal cells secrete their protein products, together with ions and water, into the ductal tree that finally converges to one or two main ducts that empty into the duodenum. The enzymes in the secreted fluid (e.g., proteases, lipases, and saccharides) play a crucial role in decomposing complex energy-rich nutrients, such as proteins, lipids, and saccharides, into elementary units for absorption into the portal blood [2].

PHYSIOLOGY AND PATHOPHYSIOLOGY OF ISLETS OF LANGERHANS AND ACINAR CELLS

Studying physiology and pathophysiology of cells of the endocrine and exocrine pancreas is of relevance to understand some human diseases, most importantly diabetes, insulinoma and other functional endocrine tumors, pancreatitis, and pancreatic carcinoma. Due to less biological variability, predictable accessibility, easy maintenance, and a high degree of structural and functional similarity to human tissue, the mouse pancreas is most commonly used as a model to study endocrine (predominantly beta cell) and exocrine (path)physiology [1]. In mouse islets of Langerhans, beta cells are electrically excitable and seem to be electrically coupled into a single functional syncytium. They respond to energy-rich nutrients (absorbed from the gut), as well as neurohormonal inputs, with a secretory response in a coordinated and oscillatory manner. Oscillations in the beta cell syncytium occur on two different time scales. Slow oscillations with a period of several minutes are believed to underlie the pulsatility in plasma insulin, whereas fast oscillations with a period of several seconds to tens of second, superimposed on the slow pattern, are currently believed to set the amplitude of the slow plasma insulin oscillations [7]. The oscillatory behavior of crucial parameters within beta cells might be crucial to prevent excitotoxicity, regulate expression of genes, and maintain a proper sensitivity of the exocytotic machinery to calcium ions, whereas at the level of the whole organism, pulsatility in plasma insulin ensures a higher level of sensitivity of target tissues (liver, skeletal muscle, adipose tissue) compared with non-oscillatory insulin elevations and changes in the ordinary pattern of plasma insulin temporal behavior are an early marker of insulin resistance and diabetes mellitus [7–9]. Thus during the fast oscillations, in individual beta cells within mouse islets of Langerhans, after stimulation, membrane potential and intracellular calcium concentration ($[Ca^{2+}]_i$) oscillate in phase [10, 11] to ensure an oscillatory secretion of exocytotic granules containing insulin [12]. Coordination of signals between individual beta cells can be brought about using depolarization waves spreading across the beta cell syncytium matched by waves of intracellular calcium increases [10, 13]. In insulinoma, the secretory response is autonomous and decoupled from the stimulatory input, which leads to hypoglycemia presenting with the Whipple´s triad of symptoms and can potentially be fatal [14]. In type 1 diabetes mellitus, beta cell mass and thus the secretory response are diminished due to autoimmune destruction, whereas in type 2 diabetes mellitus, the lack of insulin is relative, due to a combination of insulin resistance and beta-cell dysfunction [15, 16]. The latter might present itself in many different ways, an important one being that the ability of beta cells to communicate via gap junctions is diminished [17, 18]. Acinar cells are not classical electrically excitable cells, and in contrast to beta cells that are electrically excitable by glucose and some other nutrients, they rather respond to secretagogues which bind to membrane G-protein-coupled receptors, e.g., acetylcholine and cholecystokinin. Also in acinar cells, cytosolic calcium is the key secondary messenger that couples the neurohormonal input to secretion of zymogen granules and its concentration increases upon stimulation in a non-trivial oscillatory manner [19], predominantly at the apical pole where the zymogen granules are located [20, 21]. Of note, also acinar cells within individual

acini seem to be functionally coupled, and the mechanistic substrate for this coupling as well as its role in diseases of the exocrine pancreas remain to be fully elucidated [22]. A more global or even non-oscillatory calcium increase due to hyperstimulation or non-physiological stimulation of acinar cells is believed to lead to an aberrant activation of zymogen granule contents and their secretion at the basolateral side of the plasma membrane, a process which is thought to play a crucial role in the pathogenesis of pancreatitis [23–25].

METHODOLOGICAL ADVANCEMENTS IN THE FIELD

The endocrine and the exocrine physiology of the pancreas had first been studied on cell lines or acutely dispersed beta and acinar cells [26]. Upon advent of successful isolation techniques, intact isolated islets [27–29] and acini have become the method of choice due to improved morphological and functional phenotype in both islet [26] and acinar cells [30]. An even more detailed physiological assessment of beta cells and acinar cells in a yet more physiological environment has become possible with the introduction of the acute pancreas tissue slice technique in 2003 by Speier and Rupnik [31]. The development of this technique has been inspired by the brain tissue slice technique to study the electrical properties of neurons [32] and the neuroendocrine tissue slice techniques to study *in situ* the function of the pituitary [33] and the medulla of the adrenal gland [34]. The main advantage of slices is that the cellular context of the tissue with the cell-cell contacts and also paracrine modes of interaction, that are of great importance in the above types of tissue, are well preserved [5]. The pancreas slice technique requires that the ductal tree of the gland be injected with a low melting point agarose to ensure an easier manipulation of the tissue and stability during slicing. Compared with the isolation of acini and islets, slicing does not involve any enzymatic digestion of the tissue, whereas the endogenous enzymes from the exocrine part are diluted and inactivated by low temperatures employed during preparation [13, 31]. Successfully combining this method with electrophysiological recordings [4, 31, 35–37], large scale membrane potential [10], $[Ca^{2+}]_i$ [4, 13], and exocytosis [4, 38–40] measurements has advanced our understanding of function of both acinar [26, 39, 41] and beta cells [10, 13, 42] at the cellular level, as well enabled application of advanced analytical methods from the realm of complex network theory to understand the function at the higher, multicellular level of organization [18, 43, 44]. Recently, transplantation of islets of Langerhans into the optically easily accessible anterior chamber of the eye has been introduced as a method to study islet physiology *in vivo* [45, 46]. A similar approach for studying exocrine pancreas physiology will arguably be more difficult to develop [47].

THE SIGNIFICANCE AND POSSIBILITIES TO STUDY HUMAN PANCREAS PHYSIOLOGY

Some studies in the last few years have shown that in contrast to mouse islets, the human islets possess a somewhat different topology, with beta cells being interspersed with non-beta cells much more frequently than in mouse islets [48]. This may have repercussions for the communication between individual beta cells within a given islet of Langerhans. It remains controversial whether the human islet of Langerhans functions as a syncytium in terms of intercellular signaling and whether the membrane potential, $[Ca^{2+}]_i$, and exocytosis are synchronized between individual beta cells within an islet of Langerhans. Results of the handful of studies conducted over the last 20 years point to the whole range of possibilities. Namely, it has been reported that during stimulation with glucose, $[Ca^{2+}]_i$ signals in individual beta cells within human islets of Langerhans are (i) non-oscillatory (i.e., phasic) [49], (ii) oscillatory but not synchronized [18, 48], (iii) oscillatory and synchronized in smaller clusters comprising a few beta cells [50], but also that $[Ca^{2+}]_i$ signals are (iv) synchronized

across whole islets [51]. Important technical drawbacks strongly limiting our ability to draw definite conclusions are the wide variability of sources used for obtaining human tissue, as well as differences in glucose concentrations used for stimulation, transportation times, culture duration and conditions in preparing isolated islets for physiological recordings that, in the best case scenarios, allowed only a partial assessment of beta cell network properties [18, 48, 50, 51].

The differences between rodent and human islets are pertinent for understanding the etiopathogenesis of diabetes mellitus, since genetic as well as environmental factors may influence the beta cell network in a species-specific manner. The main aims of future endeavors to studying human beta cells function are therefore (i) to characterize the behavior of beta-cells in human islets of Langerhans from non-diabetic (normal) subjects, (ii) to compare it with the behavior of beta cells in islets from diabetic subjects, as well as (iii) to assess and quantify the structural and functional differences between human and mouse islets of Langerhans. Finally, (iv) attempts will have to be continued to establish glucose- and secretagogue-responsive human beta cell lines [52, 53] and to study the transdifferentiation potential of human endocrine and other parenchymal cells (e.g., ductal epithelial cells) functioning as a renewable pool of beta cell progenitors [54, 55].

Similarly, a number of structural and possibly functional differences between humans and mice have been reported for the exocrine part of the gland and these are of great translational importance when it comes to understanding pathophysiology of pancreatitis and other disorders in humans [1, 2]. As for beta cells, (i) normal physiology of acinar and possibly ductal cells will have to be addressed, together with (ii) the comparison with samples from individuals with pancreatic disease, the (iii) interspecies comparison, and (iv) further studies of the regenerative potential of the exocrine pancreas.

Fortunately, an armamentarium of experimental approaches is at hand to address the above issues. In the near future, isolated human acini, isolated and transplanted human islets, and human pancreas tissue slices obtained during pancreatectomy or from brain-dead donors, in conjunction with electro- and optophysiological approaches, modern tools to track exocytosis, such as biosensor cells and extracellular fluorescent dyes, as well as biochemical assays and genetic tools will conceivably play the main role in advancing our knowledge of pancreas physiology and pathophysiology.

CONCLUSIONS

The acute tissue slice method has proven valuable in validating findings obtained using less physiological preparations, such as dispersed cells, isolated acini, and islets, in discovering some novel aspects of endocrine and exocrine pancreas physiology and pathophysiology, and holds promise to be translatable to human tissue. Testing some of the key findings obtained in mice also on human tissue is important not only from the point of view of a developmental and comparative biologist and basic physiologist, but especially to understanding basic mechanisms of human pancreatic diseases. This shall facilitate the development of novel screening and diagnostic methods help reveal new pharmacological targets and test them in a translationally relevant *in vitro* model.

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Review article

Electrochemotherapy in hepatocellular cancer – alternative or definitive solution

Mihajlo Đokić*[1], Žan Čebron[2], Urban Stupan[2]
[1]*Department for the hepatobiliary and liver transplantation surgery, Department for abdominal surgery, University Medical Centre Ljubljana*
[2]*Medical faculty, University of Ljubljana, 1000 Ljubljana.*
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ABSTRACT

Incidence of hepatocellular carcinoma (HCC) is rising across the world. Patients with primary liver tumors can be treated radically with liver resection of the tumors and liver transplantation. When radical treatment is not indicated due to patient condition or tumor extent, some ablative therapy can offer the patients hope for longer survival. Patients, in whom those methods are not recommendable, have a stage C disease suitable only for palliative treatment. Therefore, for the treatment of patients with HCC with electrochemotherapy, a clinical trial was created at our institution.

ELECTROCHEMOTHERAPY

Electroporation is a method, where externally delivered electric field induces a sufficiently large transmembrane voltage, which creates membrane pores and therefore facilitates the entrance of different molecules into the cells. Sufficient drug accumulation in cells is one of the most important underlying mechanisms responsible for effective treatment (1–3). Electroporation can be used for delivering non-viral genes, called gene electrotransfer (4), or for poorly or non-permeant, but highly effective cytotoxic chemotherapeutics, called electrochemotherapy. Electrochemotherapy is a treatment where reversible electroporation facilitates hydrophilic drugs (5, 6), such as bleomycin or cisplatin, entrance into the cells, thus increasing their cytotoxicity locally and decreasing toxic systemic side effects of the drugs (7). The use of bleomycin is based on the clinical evidence showing that among other drugs tested; it has the highest potentiation of cytotoxicity by electroporation (up to several 1,000 times). Electrochemotherapy also has two distinct vascular effects. Since the exposure of tumors to electric fields predisposes stromal cells to drug uptake, it also affects endothelial cells of tumor vessels. This action leads to endothelial cell death (apoptosis) and consequently to abrogation of tumor blood flow. This is vascular disrupting effect (8), whereas in tumors, the vasoconstriction, was demonstrated and confirmed on

*Mihajlo Đokić, MD
Department for the hepatobiliary and liver transplantation surgery, Department for abdominal surgery, University Medical Centre Ljubljana, Zaloška Cesta 7, 1525 Ljubljana, Slovenia
E-mail: mihajlo.djokic@kclj.si

normal and tumor vessels by intravital microscopy (9). There are only a few papers showing feasibility and safety of electrochemotherapy on deep-seeded tumors such as colorectal liver metastases or liver tumors in general. One of them is the study of Edhemović et al. where besides proving safety and feasibility of electrochemotherapy as prime objective, its efficacy as a secondary objective in the treatment of colorectal liver metastases was demonstrated. The purpose of this article is to discuss whether ECT is alternative or definitive solution in treatment of patients with HCC.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) represent the biggest part of heterogeneous group of primary liver tumors (PLT). PLT are group of tumors that arise from liver cells. HCC, arising from hepatocytes, is the most common and represents more than 90% of all primary liver tumors, which together with intrahepatic cholangiocarcinoma represent 98.5% of all.

HCC is the 6th most common cancer in the world, and they are the 3rd most common cause of cancer-related death. Throughout the world, each year more than 700,000 new cases are diagnosed, and more than 600,000 deaths are attributed to HCC (10). The incidence of HCC is rising worldwide with the majority of the new cases in Asia and Africa, affecting more males than females by a factor of 2.5. The incidence is also increasing in the developed world and has tripled in USA in the last two decades. In Slovenia, incidence is 9.3 for males and 4.6/ 105 for females. The most common cause for developing HCC is infection with hepatitis B/C virus and cirrhosis. Other etiological factors include aflatoxins, alcoholic hepatitis, not-alcoholic fatty liver disease, autoimmune hepatitis, hemochromatosis, alpha-1-antitrypsin deficiency, Wilson's disease, Budd-Chiari syndrome (11) and use of anabolics.

TREATMENT OPTIONS IN HEPATOCELLULAR CARCINOMA

The treatment options for patients with primary liver tumors are surgery (including liver transplantation), radiofrequency ablation (RFA), irreversible electroporation, microwave ablation, embolization (TACE), targeted therapy and chemotherapy. Almost all patients through the course of the disease receive some combination of treatments, depending on the disease stage. That is the reason for numerous staging systems being used worldwide and all of them are trying to determine the best treatment option for each patient. The right treatment options depends on the following: location, number and size of tumors; quality of liver parenchyma, cirrhosis or absence of it and when present, the stage of cirrhosis. Other important factors to consider include age, general health and patients concerns about treatment and possible side effects. In Europe, BCLC (12) classification is commonly used for staging and treatment planning for HCC, whereas patients listed for liver transplantation are based on Milan criteria (13).

As mentioned, resection is the first line of treatment for patients with HCC in cases with solitary lesion or in patients with multi-focal tumors inside of Milan criteria or in case of mild portal hypertension in patients not suitable for liver transplant, although it is debatable, because such patients could benefit from other locoregional therapies, avoiding the risk of surgery and of liver decompensation after surgery. Radiofrequency ablation (RFA) and ethanol injection (EI) are the standard treatments for patients not suitable for surgery. RFA is recommended for small lesions up to 3cm, with the probability of complete necrosis for small tumors, (< 2 cm) away from large vessels, which progressively decreases with the increase of tumor size. TACE is the recommended treatment for BCLC stage B multinodular, as well for symptomatic tumors without vascular invasion or extrahepatic spread. Drug-eluting beads have similar efficacy to gealfoam-lipiodol with probably less adverse events.

An alternative to TACE is radioembolization. Regardless to progress that was made in the treatment of patients with primary liver tumor in the last two decades, a large number of patients never gets intent to cure treatment.

Curative Treatments of HCC

Surgical resection and liver transplantation are the only curative options available for HCC, with 5-year survival rates of 36–70 % and 60–70 %, respectively. Factors precluding surgery include stage of underlying cirrhosis, impairment of liver function, extrahepatic metastases of HCC, vascular invasion, high-risk anatomical location, excessive size or number of lesions, insufficient remnant of the liver after surgery to support life, and co-morbid conditions. Therefore, only 10–20 % of 90% of patients with HCC have disease amenable for liver resection (14). Liver transplantation is often the 100% optimal curative treatment for HCC. Unlike other treatment modalities, liver transplantation corrects underlying liver dysfunction and removes the diseased tissue that poses a risk for the development of recurrence or new HCC (15). Unfortunately, the need for donor organs exceeds organ availability in most countries; therefore, clinical criteria for liver transplantation had to be established. Factors involved in cancer recurrence after liver transplantation are the most important aspects of the eligibility criteria of the recipients. Single HCC smaller than 5 cm or up to three nodules of HCC less than 3 cm were first criteria proposed for the liver transplantation to treat HCC, also known as the Milan criteria. For patients with HCC, 4-year overall survival rate of 85 % and the disease-free survival of 92 %, selected by the Milan criteria, was observed. The Milan criteria are widely used, but strict limitations of the Milan criteria leave many patients with HCC not eligible to undergo transplantation despite the lack of major vascular invasion or lymph node metastasis. Because of the shortage of available organs for transplantation, patients stay significantly longer on waiting lists and tumor progress is expected. If patients do not receive bridging treatment to transplantation while they are waiting for a liver graft, patients may cease to be eligible for procedure. This means that pretransplantation treatment is necessary. Standard treatments include TACE, systemic chemotherapy, PEI, and RFA, with TACE being the most commonly used procedures as bridging to transplantation.

As mentioned before, surgical resection is the first line of treatment for patients with HCC with preserved liver function and solitary lesion or in patients with multifocal tumors inside the Milan criteria or in case of mild portal hypertension in patients not suitable for liver transplantation, although it is debated if such patients could benefit from other local ablative therapies, avoiding the risks of surgery mainly liver failure after resection. All other treatment regimens are palliative except RFA, which can be curative in some cases.

Local ablative treatments

Local ablative treatments are considered, except RFA, which can be curative in some cases, as non-curative treatments and are used in patients not eligible for surgical interventions or as bridging technique to liver transplantation.

Radiofrequency Ablation and Microwave Ablation (MWA)

RFA is recommended for up to three small lesions up to 3 cm in diameter, with high probability of complete necrosis for small tumors (<2 cm), away from large vessels. The likelihood of complete response and success of RFA progressively decreases with the increase of tumor size. Some studies concluded that RFA was as effective as surgical resection in the treatment of solitary and small HCC. Even more, some authors regarded RFA as the first-line treatment for small, operable HCCs (<2 cm) (16). High rate of recurrence after RFA is the leading cause of late death of patients with HCC. The risk factors for tumor recurrence after treatment include tumor size, insufficient safety

margin, multinodular tumor, and tumor location (17). Recurrences also arise because of preexisting microscopic tumor foci that are undetected by imaging modalities or malignant cells that have been disseminated during manipulation. Local recurrence is more frequent after RFA than resection. This may be a result of the safety margin of RFA being narrower than that of resection, as during resection entire anatomic segment is removed. The clearance of tumors and any potential sites of microscopic disease are more complete in patients undergoing resection. Local recurrences after RFA, therefore, may be attributable to insufficient destruction of the primary tumor and the presence of tumor venous invasion in the adjacent liver.

MWA is emerging as a valuable alternative to RFA for thermal destruction of HCC. Electromagnetic microwaves heat matter by agitating water molecules in the surrounding tissue, which produces friction and heat, thus inducing cellular death using coagulation necrosis (18). The main features of MWA technology, when compared with existing thermal ablation techniques, include consistently higher intratumoral temperatures, larger tumor ablation volumes, shorter ablation times, and an improved convection profile. As a result, the advantage of MWA over RFA is that treatment outcome is less affected by vessels in proximity to the tumor (19). Also, because MWA does not rely on an electric circuit as RFA does, multiple applicators can be used simultaneously.

Transarterial Chemoembolization (TACE)

TACE is the recommended treatment for BCLC stage B, multinodular, as well as symptomatic tumors without vascular invasion or extrahepatic spread. The effectiveness of TACE in patients with intermediate-stage HCC may be confounded as TACE is often used in combination with other treatment modalities including local and systemic therapies. As a therapeutic response to TACE approximately in 40–70 % of patients with overt hypervascular monomodular HCC with tumor size of 5 cm or less, complete tumor necrosis can be achieved, and they remain local recurrence-free for three years or more after undergoing super selective (subsegmental) TACE. Although it is difficult to compare data on the outcome of TACE due to differences in staging systems, 5-year survival rates after TACE of 39 % and 27 % are reported (20). Drug-eluting beads have similar efficacy to gel foam-lipiodol with probably less adverse events. An alternative to TACE is radioembolization with Yttrium90. Radioembolization involves the catheter-based delivery of Yttrium90 microspheres into the hepatic artery to distribute radioisotopes to the tumor. Yttrium90 is a pure beta emitter, which generates high-energy radiation with a short half-life with shallow penetration (maximum 11 mm) resulting in necrosis (21). There is significant difference in survival between radioembolization and TACE, but postembolization syndrome was significantly more severe in patients who underwent TACE(22). Further evaluation of radioembolization, including direct comparisons with TACE, is needed. Radioembolization may cause injury to the hepatic tissue and result in fibrotic changes and tissue atrophy. The loss of liver function can be compensated for by nontreated liver segments, which tend to undergo hypertrophy after radioembolization.

Electroporation

Ablative therapies are being used increasingly to treat primary and metastatic cancer in the liver. The most common techniques in current use include RFA and MWA.These techniques are used in patients who are poor candidates for resection due to the location of the tumor, comorbidities or earlier hepatic resection. There is, however, a high recurrence rate with ablative techniques, ranging from 4 % to 43 % in patients with HCC or metastatic colorectal cancer. Tumors in proximity to major portal pedicles or hepatic veins cannot be effectively or safely ablated with RFA or MWA techniques. Complications caused by thermal

damage to bile ducts or blood vessels and high recurrence rates are associated with these techniques (23). Therefore, new treatments and alternative techniques are searched for. This has prompted the development of two different methods of electroporation: irreversible electroporation (IRE) used alone, and reversible electroporation, used in combination with selected anticancer drugs, thus called electrochemotherapy (ECT). Electroporation is a method, where externally delivered electric field induces a sufficiently large transmembrane voltage, which renders membrane permeable thus facilitating entrance of different molecules into the cells. According to the field strength, this event may be reversible, and the cells survive. We differentiate two types of electroporation: IRE and reversible electroporation. As the name suggests, IRE relies on delivering electrical pulses whose strength and duration exceeds the threshold of spontaneous cell membrane repair. The permeability of the cell membrane that they induce disrupts the homeostasis of the cells, leading to cell death. By contrast, tissues subjected to reversible electroporation remain viable after the procedure. The lesser electrical strength and duration of the applied pulses during the procedure allow pores in the membrane to seal by themselves.

Irreversible Electroporation

IRE is a relatively new minimally invasive image-guided technique for oncologic treatment of soft tissue tumors. The application of ultra-short high-voltage electrical pulses leads to an increase in permeability of the cell membrane leading to cell death. Due to increased membrane permeability, cell content (most of the cell plasma) leaks out of the cell, leading to necrosis or apoptosis of cells. IRE utilizes electric field strength of at least 1,000–1,500 V/cm. The mechanism of action leads to some unique features of IRE: tissue with a comparably high density of viable cells will receive most injury, whereas fibrotic tissue with a paucity of cells will almost be left unaffected. Thermal ablation techniques induce tissue necrosis by high deposition of thermal energy, while IRE induces tissue necrosis with minimal thermal energy deposition. This basic difference leads to absence of heat-sink effect, which causes inhomogeneous heating with insufficient tissue destruction close to the vessels and to reduced destruction of the extracellular matrix, with the potential for cellular regeneration (24). Unlike thermal ablation techniques that destroy all normal and pathologic tissue and blood vessels in the ablation zone, IRE is discriminate. Normal and pathologic tissue are destroyed by IRE, but vessels and bile ducts are not (25). The endothelium of these structures is affected by IRE, but it repopulates shortly after treatment (26). There are some IRE specific advantages: short ablation time, preservation of vital structures within IRE-ablated zone, avoidance of heat/cold-sink effect, IRE-induced complete ablation with well-demarcated margin, IRE-induced apoptotic cell death, and real-time monitoring of IRE ablation. Initial clinical reports suggest feasibility and efficacy of IRE in tumor localizations in the vicinity of a large blood vessels or vital structures in the liver hilum where use of thermoablation is not recommended. Advantage of IRE lays in avoidance of injury to the bile ducts and vessels within an organ, yet still in icting tumor as well as normal parenchymal cell death (28). For these reasons, IRE is an attractive treatment option for various soft tissue tumors located in challenging locations.

Reversible electroporation and electrochemotherapy

Reversible electroporation is the approach where the membrane reorganization facilitates the diffusion of the therapeutic molecules into the cells while preserving the cells viability. Therefore, sufficient drug accumulation in cells is one of the most important underlying mechanisms responsible for effective treatment. Electroporation can be used for delivering genes, called gene electrotransfer, or for poorly or nonpermanent, but highly effective cytotoxic chemotherapeutics called electrochemotherapy. Electrochemotherapy is a

treatment where reversible electroporation facilitates hydrophilic drugs, such as bleomycin or cisplatin, accumulation in the cells, thus increasing their cytotoxicity locally. The use of bleomycin is based on the clinical evidence showing that among other drugs tested, it has the highest potentiation of cytotoxicity by electroporation and due to low doses needed the side effects are avoided. Electrochemotherapy also has two distinct vascular effects. Since the exposure of tumors to electric fields predisposes stromal cells to drug uptake, it also affects endothelial cells of tumor vessels. This action leads to endothelial cell death (apoptosis) and consequently to abrogation of tumor blood ow. This is vascular disrupting effect, whereas in tumors, the vasoconstriction was demonstrated and confirmed on normal and tumor vessels by intravital microscopy. There are couple of study showing feasibility of electrochemotherapy on deep-seeded tumors such as colorectal liver metastases or liver tumors in general. Based on optimistic results of the study on colorectal liver metastases, primary liver tumors were identified for the possible targets based on their favorable biology as being well-vascularized tumors and because the technology has already been adopted and proven to be safe.

Treatment of hepatocellular carcinoma with electrochemotherapy

In an attempt to achieve better disease control and as additional treatment option, a study assessing feasibility and evaluating toxicity and effectiveness of electrochemotherapy (ECT) with bleomycin in treatment of PLC was designed at Clinical Department of Abdominal Surgery, University Clinical Centre Ljubljana in cooperation with Institute of Oncology Ljubljana and with Faculty of Electrical Engineering, University of Ljubljana. Phase I is concluded, and results are very promising. Regardless of that ECT are still in the group of additional treatment options for treatment of HCC, and only the larger study can provide the answer whether it can be »upgraded« to curative option group.

CONCLUSION

Electrochemotherapy has, after successful translation into treatment of cutaneous tumors, progressed into translation of deep-seated tumors. Concluded phase I study shows that ECT can be effective in treatment of HCC. The treatment of HCC with electrochemotherapy has so far proven as safe and effective and is predominantly indicated in patients with tumors not amenable to surgery, RFA or TACE.

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Concomitant hepatocellular carcinoma and cavernous hemangioma in a patient with non-cirrhotic liver: a case report

Katarina Bizjak[1], Arpad Ivanecz[1]
[1]*Department of Abdominal and General Surgery, University Clinical Centre Maribor, Slovenia*
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Introduction: The coexistence of both hepatocellular carcinoma (HCC) and hemangioma in the same patient is relatively rare, with just few cases described in the literature.[1–4] We present such a case of a 66-year-old patient with several comorbidities and an absence of cirrhosis, originally admitted to hospital for gastritis related problems.

Case report: A 66-year-old patient presented to the emergency department with abdominal pain and vomiting after red wine ingestion. His medical history was notable for gastritis, diabetes, hypertension and chronic kidney disease. He denied alcohol abuse in the last four years. Physical examination revealed slightly jaundiced skin, tenderness in the upper abdomen and a liver mass in the epigastrium. With non-specific laboratory findings and a gastroscopy positive for erosive gastropathy, the patient was admitted to department of gastroenterology. Subsequent imaging techniques (abdominal ultrasound (US), contrast-enhanced US (CEUS) and computed tomography (CT)) described steatotic liver without cirrhosis and two liver lesions; one large, heterogenic, with malignant appearance in the left part, and a smaller one in the eighth segment, as a hemangioma. Additional tests for blood tumor markers alpha-feto protein (AFP), carcinoembryonic antigen (CEA) and CA 19–9 were all negative. US-guided liver biopsy of the suspected malignant lesion confirmed histopathologically as well-differentiated HCC. Finally, after multidisciplinary team discussion, the patient was admitted to our department for surgical treatment. Operation (left lateral sectionectomy) itself was uneventful; intraoperative US confirmed the smaller lesion as a hemangioma and excluded any other liver lesions. The patient was discharged from hospital on the eleventh postoperative day, making excellent recovery. Biopsy result of the resection specimen confirmed as a well-differentiated HCC in a distance of 2,1 cm from resection margin (R0 resection). At last follow-up (in April 2017), five years after the surgery, the patient was clinically fine, without any signs of recurrent disease on surveillance abdominal US, and with normal liver function tests and blood AFP level.

Discussion: Multidisciplinary approach is necessary to tailor management plan for patients with HCC; based on tumor burden, presence of metastasis, hepatic functional reserve, performance status and patient's wishes.[5] In rare cases of synchronous HCC and hemangioma, the characterization of their nature is crucial for making the treatment plan. The decision on extent of the liver resection is of primary importance to avoid unnecessary removal of liver tissue and functional consequences that follow and may be detrimental for patient's recovery.

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Intestinal malrotation with acute midgut volvulus: a rare, life-threatening condition in a 3-year old boy – a case report

Agneš Bokroš[1], Arpad Ivanecz[1], Stojan Potrč[1]
[1]*Department of Abdominal and General Surgery, University Clinical Centre Maribor, Slovenia*
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Introduction: Midgut malrotation (MM) is an anomaly of fetal intestinal rotation. The incidence of rotational anomalies of the midgut is estimated to be 1 in 6000 of all live births (1). We usually diagnose MM in newborn and young infants; up to 75% of symptomatic cases occur in newborns, and up to 90% of symptomatic cases occur within the first year of life (2). The classic description of intestinal malrotation is that of the term infant who presents with bilious emesis that prompts closer examination for duodenal obstruction. The upper gastrointestinal contrast series confirms the diagnosis by identifying the right-sided position of the duodenojejunal junction or evidence of midgut volvulus (MV). In rare cases, congenital MM can be asymptomatic during infancy and show up with acute or recurrent intestinal symptoms later in childhood, adolescence or even in adulthood.

Case Report: A 3-year-old boy was referred to our institution late at night as an emergency from another hospital, with acute abdomen and septic shock. The boy was born at term. He was healthy without any gastrointestinal disorder until he was two years old. He began complaining of recurrent abdominal pain accompanied by intermittent vomiting of ingested food, which was rarely followed by emesis of bile. After a day, the symptoms disappeared spontaneously, but they returned approximately once every two months. He was hospitalized several times; diagnostic work-up included allergy testing to foods, a lactose breath test, sweat chloride testing, stool guaiac, abdominal x-ray, and ultrasound. All study findings were reported as normal. The boy thrived normally. During the night, 24 hours before admission to our institution, the boy's symptoms reappeared: colicky abdominal pain and vomiting. By morning, the boy felt no pain, although he was a little tired. He ate and passed normal stools. In the afternoon, the symptoms returned, but now his abdomen distended as never before. He was admitted to another hospital. Symptoms progressed rapidly, and vomiting of ingested food and bile continued, with hematemesis. An abdominal x-ray showed multiple air fluid levels in dilated small bowel loops. He was referred to our institution. The boy looked severely ill; metabolic acidosis (pH - 7.2) with septic shock and severe anemia (hemoglobin: 69 g/L) were apparent. His abdomen was distended and painful, and there were no bowel sounds on auscultation.

During emergency laparotomy, MV due to MM with extensive intestinal necrosis was found. The duodenum did not cross the midline, and the duodenojejunal junction lay completely on the right side. The superior mesenteric vein (SMV) was to the left of the superior mesenteric artery (SMA) instead of to the right. The small bowel mesentery had a narrow base, and it was thickened with lymphatic and venous congestion. There was also a thrombosis of the SMV. The cecum was located at the lower part of the liver. All parts of the small

bowel (as well as the fourth part of the duodenum and cecum) were obviously necrotic and therefore had to be resected. The coloduodenal bands were divided. A primary anastomosis was performed between the third part of the duodenum and the ascending colon. In addition to a nasogastric tube, a nasoduodenal tube and a colostomy tube were inserted to protect the anastomosis. The postoperative course was uneventful, and a contrast study revealed a patent anastomosis with no leaks. Presently, nine years after the operation, the boy is on TPN, thrives normally, eats regular food with no dietary restriction, passes pap-like stool once or twice daily, with no diarrhea, and has no signs of liver failure. There is some impairment in his quality of life, but until now, he can be disconnected from TPN for 6 hours/ day, and practice almost completely normal daily activities for a child of his age.

Discussion: Our report emphasizes the need to consider the diagnosis of MM in older children who have chronic abdominal symptoms. The difficulty of diagnosis lies in both the absence of specific physical findings and the low frequency after the neonatal period (1–10). Presumably, when the symptoms of abdominal pain and vomiting of ingested food appeared for the first time by our patient, MV was present with intermittent torsion. The onset of symptoms and their severity depends on the degree and duration of vascular occlusion, which is characterized as "on and off" volvulization (3). Symptoms in children are often mistaken for milk allergy, malabsorption, celiac syndrome or even psychological disorders (3). In our case, the abdominal ultrasound (US) was read as normal. The presence of inverted superior mesenteric vessels, a "whirlpool" sign, or duodenal dilatation on abdominal US have been shown to be sensitive diagnostic criteria for malrotation in children, but the examination is highly operator-dependent and is not secure enough to exclude the diagnosis (4). An upper gastrointestinal series, with or without barium enema, remains the preferred imaging modality for diagnosing malrotation in this population (4). Delay in diagnosis, and surgical intervention remains the rule rather than the exception (5–7). It has been reported that children beyond the neonatal period who present with MM have potentially life-threatening complications of this anomaly; nearly half of symptomatic patients are admitted as an emergency, and the rate of volvulus with intestinal ischemia is 15–22% (2, 3, 8, 9). When strangulation of the bowel developed in our case, the abdomen became distended and tender to palpation.

During laparotomy, we exposed the twisted infarcted small bowel, which was obviously gangrenous. Thrombosis of the SMV probably worsened the situation and led to a shorter time interval of progression of ischemia to transmural necrosis. Although it is essential to preserve as much bowel length as possible, preferably including the ileocecal valve, we had no opportunity to preserve any length of the small necrotic bowel, except the first three parts of the duodenum. To have left any part of the small necrotic bowel in the abdomen, with the possibility of avoiding short bowel syndrome (SBS), would in our case, probably have led to further progression of septic shock and a consequent risk to the patient's life. It was estimated a probability of 10–40% that a patient with MV would require intestinal resection and develop SBS that required TPN (2). At present, TPN and small bowel transplantation remain the only viable therapeutic options for extreme SBS. However, sepsis and liver failure associated with TPN, and limited availability of donor organs and high graft rejection rates associated with transplantation, can limit their use (9.). Attempts to engineer the small intestine have achieved varying degrees of success in animal models but at present are still experimental (10).

Conclusion: In conclusion, we hope that enhanced awareness of the presentation of MM in older children will lead to shorter time to diagnosis and improved therapeutic outcomes in this rare, but potentially life-threatening disease.

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Enkapsulirajoča peritonealna skleroza: redek vzrok za ileus tankega črevesja (prikaz primera)

Tajda Božič[1], Jan Grosek[2]
[1]*University Medical Center Ljubljana, Ljubljana, Slovenia*
[2]*Klinični oddelek za abdominalno kirurgijo, Univerzitetni klinični center Ljubljana, Slovenia*
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Uvod: Enkapsulirajoča peritonealna skleroza (EPS) je redka bolezen, ki povzroči zadebelitev in fibrozo peritoneja. V zgodnjih fazah je asimptomatska, dalj trajajoča pa lahko privede do hujšanja, podhranjenosti, obstrukcije in strangulacije črevesja. Najpogosteje je opisana kot zaplet dalj časa trajajoče peritonealne dialize, redko pa predstavlja posledico avtoimunih, malignih bolezni in ostalih dejavnikov. Eden izmed sprožilnih dejavnikov za razvoj EPS je ledvična transplantacija (1).

Predstavitev primera: Naš bolnik je 45-letni gospod, ki je imel leta 2013 transplantirano kadaversko ledvico. Pred transplantacijo je imel zaradi zapletov kronične ledvične bolezni opravljeno paratiroidektomijo. Prejema imunosupresivno in antihipertenzivno terapijo. V začetku februarja 2017 je zbolel s hudimi bolečinami v trebuhu in slabostjo. Sprejet je bil na Klinični oddelek za nefrologijo UKC Ljubljana. Na oddelku so pomislili, da bi bil lahko vzrok bolnikovih težav ileus zaradi EPS. Bolnik se je pred transplantacijo več let zdravil s peritonealno dializo. Zaradi suma na ileus je bil opravljen RTG abdomna, ki ni pokazal prepričljivih znakov te bolezni. Bolnikovo stanje je bilo čedalje slabše, zato so RTG preiskavo abdomna čez dva dni ponovili. Tokrat so bili znaki za ileus prepričljivi, prav tako pa je podroben pregled rentgenske slike odkril kalcinacije v desnem delu trebuha. Še več kalcinacij je prikazal CT; vidne so bile pod obema hemidiafragmama, po peritoneju, v mali medenici in mezenteriju, kjer so bile najbolj izrazite. Bolnik je bil premeščen na Klinični oddelek za abdominalno kirurgijo, kjer je bil po krajši predoperativni pripravi operiran. Vstop v trebuh je bil zaradi v konvolut ujetega črevesja neugoden. Seroza je bila močno zadebeljena. Spremembe v abdominalni votlini so makroskopsko izgledale značilne za EPS v sklopu dolgotrajne peritonealne dalize. Med operacijo je bila opravljena kompletna adhezioliza tankega črevesja, potrebna je bila resekcija krajše vijuge tankega črevesja, kjer adheziolize ni bilo moč opraviti. Preparati, ki so bili poslani na histološko preiskavo, so diagnozo potrdili. 10 dni po operaciji je bil bolnik odpuščen v domačo oskrbo.

Zaključek: EPS praviloma zdravimo s tamoksifenom in kortikosteroidi (2). Pacienti zaradi podhranjenosti potrebujejo prehransko podporo. Najpogosteje se pri njih uvede parenteralno hranjenje (3). Ko se pojavijo obstruktivni zapleti, ki so potencialno smrtonosni, je zdravljenje izbora kirurška adhezioliza (2). Izboljšanje kirurških tehnik v zadnjem desetletju, je močno povečalo preživetje bolnikov z EPS (2).

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A rare but lethal cause of gastrointestinal bleeding – a case report of a patient with secondary aortoduodenal fistula

Brada Besarta[1], Ocepek Andreja[1]
[1]*Department of Gastroenterology, Clinic of Internal Medicine, University Medical Centre Maribor, Slovenia*
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Introduction: Gastrointestinal bleeding remains a common cause of hospital admissions. It can vary from the occult, chronic blood loss to a massive, potentially life-threatening hemorrhage. There is a wide range of etiologies, which can cause gastrointestinal bleeding, some of which are rare and difficult to diagnose (1, 2). We present a case of a rather uncommon cause – secondary aortoduodenal fistula.

Case report: 77-year old male with ulcerative colitis, ischemic cardiomyopathy and peripheral arterial occlusive disease with a history of aorto-femoral bypass surgery 15 years ago, was initially admitted to our ward due to haematemesis and melena with abdominal discomfort. On physical examination, he appeared pale but was hemodynamically stable. We performed immediate upper endoscopy. Hemorrhagic gastritis was found with no signs of active bleeding. The patient received fluid therapy, proton pump inhibitor, and blood transfusion, all of which improved his clinical status, he did not experience further discomfort. With a history of ulcerative colitis in mind we performed lower endoscopy and discovered few polyps which were removed, there were no signs of complications or active bleeding. Our patient was dismissed in a stable condition but returned after ten days, with a history of haematochezia and pain in lower abdominal region. After initial fluid therapy and blood transfusions, a computed tomographic angiography of abdominal vessels was performed on the admission day but showed no extravasation. An urgent lower endoscopy was performed, which revealed an ulcer at the site of the previous polypectomy. However, there were no signs of active bleeding. The patient was regularly monitored, his vital signs were stable, his clinical condition was improving, he experienced no further pain or any discomfort. Fecal occult blood tests were negative, and his hemoglobin values increased appropriately. Unexpectedly, on the fourth day, his clinical condition suddenly deteriorated, he became unresponsive with no vital signs and eventually died despite resuscitation attempt. An autopsy revealed the origin of bleeding; there was a communication between the distal duodenum and aortic graft – a secondary aortoduodenal fistula causing exsanguination.

Conclusion: Secondary aortoduodenal fistula is an uncommon but life-threatening complication of abdominal aortic reconstruction, usually found years after the procedure (1, 2). The most frequent presenting clinical picture is upper gastrointestinal bleeding, and the only correct treatment is an early surgical intervention (3). Unfortunately, the delay in diagnosis is common, a fact which should raise a high suspicion of possible aortoenteric fistula in all patients with a history of aortic surgical intervention presenting with sings of gastrointestinal bleeding (1).

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The Discovery of Two Rare Disorders in One Patient – Case Report

Nejc Bukovnik[1], Andreja Ocepek[1], Jernej Lučev[2], Pija Šumer Mayer[2], Stojan Potrč[3]
[1]*Department of Gastroenterology, Division of Internal Medicine, University Clinical Center Maribor, Slovenia*
[2]*Department of Radiology, University Clinical Center Maribor, Slovenia*
[3] *Department of general and abdominal surgery, Division of Surgery, University Clinical Center Maribor, Slovenia*
Gastroenterolog 2017; suplement 3: 88–89

Introduction: Superior mesenteric artery syndrome (SMAS) was first described in 1861 by Austro-Hungarian professor of anatomy Carl von Rokitansky (1). The exact pathophysiologic description and proposed solution was proposed by David Wilkie, after whom the syndrome is named (2) in the year 1921. The syndrome appears when the angle of the aorta and the superior mesenteric artery (SMA) is lowered below 25°, and the third portion of the duodenum is compressed between them (3). The reason for the compression is usually the loss of fat between both arteries as a consequence of general weight loss from numerous reasons. The frequency of the SMAS is not exactly known but is estimated to be from 0.013 to 0.3% in the general population by barium studies of upper gastrointestinal tract (4). The most common symptoms are nausea and vomiting, patients complain of heartburn and keep losing weight. If the blockage progresses, the high ileus can form. The syndrome can easily be overlooked and a long time can pass before it is diagnosed. The Treatment consists of gastric decompression, parenteral and entero-jejunal feeding. If the desired result is not achieved, a laparoscopic duodenojejunal anastomosis is performed most of the time. The result is favorable in most cases (5).

Case Report: A 39 – year old patient was admitted to the department of gastroenterology after multiple visits at the emergency department for nausea and vomiting. When she was 15 years old she was diagnosed with celiac disease, five years ago she started intermittent treatment of *autoimmune hyperthyroidism* with tiamazole. In the last six months, she had multiple visits in the clinic for thyroid diseases because of the worsening of thyroid symptoms, she lost 15 kilograms of weight and was constantly nauseous and vomited frequently. A complete blood work up was made, potassium levels were low, other than that the rest of the parameters were normal, tumor markers (CEA, CA 19–9, CA 72–4) were negative. Ultrasound of the abdomen showed a distended stomach filled with fluid. Upper endoscopy showed gastric ptosis with fluid retention; the endoscopy was possible to the second part of the duodenum to where no pathology was found. The patient was still nauseous and was vomiting. After that, a barium swallow test was performed; it showed an obstructed bowel in the part of the distal duodenum. With abdominal computed tomography we found a lowered angle between aorta and SMA. In that section, the duodenum was compressed. Also, the left renal vein was obstructed (Nutcracker syndrome). We suspected SMAS. We began the treatment with a conservative approach by parenteral feeding and gastric decompression, but after attempting enteral feeding, the nausea and vomiting relapsed. We planned to perform a Roux

duodenojejunal anastomosis. During the surgery, a tumor formation was found, so a segment resection of the small bowel was performed. A 35×28 mm large tumor was found that did not enclose the bowel; histology showed that it was an invasive adenocarcinoma. The stage of the disease was pT3 N0 M0; the tumor was removed into healthy tissue. The adjuvant therapy was not needed, the patient has frequent follow-ups. At the last endoscopic check-up, there were no signs of relapse, the patient was feeling good, she does not have nausea, and she does not vomit, she also gained weight.

Discussion: Superior mesenteric artery syndrome is a rare cause of upper bowel obstruction. We need to suspect it in selected patients who had rapid weight loss for any reason and in patients suffering from constant nausea, vomiting, abdominal pains and reflux where diagnostic procedures show bowel obstructions. Initial treatment is conservative with gastric decompression and parenteral feeding; surgery is needed where conservative approach is not successful.

We suspect that the coincidence of SMAS and partial tumorous obstruction of the small bowel lead to the appearance of the symptoms that pointed out the malignant disease. The duodenal carcinoma is a rare malignant disease (the incidence of small bowel tumors in Slovenia is 0.51 on 100 000 people, and based on the literature we can predict that only about one fourth of them are located in the duodenum) (6,7). In our patient, the duodenal carcinoma was found in an early stage. As such it probably would not be symptomatic and would metastasis before the symptoms would appear if there were no additional obstruction from aorta and SMA.

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Cecal lipoma as a rare cause of intestinal intussusception – a case report of a female patient with sever bowel obstruction

Ćeranić Davorin[1], Dajčman Davorin[1], Gajzer Borut[2], Vadnjal Đonlagić Sabina[3]
[1]*Department of Gastroenterology, Division of Internal Medicine, University Clinical Center Maribor, Slovenia*
[2] *Department of general and abdominal surgery, Division of Surgery, University Clinical Center Maribor, Slovenia*
[3]*MDT&T, Maribor, Slovenia*
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Introduction: Intussusception is condition where proximal part of intestine invaginates in adjacent distal part of intestine. It is frequent in children but uncommon in adults in Western world. It is estimated that only 5% of invaginations occur in adults. The most common etiology is underlying malignant disease, diverticular disease, adhesions, strictures, and polyps. Majority of patients need definite surgical treatment with resection.

Case Report: 63-years old lady was admitted to hospital due to abdominal pain and noninfective diarrhea. In previous years she had cholecystectomy and hysterectomy. After diarrheic period she had the onset of constipation. At the beginning, the pain was abated after spasmolytics. In the second week of disease, pain was persistent despite the therapy with Spasmolytics. Also, constipation has occurred. Inflammatory markers, liver tests, BUN, iron, protein electrophoresis and coagulation test, were normal. Tumor-like lesion with suspected invagination of the right colon was described on the ultrasound. Computed tomography revealed invagination. Laparotomy was performed, and caecoascendental invagination due to cecal lipoma was seen. Partial colon resection was performed, and histology exam confirmed lipoma, no tumor tissue was identified. Postoperative course was uneventful. Colonoscopy was performed six months later and revealed normal mucosa and ileoascendic anastomosis.

Conclusion: Intussusception in adults is a rare cause bowel obstruction and acute symptoms like abdominal pain, abdominal distension, severe vomiting, diarrhea or constipation. Immediate radiological imaging (ultrasound, CT) should be obtained. Surgical treatment is the therapeutic modality of choice.

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Duodenal perforation as a complication of E.R.C.P. after unsuccessful bile duct stone extraction and stenting

Tadej Durič[1], Davorin Dajčman[1], Saša Rudolf[2], Arpad Ivanecz[3]
[1]*Department of Gastroenterology, University Medical Centre Maribor, Slovenia*
[2]*Department of Radiology, University Medical Centre Maribor, Slovenia*
[3]*Department of General and Abdominal Surgery, University Medical Centre Maribor, Slovenia*
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Introduction: Perforation is a known complication of ERCP. Incidence of perforation ranges between 0.3 and 2%. In general, perforation regarding E.R.C.P. can be divided in four types:

- Type I: Free bowel wall perforation
- Type II: Retroperitoneal duodenal perforation secondary to periampullary injury
- Type III: Perforation of the pancreatic or bile duct
- Type IV: Retroperitoneal air alone

Case report: A 47-year-old woman was admitted to hospital care because of new onset of jaundice and pain in upper right abdominal quadrant. She also complained about nausea, but without vomiting. At admission, she was cardio – circulatory stable, icteric, no fever. Palpable pain was present in the right upper abdominal quadrant. Laboratory showed obstructive jaundice with elevated bilirubin, AF and gt. Coagulation tests were normal; percutaneous US showed a high probability for choledocholithiasis. ERCP was performed. After common bile duct cannulation and contrast application choledocholithiasis was confirmed with at least one stone of diameter 10 mm. Wide papillotomy was performed, and Dormia basket introduced. The stone was successfully captured in the basket, but due to very hard consistency of the stone, retrieval of the basket was not possible. Urgent lithotripsy was performed, and extraction of the basket was achieved. However, the impacted stone remained. A biliary stent was inserted, but it did not pass the impacted stone. The next day patient presented with acute abdominal pain and leukocytosis. X-ray and abdominal CT confirmed abdominal perforation of duodenal wall, caused by the proximal end of biliary stent. The patient was referred to OR for surgical intervention. Stent extraction, cholecystectomy, choledochotomy with stone evacuation and suture of perforation were performed. Biliary drainage through T drain was achieved, feeding jejunostomy was applied. In the post-operative treatment, patient was stable, without abdominal pain or icterus. She was discharged 12 days after surgery.

Endoscopic lithotripsy is the first line of treatment in large bile duct stones. In this case, due to very hard consistency of the stones, endoscopic lithotripsy could not be performed after the initial attempt of stone extraction. Emergency lithotripsy was performed, resulting only in basket retrieval, leaving the impacted stone. At this point, electrohydraulic lithotripsy (EHL) would be the next endoscopic step for management of common bile duct stone impaction. After confirming perforation of the duodenal wall, which was caused by stent protrusion, surgical intervention was inevitable.

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Treatment of persistent anal fistula secondary to Crohn's disease in patients after abdominoperineal excision

Urska Gajsek[1]
[1]*Department of General and Abdominal Surgery, University Clinical Centre Maribor, Slovenia*
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***Keywords**: anal fistula, Crohn's disease, PolyMem®, wound dressing*

Objectives: Several new techniques have been described for the management of cutaneous fistulas in the gluteal region after abdominoperineal excision (APE) in young patients with Crohn's disease.

Two young patients aged 33 and 27 years with chronic perineal fistulas after abdominoperineal excision surgery secondary to Crohn's disease were treated with PolyMem® Wound care dressing.

Methods: Both patients had persistent cutaneous fistula 6months after the APE, confirmed with MR, no enteral connection was seen. At the beginning of treatment, fistula canal was surgically debrided, and PolyMem® WIC® Silver Rope inserted. The fistula canals were 9 cm long, 3 cm width and 12 cm long and 3 cm width, respectively. In the first week, the dressing was changed every day then gradually less frequent (according to discharge)in the last month twice per week. MR was assessed after the treatment.

Results: After ten weeks of PolyMem® WIC® Silver Rope cavity wound dressing, the fistula shrank for 1 cm and the fistula canal started closing from above, the yellowish fluid discharge which was observed at the beginning and increased in the first week, completely stopped.

Conclusion: The multifunctional wound care dressings are an option for patients with Crohn's related fistulas. PolyMem® WIC® Silver Rope is especially appropriate for deep wounds with narrow openings, such as tunnels and can also be used in the presence of infection.

Case report of discrepancy between abdominal computed tomography and percutaneous cholangiopancreatography in diagnostic of obstructive icterus

Jerneja Golub[1], Andrej Zafošnik[1], Andreja Ocepek[1], Silva Breznik[2], Saša Rudolf[2], Davorin Dajčman[1]
[1]*Department of Gastroenterology, Division of Internal medicine, University Clinical Centre Maribor, Slovenia*
[2]*Department of Radiology, University Clinical Centre Maribor, Slovenia*
Gastroenterolog 2017; suplement 3: 93–94

Introduction: Obstructive icterus is very common clinical presentation in gastroenterology practice, and it has wide differential diagnosis. Imaging studies are very important in identifying the cause of obstruction. Non-invasive are abdominal ultrasound (US), endoscopic ultrasound (EUS), abdominal computed tomography (CT) scan and magnetic resonance cholangiopancreatography (MRCP). Invasive imaging studies that can be used for diagnostics and treatment are percutaneous transhepatic cholangiopancreatography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) (1, 2).

We are presenting a case of a patient with obstructive icterus where we observed discrepancy of results between abdominal CT scan and PTC.

Case report: A 59 – year old male was admitted to the Department for Gastroenterology due to abdominal pain and obstructive icterus. He had long term problem with mild abdominal pain for last four years. A day before the admission the pain worsened and became cramping like with intermittent attacks of pain. Normally spread through whole abdomen, but the most painful point was in epigastrium. In the time of the attack he experienced dyspnea, retching and he reported sour taste, lack of appetite and nausea. He did not vomit or lose any weight. He also noticed that his urine was darker than usual. Until now he was treated due to arterial hypertension and gastritis. In clinical examination, he was hemodynamically, respiratory stable and icteric. The abdomen was palpatory painful in epigastrium and right upper abdominal quadrant. On palpation, liver were not enlarged. Laboratory revealed hyperbilirubinemia due to direct bilirubin, high cholestatic enzymes and liver transaminases (ALT>AST). We were also observing mildly elevated tumour marker Ca 19–9. Markers of viral hepatitis were negative. We performed abdominal US that showed liver steatosis, gallstones in gallbladder, widened common biliary duct (CBD) in extrahepatic part and thickened wall of cystic duct, without clearly visible cause of obstruction. For more accurate diagnostics of visible changes, we ordered abdominal CT scan that showed suspect tumour in liver hilus, probably Klatskin tumour, with suspect lesion in 4B segment of liver and portal vein thrombosis. Because of progressive icterus and suspected tumour in liver hilus, a percutaneous biliary drainage with PTC was performed. PCT showed no signs of Klatskin tumour or other obstruction in central biliary ducts and the walls of ducts were smooth and showed no other pathology. In the CBD two filling defects suspicious of gallstones were described. After consulting with surgeons and radiologists, we concluded that icterus is more likely due to choledocholithiasis than tumour, so we performed ERCP where choledocholithiasis was confirmed, and two big gallstones were removed from CBD.

Because of suspected portal vein thrombosis, we repeated abdominal US with portal vein Doppler examination, which showed no signs of obstruction in central portal veins and hepatic veins. After the procedures, icterus in our patient rapidly declined, in control laboratory studies we also were observing normalisation of Ca 19–9. During hospitalisation he did not complain about new onset of abdominal pain, we observed no onset of acute cholangitis, and after 22 days of hospitalisation, he was discharged from hospital. He is now asymptomatic and is waiting for elective cholecystectomy.

Discussion: In our case, the greatest problem was identifying the cause of icterus. Abdominal CT scan was performed to exclude other possible causes of obstructive icterus that would demand operative treatment. It is well known that ERCP with endoscopic sphincterotomy and stent implantation is connected with several possible complications that could prolong definite operative treatment. Because we suspected that the tumour in liver hilus is the cause of obstructive icterus we firstly decided to perform percutaneous biliary drainage with PTC. If this were the case the internal drainage with ERCP would not be possible.

Abdominal CT scan is normally more accurate in diagnostic of obstructive icterus that US, but has lower sensitivity and specificity than MRCP in identifying gallstones since many of them are radiolucent and CT scanning can only image calcified stones. It is possible that tumour changes with portal vein thrombosis that were visible on CT scan were the result of at least two big gallstones and chronical inflammation of biliary ducts that is connected with choledocholithiasis (2–4). The case of this patient showed that diagnostics of obstructive icterus is very complex and sometimes demands multidisciplinary approach. Sometimes we have to repeat some laboratory and imaging studies more than one time to determine the right cause.

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Vedolizumab efficacy and safety – single center experience after one year of use

Jurij Hanžel[1], Ivan Ferkolj[1], Nataša Smrekar[1], Matic Koželj[1], Gregor Novak[1], Borut Štabuc[1], David Drobne[1]
[1]*Department of Gastroenterology, University Medical Centre Ljubljana, Slovenia*
Gastroenterolog 2017; suplement 3: 95–96

Background and aims: Vedolizumab is a humanized monoclonal antibody that targets the $\alpha_4ß_7$ integrin and thus prevents recruitment of lymphocytes to the intestinal lamina propria. It was approved for use in Slovenia in May 2016. Data on efficacy, safety, and predictors of success in real life settings are still limited. Our aim was to study mid- to long-term outcome of vedolizumab in our cohort. We report on the characteristics of our cohort and the drug retention rate at the end of follow-up.

Methods: We identified all patients treated with vedolizumab in a tertiary referral university hospital: a cohort of 52 patients (26 CD, 25 UC, 1 IBDU), largely resistant to anti-TNF agents, who received vedolizumab at our center (31 male, mean age 40 years). At the time of the first infusion the mean duration of disease was 10 years, 44 patients (85%) had been exposed to at least one anti-TNF agent, 20 (39%) were receiving systemic steroids and 6 (12%) immunomodulators, 31 (60%) had a C-reactive protein (CRP) level >5 mg/L, with a median of 6 mg/L (IQR 5–18 mg/L). Known predictors of drug failure were studied in our cohort: CRP >5 mg/L, albumin < 35 g/L, systemic steroids at induction and perianal disease as predictors of drug discontinuation and need for optimization (*1*). The main outcome was partial (need for dose optimization from 300 mg q8 weeks to 300 mg q4 weeks) or complete drug failure (withdrawal of drug due to inefficacy). The log-rank test was used to compare hazard rates in groups. Numeric variables were compared using the Mann-Whitney test.

Results: During a median follow-up of 23 weeks (IQR 10–38) 47 patients (90%) remained on treatment with vedolizumab, 12 (23%) required dose optimization, 13 (25%) reached the composite endpoint of dose optimization or discontinuation due to complete drug failure. Patients with ≥2 risk factors were more likely to require dose optimization or discontinue treatment ($P = 0.002$) (Figure 1). The five patients (1 CD, 4 UC) who discontinued the drug did so due to primary nonresponse after a median of 20 weeks: four proceeded to surgery, while one was switched to infliximab. Their median CRP levels were higher (12 vs. 6 mg/L) and albumin levels lower (38 vs. 41 g/L) compared to the cohort median, but the difference was not statistically significant. No adverse effects attributable to vedolizumab were observed during follow-up. There were no fatal outcomes.

Conclusion: We observed a 90% drug retention rate, although 23% of our cohort needed early dose optimisation. Patients with at least two poor prognostic factors (CRP >5 mg/L, albumin < 35 g/L, systemic steroids at induction and perianal disease) were more likely to require early dose optimization or discontinue vedolizumab.

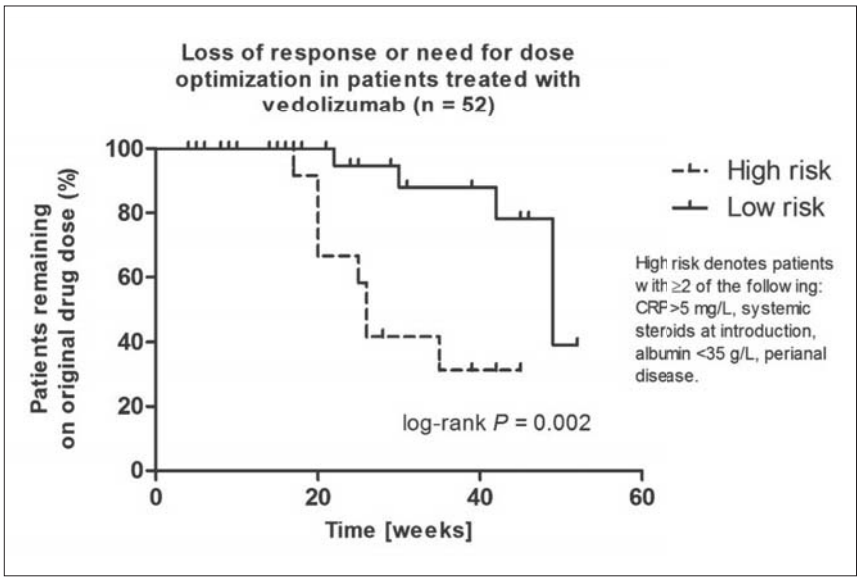

Figure 1.

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Primary Clinical Experience with the use of Duodenal–Jejunal Bypass Liner in Morbidly Obese Adolescents

Matjaž Homan[1,2], Tadej Battelino[2,3], Primož Kotnik[2,3], Rok Orel[1,2]
[1]*Department of Gastroenterology, Hepatology, and Nutrition, University Children's Hospital, University Medical Centre Ljubljana, Slovenia*
[2]*Medical Faculty, University of Ljubljana, Slovenia*
[3]*Department of Endocrinology, Diabetes, and Metabolism, University Children's Hospital, University Medical Centre Ljubljana, Slovenia*
Gastroenterolog 2017; suplement 3: 97

Objectives and study: The duodenal–jejunal bypass liner (DJBL) (Endobarrier) is an endoscopic implant that mimics the duodenal- jejunal bypass component of the Roux-en-Y gastric bypass. Studies in adults have shown relevant weight loss and improvement in type 2 diabetes. The aim of this prospective study was to investigate for the first time safety and efficacy of DJBL in severely obese adolescents with obesity complications up to 12 months after implantation.

Methods: The device was successfully implanted in 14 morbidly obese adolescents out of 17 that underwent the procedure (10 females, mean age 17.7 years (range 15.0–19.2); average BW 124,3 kg (range 93.2–158.8)). Inclusion criteria were; ≥ BMI 35 kg/m^2 with obesity complications such as hypertension, prediabetes or type 2 diabetes. They metformin was discontinued before DJBL placement. The exclusion criteria are described in details at www.ClinicalTrials.gov (NCT02183935). The procedure was performed endoscopically under general anesthesia. Subjects were under observation in the hospital for two days following the procedure for possible complications. According to the protocol, they were receiving esomeprazole 40 mg BID throughout follow-up.

Results: In the safety analyses there were no severe procedure or post procedure related complications. The most frequent adverse events were of gastrointestinal origin: nausea (6/14), abdominal pains (8/14), and diarrhea (2/14) in the first two weeks after implantation. One subject developed cholecystitis three months after endoscopy and one patient had transiently elevated pancreatic enzymes. The BMI (kg/m^2) was measured at 0, 3, 6, 9 and 12 months and decreased at all time frames (42,3 (range 36,7 to 48,8), 38,0 (range 34,1 to 44,5), 37,7 (range 33,3 to 44,8), 37,5 (range 33,1 to 45,5), 36,7 (range 32,4 to 45,9), respectively). Also, glucose metabolism significantly improved: mean HOMA-IR level at the beginning of the study was 5,6 (± 2,2) and decreased at 6 and 12 months after implantation (3,8 (± 1,6), 2,7 (± 0,9), respectively).

Conclusion: This is the first report on the use of endoscopically placed DJBL in adolescents being followed-up to 12 months. Relevant weight loss was determined in most adolescents and glucose metabolism improved in all. No serious device-related adverse effects were detected.

Disclosure of Interest: None Declared.

Pancreas pseudocyst: complication after complication

Ilijevec B.[1], Marolt U.[1], Kurečič S.[2], Arpad Ivanecz[1], Stojan Potrč[1]
[1]*Department of general and abdominal surgery, UKC Maribor, Slovenia*
[2]*Faculty of Dental medicine*
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Introduction: Pancreatic fluid collections (PFCs) are a frequent complication of pancreatitis. The revised Atlanta criteria classifies PFCs as acute (less than four weeks after pancreatitis episode) or chronic (more than four weeks after pancreatitis episode). Acute fluid collections are subdivided into acute peripancreatic fluid collections and acute necrotic collections. Chronic fluid collections are also subdivided into pseudocysts and walled-off pancreatic necrosis (WOPN). This classification is important because the management and treatment varies depending on the type of the collection (1). A pseudocyst is and encapsulated fluid collection, without the presence of solid debris, that develops because of pancreatitis a minimum of 4 weeks after initial injury, as described in revised Atlanta criteria (2). Prevalence of pseudocysts in patients with chronic pancreatitis is 20–40%. Appearance of symptoms is linked to the size and location of the pseudocyst; potential symptoms are abdominal pain, early satiety, nausea/vomiting, icterus and weight loss (3). Spontaneous resolution of pancreatic pseudocyst occurs in 80% (4). General principle to intervening for PFCs can be summarized in 3 steps: delay, drain and if necessary, debride (5). Indication for intervention is symptomatic PFC, and the first-line therapy in the management of pancreatic pseudocyst is endoscopic drainage (1, 6, 7). Should that be unsuccessful, an experienced surgeon could try another minimally invasive laparoscopic treatment (7). Walled-off pancreatic necrosis is an encapsulated collection of both fluid and solid, necrotic debris that arises from an acute necrotic collection as a consequence of necrotizing pancreatitis. Symptomatic WOPN (especially infected WOPN) has significant morbidity and mortality (8). Successful treatment of WOPN is often difficult, with rates of success as low as 25% (9). A meta-analysis summarizing the results from 12 studies involving 481 patients with infected WOPN who were treated with percutaneous or endoscopic drainage found a pooled treatment success rate of only 59% (10). This leaves a significant group of patients with infected WOPN not responding to drainage procedures that require more aggressive debridement of the necrotic debris within the collection via direct endoscopic necrosectomy or direct surgery (5). Open necrosectomy used to be the traditional approach to infected necrosis. This is an invasive procedure associated with a high risk of complications (34–95%) and mortality (11–39%) and long-term pancreatic insufficiency (8).

Case report: 71-year-old male patient, who had a history of chronic pancreatitis with acute exacerbations of pancreatitis, probably of biliary etiology in years 2013, 2014, 2015, was admitted to the Department of Gastroenterology, leading symptom being abdominal pain in the upper abdomen.

His medical history was notable for acute myocardial infarction with stent insertion in 2005, peripheral obstructive arterial disease, after thrombectomy of femoral artery, liver steatosis, arterial hypertension. He was taking Aspirin 100mg 1x1 pill, April 2,5mg 1x1 pill, Atoris 20mg 1x1 pill, Coryol 6,25mg 2x1 pill, Sintrom, Controloc 20mg 1x1 pill, Kreon 25.000mg caps between meals, Symbicort 2x2 inhalations, Spiriva 1x2 inhalations, Berodual inhalations.

Ultrasound and computed tomography were performed. Cholecystolithiasis and pseudocyst (6x4cm) anterior to the pancreas was described. Trans gastric drainage of the pseudocyst was not successful due to the density of the pseudocyst collection. Surgical drainage was not indicated since the patient was asymptomatic. Later, the patient was underwent elective laparoscopic cholecystectomy. The operation and postoperative course were uneventful. After seven months, patient was urgently admitted to the Department of Gastroenterology; leading symptom was one-month lasting abdominal pain in the upper abdomen. Clinical status of abdomen revealed distended, diffusely painful abdomen and peristalsis was heard. Laboratory tests showed elevated WBC, CRP was 160 mg/L, elevated serum amylase, and lipase. Necrosis in the region of the neck of pancreas and pseudocyst anterior from pancreas were described on the CT scan. Monitoring and antibiotic therapy was advised by consultant abdominal surgeon. It was decided by interdisciplinary committee, that gastroscopy should be performed to evaluate the possibility of trans-gastric drainage or percutaneous drainage. Next day the patient collapsed due to the septic shock and was found unresponsive and without pulse. He was reanimated and transferred to the ICU, where elevated intraabdominal pressure was measured (30 mmHg). Due to the inefficient conservative treatment, the patient was operated on 11. 11. 2016 and laparotomy. Necrosis were evacuation. After 16 days, he was cardiocirculatory stabile transferred back to the Department of Gastroenterology, where elevation of inflammatory markers was recorded despite treatment with antibiotics. Again, a vast peripancreatic fluid collection was shown on abdominal CT. Abdominal secretions from draining tubes were amylase and lipase highly positive. The patient was transferred to the Department for general and abdominal surgery because of complications of treatment of acute necrotizing pancreatitis. Additional percutaneous drainage procedure was done and flushing draining tube was inserted. Residual collection, which was not drained by the draining tube, was seen on the US. A fistula could not be confirmed by the radiographic imaging, even though the secretions from the draining tubes were still highly amylase positive. The patient was again introduced on the interdisciplinary committee to evaluate the possibility of papillotomy and relieving the main pancreatic duct to decrease the secretion on abdominal draining tubes. ERCP was performed. Histology was taken, but no neoplastic growth was described by the pathologist. New necrotic collections were shown by additional radiographic diagnostic; again percutaneous drainage was performed. Over the course of a few days, tachycardia, respiratory distress, and chest pain were developed by the patient. Elevated inflammatory indicators were recorded again. This time a larger subcapsular hematoma of the spleen, which communicated with the peripancreatic fluid collection, was shown. The patient was urgently operated on 19. 1. 2017, splenectomy, evacuation of the hematoma and necrotic tissue, lavage and drainage was performed. In the next weeks, antibiotic and antifungal treatment was concluded, physical and respiratory rehabilitation was being done by the patient. Tachycardia and dyspnea developed by the patient on 18. 2. 2017, CTA of lungs excluded pulmonary embolism. Next day the patient deteriorated. Vasoactive support was needed. Last abdominal CT images were revised by radiologist; two smaller collections were described in pancreatic region. US-guided drainage of abscess was performed on 24.2.2017. The same day cardiocirculatory instability reappeared, patient was hypotensive elevation of vasoactive support.

With the intensive treatment being exhausted, death of the patient occurred on 25. 2. 2017. Autopsy was performed, yet there was no autopsy report in the time of writing of this contribution.

Discussion: The drainage of the pseudocyst was not done since the patient was asymptomatic. Size greater than 6 cm was previously an indication for drainage, today, as per revised Atlanta criteria, size alone does not necessitate the treatment, as most of pancreatic fluid collections tend to resolve spontaneously (5). When PFC becomes, symptomatic intervention is indicated (1, 6, 7). Our patient was urgently admitted because of abdominal pain. Hence the trans-gastric drainage was attempted, it was unsuccessful because of the density of the pseudocyst collection. After the conservative treatment, the symptoms were alleviated. Laparoscopic drainage was considered since the patient was asymptomatic, further treatment was not indicated after a joint decision. Since the recurrent pancreatitis episodes were of biliary etiology, the next step was laparoscopic cholecystectomy. The procedure was uneventful. A question arises, should at the same time laparoscopic drainage be done? After the procedure, the patient had a quiet period for about six months, then abdominal pain reappeared. Again, he had signs of acute pancreatitis. Radiographic images showed necrosis in the pancreas region. Consultant abdominal surgeon advised conservative approach, and interdisciplinary committee decided that minimal invasive trans-gastric drainage or percutaneous drainage should be tried. After that, the patient collapsed was found unresponsive and pulseless. He was reanimated and transferred to the ICU, where signs of intraabdominal compartment were recorded. Operation was indicated, necrosectomy was done and draining tubes inserted. After less than three weeks, abdominal CT again shows a vast PFC; his inflammatory indicators were elevated again. Abdominal secretions from drains were amylase and lipase highly positive. Again, minimally invasive percutaneous drainage was done and was draining some fluid from the collection, but not everything. Secretions were still amylase highly positive. Pancreatic fistula was not confirmed on repeated abdominal CTs. We wanted to relieve the pancreatic duct and alleviate high amylase secretions on abdominal drains, so again minimally invasive ERCP was successfully done. Nevertheless, abdominal CT showed new necrotic collections in pancreatic region, again, percutaneous drainage was done. In next days, patient developed tachycardia, respiratory distress, and chest pain. Urgent abdominal CT showed this time subcapsular hematoma that communicated with the PFC. Urgent operation was indicated and splenectomy was done along with evacuation of the hematoma and necrotic tissue, lavage, and drainage. The patient was put on antibiotic therapy for 21 days and antifungal therapy for ten days. He was slowly beginning to get better. A month after his last operation the patient deteriorated. He needed vasoactive support. Nevertheless, drops of blood pressure were monitored and we could not stabilize the patient despite increasing the vasoactive support. The prolonged course of a tough disease with a lot of complications on the way took a toll on a heart of a patient, who already had cardiac comorbidity and the patient died. Pancreatitis is a tough disease, best treated conservatively, despite that it can have a lot of complications, percentage of which rises with the more demanding procedures. We used the three-step approach, delay, drain and if necessary, debride. Sadly, the outcome for the patient was lethal.

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Ileokolična invaginacija, redek vzrok ileusa pri odraslih – prikaz primera

Jurij Aleš Košir[1], Gregor Norčič[2], Jan Grosek[2]
[1]*University Medical Center Ljubljana, Slovenia*
[2]*Klinični oddelek za abdominalno kirurgijo, Univerzitetni klinični center Ljubljana, Slovenia*
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Uvod: Invaginacija črevesja nastane, ko se črevo uviha v del črevesja pred njim. Mezenterij uvihanega dela črevesja se pretisne, nastane venski zastoj in edem, kasneje pride do prekinitve arterijskega pretoka, ishemije in nekroze. Otečeno uvihano črevo povzroči zaporo (1). Invaginacija predstavlja večino vzrokov ileusa pri otrocih starih pol do tretjega leta, pri odraslih pa predstavlja le 1–5 % vseh mehanskih ileusov (1). 75–85 % invaginacij v otroštvu je idiopatskih, večinoma so lokalizirane ileocekalno (2). Vlogo v etiopatogenezi ima nabreklo limfatično tkivo, ki je prisotno pri večini otrok z ileocekalno invaginacijo. Pri odraslih je večina invaginacij sekundarnih zaradi potega patološke formacije, tako imenovanega vodila, v distalni del črevesja (2). Zdravljenje se zaradi različne etiologije razlikuje glede na starostne skupne. Pri otrocih se najprej poskuša razrešiti invaginacijo konzervativno s točenjem fiziološke raztopine pod nadzorom ultrazvoka ali s polnjenjem z zrakom in kontrastom pod nadzorom diaskopije z namenom, da bi se uvihani del črevesja izbočil nazaj ven. Če to ni uspešno ali če ima otrok težave že dalj časa, se odločimo za kirurško zdravljenje (3). Pri odraslih je v več kot polovici primerov vodilo maligna neoplazma, zato se zdravi predvsem kirurško z resekcijo prizadetega dela (2). Vodila so lahko tudi benigni tumorji, tujki, Meckelov divertikel, ulkusi in vnetni polipi (1).

Prikaz primera: 41-letna gospa je bila obravnavana na Kliničnem oddelku za abdominalno kirurgijo Univerzitetnega kliničnega centra Ljubljana zaradi slabosti, trebušnih bolečin in izgube 10 kg v petih tednih. Test na prikrito krvavitev v blatu je bil ob tem pozitiven. Sicer je bila gospa zdrava, brez redne terapije. Opravila je gastroskopijo, ki je v korpusu želodca pokazala izboklino, takrat sumljive za GIST želodca, vendar je histološki pregled odščipov pokazal normalno sluznico želodca. Čez nekaj dni je imela opravljeno kolonoskopijo, kjer je bil najden tumor v predelu Bauchinijeve zaklopke. Še isti dan je bila gospa sprejeta na naš klinični oddelek zaradi predvidenega operativnega zdravljenja. Dan po sprejemu je opravila CT, ki je pokazal obsežno ileokolično invaginacijo, ki je segala vse do jetrnega zavoja debelega črevesja. Kot vodilo je bil suspekten lipom velikosti 55 x 38 mm. V prihodnjih dneh je bila operirana, napravljena je bila laparoskopska desna hemikolektomija, odvzet je bil aspirat tekočine v Douglasovem prostoru in poslan na citološko preiskavo, kjer ni bilo najdenih malignih celic. Patohistološki pregled reseciranega preparata je govoril za submukozni lipom ascendentnega debelega črevesja brez zasevkov v pregledanih 15 bezgavkah. Pooperativni potek je bil ugoden in gospo smo po nekaj dnevih odpustili domov. Na kontrolnem pregledu je navajala dobro počutje brez preteklih težav.

Zaključek: Invaginacija je redek vzrok mehanskega ileusa pri odraslih. Ob sumu nanjo in s pravilnimi preiskavami je diagnoza na dlani. Za razliko od otroških primerov, ki so predvsem idiopatske etiologije, je pri odraslih večina primerov posledica malignega tumorja, zato je zdravljenje temu primerno usmerjeno s kirurško resekcijo prizadetega dela. Vzrok so lahko tudi benigne tumorske formacije.

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Limitations of diagnostic methods in evaluation of a cecal tumor – Case report

Lah Taja[1], Ocepek Andreja[1], Pernat Drobež Cvetka[1], Andromako Nikica[2]
[1]*Department of Gastroenterology, Clinic of Internal Medicine, University Medical Centre Maribor, Slovenia*
[2]*Department of Abdominal and General Surgery, University Medical Centre Maribor, Slovenia*
Gastroenterolog 2017; suplement 3: 104

Introduction: Primary lymphoma is a rare tumor of the gastrointestinal tract, representing only 0.2 to 1.2% of all malignant tumors of the colon (3). Diffuse large B-cell lymphoma is a lymphoid neoplasm of large immature lymphoid cells and is most common among non-Hodgkin lymphomas. It occurs predominantly around the age of 70, and in male patients. In addition to lymph nodes, it most commonly affects the stomach and ileocecal part of the intestine, but also many other organs and tissues (1, 2).

Case report: a 69-year-old male patient experienced moderate pain in the lower right quadrant of abdomen, occasional diarrhea and weight loss in last two months. Abdominal ultrasound performed in an out-patient setting followed by computed tomography showed thickened cecal wall and suspicious lymph nodes in the area. Patient's history revealed a removed colonic polyp years ago, chronic obstructive lung disease and gout. Clinical status was insignificant except of a painful palpable mass in the ileocecal region. Among laboratory parameters only mildly elevated C-reactive protein and tumor marker beta-2-microglobulin were discovered. Colonoscopy confirmed a large ulcerated cecal tumor, but histological finding was surprising – only granulation tissue and signs of chronic inflammation were described. Repeated colonoscopies (altogether 3) were done with multiple biopsies, revealing progression of pathology: a large fistula between sigmoid and cecal colon was found, with smaller new fistulas developing. Histology remained inconclusive. Differential diagnosis was wide: synchronous carcinoma of cecal and sigmoid colon, fistulizing Crohn's disease, colon tuberculosis (the patient had a positive quantiferon test and history of coming in contact with a tuberculosis patient in childhood) or lymphoma. Following extensive and repeated diagnostics a multidisciplinary council agreed on a surgical approach due to a progressive course of disease. During an explorative laparotomy, a right hemicolectomy with additional resection of ileum and sigmoid colon was done. Finally, histology of the resected bowel defined the tumor as diffuse large B-cell lymphoma, centroblastic type. Postsurgical course was uneventful, and the patient was referred to Institute of Oncology in Ljubljana for oncological treatment.

Conclusion: Despite repeated endoscopic examinations and multiple biopsies we could not histologically verify a cecal tumor preoperatively. Only in cooperation with abdominal surgeons and after surgical resection definite histological diagnosis could be established, necessary for appropriate oncological treatment of advanced form of this rare malignant tumor of the colon.

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„Step up“ and „Top down“ therapeutic approach in patients with inflammatory bowel disease

Marinko Žulj[1], Matej Tomić[2], Ana-Marija Vezmar[2], Kristina Steiner[2], Mladen Vukovic[2], Sabina Steiner[1], Matija Fenrich[2], J. Jakab[1], Marko Boban[1], Aleksandar Včev[1]
[1] *Department of Internal Medicine, Faculty of Medicine Osijek, Croatia*
[2] *Student at Faculty of Medicine Osijek, Croatia*
Gastroenterolog 2017; suplement 3: 105

Background: Ulcerative colitis and Crohn's disease are idiopathic autoimmune diseases whose incidence is constantly increasing, consequently representing a significant health problem of a developed Western society. They are characterized by chronic inflammation of the gastrointestinal wall and the high occurrence of relapse. Drug groups used in the treatment of inflammatory bowel disease are aminosalicylates, corticosteroids, immunomodulators and biological agents. By developing new drugs, therapeutic approach has changed from the simpler "step up" to the "top-down" approach, where more complex and more effective drugs are applied from the start. The basic goal of the treatment is to develop a deep remission and its longer duration, along with the smaller number of relapses. The aim of this study was to determine frequency of disease relapses in various types of the therapy.

Materials and Methods: The research was based on medical documentation of patients affected by inflammatory bowel disease, treated at the Department of Gastroenterology and Hepatology, at Clinical Hospital Osijek. In total, 79 patients were involved, of which 40 of them were diagnosed with ulcerative colitis and 39 with Crohn's disease.

Results: Patients with Crohn's disease achieved the longest remission, up to 2450 days, when receiving biological therapy. Much shorter remission is seen in patients taking aminosalicylates. However, there was no significant difference in remission duration between different treatment strategies (Mann-Whitney U test, P = 0,2836). For patients with ulcerative colitis, the best results, with the remission up to 2500 days, gave the combination of aminosalicylates and immunosuppressives. Still, there was no significant difference in remission duration between different treatment strategies (Mann-Whitney U test, P = P = 0,4762).

Conclusion: Almost all patients in this study started treatment with a »step-up« approach, and only at later stages of the disease were treated with biological therapy. Because of the reason mentioned above, there was no statistically significant difference between the »step up« and »top down« therapeutic approaches, and further assessment of these investigated groups is required.

IgG4-related sclerosing cholangitis and autoimmune pancreatitis

Manca Novak[1]
[1]*Gastromedica d. o. o., Murska Sobota, Slovenia*
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Background: IgG4-related sclerosing cholangitis (IgG4-SC) is a characteristic type of sclerosing cholangitis with an unknown pathogenic mechanism. Patients with IgG4-SC display increased serum IgG4 levels and dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall. IgG4-SC is frequently associated with autoimmune pancreatitis (AIP) and is part of IgG4-related disease. IgG4-related dacryoadenitis, sialadenitis, and IgG4-related retroperitoneal fibrosis are also occasionally observed in Ig4-SC. IgG4-SC should be carefully diagnosed based on a combination of characteristic clinical, serological, morphological and histopathological features. The disease commonly occurs in elderly men with a mean age of 70 years. The major presenting complaint is painless obstructive jaundice. The characteristic features of IgG4-SC can be classified into four types based on the stricture regions revealed by cholangiography and differential diagnosis. Type 1 IgG4-SC displays stenosis only in the lower part of the common bile duct and thus should be differentiated from chronic pancreatitis, pancreatic cancer, and cholangiocarcinoma. Type 2 IgG4-SC, in which stenosis is diffusely distributed throughout the intrapancreatic and extrapancreatic bile ducts, should be differentiated from primary sclerosing cholangitis (PSC) and is then further subdivided into two subtypes. Type 3 IgG4-SC is characterized by stenosis in the hilar hepatic lesions and the lower part of the common bile duct. Type 4 IgG4-SC presents with strictures of the bile duct only in the hilar hepatic lesions. Serum IgG4 level is a useful marker to distinguish IgG4-SC from pancreatic malignoma, as the value of more than twice the upper limit of normal, more than 135 g/dl, is used as a diagnostic criteria. Pathological features in IgG4-SC represent fibroinflammatory involvement mainly in the submucosa of the bile duct wall, whereas the epithelium of the bile duct is intact. Dense infiltration of lymphocytes and IgG4-SC-positive plasma cells with extensive fibrosis and obliterative phlebitis is present. IgG4-SC responds well to steroid therapy, although after steroid withdrawal relapses occur in 53%. The presence of proximal strictures is predictive of relapse. In refractory cases for oral steroids, it has been reported that steroid mini-pulse therapy, immunomodulators (azathioprine) and rituximab are useful.

Case report: We report a case of 76-year old man who was admitted to local hospital with a two-week history of jaundice, loss of appetite, pale stool and frequent urination of dark urine. On physical examination, he was icteric with mild right upper quadrant tenderness. Laboratory findings revealed high values of bilirubin (287/230 µmol/l) and cholestatic enzymes (AF 10,14 µkat/L; GGT 14,35 µkat/l) with only slightly elevated transaminases (AST 1,37 µkat/l; ALT 1,66 µkat/l). Pancreatic enzymes, inflammatory parameters, and kidney function were normal. Serum glucose was high (22,6 mmol/l), as well glucose in urine, with no signs of ketoacidosis. Cancer antigen CA 19–9 was

elevated (288 U/ml). Abdominal ultrasound (US) demonstrated dilated common bile duct to 10 mm, dilated intrahepatic bile ducts, enlarged gallbladder with gallstones and normal liver. Pancreas was diffusely enlarged, hypoechoic with no focal mass. There was no ascites. Computer tomography (CT) revealed dilated common bile duct and intrahepatic bile ducts, prominent homogenous head of pancreas, enlarged lymph nodes around pancreas, aorta, truncus coeliacus and splenoportal venous. Endoscopic retrograde cholangiopancreatography (ERCP) was performed and clearly showed stenosis in distal part of common bile duct with dilatation proximally. Successful biliary decompression was performed by internal stenting. Aspiration of bile for cytological analysis was taken and showed only inflammatory cells. The patient was transmitted to clinical center for operative treatment because of stenosis of common bile duct and suspected cholangiocarcinoma. Between the operation, a tumor was palpated in the region of the pancreas head. Macroscopically was suspicious for chronic pancreatitis. Frozen section procedure did not confirm malignancy but dense fibrosis with marked lymphoplasmacytic infiltration. The pylorus-preserving pancreaticoduodenectomy (PPPD), Whipple procedure, was performed histopathological findings in the resected specimens (resected duodenum with the head of the pancreas, peripancreatic fat tissue with lymph nodes and gallbladder) revealed extensive and dense fibrosis with marked lymphoplasmacytic infiltration and obliterative phlebitis; in all resected lymph nodes there were signs of reactive follicular hyperplasia with no neoplasia. There were signs of chronic cholangitis in the resection margin of the common bile duct and signs of chronic cholecystitis in the gallbladder wall. The histology structure of duodenum was normal. The pathologist suggested to evaluate IgG4 serum measurement because of chronic atrophic fibroproliferative pancreatitis. Serum IgG4 level was more than four times upper limit of normal. We started with oral steroids, methylprednisolone with the initial dose 0,5 mg/kg body weight/day for eight weeks. Regular laboratory check-ups were performed. Bilirubin and cholestatic enzymes dropped to almost normal range. After eight weeks we slowly tapered the dose and gradually discontinued treatment with steroids. After four weeks patient became icteric again, bilirubin and cholestatic enzymes were high, serum IgG4 was elevated more than four times. We restarted with steroids with the same dose as the first time. Because of relapse soon after the discontinuation of steroids the patient didn't stop the therapy with steroids this time but stays on minimum possible steroid dose that remains remission. He also takes medications for osteoporosis prevention and acid suppression therapy for gastric ulcer prevention. His blood sugar is in normal range with higher doses of insulin. His bilirubin values are in normal range. He might be a candidate for immunosuppressive medication, azathioprine.

Conclusions: IgG4-SC has become a distinct clinical entity of sclerosing cholangitis. IgG4-SC should be carefully diagnosed based on a combination of characteristic clinical, serological, morphological and histopathological features after cholangiographic classification and targeting of a disease for differential diagnosis.

Endoscopic management of buried bumper syndrome – case of a patient with Parkinson's disease and intestinal application of levodopa through PEG-J tube

Ocepek Andreja[1], Pernat Drobež Cvetka[1], Ademovič Tadej[1], Borak Marinka[1], Menih Marija[2], Ornik Košan Marjetka[2]
[1]*Department of Gastroenterology, Clinic for Internal Medicine, University Medical Centre Maribor, Slovenia*
[2]*Department of Neurology, University Medical Centre Maribor, Slovenia*
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Introduction: Buried bumper syndrome (BBS) is a rare, but well-known complication of percutaneous endoscopic gastrostomy (PEG). It occurs if too much pressure is exerted on an outer tube fixator over longer period. Inner bumper becomes partially or completely over-grown with stomach mucosa. We present a case of a patient with BBS that was successfully managed endoscopically.

Case report: 78-year-old female patient with Parkinson's disease had PEG tube (15 Fr diameter, AbbVie™ PEG, AbbVie Inc, North Chicago, ZDA) with jejunal catheter (9 Fr diameter, AbbVie™ J, AbbVie Inc, North Chicago, ZDA) inserted in November 2014 for continuous intestinal application of levodopa. Until March 2017 patient was doing well, she was regularly followed-up by neurologist and neurology nurse, who in March 2017 discovered that PEG tube was not mobile. Suspicion of BBS was confirmed at gastroscopy.

Avoiding potential complications of a surgical procedure decision to remove PEG-J endoscopically was made. During gastroscopy another interesting complication was discovered; jejunal catheter tip was tied in a knot. Before removing jejunal catheter, we managed to untie it with grasping forceps. Through PEG and small opening in stomach mucosa, a guide wire was inserted, which was used to safely guide a sphincterotome (normally used during endoscopic retrograde cholangiopancreatography) into the stomach. Multiple cuts were done to stomach mucosa that has over-grown the inner bumper. Also, needle knife papillotomy was used to further cut through stomach mucosa over the bumper, and with the help of endoscopic grasping forceps, it was finally pulled into the stomach cavity. The bumper was grabbed with a snare, the tube was cut and the bumper extracted through the mouth. Endoscopically defect in the stomach mucosa was evaluated for bleeding. No immediate complication was observed. Post-procedural course was uneventful, with no signs of pneumoperitoneum, peritonitis or bleeding. At follow-up gastroscopy, the defect was healed.

Conclusions: Anecdotal cases of endoscopic management of BBS have been described in literature. Skilful and resourceful endoscopists have successfully improvised using diverse endoscopic accessories to avoid surgical treatment for BBS. We also succeeded to endoscopically remove overgrown PEG-J tube, providing an older patient with a less invasive therapeutic procedure. An endoscopic accessory for managing BBS is already commercially available (Flamingo-kit®, Medwork, Hoechstadt an der Aisch, Nemčija), but it was useless in our case, as it is intended for removal of 20 Fr PEG tubes and our patient had a 15 Fr PEG tube in place.

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Risk factors for chronic liver diseases in random adult volunteers – Liver day 2017 at UMC Maribor

Ocepek Andreja[1], Brada Besarta[1], Lah Taja[1], Kolar Petra[1], Roškar Irena[1], Fideršek Manuela[1], Kramberger Alenka[1], Gregorčič Jure[1], Veingerl Tadeja[1], Ulčnik Suzana[1]
[1]*Department of Gastroenterology, Clinic for Internal Medicine, University Medical Centre Maribor, Slovenia*
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Introduction: Chronic liver diseases affect people all around the world independent of gender, age or race. Among European countries Slovenia has one of the highest mortality rates due to liver cirrhosis, main reason being excessive alcohol consumption. Other more common risk factors are non-alcoholic liver steatosis, and chronic viral hepatitis B and C, less frequent are immune-mediated inflammatory diseases (IMID), genetic factors and toxic effects of various medications, drugs, and herbs. On 19th of April 2017, World Liver Day, we organised an information booth for visitors of our clinic.

Methods: We invited random adults to participate in an observational one-day study on risk factors for chronic liver diseases. Every volunteer fulfilled a questionnaire on risk factors; we measured their body weight (BW) and height (BH), calculated body mass index (BMI), measured blood glucose (BG), total cholesterol (CHO) and triglycerides (TG). Accu-Check® glucometer and Accu-Trend® cholesterol and triglycerides measuring device was used (F. Hoffmann-La Roche AG Konzern-Hauptsitz, Basel, Switzerland).

Results: 92 adults were included in the study, 75 (81,5%) were female. None acknowledged excessive alcohol consumption, defined as more than 14 units of alcohol consumed weekly for men and more than seven units of alcohol consumed weekly for women. Average BMI was 26,05 kg/m^2 (17 to 45 kg/m^2). 43 (46,7%) volunteers had BMI over 25 kg/m^2 and 22 (23,9%) 30 kg/m^2 or more. Average level of BG was 6,44 mmol/L (3,9 to 14,6 mmol/L). 64 (69,5%) volunteers had elevated levels of CHO (over 5,1 mmol/L) and 37 (40,2%) volunteers had elevated levels of TG (over 1,7 mmol/L). In 12 (13%) volunteers, we established risk factors for infection with hepatitis B or C virus: 2 individuals acknowledged unsafe sexual behaviour, one person had a tattoo done at an unreliable tattoo-shop, ten volunteers received blood transfusion before 1992, none were i.v. Drug users. 20 (21,7%) volunteers had IMID (Crohn's disease, psoriasis, thyroid disease...). 3 (3,3%) volunteers were susceptible to genetically caused chronic liver diseases (e.g. haemochromatosis). 48 (52,2%) volunteers regularly or frequently used potentially hepatotoxic medication (mainly non-steroidal anti-inflammatory drugs (NSAID's), paracetamol and statins). 15 (16,3%) volunteers mentioned using herbal remedies and teas but were deemed liver-safe.

Conclusions: In our observational study most frequent risk factors for chronic liver diseases among random adults were elevated levels of CHO, TG, BMI and BG, which is in concordance with increasing incidence of non-alcoholic liver steatosis and steatohepatitis in developed countries. High percent of participants with IMID is likely due to enrollment among hospital visitors. More than half of participants acknowledged regular or frequent use of potentially hepatotoxic medication, mainly NSAID's. The aim of our study was not only to establish frequency of risk factors for chronic liver diseases in random adult volunteers but mostly to raise awareness of this health issue and preventive measures among general public.

Efficacy of Vedolizumab as Induction Therapy for Inflammatory Bowel Disease: Our experiences

Cvetka Pernat Drobež[1], Andreja Ocepek[1], Davorin Dajčman[1], Andrej Zafošnik[1]
[1]*Department of Gastroenterology, Clinic for Internal Medicine, University Medical Centre Maribor, Slovenia*
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Background and Aim: GEMINI 1 and GEMINI 2 trials have shown the efficacy of vedolizumab, a new type of monoclonal antibody targeting integrins, in patients with Crohn's disease or Ulcerative colitis. Our aim was to assess both efficacy and safety of vedolizumab in »real-life conditions« in patients who failed anti-tumor necrosis factor (anti-TNF) therapy.

Methods: All patients treated with vedolizumab were included without any exclusion criteria. Vedolizumab (300mg) was administered at weeks 0, 2, 6 (10 in Crohn's disease) and 14. Clinical response and clinical remission were evaluated by the end of the induction phase, using Harvey-Brashow index for Crohn's disease (CD) and partial Mayo Clinic Score for Ulcerative Colitis (UK). Side effects were collected during the induction phase.

Results: 27 patients were enrolled from September 2016, including 15 CD, and 12 UC. Mean age was 42 years for CD, and 47 years for UK; mean disease duration was 10,4 years for CD, and 11,6 years for UK. All patients completed the induction period. Previous treatment failures with 1 or 2 anti-TNF occurred in 96%, one-thirds were on an immunomodulator and 20% on systemic steroids at baseline. In CD, 56%, and 33% and UC, 57% and 29% had clinical response and steroid-free clinical remission at week 14. Adverse events occurred in 10.5%.

Conclusions: Our results support both, efficacy and safety of vedolizumab in routine use, as previously demonstrated in other »real life« studies (1, 2, 3). Vedolizumab may, therefore, be an effective and safe drug for treatment the patients with moderate to severe Inflammatory Bowel Disease.

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The impact of preoperative patient preparation: nonsurgical complications, long-term results and quality of life

Tadeja Pintar[1], Tanja Carli[2]
[1]*Abdominal Surgery, UMC Ljubljana, Ljubljana, MF Ljubljana, University of Ljubljana, Slovenia*
[2]*MF Ljubljana; Insititute of physiology, University of Ljubljana, Slovenia*
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Introduction: Consistent and accurately preoperative patients preparation based on standard recommendation scheme have been shown to be efficient in reduction of short and medium term results: non-surgical complications and weight loss. Programs included detailed dietary counseling, education to autoregulative dietary supervision and physical activity (PA) encouraging are highly efficient to obtain good long-term results. The impact of dietary counseling based on locally produced and self-preparing food is highly efficient: weight reduction and maintenance, lean body mass, adherence to PA and quality of life (QL) are improved.

Methods: Standard protocol for preoperative patient preparation prior any obesity surgery intervention have been introduced and also regular detection of OSA, BIA measurement pre- and postoperatively. Protocol augmentation based on basic dietary consultation, specific food preparation, adherence to step PA according to BMI and physical ability was introduced to the cohort of 50 patients. Advanced counseling from surgical team was started and web page recipes and local recipes introduced by interview.

Results: Average 13 kg preoperative weight loss was observed, representing 12%EWL (ranged fro 7–20 kg), average increase of lean body mass 1,5–2 kg, average reduction of BMI(kg/m^2) for 3–5, improvement of PA ability and activity: regular activity mostly light walk 3–4 times a week in the tendency of time prolongation and important improvement to QL have been observed. Average one-year EWL ranged 85%, two years 90% and three years 90% with average BMI (kg/m^2) 26 in the 3rd postoperative year. Postoperatively patients most frequently used fitness training 3–4 times/week, included dietary scheme to calory needs and dietary substrate. No metabolic complications were observed in detailed recommendations. Patient mark to satisfaction was ranged from 9,3–9,9 of 10.

Conclusion: The results of small observational study showed the importance of educational and supporting activity from bariatric team to efficient preoperative patient preparation and the impact of surgical team to patient adherence to instructions and recommendations resulting in short, intermediate and long-term results. Clear and detailed instructions also resulted in improved QL and no non-surgical complications incidence.

Clostridium difficile isolation and characterisation – results of a pilot study in IBD patients

Pintar Š[1], Rupnik M[1,2], Pavel Skok[1,3]
[1]*Faculty of Medicine, University of Maribor, Slovenia*
[2]*National Laboratory for Health, Environment and Food, Slovenia*
[3]*Department of Gastroenterology, Clinic for Internal Medicine, University Medical Centre Maribor, Slovenia*
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Introduction: Clostridium difficile (CD) infection is becoming prevalent in general population as well as in patients with inflammatory bowel disease (IBD). Ulcerative colitis and Crohn's disease are chronic diseases causing prolonged inflammation of gastrointestinal tract. These patients are often colonized with CD, but its role is inconclusive.

Study aims: To compare CD colonization and selected laboratory parameters in patients with IBD and control group.

Patients and methods: In the period between 1/12/2015 – 1/5/2016, we obtained fecal samples from 161 randomly selected patients, hospitalized at Department of Gastroenterology. Total DNA was isolated from feces and CD was detected using real-time PCR amplification of specific 16S RNA gene. Toxigenic strains were confirmed by the amplification of *tcd*B gene. After collecting patient's demographic information, inflammatory parameters and therapy (including pre-and hospital antibiotics, corticosteroids, biological therapy) we divided isolates in two groups: IBD patients and control group patients.

Results: In the final analysis were included 151 samples (male 75, female 76), 48 (31.8%) from IBD patients and 103 (68.2 %) from control group. In IBD group 23/48 samples (47.9%) were positive for CD; 7 were *TcdB*+ (7/48, 14.6%). In the control group 42/103(40.8%) were positive for CD, 11 were *TcdB*+, (11/103, 10.7%). Between the two groups, significant differences were confirmed in the use of corticosteroids and biological therapy before hospitalization, $p<0.001$. Regarding the use of antibiotics before hospitalization, differences between the two groups were not confirmed, $p=0.72$. Within IBD patients (CD positive compared to CD negative) no significant differences in inflammatory parameters were observed.

Conclusion: The results of our study suggest that IBD patients and patients from the control group were colonized with CD in comparable proportions. The majority of strains were nontoxigenic, which will not cause CD infections but could be regarded as a marker for disturbed gut microbiota.

Emergency Liver Resection after Bleeding from Spontaneously Ruptured Recurrent Hepatocellular Carcinoma in a Patient with Metabolic Syndrome without Steatosis and Cirrhosis: A Case Report

Irena Plahuta[1], Arpad Ivanecz[1], Stojan Potrč[1]
[1]*Department of Abdominal and General Surgery, University Medical Center Maribor, Slovenia*
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Introduction: Recently, an array of metabolic abnormalities regarded as *metabolic syndrome* has been strongly associated to the development of hepatocellular carcinoma (HCC) in a share of cases previously attributed to *cryptogenic* HCC. However, there are still some patients with HCC whose disease is cryptogenic. A spontaneous rupture of HCC is an unusual presentation of this disease, especially in Western countries. This article focuses on a case of a 57-year-old man who has undergone two similar episodes of an HCC complication over a 6-year period. He was diagnosed with metabolic syndrome, but pathohistological examination revealed no liver steatosis or cirrhosis.

Case presentation: In 2010, a 51-year-old male was referred to the emergency unit due to acute onset of abdominal pain. His BMI was 31; he had known arterial hypertension, diabetes mellitus type 2 and dyslipidemia. He was a construction worker and a smoker. Later auto- and heteroanamnesis for alcohol abuse were negative as well as the testing for hepatitis B and C, aflatoxin, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis and alpha-1-antitrypsin deficiency. During the examination, a hemorrhagic shock appeared. The CT scan revealed a bleeding from a solid HCC with a maximum diameter of 4.5 cm, located in the liver segment 5 (Figure 1). After the stabilization of the patient, trans-arterial embolization (TAE) was performed. The patient was classified as stage A according to BCLC classification. Four days later, an elective R0 resection of the segment five was done. The post-operative course was uneventful. During the next three years, the patient showed no signs of recurrence. For an unknown reason, he stopped attending hospital for routine follow-ups. In 2016, he was again referred to the emergency unit due to acute abdominal pain. The check-up revealed a hemorrhagic shock. The CT scan of the abdomen showed a bleeding from a HCC in the left lateral liver section with hemoperitoneum. Because of a critical hemodynamic instability, TAE was canceled and the patient was transferred to the operating theater. A suture ligature was made on the arterial branch for the left lateral segment of the liver. Multiple organ dysfunction syndrome appeared after four days. The CT scan showed expected necrotic changes in the left lateral section. There was an indication for a second-step surgery. An anatomic left lateral sectionectomy was performed. The histopathologic examination revealed an HCC with a maximum diameter of 8 cm. Margins were free of HCC infiltration. The trabecular growth pattern was described, and the histologic grade was 3 (Figure 2). There was no liver steatosis or cirrhosis in the specimens from the year 2010. The postoperative course was uneventful. The patient was doing well and showed no signs of recurrence during his 3- and 6-months follow-ups.

Discussion: Nevertheless, there is still a cluster of undiscovered pathophysiologic pathways hidden under the term "cryptogenic HCC." Spontaneous rupture of HCC is a rare, but potentially fatal condition. Routine follow-ups are hence crucial for the early detection of disease recurrence since curative therapy can still be offered and life-threatening complications can be prevented on time.

Computed Tomographic Perfusion Imaging for the Prediction of Response and Survival to Transarterial Chemoembolization of Hepatocellular Carcinoma

Peter Popovič[1], Ana Leban[1], Klara Kregar[1], Manca Garbajs[1], Rok Dežman[1], Matjaž Bunc[1]
[1]*Clinical Institute of Radiology, University Medical Centre Ljubljana, Slovenia*
Department of Cardiology, University Medical Centre Ljubljana, Slovenia
Gastroenterolog 2017; suplement 3: 114

Purpose: The purpose of this retrospective cohort study was to evaluate the clinical value of computed tomographic perfusion imaging (CTPI) parameters in predicting the response to treatment and overall survival in patients with hepatocellular carcinoma (HCC) treated with drug-eluting beads transarterial chemoembolization (DEBTACE).

Methods: Between December 2010 and January 2013 eighteen patients (17 men, one woman; mean age 69 5.8 years) with intermediate stage HCC underwent contrast-enhanced CTPI of the liver before treatment with DEBTACE (mean, 22 ± 49.7 days). Treatment response was evaluated on follow-up imaging (mean, 4.9 3.3 months after first DEBTACE) according to modified Response Evaluation Criteria in Solid Tumors (mRECIST). Pre-treatment CTPI parameters were compared between responders (complete response) and non-responders (partial response) with a Student t-test. For survival analysis patients were divided into two groups by the threshold value for each parameter.

Results: CTPI parameters of responders and non-responders to DEBTACE did not show statistical significant difference (hepatic blood flow (BF) $p = 0.271$, hepatic blood volume (BV) $p = 0.240$, time to peak (TTP) $p = 0.551$, permeability (PMB) $p = 0.616$, arterial liver perfusion (ALP) $p = 0.400$, portal vein perfusion (PVP) $p = 0.404$, hepatic perfusion index (HPI) $p = 0.322$). The mean survival time was 25.4 ± 3.2 months (95 % CI: 18.7–32.1). One-year and two-year survival was 83.3 % and 50 % respectively. Survival was statistically significantly longer in patients with BF lower than 50.44 ml/100ml/min ($p = 0.033$), BV lower than 13.32 ml/100ml ($p = 0.028$) and TTP higher than 19.035 s ($p = 0.015$).

Conclusions: CTPI enables prediction of survival in patients with intermediate stage HCC, treated with DEBTACE based on the pre-treatment values of BF, BV and TTP perfusion parameters. CT perfusion imaging can't be used to predict treatment response to DEBTACE.

Proton pump inhibitors and gastric fundic gland polyposis - Case report

Maja Potisek[1], Nataša Brglez Jurečič[1]
[1]*Internal Medicine Department, General Hospital Trbovlje, Trbovlje, Slovenia*
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Background: Proton pump inhibitors are safe and effective treatment for peptic ulcer disease. Lately, reports and studies have emerged in the literature about the adverse effects of long-term therapy with proton pump inhibitors, even though serious adverse effects seem to be rare.

Case report: 66-years old female patient presented to our endoscopic outpatient clinic in 2014 with abdominal discomfort and weight loss. Before that, upper endoscopy had been performed in 2009. Hemorrhagic chronic H pylori negative gastritis was diagnosed, and lansoprazole therapy was initiated. She had been taking lansoprazole 15 mg at first occasionally, but then continuously for at least three years. In March 2014, we performed esophagogastroduodenoscopy (EGD). We discovered numerous sessile polyps in the gastric body, ranging from 2 to 10 mm in diameter. Gastric mucosa was hyperaemic, while esophagus and duodenum appeared normal. Biopsies of several polyps were performed, and according to histological report, they were classified as gastric fundic gland polyps. Lansoprazole was discontinued immediately. In October 2014, control EGD was performed – almost complete polyp regression was evident, we found only few tiny polyps in the body. In April 2015, patient underwent another control. At the time, only three remaining gastric fundic gland polyps were still present. Two of them were completely removed during the procedure. The last control was in March 2017. The patient complained of mild dyspepsia, but she has not been taking any medications. Only one remaining sessile polyp was found in fundus, which we biopsied. No dysplastic changes were reported.

Conclusion: Fundic gland polyps are among the most common type of gastric polyps found during EGD. They are usually sessile, shiny, pale and are confined to gastric body and fundus. Sporadic fundic gland polyps are described as benign lesions with no risk of malignant transformation, although some appear to contain low-grade dysplasia. Gastric polyps can also occur in patients with familial adenomatous polyposis. They are histologically similar, but genetic markers show distinctive differences.

According to the literature, long-term therapy with proton pump inhibitors is associated with fundic gland polyp development. The polyp risk increases with the length of drug use (especially after 12 months). Chronic acid suppression therapy causes the levels of circulating gastrin to rise, which stimulates increased cell proliferation. However, most patients on chronic PPI therapy never develop fundic gland polyps, and it remains unclear, why some of them do. Our patient fits the criteria perfectly. She had been using proton pump inhibitor for more than three years, and after the discontinuation of this therapy, complete regression of fundic gland polyps occurred. However, it is always important to exclude the possibility of familial adenomatous polyposis. Therefore a detailed family history and sometimes colonoscopy are necessary. We excluded AFP according to our patient's age and absence of gastrointestinal polyps in her family. Complete regression of lesions confirmed it. Our patient seems to do well even three years after the PPI therapy cessation. However, it remains unclear whether any benefits from sporadic polyp regression outweigh potential adverse effects from disruption of antisecretory therapy.

Induction and Maintenance Trough Levels of Golimumab Predict Drug Retention Rate in Ulcerative Colitis Treated with Golimumab

Sebastian Stefanović[1], David Drobne[1], Iris Detrez[2], Anouck Thienpont[2], Borut Štabuc[1], Ivo Ferkolj[1], Nataša Smrekar[1], Gregor Novak[1], Matic Koželj[1], Marc Ferrante[3] and Ann Gils[2]
[1]*Department of Gastroenterology, University Medical Center Ljubljana, Ljubljana, Slovenia*
[2]*Department of Pharmaceutical and Pharmacological Sciences, Laboratory for Therapeutic and Diagnostic Antibodies, KU Leuven, Leuven, Belgium*
[3]*Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Leuven, Belgium*
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Background: Golimumab is a recently approved TNF inhibitor for moderate to severe ulcerative colitis. Real life data on clinical efficacy and pharmacokinetics are scarce.

Aims: We aimed to study clinical outcome and pharmacokinetics of golimumab in real life settings and to identify biochemical and clinical predictors of response.

Methods: We prospectively studied 19 patients who started golimumab for treatment of ulcerative colitis in a tertiary university referral medical IBD center. We collected clinical data and serum for golimumab trough level determination at prespecified time points after start of golimumab: day 3, week 1, 2, 3, 4, 6, 10, 14, 26, 38, 40, 44, 50. The main outcomes were short-term response (defined by absence of blood and diarrhea at week 14) and drug retention rate at the end of follow-up. Golimumab trough levels were measured after the completion of the study (ELISA, Leuven in-house assay). Statistical analysis included correlation of clinical predictors (disease duration, corticosteroid therapy at start of golimumab, disease extent, age, body weight) and golimumab trough levels with short-term response and drug retention rate. Predictors for drug retention rate were analyzed with Kaplan-Meier analysis. Differences in median induction (defined as median of day 3, week 2, 3, 4, 6 golimumab trough level) and median maintenance trough levels (defined as median of 10, 14, 26, 38, 40, 44, 50 golimumab trough levels) in responders compared to non-responders were analyzed with Mann-Whitney - U test. P value < 0.05 was considered significant.

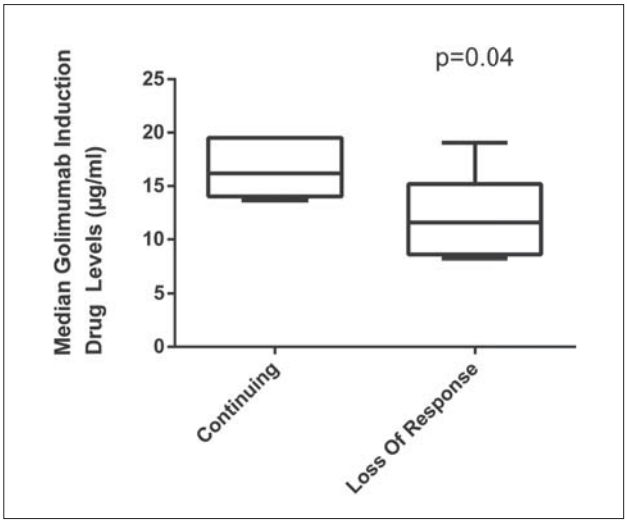
Results: 19 patients have started golimumab since 2014. Patients' demographics are given in Table 1. Short-term response was observed in 11/19 (57.9%) patients'. None of the studied parameters were predictive for short-term response. Drug retention rate after the median follow-up period of 11 months (Interquartile Range (IQR): 7.3 months to 20.8 months) was 12/19 (63.2%). The Kaplan-Meier analysis did not reveal disease duration prior to golimumab (Hazard Ratio (HR); 0.9–1.2, p=0.7), use of concomitant systemic steroids (HR: 0.1–6.3, p=0.4), age at start of golimumab (HR: 0.9–1.1, p=0.8), body weight at start of golimumab (HR: 0.9–1.1, p=0.9), disease extent (HR: 0.1–4.7, p=0.6) as predictive for drug retention rate at the end of follow-up. However, golimumab trough levels during induction and maintenance were predictive for continuous response to golimumab at the end of follow-up as golimumab trough levels were higher in end-of-follow-up responders (median induction

Table 1. Patient characteristics

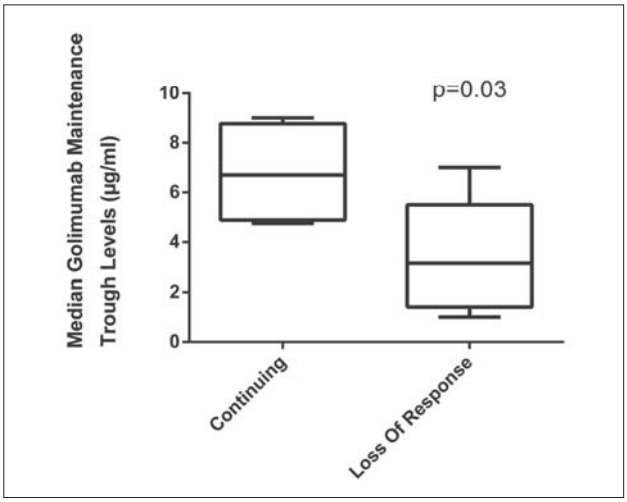
Male (%)	6/21 (31.6%)
Median (IQR) age at diagnosis (years)	36.7 (22.7–43.7)
Median age at start of golimumab (years, IQR)	46.0 (36.0–51.0)
Median weight at start of golimumab (kg's, IQR)	66.0 (59.0–81.5)
Median disease duration before golimumab (years, IQR)	9.6 (6.1–13.4)
Median follow - up (months, IQR)	11 (7.3–20.8)
Disease extent (n = 19) (%)	
E1 - proctitis	4 (21.1%)
E2 - left sided	5 (26.3%)
E3 - extensive	10 (52.6%)
Smoking status % (n = 11)	
Smokers	0 (0%)
Non - smokers	9 (81.8%)
Previous smokers	2 (18.2)
Concomitant medication at start of golimumab (%)	
Aminosalicylates	8 (73.7%)
Systemic steroids	8 (42.1%)
6-MP/AZA	8 (42.1%)
Topical steroids	5 (26.3%)
Anti - TNF-alpha naive before golimumab	17 (89.5%)
Number of patients with induction	19 (100%)

drug levels 17.9 µg/ml [IQR:14.2–20.6], median maintenance levels 6.7 µg/ml [IQR:4.9–8.8]) compared to patients who stopped golimumab due to loss of response (median drug induction levels 11.6 [IQR 8.6–15.2] median maintenance trough levels 3.15 (1.4–5.5); P-value for drug induction levels 0.04 (Graph 1), p-value for trough maintenance levels 0.03 (Graph 2). Similarly, last available maintenance trough levels were higher in patients with continuous response at the end of follow-up (12,1 [IQR: 5,4–14,4] compared to patients who lost response at the end of follow-up (3.9 [IQR: 1.3–5.9]) (p=0.055). Interestingly, none of the four patients with golimumab maintenance trough levels above six µg/ml lost response at the end of follow-up.

Conclusions: Drug retention rate of this real life, predominantly bio nad've cohort of ulcerative colitis patients, is comparable to registration trial of golimumab. Golimumab drug levels during induction and golimumab maintenance trough levels were highly correlated to drug retention rate at the end of follow-up. Clinical outcome was especially favorable for patients with maintenance golimumab trough levels > six µg/ml.



Graph 1. Prediction of Drug Retention Rate by Median Induction Drug Levels in Patients with Ulcerative Colitis Treated with Golimumab.



Graph 2. Prediction of Drug Retention Rate by Median Maintenance Trough Levels in Patients with Ulcerative Colitis Treated with Golimumab

Impact of Azathioprine Co-treatment on Clinical Outcome and Pharmacokinetics of Infliximab in Inflammatory Bowel Disease on Maintenance Infliximab Treatment

Polona Švegl[1], Saša Golob[2], Tina Kurent[3], Matic Koželj[3], Gregor Novak[3], Nataša Smrekar[3], Ivan Ferkolj[3], Borut Štabuc[2,3] and David Drobne[2,3]
[1]*University Medical Center Ljubljana, Ljubljana, Slovenia*
[2]*Medical Faculty in Ljubljana, Ljubljana, Slovenia*
[3]*Department of Gastroenterology, University Medical Center Ljubljana, Ljubljana, Slovenia*
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Background: Infliximab is indicated for treatment of inflammatory bowel disease when disease is not controlled under azathioprine. It is however not clear if continuation of azathioprine in patients started on infliximab (combination treatment) is superior regarding clinical efficacy and pharmacokinetics compared to monotherapy with infliximab (infliximab monotherapy). Furthermore, combination treatment is associated with an increased risk of malignancy and infection.

Aims: Our aim was to explore if combination treatment is clinically superior to infliximab monotherapy and whether combination treatment results in more favourable pharmacokinetics compared to infliximab monotherapy after one year of treatment.

Methods: We retrospectively studied 195 patients (114 with Crohn's disease + 81 with ulcerative colitis) who received infliximab for active inflammatory bowel disease in our tertiary university referral medical IBD centre. We reviewed electronic medical charts of all patients for demographic data and collected clinical efficacy data. Furthermore, data on infliximab trough levels were also collected. Typically, in our centre, infliximab trough levels are measured in patients after induction, at disease flare and also in patients in remission yearly (ELISA assay, Leuven). In total, infliximab trough levels after one year of treatment were available in 97/195 (49,7%) patients.

Primary outcomes were infliximab failure after one year of treatment (defined as discontinuation of infliximab due to loss of response) and pharmacokinetic outcomes after one year of treatment (proportion of patients with undetectable infliximab trough levels, proportion of patients with high (> 3 μg/ml) infliximab trough levels and median infliximab trough levels). Statistical analysis included Chi-square test and Mann Whitney U test as appropriate. $P < 0,05$ was considered significant.

Results: Patients' demographics are presented in Table 1.Combination treatment was clinically not superior to infliximab monotherapy after one year of treatment as loss of response to infliximab was comparable in both groups (combination treatment: 10 out of 113 patients (5,1%), infliximab monotherapy: 13 out of 82 patients (6,7%), p=0,134) (Figure 1). However, we did observe that pharmacokinetic outcomes after one year of treatment were superior in patients treated with combination treatment compared to infliximab monotherapy as the proportion of patients with undetectable infliximab trough levels was lower in patients treated with

Table 1: Patient characteristics

N=195	Crohn's disease (N=114)	Ulcerative colitis
(N=81)		
Sex (female)	55 (48,2%)	40 (49,4%)
Perianal involvement	44 (22,5%)	/
Number of patients on Infliximab monotherapy	47 (55,3%)	38 (44,7%)
Number of patients on combination treatment		
(Infliximab+Azathioprine)	67 (60,9%)	43 (39,1%)
Age at start of Infliximab (Median/ IQR) (years)	22 [18 to 30]	28 [20 to 35]
Duration of combination treatment before Azathioprine withdrawal (Median/IQR) (days)	296 [180 to 466]	322 [166 to 736]

combination treatment (4/97 (4,1%)) compared to infliximab monotherapy (14/97 (14,4%)) (p=0,002).

Similar was observed in median infliximab trough levels (combination treatment: 4,9 µg/ml [IQR: 2.6 to 9.88], infliximab monotherapy: 1,73 µg/ml [IQR: 0.3 to 6.7] (p=0,005)) and for proportion of patients with high infliximab trough levels (> 3 µg/ml) (combination treatment: 41/55 (74.5%), infliximab monotherapy: 19/42 (45.2%); p=0,003).

Conclusions: Combination treatment of infliximab and azathioprine was clinically not superior to infliximab monotherapy in this large single centre cohort of patients who started infliximab due to inefficiency of azathioprine. Pharmacokinetics of infliximab, however, was superior in patients treated with combination treatment compared to infliximab monotherapy.

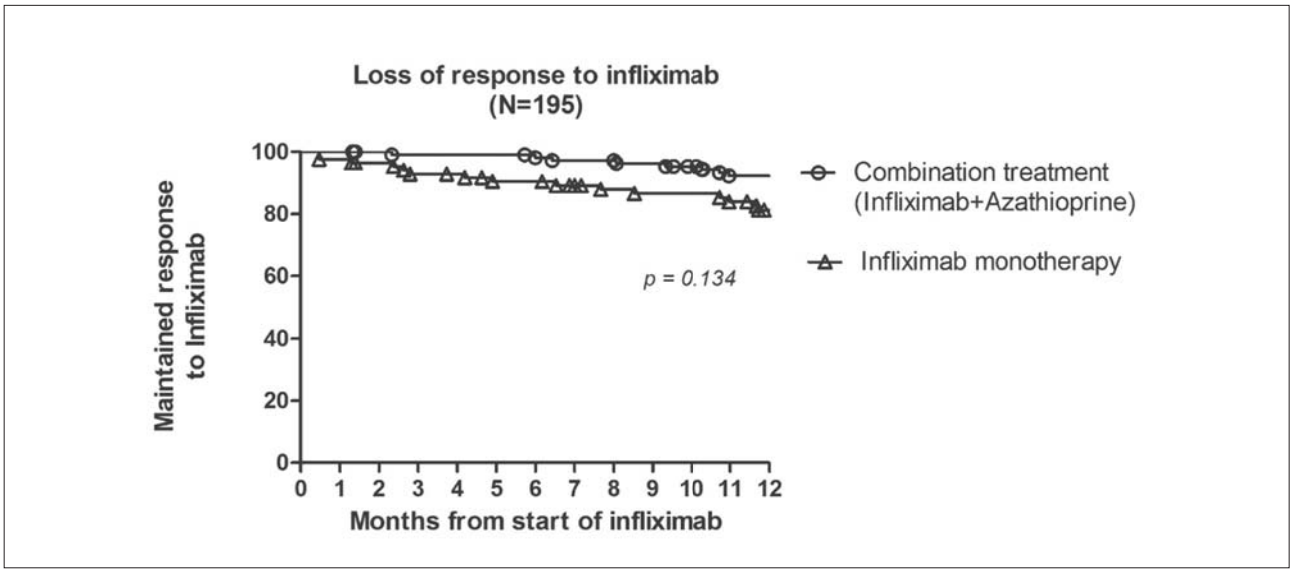

Figure 1: Infliximab failure after one year of combination treatment compared to infliximab monotherapy

Pancreatic Exocrine Insufficiency as a Consequence of Other Diseases

Miroslav Vujasinović[1], Bojan Tepeš[2], Saša Rudolf[3]
[1] *Karolinska University Hospital, Center for Digestive Diseases, Stockholm, Sweden*
[2]*AM DC Rogaška, Rogaška Slatina, Slovenia*
[3]*University Medical Center Maribor, Department of Radiology, Maribor, Slovenia*
Gastroenterolog 2017; suplement 3: 120

Background: Pancreatic exocrine insufficiency (PEI) is associated with different pancreatic illnesses and can also be associated with extrapancreatic diseases. PEI can occur in patients with diabetes mellitus (DM) and in patients after acute pancreatitis (AP). It could be present also in patients with chronic heart failure (CHF), due to decreased splanchnic circulation and tissue damage of splanchnic organs.

Patients and methods: One hundred and fifty consecutive patients with DM, mean age 59,0, were included in the study: 50 patients with type 1 DM (DM1), 50 insulin-treated patients DM type 2 (DM2-insulin) and 50 non-insulin treated patients with DM type 2 (DM2 no-insulin). Diagnosis of DM was established from health records.

One hundred patients after AP, mean age 56,5, were included in the study. There were 67 (67%) patients with mild AP, 15 (15%) patients with moderate and 18 (18%) patients with severe AP. We included 87 patients with CHF in the study; mean age was 74,7 years. CHF was classified according to New York Health Association (NYHA) criteria. There were 54 patients with NYHA II and 33 patients with NYHA III CHF. Mean time from CHF confirmation to inclusion in the study was 4,0 years. Fecal elastase-1 (FE) measurements were performed using ELISA test. FE levels >200, 100–200 and < 100 μg/g were considered as normal exocrine pancreatic function, mild and severe PEI, respectively. In patients with low FE, further workup was performed including the following laboratory tests: iron, ferritin, transferring, vitamin B12, folic acid, ionized calcium, phosphates, magnesium, potassium, sodium chloride, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, bilirubin, amylase, lipase, carbohydrate deficient transferrin, CA 19–9, alpha-1-antitripsyn, tissue transglutaminase antibodies, Hep-2 antibodies, immunoglobulin G4, protein, albumin, total cholesterol, HDL cholesterol, triglycerides, LDL cholesterol and vitamins A, D, and E. We excluded patients with any of the following: alcohol consumption over 20 g per day, medical history of abdominal surgery, any other known reason for malabsorption, previous pancreatic disease, abnormal liver function test, malignant disease, inflammatory bowel disease and autoimmune diseases.

The aims of our studies were:
- To determine prevalence of PEI in patients with DM.
- To determine prevalence of PEI in patients after AP.
- To determine prevalence of PEI in patients with CHF.
- To evaluate clinical importance of PEI.

Results: PEI was diagnosed in 8 (5,4%) patients with DM; 21 (21%) of patients after AP and 6 (6,9%) patients with CHF. In all patients with PEI at least one nutritional serum marker was decreased (vitamin D, selenium, phosphorus, zinc, folic acid and prealbumin).

Conclusions: PEI in DM occurred less frequently than in previous studies, probably due to our strict exclusion criteria (age, alcohol intake). PEI can developed after AP, regardless of its severity and etiology, suggesting that routine follow-up of patients with AP after discharge from hospital is necessary. PEI can develop in low percentage of patients with CHF. Decreased values of some serum nutritional markers are present in all patients with PEI, including patients without chronic pancreatitis.

Analysis of 60 patients with malignant polyps in national colorectal screening program Svit

Grujica Vujnović[1], Bojan Tepeš[2]
[1]*General Hospital Ptuj, Ptuj, Slovenia*
[2]*Abakus Medico d.o.o., DC Rogaška, Rogaška Slatina, Slovenia*
Gastroenterolog 2017; suplement 3: 122–123

Keywords: *malignant polyp, histologic criteria, screening program*

Objectives and study: Malignant polyps are detected in 0,75–5,6% of large bowel polyps. Definitive treatment can be endoscopic or surgical removal. There are strict histological criteria which need to be fulfilled to guarantee no further recurrence or disseminated disease (resection margin ≥1mm, depth of invasion: Haggitt level 1,2 and 3; Kikuchi level 1, well- differentiated carcinoma, no tumor budding and no lymphovascular invasion). In our retrospective study, we analyzed the validity of these criteria in our patients with malignant polyps as well as how clinicians and patients fulfill the recommendations for treatment by SVIT Multidisciplinary team of experts who carefully assess all patients with malignant polyps detected at National colorectal screening program SVIT.

Methods: We analyzed 60 patients with malignant polyps, resected in Slovenian colorectal screening program SVIT. We divided patients in three separate groups regard definitive treatment and histologic stage. We analyzed resection margin ≥1mm, depth of invasion, grade of carcinoma and lymphovascular invasion in all polyps resected.

Results: Five out of sixty patients were excluded due to inadequate data or different definitive treatment (chemoradiotherapy, no follow-up data for at least one year endoscopic or two years clinically). In the first group we have 19 patients who had only endoscopic removal and were without endoscopic recurrence (endoscopic check up after one year or more) or clinic dissemination of disease (clinical check up after two years or more). Six patients in this group did not fulfill the criteria for safe endoscopic removal and refused advised additional surgery. Resection margin ≥1mm was found in 11 patients (58%), <1mm in 4 patients (21%) and =0 in 2 patients (10,5%). Two patients (10,5%) were without confirmed resection margin due to piecemeal resection. In the second group, we have 28 patients who did not fulfill criteria for safe endoscopic removal and had an additional surgery. No residual malignant tissue were found in the surgical specimen (pT0N0). Resection margin ≥1mm was found in 5 patients (18%), three of them had lymphovascular invasion, another two were resected due to depth of invasion. Resection margin <1mm was found in 9 patients (32%) and =0 in 3 patients (11%). Eleven patients (39%) were without confirmed resection margin due to piecemeal resection. Eight patients were included in the third group. They also have not fulfilled criteria for safe endoscopic removal and have had an additional surgery. Surgical specimens showed residual disease at polypectomy site in 3 patients, in lymph nodes in 2 patients or at polypectomy site and in lymph nodes in 3 patients. 22% of all operated

patients (second and third group) had residual disease.No patient had safe resection margin in the third group, one patient (12,5%) had no safe resection margin, two patients (25%) were without confirmed resection margin, five patients (62,5%) had only partial polyp resection. Frequency of resection margin ≥1mm was significantly higher in first than second or third group ($p<0.01$). Depth of invasion was confirmed in 13 patients in the first group (mean 1,53 ± 1,12 mm), 12 patients in the second group (mean 2,16 ± 1,64 mm) and in 1 patient of third group (4,0mm). No lymphovascular invasion was confirmed in 95%, 75% and 37,5% of the first, second and third group respectively. All cancers were well and moderately differentiated and were equally distributed between groups.

Conclusions: Criteria for a definitive endoscopic treatment are good prognostic markers. Inadequate resection margin (<1mm) or piecemeal resection are the most frequent cause for additional surgery. More patients and at least five years follow-up should be included in future study before final conclusions on the importance of clinical decision criteria for surgical resection could be made.

Specificity of surgical therapy of inflammatory bowel disease considering previous conventional and combined conventional and biologic therapy

Marinko Žulj[1], Kristina Steiner[2], Sabina Steiner[2], Matej Tomić[2], Ana-Marija Vezmar[2], Mladen Vuković[2], Matija Fenrich[2], Marko Boban[1], Aleksandar Včev[1]
[1]*Department of Internal Medicine, Faculty of Medicine Osijek, Osijek, Croatia*
[2]*Student at Faculty of Medicine Osijek, Osijek, Croatia*
Gastroenterolog 2017; suplement 3: 124

Introduction: Ulcerative colitis and Crohn's disease are inflammatory bowel diseases with increased incidence over the years. Some of the affected patients undergo the surgical procedure due to disease. Anti-TNF agents have become part of standard treatment for patients with IBDs. Some of the studies show that 70% of patients affected with Crohn's disease and 35% of patients with ulcerative colitis will need the surgical treatment, and many population-based studies show that anti-TNF agents may reduce the surgical rates. The aim of this study was to compare surgical rates of patients with and without anti-TNF agents treatment, duration of remission and frequency of disease relapses in those two types of therapy.

Materials and methods: For this study, medical documentation of adult patients has been used. Those patients were treated at Clinical Hospital Osijek, at the Department of Gastroenterology and Hepatology from 2000. To 2014. They are all affected by ulcerative colitis or Crohn's disease, some of them had to undergo surgical treatment during their disease.

Results: The remission time was significantly shorter in patients who had no surgical operation in comparison with patients who had a surgical procedure along with receiving both conventional and biologic therapy (double-tailed independent T-test, p = 0.009). The duration of relapse was longer in patients who had surgical operation and received biologic and conventional therapy compared to patients who had only surgical and conventional therapy (double-tailed independent T-test, p=0.373) and those who didn't have operation (double-tailed independent T-test, p=0.143). Patients who had operation and received both biologic and conventional therapy had second operation later than patients who only received conventional therapy (double-tailed independent T-test, p=0.311).

Conclusion: Our study has demonstrated that patient who had received combined conventional and biologic therapy had better results compared to patients who had only conventional therapy. Those patients had fewer relapses which were shorter in duration, while the remission time was longer. Furthermore, the indication for the surgical procedure as final treatment option came noticeably later after the diagnose of inflammatory bowel disease.

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Avtorji morajo izpolnjevati pogoje za soavtorstvo. Prispevati morajo k zasnovi, oblikovanju oz. analizi in interpretaciji podatkov. Samo zbiranje podatkov ne zadostuje za soavtorstvo. Soavtorji lahko v spremnem pismu določijo vrstni red avtorjev prispevka.

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Izvleček in ključne besede (Abstract, keywords): druga stran naj obsega izvleček v slovenščini. Izvleček raziskovalnega članka naj bo strukturiran in naj ne bo daljši od 250 besed, izvlečki ostalih člankov naj bodo nestrukturirani in naj ne presegajo 150 besed. Izvleček naj vsebinsko povzema bistveno vsebino dela. Izogibajte se kraticam in okrajšavam. Izvleček raziskovalnega članka naj povzema:

- *Izhodišča* (*Background*): Navedite glavni problem in namen raziskave ter hipotezo.
- *Metode* (*Methods*): Opišite značilnosti izvedbe raziskave, vzorec, ki se preučuje (npr. randomizacija, dvojno slepi poskus, navzkrižno testiranje, testiranje s placebom itd.), standardne vrednosti za teste, časovni odnos (prospektivna, retrospektivna študija).
- *Rezultati* (*Results*): Opišite rezultate študije in navedite interval zaupanja in natančno raven statistične značilnosti. Pri primerjalnih študijah se mora interval zaupanja nanašati na razlike med skupinami.
- *Zaključki* (*Conclusions*): Navesti je treba le tiste zaključke, ki izhajajo iz podatkov, dobljenih pri raziskavi; treba je navesti morebitno klinično uporabnost rezultatov. Enakovredno je treba navesti tako pozitivne kot negativne ugotovitve in katere raziskave so še potrebne pred klinično uporabo.

Izvlečke prispevkov, ki nimajo običajne strukture članka (npr. primeri iz klinične prakse, pregledni članki), ustrezno prilagodite. Vsebujejo naj od 50 do 200 besed.

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Address for correspondence:
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University Medical Centre Ljubljana
SI-1525 Ljubljana, Slovenia
E-mail address: borut.stabuc@kclj.si