

## Over-the-scope clip in peptic ulcer bleeding: clinical success in primary and secondary treatment and factors associated with treatment failure

Stefan Gölder, Lukas Neuhas, Dennis Freuer, Andreas Probst, Alanna Ebigbo, Georg Braun, Juliane Brueckner, Johannes Stueckle, Alexander Meier, Helmut Messmann

### Angaben zur Veröffentlichung / Publication details:

Gölder, Stefan, Lukas Neuhas, Dennis Freuer, Andreas Probst, Alanna Ebigbo, Georg Braun, Juliane Brueckner, Johannes Stueckle, Alexander Meier, and Helmut Messmann. 2019. "Over-the-scope clip in peptic ulcer bleeding: clinical success in primary and secondary treatment and factors associated with treatment failure." *Endoscopy International Open* 07 (06): E846–54. <https://doi.org/10.1055/a-0898-3357>.

# Over-the-scope clip in peptic ulcer bleeding: clinical success in primary and secondary treatment and factors associated with treatment failure



## Authors

Stefan Gölder<sup>1</sup>, Lukas Neuhas<sup>2</sup>, Denis Freuer<sup>3</sup>, Andreas Probst<sup>1</sup>, Alanna Ebigbo<sup>1</sup>, Georg Braun<sup>1</sup>, Juliane Brueckner<sup>2</sup>, Johannes Stueckle<sup>2</sup>, Alexander Meier<sup>2</sup>, Helmut Messmann<sup>1</sup>

## Institutions

- 1 University Hospital Augsburg, Department of Internal Medicine III, Augsburg, Germany
- 2 Klinikum Dritter Orden, Department of Internal Medicine I, Munich, Germany
- 3 Chair of Epidemiology of the LMU Munich at UNIKA-T, Augsburg, Germany

submitted 9.11.2018

accepted after revision 25.3.2019

## Bibliography

DOI <https://doi.org/10.1055/a-0898-3357> |

Endoscopy International Open 2019; 07: E846–E854

© Georg Thieme Verlag KG Stuttgart · New York

eISSN 2196-9736

## Corresponding author

Dr. Stefan Karl Gölder, University Hospital Augsburg – Department of Internal Medicine III, Stenglinstraße 2, Augsburg 86156, Germany

Fax: +498214003331

[stefan.goelder@uk-augsburg.de](mailto:stefan.goelder@uk-augsburg.de)

## ABSTRACT

**Background and study aims** It is unclear if the clinical success rate of the over-the-scope-clip (OTSC) in peptic ulcer bleeding (PUB) is comparable when it is used in the first- or in the second-line of treatment.

**Patients and methods** Data on endoscopic treatment (first- vs. second-line) in PUB with OTSC and clinical data were analyzed. The primary outcome was the clinical success of hemostasis, defined as the absence of recurrent bleeding or further intervention. Secondary outcomes were factors associated with OTSC failure.

**Results** From April 2014 to March 2018, 100 patients (age 72 [20–98] y, female 36%) with PUB in the stomach or the duodenum were treated endoscopically with the OTSC. The OTSC was used as a first-line procedure (primary-OTSC) in 66 pts. Successful hemostasis could be achieved in 90.9%. After failure of an initial endoscopic treatment, 34 patients were treated with the OTSC (secondary-OTSC) and the treatment was successful in 94.1%. Recurrent bleeding occurred in n = 10 for primary-OTSC (16.7%) and in n = 7 pts in the secondary-OTSC (21.9%) ( $P=0.81$ ). Clinical success in the primary-OTSC was 75.8% and 73.5% in the secondary-OTSC respectively.

**Conclusions** The OTSC has a high rate of initial bleeding control in first- and second line treatment of PUB. OTSC failure occurs more often in the duodenum than in the stomach and results in longer intensive care unit stay, higher amount of transfusions, and a higher reimbursement per case.

## Introduction

Acute upper gastrointestinal hemorrhage remains one of the most common emergencies in internal medicine. The incidence rate of upper gastrointestinal bleeding is between 40 and 150 cases per 100,000 [1, 2]. Peptic ulcer bleeding (PUB) is still the most common bleeding source and responsible for 40% to 50% of all acute upper gastrointestinal bleeding episodes [1, 3]. Internationally accepted treatment standards and guidelines recommend early use of endoscopic therapy and proton pump inhibitors [4–6].

However, about 8% to 15% of all patients have persistent or recurrent bleeding and the mortality rate for PUB still remains between 10% to 14% [3, 7].

The over-the-scope-clip (OTSC) has been introduced as a new treatment option and in a recent prospective randomized study, Schmidt et al showed that use of the device is superior to conventional endoscopic treatment in recurrent PUB (secondary-OTSC) [8]. Until now it was unclear if the OTSC could be as helpful in first-line treatment of PUB (primary-OTSC). In our study, we compared primary-OTSC with secondary-OTSC in

► **Table 1** Baseline Characteristics of n = 100 patients with peptic gastric or duodenal ulcer bleeding (PUB) and treatment with the over-the-scope cClip (OTSC).

	Median (IQR), N, (%)
Age <sup>1</sup>	76 (62.75; 83)
Patient clinical complexity level (PCCL)	3 (1.75; 4)
<b>Gender</b>	
▪ male	64
▪ female	36
Outpatient bleeder	57
Inpatient bleeder	43
<b>Anticoagulation</b>	
▪ None	56
▪ ASS mono	8
▪ NOAK	8
▪ combinations	28
<b>NSAR</b>	
▪ No	49
▪ Yes	17
▪ Unclear	2
RockallScore	7 (6; 8)
Glasgow Blatchford Score (GBS)	16 (14; 17)
Ulcer size (mm)	20 (15; 30)
<b>Ulcer location</b>	
▪ Stomach proximal (Fundus/Corpus)	12
▪ Stomach distal (Antrum)	13
▪ Duodenal Bulb	25
▪ Duodenum posterior wall	30
▪ Duodenum anterior wall	17
▪ Duodenum distal	3
<b>Forrestclassification of the lesions</b>	
▪ Ia (n)	51
▪ Ib (n)	23
▪ IIa (n)	26
<b>Primary- versus secondary-OTSC</b>	
▪ Primary-OTSC (n)	66
▪ Secondary-OTSC (n)	34
<b>Clinical success</b>	
▪ Yes	75 (75%)
▪ No	25 (25%)
<b>Bleeding-related mortality</b>	
▪ Yes	9 (9%)
▪ No	91
IQR, interquartile range; TTS, through-the-scope clips; OTSC, over the scope clips; ICU, intensive care unit; NSAIDs, nonsteroidal antiinflammatory drugs.	
<sup>1</sup> Mean (interquartile range)	

PUB with regard to persistent or recurrent bleeding as well as the clinical success of OTSC treatment in the primary and secondary line of treatment.

## Patients and methods

Data for this evaluation were collected prospectively in an endoscopic database (Viewpoint Version 5.6, GE Healthcare GmbH, Solingen Germany). We extracted all information on use of OTSC for PUB. Before and after endoscopic treatment, clinical data for the patient cohort were recorded (► **Table 1**). Onset of bleeding, patient symptoms, baseline hemoglobin (g/L), blood-urea-nitrogen (BUN, mg/dL) and lactate (mmol/L) were documented, if available.

Prior to endoscopy, all patients received an 80-mg intravenous bolus of pantoprazole. Treatment was continued at a dose of 80 mg daily for at least 72 hours. Blood transfusion was initiated in case of Hb value <70 g/L, hemodynamic instability as well as persistent bleeding. Patients with hemodynamic instability were admitted to the intensive care unit (ICU). Length of ICU stay was also recorded.

The procedures were performed by experienced endoscopists in a 24/7 on-call service. We recorded the numbers of OTSC procedures performed by each endoscopist. To evaluate endoscopist performance relative to his/her experience, three groups were created, depending on the number of clips applied (1–5 OTSC; 5–20 OTSC and >20 OTSC).

In cases of active bleeding or a visible vessel, the OTSC was applied using a therapeutic endoscope (GIF HQ190, Olympus-Europe, Hamburg, Germany). The suction method was used in all cases. All interventions were performed with the 12-mm type-t clip mounted on a 6-mm cap (Ovesco Endoscopy AG, Tübingen, Germany) and were performed under either general anesthesia or midazolam/propofol sedation. Depending on the clinical situation and the endoscopic presentation, one or two clips were placed to control bleeding.

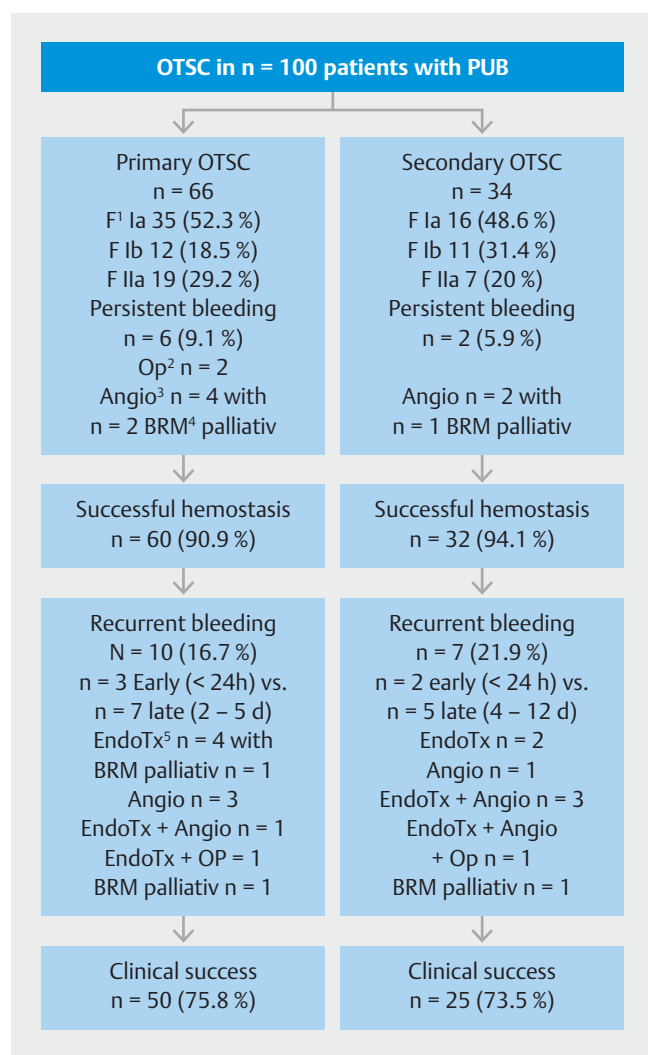
Furthermore, ulcer size (in millimeters), Forrest classification and location (stomach or duodenum) of the target lesion were documented.

Primary OTSC treatment was defined as endoscopic treatment without any prior endoscopic hemostatic approach. Secondary OTSC treatment was defined as rescue OTSC-therapy within 30 days after failed initial endoscopic hemostasis with injection therapy (adrenalin and/or fibrin glue), through-the-scope hemoclips (TTS) or a combination of injection and clip therapy (► **Fig. 1**).

The primary outcome was defined as successful initial hemostasis with no recurrent bleeding or further surgical, radiological or endoscopic treatment required.

Persistent bleeding was defined as immediate failure of endoscopic treatment proven by ongoing bleeding (oozing or squirting) after endoscopic hemostasis.

Recurrent bleeding was diagnosed if a retreatment of the target lesion was required after initial successful endoscopic treatment. Repeat endoscopy was performed if clinical symptoms of rebleeding occurred (hematemesis or recurrence of



► **Fig. 1** Flowchart of the OTSC (over-the-scope-clip) treatment in n = 100 patients with peptic ulcer bleeding (PUB). Primary-OTSC treatment was when no other endoscopic hemostatic approach had been performed. Secondary-OTSC was a rescue OTSC-therapy after failed initial endoscopic hemostasis with the combination of injection therapy and through-the-scope clips (TTS). Persistent bleeding was when the bleeding source could not be controlled by endoscopic treatment alone. If initial endoscopic OTSC treatment (primary-OTSC or secondary-OTSC) could stop the bleeding, the case was counted as successful hemostasis. Recurrent bleeding was detected by clinical presentation or endoscopy and further therapy initiated. If no other treatment modality was necessary besides the OTSC application, the case was classified as clinical success with OTSC treatment.

<sup>1</sup> F = Forrest stage of the ulcer

<sup>2</sup> OP = operative treatment of the bleeding site

<sup>3</sup> Angio = angiographic treatment of the bleeding

<sup>4</sup> BRM = Bleeding related mortality

<sup>5</sup> EndoTx = Endoscopic therapy

melena) or the patient developed signs of hemodynamic shock (tachycardia or hypotension).

A “second-look endoscopy” was not performed routinely if initial clip placement and hemostasis were deemed successful.

Secondary outcomes were clinical risk factors potentially associated with OTSC failure. We evaluated the location of bleeding onset (new admission versus in-patient bleeding), presence of anticoagulation treatment, use of nonsteroidal anti-inflammatory drugs (NSAIDs), Rockall Score, Glasgow Blatchford Score (GBS), baseline hemoglobin (g/L), blood urea nitrogen (BUN mg/dL), Lactate (mmol/L), baseline red blood cell transfusions, ulcer location (stomach versus duodenum), Forrest classification of the lesion as well as ulcer size (cm).

After discharge from the hospital, the patient clinical complexity level (PCCL), reimbursement in Euros, length of time in the intensive care unit (ICU days) and the Case Mix Index (CMI) of the German Diagnosis Related Groups (G-DRG), a measure of the financial investment in each individual case, was evaluated.

Mortality in the patient cohort was also documented. Bleeding-related mortality (BRM) was compared to clinical success of the OTSC treatment. We defined BRM as mortality from either clinical failure or events of rebleeding.

The data were collected and evaluated using Microsoft Excel 2008 for Mac, SPSS for Mac (Version 25.0 Armonk, IBM Corp. New York, United States) and R (Version 3.4.4).

Categorical variables were summarized by absolute percentages and continuous variables by median and 95 interquartile range (IQR).

Differences were evaluated by Fisher's exact or the Pearson's Chi-square test. In quantitative values, differences were measured using the Wilcoxon Rank test.

A P value < 0.05 was considered statistically significant.

Multivariate logistic regression analysis with a forward stepwise selection strategy using a likelihood ratio, including the report of relative risks and their 95% CIs, was used to identify independent risk factors for failure of bleeding control.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, in compliance with good clinical practice and according to local regulations. All patients gave written informed consent to the endotherapy. The study was not supported financially or otherwise by any external source.

## Results

From April 2014 to March 2018, 100 patients (mean age 76 [20–98] years, female 36%, male 64%) with PUB in the stomach or duodenum were treated endoscopically with the OTSC Clip in the Department of Internal Medicine III at the University Hospital Augsburg, Germany.

### Primary vs. secondary OTSC

The OTSC was used as a first-line procedure (Primary-OTSC) in 66 patients. Initial bleeding control was achieved in 90.9% (► Fig. 1), six of these patients (9.1%) suffered from persistent bleeding after technically successful OTSC placement in five cases. Subsequent salvage therapy with angiographic obliteration (4 cases) or surgery (2 cases) was performed.

After successful angiographic obliteration, two patients refused further treatment and died in a palliative situation (3.0%).

► **Table 2** Characteristics of the patients with primary- or secondary-OTSC treatment.

	Primary OTSC	Secondary OTSC	P
	n = 66	n = 34	
Age <sup>1</sup>	77 (67; 83)	71 (61; 81)	0.32
Patient clinical complexity level (PCCL) <sup>1</sup>	3 (1; 4)	3 (2; 4)	0.88
<b>Gender</b>			1
▪ male	42 (0.64)	22 (0.65)	
▪ female	24 (0.36)	12 (0.35)	
Outpatient bleed	37 (0.56)	20 (0.59)	0.83
Inpatient bleed	29 (0.44)	14 (0.41)	
<b>Anticoagulation</b>			0.37
▪ None	33 (0.5)	23 (0.68)	
▪ ASS mono	6 (0.09)	2 (0.06)	
▪ NOAK	7 (0.11)	1 (0.03)	
▪ combinations	20 (0.30)	8 (0.24)	
<b>NSAIDs</b>			0.48
▪ No	31 (0.74)	18 (0.69)	
▪ Yes	9 (0.21)	8 (0.31)	
▪ Unclear	2 (0.05)	0 (0)	
ICU (d) <sup>1</sup>	3 (2; 5)	4 (3; 7.25)	<b>0.05</b>
Rockall Score <sup>1</sup>	7 (6; 8)	7 (6; 8.75)	0.52
Glasgow Blatchford Score (GBS) <sup>1</sup>	16 (14; 17)	15 (12.5; 16)	0.14
Baseline hemoglobin (g/L) <sup>1</sup>	68 (58; 76)	66 (56.5; 73.75)	0.42
BUN (mg/dL) <sup>1</sup>	89.5 (66; 116)	82.5 (49.75; 118.5)	0.47
Lactate (mmol/l) <sup>1</sup>	2.5 (1.1; 4.5)	5.25 (2.58; 7.18)	0.07
Baseline red cell transfusions <sup>1</sup>	3 (2; 4)	4 (3; 7)	0.06
Case mix Index <sup>1</sup>	2.149 (1.16; 3.60)	2.37 (1.41; 3.56)	0.3
Reimbursement (Euro) <sup>1</sup>	7217 (3874; 11985)	7835.5 (4597; 11836.25)	0.38
Ulcer size (cm) <sup>1</sup>	2 (1.5; 3)	2 (1.5; 3)	0.61
<b>Location of the ulcer</b>			1
stomach	17 (0.26)	8 (0.24)	
duodenum	49 (0.74)	26 (0.77)	
<b>Forrest</b>			0.26
Ia (n; rel. %)	35 (0.53)	16 (0.47)	
Ib	12 (0.18)	11 (0.32)	
Ila	19 (0.29)	7 (0.21)	
<b>Technical success</b>			1
yes (rel. %)	65 (0.99)	34 (1)	
no	1 (0.015)	0 (0)	
<b>Clinical success</b>			0.81
yes (rel. %)	50 (0.76)	25 (0.74)	
no	16 (0.24)	9 (0.27)	

► **Table 2** (Continuation)

	Primary OTSC	Secondary OTSC	P
	n = 66	n = 34	
Experience Physician OTSC/endoscopist			<b>0.02</b>
<5	19 (0.29)	3 (0.09)	
5–20	5 (0.08)	8 (0.24)	
>20	42 (0.64)	23 (0.68)	
<b>Bleeding-related mortality</b>			<b>1</b>
Yes	6 (0.09)	3 (0.09)	
No	60 (0.91)	31 (0.91)	

IQR, interquartile range; TTS, through-the-scope clips; OTSC, over-the-scope clips; ICU, intensive care unit; NSAIDs, nonsteroidal antiinflammatory drugs.

<sup>1</sup> Mean (interquartile range)

The OTSC was used as a second-line procedure (secondary-OTSC) for reactivated bleeding after successful initial endoscopic hemostasis with injection of adrenalin (mean 15 mL range: 5–50 mL) or fibrin glue (mean 2 mL range: 1–4 mL). For mechanical bleeding control, only treatment with TTS (mean 4 range 1–12) was allowed in this study. In this group the bleeding source showed active bleeding (Forrest Ia or Ib) in n=27 cases. In seven cases a non-bleeding visible vessel was found (Forrest IIa). Two patients suffered from persistent bleeding (5.9%) after OTSC treatment. Both patients underwent angiographic obliteration of the feeding vessel. One patient refused further treatment and died in palliative care (2.9%).

Successful hemostasis with secondary-OTSC was achieved in 94.1%. Persistent bleeding after OTSC treatment occurred in 8% of all cases (primary- and secondary-OTSC).

Recurrent bleeding occurred 1 to 12 days after successful initial treatment, (median 3.5 d) in 16.7% (N=10) after primary-OTSC and 21.9% (N=7) after secondary-OTSC treatment ( $P=0.81$ ).

In the primary-OTSC group, ten patients (16.7%) suffered an early recurrent bleeding (<24 hours, n=3) or had late recurrent bleeding (>24 hours range 2–5 days, n=7). In four patients, a second endoscopic treatment was successful but one patient died in a palliative situation after successful bleeding control. Four patients received angiography and one surgery for bleeding control. One patient developed symptoms of recurrent bleeding but a reintervention was denied because of comorbidities and the patient's age (90 years).

In the secondary-OTSC group, seven patients (21.2%) developed early rebleeding (<24 hours, n=2) or late rebleeding (>24 hours range 4–12 days, n=5). Successful endoscopic treatment was achieved in two patients and five patients were treated with angiographic obliteration. One patient underwent surgery (► **Fig. 1**).

Recurrent bleeding occurred in 17% of all cases (primary- and secondary-OTSC).

The overall clinical success for OTSC in the primary-OTSC group was 75.8% versus 73.5% in the secondary-OTSC group ( $P=0.81$ ) (► **Fig. 1** and ► **Table 1**).

### Factors associated with OTSC failure

In the group of patients with persistent or recurrent bleeding we found no differences in risk stratification scores (Rockall and Glasgow Blatchford Score), baseline hemoglobin, BUN or lactate. Also, no differences in the frequency of antiplatelet or anticoagulant drugs or NSAID use. There were no differences between new admission- or inpatient bleeders (► **Table 2**).

The mean amount of packed red blood cells transfused in the OTSC failure group was higher (4 versus 3,  $P=0.01$ ) and ulcer size was larger (30 versus 20 mm,  $P=0.07$ ).

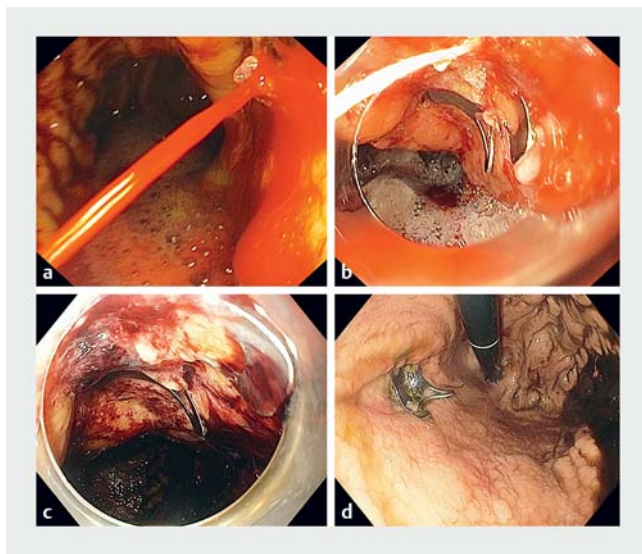
Duration of ICU treatment was longer (4 versus 3 days,  $P=0.02$ ). Reimbursement per case for the treatment failure group was higher from those successfully treated with OTSC (10055 Euro versus 6155 Euro  $P=0.04$ ) (CMI 3.036 versus 1.892  $P=0.04$ ). The trend showed a higher reimbursement and CMI in case of treatment escalation with operation or angiographic intervention.

The proportion of active oozing (Forrest Ib 23%) or spurting (Forrest Ia 51%) bleeding ulcers was 74% (► **Fig. 1**, ► **Fig. 2**) in the entire study cohort. A visible vessel (Forrest IIa) was found in 26% of ulcers (► **Fig. 3**). We found a slightly higher rate of ulcers with a visible vessel (Forrest IIa) in the primary-OTSC group (29.2% vs. 20.6%  $P=0.26$ ).

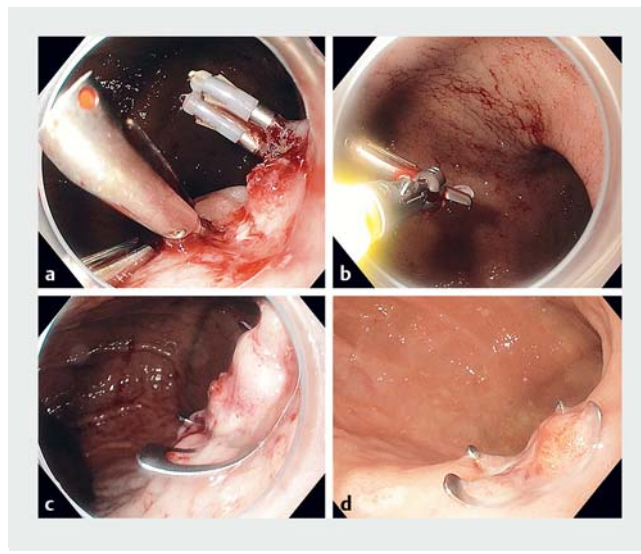
Treatment success was independent of Forrest stage of the ulcer ( $P=0.26$ ).

Endoscopic treatment was performed by 15 different physicians in our institution. To evaluate the grade of experience with the OTSC system in an active bleeding situation, we analyzed three groups: fewer than 5 OTSC applications, five to 20 or more than 20 clip applications (► **Table 3**). We found no difference in the bleeding control rate among the groups ( $P=0.58$ ). Interestingly, we had a higher rate of OTSC-unexperienced physicians (<5 OTSC) in the primary-OTSC group (28.8%) than in the middle group (5–20) 7.6% ( $P=0.02$ ). The





► **Fig. 2** Primary-OTSC. **a** Forrest Ia bleeding in the stomach diagnosed during emergency endoscopy. **b** An OTSC mounted on the therapeutic endoscope was successfully placed on the bleeding site. **c, d** After initial bleeding control and in the control endoscopy after 3 days, the clip was found in position.



► **Fig. 3** Secondary-OTSC. **a** Large ulcer with a central vessel. Prior to examination, TTS clips had been placed. **b** Because of recurrent bleeding, the TTS clips were removed. **c** An OTSC was placed on the central vessel. **d** In the second-look endoscopy the vessel was successfully closed by the OTSC.

most experienced physicians had comparable applications in the primary- or secondary-OTSC group (63.6% versus 67.7%). Logistic regression for clinical failure identified ulcer size and location in the duodenum, especially at the posterior duodenal wall, as factors associated with a higher rate of treatment failure (► **Table 4**). Also, the transfusion requirement was higher in the treatment failure group.

### Bleeding-related mortality

The rate of BRM was 6% (6 patients). In case of failure of clinically successful OTSC treatment ( $n=3$ ), all patients received angiographic bleeding control, but died due to prolonged hemorrhagic shock.

In case of recurrent bleeding, the bleeding source could be controlled by endoscopic treatment but the patient denied any further therapy.

Three patients (3%) in the successful hemostasis group also died due to prolonged hemorrhagic shock but showed no symptoms of recurrent bleeding and were also classified as BRM.

Seven patients (7%) died for reasons other than intestinal bleeding (sepsis 5×, decompensated liver cirrhosis, cardiorepiratory failure).

BRM occurred more often in the uncontrolled bleeding group (3 vs. 6 patients  $P=0.007$ ), but we found no difference between the primary-OTSC versus secondary OTSC group (6% in both groups, ► **Fig. 1**, ► **Table 1**, ► **Table 2**).

## Discussion

Our study shows that the primary-OTSC for first-line treatment of PUB has a comparably high rate of initial bleeding control with secondary-OTSC (90.9% versus 94.1%). Nevertheless, in the primary-OTSC group, we found a higher rate of salvage therapy (angiographic or surgery) of 9.1% compared to 5.9% in the secondary-OTSC group. This in part could be due to the fact that we had a per group higher rate of Forrest Ia (spurting) bleedings 53% versus 47% ( $P=0.26$ ) in the secondary-OTSC group. Forrest Ia ulcers have a higher per lesion rate of persistent and recurrent bleeding [9].

After successful initial treatment with the OTSC, recurrent bleeding occurred more often in the secondary-OTSC group than in the primary-OTSC group (21.9% vs 16.7%). This could be explained by the efficiency of the OTSC clip itself. This device has a higher compression force and therefore, obliteration of the feeding vessel is higher than with conventional TTS Clips. We also found more visible vessels (Forrest IIa) in the primary-OTSC (29.2%) compared to the secondary-OTSC group (20%) ( $P=0.26$ ). In the secondary-OTSC we might have a selection of more difficult-to-treat bleeding lesions. Therefore, a higher rate of recurrence may be explained. We also found that two recurrent bleeds occurred 8 and 12 days after the initial OTSC treatment. In one patient the clip was still in position and in one patient the clip had dislodged completely from the ulcer.

In the first prospective randomized trial comparing the OTSC as second-line therapy with conventional endoscopic retreatment, Schmidt et al. found 6.1% rate of persistent bleeding and a 9.1% rate of recurrent bleeding compared to 42.2% persistent bleeding and 16.1% recurrent bleeding for conventional endoscopic treatment. This defined the OTSC as the new stand-

► **Table 3** Factors associated with clinical failure in OTSC treatment for peptic ulcer bleeding.

	Clinical success with OTSC treatment		P
	Yes n = 75	No n = 25	
Age <sup>1</sup>	76 (62.5; 83)	72 (65; 83)	0.96
Patient Clinical Complexity Level (PCCL) <sup>1</sup>	3 (1; 4)	4 (2; 4)	0.08
<b>Gender</b>			0.16
▪ male	51 (0.68)	13 (0.52)	
▪ female	24 (0.32)	12 (0.48)	
Outpatient bleed	42 (0.56)	15 (0.6)	0.82
Inpatient bleed	33 (0.44)	10 (0.4)	
<b>Anticoagulation</b>			0.34
▪ None	40 (0.53)	16 (0.64)	
▪ ASS mono	8 (0.11)	0 (0)	
▪ NOAC	7 (0.09)	1 (0.04)	
▪ others (Combination)	20 (0.27)	8 (0.32)	
<b>NSAIDs</b>			0.76
▪ No	36 (0.735)	13 (0.684)	
▪ Yes	12 (0.245)	5 (0.263)	
▪ Unclear	1 (0.02)	1 (0.053)	
ICU (d) <sup>1</sup>	3 (2; 6)	4 (3; 9)	<b>0.02</b>
Rockall Score <sup>1</sup>	7 (6; 8)	8 (6; 9)	0.15
Glasgow Blatchford Score (GBS) <sup>1</sup>	15 (14; 17)	16 (15; 18)	0.10
Baseline hemoglobin (g/L) <sup>1</sup>	67 (57; 74.5)	70 (58; 75)	0.51
BUN (mg/dL) <sup>1</sup>	87 (57; 118)	92 (75; 116)	0.44
Lactate (mmol/l) <sup>1</sup>	2.6 (1.38; 6.8)	4.1 (2.582; 8.5)	0.23
Baseline red cell transfusions <sup>1</sup>	3 (2; 4)	4 (3; 9)	<b>0.01</b>
Case mix Index <sup>1</sup>	1.892 (1.19; 3.37)	3.036 (1.804; 4.683)	<b>0.04</b>
Reimbursement (Euro) <sup>1</sup>	6155 (3904.5; 11125)	10055 (6044; 15690)	<b>0.04</b>
Ulcer size (cm) <sup>1</sup>	2 (1; 3)	3 (2; 3)	0.07
<b>Location of the ulcer</b>			
▪ Stomach proximal (Fundus/Corpus)	10 (0.13)	2 (0.08)	<b>0.05</b>
▪ Stomach distal (Antrum)	13 (0.17)	0 (0)	
▪ Duodenal bulb	19 (0.25)	6 (0.24)	
Duodenum posterior wall	17 (0.23)	13 (0.52)	
▪ Duodenum anterior wall	13 (0.17)	4 (0.16)	
▪ Duodenum distal	3 (0.04)	0 (0)	
<b>Forrest</b>			0.26
▪ Ia	35 (0.47)	16 (0.64)	
▪ Ib	20 (0.27)	3 (0.12)	
▪ IIa	20 (0.27)	6 (0.24)	



► **Table 3** (Continuation)

	Clinical success with OTSC treatment		P
	Yes n = 75	No n = 25	
<b>Primary vs. Secondary OTSC</b>			0.81
▪ Primary OTSC	50 (0.67)	16 (0.64)	
▪ Secondary OTSC	25 (0.33)	9 (0.36)	
<b>Primary treatment (w/o) OTSC</b>			0.28
▪ Adrenalin + TTS	8 (0.33)	5 (0.46)	
▪ Adrenalin + TTS + Fibrin Clue	13 (0.54)	3 (0.27)	
▪ Fibrin Clue	3 (0.13)	2 (0.18)	
▪ OTSC in recurrent Primary-OTSC	0 (0)	1 (0.09)	
<b>Frequency of OTSC Applications/doctor</b>			0.58
▪ <5	15 (0.2)	7 (0.28)	
▪ 5 – 20	11 (0.15)	2 (0.08)	
▪ >20	49 (0.65)	16 (0.64)	

► **Table 4** Logistic regression for factors associated with clinical failure in OTSC treatment for peptic ulcer bleeding.

Factors	OR (CI)	P value
ICU (d)	1.04 (0.97 – 1.12)	0.30
Baseline red cell transfusion	1.31 (1.13 – 1.57)	0.01
Stomach vs. duodenum	4.96 (1.30 – 32.74)	0.04
Duodenum posterior wall	8.11 (1.89 – 56.94)	0.01
Ulcer size (≥ 1.5 cm)	7.19 (1.31 – 134.49)	0.07
Anticoagulation	0.64 (0.23 – 1.79)	0.40

Models were adjusted for sex and age  
ICU, intensive care unit; OR, odds ratio; CI, confidence interval.

ard in endoscopic treatment for recurrent peptic ulcer bleeding.

The clinical success rate of primary- and secondary-OTSC in our study is almost comparable (75.8% vs. 73.5%).

The clinical success rate of the first prospective randomized trial by Schmidt et al. found a final success rate of 84.8% for second-line treatment in PUB. In this study, the rate of Forrest Ia bleeding was 16.7% in a follow-up period of 30 days after initial bleeding control. Other case series or retrospective studies found rates of initial bleeding control of 77% to 100% and of re-bleeding of 7% to 42.8% [10–21].

We evaluated factors that might influence the clinical success of endoscopic treatment in PUB [22]. We found that ulcer location in the duodenum resulted in a higher rate of unsuccessful OTSC treatment. Ulcer size in the treatment failure group was larger (3 vs. 2 cm) but this did not reach statistical significance. In logistic regression we found that ulcer location

at the posterior duodenal wall was a factor associated with OTSC failure ( $P=0.01$ ). This finding is in accord with the current literature that could show a higher treatment failure for ulcers in this location [22, 23].

As a consequence of the more severe clinical scenario of failed endoscopic hemostasis, we found a longer ICU stay and a higher rate of red blood cell transfusions.

According to the German reimbursement system (G-DRG), the case mix index (CMI) and the reimbursement rate were higher for uncontrolled bleeding. There is only limited data on the reimbursement rate and cost of failed hemostasis in gastro-duodenal ulcer bleeding. A study from the United States found higher cost as well as reimbursement in case of salvage therapy with angiography or surgery [24].

Also of interest is the finding that we could not identify a difference in the experience of the endoscopist who applied the OTSC clip. This is comparable to other studies that showed a high rate of bleeding control when the OTSC system was used as the initial treatment modality. But our work is the first to show this in a real-life setting in a large referral endoscopy unit with 15 different endoscopists performing the procedure.

We found an overall mortality rate of 16% in our cohort. Seven patients died of reasons unrelated to bleeding and in three patients, bleeding was controlled but the patients died of prolonged hemorrhagic shock. Six patients died due to recurrent bleeding from the initial source. The overall rate of mortality was comparable to published data in severe ulcer bleeding and OTSC treatment of 10% to 18% [8, 12, 21].

There are some limitations to our findings. This is a retrospective evaluation of prospectively collected data, which did not compare OTSC treatment to conventional endoscopic hemostasis. Patient recruitment was performed within a time period of 4 years. Patient allocation to a treatment arm was

based on the character of the bleeding (initial versus recurrent bleeding) which could be a source of potential bias.

Recent studies show that endoscopic doppler examination of the ulcer base could direct the endoscopic therapy, this was not performed during our study [25, 26].

## Conclusion

In conclusion, the OTSC has a high rate of initial bleeding control in first- and second line treatment for PUB. The rate of recurrent bleeding was lower in first- than in second-line treatment in our study. Location of the bleeding source and ulcer size may influence the success of treatment.

## Competing interests

None

## References

- [1] van Leerdam ME. Epidemiology of acute upper gastrointestinal bleeding. *Best Pract Res Clin Gastroenterol* 2008; 22: 209–224
- [2] Hearnshaw SA, Logan RF, Lowe D et al. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut* 2011; 60: 1327–1335
- [3] Laine L, Yang H, Chang SC et al. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. *Am J Gastroenterol* 2012; 107: 1190–1195; quiz 1196
- [4] Gralnek IM, Dumonceau JM, Kuipers EJ et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015; 47: a1–46
- [5] Barkun AN, Bardou M, Kuipers EJ et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2010; 152: 101–113
- [6] Götz M, Anders M, Biecker E et al. [S2k Guideline Gastrointestinal Bleeding – Guideline of the German Society of Gastroenterology DGVS]. *Z Gastroenterol* 2017; 55: 883–936
- [7] van Leerdam ME, Vreeburg EM, Rauws EAJ et al. Acute upper GI bleeding: did anything change? Time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000. *Am J Gastroenterol* 2003; 98: 1494–1499
- [8] Schmidt A, Gölder S, Goetz M et al. Over-the-scope clips are more effective than standard endoscopic therapy for patients with recurrent bleeding of peptic ulcers. *Gastroenterology* 2018; 155: 674–686. e676
- [9] Laine L, Peterson WL. Bleeding peptic ulcer. *N Engl J Med* 1994; 331: 717–727
- [10] Albert JG, Friedrich-Rust M, Woeste G et al. Benefit of a clipping device in use in intestinal bleeding and intestinal leakage. *Gastrointest Endosc* 2011; 74: 389–397
- [11] Baron TH, Song LM, Ross A et al. Use of an over-the-scope clipping device: multicenter retrospective results of the first U.S. experience (with videos). *Gastrointest Endosc* 2012; 76: 202–208
- [12] Brandler J, Baruah A, Zeb M et al. Efficacy of over-the-scope clips in management of high-risk gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2017; 16: 690–696
- [13] Chan SM, Chiu PW, Teoh AY et al. Use of the over-the-scope clip for treatment of refractory upper gastrointestinal bleeding: a case series. *Endoscopy* 2014; 46: 428–431
- [14] Kirschniak A, Subotova N, Zieker D et al. The over-the-scope clip (OTSC) for the treatment of gastrointestinal bleeding, perforations, and fistulas. *Surg Endosc* 2011; 25: 2901–2905
- [15] Manno M, Mangiafico S, Caruso A et al. First-line endoscopic treatment with OTSC in patients with high-risk non-variceal upper gastrointestinal bleeding: preliminary experience in 40 cases. *Surg Endosc* 2016; 30: 2026–2029
- [16] Manta R, Galloro G, Mangiavillano B et al. Over-the-scope clip (OTSC) represents an effective endoscopic treatment for acute GI bleeding after failure of conventional techniques. *Surg Endosc* 2013; 27: 3162–3164
- [17] Monkemüller K, Peter S, Toshniwal J et al. Multipurpose use of the 'bear claw' (over-the-scope-clip system) to treat endoluminal gastrointestinal disorders. *Dig Endosc* 2014; 26: 350–357
- [18] Nishiyama N, Mori H, Kobara H et al. Efficacy and safety of over-the-scope clip: including complications after endoscopic submucosal dissection. *World J Gastroenterol* 2013; 19: 2752–2760
- [19] Richter-Schrag HJ, Glatz T, Walker C et al. First-line endoscopic treatment with over-the-scope clips significantly improves the primary failure and rebleeding rates in high-risk gastrointestinal bleeding: A single-center experience with 100 cases. *World J Gastroenterol* 2016; 22: 9162–9171
- [20] Skinner M, Gutierrez JP, Neumann H et al. Over-the-scope clip placement is effective rescue therapy for severe acute upper gastrointestinal bleeding. *Endosc Int Open* 2014; 2: E37–E40
- [21] Wedi E, Gonzalez S, Menke D et al. One hundred and one over-the-scope-clip applications for severe gastrointestinal bleeding, leaks and fistulas. *World J Gastroenterol* 2016; 22: 1844–1853
- [22] Ogasawara N, Mizuno M, Masui R et al. Predictive factors for intractability to endoscopic hemostasis in the treatment of bleeding gastroduodenal peptic ulcers in Japanese patients. *Clin Endosc* 2014; 47: 162–173
- [23] Elmunzer BJ, Young SD, Inadomi JM et al. Systematic review of the predictors of recurrent hemorrhage after endoscopic hemostatic therapy for bleeding peptic ulcers. *Am J Gastroenterol* 2008; 103: 2625–2632
- [24] Roy A, Kim M, Hawes R et al. The clinical and cost implications of failed endoscopic hemostasis in gastroduodenal ulcer bleeding. *United European Gastroenterol J* 2017; 5: 359–364
- [25] Jensen DM, Kovacs TOG, Ohning GV et al. Doppler endoscopic probe monitoring of blood flow improves risk stratification and outcomes of patients with severe nonvariceal upper gastrointestinal hemorrhage. *Gastroenterology* 2017; 152: 1310–1318 e1311
- [26] Jensen DM, Ohning GV, Kovacs TO et al. Doppler endoscopic probe as a guide to risk stratification and definitive hemostasis of peptic ulcer bleeding. *Gastrointest Endosc* 2016; 83: 129–136