EFFICACY AND SAFETY OF INNOVATIVE ADVANCED ENDOSCOPIC TECHNIQUES IN THE DIAGNOSIS AND PALLIATION OF UPPER GASTROINTESTINAL TRACT MALIGNANCIES

Ph.D. THESIS

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LIST OF FULL PAPERS RELATED TO THE SUBJECT OF THE THESIS

I. **Bor R**, Vasas B, Fábián A, Bálint A, Farkas K, Milassin Á, Czakó L, Rutka M, Molnár T, Szűcs M, Tiszlavicz L, Kaizer L, Hamar S, Szepes Z. Prospective comparison of slow-pull and standard suction techniques of endoscopic ultrasound-guided fine needle aspiration in the diagnosis of solid pancreatic cancer.
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LIST OF ABBREVIATIONS

AIP: autoimmune pancreatitis

CA19-9: carcinoma antigen 19-9

CBD: common bile duct

CgA: chromogranin A

CP: chronic pancreatitis

CT: computed tomography

EUS: endoscopic ultrasound

EUS-FNA: endoscopic ultrasound-guided fine needle aspiration

ERCP: endoscopic retrograde cholangiopancreatography

ESGE: European Society of Gastrointestinal Endoscopy

IPAS: intrapancreatic accessory spleen

IPM: intrapancreatic metastasis

IPMN: intraductal papillary mucinous neoplasm

GI: gastrointestinal

HCC: hepatocellular carcinoma

HE: hematoxylin-eosin

LN: lymph node

MCAC: mucinous cystadenocarcinoma

MCN: mucinous cystic neoplasm

MPD: main pancreatic duct

MRI: magnetic resonance imaging

NET: neuroendocrine tumors

NPV: negative predictive value

OGTT: oral glucose tolerance test

PDAC: pancreatic ductal adenocarcinoma

PS: plastic stents

PSCC: pancreatic squamous cell carcinoma

ROSE: rapid on-site evaluation

SEMS: self-expandable metal stent

SP: slow-pull technique

PPV: positive predictive value

SR: strain ratio

SS: standard suction technique

TEF: tracheoesophageal fistulas

1. SUMMARY

1.1. Background

Endoscopy is the gold standard for the diagnosis of upper gastrointestinal (GI) and pancreatobiliary cancers; however, conventional gastroscopy is suitable only for examination of the mucosal surface of GI tract, and it is often inadequate for detecting small lesions. The rapid advances of endoscopy led to the emergence of new diagnostic and therapeutic modalities such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS). Although international guidelines attempt to precisely define the indication of these innovative advanced endoscopic modalities, there are still several open questions. Therefore, the aims of this thesis were to compare the diagnostic yield of EUS-FNA samples obtained by slow-pull (SP) and standard suction (SS) techniques of pancreatic and extrapancreatic neoplasms and to evaluate the efficacy, safety and cost-effectiveness of endoscopic self-expandable metal stent (SEMS) placement for palliation of esophageal cancer and malignant biliary obstructions.

1.2. Methods

We compared prospectively the efficacy and quality of EUS-FNA samples obtained with SP and with SS techniques using a 5mL syringe in patient with suspicion of pancreatic or extrapancreatic malignancies. The quality of smears was assessed based on the semiquantitative scale of bloodiness and cellularity, furthermore, the number of obtained and diagnostic slide pairs was determined, as well as the diagnostic yield of samples. We retrospectively analyzed the clinical data of 212 patients with locally advanced esophageal cancer who underwent SEMS implantation. We evaluated the success and complication rate of esophageal stent implantation and determined the frequency and efficacy of repeated endoscopic interventions related to SEMS complications. We retrospectively enrolled patients who received metal (37 patients) or plastic stent (PS; 37 patients). The complication rate, the stent patency and the cumulative cost of treatment were assessed in the two group.

1.3. Results

EUS-FNA sampling of pancreatic cancer was diagnostic in 72 of 92 cases (78.3%). Diagnostic yield was 67.4% in the SS and 65.2% in the SP group. Histological samples were obtained in 60 cases (with SP: 49 cases; with SS: 46 cases). There was no difference in the diagnostic yield of histological samples between the groups (63% and 58.7%). The comparison study assessing efficacy of EUS-FNA in pancreatic and extrapancreatic cancers found that SS technique resulted higher number of smear pairs both in pancreatic (1.74 vs. 3.19; $p<0.001$) and

extrapancreatic tumors (1.62 vs. 3.28; p<0.001), however decreased the proportion of diagnostic smears (46.69% vs. 36.52%; p=0.002 and 49.17% vs. 30.67%; p<0.001) and increased the bloodiness (1.51 vs. 2.07; p<0.001 and 1.48 vs. 2.05; p<0.001). In pancreatic cancers, no difference was observed in terms of diagnostic accuracy (81.38% vs. 83.45%) and cellularity (1.44 vs. 1.27; p=0.067), however they were substantially higher in extrapancreatic tumors using SP technique (71.41% vs. 60.71% and 1.34 vs. 0.77; p<0.001). Only SP technique resulted significant difference between examiners in terms of technical success rate and quality of smears without any decrease of diagnostic accuracy.

238 SEMS implantations were performed with 99.06% technical success and 1.26% procedure related deaths rate in the enrolled 212 patients with unresectable esophageal cancer. Complications occurred in 84 patients (39.62%) and in 55 cases (25.94%) repeated endoscopic procedures were required. Early reintervention 24-48 hours after the stent implantations was necessary due to stent migration (12 cases), arrhythmia (2 cases), intolerable retrosternal pain (1 case) and dyspnea (1 case). An average of 1.98 (range 1-6; median: 2) repeated gastroscopies 13.58 (range 1.5-48; median: 11) weeks after the stent implantation were performed during the follow-up period: 37 stent repositions, 23 re-stent implantations, 15 endoscopic esophageal dilations and 7 stent removals. In 48 cases (87.3%) oral feeding of patients was made possible by endoscopic interventions.

The complication rate of SEMS for management of malignant biliary obstruction were lower (37.84% vs. 56.76), but the stent patency is higher compared with plastic stents (19.11 vs. 8.29 weeks; p=0.0041). In the plastic stent group, the frequency of hospitalization of patients in context with stent complications (1.18 vs. 2.32; p=0.05) and the necessity of reintervention for stent dysfunction (17 vs. 27; p=0.033) was substantially higher. In these group the multiple stent implantation raised the stent patency from 7.68 to 10.75 weeks. There was no difference in the total cost of treatment of malignant biliary obstruction between the two groups (p=0.848).

1.4. Conclusions

SP is an effective method with an outstanding technical success rate and efficacy compared to SS, furthermore, SP technique yields better quality smears independently from tumor consistency. The lower bloodiness of samples and decreased number of slide pairs may result in faster pathological diagnosis and more cost-effectiveness in case of SP. In contrast, SS technique reduces the diagnostic accuracy of sampling in extrapancreatic tumors. Therefore, we recommend the use of SP technique as the first sampling method.

In one quarter of SEMS implantations in patients with malignant esophageal stenosis and tracheoesophageal fistulas the occurrence of complications that can be successfully managed by endoscopic interventions, has to be reckoned with. Our experiences have shown that the individualized stent choice may substantially reduce the complications rate and make repeated endoscopic interventions easier.

In cases of primary malignant biliary obstruction, considering the cost of treatment and the burden of patients we recommend the SEMS implantation if the life expectancy of patients is more than two months. In short survival cases the multiple plastic stent implantation is recommended.

2. INTRODUCTION

Upper GI and pancreatobiliary cancers, including those of the esophagus, stomach, extrahepatic biliary tracts, and pancreas, are one of the leading causes of cancer-related morbidity and mortality worldwide. Endoscopy is the gold standard for the diagnosis of these malignancies; however, conventional gastroscopy is suitable only for examination of the mucosal surface of GI tract, and it is often inadequate for detecting small lesions. In recent decades, there have been rapid advances in the GI endoscopic technique which led to the emergence of new diagnostic and therapeutic modalities such as ERCP and EUS. ERCP is an invasive procedure that provides radiological visualization of the detailed structure and the pathological changes of the biliary tree and pancreatic ducts by injection of contrast agent into the common bile duct (CBD) and the main pancreatic duct (MPD). EUS is a minimally invasive procedure combining endoscopy with ultrasound, which allows ultrasound transducer to get close to the organs inside the body. As a result, higher ultrasound frequency is applicable, which improves the spatial resolution at the expense of depth of ultrasound waves' penetration. EUS is suitable for differentiating the layers of the gastrointestinal wall and examining the surrounding tissues and organs. Although its role is still inevitable in the staging of esophageal, stomach, pancreatic and rectal tumors, in the recent years its therapeutic significance has come to the fore. At the same time, ERCP has also transformed from a diagnostic method to an almost exclusively therapeutic procedure. Endoscopic interventions represent a less invasive therapeutic option for patients compared to surgery because it is less burdensome, does not need general anesthesia and could reduce hospital time. It is especially favorable for elderly and for patients in poor clinical condition; furthermore, it does not require the delay of initiation of oncologic treatment as opposed to surgery. Although international guidelines attempt to precisely define the indication of these innovative advanced endoscopic modalities, there are still several open questions.

Despite the increasing use of EUS-guided fine needle aspiration (EUS-FNA), there are no evidence-based recommendations about the detailed technique and processing of smears, therefore, they vary substantially across medical centers. The optimal sampling technique is expected to produce samples of satisfactory quality with high cellularity and low blood contamination.[1] The high number of smears is one of major limitations of EUS-FNA, because it increases costs and the length of pathological evaluation. These quality features are influenced by the needle and suction characteristics, as well as by vascularity and stiffness of the tumor.[2] The suction force for sampling can be generated by multiple different ways. The slow pull out of stylet during the sampling generates a small suction/capillary force (stylet capillary/slow-

pull technique; SP). In contrast, greater suction/vacuum is created attaching a 5 or 10 mL syringe to the hub of the needle after quick removal of the stylet (standard suction; SS). It is assumed that the aspiration of cells of hard, fibrotic cancers requires greater suction power, however in hypervascularized cancers the same suction force could result in increased bloodiness of smears which interferes with pathological evaluation. EUS elastography could help in determination of tissues stiffness, and based on this, in the differentiation between benign and malignant lesions,[3] however, in many medical centers elastography is not available, so the choice of sampling technique could only be based on the characteristics of the target organ. Pancreatic adenocarcinomas are typically hard lesions due to prominent desmoplastic stromal reactions.[4] Accordingly, they appear as a blue lesion on the qualitative EUS elastography images, and the strain ratio (SR; 21.80-39.08) and their optimal SR cut-off values (6.04-9.10) in the differentiation of benign and malignant lesions are also high.[5–9] In case of lymph nodes, this SR cut-off value is substantially lower, 4.5-4.61.[10,11] The benign lymph nodes are predominantly soft, green structures, the appearance of blue areas is suggestive for malignancy.[7,12] Besides the stiffness, the vascularity of the normal parenchyma of an organ influences the bloodiness of EUS-FNA samples. Liver is a typically hypervascularized organ. The technical guideline of European Society of Gastrointestinal Endoscopy (ESGE) recommends continuous suction for EUS-FNA of pancreatic solid masses and cystic lesions.[13,14] Recently published comparison studies are questioning this, although their results are contradictory. Some studies suggest that the quality of smears obtained by SP technique is better compared with SS, but others disprove this.[15–17] Numerous prospective studies with contradictory results have assessed the technical aspects of pancreatic EUS-FNA sampling. On the other hand, mainly retrospective studies have been published about the detailed sampling methods of cancers of other organs, and in these cases, only lower quality evidence-based recommendations are available.

Esophageal cancers and pancreatobiliary malignancies are often diagnosed at a locally advanced or metastatic stage, when curative resection is no longer feasible, and the therapeutic options are largely limited to the oncological treatment and palliation of symptoms.[18,19] Self-expandable metal stent (SEMS) placement is the most common mean of palliation of dysphagia caused by esophageal cancers, and it could be effective for the palliation of malignant tracheoesophageal fistulas (TEF).[20] This minimally invasive endoscopic procedure could rapidly improve the symptoms of patients, but in 30-50% of the cases minor or major complications occur with the return of dysphagia.[21] The early recognition and management of complications substantially influences the efficacy of therapy. Endoscopic treatment is firstly

recommended due to its minimal invasiveness and low burden of patients.[22] In contrast to the high technical and functional success rate of the first stent implantation, endoscopic management of SEMS complications represents a real challenge also for experienced gastroenterologists.

In approximately 70% of pancreatic cancers, some degree of biliary obstruction has occurred at the time of diagnosis, regardless of stage, and such obstruction is frequently associated with decreased length of survival.[23,24] ERCP with placement of plastic stents (PSs) or SEMSs is the first-choice procedure for the palliation of malignant obstruction of the infrahilar CBD. In the traditional approach, the choice of stent depends on the patient's clinical condition and the disease stage. The most important advantages of PSs over SEMSs are the easier insertion and favorable upfront cost; nevertheless, PSs need to be replaced every 3 to 4 months to prevent or manage the complications, such as occlusion and migration. Longer stent patency of SEMSs might compensate for its substantially higher cost. In the guidelines published in 2012, the ESGE recommended the use of 10-Fr PSs if the diagnosis of malignancy is not established or if the patient's life expectancy is less than 4 months.[25] In contrast, the newer guidelines, published in 2017, highlight the priority of SEMS usage, regardless of cancer stage.[26] Nonetheless, the use of PSs has not yet substantially decreased due to their costs. Cost effectiveness of stenting with SEMS and PS has still not been fully clarified in the daily clinical practice.

3. AIMS

3.1. Comparison of diagnostic yield of EUS-FNA samples obtained by SP and SS techniques

3.1.1. To prospectively compare the diagnostic yield of EUS-FNA samples obtained by SP and SS in patients with suspected malignant pancreatic lesions based on the number of diagnostic smear pairs, bloodiness, and cellularity.

3.1.2. To prospectively compare the efficacy of SP and SS techniques of EUS-FNA in the sampling of pancreatic and extrapancreatic tumors.

3.2. Assessment of efficacy, safety, and cost-effectiveness of endoscopic SEMS placement for palliation of upper gastrointestinal malignancies

3.2.1. To retrospectively evaluate the success and complication rate of esophageal stent implantation and to determine the frequency and efficacy of repeated endoscopic interventions related to SEMS complications.

3.2.2. To retrospectively compare the therapeutic efficacy and cost effectiveness of SEMS and PS in the treatment of primary malignant biliary obstruction in real-life settings.

4. PATIENTS AND METHODS

4.1. Prospective comparison of diagnostic yield of EUS-FNA samples obtained by SP and SS techniques

4.1.1. Technical aspects of EUS-FNAs

EUS-FNAs were performed under intravenous premedication with 5 mg midazolam, 20 mg butylscopolamine and 10-20 mg nalbuphine by the same two investigators using linear Olympus GF-UCT 140 echoendoscope (Olympus Optical, Tokyo, Japan) and 22G FNA needles (Echotip Ultra; Cook Ireland Ltd., Limerick, Ireland; EZ Shot 2, Olympus Optical, Tokyo, Japan). At least one puncture was performed using both SS and SP techniques with the same needle during approximately 7-10 back-and-forth movements done in fanning manner under continuous ultrasound control. In case of SP, suction force is generated by the slow pull out of stylet during the back-and-forth movements of the needle. In case of SS technique, 5 ml syringe was attached to the hub of the needle after quick removal of the stylet to create greater suction force compared to SP. The puncture was considered technically successful if the suction force was strong enough for mobilizing any grossly or microscopically identifiable cellular material from the target organ regardless of their diagnostic value. The obtained material from the needle was pushed on the slides with the reinsertion of the stylet. The coherent tissue species were removed from the glass slides and placed in 10% buffered formalin, smears were made from the remaining specimen and fixed in 96% methanol for at least 10 minutes. After the repeated removal of the stylet, the residual aspirated material was flushed out from the needle with saline and 5 ml air to a native sampling tube. This procedure flushed out the residual specimen from the needle. Rapid on-site evaluation (ROSE) was unavailable.

4.1.2. Pathological assessment

Pathological diagnosis was based on a combination of cytological and histological diagnosis. The formalin-fixed and paraffin-embedded tissues were processed using the standard protocol for endoscopic biopsies: standard staining with hematoxylin-eosin (HE) supplemented by special stains and immunohistochemical testing (CK7, CK20, MUC5AC, CDX-2, chromogranin A, synaptophysin, etc.) if it was necessary. The fluid in the native sampling tube obtained by flushing the EUS-FNA needle with saline was centrifuged, and smears or paraffin-embedded cell block samples were prepared. All cytological smears were stained by HE; immunocytochemistry was performed only in selected cases on smears with high cellularity.

The bloodiness and cellularity of smears was assessed in semiquantitative manners on a scale from 0 to 3.

CELLULARITY OF SMEARS	
0 - acellular	no or only a few malignant/diagnostic cells
1 – low	< 2 clusters of malignant/diagnostic cells with minimum 10 tumor cells
2 - medium	2 – 4 clusters of malignant/diagnostic cells with minimum 10 tumor cells
3 – high	>4 clusters of malignant/diagnostic cells with minimum 10 tumor cells
BLOODINESS OF SMEARS	
0 - absence	no or minimal blood contamination
1 – mild	a few blood cells which do not interfere with pathological evaluation
2 – moderate	partially covered by blood cells, but pathological evaluation is possible
3 – severe	covered by blood cells which interfere with pathological evaluation

1. Table: Semiquantitative scale for assessment of smears cellularity and bloodiness.

4.1.3. Diagnostic yield of EUS-FNA samples obtained by SP and SS in patients with suspected malignant pancreatic lesions

This prospective comparison study was carried out between January 2014 and June 2016 with collaboration between the pathology and gastroenterology department. 92 patients were enrolled who underwent EUS-FNA sampling due to suspected pancreatic cancer. The inclusion criteria were the following: 1) previously identified solid pancreatic lesions by cross-section imaging modalities which were suspicious for malignancy; 2) unresectable disease due to local invasion, dissemination to distant organs, severe comorbidity or poor general condition of the patient, or cases when the patient did not consent to surgery; 3) the cytological or histological verification of pancreatic cancer was necessary for the selection of adequate further therapy. The efficiency and diagnostic value of EUS-FNA sampling was determined based on the classification of Papanicolaou Society.[27] The sampling was considered diagnostic if it clearly confirmed the presence of non-neoplastic (Papanicolaou II category) or neoplastic pancreatic lesion (Papanicolaou IV, and VI categories), or when the cytopathologist had a high degree of certainty of the presence of carcinoma in clinically unequivocally malignant-appearing tumors (Papanicolaou V category).

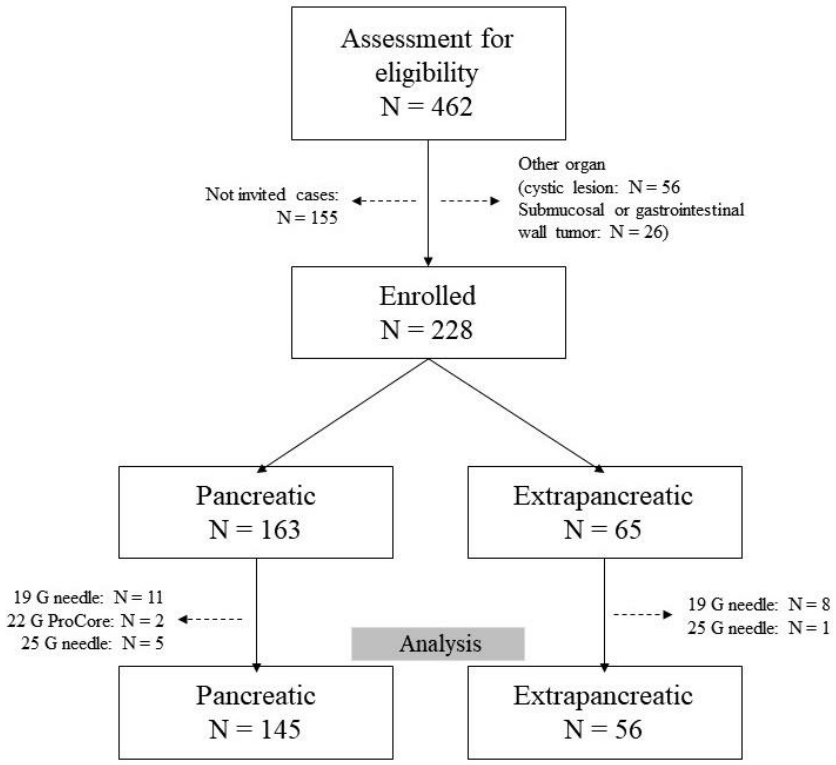
PAPANICOLAOU SOCIETY OF CYTOPATHOLOGY SYSTEM FOR REPORTING PANCREATICOBILIARY CYTOLOGY	
I. Non-diagnostic	
II. Negative (for malignancy)	Benign pancreatic tissue Acute, chronic or autoimmune pancreatitis Pseudocyst, lymphoepithelial cyst Splenule/accessory spleen
III. Atypical	
IV. Neoplastic - Benign	Serous cystadenoma Neuroendocrine microadenoma Lymphangioma
IV. Neoplastic - Other	Well-differentiated NET IPMN, all grades of dysplasia MCN, all grades of dysplasia Solid-pseudopapillary neoplasm
V. Suspicious (for malignancy)	
VI. Positive or Malignant	Ductal adenocarcinoma of the pancreas and its variants Cholangiocarcinoma Acinar cell carcinoma Poorly differentiated (small and large cell) NET Pancreatoblastoma Lymphoma Metastatic malignancy

2. Table: Classification of Papanicolaou Society for assessment of cytological sampling of the pancreatobiliary system. (NET - neuroendocrine tumor; IPMN - intraductal papillary mucinous neoplasm; MCN - mucinous cystic neoplasm).

4.1.4. Comparison of efficacy of SP and SS techniques of EUS-FNA in the sampling of pancreatic and extrapancreatic tumors

This study is a retrospective evaluation of data from prospectively enrolled consecutive patients. Patients were prospectively enrolled in this comparative study, who underwent EUS-FNA sampling between January 2014 and September 2017. In our educational institute, gastroenterologists with shorter learning curve are frequently involved in the EUS-FNA sampling. Only those patients were invited for the prospective study whose sampling were performed by one of the two experienced investigators alone. The inclusion criteria of patients were (i) suspected malignant solid pancreatic or extrapancreatic lesions identified by cross-

section imaging modalities, and (ii) cytological or histological verification of lesions necessary for the selection of adequate further therapy. Criteria of exclusion from the analysis were major protocol deviation: (i) use of 25G, 19G or ProCore needles, (ii) application of only one of the two techniques or (iii) other sampling technique.



1. Figure: The STROBE flowchart of study.

The quality assessment of EUS-FNA sampling was based on the number of obtained smear pairs, the proportion of diagnostic smear pairs, as well as on the bloodiness and cellularity of specimens. Diagnostic accuracy was determined by comparing the EUS-FNA diagnosis with the final diagnosis. On the one hand, the final diagnosis was based on the pathological assessment of samples obtained by surgical resection, autopsy, or repeated sampling with another sampling modality. On the other hand, it was determined after more than 6-months of follow-up: malignancy was confirmed by the tumor progression or metastasis formation, while the lesion was considered to be benign if clinical course did not reveal any deterioration.

4.1.5. Statistical analysis

SPSS software version 22 (SPSS Inc., Chicago, Illinois, USA), SigmaPlot 12.5 (Systat Software Inc., San Jose, California, USA) and R statistical software version 3.4.2 (R Foundation

for Statistical Computing, http://www.R-project.org) was used for the statistical analysis of data. The descriptive statistics were reported as frequencies (N), percentage (%), mean ±SD and median with ranges. The differences in the quality indicators between the SS and SP group were compared using paired sample t-tests and Mann-Whitney Rank Sum Test. Values of $p<0.05$ were considered significant. We used logistic regression analysis, Fisher's exact test and Chi Squared test to identify the factors that can modify the effectiveness and quality indicators of sampling.

4.1.6. Ethical approval and consent to participate

The study protocols were approved by the Regional and Institutional Human Medical Biological Research Ethics Committee of the University of Szeged (clinical trial registration number: 3679 SZTE). The study was carried out under the declaration of Helsinki.

4.2. Assessment of efficacy, safety, and cost-effectiveness of endoscopic SEMS placement for the palliation of upper gastrointestinal malignancies

4.2.1. Success and complication rate of esophageal stent implantation and determination of frequency and efficacy of repeated endoscopic interventions related to SEMS complications

212 patients with malignant esophageal obstruction or TEF who underwent SEMS implantation between 2007 and 2014 were retrospectively enrolled to our study. The inclusion criteria were: 1) malignant esophageal obstruction or TEF confirmed by endoscopy and/or barium swallow/meal examination; 2) pathologically diagnosed esophageal malignancy; 3) unresectable tumor with advanced stage or poor surgical candidates; 4) onco-team recommended oncological treatment and/or palliative esophageal SEMS implantation.

Stent implantations were performed under intravenous sedation (5-10 mg midazolam) with or without intravenous analgesics (10-20 mg nalbuphine). Various types of esophageal stents were used from the following manufacturers: Leufen Medical GmbH. (Berlin, Germany); Boston Scientific Corporation (Minneapolis, Minnesota, USA); Taewoong Medical Co., Ltd., (Seoul, South Korea); Changzhou Health Microport Medical Device Co., Ltd. (Changzhou, Jiangsu, China); Endo-Technik (Solingen, Germany); ENDO-FLEX GmbH. (Voerde, Germany); Accura Medizintechnik GmbH. (Karben, Germany); BVM Medical Ltd. (Trinity Lane, Leicestershire, United Kingdom); Micro-Tech (Nanjing) Co., Ltd. (Nanjing, China). The diameter of the applied stents' body was 18 or 20 mm, and the material of stents and their

coating were identical in products made by the same manufacturers (polytetrafluoroethylene, silicone, polyurethane, etc.; nitinol, steel, etc.). The pattern (weave, braided, knits, etc.) and shape of stents varied widely depending on the altered anatomical situations. The selection of the optimal stent depended on the disease location and length of obstruction. In case of tumors of the upper third of the esophagus and the cardia, specific SEMS were inserted (cardia umbrella stent, anti-reflux valve, anti-migration property, etc.) which could reduce the risk of foreign body sensation in the pharynx and the severity of gastroesophageal reflux. The choice between partially and fully covered stents was individualized, depending on the risk of restenosis and migration: fully covered SEMS was preferred in case of a long and significant stenosis, in contrast to partially covered stents, which were applied in cases with higher migration risk. The stent was at least 2 cm longer than the endoscopically measured length of stenosis. The proximal and distal ends of the neoplasia were marked with external metal markers. If the stenosis was too tight to allow the passage of the stent delivery system and the endoscopic visualization of the distal part of esophagus, endoscopic balloon or bougie dilation was performed first. After the removal of the endoscope, the stent was inserted into the right position with guidewire assistance under X-ray control, and finally the proper SEMS position was verified endoscopically.

The efficacy of SEMS implantation was characterized by technical and functional success rate. The intervention was considered technically successful if the stent was opened correctly in the proper position confirmed by X-ray and endoscopy, and functionally successful if the oral feeding of the patients became possible 24 hours after the intervention. Minor complications were defined as mild-to moderate events related to stent implantation which could be treated conservatively without the need for hospitalization (gastroesophageal reflux, emesis, retrosternal pain, mild dysphagia, etc.). All patients received opiate pain killers, and in case of distal obstruction prophylactically proton pump inhibitor therapy with or without prokinetic drugs to avoid the reflux. Major complications were defined as severe, often life-threatening complications, which required repeated hospitalization and endoscopic interventions (TEF, stent migration or obstruction, aspiration pneumonia, arrhythmia, hematemesis, etc.). We determined the rate, type, frequency, and efficacy of repeated endoscopic examinations; furthermore, we analyzed the characteristics of patients, SEMS types, and SEMS implantations to identify the risk factors and success of re-interventions.

4.2.2. Comparison of therapeutic efficacy and cost effectiveness of SEMS and PS in the treatment of primary malignant biliary obstruction in real-life settings.

We gathered retrospective data about every patient with unresectable primary pancreatobiliary malignancy who underwent endoscopic stent placement for distal biliary obstruction between 2008 and 2013. In all cases, the malignant biliary stenosis was confirmed by cross-sectional imaging and/or histological examination, and the tumor was unresectable based on the surgeon's opinion. In three cases, endoscopic biliary stenting was required because patients did not agree to surgery of resectable cancers. The exclusion criteria were; (1) surgical resection or biliary bypass performed less than 4 weeks after the first biliary stent implantation; (2) concurrent gastric outlet obstruction and malignant biliary obstruction at the time of stent placement; (3) hilar or intrahepatic malignant biliary obstruction unsuitable for endoscopic treatment.

The efficacy of stent implantation was characterized by technical and functional success rates, duration of stent patency and complication rate of stenting. The intervention was considered technically successful if the stent was placed across the stricture in the proper position, as confirmed by radiography and endoscopy. Functional success of the stent was defined as restoration of bile outflow, detected by endoscopy immediately after drainage, and as more than 30% decrease in serum bilirubin level from baseline within a week after stenting. Duration of stent patency was defined as the period between the stent placement and either functional failure or the patient's death. Functional failure was determined by the return of signs of biliary obstruction: symptoms of cholangitis (icterus, pruritus, abdominal pain, fever) and/or elevation of liver enzymes and/or elevation of serum bilirubin level. We also determined the number of hospitalizations and nursing days associated with bile duct stenting and stent complications both in PS and SEMS subgroups.

During the economic analysis, we assessed only the costs of medical treatment directly associated with the management of biliary obstruction: the cost of stents, repeated interventions (ERCP, percutaneous transhepatic drainage), and hospital stay in correlation with biliary obstruction. Palliative surgical interventions and repeated hospitalizations were required independently from biliary obstruction and endoscopic stenting due to progression of pancreatobiliary malignancy. The costs of these medical cares were not evaluated during the cost-effectiveness analysis.

COST USED FOR ANALYSIS	COST (FORINT)
SEMS	120,000
Plastic stent	5,500
PTD with plastic stent	79,086
ERCP	37,855
Cost of hospitalization/days	30,000

3. Table: Costs used in cost-effectiveness analysis of stent implantation in the management of primary malignant biliary obstruction (ERCP - endoscopic retrograde cholangio-pancreatography; PTD - percutaneous biliary drainage; SEMS - self-expandable metal stent)

4.2.3. Statistical analysis

To collect the medical documentation of patients, we used a MedSolutions medical recorder. Statistical analysis was performed using SPSS software version 22 and 24 (SPSS Inc., Chicago, Illinois, USA); *p* values of less than 0.05 were considered significant. Descriptive statistics were expressed as mean and median with ranges. Differences in continuous variables such as survival time and duration of stent patency were assessed with an independent samples t test. We used logistic regression analysis, Fisher's exact test and Chi Squared test to identify the factors that can modify the risk of SEMS complications and the cost-effectiveness of stenting.

4.2.4. Ethical approval and consent to participate

The study protocols were approved by the Regional and Institutional Human Medical Biological Research Ethics Committee of the University of Szeged (ethics approval number: 3680 SZTE). The study was carried out under the declaration of Helsinki.

5. RESULTS

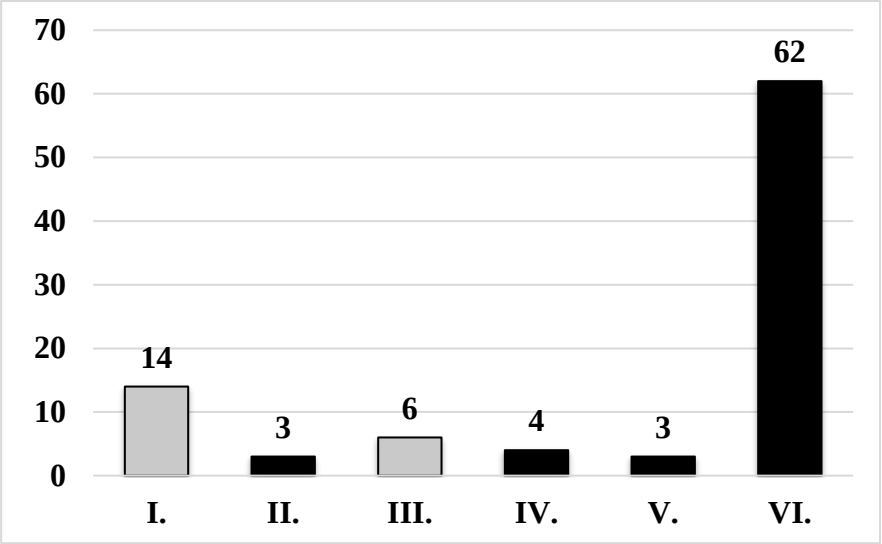
5.1. Comparison of diagnostic yield of EUS-FNA samples obtained by SP and SS techniques

5.1.1. Diagnostic yield of EUS-FNA samples obtained by SP and SS in patients with suspected malignant pancreatic lesions

92 EUS-FNA samplings of 89 patients were involved. Sampling had to be repeated in three patients due to non-diagnostic smears. There was no significant proportional variance with regard to the patients' gender. Mean age at the time of sampling was 66.1 years (range 27-95; median 69). Lesions were located most frequently in the pancreatic head (N=71; 79.8%). The mean diameter was 31.8 mm (range 7-62; median 30), and in 44 cases (47.2%) cancer antigen 19-9 (CA19-9) was elevated. There was no significant difference between the use of Cook Medical and Olympus EZ Shot 2 needles (47 vs. 55 cases). The mean number of passes for each lesion was 4 (3-7; median 4).

PATIENTS (N=89)		**SAMPLING (N=92)**	
Male/female	38/51	Examiners: Z.Sz/L.Cz	70/22
Age (year)	66.1 (27-95; median: 69)	Punctures per examination	4 (3-7; median: 4)
Tumor location		2 punctures	23 (25%)
Head	71 (79.8%)	3 punctures	47 (51.1%)
Body	7 (7.9%)	4 punctures	17 (18.5%)
Tail	8 (8.9%)	5 punctures	6 (4.3%)
Diffuse	3 (3.4%)	6 punctures	1 (1.1%)
Tumor size (mm)	31.8 (7-62; median: 30)	LMWH	10 (10.9%)
		PAI	14 (15.2%)
CA 19-9			
Elevated	44 (47.2%)	Needle type	
Normal	27 (29.3%)	Echotip	37 (40.2%)
No data	18 (19.5%)	EZ Shot 2	55 (59.8%)
CgA elevation	5 (5.6%)		

4. Table: Baseline characteristics of patients and sampling (CA19-9 – carcinoma antigen 19-9; CgA – chromogranin A; LMWH – low molecular weight heparin; PAI – platelet aggregation inhibitors)



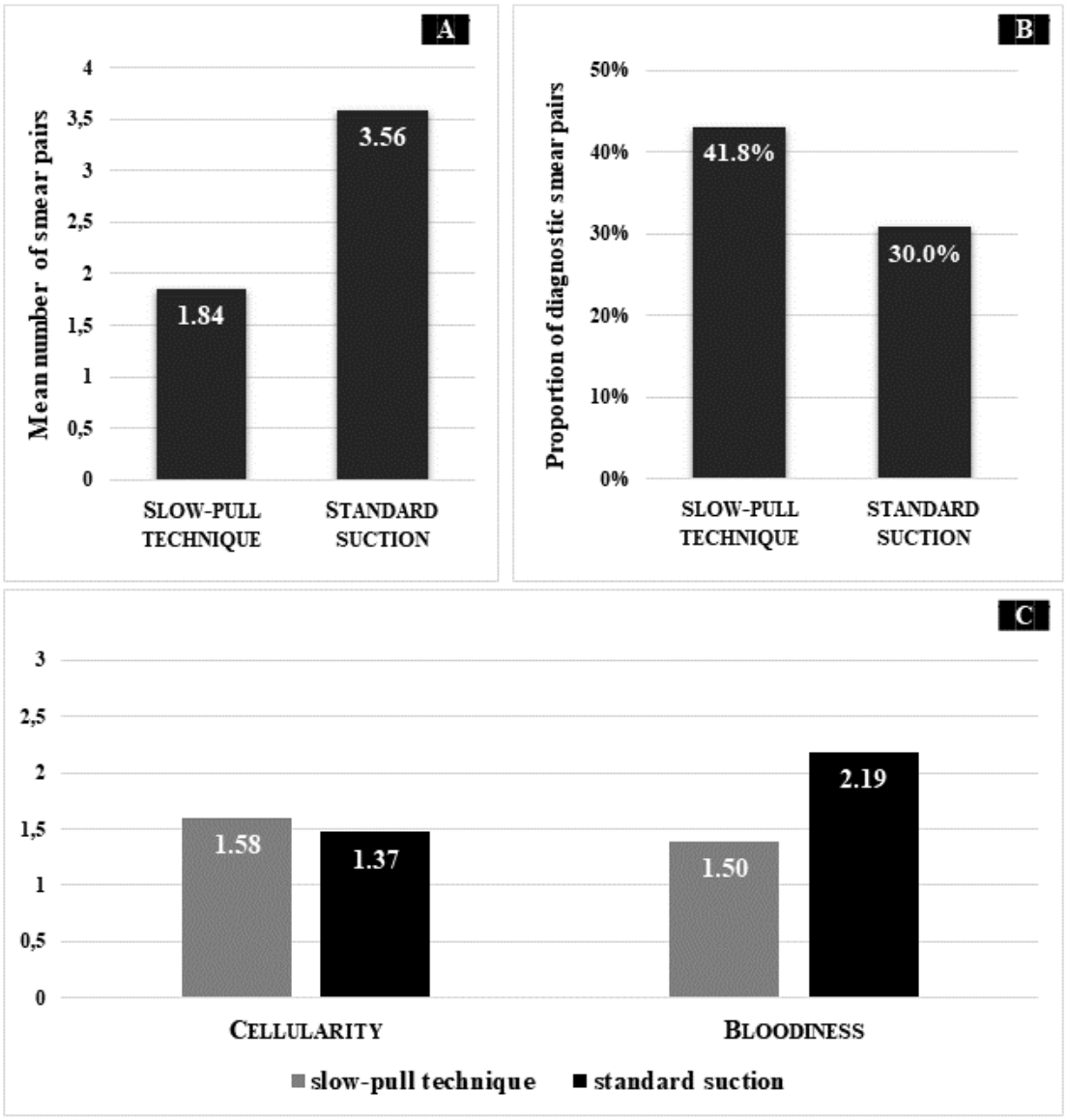
2. Figure: Efficacy of sampling according to the classification of Papanicolaou Society. Grey color shows the non-diagnostic and black the diagnostic categories

EUS-FNA sampling was diagnostic in 72 cases (78.3%): the presence of neoplasm was confirmed in 69 cases (Papanicolaou IV, V, VI) and chronic pancreatitis in 3 cases (Papanicolaou II). There was no significant difference between the diagnostic yield of SP and SS (65.2% vs. 67.4%), although the technical success rate was higher in the SS group (92.4% vs. 100%), but it was not statistically relevant. Cytological examination of the fluid obtained by flushing the needle with saline confirmed the diagnosis in 31 cases (33.7%), and in one patient the diagnosis was based only on this cytological sample. Histological samples were taken in 60 cases with similar efficiency in the SS and SP groups (50.0% vs. 53.3%). There was no detectable difference between the two groups in the diagnostic yield of histological samples (58.7% vs. 63.2%). The diagnostic yield of EUS-FNA examination was not influenced by the endosonographer, the needle type, tumor size and location.

	SLOW-PULL TECHNIQUE	STANDARD SUCTION
Technical success rate	85 (92.4%)	92 (100%)
Diagnostic yield	60 (65.2%)	62 (67.4%)
Histological sample obtained	49 (53.3%)	46 (50.0%)
Diagnostic yield of histological sample	31 (63.2%)	27 (58.7%)

5. Table: Comparison of effectiveness of standard suction and slow-pull technique

The average number of smear pairs for one pass was significantly higher in the SS group (3.56; range 1-9.5; median 3.5) compared with the SP one (1.84; range 0-7.5; median 1.5), but it was associated with considerably increased bloodiness (1.50 vs. 2.19; p<0.001). Cellularity did not differ statistically between the groups (1.58 vs. 1.37; p=0.2554). In contrast, the proportion of diagnostic smears obtained with SP was higher (41.8% vs. 30.0%; p=0.003).



3. Figure: Comparison of quality indicators of sampling obtained by SP and SS technique based on the mean number of smear pairs (A), - proportion of diagnostic smears (B), cellularity and bloodiness of smears (C)

Early complication occurred in three cases (3.2%). A 66-year old man developed mild, postprocedural acute pancreatitis, which recovered during 4-days long total parenteral nutrition.

Two patients had threefold elevation in serum amylase level without clinical symptoms. Severe and late complications were not found.

In 69 of 72 diagnostic EUS-FNA samplings pathological examination demonstrated neoplastic pancreatic lesions. Ductal adenocarcinoma was the most frequent neoplasm with 64.1% incidence rate. Five low grade and one high grade NETs were identified (6.5%). The latter was proved to be ductal adenocarcinoma by autopsy. On one occasion signet ring cell carcinoma was found. Repeated histological sampling (5 autopsies, 8 surgical samples, 2 transabdominal core biopsies) confirmed the results of EUS-FNA in 14 cases, and in the rest 55 cases the clinical course affirmed the diagnosis. In a case of chronic pancreatitis based on the FNA results, Whipple procedure was performed due to biliary obstruction. Pathological evaluation of the surgical specimen revealed pancreatic intraepithelial neoplasia 1B besides chronic pancreatitis.

In 5 out of 14 non-diagnostic EUS-FNAs (Papanicolaou I) benign disease was detected by further examinations (1 autoimmune and 3 chronic pancreatitis: 1 infection). In the rest 9 cases ductal adenocarcinoma (N=5), biliary duct carcinoma (N=1), IPMN (N=1) and metastatic renal cell carcinoma (N=2) were identified. In the background of atypia benign disorder was found only in one case (autoimmune pancreatitis). Table 6 is summarizing the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and accuracy of EUS-FNA sampling in the identification of pancreatic neoplasm determined based on the results of follow-up.

EFFICACY OF EUS-FNA IN THE IDENTIFICATION OF PANCREATIC NEOPLASM			
	INDEPENDENTLY FROM THE METHOD	SLOW-PULL TECHNIQUE	STANDARD SUCTION
Sensitivity	83.1%	69.9%	73.5%
Specificity	100%	100%	100%
NPV	39.1%	26.5%	29%
PPV	100%	100%	100%
Accuracy	84.8%	72.8%	76.1%

6. Table: Efficacy of EUS-FNA in the identification of pancreatic malignancy (NPV – negative predictive value; PPV – positive predictive value).

5.1.2. Comparison of efficacy of SP and SS techniques of EUS-FNA in the sampling of pancreatic and extrapancreatic tumors

201 patients were prospectively enrolled and analyzed in the study from which 145 patients were categorized into pancreatic tumors and 56 patients (46 lymph nodes and 10 liver lesions) into extrapancreatic tumors subgroup. The male-female ratio was 85:116. Mean age at time of sampling was 65.13 years (range 19-94; median 67).

	PANCREATIC (n = 145)	**EXTRAPANCREATIC (n = 56)**	***p*-value**
Gender (male/female)	66/79	17/39	0.058
Mean age (year)	65.64 ±12.26 (19-94; median 68)	63.72±13.93 (19-87; median 67)	0.368
Tumor size (mm)	33.56 (8-80; 31)	29.32 (8-80; median 26)	0.084
Mean number of punctures	3.99 (2-7; median 4)	3.69 (2-6; median 4)	0.828
Needle type			
EZ Shot 2	106 (73.1%)	47 (83.9%)	0.139
Echotip	39 (26.9%)	9 (16.1%)	
Examiners (exA/exB)	27/118	5/51	0.125
Final diagnosis	PDAC: 119 (82.1%) CP: 10 (6.9%) pNEN: 6 (4.1%) IPM: 3 (2.1%) AIP: 2 (1.4%) PSCC: 2 (1.4%) MCAC: 1 (0.7%) IPMN: 1 (0.7%) IPAS: 1 (0.7%)	Metastatic LN: 30 (53.6%) *(pancreas N=15; lung N=4; NET N=2; prostate N=2; melanoma N=2; leiomyosarcoma N=1; breast N=1; stomach N=1, thyroid N=1)* Reactive LN: 9 (16.1%) Liver metastasis: 5 (8.9%) non-HL: 6 (10.7%) HCC: 5 (8.9%) Endometriosis: 1 (1.8%)	

7. **Table:** Clinical characteristics of enrolled patients and EUS-FNA examinations.

(exA and exB – examiner A and B; PDAC – pancreatic ductal adenocarcinoma; CP – chronic pancreatitis; pNEN – pancreatic neuroendocrine neoplasm; IPM – intrapancreatic metastasis; AIP – autoimmune pancreatitis; PSCC – pancreatic squamous cell carcinoma; MCAC – mucinous cystadenocarcinoma; IPMN – intraductal papillary mucinous neoplasm; IPAS – intrapancreatic accessory spleen; LN – lymph node; HCC – hepatocellular carcinoma)

The EZ Shot 2 needle was significantly more frequently used compared with Echotip needle (153 vs. 48; p<0.001), and statistically significant proportional variance regarding examiner was observed (169 vs. 32; p<0.001). However, there was no substantial difference between the subgroups in terms of patients' gender and age, the investigator of EUS-FNA and the type of used needle.

An average 3.19 (range 2-7; median 4) punctures were performed during EUS-FNA examinations in which the proportion of the usage of SS and SP techniques was almost equal (1.98 [range 1-4; median 2] vs. 1.94 [range 1-5; median 2]). The overall technical success rate of EUS-FNA was 100%. The diagnostic accuracy independently from sampling technique was 88.28% in pancreatic cancers and 75.00% in the extrapancreatic tumors subgroup with high sensitivity, specificity, and positive predictive value (88.64%, 84.62% and 98.32% vs. 72.34%, 88.89% and 97.14%). In 42 cases (20.90%), the diagnosis was based on the pathological evaluation of cytological samples only, however, in the remaining 159 cases (79.10%) appropriate histological and cytological samples were obtained. The final diagnosis was benign only in 24 cases (11.94%). EUS-FNA examination confirmed the presence of malignant disorder in 90.34% of cases in the pancreatic cancer subgroup and in 82.14% of cases in the extrapancreatic cancer subgroup.

	PANCREATIC (N=145)			**EXTRAPANCREATIC (N=56)**		
	SLOW-PULL	**STANDARD SUCTION**	***p*-value**	**SLOW-PULL**	**STANDARD SUCTION**	***p*-value**
Technical success rate	134 (92.41%)	142 (97.93%)	0.788	52 (92.86%)	56 (100%)	0.869
Mean number of smears per puncture	1.74±1.09 (0-8; med. 1.5)	3.19±1.82 (0-10; med. 3)	<0.001	1.62±1.11 (0-6; med. 1)	3.28±1.19 (1-9; med. 2.5)	<0.001
Proportion of diagnostic smears	46.69%	36.33%	0.002	49.17%	30.67%	<0.001
Histological samples obtained	96 (66.21%)	94 (64.83%)	0.623	44 (78.57%)	45 (80.36%)	0.999
Diagnostic yield of histological samples	73 (76.04%)	73 (77.66%)	0.999	32 (72.72%)	31 (68.89%)	0.999

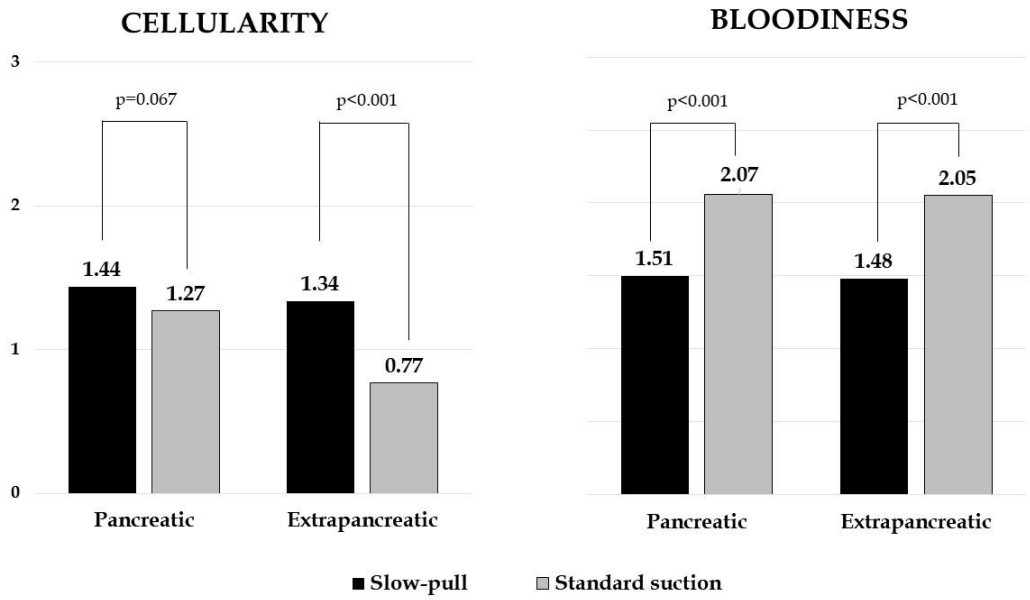
8. **Table:** Efficacy of slow-pull and standard suction techniques of EUS-FNA in the sampling of pancreatic and extrapancreatic cancers.

The technical success rate of the sampling techniques (SP vs. SS) was equally high in cases of pancreatic cancers (92.41% vs. 97.93%) and extrapancreatic tumors (92.9% vs. 100%). In the pancreatic cancers subgroup, no significant difference was observed in terms of diagnostic accuracy, sensitivity and specificity of sampling (81.38%, 81.06% and 84.62% vs. 83.47%, 83.33% and 84.62%), as well as the rate and diagnostic value of obtained histological samples (66.21% and 76.04% vs. 64.83% and 77.66%). In contrast, in the extrapancreatic tumors subgroup, the SS technique achieved substantially lower diagnostic accuracy (71.41% vs. 60.71%), however, the characteristics of obtained histological samples did not differ (78.57% and 72.72% vs 80.30% and 68.80%).

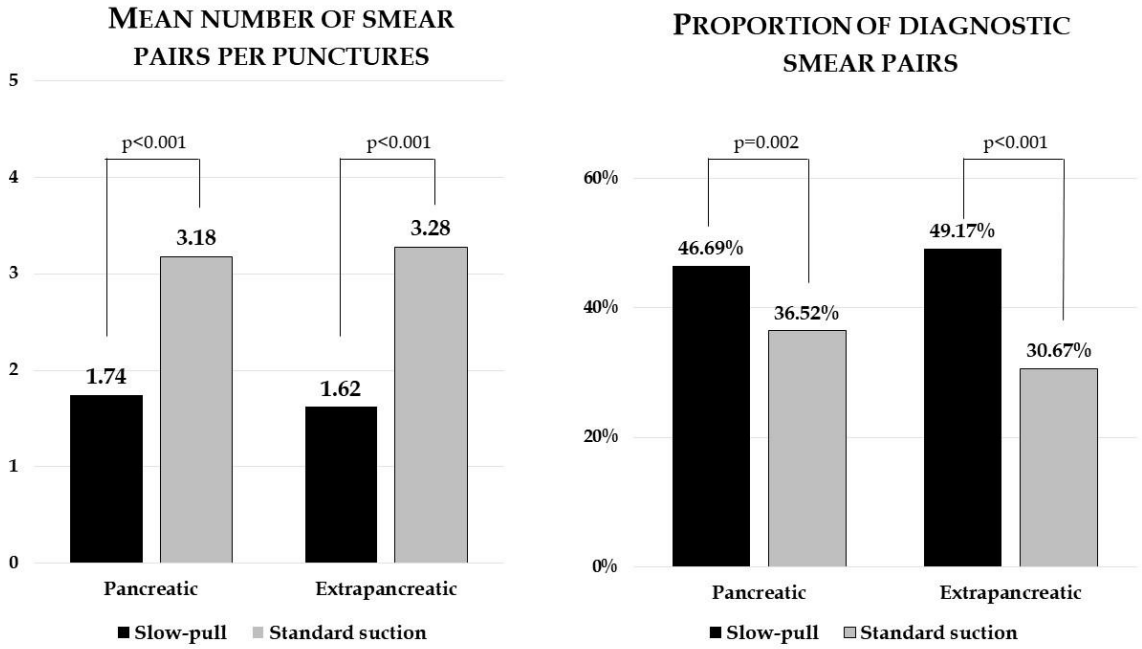
	PANCREATIC (N=145)			**EXTRAPANCREATIC (N=56)**		
	SLOW-PULL	**STANDARD SUCTION**	**OVERALL**	**SLOW-PULL**	**STANDARD SUCTION**	**OVERALL**
Sensitivity	81.06%	83.33%	88.64%	68.10%	54.17%	72.34%
Specificity	84.62%	84.62%	84.62%	88.89%	100%	88.89%
NPV	31.43%	33.33%	42.31%	34.78%	26.67%	38.10%
PPV	98.17%	98.21%	98.32%	96.97%	100%	97.14%
Accuracy	81.38%	83.45%	88.28%	71.41%	60.71%	75.00%

9. **Table:** No significant difference could be observed in terms of diagnostic accuracy of EUS-FNA sampling using slow-pull and standard suction techniques in pancreatic and extrapancreatic tumors. (NPV – negative predictive value; PPV – positive predictive value)

The SS technique resulted in significantly higher number of smear pairs for one pass in both pancreatic (1.74±1.09 vs. 3.19±1.82; $p<0.001$) and extrapancreatic tumors (1.62±1.11 vs. 3.28±1.19; $p<0.001$), but at the same time it was associated with considerably increased bloodiness (1.51±0.86 vs. 2.07±0.85, $p<0.001$; and 1.48±0.87 vs. 2.05±0.86, $p<0.001$) and the proportion of diagnostic smear pairs decreased (46.69% vs. 36.52%, $p=0.002$; and 49.17% vs. 30.67%; $p<0.001$). The type of suction did not influence the cellularity of smears in the pancreatic cancers subgroup (1.44±1.19 vs. 1.27±1.10; $p=0.067$), however in cases of extrapancreatic tumors the increased blood contamination covered the tumor cells, thereby resulted in reduced cellularity (1.34±1.10 vs. 0.77±1.01; $p<0.001$).



4. **Figure:** Quality assessment of specimens based on the cellularity and bloodiness of smears: SS technique resulted in significantly higher bloodiness in both subgroups, and in cases of extrapancreatic cancers it led to decreased cellularity.



5. **Figure:** The SS technique resulted in significantly higher number of smear pairs for one pass in both pancreatic and extrapancreatic tumors, however, it considerably decreased the proportion of diagnostic smear pairs.

The diagnostic accuracy (69.70% vs. 79.41%; p=0.699), the technical success rate (100% vs. 98.24%; p=0.998) and quality of samples obtained by SS technique (cellularity: 1.09±1.10 vs. 1.14±1.10, p=0.811; bloodiness: 2.00±0.90 vs. 2.07±0.85, p=0.678; mean number of smear pairs: 3.21±1.78 vs. 3.21±1.95, p=0.994; proportion of diagnostic smears: 32.45% vs. 35.38%, p=0.666) did not differ significantly between the EUS-FNA examiners. In contrast, substantial examiner-dependency was observed in terms of technical success rate of sampling (81.82% vs. 97.06%; p<0.001) and the quality of smears using SP techniques of FNA (cellularity: 1.03±1.26 vs. 1.48±1.20, p=0.061; bloodiness: 1.12±0.89 vs. 1.57±0.84, p=0.011; mean number of smear pairs: 0.98±0.71 vs. 1.85±1.10, p<0.001; proportion of diagnostic smears: 43.31% vs. 48.00%, p=0.597) without any decrease in diagnostic accuracy (63.64% vs. 78.82%; p=0.099). In cases of pancreatic and extrapancreatic cancers, the subgroup analysis revealed almost similar difference between the EUS-FNA examiners using SS technique. The type of needle did not influence the characteristics of EUS-FNA samples obtained by SP and SS techniques.

Mild early complications in correlation with EUS-FNA sampling occurred in five cases (2.49%). In the pancreatic tumor subgroup, four patients (2.76%) had threefold elevation in serum amylase level 24-hours after sampling, which did not cause clinical symptoms in three cases. In one case (1.56%) of an extrapancreatic tumor EUS-FNA, mild peritonitis occurred after liver sampling of a patient with significant ascites. Severe and late complications were not detected.

5.2. Assessment of efficacy, safety, and cost-effectiveness of endoscopic SEMS placement for palliation of upper gastrointestinal malignancies

5.3.1 Success and complication rate of esophageal stent implantation and determination of frequency and efficacy of repeated endoscopic interventions related to SEMS complications

In the 212 enrolled cases 238 SEMS implantations were performed due to malignant esophageal obstructions caused by predominantly primary esophageal tumors (83.49%) or lung cancers (13.68%). In 33 cases TEF was present at the time of SEMS implantation. The technical success rate of the first SEMS implantations was 99.06%.

CHARACTERISTICS OF SEMS PLACEMENTS	
Patients/SEMS	212/238
- **one SEMS placement**	189 (89.15%)
- **two SEMS placements**	21 (9.91%)
- **three SEMS placements**	1 (0.47%)
- **four SEMS placements**	1 (0.47%)
Partially/fully covered SEMS	39/199 (16.39%/83.11%)
Technical success rate	99.06%
Functional success rate	97.64%
Procedure related death	1.26%

10. Table: Characteristics of esophageal stent implantations.

CLINICAL AND DEMOGRAPHIC DATA OF PATIENTS (N=212)	
Female/Male	46/166 (21.7%/78.30%)
Mean age (year)	63.9 (range 22-93; median 63)
Malignant esophageal obstruction:	
- **lung cancer**	29 (13.68%)
- **esophageal cancer**	177 (83.49 %)
- **breast cancer**	2 (0.94%)
- **gastric cancer**	2 (0.94%)
- **hypopharyngeal cancer**	1 (0.47%)
- **mediastinal metastasis of rectal cancer**	1 (0.47%)
Location of obstruction	
- **upper third of the esophagus**	97 (45.75%)
- **middle third of the esophagus**	95 (44.81%)
- **lower third of the esophagus**	20 (9.43%)
Tracheoesophageal fistula at the time of stent placement	33 15.67%)

11. **Table:** Clinical and demographic data of patients undergone esophageal SEMS placement due to malignant esophageal stricture and/or trachea-esophageal fistula.

In two cases the cardia stent spontaneously migrated into the stomach immediately after the implantation, and reposition was not feasible. In one case intolerable retrosternal pain and severe dyspnea and in three cases development of severe complications (arrhythmia,

pneumonia) hampered the oral feeding of patients, therefore the functional success rate decreased to 97.64%. Procedure related death was 1.26%: two patients died due to malignant supraventricular arrhythmia and aspiration pneumonia less than 24 hours after stent implantation.

In total, major and minor complications were observed in 84 of 212 (39.6%) patients. Retrosternal pain (13.68%) and stent migration (6.57%) were the most frequent early complications, and they appeared less than 4 weeks after SEMS implantation. Fatal complications were seen in three cases. One patient died 24 hours after stent implantation due to aspiration pneumonia, respiratory insufficiency, and septic shock. In two cases malignant supraventricular tachycardia occurred with cardiovascular instability immediately after stenting. These patients died despite their admission to intensive care unit and the removal of the stent. After the 4-week follow-up stent obstruction caused by tumor overgrowth or ingrowth (15.09%), migration (10.38%) and new TEF formation (7.08%) were the most common complications. No correlation was found between clinical/procedural factors (gender, age, tumor type, location, necessity of dilation during stenting, coverage of SEMS, and presence of TEF at the time of stenting) and the development of complications.

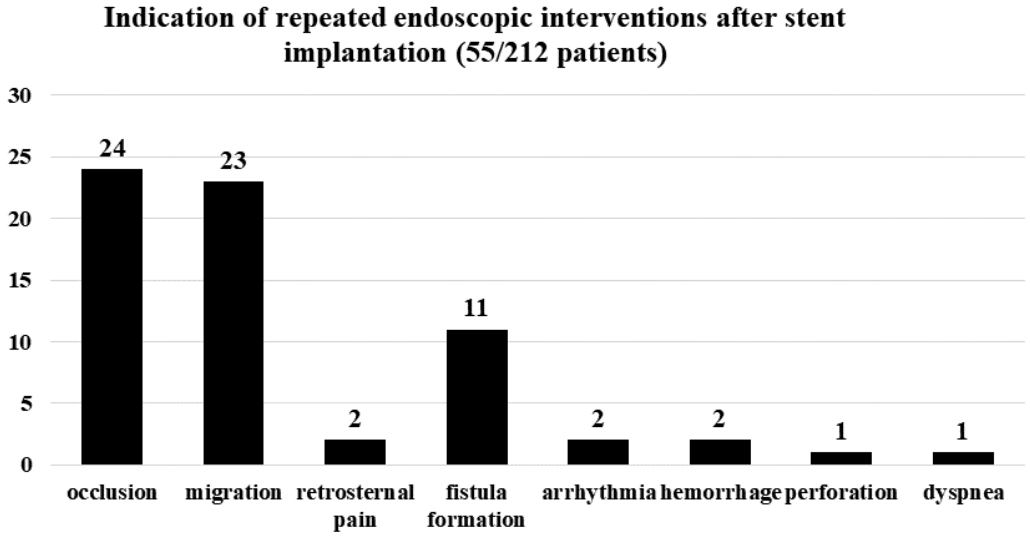
COMPLICATIONS OF SEMS PLACEMENT (N=84/212)			
ACUTE		**CHRONIC**	
retrosternal pain	29 (13.68%)	occlusion	32 (15.09%)
migration	14 (6.57%)	migration	22 (10.38%)
hemorrhage	4 (1.89%)	fistula formation	15 (7.08%)
arrhythmia	2 (0.94%)	perforation	1 (0.47%)
perforation	1 (0.47%)		
pneumothorax	1 (0.47%)		
aspiration pneumonia	1 (0.47%)		
complication of anesthesia	1 (0.47%)		

12. **Table:** Complications of esophageal SEMS implantation. Acute complications occur less than 4 weeks after SEMS implantation.

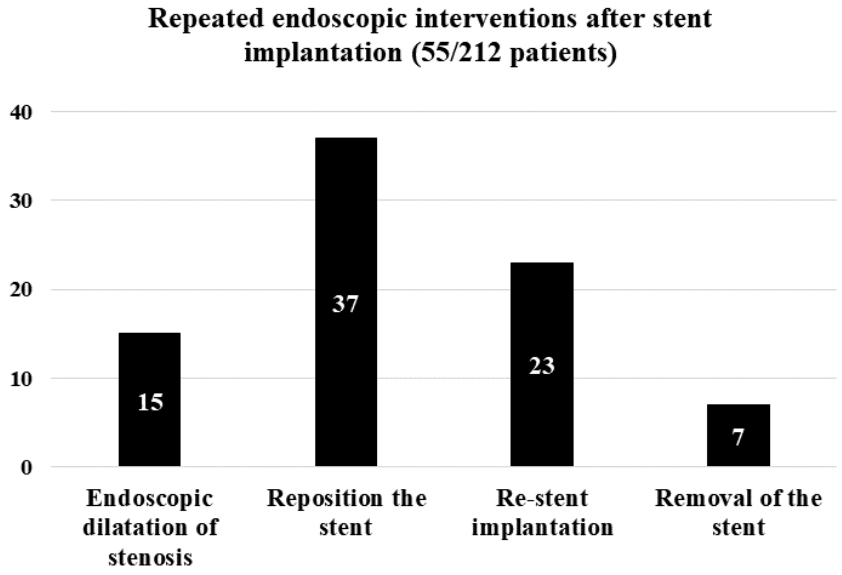
SUSPECTED RISK FACTORS	DEVELOPMENT OF COMPLICATIONS	REPEATED ENDOSCOPIC INTERVENTIONS
Gender	*p=0.216*	*p=0.272*
Age	*p=0.382*	*p=0.169*
Tumor type (esophageal or other)	*p=0.579*	*p=0.516*
Dilation of stenosis during stent implantation	*p=0.109*	*p=0.088*
Tracheoesophageal fistula at the time of stenting	*p=0.756*	*p=0.509*
Length of stenosis	*p=0.392*	*P=0.552*
Tumor location	*p=0.943*	*p=0.214*
Partially/fully covered stent	*p=0.539*	*p=0.339*

13. **Table:** Effect of clinical and procedural factors on the development of complications of esophageal stent implantation and the necessity of repeated endoscopic interventions.

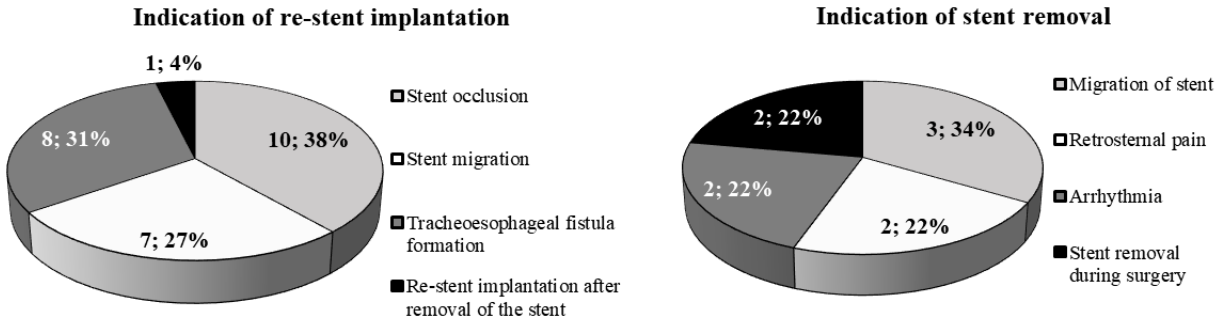
In 55 cases (25.94%) repeated endoscopic interventions were required. In 16 patients the first re-intervention was performed 24-48 hours after stent implantation; it was necessary due to early stent migration (12 cases), supraventricular arrhythmia (2 cases), dyspnea (one case) and intolerable retrosternal pain (one case). In this group, multiple endoscopies were required in every second patient during the follow-up. In case of patients with an uncomplicated early post-implantation period (24-48 hours), 1.98 (range 1-6; median 2) re-interventions were performed per patient from which the first took place at an average of 13.58 weeks (range 1.5-48; median 11) after stenting. Stent re-implantation occurred in 23 cases: 21 patients received two, one patient three and one patient four SEMSs due to stent migration (7 cases), occlusion (10 cases) or new TEF formation (8 cases). Endoscopic removal of the stent due to complications (arrhythmia, retrosternal pain, migration) was unavoidable in 7 cases. In 48 of 55 patients (87.27%) oral feeding was resolved by an endoscopic procedure, in 6 cases transient parenteral or permanent enteral feeding with gastric tube or percutaneous endoscopic gastrostomy (PEG) was feasible.



6. Figure: Indication of repeated endoscopic interventions after esophageal stent implantation.



7. Figure: Repeated endoscopic interventions after esophageal stent implantation.



8. **Figure:** Indications of esophageal re-stent implantations and stent removal.

No statistically significant correlation was found between clinical/procedural factors (gender, age, tumor type, location, necessity of dilation during stenting, coverage and manufacturer of SEMS, and presence of TEF at the time of stenting) and the necessity of repeated endoscopic interventions.

5.2.1. Comparison of therapeutic efficacy and cost effectiveness of SEMS and PS in the treatment of primary malignant biliary obstruction in real-life settings.

Of the 74 patients with primary malignant biliary obstruction, 37 were in the PS subgroup and 37 were in the SEMS subgroup. The male-female ratio was 40:34. Mean age at time of sampling was 67.64 years (range 25-94; median 68). The biliary obstruction was caused by pancreatic cancer in 46 cases (61.62%), by primary biliary duct cancer in 13 cases (17.57%) and by ampullary cancer in 5 cases (6.76%). In the rest 10 cases (13.51%), the bile duct was compressed by metastases of other organs. The clinical characteristics of patients (gender, age) and neoplasms (type of primary tumor, location of obstruction, rate of distant metastasis, and use of chemoradiotherapy) did not differ significantly.

The rates of technical success (100% vs. 97.29%) and functional success (94.79% vs. 86.49%) of SEMSs and PSs were similarly high and independent of stent type. Functional failure occurred in 2 cases in SEMS group (5.41%), while it occurred in 5 cases in PS subgroup (13.51%). Stent-related death was very low (0.014%): only one patient died of cholangiosepsis less than one week after ERCP. The complication rate of SEMS was lower compared with plastic stents (37.84% vs. 56.76%), but it was not significantly different (p=0.160). Stent occlusion was the most frequent complication. The mean follow-up time for patients was 23.41 weeks (range 1-86, median 16). Data of 31 patients in the PS and 28 patients in the SEMS

subgroup were assessed during the stent patency analysis. The mean time of stent patency were significantly higher in the SEMS group (19.11 vs. 8.29 weeks; p=0.0041).

	SEMS	PS	*p* VALUE
Technical success rate (%)	100	97.29	
Functional success rate (%)	94.59	86.49	
Average stent patency (week)	19.11	8.29	**0.0041**
Complication rate (%)	37.84	56.76	0.16
Number of hospitalizations	1.18	2.32	**0.05**
Length of hospitalization (day)	10.89	13.7	0.19
Repeated interventions (patient)	17	27	**0.033**

14. **Table:** Comparison of clinical characteristics of self-expandable metal stent (SEMS) and plastic stent (PS) implantation.

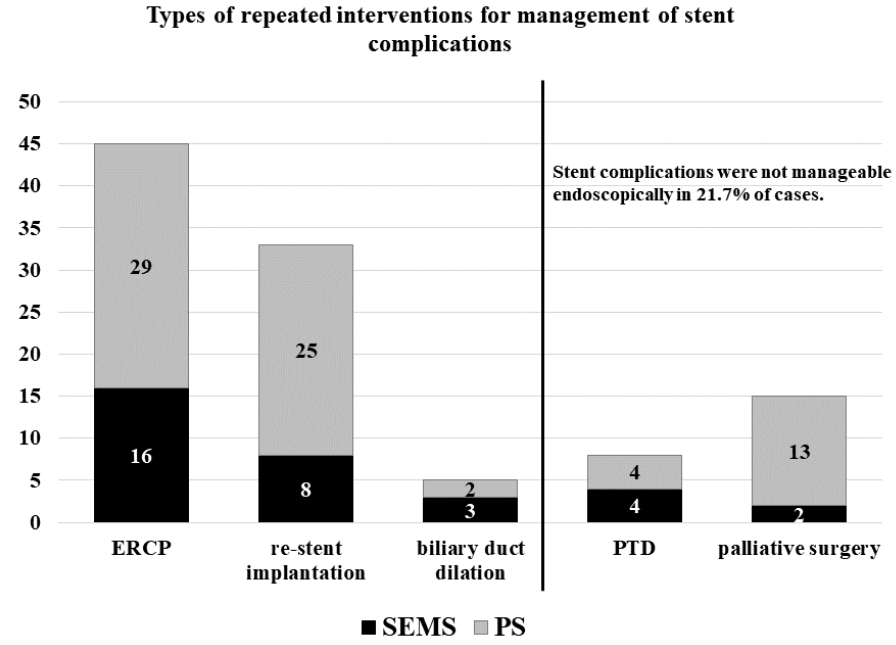
In the SEMS group the frequency (1.18 vs. 2.32; p=0.05) of re-hospitalization of patients in context with stent complications were substantially lower, but the necessity of reintervention for stent dysfunction was higher (17 vs. 27; p=0.033), in contrast, the length of hospitalization did not differed significantly between the groups (10.89 vs. 13.7 days; p=0.19). In the plastic stent group, the multiple stent implantation increased the stent patency: the second stent raised it from 7.68 to 10.75 weeks.

In 78.30% of cases the stent complications were manageable endoscopically in both groups: re-ERCP, re-stent implantation or stent replacement were performed. Percutaneous biliary drainage was required in four cases in both subgroups; however, surgical intervention was performed more frequently in the PS subgroup (13 cases vs. 2 cases).

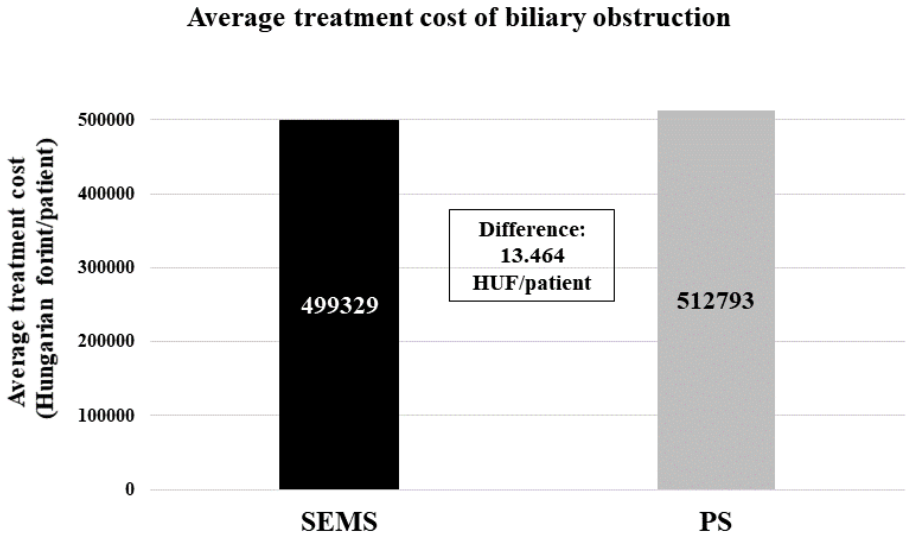
In the SEMS subgroup, uncovered metal stent was inserted in 23 (62.16%), partially covered and covered stent were used in 8 (21.62%) cases and in 5 (13.51%) cases, respectively. In the PS subgroup, an average of 1.32 stent implantation were performed during the first ERCP examination: in 26 cases only one, while in 10 cases two and in one case three PSs were inserted simultaneously. Similarly, an average of 1.38 PS was placed during the repeated endoscopic interventions. Duration of stent patency was increased by implantation of multiple stents in comparison with the use of single stents (10.75 weeks vs. 7.68 weeks, $p<0.05$).

There was no difference in the total cost of treatment of malignant biliary obstruction between the two groups (p=0.848). If the patients' survival time was more than two months, the cost-effectiveness of SEMS was better than PSs. The PS implantation was associated with

higher number of repeated hospitalizations (2.32 vs. 1.18, p=0.05) and re-interventions (17 vs. 27, p=0.033) compared with SEMS, but length of hospitalization did not differ significantly between the groups (13.7 vs. 10.89 days, p=0.19).



9. **Figure:** Management of complication of self-expandable metal stents (SEMS) and plastic stents (PS). (ERCP – endoscopic retrograde cholangiopancreatography, PTD – percutaneous transhepatic drainage).



10. **Figure:** Comparison of average treatment cost of malignant biliary obstruction using self-expandable metal stents (SEMS) and plastic stents (PS).

6. DISCUSSION

SP is a new, promising sampling method of EUS-FNA, however, the technical guideline of ESGE emphasized that in this case the suction force is not standardized, substantially depends on the speed of stylet removal, and it is estimated to be only 5% of the force generated with the SS technique.[13,28] Our knowledge regarding this method is based mainly on the results of retrospective studies, and the published data are highly controversial in terms of diagnostic yield and the quality of smears. Our prospective study simultaneously evaluated the efficiency of EUS-FNA using SP and SS techniques in which the differences between the methods were determined not only on the basis of diagnostic accuracy, but also considered the quality indicators of obtained smears and the acquisition of core tissues. The most important advantage of our two studies is the separate assessment and comparison of the diagnostic accuracy of EUS-FNA in the sampling of organs with different characteristics, but the sampling efficacy of the two techniques was assessed in the same lesions; therefore there was no difference in the tumor characteristics (size, location, vascularity, stiffness) and in the diagnostic process (premedication, endoscope, needle type and diameter, endosonographer, assistant, pathologist, etc.). Although, there are some limitations to our researches. These are single-center cohort studies with participation of two different investigators, in which relatively small number of cases were enrolled. Not being a randomized controlled trial is another drawback of our study. The study protocol exactly defined the proper execution of SP and SS techniques, but did not determine the order of sampling methods, it was based on the preference of investigator. Furthermore, the pathologists involved in smears evaluation were not blinded to the sampling technique.

Similarly to our results, most of the recently published studies did not find significant difference between the SP and SS techniques in terms of diagnostic accuracy in case of pancreatic cancer, however they suggested that the lower suction force of SP with 22G needle could improve the quality of smears, which is manifested in a higher proportion of tissue microfragments, greater cellularity of smears and lower blood contamination.[15,29–31] In contrast, Puri et al. reported significantly higher sensitivity and negative predictive value when suction technique was applied (85.7% vs. 66.7%), but it was also associated with increased number of slides (17.8±7.1 vs. 10.2±5.5; p=0.001) and higher blood-contamination.[16] Prospective study of Lee et al. contradicted this, because significantly superior diagnostic accuracy was detected when SP with fanning technique was applied compared with SS (88% vs 71%, p=0.044).[32]

Nakai et al. found a difference between SP and SS technique only when 25G needle was used (90% vs. 67%).[33] Efficiency of four types of suction (slow-pull technique, suction techniques with 5-ml/10-ml/20-ml syringes) was assessed in the retrospective study of Chen et al. in which significant differences between the groups was observed in terms of cytological diagnostic accuracy (90.3% vs. 63.2% vs. 58.8% vs. 55.6%, p=0.019), sensitivity (88.2% vs. 41.7% vs. 40.0% vs. 36.4%, p=0.009) and blood contamination (score ≥ 2 for 29.0% vs. 52.6% vs. 70.6% vs 72.2%, p=0.003).[34]

Our study also confirmed that the diagnostic accuracy and sensitivity of sampling did not differ significantly in case of pancreatic cancers between the SP and SS techniques, however substantial decrease was observed in extrapancreatic cancers (such as lymph node and liver cancers) when SS technique were used. Although the optimal sampling technique for pancreatic EUS-FNA has been examined in several studies, only few clinical trials dealt with the technical aspects of other organs' sampling. Wallace et al. analyzed the results of 42 EUS-FNAs in patients with lymphadenopathy and concluded that SS technique was associated with an increase in the cellularity, but it worsens the specimen's bloodiness compared with FNA without suction, therefore, it does not improve the likelihood of obtaining a correct diagnosis (OR 1.52: 95% CI [0.81, 2.85]).[17] The randomized controlled trial of Bansal et al. assessed the results of 300 EUS-FNA examinations of 235 lymph nodes and 65 pancreatic masses, and found that significantly more slides and blood clots were generated by the suction method compared with the capillary action and no suction subgroup. The diagnostic accuracy was similarly high in both groups (91%, 91% and 94%, p=0.67) but contrary with our results, the efficiency of FNA sampling of lymph nodes and pancreatic cancers did not differ significantly when SP or SS technique were used.[35]

The EUS-FNA using conventional needles could obtain not only cytological, but also histological specimens. Multiple immunostainings of core tissues are often essential for the accurate diagnosis of nonmalignant lesions and for precise subtyping of uncommon neoplasms or metastases. In our studies, the acquisition of tissue microfragments showed similar proportion in pancreatic and extrapancreatic cancers subgroups using both SP and SS techniques. In some cases, the formalin fixed samples contained only red blood cells because the distinction between tissue fragments and coagulum based on the macroscopic appearance was not possible in the majority of the cases. In our population, the rate of diagnostic tissue samples was 76.04% and 77.66% in pancreatic cancers subgroup using SP and SS, and 72.72% and 68.89% in case of extrapancreatic cancers. Our findings correlate with the results of other

prospective studies. Kida et al. achieved 83% tissue sampling rate for histology with a diagnostic accuracy of 85%. Despite the significantly higher sampling rate for cytology, they found no significant difference between the diagnostic accuracy of histology and cytology using 22G FNA needle (66% and 75%).[36] Park et al. found that combined analysis is more sensitive than cytology and histology alone (81.8% vs. 69.8% vs. 67.2%; $p<0.01$).[37] Wang et al. assessed the correlation between suction power of FNA and diagnostic yield of core tissues and concluded that the samples that were obtained for histopathological diagnosis using 5 ml suction were superior to those obtained using SP technique or 10 ml suction.[38] Hucl et al. showed that the average number of passes to obtain sufficient tissue was significantly lower when 22G ProCore needles were used compared with the standard 22G needles (1.2±0.5 vs. 2.5±0.9; <0.001), but the diagnostic accuracy did not show relevant difference in the two groups.[39] Vanbiervliet et al. confirmed these results, and additionally found that the overall sample quality was significantly better in case of standard 22G needle.[40]

The higher cost compared to transabdominal sampling is one of the important disadvantages of EUS-FNA. The price of the endoscopic ultrasound system and the needles in themselves are outstandingly high; the relatively high number of stained smears further increases the overall costs. The technique which reduces the number of samples without impairing the accuracy could make EUS-FNA sampling more cost-effective. Rapid on-site evaluation (ROSE) may be a good alternative. It could result up to 3.5-15% improvement in adequacy rates and accuracy of the cytological examination, and it could help to reduce the number of EUS-FNA passes and slides, which could further shorten the length of examination and pathological evaluation.[41–44] Fabbri et al. found that tissue samples obtained by ProCore needles could achieve comparable adequacy and diagnostic accuracy with rapid on-site evaluation (ROSE), and it could be more cost-effective.[45,46] ROSE was not available during the study period in our department, and previously we did not experience better adequacy rates with ProCore needles. However, capillary technique resulted in significantly lower number of smears without any impairment in cellularity and diagnostic yield.

Our retrospective observational study of 212 patients has confirmed that esophageal stent implantation is easy to perform, and a safe and effective treatment in neoplastic esophageal obstruction and malignant TEF. Additionally, our results revealed that the majority of SEMS complications could be successfully managed by endoscopic interventions (stent re-implantation, dilation of stenosis, stent reposition).

The role of SEMS placement in the palliative treatment of malignant esophageal stenosis is unquestionable because it provides immediate and potentially long-lasting relief of obstructive symptoms.[47,48] SEMS placement is superior to the remaining endoscopic procedures such as self-expandable plastic stent (SEPS) placement, dilation alone or argon plasma coagulation (APC), because it provides a more durable asymptomatic period and is associated with decreased risk for complications.[49,50] However, previous studies shown that the rate of SEMS-related adverse events is high, and varies between 22-50% depending on the location of the tumor, the presence of a fistula or tumor shelf, concomitant chemo-irradiation, tumor vascularity and the stent design.[51] Stenting of upper esophageal tumors represents a real therapeutic challenge due to pain and globus sensation, an elevated risk of TEF and aspiration pneumonia.[52] In this location the use of a specially designed stent is recommended the proximal end of which keeps a 2-cm distance from the upper esophageal sphincter after stenting. A retrospective study has analyzed clinical data of 104 patients with malignant proximal esophageal stenosis and concluded that SEMS placement is safe and effective, and the complication rate is not elevated compared to stenting in the distal esophagus.[53] The use of newly designed esophageal stents could reduce certain type of complications such as SEMS with antireflux valve or antimigration property, cardia umbrella stents.[54] Results of previous studies have shown better long-term efficacy in case of partially or fully covered stent placement compared to uncovered.[51,55,56] The appropriate use of specific designed stents could help to prevent the development of short- and long-term adverse events. In our study fully covered SEMSs were applied most frequently (partially covered 16.39% vs. fully covered 83.11%), and in every cardia or proximal esophageal tumor specially designed stents were inserted. We have noted complications in 84 cases (39.62%) which showed no correlation with tumor type, location, necessity of dilation during stenting, coverage of SEMS and presence of TEF at the time of stenting. The difference between the risk factors of complications in the published data and our study might be caused by the retrospective study design or the relatively small number of adverse events, although it could also suggest that our stent choice was adequate.

Endoscopic re-interventions can successfully treat SEMS-related complications in most of the cases.[57] Homann et al. analyzed clinical data of 133 patients with unresectable esophageal cancer. They found that delayed complications occurred in 53.4% (71 of 133 patients), these patients were successfully treated by dilatation (24%), placement of a second/third stent (27%), laser therapy (16%), and/or placement of a feeding tube (19%). Patients with repeated

endoscopic interventions had a significantly longer life expectancy (222±26 days vs. 86±14 days, $p<0.001$).[58] Recurrent dysphagia occurred in one-third of patients due to tumor over- or ingrowth via the stent, non-cancerous granulomatous tissue overgrowth or food impaction. In case of stent obstruction, either endoscopic reposition, argon plasma coagulation, exchange for a new stent or the second SEMS implantation could be effective to restore the esophageal patency.[59] Incidence of stent migration ranges from 4 to 36%. This could be asymptomatic or manifest, presenting as chest pain, recurrent dysphagia, or dyspnea. Stent reposition or removal of the stent with a new stent implantation are the effective endoscopic therapeutic options in these cases.[60] In our study in 48 of 55 patients (87.27%) with SEMS-related complications oral feeding was solved by endoscopic interventions (dilation, reposition, re-stent implantation, stent removal). We confirmed that the second SEMS placement is effective in 91.31% of the cases: one of the 23 stents migrated distally, and one was removed due to retrosternal pain. Stent reposition might be a good alternative to SEMS re-implantation due to its effectiveness, low costs, and relative simplicity.

In most cases TEF develops next to the proximal or distal end of the stent due to the radial force and resulting pressure necrosis.[59] The study performed by Shin et al. highlighted that the SEMS placement is clinically successful in 80% of patients with TEF, but during the follow up, recurrence of fistula was experienced in one third of the cases.[61] We have found that the risk of fistula formation is high in patients with TEF at the time of stenting. In 8 of 11 cases (72.73%) of new TEF formation endoscopic reposition and/or a second SEMS placement solved the oral feeding of patients. Retrosternal pain often occurs after stent implantation, but it is mild to moderate in most of the cases and could be managed with opiate analgesics. The frequency of this minor complication varies widely among different studies from 13% to 60%.[59,62] Our results correlate with the results of other studies: 29 patients (13.68%) experienced retrosternal pain, but only two of them required endoscopic intervention, stent removal (6.89%).

Our retrospective study comparing efficacy and cost-effectiveness of plastic and metal biliary stents found that the duration of patency of SEMSs (19.11 weeks) was almost twice that of PSs (8.27 weeks; $p < 0.0041$), which is consistent with the results of previously published clinical trials. In a 2016 meta-analysis, Moole et al evaluated the data of 984 patients from four retrospective and seven randomized controlled trials and demonstrated that duration of patency of SEMSs (median, 167.7 days; 95% confidence interval [CI], 159.2 to 176.3) was superior to that of PS (median, 73.3 days; 95% CI, 69.8 to 76.9), and that SEMSs had lower rates of

occlusion (odds ratio [OR], 0.48; 95% CI, 0.34 to 0.67) and reintervention (OR, 1.1; 95% CI, 0.9 to 1.3) than did PSs (OR, 1.7; 95% CI, 1.5 to 1.9).[63] Pooled analysis of randomized controlled trials did not reveal differences between PS and SEMS in overall patient survival (weighted mean difference, 0.67 months; 95% CI, -0.66 to 1.99) or in the 30-day mortality odds ratio (0.80; 95% CI, 0.52 to 1.24), but the rate of symptom-free survival at 6 months was higher (OR, 5.96; 95% CI, 1.71 to 20.81]).[64]

The early clinical trials and meta-analyses suggested that SEMS placement is the right choice for cost-effectiveness considerations only if a patient's life expectancy is more than 4 months.[65–67] According to the previous ESGE guideline published in 2012, the initial insertion of a 10-Fr PSs was recommended if the diagnosis of malignancy was not established or if expected survival was shorter than 4 months.[25] In contrast, more recent trials have demonstrated that the total cost of PS and SEMS per patient did not differ among patients with short (3-month) survival or metastatic disease despite the fact that SEMS placement was initially more expensive.[68] Furthermore, the general and disease-specific health-related quality of life of patients with inoperable malignant extrahepatic bile duct obstruction was better over time with SEMSs than with PSs.[69] In addition, a German retrospective study of the management of SEMS occlusion did not reveal significant differences in median overall duration of secondary stent patency (88 days for sSEMS, 143 days for PS; p = 0.069), median subsequent intervention rate (53.4% for sSEMS, 40.0% for PS; p = 0.501), or median case costs (5145€ for sSEMS, 3473€ for PS; p = 0.803).[70]

In view of new evidence, the ESGE (in the guideline published in 2017) now recommends SEMS insertion for palliative drainage of malignant extrahepatic biliary obstruction, regardless of the patient's life expectancy.[26] The results of our study confirmed that use of PS is not superior to that of SEMS with regard to the cumulative cost of treatment even in cases of short (≤ 2 month) survival, but the total hospitalization time is longer, and the reintervention rate is higher. The most appropriate SEMS type in the management of malignant distal biliary obstruction is still debated. Meta-analyses have revealed no significant difference between covered and uncovered metal stents with regard to the survival benefit, overall rate of adverse events, rate of stent dysfunction, and duration of primary stent patency during the period from primary stent insertion to primary stent dysfunction or patient death.[71–73] Some studies, however, have suggested that the covered SEMS is associated with a lower risk of tumor ingrowth but higher risks of tumor overgrowth, sludge formation, stent migration, and post-stenting cholecystitis.[74–76] In our cohort, the coverage of stent did not influence the

technical and functional success rate, stent patency, complication rate, or cost-effectiveness of stenting.

The main limitation of this research is its retrospective, single-center design. Thus, some differences were observed in terms of stent choice and timing of stent replacement. The designs of SEMS purchased from different manufacturers varied slightly, and the diameter and the number of PS inserted at the same time were different, but their design was uniform. We considered these differences during the statistical analysis, but the substantial difference in the sizes of subgroup populations limited the detection of statistically significant variance. Because of the retrospective nature of data collection, the only detailed information available concerned the gastroenterological treatment of pancreatobiliary malignancies performed in our tertiary-level clinical center; however, the patients frequently underwent follow-up in primary- or secondary-level medical institutions. Therefore, in the cost-effectiveness analysis, we assessed the direct cost of interventions and hospitalization in relation to malignant biliary obstruction. The concomitant oncologic treatments or coexisting diseases with potential influence on the total cost of patients' medical care would not be included in the analysis.

7. CONCLUSION

Our two prospective comparison studies of EUS-FNA techniques revealed that SP is an effective method with an outstanding technical success rate and efficacy compared to SS, furthermore, the low negative pressure suction generated by SP technique yields better quality smears independently from tumor consistency. Cellularity of smears and the rate of acquiring sufficient histological material are similar with SS; however, lower bloodiness of samples and decreased number of slide pairs may result in faster pathological diagnosis and more cost-effectiveness in case of SP. In addition, the higher negative pressure suction of SS technique reduces the diagnostic accuracy of sampling in extrapancreatic cancers, therefore, we recommend the SP technique as the first method in the EUS-FNA sampling of soft tissues, such as lymph nodes and liver cancers. In case of solid pancreatic cancers, SP may be the optimal first choice which could be supplemented by SS technique in case no histological sample could be obtained or when the macroscopic appearance of the smears suggests their inappropriateness for the diagnosis. However, the examiner-dependency of SP technique should also be taken into account. On the other hand, this can also be a favorable feature, as investigators who gained a certain amount of experience using SP technique could achieve outstanding diagnostic accuracy. However, important advantage of SS technique is that it can compensate the differences between the investigators.

Our retrospective study assessing risk factors of complications and efficacy of repeated endoscopic interventions after esophageal SEMS implantation found that in one quarter of patients we must reckon with development of complications. Despite the simplicity and high success rate of SEMS implantation, the treatment of SEMS-related complications represents the real clinical challenge. Our study has not identified any clinical factors which could help the selection of high-risk patients. Nonetheless, we consider that the individualized stent choice could help to reduce the frequency of adverse events and make repeated endoscopic interventions easier. We recommend endoscopic interventions as the first-line treatment for SEMS-related complications, because in most of the cases they make oral feeding possible. Our recommendations for the stent selection may decrease the burden of patients and could also make the treatment of stent complications more cost effective because they may reduce the frequency of stent-related complications, the number of repeated endoscopic interventions and the necessity of stent re-implantation.

Our retrospective cohort study comparing the cost effectiveness of SEMS and PS placement confirmed that SEMS is a better choice than PS in the management of unresectable primary malignant biliary obstruction not only in terms of effectiveness and longer stent patency but also in terms of cost-effectiveness. Because we found no difference in the cumulative treatment costs of patients, we recommend SEMS implantation regardless of patients' life expectancy. Our results also confirmed that multiple stent implantation and larger stent diameter increased the duration of stent patency and decreased the reintervention rate, in comparison with the use of single 7-Fr stents. Therefore, if SEMS is not available, implantation of multiple PSs is recommended.

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FIGURES

TABLES

1.sz. melléklet

Társszerzői lemondó nyilatkozat

Co-author certification

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- Daróczi T, Bor R, Fábián A, Szabó E, Farkas K, Bálint A, Czakó L, Rutka M, Szűcs M, Milassin Á, Molnár T, Szepes Z. [Cost-effectiveness trial of self-expandable metal stents and plastic biliary stents in malignant biliary obstruction]. Orv Hetil. 2016 Feb;157(7):268-74. Hungarian.