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SLOVENSKO ZDRUŽENJE
ZA GASTROENTEROLOGIJO
IN HEPATOLOGIJO



Dear colleagues,

On behalf of the organizing committee, it is my great pleasure to welcome you all to the 4th Alpe-Adria-Donava (AAD) conference organized by SAGH (Slovenian association for gastroenterology and hepatology), in conjunction with the section of medical nurses and technicians (SSMS and ZT) specializing in endoscopy and gastroenterology.

This event, scheduled from October 20th to 21st, 2023 at Brdo pri Kranju, represents a unique collaborative platform aimed at providing updates on the latest advancements in gastroenterology, hepatology, gastrointestinal endoscopy, and abdominal surgery.

This international congress boasts a remarkable lineup of international faculty from across the globe - the United States, United Kingdom, Belgium, Italy, Norway, Hungary, Portugal, Slovakia, Sweden, Croatia, Serbia, Latvia, Bosnia and Hercegovina, Montenegro, Republic of Srpska.

Their expertise, along with the rich array of topics to be discussed, underscores our commitment to fostering a conducive environment for knowledge exchange, thus propelling the fields of gastroenterology and hepatology forward.

Besides lectures, the agenda includes hands-on endoscopic workshops, where practical examples from daily practice focusing on digestive diseases will be showcased. These sessions are tailored not only for members of SAGH and SSMS and ZT but also for interested specialists from various fields, extending an invitation to our colleagues from neighbouring countries as well.

We are thrilled to announce that this conference has been awarded 16 CME credits by The Medical Chamber of Slovenia, reflecting the rich educational value of the program on offer.

In closing, I wish to express our profound gratitude to all participants, organizers, sponsors, and supporters who have made this event possible. Your presence is a testament to the collective aspiration towards advancing the medical fields of gastroenterology and hepatology. As we delve into fruitful discussions and forge new connections, let's seize this opportunity to learn from each other and contribute significantly to these vital fields.

I am looking forward to an enriching and productive experience at this 4th AAD meeting.

Thank you once again for being here.

Warm regards,

Milan Stefanovič, MD, AGAF
President of SAGH

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Grad Brdo. Vir: <https://brdo.si/objekti/grad-brdo-2/>
Brdo Castle. Source: <https://brdo.si/objekti/grad-brdo-2/>



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Ziah Rifadbegovic	Department of General and Abdominal Surgery, Univesrity Clinical Center Tuzla, Bosnia and Hercegovina

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Stevan Trbojevic	University Clinical Center Republic of Srpska, Banja Luka, Republic of Srpska
Miroslav Vujasinovic	Department for Upper Abdominal Diseases, Karolinska University Hospital, Stockholm, Sweden
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Domaći predavatelji / National Faculty

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Erik Brecelj	Institute of Oncology Ljubljana
Nejc Bukovnik	Department of Gastroenterology, University Medical Center Maribor
David Drobne	Department of Gastroenterology and Hepatology, University Medical Center Ljubljana
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Miha Petric	Department of Abdominal Surgery, University Medical Center Ljubljana
Ursa Novljan	Department of Abdominal Surgery, University Medical Center Maribor

Gregor Novak	Department of Gastroenterology and Hepatology, University Medical Center Ljubljana
Natasa Smrekar	Department of Gastroenterology and Hepatology, University Medical Center Ljubljana
Milan Stefanovic	Diagnostic Center Bled Group
Sebastian Stefanovic	Diagnostic Center Bled Group
Borut Stabuc	Department of Gastroenterology and Hepatology, University Medical Center Ljubljana
Ales Tomazic	Department of Abdominal Surgery, University Medical Center Ljubljana
Bojan Tepes	Diagnostic Center Rogaska, Rogaska Slatina
Spela Turk	Department of Abdominal Surgery, University Medical Center Maribor
Blaz Trotovsek	Department of Abdominal Surgery, University Medical Center Ljubljana
Luka Strnisa	Department of Gastroenterology, University Medical Center Ljubljana
Nina Zidar	Institute of Pathology, Faculty of Medicine

Srečanje Alpe - Jadran - Donava (AAD)

Alps - Adria - Donube Meeting

Program

Brdo pri Kranju, 20. in 21. oktober 2023
Brdo pri Kranju, 20th and 21st of October 2023

Petek / Friday, 20. 10. 2023

09:00 – 09:10 *M. Stefanovic - SAGH President*
Diagnostic Center Bled Group,
Slovenia
Welcome and Introduction Speech

Predsedstvo / Chairmen: *B. Stabuc, I. Jovanovic, I. Grgurevic, H. Ivekovic*

09:10 – 09:30 *T. Pintar*
Department of Abdominal
Surgery, University Medical
Center Ljubljana, Slovenia
*Relevance of Endoscopy in
Bariatric Procedures*

09:30 – 09:50 *S. Turk*
Department of Abdominal
Surgery, University Medical
Center Maribor, Slovenia
*Impact of obesity on complications
after laparoscopic liver resection*

09:50 – 10:10 *M. Bulajic*
Digestive Endoscopy Department,
Fatebenefratelli Isola Tiberina -
Gemelli Isola, Rome, Italy
*Advanced Endoscopic Bariatric
Therapy*

10:10 – 10:30 *J. Grosek*
Department of Abdominal
Surgery, University Medical
Center Ljubljana, Slovenia
*Robotic-assisted colorectal
resections at University Medical
Center Ljubljana - steady road
from competency to proficiency*

10:30 – 10:50

**Bronze Sponsor Satellite
Symposia (Janssen)**

G. Novak
Department of Gastroenterology,
University Medical Center
Ljubljana, Slovenia
*Detection and follow-up of
precancerous lesions in IBD patients*

10:00 – 10:30

EXHIBITION BREAK

Predsedstvo / Chairmen: *M. Stefanovic, P. Draganov, P. Hindryckx, P. Bhandari*

11:10 – 11:30 *R. Knezevic*
Diagnostic Center Bled Group,
Slovenia
*Endoscopic Full Thickness
Resection in Appendix, Issues and
Solutions (Single Center Experience)*

11:30 – 11:50 *P. Draganov*
University of Florida, Gainesville,
United States of America
*New Devices for Defect Closure
and Endoscopic Submucosal
Dissection*

11:50 – 12:10 *P. Bhandari*
University of Portsmouth,
Portsmouth, United Kingdom
*From cold to hot to ESD: How to
best remove lesions in the GI tract*

12:10 – 12:30 *P. Hindryckx*
Ghent University Hospital, Ghent,
Belgium
*Endoscopic Ultrasonography -
Assisted Management of
Hepatobiliopancreatic Disease*

12:30 – 12:50	<p><i>S. Stefanovic</i> Diagnostic Center Bled Group, Slovenia Ghent University Hospital, Ghent, Belgium <i>Recommendations for prevention and management of LAMS-related complications: an international Delphi consensus study</i></p> <hr/>	15:10 – 15:20	<p><i>D. Badovinac</i> Department of Abdominal Surgery, University Medical Center Ljubljana, Slovenia <i>Extracellular vesicles in liquid biopsy as biomarkers of radical resection in pancreatic cancer</i></p> <hr/>
13:00 – 14:00	<p>EXHIBITION BREAK WITH LUNCH</p> <hr/>	15:20 – 15:40	<p>EXHIBITION BREAK</p> <hr/>
<p>Predsedstvo / Chairmen: <i>A. Tomazic, M. Zovak, R. Salvia, A. Karamarkovic</i></p>		<p>Predsedstvo / Chairmen: <i>B. Tepes, S. Djuranovic, G. Hauser, M. Leja</i></p>	
14:00 – 14:25	<p><i>R. Salvia</i> Unit of General and Pancreatic Surgery - The Pancreas Institute Verona, Verona, Italy <i>Pancreatic cystic lesions - can we predict the risk of malignancy? The influence on decision about surgery</i></p> <hr/>	15:40 – 16:00	<p><i>M. Stefanovic</i> Diagnostic Center Bled Group, Slovenia <i>Slovenian National Screening and Early Detection Programme for Colorectal Cancer - SVIT, Our Results</i></p> <hr/>
14:25 – 14:40	<p><i>A. Tomazic</i> Department of Abdominal Surgery, University Medical Center Ljubljana, Slovenia <i>P-NETs - What's the appropriate treatment for localized disease? (Observation, enculeation, oncological resection)</i></p> <hr/>	16:00 – 16:20	<p><i>J. Carlos Silva</i> Department of Gastroenterology, Centro Hospitalar Villa Nova de Gaia e Espinho, Portugal <i>Gastric cancer screening in Europe: Where are we now?</i></p> <hr/>
14:40 – 14:55	<p><i>B. Trotošek</i> Department of Abdominal Surgery, University Medical Center Ljubljana, Slovenia Limits of pancreatic surgery - do extensive resections benefit in survival</p> <hr/>	16:20 – 16:40	<p><i>B. Tepes</i> Diagnostic Center Rogaska, Rogaska Slatina, Slovenia <i>Gastric cancer prevention in Europe – the EUROHELICAN project</i></p> <hr/>
14:55 – 15:10	<p><i>M. Petric</i> Department of Abdominal Surgery, University Medical Center Ljubljana, Slovenia <i>Indications for minimally invasive pancreatic surgery - Are there any oncological benefits</i></p> <hr/>	16:40 – 17:00	<p><i>M. Leja</i> Digestive Diseases Centre Gastro, Riga, Latvia <i>Gastric cancer prevention in Europe – the TOGAS project</i></p> <hr/>
		17:00 – 17:20	<p>Silver Sponsor Satellite Symposia (Takeda) <i>U. Kogovsek</i> Department of Abdominal Surgery, University Medical Center Ljubljana, Slovenia <i>Closing the Gap: Contemporary Relevance of Complex Perianal Fistula Closure in Crohn's disease - Insights and Prospects</i></p> <hr/>
		17:20 – 17:40	<p>EXHIBITION BREAK</p> <hr/>

Predsedstvo / Chairmen: *S. Potrc, Z. Rifadbegovic, A. Ferko, B. Edwin*

17:40 – 18:00 *A. Ferko*
Hospital Bory Bratislava,
Bratislava, Slovak Republic
*Safe colorectal anastomosis: a
new concept of surgical procedure
standardization and trans-anal
evaluation resulted in a low leak
and a diversion rate*

18:00 – 18:20 *A. Papp*
Department of Surgery, Sebészeti
Klinika Pécs, Hungary
*New aspects in esophageal cancer
surgery*

18:20 – 18:40 *B. Edwin*
Department of
Hepatopancreatobiliary Surgery,
Oslo University hospital, Norway
*The Journey of Liver Surgery and
Future Perspectives*

18:40 – 19:00 *M. Horvat*
Department of Abdominal
Surgery, University Medical
Center Maribor, Slovenia
*Prevention of post-splenectomy
infectious complications- an audit
at clinical department for
abdominal and general surgery*

20:00 **DINNER**

Sobota / Saturday, 21. 10. 2023

Predsedstvo / Chairmen: *A. Ivanecz, A. Pavlovic Markovic, B. Smolovic, S. Milic*

08:00 – 08:20 *T. Bokun*
Department of Gastroenterology,
Hepatology and Clinical Nutrition,
University Hospital Dubrava,
Zagreb, Croatia
*Endoscopic Management of GI
Fistulas*

08:20 – 08:40 *T. Pavic*
Department of Gastroenterology
and Hepatology, University
Hospital Center Sestre Milosrdnice,
Zagreb, Croatia
*EUS-Guided liver biopsy for
parenchymal liver disease*

08:40 – 09:00 *E. Brecelj*
Institute of Oncology, Ljubljana,
Slovenia
*Watch and Wait Protocol - Rectal
cancer - Our results*

09:00 – 09:20 *A. Repici*
Humanitas University and
Humanitas Research Hospital,
Milano, Italy
*Innovation in Diagnostic and
Therapeutic Endoscopy*

09:20 – 09:40 *M. Vujasinovic*
Department for Upper Abdominal
Diseases, Karolinska University
Hospital, Stockholm, Sweden
*Pancreatic exocrine insufficiency:
From diagnosis to treatment*

09:40 – 10:20 **Silver Sponsor Satellite
Symposia (Genesis Pharma)**
D. Cassiman
Department of Gastroenterology -
Hepatology, Metabolic Center at the
University Hospital Gasthuisberg,
Leuven, Belgium
*Acute Hepatic Porphyria (AHP):
Advancing diagnosis and treatment
of a rare genetic disease*

10:20 – 10:40 **EXHIBITION BREAK**

Predsedstvo / Chairmen: *D. Drobne, N. Smrekar, W. Reinisch, D. Tarabar*

10:40 – 11:00 *D. Drobne*
Department of Gastroenterology,
University Medical Center
Ljubljana, Slovenia
*Slovenian UR-CARE Inflammatory
Bowel Disease Registry: in 4 years
from scratch to top European
recruiter*

11:00 – 11:20 *J. Hanzel*
Department of Gastroenterology,
University Medical Center
Ljubljana, Slovenia
*Clinical trial design in
Inflammatory Bowel Disease -
challenges and opportunities*

11:20 – 11:40 *P. Macek*
Department of Gastroenterology,
University Medical Center
Maribor, Slovenia
*Clinical tool CDST for treatment
of IBD with vedolizumab*

11:40 – 12:00 *M. Jerala*
Institute of Pathology, Faculty of
Medicine Ljubljana, Slovenia
*Pathogenesis of Fibrostenosis in
Crohn's Disease*

12:00 – 12:20 **Silver Sponsor Satellite
Symposia (Takeda)**
D. Tarabar
University Hospital Center "Dr.
Dragisa Misovic" Belgrade, Serbia
*Chronic Pouchitis and the Role of
Vedolizumab Treatment*

12:20 – 13:00 **Silver Sponsor Satellite
Symposia (AbbVie)**

13:00 – 13:45

LUNCH WITH
EXHIBITION BREAK

Predsedstvo / Chairmen: *B. Trotovsek, S. Trbojevic, M. Banic, Z. Milosevic*

13:45 – 14:05 *G. Novak*
Department of Gastroenterology,
University Medical Center
Ljubljana
*Assessment of endoscopic and
histological activity in
inflammatory bowel disease*

14:05 – 14:25 *U. Marolt*
Department of Abdominal
Surgery, University Medical
Center Maribor, Slovenia
*Calcium imaging in intact mouse
acinar cells in acute pancreas
tissue slices*

14:25 – 14:45 *B. Ilijevec*
Department of Abdominal
Surgery, University Medical
Center Maribor, Slovenia
*Laparoscopic distal pancreatectomy
– a propensity score matched single
center experience*

14:45 – 15:05 *T. Magdalenic*
Department of Abdominal
Surgery, University Medical
Center Maribor, Slovenia
*Validation of the Institute
Mutualiste Montsouris system for
the stratification of laparoscopic
liver resections*

15:05 – 15:25 *M. Homan*
Department of Gastroenterology,
Pediatric Clinic, University Medical
Center Ljubljana, Slovenia
*Helicobacter pylori in children and
adolescents - Slovenia (our results)*

15:25 – 15:45 *R. Orel*
Department of Gastroenterology,
Pediatric Clinic, University Medical
Center Ljubljana, Slovenia
*Eosinophilic Diseases of
Gastrointestinal Tract*

15:45 – 16:00

EXHIBITION BREAK

Predsedstvo / Chairmen: *A. Ocepek, N. Rustemovic, A. Husic Selimovic, P. Dugalic*

16:00 – 16:20	<i>P. Dugalic</i> Department of Gastroenterology, University Clinical Hospital Centre Zemun-Belgrade, Serbia <i>Barrett's esophagus - How often do we think about it in everyday practice</i>
16:20 – 16:40	<i>I. Plahuta</i> Department of Abdominal Surgery, University Medical Center Maribor, Slovenia <i>What defines long term survival in patients after liver resection for colorectal metastases?</i>
16:40 – 17:00	<i>G. Hladnik</i> Department of Abdominal Surgery, University Medical Center Maribor, Slovenia <i>Preoperative Nutritional Assessment in Gastric Cancer Patients: A Single Center Experience</i>
17:00 – 17:20	<i>U. Novljan</i> Department of Abdominal Surgery, University Medical Center Ljubljana, Slovenia <i>SIBO in Upper Gastrointestinal Tract Surgery</i>
17:20 – 17:40	<i>A. Gavric</i> Department of Gastroenterology, University Medical Center Ljubljana, Slovenia <i>Comparing margin ablation techniques after endoscopic mucosal resection of large nonpedunculated colorectal polyps</i>
17:40 – 17:45	<i>M. Stefanovic</i> Diagnostic Center Bled Group, Bled, Slovenia <i>Adjourn</i>

Hands-on endoscopy workshops

Petek / Friday, 20. 10. 2023

ROOM I

14.00 – 15.00	EUS FNA/FNB <i>Endoscopist: T. Pavic</i> <i>Endoscopy tech: J. Tepina</i>
16.00 – 17.00	ERCP <i>Endoscopist: S. Plut</i> <i>Endoscopy tech: B. Rezar</i>
16.00 – 17.00	OTSC clips <i>Endoscopist: N. Bukovnik</i> <i>Endoscopy tech: T. Ademovic</i>
17.00 – 18.30	Management of post-polypectomy complications <i>Endoscopist: K. Mojškerc</i> <i>Endoscopy tech: M. Tandler</i>
17.00 – 18.30	ESD <i>Endoscopist: L. Strnisa</i> <i>Endoscopy tech: M. Sever</i>

ROOM II

14.00 – 15.00	EMR <i>Endoscopist: R. Knezevic</i> <i>Endoscopy tech: E. Turk</i>
15.00 – 16.00	EUS FNA/FNB <i>Endoscopist: M. Mervic</i> <i>Endoscopy tech: E. Budimir</i>

ROOM III

15.00 – 16.00	Colonoscopy - Tips and Tricks <i>Endoscopist: D. Dodic</i> <i>Endoscopy tech: N. Spelec</i>
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Zdravniška zbornica Slovenije podeljuje 16 kreditnih točk. *Slovenian Medical Chamber has awarded 16 CME points.*

Srečanje sekcije medicinskih sester in zdravstvenih tehnikov v endoskopiji in gastroenterologiji

Petek / Friday, 20. 10. 2023

07:30 – 08:30 REGISTRACIJA UDELEŽENCEV

08:30 – 08:40 Marija Petrinc Primožič, dipl. m. s.,
Milan Stefanovič, dr. med.
Otvoritev srečanja

1. SKLOP

Moderatoriki: Marija Petrinc Primožič, dipl. m. s.,
Mateja Zajc Čizman, dipl. m. s.

08:40 – 09:00 Ariana Hadžić, dipl. m. s.,
Čavlović Andrijana, dipl. m. s.
Prikaz primera paranteralne
prehrane na domu

09:00 – 09:20 Tara Šimac dipl. m.s.,
Žarko Mišanović, dipl. zn.
Namerno zaužitje tujka pri
pacientih s psihiatrično diagnozo –
študija primera

09:20 – 09:40 Nastja Špelec dipl. m. s.,
Tadej Ademović dipl. zn.
Nastanek ileusa zaradi žolčnega
kamna, po ERCP posegu –
prikaz primera

09:40 – 10:00 Erika Šmid, dipl. m. s.,
Anita Smajlović, dipl. m. s.
Otrok s tujkom v prebavilih –
prikaz primera

10:20 – 10:40 Veronika Koren, dipl. m. s.
Priprava na kolonoskopijo –
je dieta res pomembna

10:40 – 10:50 Vprašanja in diskusija

10:50 – 11:10 ODMOR

2. SKLOP

Moderatoriki: Mateja Sever, dipl. m. s.,
Veronika Koren, dipl. m. s.

11:10 – 11:30 mag. zdr. neg. Linda Cellner
Imunoterapija – prednosti in
slabosti

11:30 – 11:50

Špela Ferlin, ZT, Nina Križnar, ZT
Usklajevanje osebnega in
profesionalnega življenja ter
izobraževanja ob delu na KOGE

11:50 – 12:10

Mateja Sever, dipl. m. s.
Kompetence diplomirane
medicinske sestre v endoskopiji in
primeri dobre prakse

12:10 – 12:30

Carmen Bobnar Sekulić, dipl. m. s.
Ali imajo medicinske sestre dovolj
znanja o subkutani aplikaciji
biološkega zdravila?

12:30 – 12:50

Mateja Zajc Čizman, dipl. m. s.,
Mojca Poljanšek, dipl. m. s.
Čista intermitentna kateterizacija
pri bolnikih s suho urostomo

12:50 – 13:00

Vprašanja in diskusija

13:00 – 14:00

KOSILO

3. SKLOP

DELAVNICE

14:00 – 18:30

1. EUS FNA/FNB
Tajana Pavić, Janita Tepina

2. ERCP
Samo Plut, Boštjan Rezar

3. OTSC KLIPI
Nejc Bukovnik, Tadej Ademović

4. Zdravljenje zapletov po
polipektomiji
Klemen Mojskerc, Marijana Tandler

5. ESD
Luka Strniša, Mateja Sever

6. EMR
Rajko Knežević, Ernestina Turk

7. EUS FNA/FNB
Manfred Mervic, Elvana Budimir

8. Kolonoskopija – nasveti in triki
Daniel Dodić, Nastja Špelec

18:30 – 18:40

ZAKLJUČEK SEMINARJA

20:00

VEČERJA

Zdravniška zbornica Slovenije podeljuje 16 kreditnih točk. *Slovenian Medical Chamber has awarded 16 CME points.*

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Relevance of Endoscopy in Bariatric Procedures

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Highlights

- The obesity is associated with gastrointestinal diseases. The prevalence of upper GI disorders in morbid obesity is significantly high (81.5%).
- The most frequent obesity related disorders are GERD, Hiatus hernia and *Helicobacter pylori*, different grade of esophageal disorders.
- The preoperative preparation performing routine and selective upper endoscopy in of all obese patients preparing for bariatric surgery is implemented in clinical protocols.
- The routine endoscopy is the basis for the choice of MBS surgery and also the bariatric follow-up.
- Endoscopic management of MBS complications is procedure related and reduces all over rate of complications related to MBS. The endoscopic armamentarium is expanding and is providing minimally invasive treatment options for patients with post- bariatric surgery complications.

Introduction. The obesity is associated with many gastrointestinal disease conditions, most frequently GERD, Hiatal hernia, *Helicobacter pylori* and esophageal disorders ranged up to 55% and which dictates the implementation of endoscopy in pre-operative protocols in patients who are candidates for MBS (1, 2).

Esophago-gastro-duodenoscopy (EGD) (1, 2, 3) is a procedure that allows for visual inspection of the lumen and provides access for biopsying the esophagus, stomach and duodenum. EGD is an important investigative tool for the diagnosis of diseases of the upper gastrointestinal tract including hiatal hernias (HH), esophageal mucosal injury secondary to gastro-esophageal reflux disease (GERD), Barrett's esophagus (BE),

gastrointestinal stromal tumours (GISTs) and esophageal adenocarcinoma (EAC) (2, 3, 4).

EGD prior to bariatric surgery allows for the diagnosis of concomitant diseases that may preclude bariatric surgery, such as upper gastrointestinal malignancies or varices due to portal hypertension. It may also lead to the diagnosis of diseases that should be treated prior to surgery, such as peptic ulcer disease and *Helicobacter pylori* infection. EGD also allows for the diagnosis of conditions such as GERD-related esophageal mucosal injury including erosive esophagitis, esophageal ulcers, strictures and BE; and anatomical defects such as HH, which may influence the operative procedural choice and change the operative management protocols. In addition, EGD allows for a pre-operative assessment of the distal stomach which becomes inaccessible after OAGB and RYGB. For upmentioned circumstances, there is a justified urgency for the reasons set out above to perform routine EGD prior to any bariatric procedure, independent of symptoms.

Literature search reports abnormal EGD findings in at least 55.5% of patients prior to bariatric surgery. The most common reported are gastritis, HH and esophagitis; clinical conditions leading to modification or delay of are presented less commonly. 16.5% having findings that led to modification or delay of the planned procedure and in 0.2% surgery should be cancelled. 25.3% of asymptomatic patients had abnormal EGD findings. Systematic screening to pathology is supported with MBS varying effect on GERD, bile reflux, BE and malignancy risk (4), and also for the appropriate tailoring the decision regarding EGD according to the procedure planned with EGD. Risk for bile reflux is procedure related and higher in LSG

and OAGB and based on symptoms for banded procedures and RYGB (3, 4, 5).

Data extrapolated from studies based EDS after MBS procedures present a change in the pre-operative pathology detected, and also confirmed an incidence of new pathology regardless of the bariatric procedure performed (4, 5, 6).

Beneficial effects of MBS justify the relatively high and significant incidence of major complications, mandatory approached with multidisciplinary team critical for optimal outcomes. Minimally invasive protocols for complications should be implemented because of the high risk associated with reoperations. Endoscopy is important in both the diagnosis and the management of complications, and also providing therapeutic interventions for many bariatric surgical complications including anastomotic strictures, anastomotic leaks,

choledocholithiasis, sleeve stenosis, weight regain, and eroded bands (4, 5, 6, 7).

Conclusions are presenting Recommendations of the IFSO Endoscopy in Bariatric Surgery Taskforce

1. Esophago-gastro-duodenoscopy (EGD) should be considered for all patients with upper GI symptoms planning to undergo a MBS due to the frequency of pathology that may alter management.
2. EGD should be considered for patients without upper GI symptoms who are planning to undergo a MBS procedure due to the 25.3% chance of an unexpected finding that may alter management or contra-indicate surgery.
3. EGD should be routinely considered in populations where the community incidence of significant gastric and esophageal pathology is high,

Endoscopic management of bariatric complications

Surgery	Complication	Diagnosis	Management options
RYGB	Gastrojejunal anastomotic stricture	Upper GI series; Endoscopy	Endoscopic balloon dilation; Steroid injection; Needle knife radial incisions; Lumen-opposing metal stent
	Gastrogastric fistula	Upper GI series; Endoscopy	Endoscopic suturing; OTSC
	Anastomotic leaks	CT imaging; Upper GI series; Endoscopy	CSEMS; Internal drainage with pigtail stents; OTSC; Endosponge therapy; Endoscopic suturing
	Choledocholithiasis	MRCP; CT imaging; Ultrasound	Overtube-assisted ERCP; Laparoscopic-assisted ERCP; EDGE
	Weight regain	EGD-Dilated gastrojejunostomy	Stoma reduction: Endoscopic suturing; OTSC; Serial APC treatments; Radiofrequency ablation
Sleeve gastrectomy	Staple line leak	CT imaging; Upper GI series; Endoscopy	CSEMS; Internal drainage with pigtail stents; OTSC; Endosponge therapy; Endoscopic suturing
	Sleeve stenosis	Upper GI series; Endoscopy	Radial expanding balloon dilation; Pneumatic balloon dilation
LAGB	Band migration	CT imaging; Endoscopy	Mechanical lithotripter band cutting

RYGB: Roux-en-Y gastric bypass; CSEMS: Covered self-expandable metallic stent; OTSC: Over-the-scope-clip; EDGE: Endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiopancreatography; APC: Argon plasma coagulation; LAGB: Laparoscopic adjustable gastric band.

Adapted from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8776527/>

particularly when the procedure will lead to part of the stomach being inaccessible (for example RYGB and OAGB).

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5. EGD should be undertaken routinely for all patients after MBS at 1 year and then every 2–3 years for patients who have undergone LSG or OAGB to enable early detection of Barrett’s esophagus or upper GI malignancy until more data is available to confirm the incidence of these cancers in practice.
6. EGD should be performed following banded procedures and RYGB on the basis of upper GI symptoms.

In addition, endoscopic management of MBS complications is procedure related and reduces all over rate of complications related to MBS. The endoscopic armamentarium is expanding and is providing minimally invasive treatment options for patients with post-bariatric surgery complications. Post bariatric surgery patients are complex, and these complications are best managed with a multidisciplinary team with experience in this field.

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Impact of obesity on complications after laparoscopic liver resection

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INTRODUCTION

Obesity is a major public health problem in Western countries, and it is a well-known cause of multiple comorbidities (1). Moreover, it is presumably associated with an increased risk of complications after surgery. Although numerous studies have investigated the effects of obesity on surgical outcomes, there is still no consensus on the topic (2, 3).

With an increasing application of minimally invasive surgery for benign and malignant lesions of the liver, the results of laparoscopic liver resection (LLR) in obese patients are of great interest. In a recent systematic review, Kwan et al. studied the impact of body mass index (BMI) on surgical outcomes in LLR. Most of the studies included showed no significant difference in intra- and postoperative complications between different BMI groups. The authors concluded that current evidence shows LLR in obese patients is safe, however further studies are still needed (4).

Intrinsically we feel that surgery on obese patients poses a greater challenge for the surgeon during the operation, as well as for the patient on his path to recovery. Thus, with this study we aimed to objectively evaluate the impact of obesity on intra- and postoperative outcomes after LLR, in order to better understand this growing health problem in the setting of our surgical patients.

MATERIALS AND METHODS

All 225 consecutive patients undergoing LLR from the year 2008 to 2023 were retrospectively analysed. Patients were categorized into three groups based on their BMI: normal weight (18,5–24,9 kg/m²), overweight (25–29,9 kg/m²) and obese (≥ 30 kg/m²). The groups were then compared in terms of preoperative data as well as intra- and postoperative outcomes. We performed multivariate analysis using linear regression to predict intraoperative blood loss and operative time.

RESULTS

Despite higher rates of associated comorbidities in the obese patients, there were no significant differences in intraoperative blood loss, damage to surrounding structures, the rate of conversion or operative time between all three BMI groups (Table 1 and 2). Moreover, there were no significant differences in overall morbidity (33,3% vs. 27,8% vs. 26,8%, $p = 0,676$), as well as major morbidity (15,9% vs. 12,2% vs. 12,2%, $p = 0,746$) or mortality rates (1,4% vs. 1,6% vs. 0%, $p = 0,703$) (Table 3). Multivariate linear regression analysis has not shown BMI to be a predictive variable on intraoperative blood loss and operative time.

DISCUSSION

Few decades ago, obesity was generally considered a contraindication for laparoscopic surgery due to asso-

ciated technical difficulties. To date, quite a few studies have examined the relationship between BMI and peri-operative outcomes in LLR; yet there is still a significant degree of heterogeneity and applicability to the Western population is questionable (4). Overall, surgical outcomes do not seem to be overwhelmingly worse in obese patients, but some newer studies put the negative impact of obesity on LLR back into question (5,6). On the contrary to our clinical suspicion, our data showed that, when compared to normal

weight group, obese and overweight patients have similar rates of intraoperative and postoperative complications. It might be that the reason why the distinct negative correlation between BMI and perioperative outcomes can't be shown, is that BMI has a non-specific role as an anthropometric measure of obesity. This questions if maybe other measures for body fat composition would be more accurate at determining outcomes after LLR (7).

Table 1. Preoperative characteristics in the three groups

Variable	Normal weight (n = 69; 30,7%)	Overweight (n = 115; 51,1%)	Obese (n = 41; 18,2%)	P-value
Age	62,17 ± 14,123	63,48 ± 12,445	60,05 ± 10,416	0,324
Male sex	36 (52,2%)	73 (63,5%)	30 (73,2%)	0,078
ASA 3 or 4	17 (24,6%)	27 (23,5%)	22 (53,7%)	< 0,001
Comorbidities present	39 (56,5%)	78 (67,8%)	36 (87,8%)	0,003
Number of comorbidities	1,06 ± 1,235	1,30 ± 1,237	2,07 ± 1,439	< 0,001
AH	21 (30,4%)	57 (49,6%)	15 (36,6)	0,031
Diabetes	8 (11,6%)	24 (20,9%)	13 (31,7%)	0,037
Malign tumour	49 (71%)	87 (75,7%)	30 (73,2%)	0,783
Size of the largest tumour	3,8 (1-16; 4)	4,6 (0,2-18,5; 3,3)	4,2 (0,2-22; 3,0)	0,720
Proximity to IVC	13 (18,8%)	21 (18,3%)	8 (19,5%)	0,984

ASA, American Society of Anaesthesia; AH, arterial hypertension; IVC, inferior vena cava

Table 2. Intraoperative outcomes in the three groups

Variable	Normal weight (n = 69)	Overweight (n = 115)	Obese (n = 41)	P-value
Operative time (min)	160 (25-360; 95)	160 (30-450; 90)	160 (20-360; 85)	0,341
Intraoperative complication	13 (18,8%)	20 (17,4%)	9 (22,0%)	0,812
Blood loss > 775mL	3 (4,3%)	7 (6,1%)	5 (12,2%)	0,263
Damage to surrounding structures	1 (1,4%)	2 (1,7%)	0	0,703
Conversion	10 (14,5%)	14 (12,2%)	7 (17,1%)	0,721

Table 3. Postoperative outcomes in the three groups

Variable	Normal weight (n = 69)	Overweight (n = 115)	Obese (n = 41)	P-value
Morbidity (CD 1-5)	23 (33,3%)	32 (27,8%)	11 (26,8%)	0,676
Morbidity (CD ≥ 3)	11 (15,9%)	14 (12,2%)	5 (12,2%)	0,746
Mortality	1 (1,4%)	2 (1,7%)	0	0,703
LOS	6 (2–52; 6)	6 (2–79;3)	5 (2–42; 4)	0,732
Readmission rate	4 (5,8%)	7 (6,1%)	1 (2,4%)	0,657
Steatosis ^a , b	7 (10,1%)	23 (20,0%)	19 (46,3%)	<0,001
Cirrhosis ^b	11 (15,9%)	22 (19,1%)	12 (29,3%)	0,227

CD, Clavien-Dindo; LOS, length of stay. ^bconfirmed by pathohistological examination

CONCLUSIONS

General surgeons will encounter more overweight and obese patients in the future; therefore, it is important to fully understand the effect of elevated BMI on the outcomes of these patients. Our results suggest that with proper patient selection LLR in obese patients can be undertaken and performed as safely as in normal weight patients with the same risk of intra- and postoperative complications.

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Advanced endoscopic bariatric therapy - endoscopic gastroplasty for treatment of obese patients: preliminary results at 6 months follow-up from a prospective, single center, randomized controlled trial

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Introduction: Obesity awareness has recently increased following its pandemic evolution (1, 2). Besides nutritional and lifestyle modifications and pharmacological therapy, many other therapeutic strategies have been evaluated.

While surgery (i.e., sleeve gastrectomy and Roux-Y gastric by-pass) is the best approach for severe obesity, I and II grade of obesity management with intragastric balloon is the most prevalent therapeutic option, with an estimated efficacy of 12% total body weight loss and a frequent relapse after its removal (3, 4).

Other techniques (5), among which the Endoscopic Gastroplasty (EG), were recently evaluated (6).

EG is based on gastric body remodeling by multiple full-thickness bites through specific suture devices that are attached to the scope, allowing a mini-invasive incisionless gastric reduction. Nowadays three different techniques are described: endoscopic sleeve gastroplasty (ESG) (Overstitch; Apollo Endosurgery, Austin, TX), endoluminal vertical gastroplasty (EVG) (Endo-mina; Endo Tools SA (ETT), Gosselies, Belgium), and distal primary obesity surgery endoluminal (POSE-2) (Incisionless Operating Platform; USGI Medical, San Clemente, CA).

They showed similar results in terms of weight loss and improvement of obesity (1, 6).

Aims & Methods: Our study aimed to assess feasibility, safety, and efficacy of these three techniques compared to a control group. This was a prospective, single center, randomized controlled trial (ClinicalTrials.gov NCT04854317) of patients who underwent EG (through ESG or EVG or D-POSE) or a low-calorie Mediterranean diet (1600 and 1400 Kcal/day for men and women, respectively; 50% carbohydrates, 30% fats, 20% proteins) for treatment of obesity. Outcomes included technical success rate, serious adverse event rate, and efficacy of the three EG procedures at inducing weight loss, improving obesity-related comorbidities and quality of life, compared to the diet group.

Results: Between July 2020 and October 2021, 120 obese (body mass index 37.5 ± 3.5 kg/m) patients (mean age, 46 ± 10 years; females 87.8%; obesity class II as the main obesity class in 58.3% cases; hepatic steatosis as the main comorbidity with a 70% frequency) underwent EG (through ESG or EVG or D-POSE, with 30 patients for each procedure, 90 patients in total) or a low-calorie diet (30 patients). In the EG group the technical success rate was 100%. The serious adverse event rate was 0%. At 6 months, 63/90 (70%) patients attended their follow-up visit. They experienced $16\% \pm 6\%$ total body weight loss

(TBWL) and $39.7\% \pm 14.9\%$ excess weight loss (EWL), with no significant difference among the three techniques in both of parameters ($p > 0.62$ in TBWL% and $p > 0.94$ in EWL% ANOVA tests). Concerning the low-calorie diet group, 18/30 (60%) patients attended their 6 months follow-up visit; they experienced $1.1\% \pm 4.7\%$ TBWL ($p < 0.001$ versus EG group) and $2.3\% \pm 9.8\%$ EWL ($p < 0.001$ versus EG group). Sixty out of sixty-three (95.2%) patients achieved at least 5% TBWL, and 54/63 (85.7%) achieved at least 25% EWL in the EG group, compared to 2/18 (11.1%) and 1/18 (5.6%) in the diet group, respectively. Fatty liver disease, hypertension, hyperlipidemia, diabetes, and obstructive sleep apnea improved after the EG procedure, while no improvement was observed in the diet group. Also, the quality of life measured by EQ-5D test improved at 6-month follow-up ($p < 0.01$) in the EG group, while no significant improvement was detected in the diet group.

Conclusion: EG through ESG, EVG and D-POSE, focusing on gastric body reduction and sparing the fundus and antrum, are technically feasible and safe, and appear to be effective in the short-term (6 months follow-up) for the treatment of obese patients, compared to diet.

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Robotic colorectal resections at UMC Ljubljana - steady road from competency to proficiency

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Advances in surgery have allowed the widespread use of minimally invasive approaches, becoming the standard of care for more and more diseases. Robotic resections represent a novel but increasingly popular approach to treatment of colorectal cancer. Robotic surgical systems help surgeons to overcome limitations of laparoscopic surgery, offering better visualisation with three-dimensional magnified view and stable camera platform, stabilization of tremors and greater dexterity of movements. Moreover, they also improve the ergonomics for the operating surgeon (1).

The evolution and usage of robotic platform is well illustrated by bibliometric data, as more and more manuscripts are being published each year, from feasibility studies to case series and reviews, and, finally, more and more multi-centre trials. The abundance of published research clearly shows, how robotic assisted surgery has gained acceptance not only in the field of colorectal surgery but across many surgical specialties (2).

Da Vinci Xi robotic platform was introduced at University Medical Centre Ljubljana in 2018, when urologists started with robotic operations. We followed in 2020, and since then more than 1000 robotic operations (700 urological and 400 abdominal) were done.

With the introduction and implementation of a new surgical approach, surgeons need to climb a learning curve, representing the amount of procedures, required to achieve an adequate surgical performance, regarding safety, efficacy and also efficiency (3). The ideal minimal invasive procedure has a short learning curve

and is therefore easy to master. Moreover, the period in which the surgeon »climbs« the learning curve, should not result in additional morbidity, worsened oncological outcomes or even mortality for the patient.

Our path is generally summarized in figure 1 and it started with gaining knowledge of robotic surgery principles, including robotic system components, console operation, robotic instrument handling and trocar placement. This was achieved through on-site (our operating theatre) »dry-lab« training, well organized by the Intuitive representatives, followed by cadaveric training in Naples, Italy. These training programs were focused on general robotic principles and also specifically on colorectal procedures. Participation enabled learning with the help of didactic sessions, virtual simulations and with already mentioned hands-on



Figure 1. Robotic training pathway

training using surgical robotic systems. To further strengthen our robotic programme and accelerate our learning curve climb, we established a collaboration with an experienced robotic surgeon, prof. Morpurgo from Camposampiero, Italy. Our partnership started with visitation to Camposampiero and observing typical robotic colorectal resections performed by prof. Morpurgo and his team. Thereafter, when starting with our own initial cases, our collaboration continued by inviting prof. Morpurgo to UMC Ljubljana for proctorship and guidance.

Transitioning from mere competency to proficiency in performing robotic colorectal resections requires a systematic and stepwise approach and this is exactly how we chose to implement this new technology at University Medical Centre Ljubljana.

By selecting less complex cases at first, such as sigmoidectomies or right colectomies for benign disease or locally non-advanced tumors, we assured the safety of our patients and quality of surgery, hence the treatment results were not compromised.

Even when starting more challenging cases, only patients with colon and later on upper rectal cancer were operated at first, because we deemed middle and low rectal cancers not suitable due to technical demands of pelvic surgery. Only later on did we start, successfully, performing even the most technically demanding robotic colorectal resections (4, 5).

From the very beginning, we established a database (a simple registry), which is prospectively populated with all the relevant clinical data (patient demographics, operative characteristics, postoperative follow-up,...). Only through analyzing this data we can appreciate, how good or bad our results are, in terms of postoperative morbidity, mortality and long term survival in case of cancer patients. To have a successful and long-lasting surgical program, it is crucial to analyze outcomes and complications to identify areas of improvement and facilitate the adoption of best practices.

It has to be appreciated, that before embarking on a road of robotic colorectal resections our surgical department had an established competency in colorectal surgery in terms of traditional open or laparoscopic approaches. This probably played a role in faster acquisition of skills on the robotic platform. However, this journey from competency to proficiency is not something to achieve and then just stop when one feels skilled or proficient enough. The surgeon and all the team must stay dedicated and work together to persevere through difficulties they will encounter and continuously seek to refine their skills and experiences. It is important to stay updated with the latest literature, attend conferences and engage with professional societies.

This is how the continuity of the robotic program can be accomplished, allowing for a proper surgical volume for every robotic surgeon, which is crucial for maintaining and enhancing proficiency and continuous improvement.

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Endoscopic full thickness resection in appendix, issues and solutions (a single center experience)

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ABSTRACT

Gastrointestinal neoplasms were traditionally treated by surgical resection. Endoscopic techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have become conventional, effective and safe treatment methods in the last decades. However, those techniques are restricted to superficial neoplasms. Endoscopic full thickness resection (EFTR) is an emerging and evolving technique that can not only yield adequate tissue for histopathological diagnosis, but also spare surgical therapy in selected cases.

Standard and advanced endoscopic techniques (such as EMR and ESD) are sufficient for removal of most gastrointestinal neoplasms, which involve the mucosal and submucosal layer of the gastrointestinal wall, but they have some limitations. Non-lifting lesions, lesions arising from deeper layers, and lesions in difficult locations pose a significant challenge. Due to increased risk of perforation with the use of standard methods, endoscopic full thickness resection (EFTR) with secure gastrointestinal (GI) wall defect closure provides a safe and minimally invasive - compared to surgery - therapeutic option.

The first over-the-flexible-scope device for EFTR was introduced in 2001 by Schurr and colleagues (1), but it was cumbersome and never entered clinical practice. In the following years the extensive research in the field of Natural Orifice Transluminal Endoscopic

Surgery (NOTES) led to improved conservative endoscopic management of iatrogenic GI wall defects. The introduction of over-the-scope clip (OTSC) closure technique opened the door for the development of over-the-scope full-thickness resection device in 2011.

Since then, the method has been gaining ground in clinical use. Several EFTR devices were developed, all of which utilize either suturing or clipping the GI wall before resecting it, thus avoiding opening and contaminating the peritoneal cavity. The vast majority of published studies and reports were performed using the FTRD® System, developed by Ovesco Endoscopy, Tübingen, Germany.

The indications for use of EFTR are versatile and complement the spectrum of standard interventional endoscopic techniques: non-lifting adenomas (treatment naïve or recurrences), adenomas in difficult locations (diverticulum, appendix), re-resection of malignant polyps, subepithelial tumors, early carcinoma, and diagnostic full-thickness resection (e.g., for motility disorders).

Its use is contraindicated in case of known adhesions of GI wall with adjacent organs, near a stenosis, if it is clear that the target tissue cannot be completely excised, and when clipping or surgery is contraindicated due to patient comorbidities (e.g., immunosuppression, anticoagulation therapy).

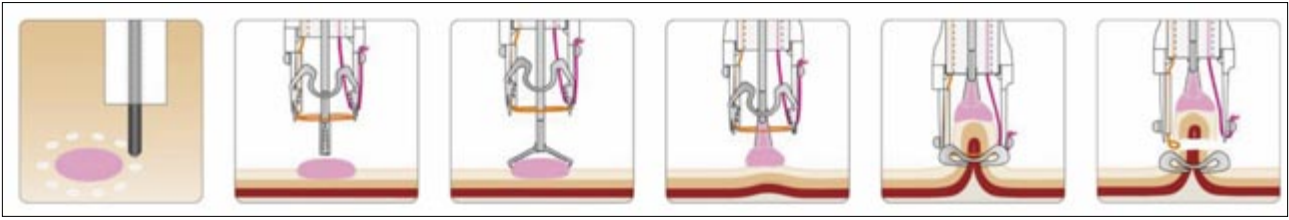


Figure 1. Procedural steps (source: Ovesco Endoscopy AG)

The procedural steps (Fig. 1) when using the FTRD System are: marking the lesion with the FTRD Marking Probe; inserting the endoscope with the mounted FTRD System to the resection site and adjusting the lesion; grasping and mobilizing the lesion with the FTRD Grasper; ensuring the lesion is completely in the cap; deploying the clip; resecting tissue and retrieving the specimen.

The clinical data published on FTRD show overall comparable results in terms of technical success, R0 resection rate and complications rate across different indications (2, 3, 4). The procedure was technically successful in 83–89%, R0 resection was achieved in 76–82%, and complication rate was 9–12%, with surgery due to adverse events needed in 2.0–2.7% of cases.

EFTR at the base of the appendix offers a minimally invasive method of resection and is technically feasible (5). However, the patients should be informed about the risk of possible appendicitis (occurring in 8–17% of cases) and subsequent need for surgical intervention. At present, prophylactic antibiotic therapy is usually administered over the course of three days for such interventions.

In Diagnostic Centre Bled we performed 41 FTRDs between January 2020 and June 2023, 14 of which were at the appendix (Fig. 2). Procedures were done by two endoscopists. 8 patients were female, and 6 were male. Their median age was 68.2 years. The median size of the lesion removed was 12.6 mm. Median procedure time was 51 minutes. The procedures were performed with conscious sedation, using intravenous combination of midazolam and piritramide or fenta-

nyl. Technical success rate, and R0 resection rate were all 85.7%.

Histologically, resected specimen were sessile serrated lesions in 8 cases, low-grade dysplastic tubular adenomas in 5 cases, and high-grade dysplastic tubular adenoma in one case. We performed one re-resection after previous R1 resection of low-grade dysplastic adenoma.

Duration of prophylactic antibiotic therapy administered was 1–3 days.

2 patients (14.3%) needed surgery due to postprocedural appendicitis. Surgery was also needed in two additional patients. One because of R1 resection of low-grade adenoma and one because of subepithelial mucinous neoplasm found at follow up.



Figure 2. Appendiceal EFTR (source: Diagnostic Center Bled)

Our series shows data comparable to reports found in the literature, which confirms the value of this method as feasible and minimally invasive alternative to surgical resection of neoplasms found at the appendiceal orifice.

The procedure is technically demanding, which can be alleviated by careful selection of suitable cases, obtaining a certification for use of the FTRD System and adhering meticulously to the procedural steps.

The location-specific, relatively higher rate of complications, compared to other EFTR procedures - namely appendicitis - calls for further look into the duration and choice of periprocedural antibiotic regimen and possibly use of prophylactic intraluminal appendiceal drainage.

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Endoscopic Ultrasonography-Assisted Management of Biliopancreatic Disease

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Since many year, endoscopic retrograde cholangio-pancreaticography (ERCP) is the first-line approach to manage both benign and malignant biliopancreatic obstruction. However, even in experienced hands, ERCP fails in 5–10% of cases because of impossible cannulation or inaccessibility of the papilla (eg due to surgically altered anatomy or a duodenal stenosis) (1). Moreover, ERCP can be complicated by pancreatitis, cholangitis, bleeding, perforation or stent dysfunction requiring reintervention (2). Until recently, percutaneous transhepatic biliary drainage (PTBD) was the only non-surgical alternative to achieve biliary drainage in cases of failed or impossible ERCP. However, reported adverse rates of PTBD are high (~25%) (3). In addition, PTBD can not be used to achieve pancreatic duct drainage.

Endosonographic-guided biliary drainage (EUS-BD) or pancreatic duct drainage (EUS-PD) techniques have recently been introduced as an alternative to PTBD and surgery in patients with failed ERCP. It is now clear that EUS-BD is associated with fewer adverse events as compared to PTBD and should be preferred if the expertise is available (4).

In patients with benign biliopancreatic obstruction and normal access to the papilla, an EUS-guided rendezvous technique is often used if retrograde cannulation has failed. During this procedure, the dilated bile duct or pancreatic duct is punctured with a 19G needle and a wire is advanced through the needle and through the papilla into the duodenum. The wire is retrieved with the duodenoscope and the sphinctero-

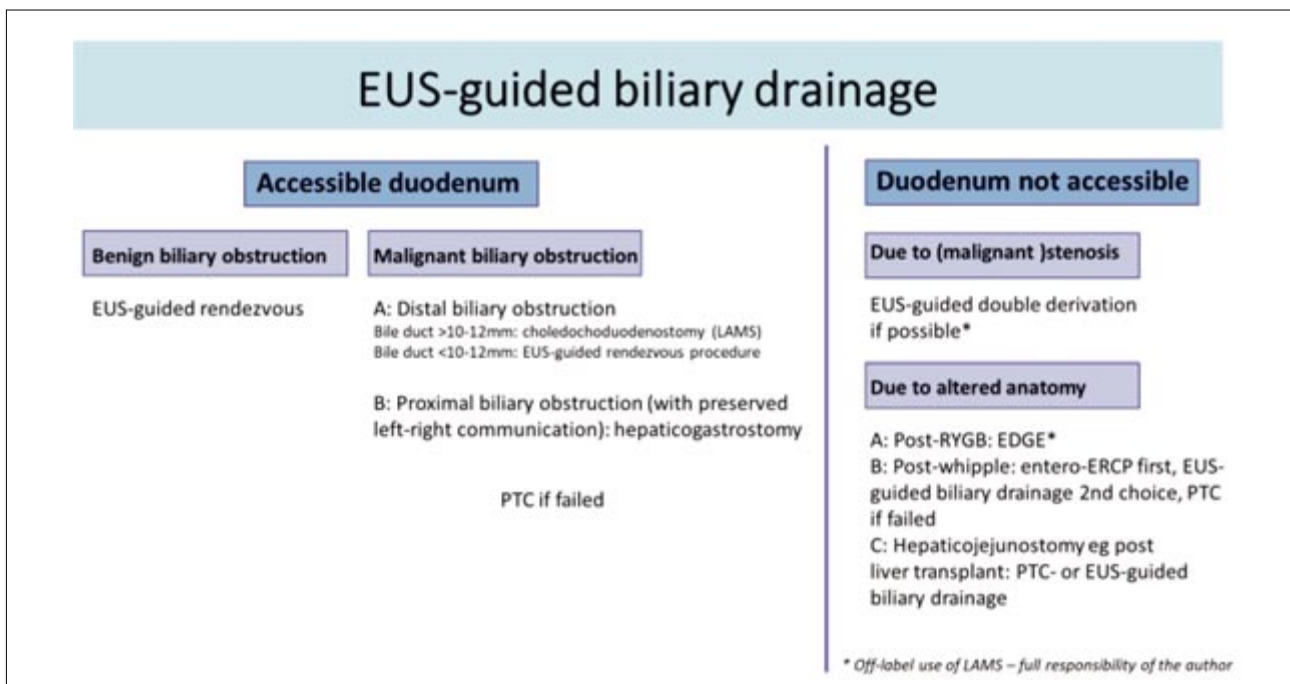


Figure. Flowchart: EUS-guided biliary drainage in case of failed or impossible ERCP

tome if advanced over the wire to cannulate the duct (5, 6).

In patients with malignant biliary obstruction and failed ERCP, direct EUS-guided biliary drainage can be achieved with either a lumen-apposing metal stent (LAMS) from within the duodenum for distal biliary obstruction (choledochoduodenostomy) or a stent between the stomach and the left liver lobe (hepaticogastrostomy). The choice between these two techniques depends on the site of biliary obstruction, the operability of the patient and the level of bile duct dilatation (6). Preliminary data suggest that EUS-guided drainage might replace ERCP as the first-line modality of biliary drainage in palliative patients with malignant distal biliary obstruction mainly since it eliminates the risk of post-ERCP pancreatitis (7, 8).

EUS-guided interventions are also of value in patients with altered anatomy. A direct connection (with a broad diameter LAMS) can be created between the gastric pouch and the excluded stomach to create endoscopic access to the excluded stomach in patient with previous gastric bypass (eg. to perform ERCP). In patients with a hepaticojejunostomy (eg after Whipple, after liver transplantation,...), a temporary hepaticogastrostomy can be placed to create a fistula that allows for further biliary interventions (such as dilatation and stenting of a narrowed biliodigestive anastomosis, stone removal,...) (10). Similarly, a gastropancreaticostomy can be created to drain the pancreatic duct and allow for future interventions through the fistula (stone lithotripsy, further stenting,...).

There is no doubt that EUS-guided biliopancreatic interventions will further expand and receive increasing popularity in the next coming years. The development of dedicated endoscopic tools will facilitate many of these EUS-guided procedures.

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Recommendations For Prevention and Management Of LAMS-Related Complications: An International Delphi Consensus Study

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INTRODUCTION

Lumen-apposing metal stents (LAMS) have become an essential tool in endoscopic procedures for a variety of in- and off-label indications. While LAMS can provide significant clinical benefit for many patients, it's critical to be aware of potential adverse events related

to the procedure. These events have been reported in up to 21.3% of cases (1, 2).

There is an obvious need for consensus regarding the safe use of LAMS to guide practitioners and minimize complications. We sought to develop recommendations on the safe use of LAMS for in- and off-label

indications through a Delphi process with the aim to offer a standardized approach to LAMS placement in different on- and off-label indications.

AIMS AND METHODS

20 international experts were identified and invited to participate in a modified Delphi process to develop consensus recommendations for the safe use of LAMS.

Nineteen experts responded to the survey. Our Delphi process consisted of three rounds. In two round participants had the option of either agreeing or disagreeing with the statements or adding their own comments. Each statement was also provided with the evidence level based on the GRADE methodology.

Comments were then reviewed and statements where no consensus was reached revised and offered in the next round for additional voting. Anonymized comments were also available for other participants to review before voting. The threshold for accepting a statement was set at 80% agreement.

RESULTS

We accepted 56/60 (93.3%) statements during the three Delphi rounds. In first round 35 (58.3%), in second round 17 (28.3%) and in third round 4 statements (6.6%) were accepted. We could not reach consensus in 4 statements (6.6%), so these were removed from final recommendations.

The accepted statements were grouped into the following categories: general safety measures, peripancreatic fluid collections, biliary drainage, gallbladder drainage, and gastroenterostomy (GATE). Consensus was reached on essential safety measures, such as appropriate patient selection, pre-procedural imaging, LAMS placement technique, and post-procedural management. Specific recommendations were developed for each of the aforementioned indication, emphasizing the importance of careful assessment, technique adjustments, and clinical follow-up to minimize complications.

CONCLUSION

Through a modified Delphi process, we developed a consensus on the safe use of LAMS for in- and off-label indications, including general safety measures and recommendations for specific clinical scenarios.

This consensus aims to provide a practical and evidence-based guideline for clinicians to ensure the safe and effective use of LAMS in various endoscopic procedures.

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Do extensive pancreatic resections improve survival?

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INTRODUCTION

Despite the progress in diagnostics, surgical techniques, neoadjuvant and adjuvant therapy there is a lack of improvement in outcomes of the patients with pancreatic cancer. Surgical resection is the only potential curative treatment, however only 15 to 20% of patients are candidates for surgery at the time of the diagnosis. Even after a curative resection, the prognosis is relatively poor, with a median survival of 15–23 months and a 5-year survival of 30% for node negative and 10% for node positive disease (1). The prognosis of a patients undergoing surgical resection is highly dependent on margin status. Resections with histologically negative margins provide the best outcome while resections with positive histological margins have reduced survival rate and resections with residual tumor have a prognosis similar to patients treated with non-operative therapies (1). Only patients with high probability of R0 resection are good candidates for upfront surgery (2).

In pancreatic cancer patients with involvement of the adjacent vascular structures, lymph node involvement beyond the field of resection and distant metastasis are deemed unresectable. Resectability of a pancreatic tumor is determined by preoperative imaging evaluation. Thin-cut pancreatic protocol computed tomography (CT) scan is the method of choice for pancreatic cancer diagnostics. Positive predictive value of a CT scan for unresectability (89–100%) is high, however the positive predictive value of CT scan for predicting resectability is low (45–79%) (3). Magnetic reso-

nance imaging (MRI) can be useful in detection of hepatic lesions that cannot be characterized by a CT (2). The sensitivity and specificity of a CT scan for lymph nodes are low, especially after a patient has undergone neoadjuvant treatment. In such cases exploration might be the only method to assess true resectability. The value of diagnostic laparoscopy is not universally accepted and should be limited to patients with the highest likelihood of occult metastatic disease.

Preoperative histological verification in patients with a typical clinical presentation and resectable malignant disease on imaging is not necessary. It is reasonable to proceed to surgery, due to high negative predictive value of a biopsies.

RESULTS

According to the guidelines from the National Comprehensive Cancer Network (NCCN) all patients with distant metastases and metastases to the lymph nodes beyond resection are deemed unresectable. Patients are considered unresectable also when tumor surrounds $> 180^\circ$ of SMA or celiac axis or is in contact with the first jejunal SMA branch, and if SMV or portal vein due to tumor involvement or occlusion can't be reconstructed. While unresectable disease definitions are widely accepted there is less consensus on the definition of the "borderline" resectable disease (1). European Society for Medical Oncology (ESMO) recommends chemotherapy for patients with locally advanced disease and recognizes a minor role in of the addition of chemoradiation. If sufficient downsta-

ging response is achieved, subsequent surgical exploration can be considered. Oncological treatment is adjusted based on the patient's performance status.

The NCCN considers patients as borderline resectable when tumor is in contact with the IVC or surrounds SMV or portal vein in more than $> 180^\circ$ and in presence of vein thrombosis when resection and reconstruction is possible. Tumors in contact with common hepatic artery without involvement of celiac axis or hepatic artery bifurcation and SMA $\leq 180^\circ$ allowing resection and reconstruction are also considered resectable. Tumors of body and tail are considered as borderline resectable when tumor is in contact less $\leq 180^\circ$ with the celiac axis or more but without involvement of the aorta and with an intact and uninvolved gastroduodenal artery.

Due to high probability of an incomplete resection of borderline resectable tumors, strategies to "downstage" the tumour prior to the resection, using chemotherapy with or without radiotherapy, developed. ESMO and NCCN all favor initial period of chemotherapy followed by a reassessment of resectability (4). However, there is no consensus for the best approach to those patients and it is unclear whether neoadjuvant therapy provides benefit compared to modern adjuvant therapy. Most institutions and guidelines encourage enrolment of such patients in trials.

Portal vein (PV) or superior mesenteric vein (SMV) resection is supported when a R0 or R1 resection can be accomplished and if good inflow and outflow veins are present. It is suggested that in high-volume centers patients undergoing venous reconstructions have similar morbidity and perioperative mortality and it is recommended for selected groups of patients where R0/R1 resection can be accomplished (5).

While venous resection is supported, arterial resection is generally not recommended by guidelines such as ESMOs (6). However, with the advancements in operative techniques current evidence suggests that it might be appropriate for selected group of patients.

In high volume centers this is a viable option and may provide survival benefit (6).

Lymph node status is one of the most important prognostic factors after pancreatectomy and at least 15 lymph nodes should be sampled. Early recurrence and poor survival is inevitable when paraaortic nodes are infiltrated. Extended lymphadenectomy does not improve long term survival or lower recurrence rate in pancreatic cancer surgery and is not recommended (7).

Prognosis of patients with liver metastasis from pancreatic cancer is very poor and hepatic resection is generally not recommended. However, some authors have shown survival benefit in patients with synchronous solitary metastasis (8). A multicentric, prospective, randomized phase III control trial (CSPAC-1) is currently in progress to evaluate the benefits of synchronous resection of pancreatic cancer and liver metastases (9).

Sometimes resection of nearby organs is necessary to achieve radical resection. There is limited data on such resections and their oncological benefit remains controversial.

A systematic review of pancreaticoduodenectomy with colon resections showed that they are associated with increased morbidity and mortality compared to a standard resection, however survival was comparable (10).

CONCLUSIONS

Although surgical resection is the only potentially curative treatment of pancreatic cancer for now, due to poor results, it is obviously not the best or the last answer.

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Indications for minimally invasive pancreatic surgery: are there any oncological benefits?

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ABSTRACT

Currently, surgery in combination with systemic treatment is associated with the best survival outcome in patients with pancreatic adenocarcinomas. The open surgical approach is considered the standard method of choice, with acceptable mortality rates of less than 3 to 5% in high-volume centers. However, it is still associated with an unacceptably high rate of morbidity, mainly due to the occurrence of pancreatic fistula. Minimally invasive surgery, with its advantages over open surgery in other surgical fields, offered hope for patients with PA for a lower complication rate and better overall survival compared with a higher percentage of patients receiving adjuvant systemic chemotherapy. Anatomical considerations and limitations of laparoscopic technology resulted in the acceptance of laparoscopic modality in pancreatic surgery, where the reconstruction phase was not needed. The laparoscopic technique is applicable for left-sided pancreatic resections and has been adopted worldwide with results comparable to those of open surgery. The complexity of pancreatic head resection has resulted in the adoption of laparoscopic techniques in a relatively low number of centers worldwide, performed by a small number of highly skilled surgeons. If a surgical method is not reproducible and acceptable worldwide, it is difficult to state that it is equivalent to well-established open surgical procedures. Advances in technology have resulted in the development of robotic surgery platforms. The robotic surgery platform, with its stability combined with the three-dimensional, magnified high-definition vision, increased degrees of freedom of the instruments, and tremor filtering, allows

for the same movements as open surgery. Thus, despite their relatively young age, robotic platforms have been accepted as a minimally invasive surgical method that enables all types of pancreatic surgical procedures including pancreatic head resection. The main limitations of the worldwide acceptance of robotic platforms are associated with higher costs and steep learning curves. Despite the possibility of using a high-tech tool, surgeons should focus primarily on patient well-being and achieve the best possible results regardless of the surgical method used. The new method can be applied as the new method of choice only when producing the same or better results than the standard open surgical approach. In the literature, several parameters have been used to compare the effectiveness and applicability of different methods. Most often used are the time of surgery, blood loss, rate of conversion, postoperative pain, complication rate, mortality rate, oncological outcomes, and aesthetic effect. The authors opined that the main factors to be considered when comparing different methods are the rate of complications, mortality rate, and oncological outcomes. These factors profoundly influence patients' well-being and long-term survival. In 2016, de Roojis published a meta-analysis in which outcomes after MIPS seemed promising in comparative cohort studies, despite the presence of bias, whereas registry studies reported higher mortality in low-volume centers. The authors concluded that the introduction of MIPS should be closely monitored and performed only within structured training programs in high-volume centers. If we look at the data comparing open pancreatic surgery (OPS) to minimally invasive pancreatic surgery (MIPS), the rate of surgical site com-

lications (88 (44.4%) vs. 87 (43.9%); $P > .99$) was similar, whereas the rate of non-surgical site complications (35 (17.7%) vs. 56 (28.3%); $P = .02$) differed in favor of MIPS. MIPS was associated with a higher rate of clinically relevant pancreatic fistula (22.2% vs. 12.6% after OPS ($P = .02$)) and a lower rate of delayed gastric emptying (5.6% vs. 24.7%; $P < .001$). Another study showed that outcomes in MIPS are equal to or more beneficial compared to the open approach when applied to elderly and obese patients. A series of 500 robotic pancreatoduodenectomies showed that robotic pancreatic surgery is associated with a low complication rate (Clavien score > 2 , less than 24%) and clinically relevant postoperative pancreatic fistula in 7.8% and 30- and 90-day mortality rates of 1.4% and 3.1%, respectively. Even in patients with periampullary carcinoma, MIPS is not inferior in terms of short-term morbidity or mortality. In 2018, van Hilst et al. showed that in patients with PDAC, MIPS was associated with comparable survival, R0 resection, and use of adjuvant chemotherapy, but a lower lymph node yield, as compared to OPS. The DIPLOMA trial reported comparable survival rates after MIPS and OPS for PDAC. However, the opposing differences in R0 resection rate, resection of Gerota's fascia, and lymph node retrieval strengthen the need for randomized trials to confirm the oncological safety of MIPS. The LEOPARD trial showed that MIPS was associated with a reduced time to functional recovery. MIPS was associated with less delayed gastric emptying and a better quality of life without increasing costs; however, the overall rate of complications was not reduced. A recently published meta-analysis showed that laparoscopic pancreatoduodenectomy (LPD) is associated with non-inferior short-term surgical outcomes and oncologic adequacy compared to open resection when performed by experienced surgeons at large centers. Comparable results were reported by Uijterwijk et al. Robotic pancreatoduodenectomy (RPD) is a safe and feasible surgical treatment for malignant or benign disease of the pancreatic head and periampullary region, with comparable results in terms of surgical radicality, including R0 curative resection and the number of harvested lymph nodes with OPD. Long-term surgical and oncological outcomes of MIPS for

distal cholangiocarcinoma are acceptable compared with those of OPD. Surgical outcomes seem to favor RPD over LPD, but more data are needed. In conclusion, open resection remains the cornerstone of pancreatic surgery. Most surgical communities appreciate the adoption of MIPS as the method of choice for a selected population of patients. It is safe and oncologically comparable to open surgery if performed in a high-volume center with experienced surgeons following standardization of operative procedure protocols. However, to establish the role of new minimally invasive modalities, further high-quality evidence is required.

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Slovenian National Screening and Early Detection Programme for Colorectal Cancer - SVIT, Our Results

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INTRODUCTION

Colorectal cancer (CRC) is a significant health burden globally, and its management and outcomes vary substantially across countries. European Union faces approximately 350,000 new cases of colorectal cancer annually, and 156,105 deaths yearly. With one in every 35 women and one in every 22 men likely to develop CRC in their lifetime, it is imperative to focus on preventive measures and early detection strategies.

Slovenia recorded a CRC incidence of 56.4 per 100,000 inhabitants in 2020, ranking sixth among European Union countries. The SVIT Program, initiated in 2009, stands as Slovenia's response to this rising health challenge, aiming to curb CRC incidence through enhanced primary and secondary preventive measures (1, 2).

THE SVIT PROGRAM

Initiated in 2009, the SVIT Program is Slovenia's national response to CRC, inviting approximately 600,000 individuals, aged between 50 and 74 years, for screening every two years. Employing an immunochemical test for occult bleeding in stool, the program refers individuals with positive results for colonoscopy. Persons undergoing diagnostic or therapeutic treatment for colorectal cancer and patients with IBD (Ulcerative colitis, Crohn's disease) are excluded

from the screening program. Persons with negative colonoscopy findings in the past 5 years are temporary excluded from the screening program. All participants however are instructed to return the signed Declaration of Participation to the SVIT Program regardless of the presence of an exclusion factor (3).

Functioning on an estimated budget of 7,114,708 €, it is meticulously organized and ensures short waiting times, personalized communication, regional accessibility, and special care for people with special needs, with an emphasis on continual improvements and adherence to the newly renewed Slovenian guidelines (3).

Funds for running the program, invitations, sending testers, purchasing testers and means for cleaning the intestines before colonoscopy are 3,466,568 €, and for screening colonoscopies and screening histopathological examinations are in the amount of 3,648.140 €.

The implementation and management of the program adhere to legal acts and regulations framed by the Slovenian government (Rules on the implementation of national screening programs for the early detection of precancerous changes and cancer (UL 68/2019) and Act on data collections in the field of health care (4–5).

OPERATIONAL FRAMEWORK AND RESULTS (Figure 1)

The program has been well-received, with a 65% responsiveness to invitations and a 94% colonoscopy rate after a positive FIT. However, responsiveness disparities exist, particularly among men (58.8% compared to women's 69.9%) and in specific regions of the country. The program's success relies significantly on the quality of colonoscopies performed and the continual training and inspections of the endoscopists involved, ensuring the high reliability of the screening process.

It is important that qualified colonoscopists enter the program. However, this factor in itself is not sufficient. To ensure the proper quality level of performing colonoscopies and to improve it, we perform regular, continuous checks. The control of the indicators certainly reduces the potential occurrence of interval colorectal carcinoma and serious complications, as well as provide better cooperation by all individuals involved in the program.

Sixty-eight colonoscopists from 29 endoscopy units participated in SVIT from April 2009 to January 2015. A group of 3 supervising endoscopists from the SVIT

Program Council performed 91 inspections and provided regular annual training.

A total of 891,364 (58.2%) Slovenian citizens participated in the first three screening rounds.

Among 46,552 (6%) positive individuals, 42,866 (92.1%) underwent a first colonoscopy. Total colonoscopies were performed in 98% of endoscopies ($p = 0.459$ between cycles), mean ADR was 51.8% ($p = 0.872$ between cycles), mean right colon ADR was 37.5% ($p = 0.227$ between cycles), mean MAP was 1.1 ($p = 0.981$ between cycles), mean MAP+ was 2.0 ($p = 0.824$ between cycles), and the mean SSL detection rate was 3% ($p < 0.001$).

We observed large differences in quality indicators between endoscopists and a significant increase in MAP, ADR in the right part of the colon and detection of SSL per endoscopist over a 6-year period (5).

The emphasis on quality assurance and regular monitoring has led to an increase in the Adenoma Detection Rate (ADR) to 58% in 2023. The introduction of SVIT has correspondingly seen a decrease in CRC incidence and mortality, with a 3% annual decrease for men and a 2% annual decrease for women since 2010 (5–6).

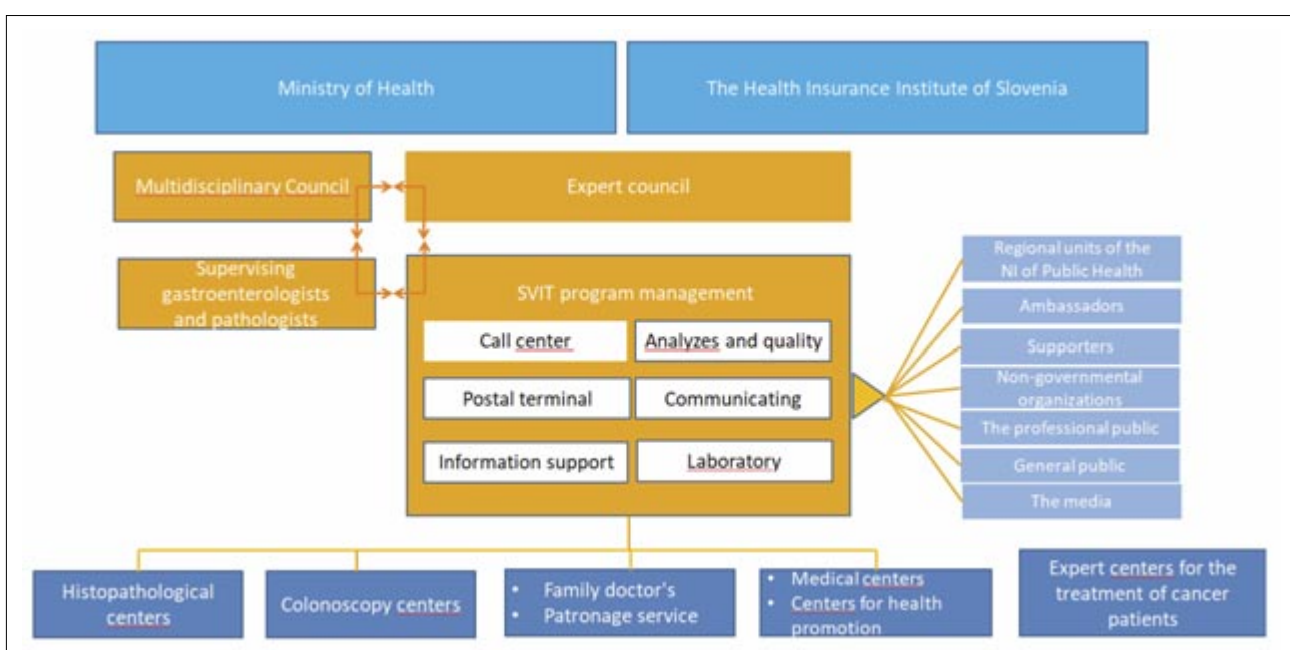


Figure 1. Organizational chart of Program SVIT

SURVIVAL RATES AND IMPACT ASSESSMENT

The post-program era has seen a rise in five-year survival rates, from 54% in 2000–2004 to 62% in 2010–2014 for colon cancer patients. Notably, rectal cancer patients have experienced an increase in survival from 49% to 60% within similar periods. Additionally, the program has enabled catching up of the survival rate of individuals below 50 with those aged between 50 and 74 (5–6). Five-year net survival is more than 94% for cancer detected in a limited stage, 71% for an extended stage, and survival is only slightly less than 10% for patients with diffuse disease at the time of diagnosis (7).

CONCLUSION

Fifteen years of the SVIT program reflect a promising advancement in colorectal cancer management in Slovenia. The outcomes highlight an increase in limited disease diagnosis, continual improvements in ADR, and a significant reduction in CRC incidence and mortality. The structured and quality-centric approach of SVIT provides valuable insights and underscores the importance of nationally implemented, meticulously organized screening programs in combating colorectal cancer. The blend of preventive strategies, quality assurance, and targeted improvements resonate as foundational elements in achieving substantial progress in colorectal cancer management globally.

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Gastric cancer screening in Europe: where are we now?

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Gastric cancer (GC) incidence rates are highest in Eastern Asia and Eastern Europe, whereas rates in Northern America and Northern Europe are generally low (1). When a population-based GC cancer screening program is implemented in a given country/region, several factors must be considered, especially the age-standardized incidence rate (ASR) and the impact on the mortality. For GC, three risk areas can be determined: 1) High-risk areas: ASR ≥ 20 per 100,000 (e.g., Japan, Korea, and China); 2) Intermediate risk areas: ASR ≥ 10 and <20 per 100,000 (e.g., Portugal, Lithuania, Romania, and Slovenia); 3) Low-risk areas: ASR < 10 per 100,000 (e.g., the USA, UK, Sweden, and Germany) (2).

Currently, GC screening is offered to healthy asymptomatic individuals in 3 Eastern countries with a high disease incidence (ASR ≥ 20 per 100,000), namely Japan, South Korea and China. In Japan, Upper Gastrointestinal Series (UGIS) or Upper GI Endoscopy (UGIE) are both first-line options for asymptomatic individuals ≥ 40 years old. The National Cancer Screening Program for GC in South Korea offers biennial UGIS or UGIE to individuals ≥ 40 years old. In China screening through UGIE is available in high-risk areas, for individuals aged 40–69 years old (3). Two meta-analyses showed that GC screening is associated with significantly lower GC mortality rates, either through endoscopic screening or UGIS (3, 4). Comparing GC screening methods, UGIE was associated with higher diagnostic yield, while UGIS and Serum Pepsinogen (PG) tended to higher adherence rates. Screening uptake was predominantly impacted by recruitment

strategies independently of the adopted method (3). Even in high-risk countries where GC screening is well-established, significant challenges arise, namely insufficient endoscopy services, availability of qualified endoscopists and budget constraints (2).

In European countries, the current role of endoscopy in GC early detection represents that of a surveillance tool for pre-defined high-risk individuals, according to MAPS II recommendations, in the setting of opportunistic prevention rather than a screening modality to address the general population (5). The European Society of Gastrointestinal Endoscopy (ESGE) position statement on the role of endoscopy in digestive cancer screening argues that for intermediate-risk regions, endoscopy may have a role for primary screening if cost-effectiveness is proven in the particular country (6). This strategy is supported by a European cost-utility analysis that concluded that endoscopic GC screening every 5 years was cost-effective if combined with a screening colonoscopy in individuals between 50–75 years presenting a positive fecal occult blood test (FOBT) (7). A recent meta-analysis showed that there is an appreciable prevalence of upper gastrointestinal cancers and other clinically significant lesions in FOBT positive subjects, regardless of the presence of colonic pathology (8).

Serological biomarkers (e.g., serum pepsinogen (PG) I and II, gastrin 17, serum anti-*Helicobacter pylori* IgG antibody) poses as an alternative screening method for GC. Despite most studies on the utility of serologic testing originate from high-risk areas for GC,

European studies have been evaluating its role in GC screening (3). A Slovenian study used serologic biomarkers in a population of FOBT positive patients, to identify those with gastric preneoplastic conditions, eligible for further endoscopic screening and found a combined accuracy of 87.5% (9). Similarly, a study from Germany, concluded that patients with a high-risk GC profile according to the Operative Link of Gastritis Assessment (OLGA; stages III and IV) could be identified by a serum PG assessment, and suggested that serological GC screening could be combined with a CRC-screening program, and individuals with a positive PG test should be offered an additional UGIE in addition to a screening colonoscopy (2). Despite the interest in serological testing, the GISTAR study from Latvia found that the low sensitivity of the PG panel may be a limit its use in a population-based screening setting (2).

It is well known that eradication of *H pylori* infection is associated with reduced incidence of GC and the benefits of eradication vary with baseline incidence rates (10). Data on cost-effectiveness of mass screening and eradication from Asian countries show that only in the setting of intermediate to high GC incidence rates and high *Helicobacter pylori* infection rates it is advisable (10). In high GC incidence countries, this strategy is more cost-effective when the starting age of screening is at 20–30 years than at older age (10).

A cross-sectional assessment of ongoing gastric cancer screening programs was performed in 2022, and despite the low response rate (22%), only 2 European countries (Sweden and Serbia) reported opportunistic GC screening in high-risk individuals.

GC screening is well established in Eastern countries, namely Japan, Korea, and China and evidence on screening outcomes largely arises from high-risk populations. Data on population-based screening in European countries/regions is scarce (3), and to date, outside opportunistic screening setting, no program has formally been implemented. In Europe, for intermediate-risk populations endoscopic GC screening combined with a screening colonoscopy may have a role

for primary screening if cost-effectiveness is proven. A population-based *H. pylori* test and treat program may be cost-effective pending on GC incidence and *Helicobacter pylori* infection rates. European health policies for GC screening have recently been revised and supported pilot programs to further reinforce the need for GC screening implementation.

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Gastric cancer prevention in Europe – the EUROHELICAN project

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H. pylori was the first bacterium to be declared a Class I carcinogen by WHO, the International Agency for Research on Cancer -IARC in 1994 (1). In 2018, 2.2 million cases of cancer attributable to infections and theoretically preventable were diagnosed worldwide. The primary causes of infectious cancers is *Helicobacter pylori*, which was responsible for 89% of non-cardiac gastric cancers (810,000 cases, age-standardized incidence -ASIR 8.7 cases per 100,000 person-years), following by a human papillomavirus (690 000.8-0), hepatitis B virus (360 000). , 4-1) and hepatitis C viruses (160,000, 1-7; 2).

A recent meta-analysis of seven randomized controlled trials with 8323 asymptomatic healthy participants found that *H. pylori* infection eradication reduced the incidence of gastric cancer (GC; RR = 0.54, 95% CI 0.40 to 0.72, number needed to treat to prevent one GC (NNT) was 72) and GC mortality (RR = 0.61, 95% CI 0.40–0.92, NNT was 135). More importantly, the study found that 8,743,815 disease-adjusted life years (DALYs) would be gained if population-based search and treatment programs were implemented globally (3). Population-based *H. pylori* screening and treatment programs have been recommended to prevent gastric cancer, particularly in medium to high-incidence areas (4–7), and decision models consistently find the strategy to be cost-effective in these regions (8, 9).

The results of six rounds of population-based *H. pylori* screening and treatment programs from 2004 to 2018 for a high-risk population aged 30 years or older infected with *H. pylori* In Matsu Island, Taiwan were published (10). The strategy resulted in a significant

reduction in the prevalence of *H. pylori* in the population (from 64.2% to 15.0%), along with a reduction in the presence and severity of atrophic gastritis and intestinal metaplasia, as well as the incidence of gastric cancer (for 53%) and mortality (for 25%). During the period of detection and treatment there were no significant changes in rates of antibiotic resistance and other gastrointestinal cancers.

Eradication of *H. pylori* infection has additional health benefits in addition to preventing gastric cancer, such as prevention of gastric and duodenal ulcers, dyspepsia, iron deficiency, MALT lymphoma, and idiopathic thrombocytopenic purpura (6).

Based on the current evidence, population-based *H. pylori* screening and treatment programs should be immediately included as a health care priority, especially in regions with medium to high burden of gastric cancer. Screening programs for *H. pylori* infection and treatment of the infection should ideally be aimed at the younger adult population, aged 20–40 years, before preneoplastic changes in the gastric mucosa appear. This would also reduce the possibility of transmitting the infection to their children (5). Locally validated high-sensitivity *H. pylori* serology could be used to detect *H. pylori*, and the infection is then confirmed by the ¹³C-urea breath test (UDT). In the EU Beating Cancer Plan 2022–2032, the EU Commission wrote that it would be necessary in countries with a medium and high incidence of stomach cancer to start screening for *H. pylori* infection as a method of primary prevention of stomach cancer. Slovenia-NIJZ leads the EUROHELICAN project and part of

the TOGAS project, which represent the implementation of this approach for the first time in the EU.

In our pilot study, which is part of the EUROHELLCAN project, 2,000 asymptomatic residents aged between 30–34 in ZD Maribor will be included as part of regular preventive examinations. Along with other risk factors (BS, lipids, RR, obesity, smoking...) we will also perform a serological test for the presence of H pylori infection. We assume that 20% of the subjects will be serologically positive (13). For confirmation, we will perform UDT and treat positive patients with 14-day therapy according to European and Slovenian (SAGH) recommendations (14). Patients will receive Esomeprazole 2 x 40 mg, Amoxicillin 4 x 500 mg, Metronidazole 4 x 400 mg and Bismuth Oxide Krka 4 x 120 mg. In case of allergy to penicillin, patients will be treated with the scheme: Esomeprazole 2 x 40 mg, Clarithromycin 2 x 400 mg, Metronidazole 4 x 500 mg and Bismuth Oxide Krka 4 x 120 mg (resistance to Clarithromycin in Slovenia is < 15%). One month after the end of the treatment, patients will be tested with UDT. In the case of a positive result (< 7% of patients; 15), they will receive second-line treatment with Esomeprazole 2 x 40 mg, Levofloxacin 500 mg, Metronidazole 4 x 400 mg and Bismuth Oxide Krka 4 x 120 mg according to the SAGH recommendations. UDT will be performed 1 month after the end of treatment. Second-line treatment failure is expected in < 2% of patients. They will be referred to a gastroenterologist for susceptibility based treatment.

At the end of 2023, we will start with the EU project TOGAS, where 6 EU countries will be involved in the research on screening for H pylori as a method of primary prevention of gastric cancer. The research will be carried out under the coordination of NIJZ. ZD Ljubljana will be included in the research with 3000 examinees in the age group 30–34 years.

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Safe colorectal anastomosis: a new concept of surgical procedure standardization and trans-anal evaluation resulted in a low leak and a diversion rate

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INTRODUCTION

Dehiscence of colorectal anastomosis is a serious complication that is associated with increased mortality (1), impaired functional and oncological outcomes (3). The hypothesis was that anastomosis reinforcement and vacuum trans-anal drainage could eliminate some risk factors, such as mechanically stapled anastomosis instability and local infection.

MATERIAL AND METHOD

Patients with rectal cancer within 10 cm of the anal verge and low anterior resection with double-stapled technique were included consecutively. A stapler anastomosis was supplemented by trans-anal reinforcement and vacuum drainage using a povidone-iodine-soaked sponge. Modified reinforcement using a circular mucosa plication was developed and used. Patients were followed up by postoperative endoscopy and outcomes were acute leak rate, morbidity, and diversion rate.

RESULTS

The procedure was successfully completed in 52 from 54 patients during time period January 2019-October 2020. The mean age of patients was 61 years (lower-upper quartiles 54–69 years). There were 38/52 (73%) males and 14/52 (27%) females; the neoadjuvant radiotherapy was indicated in a group of patients in 24/52 (46%). The mean level of anastomosis was

3.8 cm (lower-upper quartiles 3.00–4.88 cm). The overall morbidity was 32.6% (17/52) and Clavien-Dindo complications ≥ 3 grade appeared in 3/52 (5.7%) patients. No loss of anastomosis was recorded and no patient died postoperatively. The symptomatic anastomotic leak was recorded in 2 (3.8%) patients and asymptomatic blind fistula was recorded in one patient 1/52 (1.9%). Diversion ileostomy was created in 1/52 patient (1.9%).

CONCLUSION

Reinforcement of double-stapled anastomosis using a circular mucosa plication with combination of vacuum povidone-iodine-soaked sponge drainage led to a low acute leak and diversion rate. This pilot study requires further investigation.

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New aspects in esophageal cancer surgery: our experiences

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25 years ago in Hungary, we mostly found esophageal squamous cell carcinoma, with a squamous cell carcinoma to adenocarcinoma ratio of 10:1. Patients with advanced cancer underwent open surgery, with a perioperative mortality rate of around 10–15%, and an expected 5-year survival rate of below 20%.

Epidemiology: We performed a cross-sectional study using data from esophageal cancer patients diagnosed between 1992 and 2018 at eight tertiary referral centers in four major cities of Hungary. We retrospectively identified cases in the electronic databases of each center and collected data on gender, age at diagnosis, year of diagnosis, specialty of the origin center, histological type and localization of the tumor. Patients were grouped based on the two main histological types: AC or SCC. We extracted data on 3283 patients with esophageal cancer. 2632 of these were diagnosed with either of the two main histological types; 737 had AC and 1895 SCC. There was no significant difference in the gender ratio of the patients between AC and SCC (80.1% vs 81.8% males, respectively; $p = 0.261$). The relative incidence of AC increased over the years ($p < 0.001$, $b = 1.19$ 54 CI: 0.84–1.54). AC patients were older at diagnosis than SCC patients (64.37 ± 11.59 vs 55.60 ± 10.07 years, $p < 0.001$). The age of patients at the diagnosis of primary esophageal cancer increased over time ($p < 0.001$, $R = 0.119$). The rapid increase in the relative incidence of AC and simultaneous decrease of the relative incidence of SCC suggest that this well-established Western phenomenon is also present in Hungary. (1)

Neoadjuvant therapy: In 1997, we were the first in Hungary to use neoadjuvant treatment for esophageal cancer. As is well known, this is now evidence-based. However, based on our initial experience, it was an interesting observation that upper third tumors responded better to treatment, and we observed more complete remissions. (2) As a result, we introduced organ-preserving resections for tumors at the entrance of the esophagus. (3)

Predictive factors: These above-mentioned observations then prompted us to search for clinical factors which can predict the effectiveness of treatment. At that time, we confirmed that certain heat-shock proteins show correlation with the response to treatment. We showed that high levels of Hsp 16.2, Hsp 90, p-Akt and SOUL were negative prognostic factors in response to therapy and that a high level of these proteins was correlated with decreased 3-year overall survival. These findings underline the significance of these markers as potential predictors of response which possibly can be applied in clinical practice. (4, 5) In a similar study, we also confirmed the presence of HPV infection in esophageal cancer for the first time in Hungary and found a correlation between the response to treatment, the presence of HPV infection, and the expression of HSP proteins. (6)

Surgical technic: In the past decade, there have been significant changes in the surgery of esophageal cancer in our country as well. It has become clear that minimal invasiveness is a clear advantage in the case of esophageal resections. In Hungary, we were among

the first to introduce minimal invasive esophageal resections, and today about 40–50% of our surgeries are performed this way. We conducted and published a meta-analysis to demonstrate the advantages of minimal invasive esophageal resections (MIE). (7) In addition, we introduced robot-assisted surgery last year and after the learning period, we started performing robot-assisted esophageal resections (RAMIE). However, the introduction of the minimal invasive technique has also resulted in the abandonment of the previously mandatory pylorus plasty during the operation. To demonstrate the validity of this decision, we also conducted a meta-analysis using data from the literature.

Preoperative patient care: The advantages provided by MIE result in earlier discharge of patients. However, according to previous principles, patients should not consume anything orally for 5–7 days after esophageal resection, thus reducing the likelihood of anastomotic insufficiency. The application of this rule significantly increases the length of hospital stay. The use of ERAS principles is increasingly spreading in surgery around the world, including in UGI surgery. With the help of prehabilitation, early per oral nutrition during UGI surgical interventions can be started without increasing the number of complications. We conducted a meta-analysis to prove the correctness of this proposition (8), and in line with this, we demonstrated the application of new principles by conducting a propensity score matching study on our own patient material.

Special reconstructions: We consider it extremely important to centralize esophageal surgery to ensure the appropriate level of care, which has only just begun in Hungary. One of the most important reasons for this is that one or two skilled esophageal surgeons are not enough to ensure good results; this can only be achieved through highly trained teamwork in the treatment of esophageal diseases. This also includes cases where classical surgical methods are no longer effective. In such situations, plastic surgeons can be of great help, aiding with free jejunum or supercharged colon replacements, as well as employing other

seemingly hopeless situations using plastic and microsurgical methods to find successful solutions. As this is available at our clinic, we have published several articles on the possibilities of special esophageal replacements. (9, 10) We believe that such a possibility should be available in a serious esophageal surgical center to ensure quality care.

SUMMARY

Our retrospective cross-sectional study aimed to confirm or disprove the presence of the so-called “esophageal adenocarcinoma epidemic” in Hungary.

Neoadjuvant treatment is now clearly evidence-based, and the new immunotherapy further enhances its effectiveness. Our description of better treatment response for tumors located in the upper part of the esophagus has created the possibility of performing organ-preserving surgeries.

During the examination of predictors of treatment response, the expression of tumor-associated proteins, including Hsp, showed a clear correlation with treatment response. Similarly, interesting correlations were seen in the case of HPV infection, Hsp expression, and treatment response.

In terms of surgical technique, MIE and now perhaps RAMIE clearly provide an advantage over open surgeries. The introduction of minimally invasive techniques resulted in the abandonment of pylorusplastica, which was previously considered obligatory, and our own study supports this.

Another major change in perioperative patient management is the introduction of ERAS principles, including prehabilitation and early oral feeding, which not only shorten hospital stays and improve quality of life but also do not increase complications or perioperative mortality.

Finally, it is important to centralize care in centers with appropriate quality indicators where high-level teamwork takes place. This includes involving plastic

surgeons, who can help achieve good results even in previously hopeless situations.

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The Journey of Liver Surgery and Future Perspectives

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ABSTRACT

Liver surgery has undergone a remarkable evolution, marked by the contributions of pioneering surgeons, advancements in surgical techniques, and the integration of innovative technologies. This abstract delves into the historical development of liver surgery, its anatomical intricacies, surgical innovations, and its promising future horizons. The exploration begins with an introduction to liver anatomy, emphasizing the groundbreaking work of Claude Couinaud, who classified the liver into distinct segments based on portal blood distribution.

The emergence of liver tumors, both benign and malignant, has spurred the need for effective surgical interventions. Various types of liver resections are discussed, ranging from formal anatomical resection, anatomical segmentectomies to atypical resections. The Brisbane 2000 Terminology of Liver Anatomy and Resections serves as a framework for understanding liver surgery nomenclature. Notably, the liver's regenerative capacity enables the removal of up to 70% of its mass without compromising its essential functions.

Key innovations that have facilitated successful elective abdominal operations are highlighted. These include the introduction of anesthesia by Morton in 1846, Pasteur's discovery of microorganisms causing diseases, Lister's development of antiseptics in 1867, and the utilization of Paquelin's Thermo-Cautery. Sterilization through steam, pioneered by Von Berg-

mann in 1886, revolutionized surgical practices. The presentation also chronicles significant historical milestones, such as German surgeon Carl Johann August Langenbuch's first successful hepatic resection in 1888 and subsequent resections of metastatic liver cancers by Bruns and hemangiomas by von Eiselberg.

Hemorrhage emerged as a major challenge in early liver surgeries, with techniques like Pringle's Maneuver being developed to achieve hemostasis. A multicenter analysis from 1977 underscored the operative mortality rates associated with hepatic resections, prompting further refinement of techniques. The concept of Future Liver Remnant (FLR) gained prominence, emphasizing the importance of preserving adequate liver function after resection. The 1980s and 1990s marked a period of acceptance for liver surgery, driven by improved anatomical understanding and advancements in anesthetic care, transection techniques, and hemostatic methods.

A paradigm shift occurred with the advent of minimally invasive surgery, particularly laparoscopy, which earned recognition as "patient-friendly surgery." The presentation elucidates various surgical approaches, including open, minimally invasive, and parenchyma-sparing techniques. Multimodal treatment strategies, combining surgery with other therapeutic modalities, gained traction, requiring robust evidence through frameworks like IDEAL (Idea, Development, Exploration, Assessment, Long-term follow-up).

The presentation underscores the significance of evidence-based practice in liver surgery, highlighting the importance of matched series, systematic reviews, meta-analyses, and randomized controlled trials. European guidelines provide a comprehensive framework for standardizing liver surgical practices. As the field looks to the future, the abstract anticipates the integration of value-based healthcare, the fusion of medicine with technology, and the role of robotics, navigation technologies, and hybrid operating rooms. The potential of localized ablation of liver tumors, the transformative power of big medical data, and the advent of personalized cancer treatments also shape the landscape of liver surgery.

In conclusion, this presentation encapsulates the journey of liver surgery from historical breakthroughs to modern advancements and envisions its promising future. It underscores the importance of interdisciplinary collaboration, evidence-based practice, and the harmonious amalgamation of surgical expertise with cutting-edge technology as the catalysts for continued success in liver surgery.

Prevention of post splenectomy infectious complications – an audit at Clinical Department for Abdominal and General Surgery in Clinical Centre Maribor

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Keywords: antibiotic prophylaxis; education; overwhelming infections; post-splenectomy; vaccination

ABSTRACT

Patients who have had splenectomies are at increased risk for severe infections and overwhelming sepsis. Prophylactic measures are important to reduce mortality in this group; among them are vaccinations, antibiotic prophylaxis, and education. We performed a retrospective audit of post-splenectomy prophylactic measures, focusing on vaccinations and antibiotic prophylaxis coverage.

We included 156 adult patients who had splenectomies between January 2013 and December 2021 in a study conducted at a single tertiary medical center. Data regarding vaccinations, antibiotic prophylaxis, and severe infections in the post-splenectomy period were obtained from medical records and supplemented by a patient-devised questionnaire.

Our study shows that there is adequate basic pneumococcal vaccination coverage among patients after a splenectomy particularly after an elective splenectomy, but there is a lack of and an inadequate implementation of other prophylactic measures.

INTRODUCTION

An overwhelming post-splenectomy infection (OPSI) caused by encapsulated bacteria was first described 1952 in a cohort of children who had splenectomies. Not only pneumococcal infection, but also infections with other encapsulated bacteria such as *Neisseria meningitidis*, *Haemophilus influenzae*, intra-erythrocytic parasitic infections and animal bites can be fatal in asplenic patients. The incidence of post-splenectomy sepsis is reported to be the highest in the first two to three years after splenectomy. Because of a possibly fatal outcome of infections in patients who have had splenectomies, it is important to implement preventive measures to reduce the risk of severe infections in this special group. Preventive measures in patients who have had splenectomies include vaccinations, antibiotic prophylaxis, and patient education. If there is an overall consensus regarding the vaccinations there are varying approaches regarding the recommended antibiotic prophylaxis after a splenectomy.

PATIENTS AND METHODS

We conducted a retrospective cohort study. We included the medical data of all adult patients who had splenectomies for various reasons at the University Medical Centre Maribor (UKC MB) between January 2013 and December 2021 who were still alive at the end of 2021. We observed the compliance of post-splenectomy preventive measures, focusing on vaccination coverage and the post-splenectomy antibiotic prophylaxis. We also observed the number of severe infections in the post-splenectomy period. Severe infections were defined as infections that required hospitalization. We collected data on the administered vaccinations from the Maribor regional unit of the National Institute of Public Health. We fulfilled the questionnaire by a telephone interview. In surviving non-responders, the questionnaires were sent per mail.

RESULTS

Between January 1, 2013 and December 31, 2021 (nine years), 279 patients had splenectomies at our institution for various reasons. One hundred twenty (43.0%) patients died before December 2021, mostly because of malignancies. Among 120 deceased patients, none died from OPSI or a severe infection. Of 159 surviving patients, the data from 146 patients were obtained from their medical records and a questionnaire completed either by a telephone interview or by mail.

We observed the highest coverage in pneumococcal vaccination. Overall, 77.5% of patients received a basic pneumococcal vaccination. Antibiotic prophylaxis with phenoxymethylpenicillin or an alternative for two years was recommended at hospital discharge only for 57 (39.0%) patients. Among them, only half of the patients (52.6%) followed the recommendation completely and continued the antibiotics for a total of two years after splenectomy. Most patients, 128 (87.7%), did not suffer severe infections in the observed period. Most patients, 128 (87.7%), did not suffer severe infections in the observed period.

CONCLUSION

Our study presents the current situation of prophylactic measures among asplenic patients in a Slovenian tertiary care center, with adequate basic pneumococcal vaccination coverage yet a low re-vaccination rate, as well as a low proportion of patients receiving antibiotic prophylaxis. Our findings indicate that among all prophylactic measures, education seems to be a core preventative measure, because it could improve compliance with the other two arms of prophylaxis: vaccination and antibiotic prophylaxis.

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EUS-guided liver biopsy for parenchymal liver disease

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In recent years we have witnessed the emergence of endoscopic-ultrasound-guided liver biopsy (EUS-LB) as an effective alternative to traditional liver biopsy techniques. Since the first published cases of EUS-LB in 2007 using a novel Tru-Cut core biopsy needle (QuickCore; Cook Medical, Winston Salem, NC, USA), comparative studies have demonstrated that both endoscopic and non-endoscopic approaches are similar in terms of diagnostic adequacy, accuracy, and adverse events (1). However, EUS-LB still affords many advantages over percutaneous (PC-LB) and transjugular approaches. Due to the proximity of the ultrasound device to the liver, EUS allows for a detailed view of a patient's anatomy in real-time and the avoidance of other structures, including the adjacent vasculature and major bile ducts, thus reducing procedure-related complications (2). In this way, multiple cores from both right and left liver lobes can be obtained, increasing the adequacy and yield of tissue (3). Additionally, EUS-LB is performed with either conscious sedation or under anesthesia, significantly improving patient tolerance and comfort (4). The procedure is quick, adding only a few minutes to the overall procedure time. We often perform EUS for the evaluation of elevated liver enzymes in patients with a dilated common bile duct, and in case of non-diagnostic findings, patients can undergo EUS-LB in the same session, which is likely to reduce overall time, cost of multiple procedures, and expedite clinical management (3). Finally, EUS-LB has a shorter average recovery time compared to conventional LB methods (4).

The latest meta-analysis which included twenty-three studies with a total of 1326 patients using both 19G

and 22G FNA/FNB needles showed a high diagnostic yield of more than 90% which is comparable with the yield of PC-LB. Moreover, after excluding studies using EUS-TB technique with QuickCore™ needle which is not available in the market anymore due to the technical difficulties associated with higher failure rates, diagnostic yield increased to $\geq 95\%$ using EUS-FNB technique with either standard or core-type needles (5). In the past several years, multiple dedicated EUS-guided fine-needle biopsy (FNB) devices with enhanced tip designs for maximal tissue acquisition have been made available for commercial use. When comparing 22G FNB versus 19G FNA needles, tissue adequacy is higher for the 19G FNAs (88% vs. 68%, $p = 0.03$), mainly because samples obtained from a smaller caliber needle are more prone to fragmentation during specimen processing (6). Specimen fragmentation remains a significant limitation of EUS-LB because it can significantly compromise diagnostic accuracy. Recent data suggest that EUS-LB with a 19 G FNB needle provides better histologic specimens than does the technique in which FNA needles are used (7). In a recent systematic review and meta-analysis to compare the safety and efficacy of EUS-LB with second-generation needles and PC-LB that included five studies with 748 patients, pooled diagnostic adequacy and overall adverse events were not significantly different between PC-LB and EUS-LB (96.6% versus 94.9%, OR: 0.81 (95% CI: 1.65–0.03; I2 0%), $P = 0.06$.), the former was superior in terms of the mean number of complete portal tracts (CPT) and total specimen length (8). Beyond the needle design and size, there is also the issue of optimal technique to improve the diagnostic yield of EUS-LB. Many endoscopists use suction or slow-pull techniques with FNA.

The wet suction technique, which uses a saline-filled pre-vacuum syringe, showed high effectiveness for EUS-LB, using the 19G Sharkcore or a standard 19G FNA needle even with a single pass and one actuation, as reported in a retrospective study on 165 patients (9). Furthermore, priming the needle with dilute heparin instead of saline can decrease the formation of blood clots in the needle and improve tissue handling. It has been demonstrated that heparin priming does not lead to bloodier specimens, nor does it increase adverse events of FNA. In a prospective study on 40 patients, using heparin-primed needles improved tissue adequacy compared with dry suction techniques (10). The most recent meta-analysis indicates that using an FNB needle with the slow-pull technique may provide better specimen quality and higher diagnostic yield (5). Nevertheless, we need more prospective comparative studies to assess the superiority of various EUS-LB techniques more precisely.

There are several limitations to the widespread utilization of this technique. EUS requires a prolonged learning curve to achieve competency in comparison to conventional techniques, which require less technical expertise. Endoscopic equipment and the devices utilized for the procedure are expensive. Conscious sedation or anesthesia further increases the cost, and there are also certain risks in an endoscopic procedure. However, EUS-LB is an evolving technique that already has an important role in settings with relevant expertise, mainly because of the superior control of the operating field, low incidence of adverse events, accessibility of the various parts of the liver, and greater patients' comfort (1).

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Watch and Wait Protocol - Rectal cancer - Our results

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To improve local control and resectability of locally advanced rectal cancer, patients are treated with neoadjuvant therapy: radiotherapy/chemoradiotherapy or total neoadjuvant treatment followed by total mesorectal excision. About 20 to 30% of patients developed a complete pathological response after neoadjuvant treatment with the disappearance of the tumor (1, 2). The excellent oncologic outcome in patients who achieved pathologic complete response after neoadjuvant treatment questioned the need for radical surgery. Major resection surgery for rectal cancer is associated with significant morbidity, mortality, and functional impairment and can lead to temporary or permanent colostomy, compromising quality of life. Because of the negative impact of rectal cancer surgery, organ preservation strategies after the achievement of complete clinical response (cCR) to neoadjuvant therapy have developed. One of these strategies with no immediate surgery and close surveillance of patients with complete clinical response is the Watch and Wait (W&W) strategy, first described in 1998 (3).

The goal of the W&W strategy is to avoid surgical treatment of patients with cCR after neoadjuvant therapy. Tumor response to neoadjuvant therapy is time-dependent, but even if a longer time is allowed for tumors to respond, not every patient will achieve a cCR. Most tumor response after neoadjuvant therapy occurs within the first 6 weeks after RT completion. The initial evaluation of tumor response to treatment should be about 6–8 weeks after the end of neoadjuvant therapy. Careful local surveillance includes digitorectal examination, proctoscopy, and MRI. Patients with cCR after neoadjuvant therapy rarely achieves

all clinical, endoscopic, and radiological criteria for cCR at first assessment. Most patients with cCR presented all 3 strict criteria for a cCR after 16 weeks from RT completion, and very few patients required more than 6 months to achieve a cCR.

To identify a complete clinical response, a digitorectal examination confirmed a normal bowel wall without ulcer, irregularity, stenosis, or palpable tumor. On endoscopic examination, a white scar with telangiectasias and hyperemia often confirmed cCR with no ulceration or tumor. MRI is the most essential radiological examination to assess tumor response to neoadjuvant treatment. PET/CT is also important in identifying patients with complete responses. A biopsy of the tumor or scar to confirm the local regrowth is not recommended. Patients with near-complete responses frequently have negative endoscopic biopsies (4). Surveillance after achieving a cCR is for detecting local regrowth and the distant progression of the disease. Despite cCR, patients are at risk for developing distant metastases. About 30% of patients who achieve cCR will develop tumor regrowth. If a local regrowth develops, it should be detected as soon as possible when surgical salvage is still possible with radical resection. The risk for local regrowth decreased after 3 years to less than 5%. Because of this, they recommended intensive follow-up during the first 3 years every 3 months. The intensity of active surveillance in patients managed by a W&W strategy could be reduced if they achieve and maintain a cCR within the first 3 years of starting this approach (5). Proctoscopy is very important because more than 95% of local regrowth is located in the bowel wall, and only 3% of patients are dia-

gnosed with regrowth only in the regional lymph nodes (6). In patients with cCR, local regrowth at any time is a risk factor for distant metastases. Patients with local regrowth showed a 5-fold higher risk of developing distant metastases than those without local regrowth (7).

In the last 5 years, in our hospital, more than 40 patients with complete clinical response after neoadjuvant treatment had been managed by watch & wait strategy. Out of 42 patients, 10 developed local regrowth, all in the first year after the end of neoadjuvant therapy. Seven patients were successfully (R0 resection) treated with salvage surgery based on the principles of TME, one patient with local excision, and one with R1 resection elsewhere. In a group of 7 patients with cCR, distant metastases were confirmed; 5 patients developed local regrowth with distant metastases and only two distant progressions without local regrowth. Two patients, one with local regrowth and one without, died because of the distant progression of the disease.

Conclusions: Watch & Wait strategy seems safe with reasonable local control after achieving a cCR. W&W can be an excellent alternative to surgery. Selection of patients is critical, and surveillance should be done very carefully. Local regrowth is a risk factor for developing distant metastases. Our results with patients with cCR managed by W&W strategy are in accordance with other studies.

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Pancreatic exocrine insufficiency: from diagnosis to treatment

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ABSTRACT

Pancreatic exocrine insufficiency (PEI) is defined as a reduction of pancreatic exocrine secretion and/or intraluminal activity of pancreatic enzymes below a level that permits normal digestion of nutrients. PEI is associated with malabsorption of nutrients and, therefore, it may cause intestinal symptoms and/or nutritional deficiencies. The clinical manifestation of PEI is variably influenced by other relevant factors, such as intestinal anatomy, intraluminal pH, and compensatory activity of non-pancreatic digestive enzymes, intestinal function, dietary habit, and nutritional needs. Consequently, the amount of secreted pancreatic enzymes needed for normal digestion, and therefore the threshold for clinical manifestation of PEI, differs amongst patients. The concept of PEI implies that pancreatic enzyme replacement therapy (PERT) can restore digestion and absorption of nutrients. In patients with pancreatic disease or previous pancreatic surgery, the presence of symptoms of maldigestion supports the diagnosis of PEI. The presence of clinically evident steatorrhea might be sufficient to make a diagnosis of PEI in these patients, but additional nutritional evaluation and pancreatic function testing are recommended. Symptoms commonly related to PEI are steatorrhea, voluminous and foul-smelling stools, diarrhea, flatulence, bloating, abdominal discomfort, and weight loss. The evaluation of symptoms in patients without a known diagnosis of pancreatic disease or previous pancreatic surgery might be extremely challenging considering the low specificity of symptoms for PEI. Due to its limited specificity, diagnosis of PEI cannot be only based on the fecal el-

stase test. Therefore, the combined evaluation of symptoms, nutritional markers and pancreatic function in the appropriate clinical context is recommended for the diagnosis of PEI in clinical practice. In patients with a very high probability of PEI, such as those with pancreatic cancer located in the head of the pancreas, and those after pancreaticoduodenectomy or total pancreatectomy, confirmation of PEI by pancreatic function tests is not always required. If the diagnosis of PEI cannot be established after evaluation of symptoms, nutritional status and pancreatic function, evaluation of the clinical response to empirical PERT could be of help to support the diagnosis of PEI in the appropriate clinical context. PERT should be administered to all patients with clinical symptoms of PEI or maldigestion in accordance with the guidelines for chronic pancreatitis. Pancreatic enzyme replacement therapy (PERT) is beneficial and tolerated in patients with exocrine pancreatic insufficiency. Pancreatic enzyme preparations differ in their content of lipase, amylase, and protease enzymes and are labeled depending upon their lipase activity. PERT preparation should intersperse well with chyme, resist inactivation by gastric juices, empty from the stomach simultaneously with nutrients, and release enzymes rapidly in the proximal small intestine. Particle size and size distribution of the pellets of pancreatic enzyme preparations have been shown to have implications for their clinical efficacy. Therefore, pancreatic enzyme preparations are pH-sensitive, enteric-coated, mini-microspheres that protect the enzymes from gastric acidity and allow them to disintegrate rapidly at pH 5.5 in the duodenum to release the enzymes. Several studies have shown that particles less than 2 mm in

size allow for better dispersal with chyme and simultaneous emptying with chyme from the stomach to the duodenum. The most frequently used PERT preparations are of porcine origin. Patients should be made aware of the porcine origin of PERT before commencing therapy. PERT dosages are based on lipase activity. Initial dose should be about 10% of the physiologically secreted dose of lipase into the duodenum. In general, although there are no randomized trials comparing different doses of enzymes, studies have shown that clinical efficacy is achieved with the administration of a minimum dose of 40,000–50,000 Ph.Eur.U (Pharmacopoeia European Units) of lipase at each main meal and half of that dose (20,000–25,000 Ph.Eur.U.) with snacks for adult patients. If there is no response to the initial dose, it should be titrated up, until it achieves clinical relevance. A higher starting dose (e.g., 75,000 units, with main meals and 50,000 Ph.U. with snacks) has been reported as effective in patients with more severe PEI, e.g., after pancreas resection. Successful PERT can be defined as resolution of malnutrition, symptoms and signs associated with pancreatic exocrine insufficiency in an individual patient. Patients who are non-responders or partial responders to PERT adherence problems, errors in the administration of PERT, and signs and symptoms of other diseases should be evaluated. Dose escalation and/or treatment with PPI, as well as testing to rule out other diseases should be applied on an individualized basis.

Slovenian UR-CARE Inflammatory Bowel Disease Registry: in 4 years from scratch to top European recruiter

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The burden of inflammatory bowel disease is increasing worldwide including in Slovenia. Slovenia has limited epidemiological data, as these are based on occasional cohort reports. Because of this, in 2019, an initiative for joining the European Registry of Inflammatory Bowel Disease (UR-CARE) (1) was started in Slovenia. In 2020, all the necessary procedures for joining UR-CARE were finished. Currently, 8/15 inflammatory bowel disease centers are using the registry.

Inclusion of patients is fast, but currently still only one half of all Slovenian patients are included. Until September 2023, Slovenia included around 3600 patients (Figure 1). First analysis of UMC Ljubljana data revealed that improved accessibility of biological drugs resulted in improved outcome of patients. Drug survival of biologicals improved after 2019 when the constraints on the choice of first line biological were removed. Real-time analyses of these data (any many

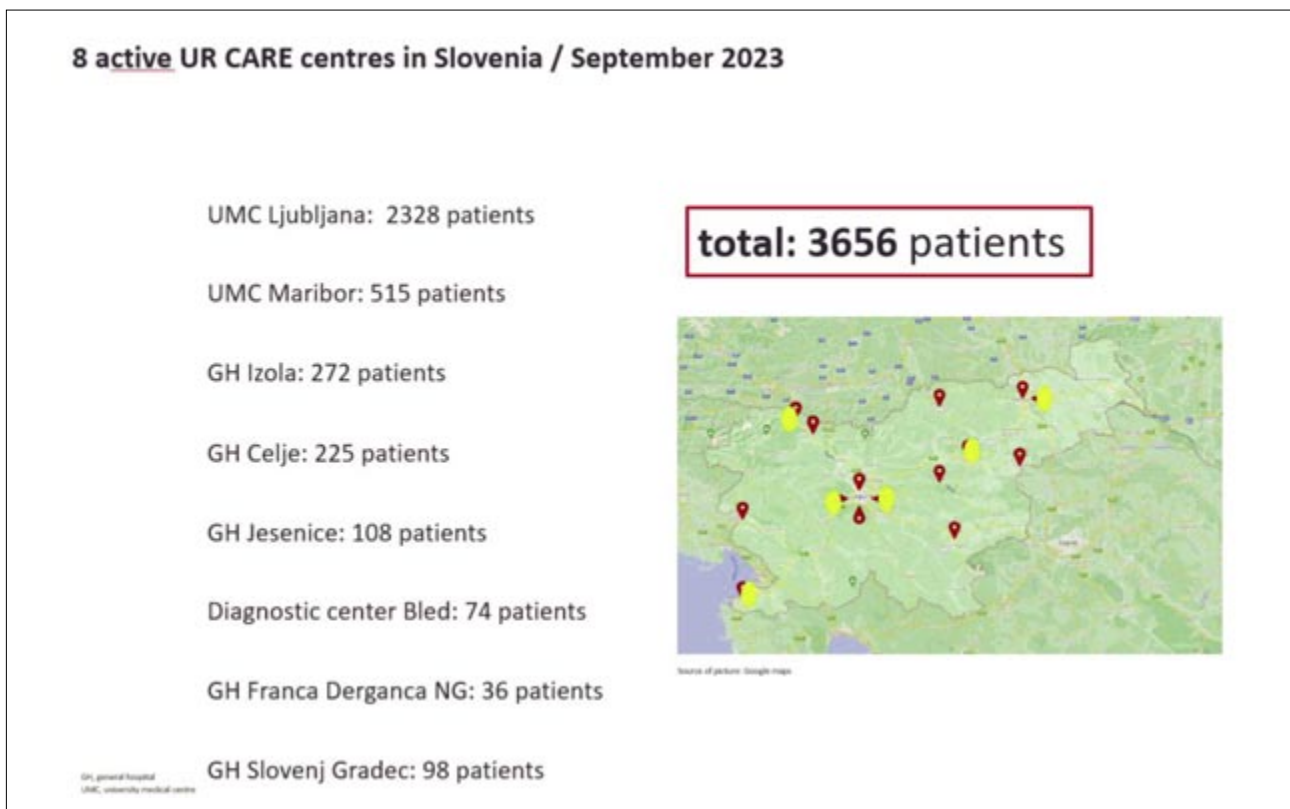


Figure 1. Inclusion of patients into the UR-CARE Registry in Slovenia

others) are possible by means of UR CARE registry. Thus, UR CARE registry is an important tool for monitoring medical care of patients with inflammatory bowel disease at the national level. Some reports on data obtained from the registry are available in recent reports published in Slovenian Journal of Digestive Diseases / Gastroenterolog. (2–4)

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Clinical tool CDST for treatment of IBD with vedolizumab

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INTRODUCTION

The goal of medical treatment of inflammatory bowel disease (IBD) is not only to induce and maintain clinical remission, but above all to achieve healing of the intestinal mucosa, as this is the only way to prevent long-term complications of the disease (1). Currently, the decision on the form of medical therapy is based on clinical information about location and severity of the disease and the intensity of the inflammatory process, the patient's treatment history, previous complications and comorbidities (2). Recommendations from professional associations based on evidence-based medicine or clinical research are helpful in deciding on type and regime of biological therapy, but the final decision is based on clinical judgement. In 2018, Dulai *et al* developed and validated a scoring system to identify patients with Crohn's disease (CD) most likely to respond to 26 weeks of vedolizumab (VDZ) therapy. For the development of clinical decision support tool

(CDST) they used data from GEMINI 2 and VICTORY consortium cohorts to identify factors associated with clinical, corticosteroid-free, and durable remission and they divided the patients into three probability groups, regarding their response status: low (< 25%), intermediate (25–75%) and high probability (> 75%). Each variable was weighted for the final single prediction model equation (table 1). This prediction model was derived and externally validated for accurately predicting clinical remission, corticosteroid-free remission, mucosal healing and deep remission with VDZ therapy in patients with CD (3). This way they derived a tool for identifying patients with CD most likely to respond to treatment with VDZ which may be routinely used in clinical practice to guide optimisation of treatment outcomes and as part of the shared decision-making process (3, 4).

In 2020, the same expert group also developed the CDST for VDZ treatment in ulcerative colitis (UC).

Table 1. CDST variables for Crohn's disease

No prior bowel surgery	+ 2 points
No prior TNF-antagonist therapy	+ 3 points
No prior fistulising disease	+ 2 points
Baseline albumin	+ 0.4 points per g/L
Baseline CRP	- 0.5 points if 3.0–10.0 mg/L - 3.0 points if > 10 mg/L

Table 2. CDST variables for ulcerative colitis

Disease duration ≥ 2 years	+ 3 points
No prior TNF-antagonist therapy	+3 points
Baseline endoscopy moderate activity	+ 2 points
Baseline albumin	+ 0.65 points per g/L
TNF = tumor necrosis factor, CRP = C-reactive protein	

They used data from the GEMINI 1 and VICTORY consortium cohort. They considered following inclusion variables: disease duration, previous TNF antagonist exposure, baseline endoscopy and baseline albumin. The chosen variables were assigned certain points and similarly to CDST for CD patients were assigned into three groups according to probability of response to VDZ (table 2). This prediction model was derived and validated for predicting differences in measured VDZ drug exposure, onset of action and VDZ treatment effectiveness, as well as identification of patients who would most likely benefit from VDZ interval shortening for response optimization (5).

The aim of our retrospective study, based on data collected in the UR-CARE registry, was to determine the potential correlation of CDST in our cohort of patients with CD and UC with VDZ treatment decision-making.

CONCLUSION

The ability to identify patients with IBD who are more likely to respond well to a specific drug before initiation of treatment would allow more effective treatment of the disease, avoid adverse effects and potentially reduce healthcare costs (6). Prospective studies are expected.

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Pathogenesis of Fibrostenosis in Crohn's Disease

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Intestinal fibrosis with stenosis is an important complication of Crohn's disease (CD), where it is the cause of significant morbidity, leading to intestinal obstruction and necessitating surgical intervention (1). Despite advances in the treatment of inflammation, fibrosis is still poorly understood (2). Fibrosis is the final result of injury in most human organs and follows similar pathways of activation and propagation. The major effector cell in fibrosis are activated myofibroblasts, which proliferate and deposit extracellular matrix components in response to pro-fibrotic stimuli (3). By examining fibrosis in different organs, we can identify common pathways, which are specific to fibrosis, regardless of the tissue in which it is occurring. Bioinformatics allows us to identify common genes, which are activated, both in kidney fibrosis and in liver cirrhosis. We showed that these genes common to kidney and liver fibrosis show strong activation in fibrotic CD, but no or only weak activation in CD without fibrosis or ulcerative colitis, confirming their specificity to fibrosis (4). On further analysis of two of these common genes (MGP and THBS2) in CD with fibrosis we showed that the genes showed much stronger expression in the outer layers of the bowel wall (subserosa) than in the inner layers (submucosa) (5). We know that subserosa is a hotspot for fibrosis in CD, representing one of the key differences from UC (6). The difference in pro-fibrotic gene activation in different layers of the bowel suggests, that the bowel contains several fibroblast populations, that inhabit different layers. Looking again at other organs where fibrosis is better characterised, we see that skin has been shown to contain different fibroblasts populations, that show similar patterns of gene activity as we observed in the bowel (7). Superficial injury to the skin results in restoration without scar formation,

while deeper injury leads to activation of fibroblasts inhabiting the deeper layers in healing with scar formation (8, 9). Analogous, in the bowel superficial injury (such as the inflammation in ulcerative colitis) results in no fibrosis or a limited fibrotic response. Injury to the outer bowel layers (such as strong transmural inflammation as seen in CD) which represents a threat of perforation to the organism, results in a strong fibrotic response in an effort to maintain the integrity of the bowel, but potentially resulting in stenosis.

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Helicobacter pylori in children and adolescents (data from Slovenia)

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Helicobacter pylori (*H. pylori*) infection is acquired mainly in childhood and persist through life unless it is treated with specific eradication therapy (1). Transient infection is described but only in infants and in rare occasions. According to recent review more than half of the world population is still infected. This means that, based on regional prevalence estimates, there were approximately 4.4 billion individuals with *H. pylori* infection worldwide in 2015 with a wide variation in the prevalence of *H. pylori* between countries (2). In children, a comprehensive review and meta-analysis of original pediatric studies from 2011 to 2016 performed on healthy children estimated an overall seroprevalence rate of 33% (95% confidence interval (CI) 27–38) (3). The prevalence of *H. pylori* infection in children is decreasing in developed countries. The study from Iceland involved 205 children aged 7–17 years and found only 3.4% of infection (4). In a recently finished Slovenian study 240 children of similar age as in study from Iceland were included and 10.5% of infection were confirmed with monoclonal stool antigen test.

Children are not little adults, and this is especially true with respect to *H. pylori* infection. Infected children have a low rate of severe diseases such as peptic ulcer disease associated with *H. pylori* and almost an absence of gastric malignancies (5). Longstanding active chronic gastritis in adults may result in gastric mucosal atrophy with intestinal metaplasia. In the minority, these premalignant mucosal changes progress to dysplasia and cancer. However, the possible association between such kind of histological changes and gastric cancer is still controversial in the pediatric

population. In addition, the prevalence of premalignant changes is not consistent among published pediatric studies, for example in Slovenia the atrophy was observed in 32.5% of infected children, mostly of mild degree, and intestinal metaplasia was detected in 5.5% of children (6). Different factors can influence on the severity of clinical outcome of chronic infection including certain *H. pylori* genotypes. To date, *cagA* and certain allelic variants of *vacA* have been most consistently associated with severe gastroduodenal diseases in both children and adults. The prevalence of *cagA* gene and *vacA* alleles in children varies among different countries/regions. In Slovenia gene *cagA* have been found in 59,6% of cases, whereas pediatric *H. pylori* strains more commonly contain *vacA* s1 and m2 than *vacA* s2 and m1, with most strains harboring the *vacA* s1/m1 genotype (6, 7, 8).

Treatment failure is increasing worldwide because of a general increase in the antimicrobial resistance of *H. pylori*. The resistance rate of most used antibiotics in the eradication protocols is very high. Primary antimicrobial resistance rates of *H. pylori* in Slovenia were 23.4% to clarithromycin and 20.2% to metronidazole (9). With that keeping in mind the last published pediatric guidelines from 2017 suggested tailored eradication therapy according to the antibiotic susceptibility testing (10). A pediatric study from Slovenia provided strong evidence that in countries with a high prevalence of resistant *H. pylori* strains tailored therapy is essential. Eradication rate was achieved in 85,9% of pediatric patients (9). Although triple therapy tailored to antimicrobial susceptibility was highly successful in our study, an eradication rate greater than

90% was not achieved. Higher failure rates in single-resistant strains despite tailored treatment indicate missed resistance by sampling error. Therefore, two or more biopsies (antrum and corpus) for antibiotic susceptibility testing was suggested to detect resistant bacterial strains in case of mixed infection, having an uneven distribution of clarithromycin-susceptible and clarithromycin-resistant *H. pylori* strains in the stomach (11, 12). In addition, patient/parents' education is crucial for high adherence to therapy.

In adults it is accepted that *H. pylori* gastritis is an infectious disease, and that infection must be treated irrespective of symptoms due to possible serious consequences such as gastric carcinoma. Mass screening in areas with high gastric carcinoma burden have been implemented or considered. However, in childhood *H. pylori* infection rarely causes complications. Moreover, the growing evidence for a possible beneficial role of *H. pylori* infection against some chronic conditions like asthma and allergies. The advent of more sophisticated techniques for assessing the proteome as well as machine learning algorithms may lead to the identification of biomarkers that determine which infected children need eradication therapy because of higher risk of complications such as gastric cancer later in life.

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Eosinophilic Diseases of Gastrointestinal Tract

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Eosinophilic gastrointestinal diseases (EGIDs) are chronic inflammatory disorders of the gastrointestinal (GI) tract characterized clinically by the presence of gastrointestinal symptoms and histologically by eosinophilic predominant inflammation of the GI tract, in the absence of an identifiable secondary cause. Eosinophilic esophagitis (EoE) has relatively high and growing global prevalence, estimated to be 74.42 (95% CI, 39.66–109.19 cases per 100,000 inhabitant-years in the period 2017–2022 (1). EGIDs beyond the esophagus are rare and ill-defined diseases. With intention to define and classify these diseases better, a special international task force of 92 experts from various fields (gastroenterology, allergy, pediatrics, pathologists, researchers) was formed. We published new nomenclature for non-EoE EGIDs based on the location of eosinophilic inflammation and the organ involved in the inflammatory process: eosinophilic gastritis (EoG); eosinophilic enteritis (EoN) with subcategories of eosinophilic duodenitis (EoD), eosinophilic jejunitis (EoJ), eosinophilic ileitis (EoI); and eosinophilic colitis (EoC) (2). When clinically known, subclassification of the different layers of the GI tract should be also described as mucosal, muscular or serosal. Frequently, a term eosinophilic gastroenteritis (EGE) appears in a literature, which includes both EoG and EoN. We recommend to use more accurate recent nomenclature in future publications.

We do not have accurate data on incidence and prevalence of EGIDs beyond the esophagus because most publications to date have focused on case reports and small retrospective series. Estimates of prevalence based on information from insurance databases in North America, over a 2-year period (2009–2011) with data from more than 75 million individuals (ages

0–64 years) suggest that the prevalence of EoG, EGE, and EoC is 6.3 per 100,000, 8.4 per 100,000, and 3.3 per 100,000, respectively (3). Another important problem is that defined and internationally accepted criteria for making a diagnosis exist only for EoE, while for the other EGIDs very different definitions have been used, especially regarding numbers of eosinophils in the biopsies.

Therefore, one of the main goals of the first international international guidelines for diagnosis and treatment of EGIDs beyond EoE was to establish uniform diagnostic criteria, including the number of eosinophils per high power field (4). Although this paper is focused on pediatric population, it includes data from adult patients and presents the first international consensus on this topic. Similarly to EoE, both clinical symptoms and histologic inflammation are required to establish the diagnosis.

Symptoms and signs depend on part of GI tract and layer of the wall affected. They are not specific for non-EoE EGIDs, and alternative conditions should be considered before the confirmation of the diagnosis. Abdominal pain, GI bleeding, vomiting and diarrhea are most frequent. Loss of appetite, weight loss and hypoproteinemia may be present in some patients. When muscular layer is affected mechanical obstruction and motility problems appear. The typical sign of serosal involvement is ascites. Its analysis reveals feature of exudate with high number of eosinophils.

Although elevated eosinophil blood count may be present in some patients it is neither frequent or specific. Endoscopy with multiple biopsies is fundamental for EGIDs diagnostics. Endoscopy may show deep ulcers

that can bleed and even perforate through the gastrointestinal wall, shallow mucosal erosions, diffusely friable and bleeding-prone mucosa, thickened gastric or small bowel folds, pronounced nodularity or granularity, to mucosal edema and redness. However, even more frequently macroscopic appearance of the mucosa is normal and only histologic examination reveals eosinophilic inflammation (5). In patients with muscular layer involvement, narrowing of the lumen can sometimes be seen, and several cases of gastric outlet obstruction mimicking pylorostenosis have been reported. Sometimes surgical full bowel wall thickness biopsy is needed to establish diagnosis.

Unlike the esophagus, which does not contain eosinophils, the immune milieu of the gastrointestinal (GI) tract distal to the esophagus contains a resident population of eosinophils. Therefore, when preparing diagnostic criteria for non-EoE EGIDs, we focused on studies dealing with normal numbers of eosinophils in different parts of GI tract to establish threshold numbers for histologic diagnosis. They are represented in a Table 1.

Etiopathology of majority of EGIDs is poorly understood. While EoE is clearly predominantly Th2 mediated immune disorder triggered by environmental, mostly food allergens, it seems that very different immune mechanisms play the role in other EGIDs (4). The role of food allergy in the pathogenesis of EoG, EoN, and EoC is likely as diverse. some patients

respond to dietary avoidance treatment, a non-IgE-mediated food allergy may be responsible, whereas the others require the use of topical or systemic steroids, suggesting an alternative inflammatory response. Etiopathology of EoC is the least well understood. Its molecular profile is not consistent with Th2 inflammatory pattern, however, a clinical series has identified patients with non-IgE-mediated food allergic reactions.

Topical steroids, proton pump inhibitors (PPIs) as well as elimination diets are recommended first-line therapy for EoE, both for induction and maintenance of remission (6,7). Better understanding of underlying immune mechanisms is leading to development of new drugs targeting specific immune pathways. Anti-IL-4 and anti-IL-13 monoclonal antibody dupilumab is the first biologic drug that gain regulatory approval for the treatment of EoE, while several other new drugs are in the pipeline (8). As all non-EoE EGIDs are rare, all data about efficiency of different therapeutically approaches have been extrapolated from case reports and case series (4). Systemic oral steroids have been effective in inducing clinical and histological remission in non-EoE EGIDs, however, there are no data on selection criteria of which patients should be treated with oral steroids, nor on the optimal dose or duration of treatment. There is much less evidence about the efficiency of topical steroids, but they may be useful in selected patients. Elimination diets may also induce clinical improvement or remission in a proportion of patients with non-EoE EGIDs but there

Table 1. Suggested threshold peak eosinophil counts for the diagnosis of non-EoE-EGIDs

Site	Consensus threshold peak eos/0.27 mm ² HPF	Consensus threshold peak eos/mm ²
Stomach	≥ 30	≥ 110
Duodenum	≥ 50	≥ 185
Terminal Ileum	≥ 60	≥ 220
Cecum and Ascending Colon	≥ 100	≥ 370
Transverse and Descending Colon	≥ 80	≥ 300
Rectum and Sigmoid Colon	≥ 60	≥ 220

are very limited data on histological response. Case series suggest that avoidance of cow's milk may be effective in some children. Equally than in EoE patients, there is no evidence to support the use of food allergy tests to guide dietary restriction therapy. At this moment there is insufficient data to make a recommendation for or against the use of antihistamines, leukotriene inhibitors, mast cell stabilizers, PPIs, immunomodulatory or biological drugs as treatment of non-EoE EGIDs. Endoscopic dilation and surgery may be considered in selected cases with significant objective signs of obstruction.

The natural history of non-EoE EGIDs is uncertain. Some patients may have waxing and waning courses while the others seem to permanently cured. There are no studies that have examined the role of maintenance treatment in patients with non-EoE EGIDs. Therefore, the potential benefits and risks of long-term treatment should be discussed with patients.

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What defines long-term survival in patients after liver resection for colorectal metastases?

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BACKGROUND

Colorectal cancer is the third most frequent malignant disease, with 1,800,000 people affected worldwide (1). At diagnosis, the disease is disseminated in 15% to 25% of patients, and the liver is the most frequent site of distant metastases (1). Another 25% of patients develop metachronous metastases (1). The 5-year overall survival (OS) after radical resection of colorectal liver metastases (CLMs) in well-selected patients is 47–60%. However, the disease recurs in 40–75% of patients, and the liver is involved in half of such patients (1). Traditionally, factors associated with prognosis in patients with CLM were explored that derived from the characteristics of a primary tumor or the CLM, including somatic mutations (2). So far, more than a dozen prognostic scoring systems (PSSs) were developed, and some were externally validated (3). Recently, the paradigm of prognostication shifted toward a host immune system (4). Furthermore, ratios between blood cells or proteinaceous inflammatory markers (PIMs) of the acute phase response could express an inflammatory response (5, 6). These could be C-reactive protein (CRP), albumins, and fibrinogen (7, 8). In 2019, Dupre et al. (9) developed and validated the Liverpool score. It is a PSS that includes the

systemic inflammatory response expressed as the neutrophil-to-lymphocyte ratio (NLR) to predict the survival of patients undergoing surgical therapy for CLM (9). Although prognostic factors used in PSSs are usually part of routine processing, missing variables, which cannot be obtained retrospectively, represent a challenging issue for validation (3). The aim of the study was to rank original variables and candidate PIMs that could replace the NLR in further validating the PSS for patients treated with curative intent for CLM.

MATERIALS AND METHODS

In our research we conducted a retrospective review of a prospectively maintained database of 632 patients who underwent surgical treatment of CLM. For this study, a cohort of 371 patients who had undergone the first liver resection was selected. The study was based on the intention-to-treat principle. Routinely available variables were obtained from the database and analyzed since the patients were subjected to routine diagnostics. The diagnostics included a colonoscopy, blood work, and medical imaging and has already been described elsewhere (10). Patients were considered by a multidisciplinary team (1), and those with metastases confined to the liver were considered

for liver resection, radiofrequency ablation, or a combination (1). A major liver resection involves three or more adjacent liver segments. The routine blood work did not include determining the white blood cell count but PIMs: CRP, albumins and fibrinogen (8). PIMs were measured by automatized analyzers from the peripheral vein blood of patients one day before the scheduled liver procedure. Fibrinogen was obtained in a standard coagulation panel. A postoperative histopathological examination confirmed the diagnosis of CLM in all patients.

The study's endpoint was to find the most appropriate PIM by ranking the variables of the Liverpool score and candidate PIMs. For each variable, the cohort was divided into two groups. The main assumption was that the greater the two groups differed in OS, the greater was the importance of the variable in the OS of a patient. Nine variables were analyzed by the Kaplan–Meier method, by the integral between the Kaplan–Meier curves, by univariate Cox regression analysis, and by multivariate Cox regression analysis and ranked for survival.

Table 1. Four ways of ranking of survival factors

Variable	Kaplan-Meier		Integral I _p		Univariate Cox analysis		Multivariate Cox analysis	
	Chi-square	Rank	I _p [months]	Rank	Hazard ratio (Exp(b))	Rank	Hazard ratio (Exp(b))	Rank
Infiltrated lymph nodes of a primary tumor	21.6	1	26.6	2	2.04	1	1.79	1
Positive resection margin	20.0	2	28.1	1	1.65	2	1.55	2
C-reactive protein > 6 mg/L	16.5	3	20.6	3	1.53	3	1.35	3
ASA classification 2/3	8.4	4	16.6	4	1.35	4	1.33	4
Albumins < 38 g/L	6.7	5	14.7	5	1.33	5	1.14	8
The multiplicity of liver metastasis	5.1	6	12.3	7	1.30	6	1.24	5
The largest liver metastasis > 3.30 cm	4.8	7	11.1	8	1.26	7	1.21	6
Primary tumors on the right side	4.2	8	13.3	6	1.25	8	1.14	7
Fibrinogen > 4.1 g/L	0.5	9	3.2	9	1.080	9	0.982	9

ASA, American Society of Anesthesiologists

RESULTS

There were 243 (65.5%) males and 128 (34.5%) females. Their median age was 65 (27–85, IQR 15) years. There were 263 (70.9%) minor and 108 (29.1%) major liver resections.

Ranking is given in Table 1.

DISCUSSION

The most important finding of our study was that elevated CRP levels were ranked high using all four statistical methods.

First rank was radicality of liver resection in terms of whether R0 resection could be achieved, where an R1 resection was linked to a significantly worse OS (1). Second was lymph node infiltration by the primary colorectal cancer with infiltration contributing to lower survival rates (3). Third was elevated CRP, which was shown to increase the chance for worse OS (7). Fourth was the American Society of Anesthesiologists (ASA) classification, where ASA grade 2 or 3 was linked with worse OS than ASA 1. Fifth was the site of primary colorectal cancer, specifically right-sided cancer, which showed a worse prognosis than left-sided colorectal cancer (3). Sixth was the multiplicity of CLM, with multiple metastases being linked with worse OS, followed by the size of CLM at seventh, specifically with the size of the lesion greater than 3.3 cm (1). Blood albumin levels, specifically lower levels were linked with a worse outcome and placed at eighth (6). Finally, fibrinogen levels, specifically hyperfibrinogenemia, were placed at number nine with no statistical significance (8).

CONCLUSION

CRP levels were ranked high using all four statistical methods, which showed that it could be a promising factor in predicting outcomes for patients with CLM and could prove to be a proper replacement for NLR in future research regarding the validation of the Liverpool score.

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Preoperative Nutritional Assessment in Gastric Cancer Patients: A Single Center Experience

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ABSTRACT

Introduction: Gastric cancer (GC) is one of the most frequently diagnosed cancers worldwide and is the leading cause of cancer-related deaths. Over half of the patients who undergo gastric resection for gastric cancer are at moderate to severe risk malnutrition (1, 2, 3). Recent research has shown that preoperative malnutrition in patients undergoing gastric cancer resection is associated with higher rates of complications, longer hospital stays, increased mortality, readmissions, and higher healthcare costs (2, 4–8). Screening for malnutrition before major surgery is essential, as it can identify patients at risk of malnutrition who may benefit from preoperative nutritional interventions. There are numerous screening tools available, but according to ESPEN guidelines, the recommended screening tool is the nutrition risk screening 2002 (NRS-2002). GC patients identified as being at nutritional risk through screening should be referred to a registered dietitian nutritionist for a comprehensive nutrition assessment and intervention. However, managing the preoperative nutritional status of GC patients presents several challenges, including a lack of knowledge and established protocols, time constraints, and limited access to registered dietitian nutritionist. The purpose of this study is to evaluate the current provision of preoperative nutritional assessment and intervention pathways in GC patients before elective operation.

Patients and methods: Currently, at the Department of General and Abdominal Surgery, University Medical Centre Maribor, we are engaged in an ongoing study

titled 'Irisin as a Prognostic Biomarker for Gastric Cancer Patients: Assessing Its Predictive Value in the Context of Sarcopenia.' As part of our ongoing research efforts, we have conducted a partial analysis of the data collected thus far, focusing on specific aspects related to preoperative nutritional assessment pathways for gastric cancer patients undergoing surgical resection between August 2022 and August 2023 at our institution. Data was collected prospectively. All patients were discussed at our multidisciplinary meeting and procedures were performed according to outcome of these discussions. Only patients who underwent R0 surgical procedures (subtotal or total gastrectomy) were included in this analysis.

Results: 57 patients were included in this descriptive study (64.3% men, 35.7% women). The mean age was 69.9 ± 10.1 years (43–87 years; ≥ 70 years: 60.7%). The mean weight of the patients before the surgical resection was 81.1 ± 17.9 kg and the mean BMI was 27.9 ± 5.8 kg/m². A total of 57 patients (100%) underwent preoperative screening for nutritional risk prior to the surgical resection. Of these, 13 patients (22.8%) had an NRS-2002 score of 2, 15 patients (26.3%) had an NRS-2002 score of 3, 7 patients (12.3%) had an NRS-2002 score of 4, 10 patients (17.5%) had an NRS-2002 score of 5, and 12 patients (21.1%) had an NRS-2002 score of 6. Notably, 44 patients exhibited nutritional risk before the surgical procedure, with 22 of them (39.3%) classified as having severe nutritional risk. Furthermore, 20 (46.5%) of them received nutritional support following consultations with a registered dietitian nutritionist. It's worth noting that only five patients with severe nutritional risk were referred

to an RDN. The duration of preoperative nutritional treatment varied among the patients: 2 patients (10%) received treatment for less than 1 day, 3 patients (15%) for 5 days, and 14 patients (70%) for more than 7 days. The study subsequently conducted an analysis to compare the incidence of general and surgical complications between patients with severe nutritional risk and those without it. The incidence of general complications was notably higher in patients with severe nutritional risk (11.76% vs. 45.45%, $p = 0.004$). Nevertheless, the overall incidence of surgical complications displayed no significant difference (17.65% vs. 31.82%, $p = 0.220$).

Conclusions: Preoperative malnutrition is a widely prevalent and modifiable risk factor in patients undergoing surgery for GC. At the University Medical Centre Maribor, nearly half of all patients participating in the study underwent thorough preoperative nutritional assessment and received appropriate preoperative nutritional support, following established guidelines. These outcomes are comparable to those observed in other, generally more developed countries with advanced healthcare systems. The proven benefits for the patients justify the considerable efforts to foster implementation of these current guidelines in clinical practice.

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SIBO in Upper Gastrointestinal Tract Surgery

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Highlights

- Surgery related to gastric cancer, pancreatic cancer, IBD and metabolic surgery is related to high incidence of SIBO (31%), confirmed in our study. SIBO is related to metabolic complications in patients with solid organ transplantation related to increased mortality.
- The incidence of SIBO is currently underestimated and related to high incidence of metabolic consequences which urgently require appropriate intervention and treatment.
- SIBO further exacerbates and impairs the mechanisms triggered by surgery, chemotherapy and radiotherapy, with consequent micronutrient deficiencies, limited immunosuppressive resorption and efficiency, also in patients with solid organ transplantation and impact clinical signs presentation.
- SIBO should be systematically screened and treated in patients undergoing longer upper gastrointestinal tract resections and solid organ transplantation which already are in higher risk of post-surgical nutritional deficiency to significantly improve treatment outcomes and prevent the development of short and long-term complications.

Background. Longer surgical resections of upper gastrointestinal tract are at higher risk for developing Small Intestinal Bacterial Overgrowth (SIBO); SIBO is characterized as an excessive growth of bacteria in the small bowel, prompting a wide variety of enteral and systemic symptoms and is related to development of short – and long-term complications (1, 2). The predominant phyla in normal gut microbiota are Bacte-

roidetes (19,7%), Firmicutes (40%), Actinobacteria (20%) and Proteobacteria (2,15%) (1, 3, 4). In dysbiotic SIBO environment an excess number of colon dominant bacteria colonizing the small intestine, responsible for digestive symptoms such as bloating, abdominal pain, nausea, and diarrhea (5–8). The suggested pathophysiologic mechanisms of SIBO in upper abdominal surgery include changes in anatomical features due to technical reconstruction to priory and other surgery, adhesions after surgery, influx of substances in the intestine and changed gastric acidity (9–11).

Despite considerable advances in upper gastrointestinal cancer, metabolic and bariatric surgery, and solid organ transplantation (12) the underestimated incidence of malabsorption, small intestinal bacterial overgrowth, and the consequences due to the surgery itself significantly reduces the quality of patients care, affects the incidence of postoperative and metabolic complications, irrespective of the type of surgical resection (13). In patients with solid organ transplantation SIBO is associated with a reduced likelihood of recipient survival, increased prevalence of antibiotic resistance genes and graft survival due to reduced metabolization of the immunosuppressive drugs. Also, dysbiotic environment in solid organ transplantation patients is interfere in degradation, biosynthesis, and negative energy metabolism with metabolic deterioration.

Malnutrition triggers a weight loss, muscle mass reduction, and essential nutrient deficiencies, it increases the risk of tumor recurrence thus detrimentally impacting patients' quality of life and prognosis (12, 13). In addition, gut and pancreatic insufficiency represent

modifiable targets in the interdisciplinary approach to recovery of high quality of life (13). Mandatory therapeutic interventions in group of organ transplantation patients suffering SIBO is related to improved organ functioning, reduced incidence of infection complications and reduced incidence insufficient immunosuppressive profile/treatment related to graft rejection.

Micronutrient deficiencies are also prevalent after upper gastrointestinal resection surgery, as functional and anatomical modification because of surgical resection and reconstruction impact their absorption (12). Surprisingly, these deficiencies appear to be similarly prevalent in patients who have undergone surgery, with iron, vitamins A, B1, B12, D and E deficiencies commonly observed in up to 78,3% of patients (12, 13). Recognizing and treating the distinct consequences associated with each type of deficiency underscores the importance of implementing preventive measures, early detection, and prompt management (12, 13).

Aims. The aim of our study was to evaluate the exact incidence of SIBO after total and subtotal gastrectomy due to gastric carcinoma, after pancreatic carcinoma surgery, after bypass bariatric surgery and reconstruction due to inflammatory bowel disease. The objective of the study was first to compare symptoms, (neo)adjuvant chemo/radiotherapy, treatment and eating patterns in patients with and without SIBO and secondly to evaluate the importance of diagnosing SIBO and treatment to prevent SIBO – related short- and long-term complications.

Methods. In observatory randomized analytical cross – sectional study, 157 patients after longer partial gastrointestinal tract resections underwent a hydrogen (H₂) breathing test (BT) with glucose substrate (25 g/200 mL of water). Participants were instructed to ingest a low-fermentation diet 24 h before the exam and avoid smoking and physical activity on the day of the exam. Subjects fasted overnight (12 h) and during the H₂ BT. At the start of the test, a basal sample of expired air was collected by means of an H₂ BT device. If the first measure of H₂ was < 10 ppm, the participants ingested 25 g of glucose diluted in

200 mL of water. Every 20 min, in total 120 min 6 expired air samples were collected. An elevation of more than 12 ppm according to the basal value, within 120 min was deemed to be a positive result, indicating SIBO. Demographic, anthropometric data, symptoms, antibiotic treatment, (neo)adjuvant chemo/radiotherapy and eating patterns were analyzed with a questionnaire.

Results. Of the 157 patients included 56 had bypass bariatric surgery, 7 had subtotal gastrectomy, 30 had total gastrectomy, 9 had subtotal pancreatectomy, 29 had cephalic duodeno-pancreatectomy or total pancreatectomy and 26 had resection of the small bowel due to Chron's disease. Glucose H₂ BT was positive in total of 48/157 (31%) patients. A positive test was associated with flatulence and bloating ($p = 0,002$) and taking antibiotics as a child ($p = 0,011$). There was no statistically significant difference in demographic data, eating patterns and quality of life.

Conclusions. The incidence of SIBO in patients that underwent subtotal and total gastrectomy, pancreatic resection due to pancreatic carcinoma, bypass bariatric surgery procedure and surgical reconstruction due to inflammatory bowel disease is worryingly high, being 31% in total. SIBO occurs more frequently in patients with longer upper gastrointestinal tract resections related to cancer due to altered physiological defense mechanisms, cancer related cachexia and nutritional disorders. SIBO further exacerbates and impairs the mechanisms triggered by surgery and chemotherapy and radiotherapy, with consequent micronutrient deficiencies and clinical signs. The incidence of SIBO is currently underestimated, which could be connected to developing systemic complications, malabsorption, and its consequences. The results of our study confirm that there we need to systematically address diagnosis and treatment of SIBO in patients undergoing longer upper gastrointestinal tract resections which already are in higher risk of post-surgical nutritional deficiency to significantly improve treatment outcomes and prevent the development of short and long-term complications.

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Comparison of Endoscopic Mucosal Resection of large colorectal polyps with or without thermal ablation of the resection base and margins

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ABSTRACT

Background: Large non-pedunculated colorectal polyps are commonly removed using endoscopic mucosal resection (EMR). EMR combined with ablation of the resection margin significantly reduces recurrence rate. It is unclear which margin ablation technique yields lowest post-EMR recurrence rates. This study compared local recurrence rate (LRR) after EMR using different ablation techniques.

Methods: A retrospective analysis was performed from prospectively collected EMR databases that enrolled 18–89-year-old patients undergoing hot EMR of ≥ 20 mm non-pedunculated polyps between 2018 and 2023, who had at least one follow-up colonoscopy. We compared recurrence rates after EMR without margin ablation, ablation of the margin alone, and ablation of the margin and the defect base. The pri-

mary outcome was histologic LRR at the first surveillance colonoscopy.

Results: 391 patients with 427 LNPCPs were included. EMR was performed in 144 cases without ablation, 170 with margin ablation, 113 with margin+base ablation. LRRs were significantly lower in the margin+base ablation group (0.9%) compared with the margin ablation group (8.8%; $p = 0.005$), and no ablation group (23.4%; $p = 0.001$). LRRs for lesions ≥ 40 mm were significantly lower for the margin+base ablation group compared with the margin ablation and no ablation group (2.4 vs 12.5 vs 28.1%; $p = 0.005$). Bleeding rates were similar across all groups (2.1%; 1.9%; 3.0% for margin+base, margin, and no ablation respectively). 1 perforation was observed in the margin+base ablation group, and 2 in the no ablation group.

Conclusion: Margin and base ablation resulted in almost no recurrence (< 1%) compared to all other modalities. Margin ablation alone significantly reduced LRR compared to no ablation. A randomized controlled trial should follow to confirm the results observed for margin and base ablation.

Pancreatic neuroendocrine tumors – what is the appropriate treatment for localised disease

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Introduction. Appropriate management of localised pancreatic tumors is complex and challenging for surgeons. Incidence of this tumors has increased in the past years, probably also due to widespread use of imaging modalities and they represent 3–5% of all diagnosed pancreatic tumors. Surgical options have evolved, from extended oncological resections to parenchyma sparing resections and finally nowadays in some cases we follow wait and see policy.

Surgical treatment. Better understanding of natural history of the disease and biological behavior supports conservative strategies for selected patients. Radical surgery is not mandatory and may be avoided in small, indolent tumors. Variable behavior of these tumors precludes a single surgical strategy. Without doubt some pNETs must be resected: symptomatic non-functioning pNETs, non-functioning pNETs greater than 2–3 cm, non-functioning pNETs with atypical imaging (main duct dilatation) and all functioning pNETs (insulinomas, gastrinomas, VIPomas, somatostatino-mas etc.).

Standard pancreatic resections, distal pancreatectomy and pancreaticoduodenectomy, should be performed for pNETs with risk of nodal involvement. Regional lymphadenectomy is necessary, because nodal involvement is a strong prognostic factor in regard of survival. In left-sided tumors spleen preserving distal pancreatectomy can be considered, depending on the location of the tumor from splenic vessels and the hilum of the spleen.

Parenchyma sparing resections are enucleations and central pancreatectomy. If we decide for parenchyma

sparing resection, lymph node sampling can be performed to assess node invasion. The value of performing lymphadenectomy at time of primary resection remains an area of investigation. Lymph node metastases were associated with survival in several studies, however there are also studies reporting no correlation between lymphnode metastases and oncologic outcomes. Enucleation can be performed for small low grade tumors, that are located more than 2–3 mm from the main pancreatic duct. This is particularly applicable to small and superficial tumors, but less possible for tumors with abutment of pancreatic duct or deeper in the pancreatic parenchyma. In some studies, enucleation has demonstrated similar 10-year survival as formal resections. Localisation of small insulinomas is sometimes difficult and use of selective calcium stimulation angiogram may be needed to guide resection. Central pancreatectomy is an option for tumors located in the neck or the first part of the body. In this case, there is higher risk of pancreatic fistula, because of two stumps.

Open approach is the standard procedure. Regarding pancreaticoduodenectomy, laparoscopic approach did not show any advantage over open pancreatoduodenectomy. Recent Dutch randomized controlled study has been even prematurely stopped due to increased mortality in the laparoscopic arm. Story is different in distal pancreatectomy. Several studies have reported, that laparoscopic approach is safe and effective with reduced complication rate and shorter hospital stay. Robotic surgery is promising for the future, already nowadays there are some encouraging results in experienced centers not only with distal pancreatectomies but also with pancreatoduodenectomies.

Non-surgical management can be considered for asymptomatic sporadic pNETs smaller than 2 cm, MEN-1 non-functioning pNETs and MEN-1 gastrinomas smaller than 2 cm. Accepting this strategy may result in undertreatment of 10% of patients, with possible nodal metastatic involvement. In case of observation the rate of secondary resection ranges from 10–25%, metastases develop in less than 10% of patients.

Oncological outcomes after surgery depend on tumors grade, size and lymphnode involvement. In patients without liver metastases, 5-year disease free survival is greater than 90%. On the other hand, tumor recurrence is a frequent event, it occurs in 27% within 3 years and in 40% within 5 years after resection. After standard resections, exocrine and endocrine pancreatic insufficiency range from 9–30% and 5–25%. It decreases below 5% in enucleations, however the rate of pancreatic fistula after enucleation is high (45%).

Before operation it is important to weigh carefully the risk-benefit balance.

Alternative to surgery would be ablative methods, radiofrequency ablation (RFA) or microwave ablation (MWA), which can be administered percutaneously, intraoperatively or intraluminally by EUS. The techniques might be offered as an alternative for selected patients in poor general condition with an increased risk of postoperative complications. The rate of clinical success of RFA was 85–100%. Problem of this method are possible thermal injuries of the surrounding structures. Pancreatitis was the most frequent adverse event, sometimes related to thermal injury of the main pancreatic duct.

Conclusion. Surgery is the only treatment that can cure functional and non-functional tumors. In the last several years surgical management has evolved. However, in many cases surgery will still be the first type of treatment applied in in these patients. Data continue to support active surveillance rather than resection for selected, incidentally identified nonfunctional pNETs.

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Barrett's esophagus - How often do we think about it in everyday practice?

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INTRODUCTION

Barrett's oesophagus (BE) is the precursor to oesophageal adenocarcinoma, which carries a poor prognosis and it is likely that all endoscopists and gastroenterologists will encounter Barrett's oesophagus in their clinical practice. Careful assessment and management of patients who have Barrett's oesophagus with endoscopic surveillance and endoscopic endotherapy aims to reduce the risk of progression to invasive adenocarcinoma.

But how often we think about BE?

One of our big mistake during practical work is not allowing sufficient time for careful inspection of the oesophagus during endoscopy. At least 1 minute should be spent inspecting each centimetre segment. The mucosa should be cleaned with a mucolytic agent and the patient made comfortable with proper sedation. Attention should be paid to the right wall and proximal segment as this is where early cancers are most commonly found.

GEJ, as defined in North America, is the junction between the tubular esophagus and proximal stomach. The location of GEJ is approximated by the most proximal extent of the gastric folds. In Asia, this is determined by locating the distal extent of palisade of longitudinal veins. The squamocolumnar junction (SCJ), also known as the Z-line, is the junction of the squamous mucosa and columnar mucosa. It is normally somewhat irregular in appearance. The location of SCJ and GEJ may not coincide endoscopically.

The normal person has no columnar-lined esophagus (CLE), defined as metaplastic cardiac epithelium (with and without parietal and/or goblet cells). The esophageal squamous epithelium normally transitions directly to gastric oxyntic epithelium at the gastroesophageal junction (GEJ) without interposed cardiac epithelium.

The occurrence of cardiac metaplasia at the normal GEJ results from exposure of the most distal esophageal squamous epithelium to gastric contents during times of gastric overdistension.

A diagnosis of **Barrett's esophagus** requires evidence on endoscopy with biopsy confirmation of intestinal metaplasia extending at least 1 cm into the esophagus proximal to the gastroesophageal junction, or Z line.

Barrett's esophagus has been generally accepted as *a complication of chronic and severe GERD*.

Squamous islands are discrete areas of whitish or pale-colored squamous epithelium, seen at endoscopy, that are surrounded by columnar Barrett's epithelium.

Columnar islands are discrete areas of columnar BE, seen at endoscopy, surrounded by paler-colored squamous esophageal epithelium and discontinuous from the circumferential and maximal extent of Barrett's segment.

In pts with **classic esophagitis**, biopsies are usually **not taken** unless necessary to exclude *neoplasm, infection, pill injury, or bullous skin diseases*.

Therefore, the current **primary indication for esophageal biopsies** is to determine the presence of **Barrett's epithelium**. When this diagnosis is suspected, biopsies are mandatory and best done *when esophagitis is healed*

Short segment Barrett esophagus is defined by the presence of columnar-appearing mucosa in the distal esophagus (< 3 cm in length) with intestinal metaplasia on biopsy. **SSBE** is defined as ≥ 1 cm to < 3 cm BE. **LSBE** is defined as ≥ 3 cm Barrett's esophagus.

Surveillance today involves early detection of dysplasia by high definition - white light microscopy (HD-WLM) with *random 4-quadrant biopsies every 2 cm* (or every 1 cm if dysplasia is known or suspected) followed by *biopsy of mucosal irregularity* (nodules, ulcers or visible lesions).

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Endoscopic Management of GI Fistulas

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In general, a fistula is defined as an abnormal connection between an organ or vessel and another organ, vessel, or skin. Mostly, fistulas are rather thin tube-like structures of various length and can be iatrogenic - caused by injury or surgery, or spontaneous - caused by inflammation, infection, neoplasia, or foreign body.

GI fistulas represent abnormal communication between the part of GI tract and other organ, vessel, or skin. Similarly to a fistula, the GI sinus tract is a tube-shaped structure that begins from the GI tract but ends blindly in the surrounding structures. Fistulas can be asymptomatic or cause symptoms of various intensity. The main concerns are infective complications and sepsis, dehydration, and malabsorption with malnutrition.

GI fistulas are named according to the site of origin and the site of termination, the site of origin forming the first part of the name, and the site of termination the last part (eg, enteroenteric, enterocolic, gastroenteric, gastrocolic, cholecystocolic, choledochocolic, colovesical, rectovaginal, enterocutaneous, oesophagotracheal, etc.)

The therapeutic approach depends on presentation, type of fistula, aetiology, and patient condition and preferences. In acute presentation, the first step is to control infection/sepsis and electrolyte imbalance if present, following nutritional support and control of fistula output. Once patient is stabilized thorough diagnostic evaluation is needed. This includes clinical examination, radiological methods such as MDCT, magnetic resonance imaging, and GI con-

trast studies, fistulography, endoscopy, and fistuloscopy. The treatment of chronic fistula can be very challenging. It includes medications to control underlying disease, nutrition support, endoscopy, and / or surgery, all in multidisciplinary fashion with various specialists and therapists. However, it is not uncommon for fistulas to close spontaneously, depending on aetiology (postoperative and acute inflammatory more likely to close), site (gastric, at the level of Treitz and ileal are less likely to close), defect size (the smaller the better) and length of the fistula tract length (the longer the better), condition of adjacent GI tract, and presence of abscess or distal obstruction.

Endoscopy has the role in diagnostic evaluation of GI tract fistulas, and can be used in selected patients with therapeutic intention. In addition to visualising and analysing the fistula opening in the GI tract, endoscopy can be used to inject dye (eg, methylene-blue or indigo-carmin) into the GI tract orally to the fistula or directly to the opening / cannal of the fistula, allowing 'functional' diagnostics. On the other hand, endoscopy plays an important role in the evaluation of the surrounding GI tract mucosa and the underlying disease.

Endoscopy plays an important role in the management of early postoperative leaks and perforations that can be closed by through-the-scope (TTS) or over-the-scope (OTS) clips, and suturing devices, the latest with limited clinical experience. Another approach in acute/early setting is stenting via covered metal stent, which can serve as an escape or bridging therapy, but sometimes proves to be definitive, espe-

cially if defects are small. The main concern is stent migration which occurs in around one third of the patients and necessitates reintervention but also can cause serious adverse events such as perforation and obstruction of the GI tract. TTS clips are relatively ineffective for the closure of chronic fistulas, but the effectiveness of OTS clips is greater, with higher rates of fistula closures. This tool encompasses a large clip that can be used in combination with a tool to anchor-and-pull or to grasp-and-pull the fistula opening into the device for firm capture of the tissue. Data from the literature shows promising results, with good technical success, but clinical success in follow-up of around 50%. Endoscopic suturing is a complex new endoscopic technique allowing full-thickness suturing theoretically translating to high closure rates. However, clinical experience in this setting is very limited, and more clinical data are eagerly awaited. The application of endoscopic tissue sealants (fibrin glue or cyanoacrylate) can also be effective in selected group of patients, i.e., patients with thin long and low output fistulas. This method can be combined with other methods such as clipping. Endoscopic therapy is especially interesting for patients who are not good surgical candidates.

Conclusion: Management of GI tract fistulas is very complex and must include various experts in a multidisciplinary approach. Endoscopy has a role in diagnostic workup and is the first line therapeutic option in the acute setting such as early postoperative leaks. There is an increasing role for new endoscopic modalities such as stenting, OTS clipping, application of tissue sealants, and endoscopic suturing in chronic fistula management, which are less invasive compared to surgery and have the potential to replace complex surgical procedures for the management of these conditions. Even though widely acceptable algorithm that covers endoscopic therapy for GI fistulas is not available, endoscopists should be familiar with endoscopic therapeutic options as well as the site and other fistula features defining suitability for endoscopic therapy. Only experienced therapeutic endoscopist should perform therapeutic procedures for GI fistula closure.

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Calcium imaging in intact mouse acinar cells in acute pancreas tissue slices

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With the increasing number of patients suffering from diabetes mellitus, pancreatitis, and pancreatic cancer, understanding the normal and pathologic physiology of the pancreas is becoming increasingly important (1). The physiology and pathophysiology of the exocrine pancreas are closely related to changes in the intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$ concentration) of the acinar cells. Thus, understanding the regulatory mechanism of $[\text{Ca}^{2+}]_i$ concentration may lead to new treatments for diabetes mellitus, pancreatitis, and pancreatic cancer. Ca^{2+} is liberated from intracellular stores (the endoplasmic reticulum and acid Ca^{2+} pools) into the cytosol after stimulation by neurotransmitters and hormonal secretagogues, for instance, acetylcholine (ACh) and cholecystinin (CCK) (2). Under physiological conditions, the increase in $[\text{Ca}^{2+}]_i$ concentration is mainly confined to the apical region in the form of short-lasting and repetitive local signals responsible for exocytosis and acinar fluid secretion. Eventually, the secretagogue stimulus is sufficient to increase $[\text{Ca}^{2+}]_i$ concentration globally toward the basal cell pole, affecting ion transport, protein synthesis, and cell metabolism (3). Sustained elevation in $[\text{Ca}^{2+}]_i$ concentration evoked by pathological agents, such as bile acids, fatty acids, and non-oxidative alcohol metabolites (fatty acid ethyl esters), leads to bioenergetic collapse of the acinar cell, resulting in inappropriate intracellular trypsin and nuclear factor- κB activation, cytoskeletal damage, mitochon-

drial dysfunction, vacuolization, and necrosis, causing cell injury and acute pancreatitis (4). The main studies to understand the intracellular mechanisms responsible for acinar cell enzyme synthesis and secretion have been performed on cell lines, freshly isolated acinar cells, and isolated pancreatic acini (5). The isolation protocols used in these methods involve digestion by enzymes, a process that results in structural and functional changes (6). To overcome these drawbacks and to allow the study of exo- and endocrine cells in a more natural setting, which could lead to more meaningful results, the acute pancreas tissue slice technique was introduced in 2003 in analogy to successful similar approaches in other tissues (7,8). The main advantage of this approach is the short preparation time without the need for overnight cultivation and enzyme degradation, with initial slices available for experiments in less than an hour (9).

The main aim of our study was to characterize the responses of acinar cells to stimulation with ACh and to compare them with the responses to cerulein in pancreatic tissue slices, focusing on intercellular and interacinar heterogeneity and coupling.

To verify the viability and morphological integrity of acinar cells in mouse acute pancreas tissue slices following isolation, cutting, and loading of the dye, we performed a set of four different and comple-

mentary assessments of their structure and ultrastructure. First, high-resolution imaging of the tissue loaded with the fluorescent Ca^{2+} sensitive dye (Oregon Green 488 BAPTA-1 or Calbryte 520 AM) revealed pyramidal-shaped acinar cells distributed concentrically around an intercalate duct or lumen, forming a typical acinus. Second, the slicing procedure hardly affected the viability of the acinar cells as the majority of the cells appeared viable and only a few cells close to the cutting surface appeared dead on the LIVE/DEAD assay. Third, transmission electron microscopy showed the typical acinar cell ultrastructure. Finally, immunohistochemical staining revealed that the acinar cells abundantly expressed the enzyme amylase, the end product of acinar cells, and stimulation of slices by 0.1 nM cerulein resulted in a significant increase in amylase secretion. Immunofluorescence against the basic helix-loop-helix transcription factor Mist-1 showed that the exocrine pancreas organization and acinar cell identity were maintained in the tissue slices.

We have resorted to functional multicellular confocal imaging of mouse acinar cells $[\text{Ca}^{2+}]_i$ dynamics to characterize their response to ACh and cerulein in tissue slices. We show that acinar cells respond to ACh stimulation with repetitive $[\text{Ca}^{2+}]_i$ oscillations up to 1000 nM and to the CCK receptor agonist cerulein up to 100 pM. We demonstrated that increasing the ACh stimulation concentration increased both the frequency and duration of the oscillations. The total activity of cells was assessed by calculating the active time, which indicates the fraction of time occupied by oscillations. Given the modulation of frequency and duration described above, the active time is a combination of both, and the average relative active time increased accordingly with increasing ACh concentration. Finally, to evaluate the regularity of the oscillations, we calculated the coefficient of interoscillation interval variability. A significant decrease in interval variability was observed for the most extreme of the tested concentrations, which showed that oscillation became more regular with increased ACh concentration. To quantify the level of intercellular sync-

hronization, we calculated the average coactivity between pairs of cells. The activity was well synchronized only between cells from the same acinus, while the activity pattern differed considerably in the neighboring acini. Therefore, functional connections, reflecting well-synchronized cellular activity, were established only between cell pairs within the same acini and not between the cells from the neighboring acini. Furthermore, the oscillations from the same acinus were similar in shape. To test whether acinar cells in slices also respond to cerulein, a decapeptide cholecystokinin receptor agonist, and to compare its effect on $[\text{Ca}^{2+}]_i$ oscillations with responses to ACh, we stimulated slices with cerulein at a 10 pM, 100 pM, and 1000 pM concentration (10). The oscillations after stimulation with 10 pM cerulein and 100 pM cerulein were the result of repetitive, semiregular cycles of elevated and subsequently decreasing $[\text{Ca}^{2+}]_i$ levels. The observed oscillations were similar in the same acinus but typically differed between acini, analogous to what we observed in the case of ACh. Quantitative analysis revealed a dose-dependent $[\text{Ca}^{2+}]_i$ response to cerulein. We observed a significant increase in the duration of oscillations and relative active time at higher cerulein concentrations. In contrast, the frequency of oscillations, their regularity, and the degree of intercellular synchronization were not found to be concentration-dependent.

In conclusion, our results proved that various calcium oscillation parameters depend monotonically on the stimulus concentration and that the activity is rather well synchronized within acini, but not between acini. The acute pancreas tissue slice represents in our eyes a viable and reliable experimental approach for the evaluation of both intra- and intercellular signaling characteristics of acinar cell calcium dynamics. It can be utilized to assess many cells simultaneously with high spatiotemporal resolution, thus providing an efficient and high-yield platform for future studies of normal acinar cell biology, pathophysiology, and screening of pharmacological substances.

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