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Diagnosis agreement between capsule endoscopy and double-balloon enteroscopy in obscure gastrointestinal bleeding at a referral center

Enrique Pérez-Cuadrado Robles, PILAR ESTEBAN DELGADO, Blanca Martinez Andrés, Luis Eduardo Zamora Nava, Jose Luis Rodrigo Agudo, Silvia Chacón Martinez, Emilio Torrella Cortés, Jamal Shanabo, Antonio Lopez Higueras, Eduardo Muñoz Bertrán, Hacibe Hallal, RAFAEL LATORRE REVIRIEGO, OCTAVIO LÓPEZ-ALBORS, FEDERICO SORIA GÁLVEZ, Paloma Bebia Conesa, Enrique Pérez-Cuadrado Martínez

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1 Small Bowel Unit. Department of Gastroenterology. Hospital Morales Meseguer. Murcia, Spain. 2 National Institute of Medical Sciences and Nutrition Salvador Zubirán. México City, Mexico. 3 Department of Anatomy. Universidad de Murcia. Murcia, Spain. 4 Minimally Invasive Surgery Center “Jesus Usón”. Cáceres, Spain

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Correspondence: Enrique Pérez-Cuadrado Robles. Servicio de Aparato Digestivo. Hospital Morales Meseguer. Avda. Marqués de los Velez, s/n. 30008 Murcia
e-mail: kikemurcia@gmail.com

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ABSTRACT
Capsule endoscopy and double-balloon enteroscopy are well-recognized procedures in obscure gastrointestinal bleeding, with many factors that may influence their diagnosis yield. The aim of the present study was to characterize the degree of agreement
between both techniques with focus on the type of lesion in a large cohort of patients at a referral center. One thousand two hundred and nine capsules were administered in 1,078 patients and 381 enteroscopies were performed in 361 patients with obscure-gastrointestinal bleeding from 2004 to 2014. Both procedures were carried out in 332 patients (mean age: 65.22 ± 15.41, 183 men) and they have a similar diagnosis yield (70.5% vs. 69.6%, p = 0.9). Overall enteroscopy diagnosis yield was higher within patients with a previous positive capsule endoscopy (79.3% vs. 27.9%, p < 0.001).

The degree of agreement was very good for polyps (0.89 [95% CI: 0.78-0.99]), good for vascular lesions (0.66 [95% CI: 0.55-0.77]) and tumors (0.66 [95% CI: 0.55-0.76]) and moderate for ulcers (0.56 [95% CI: 0.46-0.67]). Diverticula (0.39 [95% CI: 0.29-0.5]) achieved a fair agreement. The results of CE and DBE differed in 73 patients (22%). In conclusion, the present study confirms that although overall diagnostic yield by capsule endoscopy and double-balloon enteroscopy is similar, there are many factors which can modify these values, mainly the type of lesion.

Key words: Enteroscopy. Obscure gastrointestinal bleeding. Capsule endoscopy. Dieulafoy’s lesion. Angiodysplasia.

INTRODUCTION
Capsule endoscopy (CE) and double-balloon enteroscopy (DBE) have widely demonstrated their usefulness in obscure gastrointestinal bleeding (OGIB) of the small bowel (SB) (1), but have also been reported to miss some lesions (2,3). However, the overall diagnostic yield of both techniques and their degree of agreement for different types of lesion is not well-established, with different predominant etiologies in Western and Eastern World (4,5). Regarding the agreement by type of lesion, most studies to date are short series, with low quality evidence. There are few meta-analysis comparing CE and DBE in OGI (6,7), concluding similar diagnostic yields between these modalities with differences statistically significant for fresh/blood clots and diverticulum.

The aim of this study was to assess the diagnosis agreement between both techniques and analyze the different factors that might be involved in these values at a referral
METHODS

Patients
All patients with OGIB in whom a CE and DBE were performed between January 2004 and April 2014 at our hospital were included. OGIB was defined according to the published position statement of the American Gastroenterological Association (8) and the type of bleeding (obscure-overt vs. obscure-occult) was considered. All patients had an upper endoscopy and colonoscopy as well as other imaging techniques with no appreciable findings that could explain the bleeding. Most of the patients had been referred to our hospital from other clinics. Patients with previous diagnosis that could explain the OGIB, as Crohn’s disease, were excluded.

Concepts
Positive CE or DBE was achieved when a bleeding source was detected even if the underlying lesion was not identified. The findings were considered clinically significant (positives) if they could explain the clinical presentation of the patient. Otherwise, the procedure was considered negative. Lymphangiectasia, indeterminate red spots, isolated erosions and any entity that could not explain the OGIB were therefore classified as negative. For both procedures, when several potentially bleeding lesions were diagnosed, only the one with the highest potential was considered for the analysis. Findings identified by CE and/or DBE were categorized in the followings groups: Vascular lesions, ulcers or multiple erosions, tumors, polyps, diverticulum and intraluminal bleeding with no lesion identified. All patients provided written informed consent in order to perform both procedures. The present study was reviewed and approved by the Ethical Committee of the Hospital Morales Meseguer (Murcia, Spain).

Procedures: Capsule endoscopy and double balloon enteroscopy
CE (Given Imaging Ltd, Yoqneam, Israel) was swallowed by the patient or administered by a capsule endoscopy delivery device after 8 hours fast. The location of the lesion was determined by the transit time ratio relative to the pylorus and/or the ileocecal
valve. Gastric and SB transit times were considered. Total enteroscopy of the entire SB by CE was achieved when the CE reached the cecum within the recording time and the cleansing was enough. Expert endoscopists (EPCM, ALH, HH) read the procedures. All the CE performed during the same period but after the DBE were not considered.

DBE was performed under deep sedation or general anesthesia. There was no special preparation for the anterograde approach besides 12 hours fast before the procedure. For the retrograde approach, all patients underwent bowel preparation similarly to colonoscopy. Three types of endoscopes with the system from Fuji Film® (Saitama, Japan) were used: EN-450p5, EN-450t5 and EN-580T with a different outer diameter, diameter-working channel and overtube. The approach (anterograde, retrograde), location of the lesion and the time of the procedure were collected. The decision of the first-line anterograde or retrograde approach was based in clinical presentation and CE findings. When the ideal approach was not clear, oral route was preferred. Three expert endoscopists performed DBE (EPCM, JSRA, PED). All of them knew the results of CE at the time of DBE. Tattoo injection was performed to mark the maximum length of bowel inspected and/or the location of the lesion. Finally, complications procedure-related complications were noted.

**Statistical analysis**

Categorical variables were compared using \( \chi^2 \) test or Fischer’s exact test. Normally distributed continuous variables were analyzed by Student \( t \) test and non-normally distributed variables by the Mann-Whitney U-test. McNemar’s test for paired data was used. A p-value < 0.05 was considered as statistically significant. Finally, the diagnosis agreement between the results of CE and DBE was defined as the identification of the same type of lesion by both procedures for the same patient and process. The degree of diagnosis agreement was assessed by kappa index with a Confidence Interval (CI) as follows: 0 to 0.19 (slight), 0.2 to 0.39 (fair agreement), 0.4 to 0.59 (moderate), 0.6 to 0.79 (good) and 0.8 to 1.0 (very good). The 95% confidence interval (CI) for kappa index was calculated. SPSS version 21 was used (IBM, SPSS Inc, IL, USA).

**RESULTS**
Capsule endoscopy and double-balloon enteroscopy

All the procedures performed are presented in the flowchart in figure 1. From 2004 to 2014, 1768 capsules have been administered. Of these, 1209 (68.4%) were performed in 1078 patients with overt-OGIB (n = 249, 23.1%) or occult-OGIB (n = 829, 76.9%). Endoscopy-assisted delivery device of the capsule (AdvانCE® delivery device, US endoscopy, Ohio, USA) was necessary in nine patients. Seventy-one procedures (5.9%) were considered unsatisfactory due to complications as CE retention (n = 34), technique/software failure (n = 12) and inadequate cleansing (n = 25). CE retention was located in the SB in 10 cases because of Crohn’s stenosis (n = 6), tumors (n = 3) and adhesions (n = 1). They were resolved by DBE (n = 5), surgery (n = 2) and spontaneously (n = 3). Other retentions were located in stomach (n = 20) and esophagus (n = 4), and they were resolved by upper-endoscopy removal of the capsule (n = 14) or spontaneously (n = 10). Since a proportion of unsatisfactory capsules were repeated, they were finally considered null in only 41 patients (3.8%).

During the same period of time, a DBE was performed in 621 patients at our center, being 261 of them (58.1%) because of OGIB. Three-hundred and eighty-one DBE were performed by an anterograde (n = 277, 76.7%), retrograde (n = 64, 17.7%) or combined (n = 20, 5.5%) approach. Tattoo injection was performed in the 85.7% of the total of patients. Concerning procedure-related complications, there were two perforations and one acute pancreatitis (9). All patients recover with conservative management, except one in which a sigma perforation at the beginning of the procedure required emergency surgery.

Comparative analysis

Considering the combined approach with both techniques, CE and DBE were performed in 332 patients (mean age: 65.22 ± 15.41 years, 183 men) with a median time of 30 days (range: 0-352) between both procedures. Among 37 patients (11.1%) a DBE was performed with an interval time greater than 90 days because of the following: Delay of the procedure because of the high anesthetic risk (n = 15), initial patient refusal (n = 9), other reasons (n = 13). Regarding the CE, gastric and SB median times were 18 (range: 1-480) and 237 (range: 28-518) minutes respectively. The entire
exploration of the SB by CE was achieved in 298 patients (89.8%). The median DBE time was 75 minutes (range: 7-220) and only in 18 patients the enteroscopy was incomplete. Most of the patients who underwent a direct-DBE with no previous CE performed had a massive and/or emergency OGIB, post-surgical alterations or contraindications to CE.

Overall diagnosis yield by DBE was higher within patients with a previous positive-CE compared to those who have a negative-CE for positive findings (79.3% vs. 27.9% respectively, \( p < 0.001 \)) and for the detection of SB lesions (79.5% vs. 46.9%, respectively, \( p < 0.001 \)). Overall diagnosis yield for positive findings was statistically superior by CE compared to DBE (81.6% vs. 69.9% respectively, \( p < 0.001 \)) (Table I).

Two-hundred thirty-four SB lesions in 271 positive findings were confirmed by CE, therefore 37 patients (13.6%) had a SB bleeding confirmed by CE with no underlying lesion identified. Of these 37 patients, 29 were confirmed by DBE to have the following: Angiodysplasia \( (n = 12) \), Dieulafoy’s lesion (DL) \( (n = 8) \), ulcers \( (n = 4) \), tumors or polyps \( (n = 1) \), diverticula \( (n = 1) \), jejunal varices \( (n = 1) \), arteriovenous malformation \( (n = 1) \) and bleeding with no underlying lesion identified \( (n = 1) \). The remaining 8 patients with a bleeding and no underlying lesion identified by CE had a negative-DBE. Thus, regarding only positive findings with a confirmed lesion, the CE and DBE achieved similar diagnosis yields (70.5% vs. 69.6%, \( p = 0.9 \)) (Table II).

The results of CE and DBE differed in 73 patients (22%) (56 CE-positive DBE-negative and 17 CE-negative DBE-positive cases). Among the 56 CE-positive DBE-negative patients, CE diagnosed angiodysplasias \( (n = 22, 39.28\%) \), ulcers \( (n = 17, 30.4\%) \), tumors \( (n = 6, 10.7\%) \), polyps \( (n = 2, 3.6\%) \), diverticula \( (n = 1, 1.8\%) \) and bleeding with no underlying lesion identified \( (n = 8, 14.3\%) \). Most of these lesions \( (n = 50, 89.3\%) \) were located in jejunum and the approach was by oral route in 45 cases (80.4%). The time interval between CE and DBE in these 56 false negatives of DBE was not statistically different compared to the time interval of all patients (median: 31, range: 2-310 days).

It is interesting to note that in 5 patients (29.4%) in whom the CE diagnosed one or more ulcers, non-significant isolated erosions were described by DBE considering this technique as negative result. In addition, in 6 patients (27.3%) in whom CE detected one or more angiodysplasias, DBE described the presence of indeterminate red spots
or isolated petechiae. These lesions were considered not sufficient to explain the OGIB and therefore categorized as negative result. However, the 17 CE-negative patients with a positive finding by DBE were diagnosed as follows: Angiodysplasia \((n = 5, 29.4\%)\), ulcers \((n = 4, 23.5\%)\), tumors \((n = 5, 29.4\%)\), diverticula \((n = 2, 11.8\%)\) and DL \((n = 1, 5.9\%)\). Furthermore, incomplete stenosis was observed by CE in 4 cases and it was confirmed in only one of them by DBE.

A comparison between diagnosis findings by both techniques is shown in table III. All lesions were identified similarly by both procedures. The only findings with a difference statistically significant in their diagnosis yield by CE and DBE were the bleeding with no underlying lesion identified \((11.1\% \text{ vs. } 0.3\% \text{ respectively, } p < 0.001)\) and the DL \((0.9\% \text{ vs. } 3.6\% \text{ respectively, } p = 0.004)\). Ulcers were detected in 12.7\% of patients by CE and 9.9\% of them by DBE, but this difference was not significant \((p = 0.1)\). Regarding tumors, the CE and DBE had 7 and 8 false negatives respectively \((30.4\% \text{ vs. } 33.3\%, p = 0.8)\).

Altogether, the kappa index for positive findings was moderate \((0.41 [95\% CI: 0.31-0.51])\). However, the degree of agreement between the results of CE and DBE by each type of lesion obtained varied values. This degree of agreement was very good for polyps \((0.89 [95\% CI: 0.78-0.99])\), good for angiodysplasias \((0.73 [95\% CI: 0.62-0.84])\) and tumors \((0.66 [95\% CI: 0.55-0.76])\) and moderate for ulcers \((0.56 [95\% CI: 0.46-0.67])\). Diverticula \((0.39 [95\% CI: 0.29-0.5])\) and DL \((0.39 [95\% CI: 0.31-0.48])\) achieved a fair agreement between both procedures.

**DISCUSSION**

The present study describes the degree of diagnosis agreement between CE and DBE in a series of 332 patients presented with OGIB, concluding a high diagnosis yield by both procedures assessed separately \((81.6\% \text{ vs. } 69.9\%)\). Despite of the moderate overall degree of agreement for positive findings, some variability for each type of lesion has been observed. The highest degree of agreement was achieved by polyps \((k = 0.89)\), vascular lesions \((k = 0.66)\) and tumors \((k = 0.66)\).

CE and DBE are well-recognized procedures to evaluate the SB in patients with OGIB. In these patients, strong evidence-based data suggest that CE should be used first \((10)\).
Most studies results concluded that the diagnostic yields of both procedures were similar (10-12). A meta-analysis of 2011 (7) showed that the pooled diagnostic yield for CE and DBE were 62% and 56% respectively. In our series, diagnosis yields for detecting SB lesions between both procedures were also similar (70.5% vs. 69.6%), having higher detection rates. DBE also clarified the origin of OGIB in 78.4% of patients with only ongoing-bleeding detected by CE with no underlying lesion identified. However, the diagnosis yield varies depending on several factors. Thus, within patients presented with overt-OGIB or previous positive CE, the rate of positive findings by DBE was higher. Recent data suggest that DBE should be proactively performed in patients with inconclusive or even negative CE findings (14, 15). In this sense, of 17 CE-negative patients, 7 (41.2%) were confirmed of having lesions by DBE (CE false negatives) in our study. Furthermore, several factors may have influenced the DBE false negatives (56 CE-positive DBE-negative cases).

The elapsed time between both procedures and the low-rate of DBEs exploring the entire SB could have justified the lack of positive findings in these patients. The difficulty in some cases to precisely locate distal jejunum/proximal ileum lesions by CE may also have influenced the endoscopic approach.

Concerning the variability in the agreement by type of lesion, in a recent meta-analysis (6), the DBE and CE diagnosis yields were similar for vascular disease, ulcerative and inflammatory lesion and tumors, with statistically different rates for polyps and fresh hemorrhage/clots. In our series, CE and DBE detected equally vascular lesions (44.6% vs. 47%), tumors (7.2% vs. 6.9%), polyps (4.8% vs. 3.9%) and diverticula (1.2% vs. 1.8%). Marmo et al. (16) reported 193 patients in whom the agreement for vascular and inflammatory lesions was good but not for polyps or tumors. Conversely, in our study, polyps and tumors achieved very good and good concordance values, respectively. In contrast with other studies (17), our results have shown a similar diagnosis rate for angiodysplasias and diverticula. The only findings with a difference statistically significant in the diagnosis yield between both procedures were the bleeding with no underlying lesion identified and the DL.

Considering the agreement within vascular lesions, even if the reliability was good (0.66 [95% CI: 0.55-0.77]), different subtypes obtained different values, with a kappa
index from 0.39 for the DL to 0.73 for angiodysplasias. It is interesting to note that the well-recognized multiplicity of this entity may have increased its diagnosis yield and degree of agreement for both techniques, especially within angiodysplasias. Furthermore, within the 37 patients with ongoing-bleeding and no underlying lesion detected by CE, 20 (54%) had vascular diseases confirmed by DBE (12 angiodysplasias, 8 DL). Thus, the DL is probably underdiagnosed and it can be responsible of approximately 21% of bleedings detected by CE with no cause identified, especially in patients with recurrent OGIB (18,19). Moreover, although the diagnostic agreement is good for ulcers and erosions, differential diagnosis between different enteritis may pose a greater difficulty by CE than by DBE, particularly between Crohn’s disease and non-steroidal anti-inflammatory drug-induced enteropathy. The incomplete stenosis, which allows the transit of the CE, is frequently associated with Crohn’s disease and may be overdiagnosed by this technique. In our study, DBE confirmed this finding in only 25% of cases. However, complete stenoses with CE retention were mostly confirmed by DBE and endoscopic extraction was performed confirming this finding. In addition, special consideration should be given to some lesions such as diverticula. This finding requires an associated bleeding to attribute the cause of OGIB, resulting in false negatives. Therefore, we are confident that it is important in clinical practice to rigorously assess the bleeding potential of different lesions in order to establish their significance on the clinical picture of each patient, facilitating further management and follow-up. Vascular lesions are very common and can be simply findings, presenting with other lesions with higher bleeding potential that may be the real cause of anemia. Thus, its true value should carefully interpreted in each case. It is also interesting to note that in our series, multiple angiodysplasias were detected in a higher ratio by CE than by DBE. This is probably related to several passages of the CE through the same SB segment, overestimating the number of these lesions. There are many limitations of our study. Firstly, this is a retrospective study with a referral bias because most patients were referred from other clinics, presenting with severe and/or recurrent OGIB, which has probably increased the overall diagnosis yield. In addition, the interobserver variability, the elapsed time between CE and DBE
and the different cleansing regimens previously administered to retrograde DBE may also have influenced the results. Because of the wide time interval in which the agreement is analyzed, the learning curve for endoscopists and the fact that they previously know the outcome of the CE are other factors to consider. Other limitation of our study is the possibility to detect many different types of lesions in one of the procedures, while the other procedure fail to detect the lesion with the highest bleeding potential. This may decrease the degree of agreement between both even if they have detected at least one of the lesions.

In conclusion, the present study confirms that although overall diagnostic yield by CE and DBE is similar with a moderate agreement between both, there are many factors which can modify these values, mainly the type of lesion. Thus, the agreement characteristics by type of lesion should be considered in order to correctly interpret the results of CE and DBE and apply them properly in the diagnostic-therapeutic algorithm of OGIB.

REFERENCES
### Table I. Positive findings detected by capsule endoscopy (CE) and double-balloon enteroscopy (DBE)

<table>
<thead>
<tr>
<th>CE</th>
<th>DBE</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>215</td>
<td>56</td>
</tr>
<tr>
<td>Negative</td>
<td>17</td>
<td>44</td>
</tr>
<tr>
<td>Total (%)</td>
<td>232</td>
<td>100</td>
</tr>
</tbody>
</table>

CE: Capsule endoscopy; DBE: Double-balloon enteroscopy.
Table II. Small bowel lesions detected by capsule endoscopy (CE) and double-balloon enteroscopy (DBE)

<table>
<thead>
<tr>
<th></th>
<th><strong>CE</strong></th>
<th><strong>DBE</strong></th>
<th><strong>Total (%)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>186</td>
<td>48</td>
<td>234 (70.5%)</td>
</tr>
<tr>
<td>Negative</td>
<td>46</td>
<td>52</td>
<td>98 (29.5%)</td>
</tr>
<tr>
<td><strong>Total (%)</strong></td>
<td>232 (69.9%)</td>
<td>100 (30.1%)</td>
<td>332</td>
</tr>
</tbody>
</table>

CE: Capsule endoscopy; DBE: Double-balloon enteroscopy.
### Table III. Comparative analysis of the diagnosis yield between capsule endoscopy (CE) and double-balloon enteroscopy (DBE) in 332 patients

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>CE (%)</th>
<th>DBE (%)</th>
<th>p</th>
<th>Kappa Index (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular lesions</td>
<td>148 (44.6%)</td>
<td>156 (47%)</td>
<td>0.3</td>
<td>0.66 (0.55-0.77)</td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>143 (43.1%)</td>
<td>139 (41.9%)</td>
<td>0.8</td>
<td>0.73 (0.62-0.84)</td>
</tr>
<tr>
<td>Dieulafoy’s lesion</td>
<td>3 (0.9%)</td>
<td>12 (3.6%)</td>
<td>0.004*</td>
<td>0.39 (0.31-0.48)</td>
</tr>
<tr>
<td>AVM</td>
<td>1 (0.3%)</td>
<td>3 (0.9%)</td>
<td>-</td>
<td>0.50 (0.41-0.59)</td>
</tr>
<tr>
<td>Varices</td>
<td>1 (0.3%)</td>
<td>2 (0.6%)</td>
<td>-</td>
<td>0.67 (0.56-0.77)</td>
</tr>
<tr>
<td>Ulcers or erosions</td>
<td>42 (12.7%)</td>
<td>33 (9.9%)</td>
<td>0.1</td>
<td>0.56 (0.46-0.67)</td>
</tr>
<tr>
<td>Tumors</td>
<td>24 (7.2%)</td>
<td>23 (6.9%)</td>
<td>-</td>
<td>0.66 (0.55-0.76)</td>
</tr>
<tr>
<td>Polyps</td>
<td>16 (4.8%)</td>
<td>13 (3.9%)</td>
<td>0.2</td>
<td>0.89 (0.78-0.99)</td>
</tr>
<tr>
<td>Diverticulum</td>
<td>4 (1.2%)</td>
<td>6 (1.8%)</td>
<td>0.6</td>
<td>0.39 (0.29-0.50)</td>
</tr>
<tr>
<td>Bleeding without lesion</td>
<td>37 (11.1%)</td>
<td>1 (0.3%)</td>
<td>&lt;</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

**Positive findings**

<table>
<thead>
<tr>
<th>CE (%)</th>
<th>DBE (%)</th>
<th>p</th>
<th>Kappa Index (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>271 (81.6%)</td>
<td>232 (69.9%)</td>
<td>&lt;</td>
<td>0.41 (0.31-0.51)</td>
</tr>
</tbody>
</table>

**Positive lesions**

<table>
<thead>
<tr>
<th>CE (%)</th>
<th>DBE (%)</th>
<th>p</th>
<th>Kappa Index (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>234 (70.5%)</td>
<td>231 (69.6%)</td>
<td>0.9</td>
<td>0.33 (0.23-0.44)</td>
</tr>
</tbody>
</table>

*Statistically significant. CE: Capsule endoscopy; DBE: Double-balloon enteroscopy. AVM: Arteriovenous malformation.
Fig. 1. Flowchart of patients in whom a CE and/or DBE was performed.

Total CE performed between 2004-2014
n = 1,768
CE performed for OGIB
n = 1,209 (68.4%) in 1,078 patients
Valid CE
n = 1,037 (41 null)
\( n = 978 \) (excluding 59 CE with lesions outside the SB)
CE diagnosis yield
- 487 positive-CE (47%), of which 428 (43.8%) in SB
- 550 negative-CE (53%)

Total DBE performed between 2004-2014
n = 621 patients
Total DBE performed for OGIB
n = 381 DBE in 361 patients (58.1%)
DBE performed for OGIB within patients with previous CE
n = 332
DBE performed for OGIB within patients without previous CE
n = 29
Overall DBE diagnosis yield
270 positive-DBE (74.8%) \( \text{vs} \) 260 positives for the SB (72%)
85/97 (87.6%) positives in overt-OGIB and 175/264 (66.3%) in occult-OGIB

Comparative analysis (n = 332)
- Overall diagnosis yield for positive findings between CE and DBE: 81.6% vs. 69.9%, \( p < 0.001 \)
- Overall diagnosis yield for lesions diagnosed by CE and DBE: 70.5% vs. 69.6%, \( p = 0.9 \)
- The results of CE and DBE differed in 73 patients (22%)