THE ROLE OF ENDOSCOPIC ULTRASOUND IN THE DIAGNOSIS AND MANAGEMENT OF GASTROINTESTINAL MALIGNANCIES

Ph.D. THESIS

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2021

LIST OF FULL PAPERS RELATED TO THE SUBJECT OF THE THESIS

I. **Fábián A**, Bor R, Farkas K, Bálint A, Milassin Á, Rutka M, Tiszlavicz L, Wittmann T, Nagy F, Molnár T, Szepes Z: Rectal Tumour Staging with Endorectal Ultrasound: Is There Any Difference between Western and Eastern European Countries?
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Number of full publications**:**	**34**
Cumulative impact factor:	**88.759**

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LIST OF ABBREVIATIONS

CENTRAL: Cochrane Central Register of Controlled Trials

CI: confidence interval

CRC: colorectal cancer

CRT: chemo-radiotherapy

ERCP: endoscopic retrograde cholangio-pancreatography

ERUS: endorectal ultrasound

ES: effect size

ESMO: European Society for Medical Oncology

EUS: endoscopic ultrasound

EUS-BD: endoscopic ultrasound-guided biliary drainage

EUS-FNA: endoscopic ultrasound-guided fine needle aspiration

GEA: gastroenteric anastomosis

GI: gastrointestinal

IQR: interquartile range

MRI: magnetic resonance imaging

NOS: Newcastle–Ottawa Scale

NPV: negative predictive value

PPV: positive predictive value

PTD: percutaneous transhepatic drainage

RBO: recurrent biliary obstruction

RDO: recurrent duodenal obstruction

SD: standard deviation

TEM: transanal endoscopic microsurgery

1. SUMMARY

1.1. Background

Endoscopic ultrasound (EUS) is a minimal-invasive modality that combines endoscopy with ultrasound providing a possibility to visualize the wall of the gastrointestinal tract and adjacent tissues and organs. Recent advancements in EUS technology have led to increasingly broadening indications: besides the diagnostic indications, therapeutic indications have also expanded greatly. While certain indications are firmly established, others may overlap with other procedures like endoscopic retrograde cholangio-pancreatography (ERCP) and percutaneous transhepatic drainage (PTD), and their exact place in the therapeutic algorithm is yet to be defined. Even in well-established diagnostic indications, like locoregional tumor staging, there are still issues to be clarified. Therefore, the aim of this thesis was to assess the accuracy of endorectal ultrasound (ERUS) in rectal cancer staging and the impact of neoadjuvant treatment on the staging accuracy, and to clarify the feasibility of EUS-guided biliary drainage (EUS-BD) as part of double endoscopic stenting in the palliative treatment of combined malignant duodenal and biliary obstruction.

1.2. Methods

To determine staging accuracy of ERUS in rectal cancer staging, we retrospectively compared the results of ERUS examinations performed at our tertiary endoscopic center with the histopathological results after surgical resection both in terms of depth of invasion (T-staging) and nodal involvement (N-staging). For the assessment of the impact of neoadjuvant treatment, accuracy of ERUS examinations was assessed separately for patients who received neoadjuvant chemo-radiotherapy (CRT) based on their initial staging results and for those who did not.

A systematic literature search of four major databases was performed to assess the feasibility and optimal method of double stenting for combined malignant duodenal and biliary obstruction compared with surgical double bypass in terms of technical and clinical success, adverse events, reinterventions, and survival. Event rates with 95% confidence intervals (CI) were calculated. In the subgroup analysis, outcomes were compared between the different methods of biliary stenting as part of double stenting, i.e. ERCP, PTD, and EUS-BD.

1.3. Results

During the initial six-year study period (2006–2012), 311 of the 647 ERUS assessed locoregional extension of rectal tumors. Histopathologic comparison was available in 177 cases: 67 patients underwent surgery alone; 110 received neoadjuvant CRT; ERUS preceded CRT in 77 and followed it in 33 patients. T-staging was accurate in 72% of primarily operated patients. N-staging was less accurate (62%). CRT impaired staging accuracy (64% and 59% for T- and N-staging). Rigid probes were more accurate (79%). At least 30 examinations are needed to master the technique.

In the extension of the previous study (2006–2014) focusing on the impact of neoadjuvant treatment on the staging accuracy of ERUS, the accuracy of T-staging decreased to 61% after neoadjuvant treatment (compared to the 70% accuracy of initial staging in the control group that did not receive CRT). Rate of overstaging was as high as 31% after neoadjuvant treatment. None of the ypT0 cases were identified. N- staging accuracy was 64% in the control group and 61% in restaging.

Seventy-two retrospective and 8 prospective studies published until July 2018 were included in the systematic review and meta-analysis of the feasibility of double endoscopic stenting (and particularly EUS-BD as a method of biliary stenting in malignant bilio-duodenal obstruction). Technical and clinical success rates of double stenting were 97% (95%–99%) and 92% (89%–95%), respectively. Clinical success of endoscopic biliary stenting was higher than that of surgery (97% [94%–99%] vs 86% [78%–92%]). Double stenting was associated with less adverse events (13% [8%–19%] vs 28% [19%–38%]) but more frequent need for reintervention (21% [16%–27%] vs 10% [4%–19%]) than double bypass. No significant difference was found between technical and clinical success and reintervention rate of ERCP, PTD and EUS-BD. ERCP was associated with the least adverse events (3% [1%–6%]), followed by PTD (10% [0%–37%]) and EUS-BD (23% [15%–33%]).

1.4. Conclusions

Based on the results of our retrospective studies investigating the accuracy of ERUS in rectal cancer staging, the sensitivity of ERUS examinations performed in our center complies with the literature. ERUS has a relatively short learning curve and provides more reliable results in early stages than in advanced ones. Staging accuracy was found to be similar in Western and Central Europe, suggesting its possible use as an alternative for pelvic MRI in regions with limited access to MRI. Neoadjuvant treatment significantly impairs staging accuracy, therefore

the use of ERUS cannot be recommended for the assessment of the efficacy of oncologic treatment and for surgical planning.

According to our systematic review and meta-analysis investigating the optimal palliative treatment for combined malignant biliary and duodenal obstruction, substantially high technical and clinical success can be achieved with double stenting. Based on the adverse event profile and reintervention rate, EUS-BD falls short to ERCP that – based on the currently available data – remains the first choice for biliary stenting as part of double stenting. Further prospective comparative studies with well-defined outcomes and cohorts are needed to clarify the exact place of EUS-BD in the therapeutic algorithm of combined malignant bilio-duodenal obstruction.

2. INTRODUCTION

Gastrointestinal (GI) malignancies are among the most frequent malignancies worldwide, accounting for 26% of global cancer incidence and 35% of all cancer-related deaths according to a recent database analysis, and considering the ongoing population aging incidence rates are about to remain persistently high in the following years. Cancer-related burden of GI malignancies varies across countries with the majority of colorectal and pancreatic cancer occurring in countries with high Human Development Index, Hungary being one of the countries with the highest global incidence and mortality rates of both cancer types. [1]

Disease stage at the time of the diagnosis plays a crucial role in the optimal management of malignancies. A precise knowledge of the TNM-stage is particularly important in the case of rectal cancers to select potential candidates for transanal endoscopic microsurgery (TEM), to determine the necessity of preoperative oncologic treatment and the extent of surgery. [2] As opposed to colorectal cancer (CRC) where introduction of population-based screening programs enhances the detection of the disease at an earlier stage with favorable curative treatment options available, pancreatic malignancies tend to be diagnosed at an advanced stage with poor prognosis and palliative options playing a major role in their management.

Endoscopic ultrasound (EUS) is a minimal-invasive modality that combines endoscopy with ultrasound providing a possibility to visualize the wall of the gastrointestinal tract and adjacent tissues and organs. The ultrasound probe attached to the tip of the endoscope contains piezoelectric crystals that change their shape in response to the applied timed, high-amplitude voltages, and convert electrical energy to mechanical one by producing sound waves. The transmitted sound waves are reflected from the target tissue and converted back to electrical signals that are interpreted by the ultrasound processor which produces an ultrasound image on the monitor. Amplitude of the soundwaves reflected from the target organs determine the image brightness. Electronic EUS transducers are able to alter focal distance and use tissue harmonic enhancement in order to improve the image resolution. Using higher scanning frequencies can further improve the resolution at the expense of penetration, i.e. only nearby structures (e.g. within 2 cm from the probe) can be visualized this way. The scanning frequency of standard EUS probes usually ranges between 5 and 12 MHz, while miniprobes might be able to scan at higher frequencies as well. Based on the orientation of the individual piezoelectric crystals, two EUS designs are available: radial-array and linear-array. In the former design, the crystals are arranged in 360° around the distal tip of the scope producing an image in the plane perpendicular to the long axis of the endoscope. This design has only diagnostic capability, with

the primary indication being the local (T- and N-) staging of GI malignancies including esophageal, gastric, pancreatic, and rectal cancers. The linear-array design provides images in a plane parallel to the long axis of the endoscope in a sector between 100° and 180°. This setting allows simultaneous visualization of the EUS needle and the target lesion, therefore it creates the opportunity for EUS-guided tissue acquisition and therapeutic procedures. [3] Recently, besides the diagnostic indications (incl. locoregional tumor staging, EUS-FNA sampling of solid and cystic pancreatic lesions, lymph nodes and subepithelial lesions, assessment of choledocholithiasis and acute and chronic pancreatitis), therapeutic EUS indications have also expanded greatly, including celiac plexus block and neurolysis, drainage of fluid collections (e.g. pancreatic pseudocyst, perirectal collections, liver abscess, biloma), biliary and pancreatic drainage (incl. biliary and/or pancreatic access in patients with difficult cannulation, direct biliary stent placement via transhepatic or transduodenal route, and direct pancreatic stent placement), fiducial marker placement, and cancer-directed therapies (incl. alcohol ablation, injection of chemotherapeutic agents, radiofrequency ablation, and brachytherapy). [3, 4] While certain indications are firmly established, others may overlap with other procedures like endoscopic retrograde cholangio-pancreatography (ERCP) and percutaneous transhepatic drainage (PTD), and their exact place in the therapeutic algorithm is yet to be defined.

EUS has long been playing an important role in the loco-regional staging of rectal cancer together with magnetic resonance imaging (MRI). Currently, the 2017 guideline of the European Society for Medical Oncology (ESMO) on rectal cancer declares pelvic MRI as the most accurate tool for locoregional staging that can detect extramural vascular invasion, determine T-stage and distance to the circumferential resection margin, and predict the risk of recurrence and synchronous/metachronous distant metastases. [2] ERUS is considered a valuable complementary tool for the earliest rectal tumors (tumors with invasion limited to the submucosa) where TEM or with the recent advancements in endoscopy, even endoscopic resection might be a feasible treatment option. [5] In reality, the limited regional availability and costs related to MRI might make the choice of the optimal staging tool for rectal cancer ambiguous. Still, the reported staging accuracy of ERUS varies widely in the literature with a T-staging accuracy ranging from 63% to 96%. [6, 7] The largest meta-analysis dealing with this topic by Puli et al. calculated the pooled sensitivity and specificity of ERUS to be 87.8% (95% confidence interval [CI]: 85.3%–90.0%) and 98.3% (95% CI: 97.8%–98.7%), respectively, for T1 lesions; 80.5% (95% CI: 77.9%–82.0%) and 95.6% (95% CI: 94.9%–96.3%), respectively, for T2 lesions; 96.4% (95% CI: 95.4%–97.2%) and 90.6% (95% CI: 89.5%–91.7%), respectively, for T3 lesions; and 95.4% (95% CI: 92.4%–97.5%) and 98.3%

(95% CI: 97.8%–98.7%), respectively, for T4 lesions. [8, 9] However, subsequent studies have pointed out a potential discrepancy between literature and real-life data and emphasized the importance of operator-dependency and expertise, as well as that of the annual case volume. [10] According to the meta-analysis of Puli et al., the modest positive likelihood ratio (2.84 [95% CI: 2.16–3.72]) and low negative likelihood ratio (0.42 [95% CI: 0.33–0.52]) of ERUS in nodal staging led to the conclusion that ERUS can better exclude nodal invasion than confirm it. Pooled sensitivity and specificity were also found to be only 73.2% (95% CI: 70.6%–75.6%), and 75.8% (95% CI: 73.5%–78%), respectively. [8, 9] Prediction of nodal involvement based on morphological criteria (e.g. echogenicity, size, shape, and borders) leads to further challenges, as well as the limited capability of ERUS to identify lymph nodes located further from the rectum. [11] Neoadjuvant chemo-radiotherapy (CRT) is a standard treatment option for locally advanced rectal cancer. Accurate restaging after neoadjuvant treatment would be of crucial importance in determining response to treatment, and the consequent management option. However, tissue changes occurring as a result of neoadjuvant treatment may alter the accuracy of staging modalities like ERUS and MRI significantly, potentially making them unsuitable for restaging. [9, 12]

Unresectable pancreato-biliary, gastro-duodenal, and metastatic malignancies can lead to concomitant biliary and duodenal obstruction. Biliary obstruction may be present in 51–72% of advanced pancreato-biliary cancers [13, 14], while duodenal obstruction's rate has also recently risen to 38% due to oncologic advances and consequently longer patient survival. [15] Historically applied double surgical bypass (gastroenterostomy combined with biliodigestive anastomosis) is often associated with substantial perioperative mortality and morbidity due to poor performance status and frequent co-morbidities. [14, 16, 17] As duodenal obstruction usually develops after biliary obstruction and it may occur in up to 20% of those who underwent single biliary bypass, creation of prophylactic gastroenteric anastomosis (GEA) was proposed in patients with unresectable disease confirmed at surgical exploration. [14, 18] Prophylactic GEA use reduces the chance for developing duodenal obstruction without impairing short-term outcomes in pancreatic and periampullary cancer. [18, 19] Therefore, most studies reporting double surgical bypass involve cases where biliary bypass was combined with prophylactic GEA. [20–22] Recently, endoscopic placement of plastic or self-expandable metal stents has offered minimal-invasive palliation alternative for patients unsuitable for surgery. Currently, transpapillary stenting via ERCP is considered the standard palliative treatment of malignant biliary obstruction alone. [23, 24] In the case of ERCP failure (which is reported in about 10% due to altered anatomy or duodenal obstruction), biliary stenting can be performed via PTD or

endoscopic ultrasound-guided biliary drainage (EUS-BD). [25] Recently, first-line use of EUS-BD in malignant biliary obstruction was also proposed based on comparable technical and clinical success, and favorable adverse event and reintervention rates over ERCP. [26] In 2018, a Cochrane Database Systematic Review comparing stent placement and surgical palliation for malignant gastric outlet obstruction found quicker resumption of oral intake and reduced hospital stay as benefits and higher reintervention rate as a drawback of duodenal stenting over surgery. [27] Combined biliary and duodenal stent placement (double stenting) was first reported in 1994. [28] Adequate modality for double stenting should be chosen based on the type of duodenal obstruction (whether it is located above [type I], at the level [type II], or below the ampulla [type III]) and sequence of biliary and duodenal stenting (biliary first, duodenal first, or simultaneous). Although technically challenging, biliary stenting can also be performed through the mesh of a duodenal stent. [23] Nevertheless, efficacy data of double stenting (particularly that performed as a combination of a duodenal stent insertion and EUS-BD) are limited, as usually there are few cases with concomitant biliary and duodenal obstruction in a single center [29], especially as biliary and duodenal obstruction may develop sequentially, and its place in the therapeutic algorithm is not clearly specified.

3. AIMS

3.1. Assessment of staging accuracy of ERUS in patients with rectal cancer

3.1.1. Retrospective assessment of staging accuracy of ERUS in rectal cancer compared to histopathological results after surgical resection in terms of depth of tumor invasion and lymph node involvement

3.1.2. Assessment of the influence of neoadjuvant treatment on the staging accuracy of ERUS in rectal cancer

3.2. Assessment of feasibility of EUS-BD as part of double stenting in the case of combined malignant biliary and duodenal obstruction in a systematic review and meta-analysis

3.2.1. To assess the feasibility of double stenting in malignant bilio-duodenal obstruction compared to surgical double bypass

3.2.1. To investigate the feasibility of EUS-BD as part of double stenting compared to ERCP and PTD

4. PATIENTS AND METHODS

4.1. Assessment of staging accuracy of ERUS in patients with rectal cancer

4.1.1. Retrospective assessment of staging accuracy of ERUS in rectal cancer compared to histopathological results after surgical resection in terms of depth of tumor invasion and lymph node involvement

ERUS examinations performed between November 15, 2006, and December 31, 2012 at the tertiary endoscopic center of the First Department of Internal Medicine, University of Szeged aiming to determine the depth infiltration and lymph node metastases of rectal tumors were retrospectively evaluated. Before the examinations, full-bowel preparation (polyethylene glycol-electrolyte solution or sodium picosulfate) was applied to empty the rectum. ERUS examinations were performed with a rigid rectoscope (Hitachi Aloka ASU-67 with mechanical radial (360°) transducer using 7.5–10 MHz frequency range) or a flexible echoendoscope. Two flexible probes were available: Olympus GF-UE 160 and Fujinon EG-530 UR (electronic radial (360°) probes, with 4 frequency options in the 5–10 and 5–12 MHz frequency range). ERUS examinations were carried out by two gastroenterologists with expertise in both endoscopic techniques and ultrasound diagnostics. In the initial period, several experts familiar with ultrasound diagnostics were present during the examinations, and images were interpreted based on their common consensus. Later, the examiner interpreted the endosonographic image alone. Staging was based on the TNM classification. The endosonographically defined clinical stage was indicated with uT and uN. According to the clinical staging results, the tumorous lesion was removed surgically or endoscopically, or neoadjuvant therapy was first administered, according to the applicable oncological protocols. Besides the ERUS for initial staging, a second one was carried out on some of the patients who received neoadjuvant treatment, aiming to determine the current stage before surgery, to estimate downstaging, if there had been any. The final stage was determined after the pathological procession of the surgical specimens (pT, pN and ypT, ypN in case of patients who received neoadjuvant treatment). The required data were collected from MedSolution patient recording system. Only those patients were involved in the analysis whose histopathological results with the final tumor stage were available. Patients were divided into three groups depending on the neoadjuvant treatment. Patients in the first group underwent surgical intervention without previous oncological treatment. ERUS was performed after chemoradiotherapy on patients of the second group. In the third group, ERUS was performed first, but CRT was also necessary before

surgery, because of the advanced stage of the disease. In the latter case, the later date of the histopathological findings, as well as the effect of CRT on staging, had also been taken into consideration in the evaluation of the accuracy. The accuracy of endorectal ultrasonography was evaluated by comparing uT, uN and yuT, yuN stages with the final pT, pN and ypT, ypN stages. The measure of correspondence was determined and was also characterized by Cohen's kappa coefficient. The overstaging and understaging rates were investigated as well. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ERUS were calculated for each tumor stage. Evaluating the N-staging accuracy, the ability of ERUS to recognize metastatic lymph nodes was investigated; therefore, no difference was made between N1- and N2-stages. The operator-dependency of ERUS was also investigated as well as the extent to which the experience of the endosonographer (learning curve) affects the accuracy. The learning curve was determined on the group that did not receive neoadjuvant treatment. The correctness of the endosonographic diagnoses from a single examiner was also evaluated in correlation with the number of examinations performed. Our results were compared to the largest multicenter, prospective, countrywide, and real-life study conducted by Marusch et al. in Germany, as a representative of the staging accuracy of ERUS in Western Europe. [10]

4.1.2. Assessment of the influence of neoadjuvant treatment on the staging accuracy of ERUS in rectal cancer

In this retrospective single center study, the accuracy of ERUS examinations performed with the aim of restaging rectal cancer after neoadjuvant CRT between November 2006 and December 2014 at the First Department of Internal Medicine, University of Szeged was investigated in terms of depth of invasion (T-staging) and nodal involvement (N-staging). Similarly to the previous study, histopathological results after surgical resection were used as a comparator, and correspondence was determined. T- and N-staging results were assessed separately, as well as T-staging results for each T stage. Patients undergoing surgical resection without neoadjuvant treatment were also included in the study as a control group. During the study period, a rigid rectoscope and two flexible echoendoscopes were used (see technical data above). After the initial learning phase, when several experts were present at the examination and determination of the T- and N-stage was based on a consensus, ERUS examinations were performed by one of two experts. Endosonographically defined clinical stage was indicated with uT and uN, and yuT and yuN in the case of primary staging and restaging, respectively, while final pathological stage was indicated with pT and pN without neoadjuvant treatment,

and ypT and ypN after neoadjuvant treatment. Both studies were conducted in accordance with the principles of the Declaration of Helsinki.

4.2. Assessment of feasibility of EUS-BD as part of double stenting in the case of combined malignant biliary and duodenal obstruction in a systematic review and meta-analysis

4.2.1. Protocol and registration

This work was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 Statement. [30] The study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42018103101.

4.2.2. Eligibility criteria

We included studies reporting the following outcome measures in patients with concomitant malignant biliary and duodenal obstruction treated either with combined duodenal and biliary stenting (via ERCP, PTD, or EUS-BD) or with double surgical bypass (gastroenterostomy with biliodigestive anastomosis): technical and clinical success, survival, adverse events, and reintervention rates. Studies reporting about temporary stenting were excluded. Studies reporting about prophylactic GEA were included; however, technical and clinical success could only be interpreted as that of biliary bypass in such cases. Both experimental and observational studies (either prospective or retrospective) without respect to their primary objectives were included. Conference abstracts were included to minimize publication bias. Case reports and case series reporting about less than 5 patients were excluded from quantitative analysis. Eligible articles were written in English or had an English abstract (data were obtained from the abstract in such cases).

4.2.3. Information sources and search strategy

A systematic literature search limited to human studies without language filters was performed by 2 reviewers in the PubMed (MEDLINE), EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases with the terms “([biliary obstruction AND duodenal obstruction] OR bilio-duodenal obstruction)

AND (stent OR surgery).” The final search was performed on July 17, 2018. Reference lists of included articles were also investigated to capture all relevant studies.

4.2.4. Study selection and data collection process

After the removal of duplicates, the following data were extracted by 2 independent authors: age, gender, type of underlying malignancy, type of duodenal obstruction, method of biliary drainage, type of biliary and duodenal stents, timing of stent placement, technical and clinical success, adverse events, reintervention rate, survival, and follow-up.

4.2.5. Risk of bias assessment

Risk of bias was assessed using a modified version of the Newcastle–Ottawa Scale (NOS) by 2 independent review authors. Disagreements were resolved by discussion, with involvement of a third review author, when needed. The modified NOS contained 7 items covering 2 main domains (selection and outcome) as comparability domain was not applicable because of the lack of head-to-head comparative studies: representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, demonstration that the outcome of interest was not present at the study’s start (selection domain), assessment of outcome, and length and adequacy of follow-up (outcome domain). Studies could be awarded a maximum of one star for each item. Each item was rated as “high risk” (zero stars) or “low risk” (one star).

4.2.6. Data synthesis and statistical methods

Pooled event rate was calculated for events, and pooled mean was calculated for continuous data with 95% CIs. A random-effect model was applied in all analyses with the DerSimonian–Laird estimation. Statistical heterogeneity was analyzed using the I^2 and χ^2 tests to gain probability values; $P < 0.10$ was defined to indicate significant heterogeneity. The I^2 test represents the percentage of total variability across studies because of heterogeneity. I^2 values of 30%–60%, 50%–90%, and 75%–100% corresponded to moderate, substantial, and considerable heterogeneity, respectively, based on Cochrane’s handbook. [31] Statistical analyses were performed with Comprehensive Meta-Analysis Software and STATA. Forest plots displayed the results of the meta-analysis.

4.2.7. Outcome measures

Overall technical success was defined as adequate placement of both biliary and duodenal stents or successful performance of double bypass in the case of manifest gastric outlet and biliary obstruction. [16, 32, 33] Clinical success of biliary stenting was usually defined as a postprocedural reduction in serum bilirubin level within 2 weeks. However, this definition varied remarkably across studies: One study required normalization of serum bilirubin level [34], whereas others considered clinical success when a 25% or 50% reduction in bilirubin was observed [29, 33, 35] or only stated improvement of biliary obstruction symptoms without further clarification [16, 36]. Clinical success of duodenal stenting, when clarified other than clinical improvement of symptoms [16, 36], mainly referred to a better score on the gastric outlet obstruction scoring system [33, 35]. Technical and clinical success was determined for that of biliary stenting/bypass and duodenal stenting/bypass together and separately as well. Cases of prophylactic GEA were also included in the meta-analysis because it is recommended and commonly applied in the surgical treatment of pancreatic tumors. However, when prophylactic GEA was included in the surgical group, technical and clinical success could only be interpreted as that of biliary bypass, and accordingly, this was compared with technical and clinical success of biliary stenting. Survival was determined as the time to death from both stents' placement (or creation of double bypass). For sequential biliary and duodenal stenting, survival was calculated from placement of the later stent. The following adverse events were investigated: pancreatitis, cholangitis, cholecystitis, bleeding, bile leakage, perforation, pneumoperitoneum, abdominal pain, wound infection, pneumonia, and others (including symptomless amylasemia, atrial fibrillation, cardiac arrest, aspiration, intra-abdominal abscess, and deep vein thrombosis). Stent migration, recurrent biliary obstruction (RBO; defined mostly as per the Tokyo criteria) [37], and recurrent duodenal obstruction (RDO; reoccurrence of gastric outlet obstruction symptoms) were also investigated. Adverse event rate was given as the number of patients with one or more adverse events. Reintervention rate was defined as the number of patients who required endoscopic or surgical intervention to treat RBO or RDO.

5. RESULTS

5.1. Assessment of staging accuracy of ERUS in patients with rectal cancer

5.1.1. Retrospective assessment of staging accuracy of ERUS in rectal cancer compared to histopathological results after surgical resection in terms of depth of tumor invasion and lymph node involvement

In the six-year study period, a total of 647 endorectal ultrasounds were performed. 311 of the examinations aimed to determine locoregional extension of a tumor. 30 examinations failed due to inaccessible lesions (significant stenosis or lesion located above the distance accessible with the probe), probe failure, or inadequate bowel preparation. Histopathological results with the final tumor stage were available in only 177 cases. In the other cases, the surgery and pathological procession was performed in another institution, and only the staging with ERUS was performed in our institution. 67 of the 177 patients underwent surgery without previous CRT within an average interval of 24 days after the endosonographic staging (Group I); the other 110 patients received oncological treatment prior to the surgery: ERUS was performed before the neoadjuvant treatment in 77 patients (Group III) and after that in 33 patients (Group II).

5.1.1.1. Accuracy of T-staging

In terms of the T-staging accuracy, a significant difference was noted between the three groups. The correspondence was highest (72%) in the group that did not receive CRT (Group I), with Cohen's kappa coefficient of 0.482, indicative of a moderate correspondence. 11 cases (16%) were overestimated and 8 were underestimated (12%).

	Group I (n = 67)	Group II (n = 33)	Group III (n = 77)
(y)uT–(y)pT correspondence	72%	64%	34%
Kappa coefficient	0.482	0.390	0.019
Overstaging	16%	27%	57%
Understaging	12%	9%	9%

Table 1. Overall accuracy of T-staging during the study period (2006-2012)

In this patient group, the pathological examination of the resected tissue revealed T3 stage in 12 patients; thus, primary oncological treatment would have been necessary according to the current therapeutic protocols. ERUS reported uT3 stage in 7 and uT2N1 in one of the cases; therefore, understaging led to inappropriate treatment in only 4 patients. It should be

noted, however, that in these 4 cases the time interval between ERUS and surgery was longer (an average of 38 days). The accuracy rate of ERUS was lower after neoadjuvant treatment (64%). In this group, overstaging was more frequent (27%) and 3 cases were understaged (9%). ERUS before CRT complied with the histopathological results in only 34% of the cases, accompanied by Cohen's kappa coefficient of 0.019 indicating poor correspondence. The overstaging rate was prominently high in this group (57%).

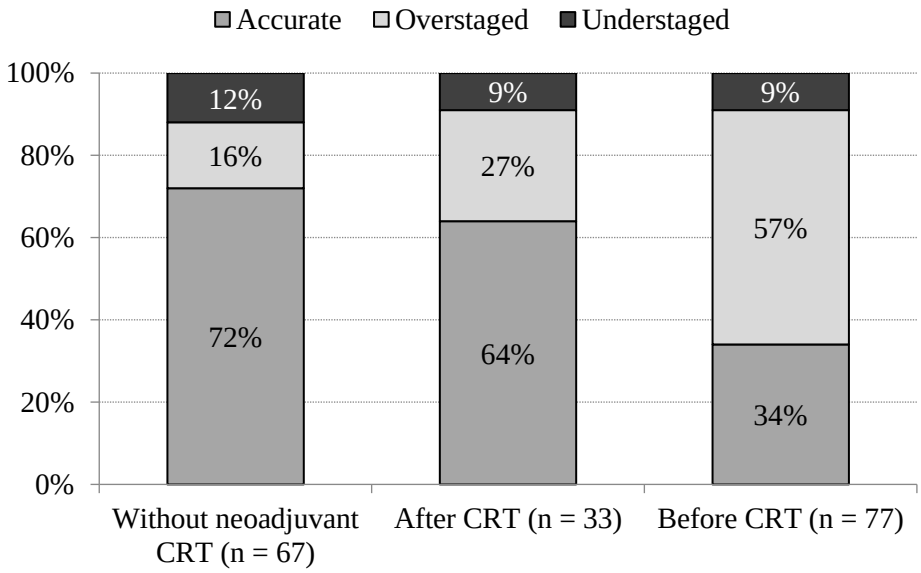

Figure 1. Accuracy of T-staging in each patient group

In the majority of patients who did not receive CRT, early stage tumors were detected (the histopathological examination revealed pT1 in 61%, pT2 in 16%, and pT3 in 18% of the cases). At least moderate correspondence could be observed for each tumor category; the correspondence was highest for T3 tumors (κ = 0.606). Three-quarters of pT1 and pT2 tumors were identified correctly with ERUS (with a sensitivity of 75% and 73%, resp.), but, in case of T3 tumors, the sensitivity was only 58%. Unlike the high positive predictive values for T1 and T3 tumors, only 42% of the endosonographically defined T2 tumors were proved to be T2. The majority of uT2 cases were overestimated, as ERUS reported T2 instead of T1.

	uT1	uT2	uT3
uT–pT correspondence (κ coefficient)	0.465	0.411	0.606
Sensitivity	75%	73%	58%
Specificity	74%	80%	96%
PPV	85%	42%	78%
NPV	61%	94%	91%

Table 2. Accuracy of ERUS for each T stage without neoadjuvant therapy (n = 67)

In accordance with the current protocols, the majority of the patients who received neoadjuvant treatment had T3 tumors. In two cases, pathological results showed complete regression; no residual tumor tissue was detectable in the resected tissue. None of these could be identified endosonographically; the lesions were overestimated. It has been proven that ERUS results of patients who received oncological treatment shifted towards overstaging compared to those who underwent surgery as a primary intervention (27% and 57% of the lesions were overstaged after and before the neoadjuvant treatment, respectively.) (Figure 1). After neoadjuvant CRT, the level of correspondence was lower for all T1-T3 stages. Correspondence was highest (κ = 0.525) for T3 tumors, 70% of the lesions described as yuT3 proved to be actually ypT3, and the sensitivity was 82%. A lower level of correspondence was observed in less advanced lesions; in T1 tumors, the sensitivity was only 20% and the positive predictive value was 50%.

	yuT1	yuT2	yuT3
uT–pT correspondence (κ coefficient)	0.218	0.415	0.525
Sensitivity	20%	67%	82%
Specificity	96%	83%	63%
PPV	50%	60%	70%
NPV	87%	87%	77%

Table 3. Accuracy of ERUS for each T stage after neoadjuvant therapy (n = 33)

5.1.1.2. Accuracy of N-staging

Lymph node involvement was both reported with ERUS and mentioned in the histopathological findings in 123 patients. 29 of these patients underwent surgery as a primary treatment (Group I); the endosonographic staging preceded (Group III) and followed (Group II) CRT in 29 and 65 cases, respectively. In Groups I and II, the tumor stage seen with ERUS

corresponded with the N-stage in the pathological results in 62%and 59% of the cases, respectively. This rate was significantly lower in Group III (45%). Understaging was more frequent in the former two categories (21% and 28%), while overstaging prevailed in the third one (40%).

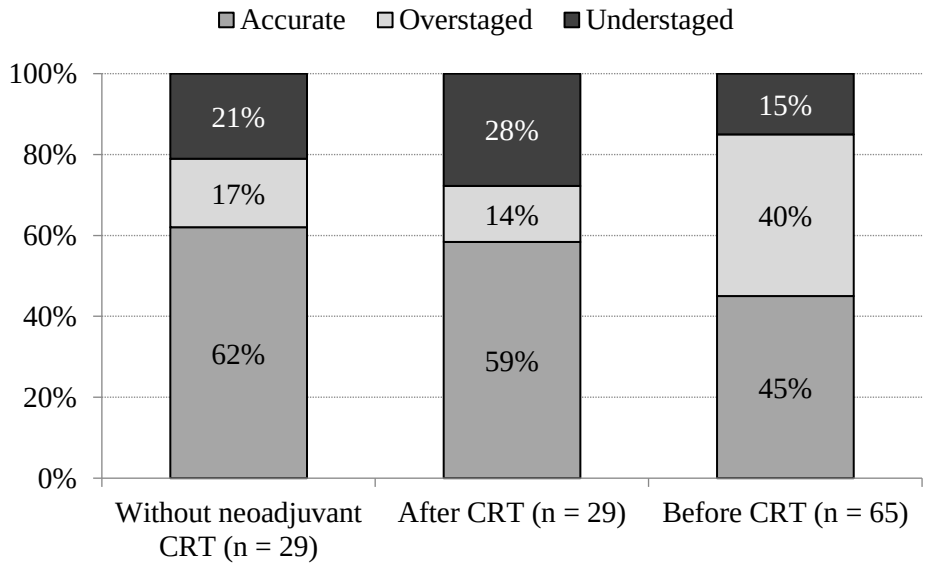

Figure 2. Accuracy of N-staging in each patient group

It could also be noted that ERUS could more reliably recognize the absence of lymph node metastases than their presence.

	Group I (n = 29)	Group II (n = 29)	Group III (n = 65)
Sensitivity	14%	11%	50%
Specificity	77%	80%	42%
PPV	17%	20%	28%
NPV	74%	67%	66%

Table 4. Accuracy of N-staging in each patient group

5.1.1.3. Learning curve

The time needed for gaining appropriate experience was investigated in the group that did not receive CRT; these 67 patients were divided into two groups; the 33 results of the initial period were compared to the subsequent 34.

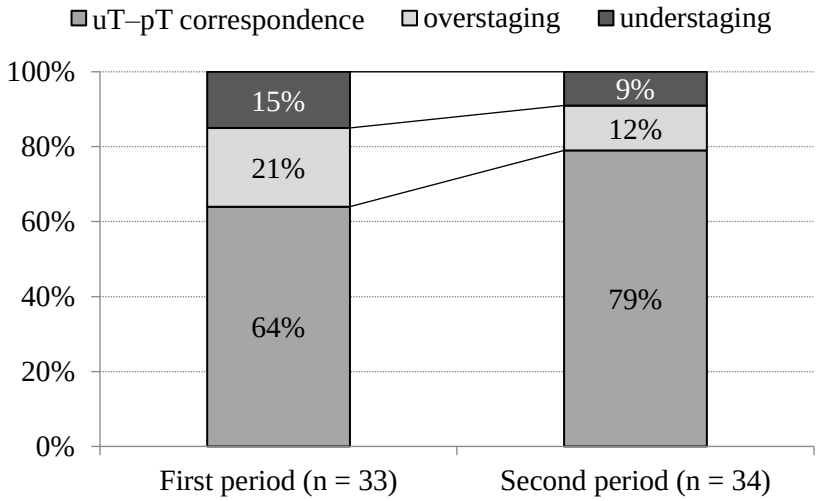

Figure 3. The accuracy of ERUS over time

The uT-pT correspondence was found to be significantly higher in the later period than in the initial one (p = 0.034). Furthermore, the understaging and overstaging rates both decreased. When taking into account only the cases from the later period, the sensitivity of ERUS reached 75% in all T-stages. All of the endoscopic T3 tumors were identified correctly.

	uT1	uT2	uT3
uT–pT correspondence (κ coefficient)	0.643	0.519	0.821
Sensitivity	80%	83%	75%
Specificity	86%	82%	100%
PPV	89%	50%	100%
NPV	75%	96%	93%

Table 5. Accuracy of ERUS for each T stage without neoadjuvant therapy, in the later study period after reaching a plateau in the learning curve (n = 34)

The learning curve of one of the examiners was determined based on 43 ERUS examinations, by comparing the accuracy of the results divided into groups of 10 cases. The level of correspondence was found to be significantly higher after 30 examinations, suggesting a plateau phase or even a further increasing tendency.

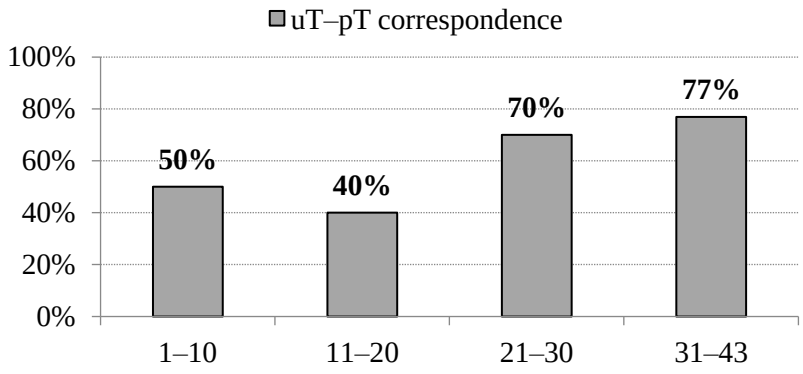

Figure 4. The performance of a single examiner after each 10 examinations

Our case number was insufficient for determining the learning curve of the N-staging.

5.1.1.4. Accuracy of rigid and flexible probes

Rigid and flexible probes were compared based on their results in patients who did not receive CRT. 29 examinations were carried out with the rigid Aloka ASU-67 probe and 38 were carried out with the flexible Olympus GF-UE 160, Fujinon EG-530UT, and EG-530UR probes. The uT stage determined with the rigid probe showed a higher rate of correspondence with the final pT stage than the one defined with flexible probes (79% and 66%).

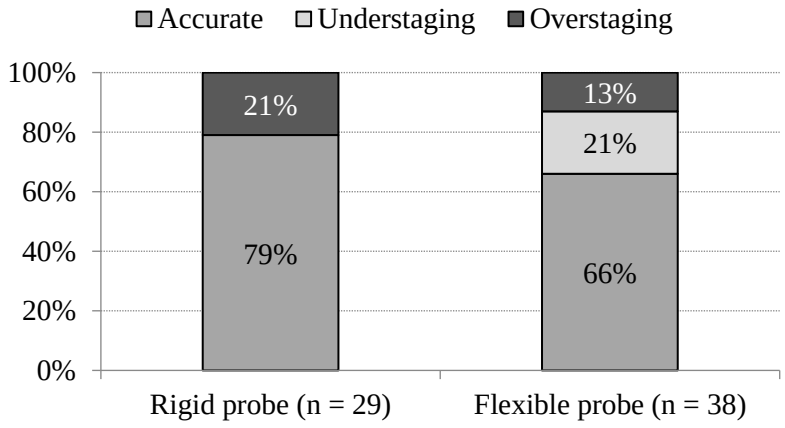

Figure 5. Accuracy of T-staging in case of flexible and rigid probes

Inaccuracy of the rigid probe was exclusively due to overestimation, while underestimation could also be observed with the flexible devices; moreover, it was more frequent than overestimation. N-staging of the rigid probe could only be evaluated in six cases; the uN-pN stages were identical in five cases, and, in one case, the lymph node detected with

ERUS did not prove to be metastatic. In case of the flexible devices, the results corresponded in 13 of the 23 cases; lymph node involvement was underestimated in six cases.

5.1.2. Assessment of the influence of neoadjuvant treatment on the staging accuracy of ERUS in rectal cancer

During the study period, a total of 849 ERUS examinations were performed in our institute from which the suspicion of a rectal malignancy arose in 507 cases, and the examination aimed to determine T- and N-stage in 385 of these cases. In terms of depth of invasion, histopathologic results were available as a comparator in 81 cases in the control group (those who underwent primary surgical resection without neoadjuvant CRT), and in 36 cases of those who underwent neoadjuvant CRT. As for nodal staging, histopathologic results were available for 46 patients in the control group, and for 33 patients who underwent restaging after neoadjuvant treatment. Mean age of patients was 63 years (range: 24–90 years) in the control group and 64 years (range: 40–81 years) in the restaged group, respectively. The tumor was located at an average of 4.7 cm above the anus (8.5 cm in the control group). The average time between restaging and surgery was 30 days (range: 1–127 days), while in the control group, surgery followed ERUS staging with an average of 26 days (range: 1–233 days).

5.1.2.1. T-staging accuracy

Distribution of different yuT-ypT stages after neoadjuvant treatment are listed in Table 6, and case numbers according to uT-pT stages in the control group are in Table 7 (yuT indicates T-stage determined with ERUS after neoadjuvant treatment, and ypT stands for the pathological stage after neoadjuvant treatment).

	ypT0	**ypT1**	**ypT2**	**ypT3**	**ypT4**	**Total**
yuT0						0
yuT1	2	1				3
yuT2		1	6	3		10
yuT3	1	2	3	15		21
yuT4		1		1		2
Total	3	5	9	19	0	36

Table 6. Case numbers after neoadjuvant treatment

	pT1	pT2	pT3	Total
uT1	36	4	3	43
uT2	10	12	4	26
uT3	3		9	12
Total	49	16	16	81

Table 7. Case numbers in the control group

While histopathologic assessment reported early stage tumors (T1-2) in 80% of the cases in the control group, more than half of the resected specimens proved to be of ypT3 stage after neoadjuvant treatment.

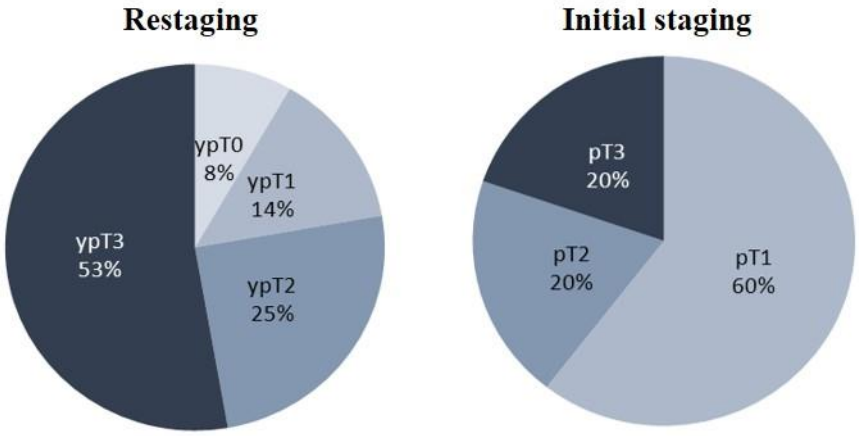

Figure 6. Proportion of each T-stage after neoadjuvant treatment (N=36) and in the control group who did not receive neoadjuvant treatment (N=81)

In case of patients who received neoadjuvant CRT, 61% of yuT and ypT stages corresponded to each other. Overstaging was more frequent than understaging (31% and 8%, respectively). Accuracy of ERUS was found to be lower compared to the control group (70%), but the difference was not significant at $p<0.05$ ($p=0.077$). Besides, overstaging was more common after neoadjuvant treatment, as opposed to the control group where the proportion of overstaging and understaging was similar.

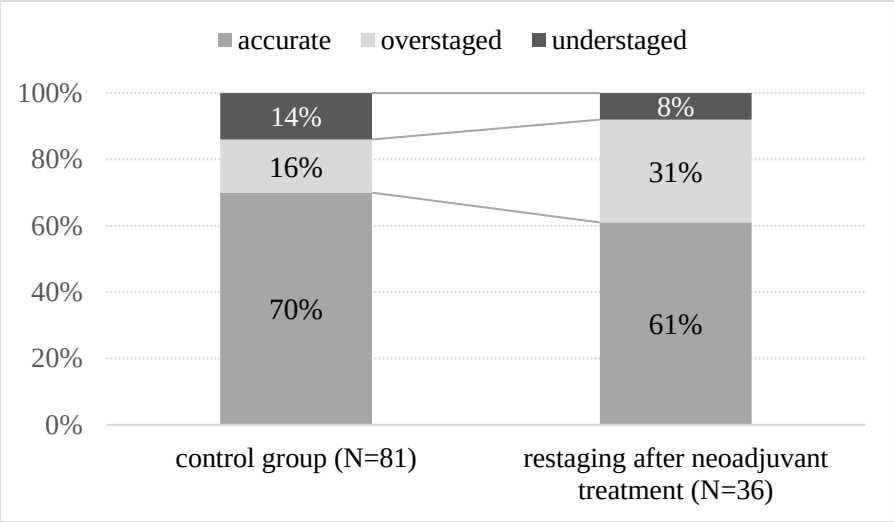

Figure 7. Accuracy of T-staging in case of initial staging (control group) and restaging after neoadjuvant treatment

During restaging, locally advanced tumors (ypT3) could be found in a greater proportion (in nearly 80%) even after neoadjuvant treatment, while complete tumor regression could be confirmed in none of the 3 cases.

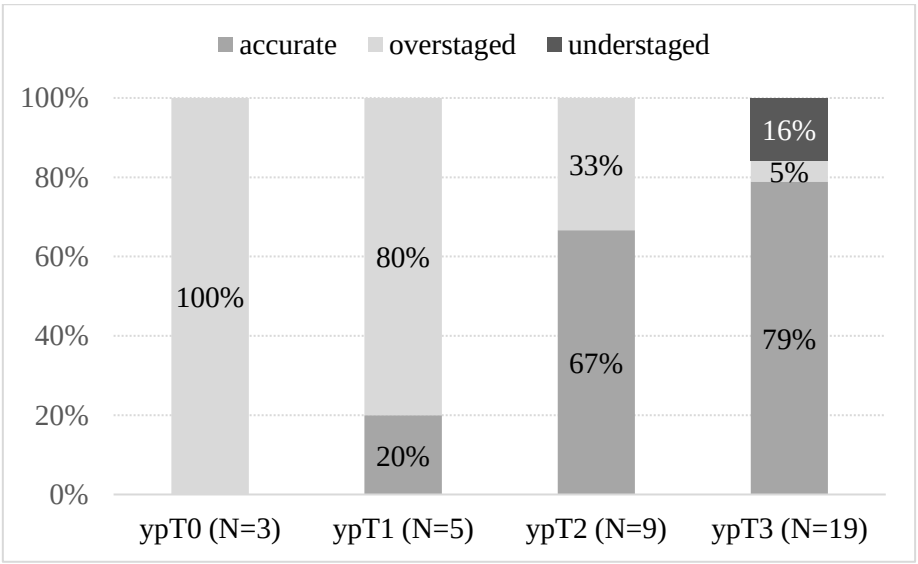

Figure 8. Staging accuracy of ERUS after neoadjuvant treatment for each T-stage

In contrast, early-stage tumors were detected more frequently in the control group (73% and 75% for pT1 and pT2, respectively).

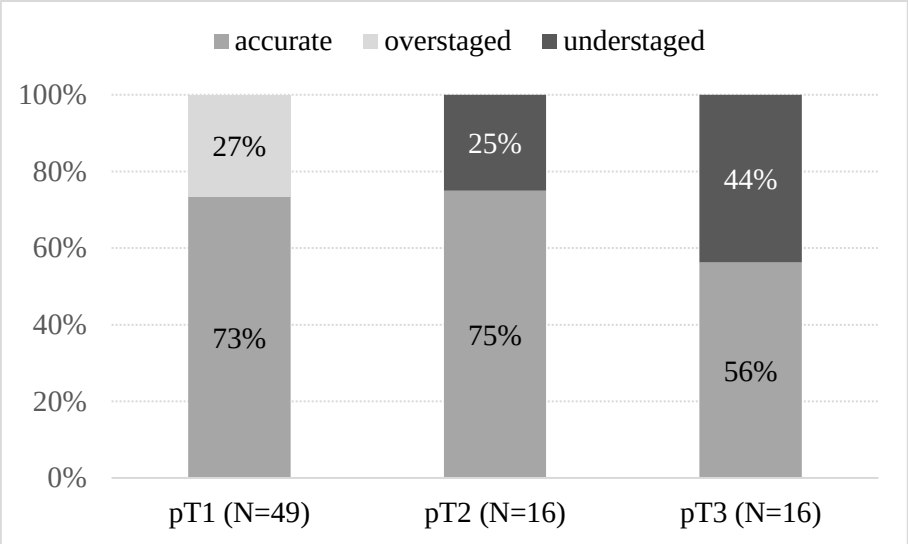

Figure 9. Initial staging accuracy of ERUS for each T-stage (control group)

5.1.2.2. N-staging accuracy

In terms of nodal involvement, no significant difference was found in the accuracy of ERUS between the group who received neoadjuvant treatment and the control group.

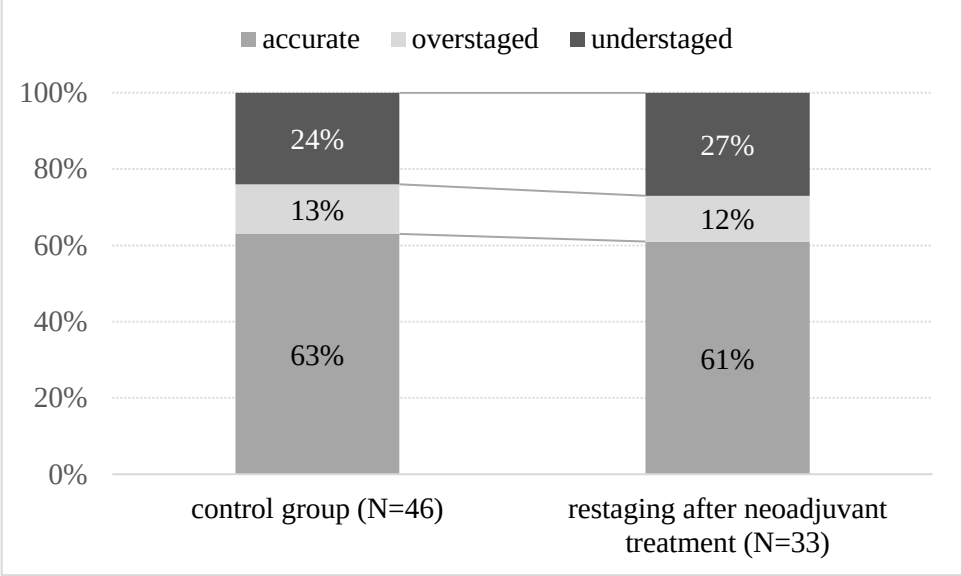

Figure 10. Accuracy of N-staging in case of initial staging (control group) and restaging after neoadjuvant treatment

Sensitivity, specificity, PPV and NPV of N-staging in the case of primary staging and restaging are listed in Table 8. It can be stated in both cases that ERUS can exclude lymph node enlargement more reliably than confirm it.

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
N-staging	15%	82%	25%	71%
N-restaging	18%	82%	33%	67%

Table 8. Accuracy of initial N-staging and N-restaging

5.2. Assessment of feasibility of EUS-BD as part of double stenting in the case of combined malignant biliary and duodenal obstruction in a systematic review and meta-analysis

5.2.1. Study selection and characteristics

A total of 2,765 records were identified through a database search: 833 in PubMed, 1,531 in EMBASE, 382 in Web of Science, and 19 in CENTRAL. Nine additional records were found from the reference list of relevant articles. After removing duplicates and irrelevant records, 121 studies were found eligible. From these, 41 case reports and case series were excluded from quantitative synthesis.

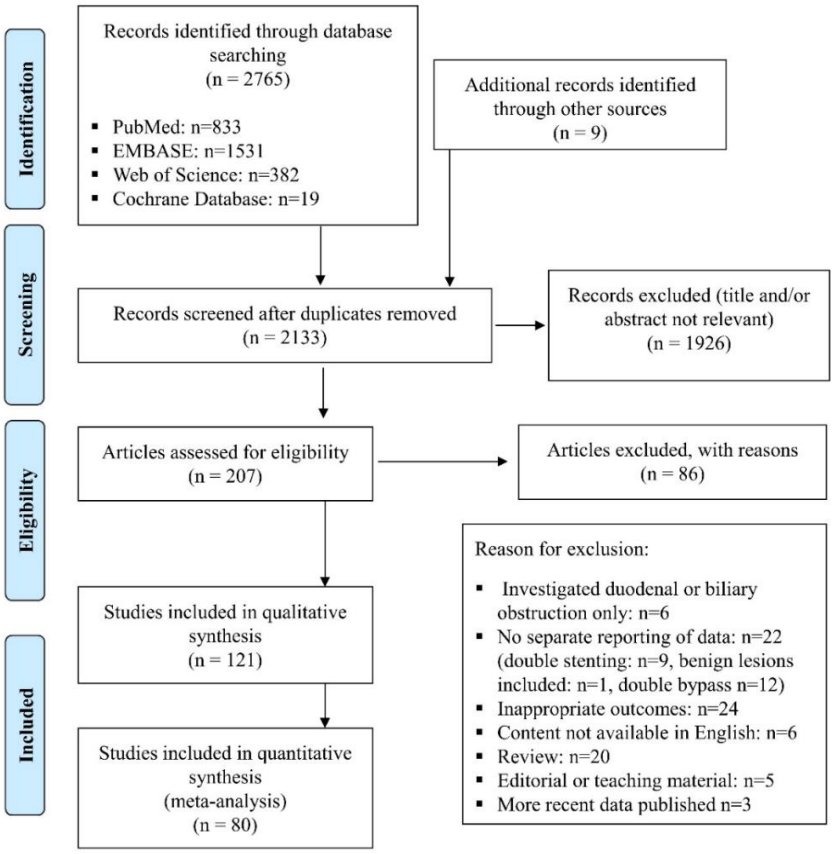

Figure 11. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart

Table 9. Characteristics of included studies dealing with endoscopic double stenting

Endoscopic

Study	Design	Centers (N^0)	N^0 pts	Age				Sex (female% of total)	Duodenum obstruction			Type of malignancy	Biliary stenting			Type of biliary stent	Type of duodenum stent	Timing			Follow-up (days)				
				Mean	Median	SD	Range		Type I	Type II	Type III		ERCP	EUS-BD	PTD			Biliary first	Simultaneous	Duodenal first	Mean	Median	SD	IQR	Range
Kaw [38], 2003	retrospective	1	18	65	-	-	46-85	39%		NA		pancreatic, bile duct, metastatic, other	18	0	0	SEMS	NA		NA				NA		
Vanbiervliet [39], 2004	retrospective	1	18	72	-	-	60-83	39%		NA		pancreatic	18	0	0	SEMS	NA	0	0	18			NA		
Choi [40], 2005 (abstract)	retrospective	1	23		NA			NA		NA		pancreatic, ampullary, gastric, bile duct, gallbladder	11	0	12	NA	NA	17	0	6			NA		
Olsen [41], 2005 (abstract)	retrospective	1	29		NA			NA		NA		pancreatic, gastric, bile duct, other	29	0	0	SEMS	NA	27		2			NA		
Maire [42], 2006	retrospective	1	23	-	65	-	32-85	NA		NA		pancreatic	23	0	0	PS, SEMS	NA	16	6	1			NA		
Sulieman [43], 2006 (abstract)	retrospective	NA	14		NA			NA		NA		pancreatic, gallbladder, metastatic	14	0	0	SEMS	NA	7	4	3			NA		
Wang [44], 2006 (abstract)	retrospective	1	20	62	-	-	-	15%		NA		NA	0	0	20	NA	NA	16	4	0			NA		
Akinci [45], 2007	retrospective	1	9	61	-	-	42-80	33%		NA		pancreatic, duodenal, bile duct	0	0	9	SEMS	NA	5	4	0			NA		
Hou [46], 2007 (abstract)	retrospective	1	12		NA			NA		NA		NA	0	0	12	SEMS	NA		NA				NA		
Mutignani [47], 2007	prospective	1	64	68.5	-	12.9	-	47%	31	25	8	pancreatic, gastric, metastatic, other	62	0	2	PS, SEMS	uSEMS	46	14	4			NA		
Moon [48], 2009	prospective	1	8	72.8	-	-	51-85	38%	3	5	0	pancreatic, ampullary, gastric, bile duct, metastatic	8	0	0	SEMS	uSEMS	2	6	0			NA		
Katsinelos [49], 2010	retrospective	4	32	-	77	-	52-89	34%		NA		pancreatic		NA		SEMS	NA	25	7	0			NA		
Keranen [50], 2010	retrospective	1	57	-	72	-	40-89	59%		NA		pancreatic, duodenal, gastric, bile duct, other	52	0	5	PS, SEMS	NA	46	11	0	-	62	-	-	1-933
Iwamuro [51], 2010	retrospective	1	7	73	-	-	58-86	29%		NA		pancreatic, ampullary	0	7	0	PS	cSEMS	0	2	5	89	-	-	-	37-186
Zheng [52], 2010 (abstract)	retrospective	1	22		NA			NA		NA		NA	22	0	0	NA	NA		NA		180	-	-	-	-
Li [53], 2011 (abstract)	retrospective	1	18		NA			NA		NA		pancreatic, duodenal, bile duct, metastatic		NA		SEMS	NA	14	4	0			NA		
Price [54], 2011 (abstract)	prospective	1	42		NA			NA		NA		pancreatic, gastric, bile duct, gallbladder	33	0	9	PS, SEMS	NA	40	0	2			NA		

Table 9. Characteristics of included studies dealing with endoscopic double stenting (cont.)

Endoscopic

Study	Design	Centers (N^0)	N^0 pts	Age				Sex (female% of total)	Duodenum obstruction			Type of malignancy	Biliary stenting			Type of biliary stent	Type of duodenum stent	Timing			Follow-up (days)				
				Mean	Median	SD	Range		Type I	Type II	Type III		ERCP	EUS-BD	PTD			Biliary first	Simultaneous	Duodenal first	Mean	Median	SD	IQR	Range
Ardengh [55], 2012 (abstract)	retrospective	1	22	22	59	-	26-87	NA		NA		pancreatic		NA		NA	NA	0	22	0			NA		
Hamada [56], 2012	retrospective	5	33	69	-	-	62-77	40%	23	5	5	pancreatic, bile duct, other	33	0	0	SEMS	cSEMS	20	11	2			NA		
Kanno [57], 2012 (abstract)	retrospective	1	21	72	-	-	-	62%		NA		NA	13	6	2	NA	NA	12	9	0			NA		
Khashab [58], 2012	retrospective	2	9	71.1	-	-	-	44%	2	7	0	pancreatic, duodenal, other	0	9	0	SEMS	NA	0	3	6			NA		
Kim [59], 2012	retrospective	1	24	71	-	11.6	43-89	50%	4	13	7	pancreatic, gastric, bile duct	13	0	11	PS, SEMS	NA	23	0	1			NA		
Maluf-Filho [60], 2012	retrospective	1	5	70	72	7	46-88	60%		NA		pancreatic, other	0	5	0	SEMS	uSEMS	0	5	0	37.2	17	16.3	-	4-90
Kushnir [61], 2013 (abstract)	retrospective	1	62	65	-	11.6	-	45%		NA		pancreatic, metastatic	62	0	15*	NA	NA		NA				NA		
Pan [62], 2013 (abstract)	retrospective	1	10		NA			NA	6	3	1	pancreatic, ampullary, bile duct, gallbladder	6	4	0	NA	NA	3	1	6			NA		
Tonozuka [63], 2013	retrospective	1	11	68.5	-	8.1	-	27%	1	10	0	pancreatic	3	8	0	SEMS	NA	6	4	1			NA		
Valeshabad [64], 2013 (abstract)	retrospective	6	35	65.9	-	-	-	49%	NA	18	NA	NA	35	12*	9*	PS, SEMS	NA	0	0	35	78.4	-	-	-	1-500
Waidmann [65], 2013	retrospective	1	17	70	-	11	50-85	47%		NA		pancreatic, gastric, bile duct, gallbladder, metastatic, other	17	0	0	PS, SEMS	cSEMS, uSEMS		NA		57	-	71	-	1-275
Carvalho [66], 2014 (abstract)	retrospective	3	50		NA			NA	35	22	4	NA	42	0	8	NA	NA		NA				NA		
Canena [35], 2014	retrospective	4	50	71.2	70	-	46-90	42%	35	11	4	pancreatic, duodenal, ampullary, gastric, bile duct, gall bladder, other	42	0	8	SEMS	uSEMS	29	15	6			NA		
Hamada [67], 2014	retrospective	3	20	66.6	65	1.1	58-76	45%	9	5	6	pancreatic, ampullary, gastric	13	7		PS, SEMS	cSEMS, uSEMS	0	0	20			NA		
Khashab [68], 2014	retrospective	6	35	64.6	-	13.5	-	45%	6	19	2	pancreatic, duodenal, metastatic, other	11#	13*	9*	PS, SEMS	uSEMS	0	0	35			NA		
Lee [69], 2014	retrospective	1	45	61.3	-	11.6	38-83	47%	21	19	5	pancreatic, duodenal, gastric, bile duct, gallbladder, other	0	0	45	SEMS	cSEMS, uSEMS	14	0	31	-	132	-	-	8-920
Yu [70], 2014	retrospective	1	17	76.6	-	6.5	62-87	18%	7	8	1	pancreatic, duodenal, bile duct	17	0	0	NA	NA	17	0	0			NA		

Table 9. Characteristics of included studies dealing with endoscopic double stenting (cont.)

Endoscopic

Study	Design	Centers (N⁰)	N⁰ pts	Age				Sex (female% of total)	Duodenum obstruction			Type of malignancy	Biliary stenting			Type of biliary stent	Type of duodenum stent	Timing			Follow-up (days)				
				Mean	Median	SD	Range		Type I	Type II	Type III		ERCP	EUS-BD	PTD			Biliary first	Simultaneous	Duodenal first	Mean	Median	SD	IQR	Range
Di Mitri [71], 2015 (abstract)	retrospective	1	35	72.4	-	10.1	-	37%		NA		pancreatic, duodenal, bile duct, other	35	0	0	NA	NA	0	0	35			NA		
Kubo [72], 2015 (abstract)	retrospective	1	44	75.4	-	-	-	48%		NA		NA	34	0	10	NA	NA	33	11	0			NA		
Manta [73], 2015	retrospective	1	15	65.6	-	-	38-80	20%		NA		pancreatic	3	12	0	SEMS	uSEMS	12	0	3			NA		
Matsumoto [74], 2015 (abstract)	retrospective	1	47		NA			NA		NA		pancreatic	32	15	0	NA	NA		NA				NA		
Sanchez-Ocana [75], 2015 (abstract)	retrospective	1	61	77	-	-	30-92	69%	26	34	1	pancreatic, gastric, other	37	24	0	NA	NA	25	9	27			NA		
Sano [76], 2015 (abstract)	retrospective	1	21		NA			NA	13	6	2	pancreatic		NA		NA	NA	17	4	0			NA		
Williamson [20], 2015	retrospective	2	7	-	70	-	42-81	38%		NA		pancreatic, duodenal, ampullary, bile duct, other		NA		PS, SEMS	NA	7	0	0			NA		
Fu [34], 2016	retrospective	1	22	64.7	-	9.3	-	30%		NA		pancreatic	0	0	22	NA	NA		NA				NA		
Ogura [77], 2016	retrospective	1	39	70.3	-	9	-	46%	28	11		pancreatobiliary, other	0	39	0	SEMS	uSEMS	0	0	39			NA		
Paik [78], 2016 (abstract)	retrospective	1	43		NA			NA		NA		pancreatic, duodenal, bile duct, gallbladder, metastatic, other	11	0	32	NA	NA	0	0	43			NA		
Sato [36], 2016	retrospective	1	43	65.4	-	9.8	-	49%	12	18	13	pancreatic, duodenal, gastric, bile duct	26	17	0	SEMS	uSEMS		NA		90	-	-	-	-
Yao [79], 2016 (abstract)	retrospective	1	42		NA			NA		NA		NA	42	0	0	NA	NA	0	0	42			NA		
Zhao [80], 2016	retrospective	1	20	63.1	-	8.2	35-72	35%		NA		pancreatic, duodenal, bile duct, metastatic	0	0	20	NA	NA	16	1	3			NA		
Bulut [81], 2017 (abstract)	retrospective	1	21	58.7	-	15	-	38%		NA		pancreatic, duodenal, ampullary, gastric, bile duct, metastatic, other	0	0	21	NA	uSEMS	14	7	0	112.6	-	152	-	-
Fukushima [82], 2017 (abstract)	retrospective	1	15		NA			NA	7	5	3	NA		NA		NA	NA		NA				NA		

Table 9. Characteristics of included studies dealing with endoscopic double stenting (cont.)

Endoscopic

Study	Design	Centers (N^0)	N^0 pts	Age				Sex (female% of total)	Duodenum obstruction			Type of malignancy	Biliary stenting			Type of biliary stent	Type of duodenum stent	Timing			Follow-up (days)				
				Mean	Median	SD	Range		Type I	Type II	Type III		ERCP	EUS-BD	PTD			Biliary first	Simultaneous	Duodenal first	Mean	Median	SD	IQR	Range
Gutierrez [83], 2017	retrospective	3	7	64.7	-	12.5	-	57%		NA		pancreatic	0	7	0	SEMS	LAMS	0	7	0	-	106	-	66-235	-
Kim [84], 2017	retrospective	1	58	61.1	-	12	-	38%		NA		pancreatic, duodenal, gastric, bile duct, gallbladder, metastatic	58	0	0	SEMS	cSEMS	58	0	0			NA		
Lee [85], 2017	retrospective	1	12	67.5	-	-	38-82	50%	4	3	5	pancreatic, ampullary, bile duct, gallbladder	11	0	1	SEMS	uSEMS		6	6			NA		
Matsumoto [33], 2017	retrospective	1	81	-	66	-	41-91	40%	38	32	11	pancreatic, ampullary, gastric, bile duct, gall bladder, metastatic	62	19	0	PS, SEMS	cSEMS, uSEMS	50	31	0			NA		
Hamada [29], 2017	retrospective	16	110	68.8	-	11.5	-	52%	45	46	19	pancreatic, ampullary, gastric, bile duct, gall bladder, other	90	20	0	PS, SEMS	NA	67	29	14			NA		
Hori [16], 2017	retrospective	8	109	-	70	-	39-96	44%	23	74	12	Pancreato-biliary, gastric, other	101	0	8	SEMS	cSEMS, uSEMS	88	12	9			NA		
Rai [86], 2017 (abstract)	prospective	1	12	NA				67%		NA		NA	7	5	0	SEMS	NA		NA				NA		
Staub [32], 2018	retrospective	2	71	66.87	-	-	31-92	38%	46	21	4	pancreatic, duodenal, ampullary, other	71	0	0	PS, SEMS	NA			71			NA		
Yamao [87], 2018	retrospective	5	39	68.5	-	11.3	-	41%	11	16	12	pancreatic	25	14	0	PS, SEMS	NA	9		30			NA		

Table 9. Characteristics of included studies dealing with endoscopic double stenting

NA – not available; SD – standard deviation; ERCP – endoscopic retrograde cholangio-pancreatography; EUS-BD – endoscopic ultrasound guided biliary drainage; PTD – percutaneous transhepatic drainage; IQR – interquartile range; SEMS – self-expandable metallic stent; PS – plastic stent; cSEMS – covered self-expandable metallic stent; uSEMS – uncovered self-expandable metallic stent; LAMS – lumen-apposing metallic stent

† EUS-BD and/or PTD was performed in case of ERCP failure

‡ 13 patients underwent successful biliary cannulation with ERCP, but stent was inserted only in 11 patients

Table 10. Characteristics of included studies dealing with double surgical bypass

Surgical

Study	Design	Centers (N^0)	N^0 of pts	Age					Sex (female% of total)	Type of malignancy	Prophylactic GEA	Follow-up (days)			
				Mean	Median	SD	IQR	Range				Mean	Median	SD	Range
Levi [88], 1982	retrospective	1	18			NA			NA	pancreatic	NA				NA
Wongsuwanporn [89], 1983 (abstract)	retrospective	1	26			NA			NA	pancreatic	NA				NA
Lee [90], 1984	retrospective	1	65			NA			NA	pancreatic, ampullary	NA				NA
Parker [91], 1985	retrospective	1	13	59	-	11	-	-	0.5%	pancreatic	NA				NA
Ferla [92], 1987	retrospective	1	14	65	-	-	-	45-92	36%	pancreatic	14				NA
Singh [93], 1990	retrospective	1	70	63	-	-	-	12-88	46%	pancreatic	20				NA
Casaccia [94], 1999	prospective	1	2	-	64	-	-	53-72	33%	pancreatic	0	12.5	-	-	7-18
Hamade [95], 2005	retrospective	1	8	-	70	-	-	26-81	43%	pancreatic, duodenal, bile duct	5				NA
Hao [96], 2005	retrospective	1	22	63	-	-	-	52-76	NA	pancreatic, ampullary, bile duct, duodenal	22				NA
Khan [97], 2005	retrospective	1	2	77	-	-	-	63-90	53%	pancreatic, duodenal, gastric, bile duct	0				NA
Mortenson [98], 2005	retrospective	1	38	61	-	11	-	-	NA	NA	NA				NA
Tang [99], 2005 (abstract)	retrospective	1	35	-	69	-	-	-	62%	NA	NA				NA
Ghanem [100], 2006	prospective	1	8	-	67	-	-	26-81	59%	pancreatic	3				NA
Lesurtel [101], 2006	retrospective	1	83	64	-	11	-	-	46%	pancreatic	72	270	-	270	-
Mann [102], 2009	retrospective	1	102	-	65	-	-	36-86	39%	pancreatic, duodenal, ampullary, bile duct, metastatic	92				NA
Ausania [103], 2012	prospective	1	50	-	64	-	-	39-79	34%	pancreatic, duodenal, ampullary, bile duct, other	50	-	300	-	120-990
Lyons [22], 2012	retrospective	1	60	65	-	-	-	-	45%	pancreatic	50				NA

Table 10. Characteristics of included studies dealing with double surgical bypass (cont.)															
Surgical															
Study	**Design**	**Centers (N^0)**	**N^0 of pts**	**Age**					**Sex (female% of total)**	**Type of malignancy**	**Prophylactic GEA**	**Follow-up (days)**			
				Mean	**Median**	**SD**	**IQR**	**Range**				**Mean**	**Median**	**SD**	**Range**
Malde [104], 2012 (abstract)	retrospective	1	48	-	-	-	-	-	40%	pancreatic	NA				NA
Valeshabad [64], 2013 (abstract)	retrospective	6	3*	65,9	-	-	-	-	49%	NA	0				NA
Bartlett [17], 2014	retrospective	315	351	66	-	-	59-75	-	45%	pancreatic	NA				NA
Kohan [21], 2014	prospective	1	42	64	-	-	-	38-88	56%	pancreatic	28				NA
Kofokotsios [105], 2015	retrospective	1	11	-	70	-	-	48-77	36%	pancreatic	11				NA
Williamson [20], 2015	retrospective	2	59	-	66	-	-	39-81	NA	pancreatic, duodenal, ampullary, bile duct, other	59				NA
Fu [34], 2016	retrospective	1	31	61	-	9,4	-	-	NA	pancreatic	31				NA
Giuliani [106], 2016 (abstract)	retrospective	1	12	-	67	-	-	41-83	42%	pancreatic	0	-	323	-	30-3296

Table 10. Characteristics of included studies dealing with surgical double bypass

SD – standard deviation; IQR – interquartile range; GEA – gastroenteric anastomosis; NA – not available

* Surgery was performed in case of ERCP failure

Therefore, 80 studies were included in the pooled analysis: 8 prospective and 72 retrospective observational studies (Tables 9 and 10). No randomized controlled trials were available. Fifty-five studies including 5,026 patients reported about double stenting, 22 with 1,080 patients about double bypass, and only 3 about both the techniques (including 64 patients who underwent double stenting and 93 with double bypass) [20, 34, 64]. However, insufficient outcome reporting hindered the direct comparison of outcomes. Underlying malignancy was specified in 73% of cases: pancreatobiliary cancer in 4,149, gastroduodenal cancer in 212, metastatic cancer in 49, and other malignancies in 144 cases. Duodenal stenosis was located above and at the ampullary level in 43.7% each and below the ampulla in 12.5% of reported cases. Seventeen studies reported about prophylactic GEA, and it was applied in 69% of surgical cases. In case of double stenting, biliary stenting was performed via ERCP in 69%, PTD in 17%, and EUS-BD in 14% of patients. Biliary and duodenal stents were placed simultaneously in 25.5% of reported cases; biliary stenting preceded duodenal in 45.7% and followed it in 28.8%. The mean interval between stent placements was 114 ± 106 days (201 ± 173 days for biliary first and 74 ± 75 days for duodenal first). In post hoc analysis, the mean age of patients who underwent double stenting was significantly higher (67.9 years [95% CI: 67.0–68.9 years; I^2 = 88.0%]) than that of those who underwent double bypass (63.7 years [95% CI: 62.3–65.0 years; I^2 = 89.2%]). Gender distribution showed no difference between the groups.

5.2.2. Risk of bias assessment

Risk of bias of individual studies was assessed with the NOS (see Table, Supplementary Digital Content 1, http://links.lww.com/CTG/A243). Baseline characteristics were reported in almost all journal articles but were only partially available in conference abstracts (Tables 9 and 10). Clinical success rate's definition varied, and other outcome measures were defined mostly uniformly [16, 29, 33–36]. Although assessment of different outcomes was reported reliably in more than 90%, outcomes were reported heterogeneously (see Tables, Supplementary Digital Content 2 and 3, http://links.lww.com/CTG/A244 and http://links.lww.com/CTG/A245). Adequate follow-up data were available in only approximately 40%, but the length of follow-up was appropriate for assessment of outcomes, when reported.

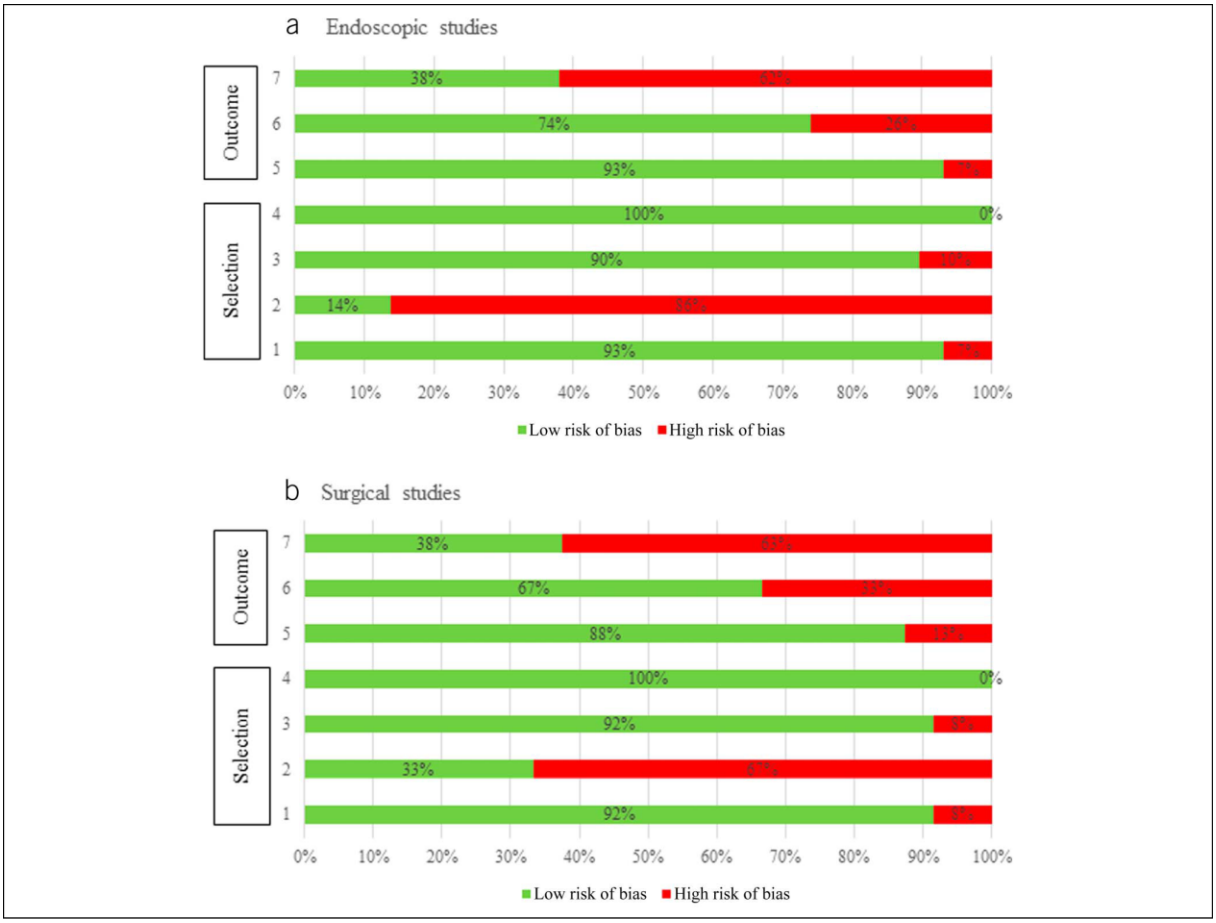

Figure 12. Risk of bias assessment of individual studies according to the modified Newcastle–Ottawa Scale. (a) Endoscopic studies and (b) surgical studies.

Each item was rated as "high risk" (zero stars) or "low risk" (one star). Selection domain: (i) representativeness of the exposed cohort, (ii) selection of the nonexposed cohort, (iii) ascertainment of exposure, and (iv) demonstration that the outcome of interest was not present at the start of study. Outcome domain: (v) assessment of outcome, (vi) length of follow-up, and (vii) adequacy of follow-up.

5.2.3. Meta-analytical calculations

5.2.3.1. Technical and clinical success

Overall technical and clinical success rates of double stenting were 97% (95% CI: 95%–99%) and 92% (95% CI: 89%–95%), respectively. Subgroup analysis of different biliary stenting modalities found no difference in technical and clinical success (see Figures, Supplementary Digital Content 4 and 5, http://links.lww.com/CTG/A246 and http://links.lww.com/CTG/A247). Considering frequent prophylactic GEA use during surgical double bypass, technical and clinical success in this group could only be assessed for biliary bypass. No difference was found between technical success of endoscopic stenting and surgical

biliary bypass (see Figure, Supplementary Digital Content 6, http://links.lww.com/CTG/A248), whereas clinical success of endoscopic biliary stenting was higher (97% [95% CI: 94%–99%; I^2 = 67.3%] vs 86% [95% CI: 78%–92%; I^2 = 19.9%], respectively). Technical and clinical success of duodenal stenting was 99% (95% CI: 97%–100%) and 97% (95% CI: 94%–99%), respectively.

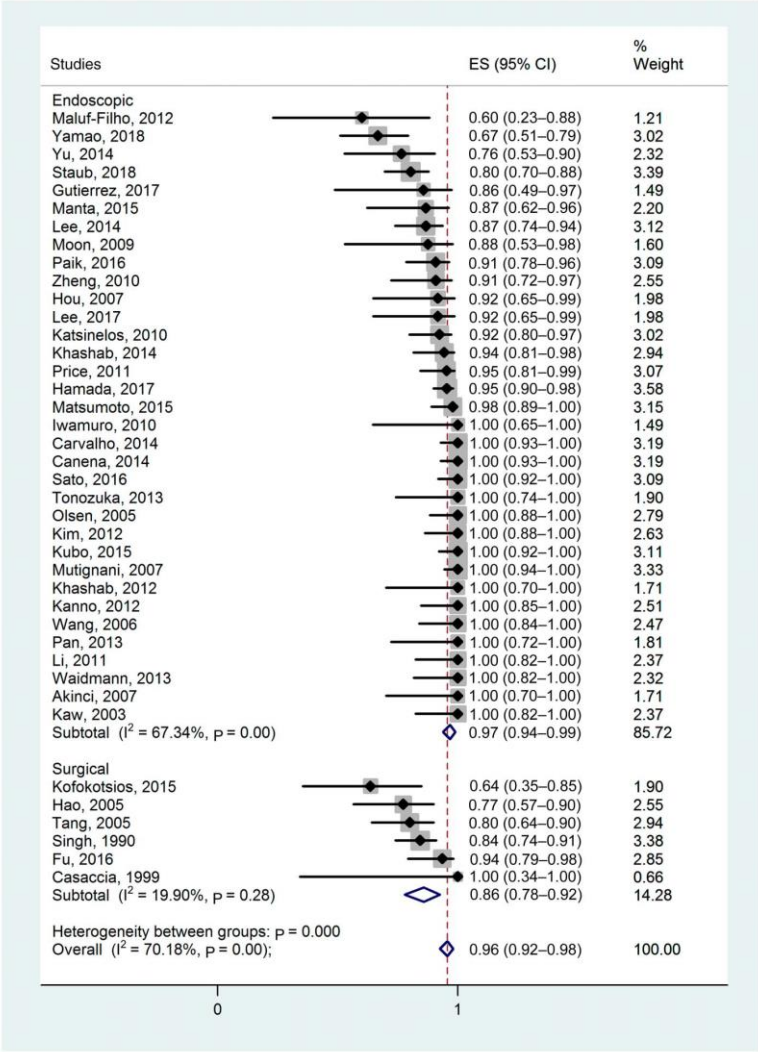

Figure 13. Clinical success of biliary bypass in case of double stenting and double surgical bypass (including cases with prophylactic GEA).

5.2.3.2. Adverse event rate

Double stenting was associated with less adverse events compared with surgical double bypass (13% [95% CI: 8%–19%; I^2 = 86.3%] vs 28% [95% CI: 19%–38%; I^2 = 89.3%]).

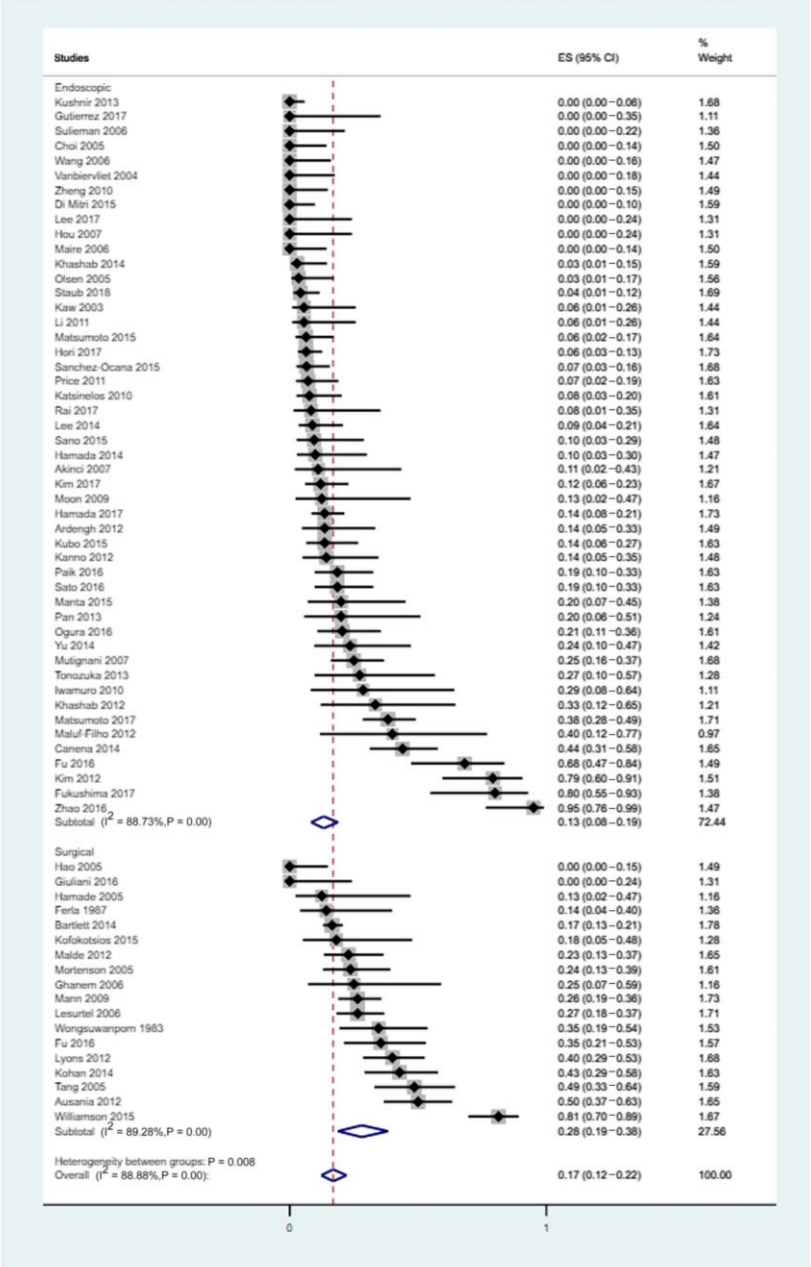

Figure 14. Adverse events related to double stenting and double surgical bypass.

See Table (Supplementary Digital Content 7, http://links.lww.com/CTG/A249) for details of adverse events associated with double stenting and double bypass. Adverse events occurred at 67.8 days on average (95% CI: 5.1–128.4 days) post-procedure. There was no difference between adverse events' occurrence time after double stenting and double bypass (52.8 days [95% CI: 23.7–129.3 days] vs 108.7 days [95% CI: 123.2–340.6 days], respectively). ERCP was associated with the least adverse events (3% [95%CI: 1%–6%; I^2 = 42.8%]), followed by PTD (10% [95% CI: 0%–37%; I^2 = 90.2%]) and EUS-BD (23% [95% CI: 15%–33%; I^2 = 1.8%]). The difference was significant between ERCP and EUS-BD.

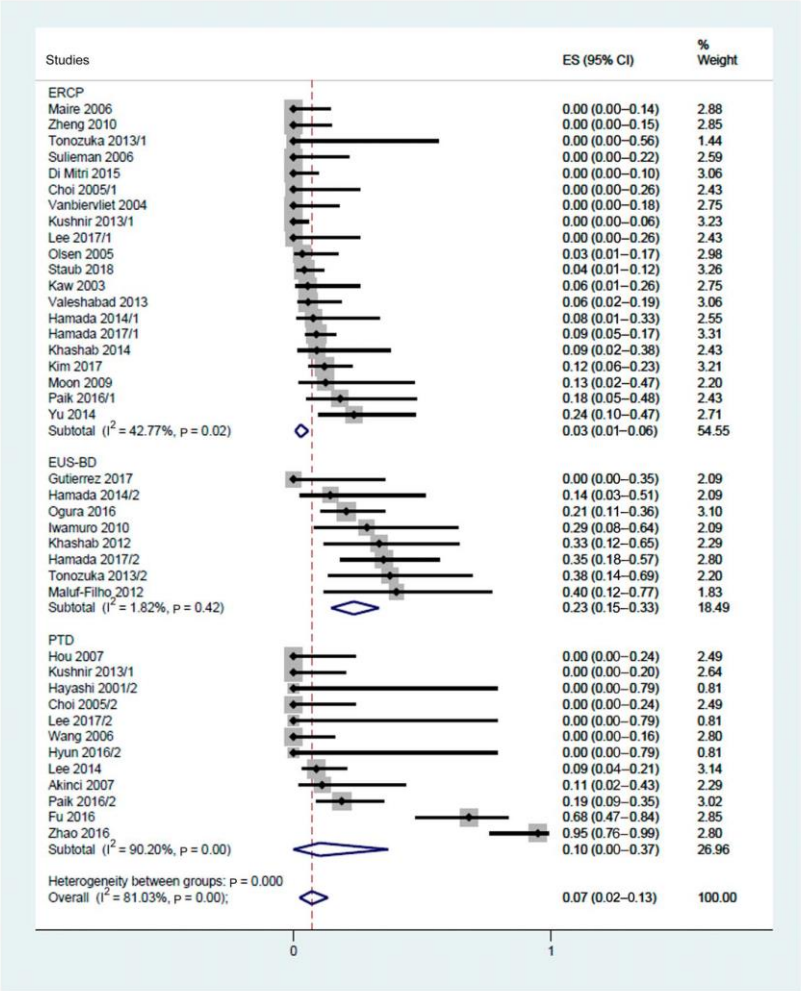

Figure 15. Adverse events related to ERCP, EUS-BD, and PTD.

5.2.3.3. Reintervention rate

More reinterventions were needed after double stenting than after double bypass (21% [95% CI: 16%–27%; I^2 = 79.4%] vs 10% [95% CI: 4%–19%; I^2 = 90.2%]) (see Figure, Supplementary Digital Content 8, http://links.lww.com/CTG/A250). In subgroup analysis, reinterventions were least likely to be necessary after PTD (4% [95% CI: 0%–15%]), followed by ERCP and EUS-BD (16% [95% CI: 9%–24%] and 32% [95% CI: 15%–50%], respectively).

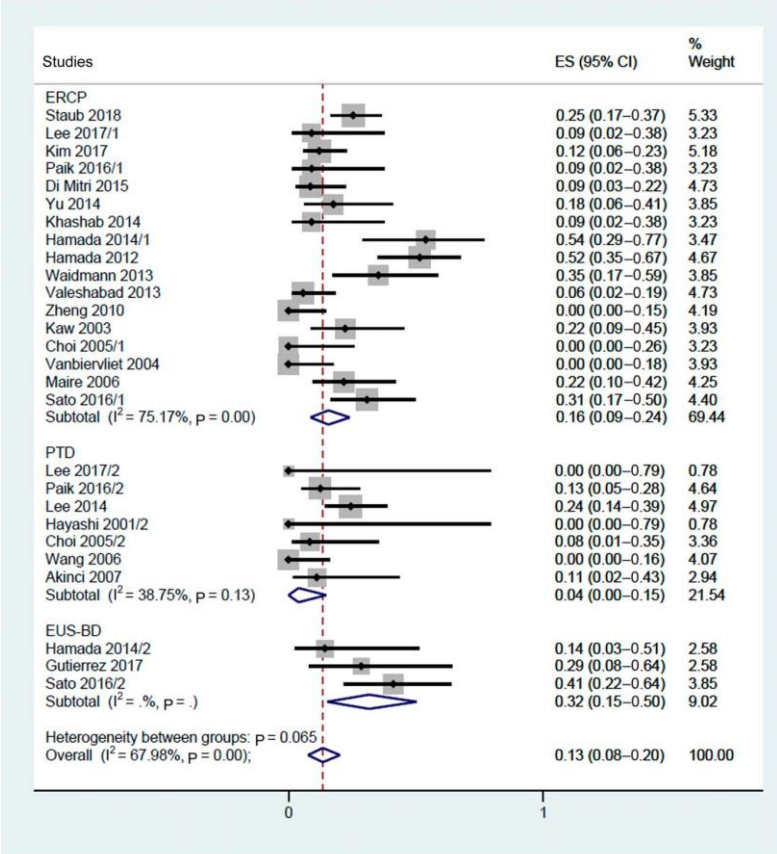

Figure 16. Reintervention rate related to ERCP, PTD, and EUS-BD.

Although only 2 surgical studies specified whether reintervention was necessary because of RBO or RDO [64, 101], several endoscopic studies investigated RBO and RDO separately (see Table, Supplementary Digital Content 2, http://links.lww.com/CTG/A244). RBO was reported in a total of 285 cases, whereas RDO was reported in 100 cases. The mean time until the occurrence of RBO and RDO was 167.3 days (95% CI: 93.0–241.6 days; I^2 = 96.0%) and 106.0 days (95% CI: 56.7–155.3 days; I^2 = 51.1%), respectively.

5.2.3.4. Survival

Cumulative mean survival of patients after double stenting was 156.4 days (95% CI: 128.3–184.5 days). Subgroup analysis of the different biliary stenting methods as part of double stenting revealed no difference in mean survival (see Figure, Supplementary Digital Content 9, http://links.lww.com/CTG/A251). A small number of surgical studies and frequent GEA use in the surgical cohort prevented comparison of survival in the endoscopic and surgical cohorts.

6. DISCUSSION

6.1. Assessment of staging accuracy of ERUS in patients with rectal cancer

6.1.1. Retrospective assessment of staging accuracy of ERUS in rectal cancer compared to histopathological results after surgical resection in terms of depth of tumor invasion and lymph node involvement

The overall accuracy of ERUS in determining the depth invasion of the primary tumor (T-stage) was found to be 72% in the patient group that did not receive CRT, with Cohen's kappa coefficient indicating moderate correspondence, which complies with the international data [10, 107]. According to a multicenter study performed in Germany, the overall accuracy of ERUS was determined as 73.1% for hospitals performing >30 ERUS/year [10]. This rate was accomplished in our center as well. Overstaging was the most frequent mistake in all three patient groups (16%-27%-57%). The reason for this might be the so-called peritumoral inflammatory reaction, which cannot be distinguished endosonographically from the tumor itself. [108, 109] Understaging was mainly due to microscopic tumorous infiltration, which is impossible to detect with endosonography. It might as well occur in extensive tumors and when the upper part of the lesion is inaccessible for the probe. As the depth of invasion varies throughout the longitudinal extension of the tumor, an impairment in accuracy occurs when the tumor tissue cannot be examined as a whole. [110, 111] Differentiating between T1/T2 and T2/T3 tumors can raise further problems, as the penetration through the wall layers is often ambiguous; it might only be indicated by the irregularity of the surface between the layers. In case of extensive tumors, determining submucosal involvement might as well be difficult, as it can be easily mistaken for the widening of the muscular propria. [110, 111] Differentiating between T2/T3 tumors plays an important role in clinical decision-making, as the necessity of CRT depends on it. Out of the 67 cases five pT3 lesions were underestimated (three were reported as uT1 and two were reported as uT2); The overall clinical stage for one of the uT2 tumors was uT2N1. This means that, based solely on the endosonographic staging, 94% of the patients could receive adequate therapy, appropriate for the pathological stage. A significant variation in sensitivity was observed between T1-T2 and T3 stages in patients who underwent surgery without neoadjuvant CRT (75%-73% and 58%). It is ascertainable that while ERUS is a good diagnostic choice in case of early rectal malignancies, MRI is recommended for staging advanced lesions, due to its higher sensitivity. [2, 112, 113] A significant difference was shown in terms of all investigated parameters between the patient group that underwent surgery alone and the one that received oncological treatment. This might be a result of the effect of chemo-

irradiation on tissues: inflammation, fibrosis, and necrosis occurring as a consequence of the treatment can hardly be differentiated endosonographically from the tumorous tissue. [114, 115] The overstaging rate was 27–57% for Groups II and III, respectively. Considering the lower positive predictive value of the method and the fact that the level of yuT-ypT correspondence is only sufficient ($\kappa = 0.390$), it can be stated that ERUS itself is not appropriate for restaging after CRT. The yuT stage is not acceptable for evaluating the effectiveness of neoadjuvant therapy. ERUS performed prior to CRT reported a more advanced lesion than the final stage in a great percentage of the cases. Effective neoadjuvant treatment leads to a decrease in the tumor stage, which results in a discrepancy in the level of uT-pT correspondence and the overstaging rate compared to the patients who received no CRT. [10]

The accuracy of N-staging was only 62%, and neither the sensitivity nor the positive predictive value of ERUS is acceptable. Therefore, it is inappropriate for the identification of metastatic lymph nodes. Currently, this is the greatest limiting factor of ERUS in rectal cancer staging. The method can only draw conclusions from the morphological features of lymph nodes to decide whether they are metastatic or not; however, there is no consensus about the staging criteria to be used. [109, 116] Most questions are being raised about the determination of the lymph node size that should be considered to be pathologic, as normal sized lymph nodes may also contain metastatic deposits, and, on the other hand, lymph node enlargement is not necessarily due to metastasis formation. The facts that the evaluation of the perirectal fat is of limited availability on higher frequencies and that only lymph nodes adjacent to the rectum can be investigated with ERUS raise further problems. [111]

Another limiting factor of ERUS is its operator-dependency. At the same time, this also means that in the hands of an experienced diagnostician it is a reliable method providing a great amount of information. [117, 118] According to our results, the learning curve is relatively short; after 30 examinations it is possible to evaluate the depth invasion of rectal cancers with confidence. Above this case load, the staging accuracy reached a significantly higher level (from 64% to 79%), which complies with the international statistics. [10, 119] Moreover, in the later period, after reaching the plateau phase of the learning curve, the sensitivity of ERUS for each tumour stage exceeded the results reported from a multicentre study from Germany (80%-83%-75% versus 58%-64%-71%). [10] The reason for the better results in the initial period (first 10 examinations) after the introduction of ERUS to our institution might be the fact that several experts were present at the examinations and the endosonographic images were

interpreted based on a common consensus. This could be a promising possibility for increasing the accuracy of ERUS in case of investigators without sufficient experience. Inevitably, regular practice is also crucial for high-level staging.

Flexible probes have several advantages over rigid ones: they are easier to maneuver with; due to their smaller diameter they can traverse a narrower lumen and to access higher locations than the rigid ones. Besides, a great advantage of flexible devices is the possibility of visual control, which is not available with rigid ("blind") probes. [110] However, our results seem to support the fact that they stay behind the rigid probes in terms of both T- and N-staging. Thus, rigid probes are still favorable over flexible ones, due to their lower costs and higher accuracy. [120]

6.1.2. Assessment of the influence of neoadjuvant treatment on the staging accuracy of ERUS in rectal cancer

According to our results, in terms of T-staging, accuracy of ERUS in rectal cancer restaging after neoadjuvant CRT falls short of the one determined for the control group, i.e. patients who had not received neoadjuvant treatment (61% and 70%, respectively). The frequency of overstaging the depth of invasion is also significantly increased (31%) after neoadjuvant treatment. ERUS was most accurate in case of T3 tumors (T-stage was correctly assessed in 79% of these cases), as opposed to the control group, where staging was more reliable in case of early tumors (staging was accurate in 73% and 75% of T1 and T2 tumors, respectively). In terms of N-staging, neoadjuvant CRT had no impact on the staging accuracy (63% and 61% for the control group and the one that received CRT, respectively). Specificity of ERUS in N-staging (82%) was higher in both groups than its sensitivity (15% and 18% for the control group and the one that received CRT, respectively).

According to the literature, accuracy of ERUS in terms of restaging depth of invasion varies in a wide range between 27% to 75%. [114, 115, 121–130] Marone et al. compared staging accuracy of ERUS in advanced rectal cancer to that of restaging after neoadjuvant treatment over a 6-year period with the inclusion of 85 patients. They reported a significant deterioration in results after CRT in terms of T-staging (61% compared to 86% in case of initial staging), while staging accuracy of nodal staging remained nearly the same (58% vs. 59%). [124] Correspondence to the histopathologic T-stage was reported to be 54% in the prospective study of Pastor et al. [125], 46% in the study conducted by Mezzi et. al. assessing results of 39 patients [126], and 48% according to Vanagunas et. al. who examined 82 patients and found a

38% rate of overstaging [127]. Restaging advanced rectal cancers after neoadjuvant treatment, Huh et al. reported an even lower staging accuracy for T-staging (38.3%) [115]. In our study, proportion of overstaged cases (36.7%) was almost as high as that of accurately staged ones. None of the 10 tumors determined to be ypT0 stage based on the histopathologic assessment could be staged correctly with ERUS. Identification of ypT0 tumors was also considered to be a challenge according to Radovanovic et al. who reported correct stage with ERUS only in one out of five cases, even with a 75% overall accuracy for T-restaging. [114] Assessing staging accuracy separately for each T-stage, Martellucci et al. found exceedingly high accuracy in case of T3 tumors (96%). [128] This was further confirmed by the meta-analysis of Zhao et al. that calculated staging accuracy of T3 tumors significantly higher than that of the overall T-restaging (79.4% vs. 54.6%, respectively) analyzing data about restaging between 1985 and 2013. [122]

Tissue changes resulting from CRT might be the reason of the lower staging accuracy after oncologic treatment as peritumoral inflammation, edema, fibrosis, and necrosis of the tumor tissue may develop as a consequence of the treatment. As a result, the integrity of the wall structure impairs further resulting in a difficulty in the identification of the wall layers. [127] Fibrotic tissue changes resulting from CRT appear hypoechoic on the ultrasound image, therefore fibrotic areas can hardly be distinguished from the tumor tissue itself. [129] Tissue regeneration after CRT takes a considerable time and certain areas are not recovering at all, therefore, timing of restaging can also be an important factor in the accuracy. [123]

Accuracy of N-restaging is reported to be between 39% and 83% in the literature [114, 115, 121–130], a review study determined average accuracy to be 70% [131]. Usually in the initial staging, the accuracy of N-staging falls short to that of T-staging [121], but this difference is not significant in case of restaging, and impairment of staging accuracy can be observed less frequently. In certain cases, N-restaging was even more accurate than initial N-staging. [124] The meta-analysis of 11 studies by Zhao et al. calculated sensitivity and specificity of nodal staging after CRT to be 0.48 (0.42–0.54) and 0.81 (0.78–0.84), respectively. [122] Specificity was found to be higher by Pastor et al. (91%), however, sensitivity was only 39%. [125]

The main challenge in determining nodal involvement is that assumptions regarding metastatic involvement of lymph nodes can only be made based on morphological features (size, shape, peritumoral location, hypoechoic appearance). On the other hand, 95% of lymph nodes are smaller than 5 mm after neoadjuvant CRT and 50% of metastatic lymph nodes are smaller than 3 mm [132], which greatly limits assessment of nodal involvement [12]. The ability

of ERUS to visualize only perirectal and mesorectal lymph nodes is another important limiting factor. [121]

Limitations of our study include its retrospective nature and relatively small case number that is partly due to the fact that being a tertiary endoscopic center, only ERUS examinations were performed at our institute and both the surgical resection and pathologic assessment took place elsewhere. Although initially ERUS-staging was based on a consensus of several experts, the learning curve also needs to be considered when interpreting the results.

6.2. Assessment of feasibility of EUS-BD as part of double stenting in the case of combined malignant biliary and duodenal obstruction in a systematic review and meta-analysis

Although double stenting for combined malignant biliary and duodenal obstruction has been a treatment option for 25 years [28], its place in the therapeutic algorithm has not been clearly specified, and reliable efficacy data are still lacking because of the rare concomitant occurrence of these conditions [29]. To the best of our knowledge, this is the first systematic review and meta-analysis dealing with the feasibility of double endoscopic stenting in this scenario. According to our findings, high cumulative technical and clinical success rates can be achieved with double stenting in this difficult-to-treat population. Success rates were comparable with traditionally applied surgical bypass regarding biliary bypass; moreover, clinical success rate of endoscopic biliary bypass was even higher than that of surgery. The importance of this finding lies in the fact that those underwent double stenting were significantly older compared with those with double bypass, suggesting a potential superiority of double stenting in the elderly. The adverse event profile of double stenting was favorable over that of double bypass in terms of not only numbers but also severity (death was only reported in the surgical cohort). However, the occurrence of adverse events depends on the method of biliary stenting: ERCP was associated with significantly fewer adverse events than EUS-BD. A previous meta-analysis about EUS-BD reported a similarly high cumulative adverse event rate (23.32%). [133] The high proportion of ERCPs in the double stenting cohort may also contribute to the overall adverse event rate. However, double stenting was associated with higher reintervention rate independently of the biliary stenting method. Duodenal stent placement alone was found to require more reinterventions than surgery [27], and a recent multicenter randomized controlled trial comparing ERCP and EUS-BD as the primary treatment modality of malignant biliary obstruction reported reintervention rates of 42.6% and 15.6%, respectively [26]. These facts, and plastic biliary stents' use in numerous studies and

inclusion of early studies dealing with double stenting, might also contribute to high reintervention rates. [134] Considering cumulative survival and mean time until RBO or RDO, generally one reintervention will be necessary for patients undergoing double stenting. Nevertheless, PTD and EUS-BD were mostly second-line treatments after ERCP failure, and the exact number of sessions required to stent placement (especially for PTD, when stenting is often performed in a second session after temporary external biliary drainage) was generally not reported; therefore, complete burden of interventions cannot be reliably assessed. Common prophylactic GEA use in double bypass also needs to be considered. Because it is associated with a lower risk of development of duodenal stenosis [18, 19], lower rates of reinterventions for RDO are expected in the surgical cohort, which consists mostly of cases with prophylactic GEA. Therefore, cumulative overall reintervention rates might also be lower; however, details of conditions requiring reintervention in this cohort were generally not reported. Another aspect related to prophylactic GEA use is the impossibility to compare overall success rates of the cohorts because technical and clinical success of duodenal bypass is not applicable in such cases.

The main limitation was the lack of head-to-head comparative studies assessing double stenting and double bypass; therefore, only an indirect comparison could be provided with significant heterogeneity between studies. Different timing of biliary and duodenal interventions and frequent second-line use of PTD and EUS-BD increase heterogeneity further. Numerous studies were retrospective or not available as full text, and being a relatively rare entity, a huge part of literature (particularly for EUS-BD) consists of case reports and case series. Results of double stenting and double bypass must be compared with caution because the cohorts may not consist of the exact same population (double stenting was traditionally an alternative for patients unfit for surgery). The higher age of those underwent double stenting seems to be confirming this; however, objective measures to assess operative risk (e.g., the American Society of Anesthesiologists classification system), which might serve as a basis for such a distinction, were not reported.

7. CONCLUSIONS

Our retrospective study investigating the accuracy of ERUS in rectal cancer staging collected the most extensive data in this topic in the Central and Eastern European region so far and found ERUS to be of high accuracy in accordance with the literature. No significant difference was found between the accuracy of the modality in Central and Western European countries. After the relatively short learning curve, our results were even above the Western European standards, although they only represent the performance of a single center not a countrywide analysis. Considering its simplicity, efficacy, low costs, and the fact that it is relatively well tolerated by patients, ERUS can be the method of choice for determining the depth invasion of the primary lesion in early malignancies, especially in regions where access to MRI is limited. However, it cannot be recommended for the evaluation of downstaging because of the decreased efficiency resulting from the inflammatory tissue reaction after CRT.

The effect of neoadjuvant treatment was further investigated in our second retrospective study where the staging accuracy of ERUS in rectal cancer was compared in those who received neoadjuvant treatment and those who were operated without oncologic treatment. Accuracy of T-staging impairs as a result of CRT, however, ERUS proved to be particularly accurate in restaging T3 tumors after neoadjuvant treatment. The modality is inappropriate for the identification of ypT0 stage and thereby complete regression cannot be determined with ERUS. On the other hand, neoadjuvant treatment has little impact on the accuracy of N-staging, but it should be noted that ERUS is not completely reliable even in the initial nodal staging. Therefore, ERUS is not feasible for restaging rectal cancer after neoadjuvant CRT, it cannot serve as a basis for surgical planning, it can only assess the tendency of change in tumor size.

Our systematic review and meta-analysis investigating the feasibility of double endoscopic stenting for combined malignant biliary and duodenal obstruction concluded that high technical and clinical success rates, especially the higher clinical success rate of endoscopic biliary stenting compared with surgical bypass, and the lower adverse event rate suggest a justification of minimally invasive techniques in this setting, but high reintervention rates should also be acknowledged. Investigating the different biliary stenting methods further, technical and clinical success rate of double stenting with EUS-BD as the biliary access method were both outstandingly high. Nevertheless, based on the currently available literature data and considering the relatively high adverse event rate and frequent need for reinterventions associated with EUS-BD, ERCP can be still recommended as the first-choice method for biliary

stenting also in case of duodenobiliary stenosis, but high reintervention rates and frequent sequential development of duodenal stenosis do not allow to make general recommendations. Caution should be taken because of the limited and substantially heterogeneous available evidence. To define the cohorts that can benefit most from double stenting, there is a pressing need for multicentric, prospective, comparative studies with well-defined outcome measures and carefully chosen cohorts. Aspects such as prophylactic GEA use, selection of patients "unfit for surgery" based on the well-defined scoring systems for risk stratification, and the possible use of EUS-BD as the primary treatment option should also be considered.

ACKNOWLEDGEMENTS

I would like to extend my sincere thanks to all people who have helped and inspired me during my doctoral study.

I would like to extend my deepest gratitude to my supervisor **Dr. Zoltán Szepes** for all his support and guidance, as well as for his valuable ideas and remarks, and the insight he gave into endoscopic ultrasound. In addition, a special thank goes to **Dr. Renáta Bor** for her constructive advices, understanding, and encouragement throughout the duration of this project. I appreciate all their contributions of time, ideas, and funding to make my Ph.D. experience productive and stimulating.

I am deeply grateful to **Prof. Dr. Tamás Molnár** and **Dr. Klaudia Farkas** for their assistance, practical suggestions, and constructive advices. Furthermore, I would like to recognize the assistance that I received from the members and assistants of the colorectal study group, from **Dr. Kata Szántó**, **Dr. Mariann Rutka**, **Dr. Anita Bálint**, **Dr. Ágnes Milassin**, **Tibor Tóth**, **Dr. Tamás Resál**, **Dr. Daniella Pigniczki**, **Péter Bacsur**, **Csilla Tóth-Káli** and **Gabriella Pócsik**.

I am grateful to **Prof. Dr. Tibor Wittmann**, **Prof. Dr. György Ábrahám and Prof. Dr. Csaba Lengyel**, former and current heads of the First Department of Medicine, University of Szeged who gave me the opportunity to work in their Department.

Lastly, I would like to thank my **family** and **friends** for all their love, never-ending support, endless patience, and encouragement.

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FIGURES

TABLES