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

Ph.D. THESIS

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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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II. **Fábián A**, Bor R, Bálint A, Farkas K, Milassin Á, Rutka M, Tiszlavicz L, Nagy F, Molnár T, Szepes Z: [Neoadjuvant treatment as a limiting factor to rectal ultrasonography].
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III. **Fábián A**, Bor R, Gede N, Bacsur P, Pécsi D, Hegyi P, Tóth B, Szakács Z, Vincze Á, Ruzsics I, Rakonczay Z Jr, Erőss B, Sepp R, Szepes Z: Double Stenting for Malignant Biliary and Duodenal Obstruction: A Systematic Review and Meta-Analysis.
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LIST OF FULL PAPERS NOT RELATED TO THE SUBJECT OF THE THESIS

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Number of full publications**:**	**34**
Cumulative impact factor**:**	**88.759**

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

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. INTRODUCTION

Gastrointestinal (GI) malignancies are among the most frequent malignancies worldwide 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. 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. 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. Recent advancements in EUS technology have led to increasingly broadening indications: besides the relatively firm diagnostic indications, therapeutic indications have also expanded greatly. While certain indications are well-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.

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 ESMO guideline 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. 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. 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%. 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. 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. 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. 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. 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.

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, while duodenal obstruction's rate has also recently risen to 38% due to oncologic advances and consequently longer patient survival. 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. 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. Prophylactic GEA use reduces the chance for developing duodenal obstruction without impairing short-term outcomes in pancreatic and periampullary cancer. Therefore, most studies reporting double surgical bypass involve cases where biliary bypass was combined with prophylactic GEA. 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. 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). 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. 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. Combined biliary and duodenal stent placement (double stenting) was first reported in 1994. 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. Nevertheless, efficacy data of double stenting (particularly that performed as a combination of a duodenal stent insertion and EUS-BD) are limited, and its place in the therapeutic algorithm is not clearly specified.

2. AIMS

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

2.1.1. 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

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

2.2. 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

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

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

3. PATIENTS AND METHODS

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

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. 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 after full bowel preparation. 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 experts. Initially, several experts familiar with ultrasound diagnostics were present during the examinations, and images were interpreted based on their common consensus. Staging was based on the TNM classification. The endosonographically defined clinical stage was indicated with uT and uN. Based on 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 update tumor stage before surgery, and to estimate downstaging, if there had been any. The final stage was determined after histopathological procession of the surgical specimens (pT, pN and ypT, ypN in case of patients who received neoadjuvant treatment). Data were collected from MedSolution patient recording system. Only patients with available histopathological results about the final tumor stage were included. Patients were divided into three groups depending on neoadjuvant treatment. Patients in the first group underwent surgical intervention without previous oncological treatment. ERUS was performed after CRT 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 disease stage. 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. Overstaging and understaging rates were investigated as well. 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.

3.1.2. 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 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.

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. Protocol and registration

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

3.2.2. 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 (GEA 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).

3.2.3. 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)." Final search was performed on July 17, 2018. Reference lists of included articles were also investigated to capture all relevant studies.

3.2.4. Study selection and data collection process

After 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.

3.2.5. Risk of bias assessment

Risk of bias was assessed using a modified version of the Newcastle–Ottawa Scale (NOS) by 2 independent review authors. 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).

3.2.6. 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. Statistical analyses were performed with Comprehensive Meta-Analysis Software and STATA. Forest plots displayed the results of the meta-analysis.

3.2.7. 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. 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, whereas others considered clinical success when a 25% or 50% reduction in bilirubin was observed or only stated improvement of biliary obstruction symptoms without further clarification. Clinical success of duodenal stenting, when clarified other than clinical improvement of symptoms, mainly referred to a better score on the gastric outlet obstruction scoring system. 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 (incl. 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), 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.

4. RESULTS

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

In the six-year study period, a total of 647 ERUS examinations were performed. 311 of them 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 ERUS staging 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 oncologic 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).

4.1.1.1. Accuracy of T-staging

There was a significant difference in T-staging accuracy between the three groups. The correspondence was highest (72%) in 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%). In this patient group, 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 of ERUS was lower after neoadjuvant treatment (64%) with more frequent overstaging (27%). 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. Overstaging rate was prominently high in this group (57%).

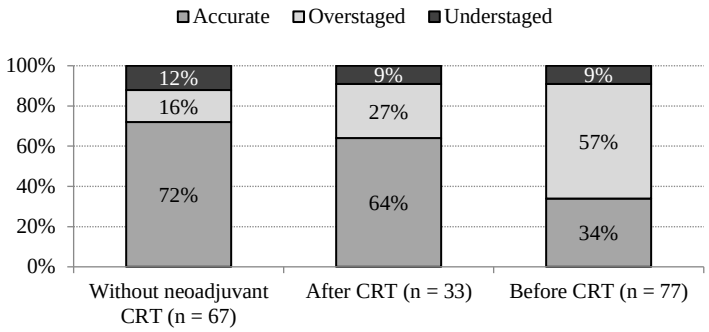

Figure 1. Accuracy of T-staging in each patient group

In most patients who did not receive CRT, early stage tumors were detected (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 PPVs 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.

	Without neoadjuvant treatment (N=67)			After neoadjuvant treatment (N=33)		
	uT1	uT2	uT3	yuT1	yuT2	yuT3
uT–pT correspondence (κ coefficient)	0.465	0.411	0.606	0.218	0.415	0.525
Sensitivity	75%	73%	58%	20%	67%	82%
Specificity	74%	80%	96%	96%	83%	63%
PPV	85%	42%	78%	50%	60%	70%
NPV	61%	94%	91%	87%	87%	77%

Table 1. Accuracy of ERUS for each T stage

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 with no residual tumor tissue in the resected tissue. None of these could be identified endosonographically; lesions were overestimated. 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 ypT3, and the sensitivity was 82%.

4.1.1.2. 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%). ERUS could more reliably recognize the absence of lymph node metastases than their presence.

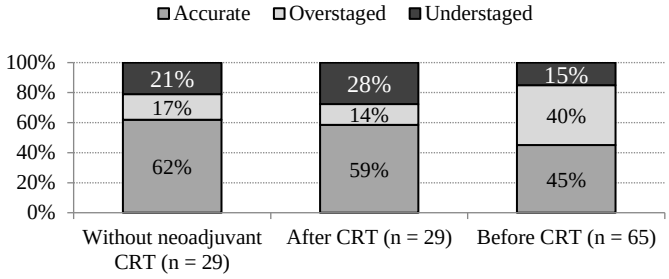

Figure 2. Accuracy of N-staging in each patient group

	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 2. Accuracy of N-staging in each patient group

4.1.1.3. 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. The uT-pT correspondence was found to be significantly higher in the later period (79% vs. 64%, p = 0.034) with both understaging and overstaging rates decreasing (from 15% to 9%, and from 21% to 12%, respectively). Investigating only the cases from the later period, the sensitivity of ERUS reached 75% in all T-stages. All 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 3. 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. Our case number was insufficient for determining the learning curve of the N-staging.

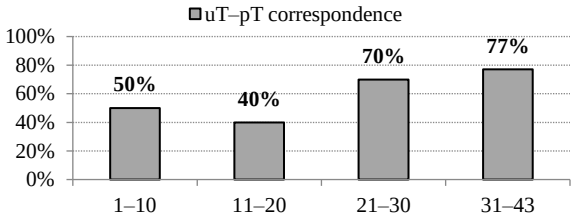

Figure 3. The performance of a single examiner after each 10 examinations

4.1.2. 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 ERUS 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, 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).

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 (53%) after neoadjuvant treatment (proportion of ypT0, ypT1 and ypT2 was 8%, 14% and 25%, respectively). After CRT, 61% of yuT and ypT stages corresponded to each other with overstaging being more frequent than understaging. Accuracy of ERUS was found to be lower compared to the control group, but the difference was not significant at $p<0.05$ ($p=0.077$). 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. Sensitivity, specificity, PPV and NPV of N-staging after CRT were 18%, 82%, 33% and 67%, respectively, whereas in the control group, 15%, 82%, 25% and 71%, respectively.

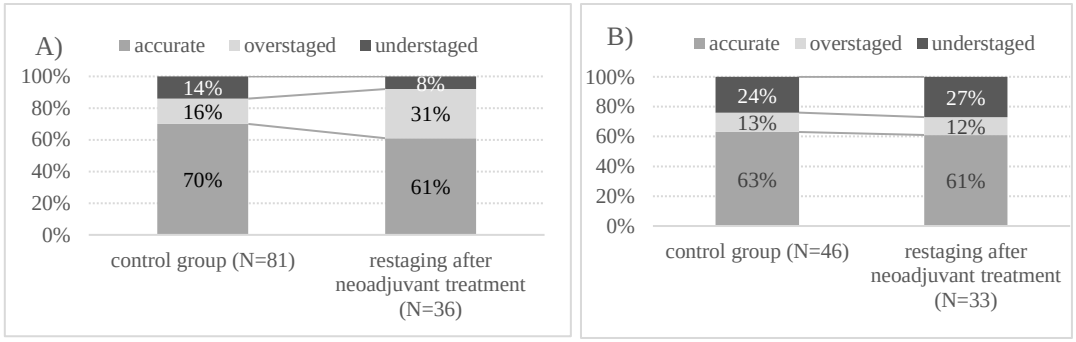

Figure 4. Accuracy of T-staging (A) and N-staging (B) in case of initial staging (control group) and restaging after neoadjuvant treatment

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 not be confirmed in any of the 3 cases. In contrast, early-stage tumors were detected more frequently in the control group (73% and 75% for pT1 and pT2, respectively).

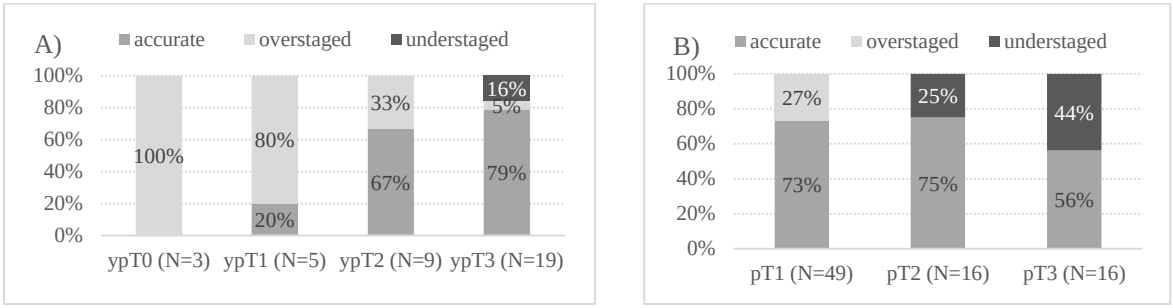

Figure 5. Staging accuracy of ERUS after neoadjuvant treatment (A) and initially (control group) (B) for each T-stage

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. Study selection and characteristics

A total of 2,765 records were identified through 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. Therefore, 80 studies were included in the pooled analysis: 8 prospective and 72 retrospective observational studies. 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). 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.

4.2.2. *Risk of bias assessment*

Baseline characteristics were reported in almost all journal articles but were only partially available in conference abstracts. Clinical success rate's definition varied; other outcome measures were defined mostly uniformly. Although assessment of different outcomes was reported reliably in more than 90%, outcomes were reported heterogeneously. Adequate follow-up data were available in only approximately 40%, but the length of follow-up was appropriate for assessment of outcomes, when reported.

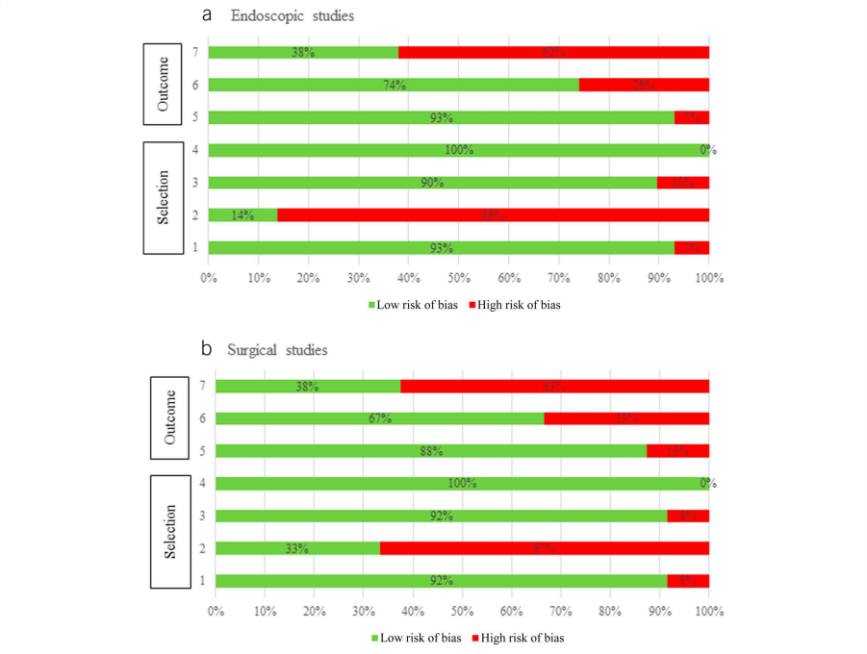

Figure 6. Risk of bias assessment of individual studies according to the modified Newcastle–Ottawa Scale. (a) Endoscopic studies and (b) surgical studies.

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.

4.2.3. *Meta-analytical calculations*

4.2.3.1. *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. 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, 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.

4.2.3.2. 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%]). 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.

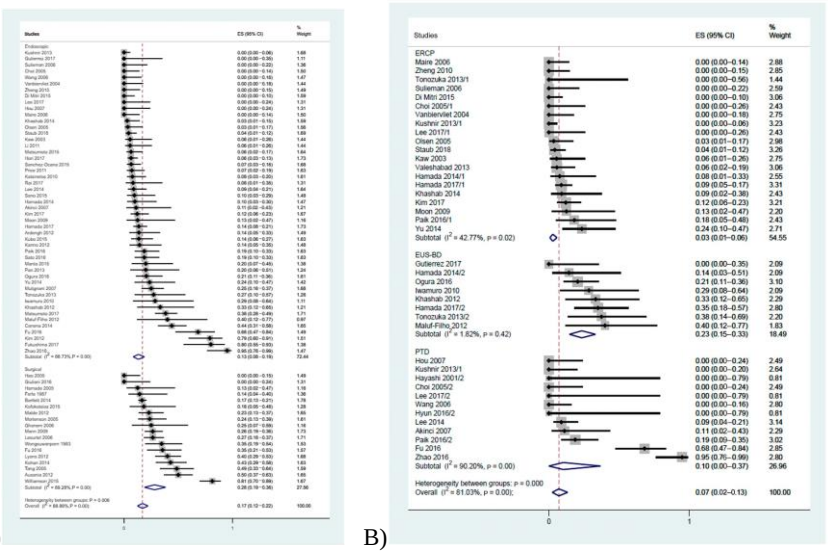

Figure 7. Adverse events related to double stenting and double surgical bypass (A) and to ERCP, EUS-BD, and PTD (B).

4.2.3.3. 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%]). 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). Although only 2 surgical studies specified whether reintervention was necessary because of RBO or RDO, several endoscopic studies investigated RBO and RDO separately. 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.

4.2.3.4. 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. A small number of surgical studies and frequent GEA use in the surgical cohort prevented comparison of survival in the endoscopic and surgical cohorts.

5. DISCUSSION

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

The overall accuracy of ERUS in determining the depth invasion of the primary tumor 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. According to a multicenter study performed in Germany, the overall accuracy of ERUS was determined as 73.1% for hospitals performing >30 ERUS/year. This rate was accomplished in our center as well. Overstaging was the most frequent mistake in all three patient groups (16%-27%-57%). This can be a result of the peritumoral inflammatory reaction, which cannot be distinguished endosonographically from the tumor itself. Understaging was mainly due to microscopic tumorous infiltration impossible to detect with EUS and could be observed in extensive tumors (where depth of invasion may vary throughout the longitudinal extension of the tumor) and when the upper part of the lesion is inaccessible for the probe. Differentiating between T1/T2 and T2/T3 tumors can raise further problems, as penetration through the wall layers is often ambiguous; it might only be indicated by the irregularity of the surface between the layers. In extensive tumors, submucosal involvement can also be easily mistaken for the widening of the muscular propria. Differentiating between T2/T3 tumors is important 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 could be still recommended for staging advanced lesions. A significant difference was shown in 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 tissue changes resulting from CRT: inflammation, fibrosis, and necrosis occurring as a consequence of the treatment can hardly be differentiated endosonographically from the

tumorous tissue. Overstaging rate was 27–57% for Groups II and III, respectively. Considering the lower PPV of the method and the only sufficient level of yuT-ypT correspondence (κ = 0.390), it can be stated that ERUS is not appropriate for restaging after CRT. 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.

The accuracy of N-staging was only 62%, and neither sensitivity nor PPV 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. 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.

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. 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. Moreover, in the later period, after reaching the plateau phase of the learning curve, the sensitivity of ERUS for each tumor stage exceeded the results reported from a multicenter study from Germany (80%-83%-75% versus 58%-64%-71%). 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-quality staging.

5.1.2. 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 patients who had not received neoadjuvant treatment (61% and 70%, respectively) with common overstaging of the

depth of invasion (31%). 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. 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%. 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%). The studies conducted by Pastor et al., Mezzi et al., and Vanagunas et al. reported the correspondence to histopathologic T-stage to be 54%, 46%, and 48%, respectively. In the last study, overstaging rate was 38%. Restaging advanced rectal cancers after CRT, Huh et al. reported an even lower T-staging accuracy (38.3%). 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 a challenge for 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. Assessing staging accuracy separately for each T-stage, Martellucci et al. found exceedingly high accuracy in case of T3 tumors (96%). 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.

Tissue changes resulting from CRT might be the reason of the lower staging accuracy: peritumoral inflammation, edema, fibrosis, and necrosis of the tumor tissue impair the integrity of the wall structure making the wall layers difficult to identify. Fibrotic tissue changes resulting from CRT appear hypoechoic on the ultrasound image, therefore fibrotic areas can hardly be distinguished from the tumor tissue itself. 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.

Accuracy of N-restaging is reported to be between 39% and 83% in the literature, a review study determined average accuracy to be 70%. Usually in the initial staging, the accuracy of N-staging falls short to that of T-staging, 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. 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. Specificity was found to be higher by Pastor et al. (91%), however, sensitivity was only 39%. 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). Meanwhile, 95% of lymph nodes are smaller than 5 mm after neoadjuvant CRT and 50% of metastatic lymph nodes are smaller than 3 mm. The ability of ERUS to visualize only perirectal and mesorectal lymph nodes is another important limiting factor.

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.

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

Although double stenting for combined malignant biliary and duodenal obstruction has been a treatment option for 25 years, 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. 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%). 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, 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. 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. 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 can result in a lower risk of development of duodenal stenosis, therefore, lower rates of reinterventions for RDO are expected in the surgical cohort. Consequently, 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.

6. 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 depth invasion of the primary lesion in early malignancies, especially in regions with limited access to MRI. However, tissue changes after CRT make the modality unsuitable for the evaluation of downstaging.

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 after 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, 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.

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