# Supplementary Material

Endoscopic papillectomy for ampullary lesions: a pooled analysis with meta-regression analysis of outcomes

Marco Spadaccini, Gianluca Franchellucci, Matteo Colombo, Cecilia Binda, Maria Terrin, Giacomo Marcozzi, Valeria Poletti, Marta Andreozzi, Alessandro De Marco, Roberto De Sire, Daryl Ramai, Silvia Carrara, Cesare Hassan, Benedetto Mangiavillano, Alessandro Fugazza, Amrita Sethi, Carlo Fabbri, Antonio Facciorusso, Andrea Anderloni, Alessandro Repici; and the endoscopic papillectomy study group

CONTENTS





Endoscopy | DOI 10.1055/a-2724-3905 | 

## Appendix 1s

### Search strategy

A specialist with expertise in systematic reviews designed the search strategy (M.S.). The studies were identified using specific medical subject headings (MeSH) and keywords like “endoscopic papillectomy” and “endoscopic ampullectomy.” The search was limited to articles published in English.

The Medline search strategy employed was: "endoscopy"[MeSH Terms] OR "endoscopy"[All Fields] OR "endoscopic"[All Fields]) AND papillectomy[All Fields] OR ("endoscopy"[MeSH Terms] OR "endoscopy"[All Fields] OR "endoscopic"[All Fields]) AND ampullectomy[All Fields].

### Selection Process

Two authors of the review (M.S. and G.F.) independently evaluated the titles and abstracts from the search based on the inclusion criteria. Full reports were obtained for titles that seemed to meet the criteria or where there was any doubt. The pairs then reviewed the full texts and abstracts to determine if they fit the inclusion criteria, resolving disagreements through discussions among all authors. The reasons for excluding trials were documented. Neither review author was blinded to the journal titles or to the authors or institutions of the studies. If multiple articles were available for a single study, we considered the most recent publication, supplementing it with data from a more comprehensive version if needed.

### Data Extraction

Using standardized forms, two reviewers (M.S. and G.F.) independently extracted data from each eligible study in duplicate. Disagreements were resolved through discussion, with unresolved issues referred to two arbitrators (A.R. and A.F.). The extracted data included publication status, study design and location, number of centers involved, enrollment period, total number of lesions treated, number of sporadic or familial lesions, average number of lesions per center per year, patient demographics (average age, gender), average tumor size, intraductal growth, preoperative assessments, use of prophylactic biliary or pancreatic stenting, numbers of lesions completely resected, en-bloc resections, curative resections, need for adjunctive treatments during the same session, adverse events (such as bleeding, perforations, pancreatitis, cholangitis, papillary stenosis, deaths), required treatments (like blood transfusions or surgeries), histological types of resected lesions (e.g., adenoma, submucosal cancer, deep infiltration, other histologies), mean follow-up duration, recurrence counts, endoscopic re-treatments, surgeries due to incompleteness or recurrence, overall surgical needs, number of patients with curative resections without recurrences, and patients managed solely by endoscopy.

### Quality assessment

Quality assessment was performed according to the modified Newcastle-Ottawa Scale for non-randomized studies, ranging from 0 (low-quality) to 5 (high-quality). Two different reviewers (MS, GF) assessed quality measures for included studies and discrepancies were adjudicated by discussion.



Endoscopy | DOI 10.1055/a-2724-3905 | 

**Table 1s:** Newcastle–Ottawa scale for quality assessment

| Author (Reference) | Publication year | Selection | Comaparability | Exposure | Total Score |
|---|---|---|---|---|---|
| Norton | 2002 | 2 | 1 | 3 | 5 |
| Catalano | 2004 | 2 | 1 | 3 | 6 |
| Cheng | 2004 | 2 | 1 | 2 | 5 |
| Katsinelos | 2006 | 2 | 1 | 3 | 6 |
| Jung | 2009 | 2 | 1 | 3 | 6 |
| Ghidirim | 2009 | 2 | 1 | 2 | 5 |
| Boix | 2009 | 2 | 1 | 2 | 5 |
| Kim | 2009 | 3 | 1 | 2 | 6 |
| Irani | 2009 | 3 | 1 | 2 | 6 |
| Hwang | 2010 | 3 | 0 | 2 | 5 |
| Patel | 2011 | 3 | 0 | 2 | 5 |
| Ito | 2012 | 3 | 1 | 2 | 6 |
| Salmi | 2012 | 2 | 1 | 2 | 6 |
| Ceppa | 2013 | 3 | 1 | 2 | 6 |
| Kim SH | 2013 | 3 | 1 | 2 | 6 |
| Laleman | 2013 | 3 | 0 | 2 | 5 |
| Will | 2013 | 3 | 0 | 2 | 5 |
| Ridtitid | 2014 | 3 | 1 | 2 | 6 |
| Onkendi | 2014 | 3 | 0 | 2 | 5 |
| Napoleon | 2014 | 3 | 1 | 2 | 6 |
| Ma | 2014 | 3 | 0 | 2 | 5 |
| Shim | 2014 | 3 | 0 | 2 | 5 |
| De Palma | 2015 | 3 | 0 | 2 | 5 |
| Lee | 2016 | 3 | 1 | 2 | 6 |
| Tsuji | 2015 | 3 | 1 | 2 | 6 |
| Soma | 2015 | 2 | 1 | 2 | 5 |
| Dubois | 2016 | 2 | 0 | 2 | 4 |
| Kang | 2017 | 2 | 0 | 2 | 5 |
| Klein | 2018 | 3 | 1 | 2 | 6 |
| Abe | 2022 | 3 | 1 | 2 | 6 |
| Attila | 2018 | 2 | 1 | 1 | 4 |
| Camus | 2018 | 3 | 1 | 2 | 6 |

| | | | | | |
|---|---|---|---|---|---|
| Cho | 2023 | 3 | 1 | 2 | 6 |
| Choi S | 2022 | 2 | 1 | 2 | 5 |
| Choi JH | 2023 | 2 | 1 | 2 | 5 |
| Chung | 2018 | 3 | 1 | 2 | 6 |
| Cui | 2022 | 3 | 1 | 2 | 6 |
| Gondran | 2022 | 3 | 1 | 2 | 6 |
| Han | 2023 | 2 | 1 | 2 | 5 |
| Iwasaki | 2020 | 3 | 2 | 1 | 6 |
| Kagawa | 2019 | 3 | 0 | 2 | 5 |
| Li S | 2018 | 3 | 1 | 2 | 6 |
| Lee Kj | 2022 | 3 | 2 | 2 | 6 |
| Meunier | 2021 | 2 | 1 | 2 | 5 |
| Miwa | 2021 | 3 | 1 | 2 | 6 |
| Miyamoto | 2023 | 2 | 1 | 2 | 5 |
| Nam | 2018 | 2 | 1 | 3 | 6 |
| Perez Cuadrato Robles | 2019 | 2 | 1 | 3 | 6 |
| Sahar | 2019 | 2 | 1 | 3 | 6 |
| Seyfried | 2022 | 2 | 1 | 3 | 6 |
| Singh | 2024 | 2 | 1 | 3 | 6 |
| Suzuki | 2023 | 2 | 1 | 2 | 5 |
| Takada | 2023 | 2 | 1 | 2 | 5 |
| Trung | 2023 | 2 | 1 | 3 | 6 |
| Wang | 2023 | 2 | 1 | 3 | 6 |
| Xie | 2023 | 2 | 1 | 3 | 6 |
| Yamamoto | 2018 | 2 | 1 | 3 | 6 |
| Yoon | 2023 | 2 | 1 | 3 | 6 |
| Binda | 2024 | 2 | 1 | 3 | 6 |
| Hyun | 2018 | 2 | 1 | 3 | 6 |
| Park | 2022 | 2 | 1 | 3 | 6 |

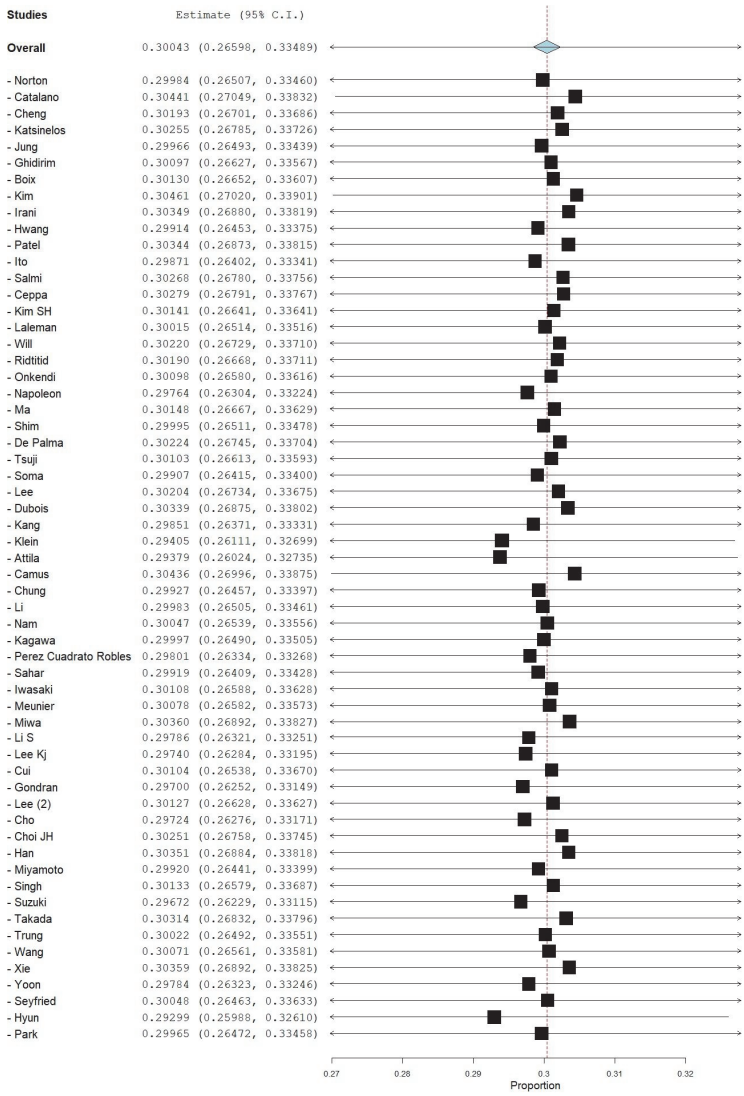


Endoscopy | DOI 10.1055/a-2724-3905 | 

**Table 2s:** Adverse events; Subgroup Analysis

| Variables | | RR | 95%CI | $I^2$ (%) | $\tau^2$ |
|---|---|---|---|---|---|
| **Study design** | Prospective | 32.6 | 22.2-42.7 | 88.23 | 0.01 |
| | Retrospective | 29.5 | 25.7-33.3 | 87.97 | 0.01 |
| **Geographical area** | Eastern | 34.8 | 28.7-40.9 | 92.16 | 0.02 |
| | Western | 25.7 | 21.6-29.8 | 84.96 | 0.01 |
| **Pubblication year** | Before 2021 | 28.9 | 23.9-33.9 | 89.43 | 0.02 |
| | 2021 and after | 31.9 | 27.7-35.9 | 81.56 | 0.01 |

**Figure 1s:** Overall adverse events: leave-one-out sensitivity analysis.






Endoscopy | DOI 10.1055/a-2724-3905 | 

**Figure 2s:** Bleeding; Forrest plot.

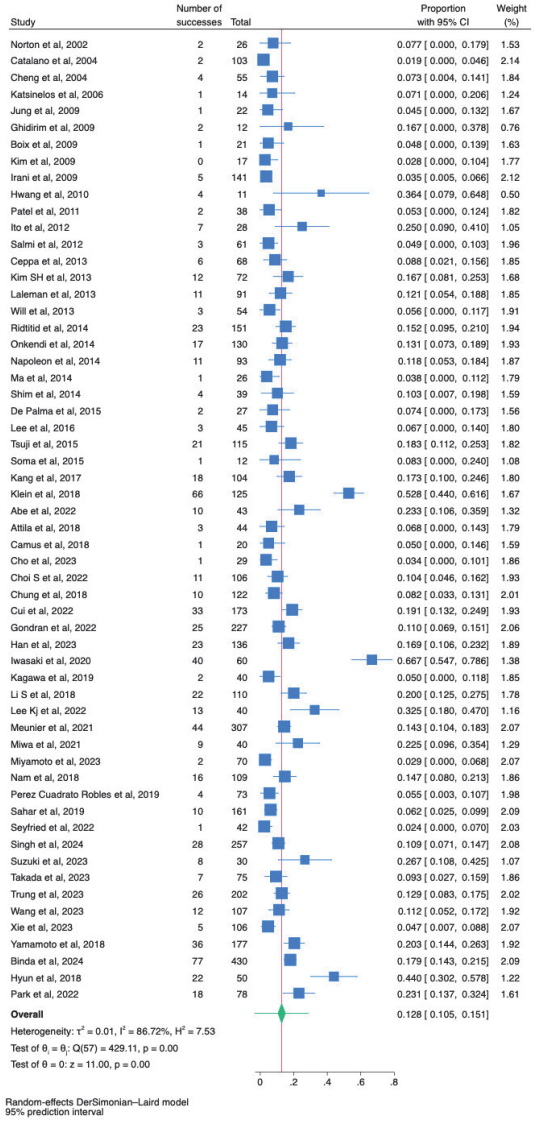



**Table 3s:** Bleeding: Meta Regression analysis

| Covariate | Coefficients | Lower Bound | Upper Bound | Standard Error | P-value |
|---|---|---|---|---|---|
| Age | 0.003 | -0.002 | 0.008 | 0.002 | 0.243 |
| **Female** | **-0.221** | **-0.498** | **- 0.02** | **0.121** | **0.048** |
| Lesions for center/year | -0.003 | -0.015 | 0.009 | 0.006 | 0.654 |
| Size (mm) | -0.001 | -0.002 | 0.001 | < 0.00 | 0.315 |
| Intraductal | 0.002 | - 0.003 | 0.006 | 0.002 | 0.497 |
| RFA | 0.019 | - 0.165 | 0.203 | 0.094 | 0.837 |



Endoscopy | DOI 10.1055/a-2724-3905 | 

**Figure 3:** Pancreatitis; Forrest Plot.

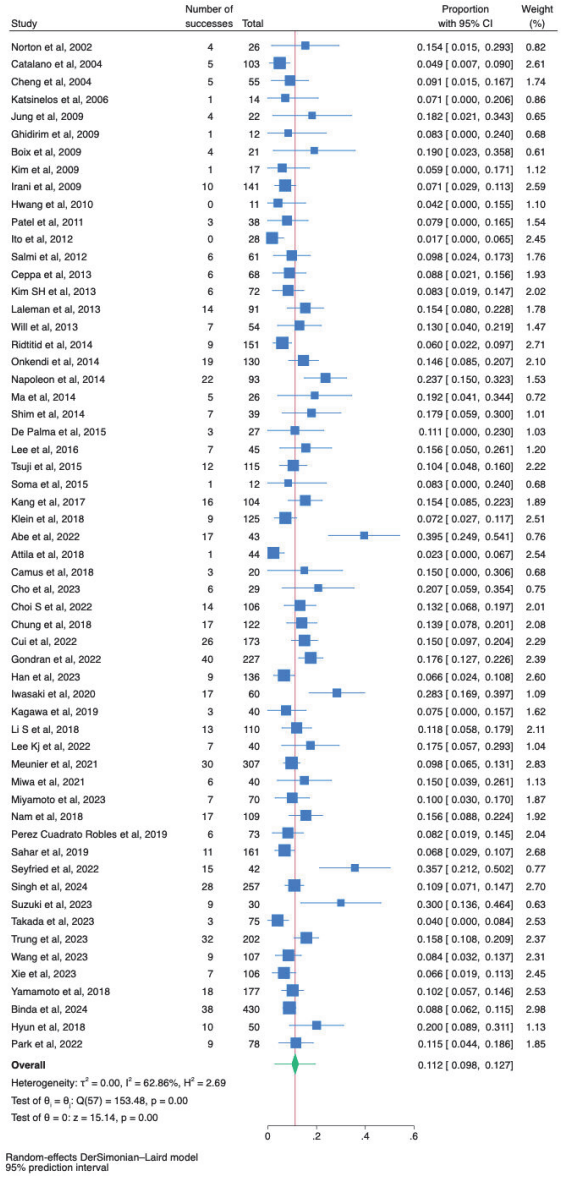



**Table 4s:** Pancreatitis: Meta Regression analysis

| Covariate | Coefficients | Lower Bound | Upper Bound | Standard Error | P-value |
|---|---|---|---|---|---|
| **Pancreatic Stent** | **-0.095** | **-0.182** | **--0.009** | **0.044** | **0.031** |
| Age | 0.000 | -0.001 | 0.002 | < 0.001 | 0.689 |
| Female | -0.024 | -0.05 | 0.098 | 0.038 | 0.528 |
| Lesions for center/year | 0.001 | -0.002 | 0.003 | 0.01 | 0.610 |
| Size (mm) | -0.000 | -0.006 | 0.006 | 0.003 | 0.954 |
| Intraductal | 0.060 | - 0.176 | 0.295 | 0.120 | 0.619 |
| RFA | 0.020 | - 0.073 | 0.113 | 0.047 | 0.680 |

**Figure 4s:** Post Procedural Cholangitis; Forrest Plot

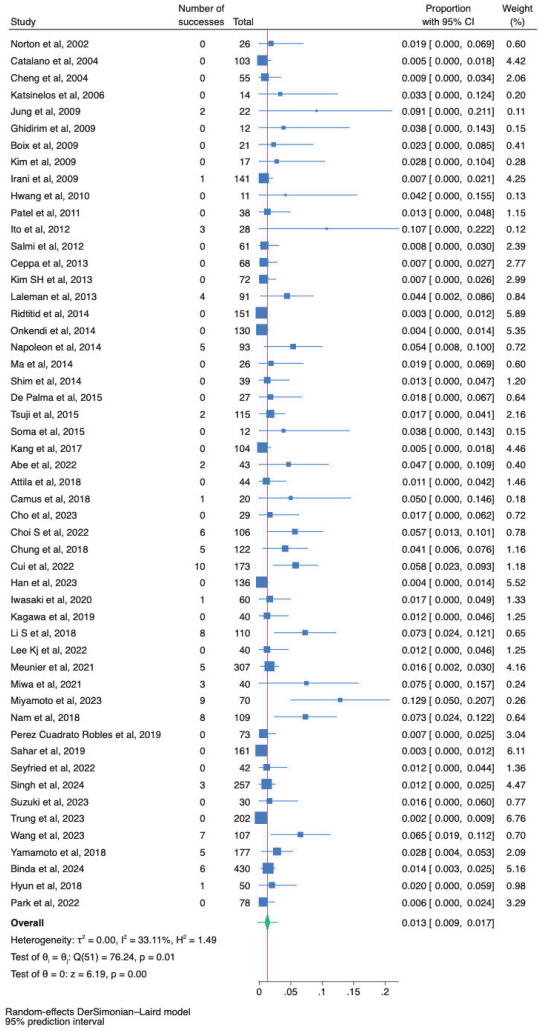



**Table 5s:** Cholangitis: Meta-regression analysis

| Covariate | Coefficients | Lower Bound | Upper Bound | Standard Error | P-value |
|---|---|---|---|---|---|
| Biliary Stent | - 0.017 | -0.042 | 0.008 | 0.013 | 0.180 |
| Age | 0.000 | -0.001 | <0.001 | <0.001 | 0.944 |
| **Female** | **-0.019** | **-0.030** | **- 0.008** | **0.006** | **<0.001** |
| Size | -0.001 | - 0.002 | 0.001 | < 0.001 | 0.315 |
| Lesions for center/year | 0.000 | - 0.001 | 0.001 | < 0.001 | 0.940 |
| Intraductal | 0.008 | - 0.053 | 0.068 | 0.031 | 0.807 |
| RFA | -0.015 | -0.040 | 0.010 | 0.013 | 0.234 |

**Figure 5s:** Post Procedural Perforations; Forrest Plot

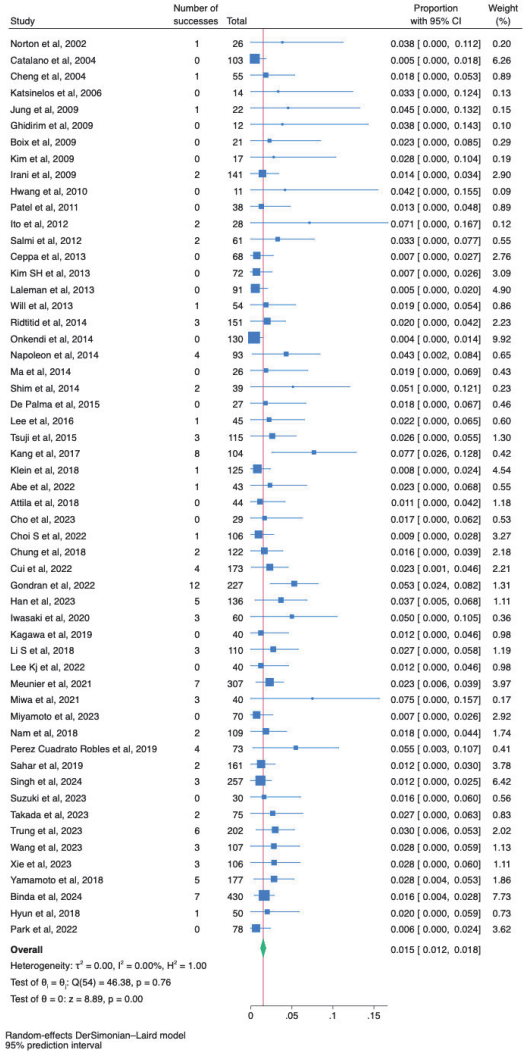



**Table 6s:** Perforation; Meta Regression analysis.

| Covariate | Coefficients | Lower Bound | Upper Bound | Standard Error | P-value |
|---|---|---|---|---|---|
| Biliary Stent | -0.017 | -0.042 | 0.008 | 0.013 | 0.180 |
| Age | 0.000 | -0.001 | 0.001 | < 0.001 | 0.944 |
| Female | -0.005 | -0.024 | 0.015 | 0.010 | 0.630 |
| Lesions for center/year | 0.000 | -0.001 | 0.001 | <0.001 | 0.940 |
| Size (mm) | -0.001 | -0.002 | 0.001 | < 0.00 | 0.315 |
| **Intraductal** | **0.044** | **0.027** | **0.125** | **0.031** | **0.038** |
| RFA | 0.015 | - 0.040 | 0.010 | 0.013 | 0.234 |

**Figure 6s:** Post Procedural Strictures; Forrest Plot

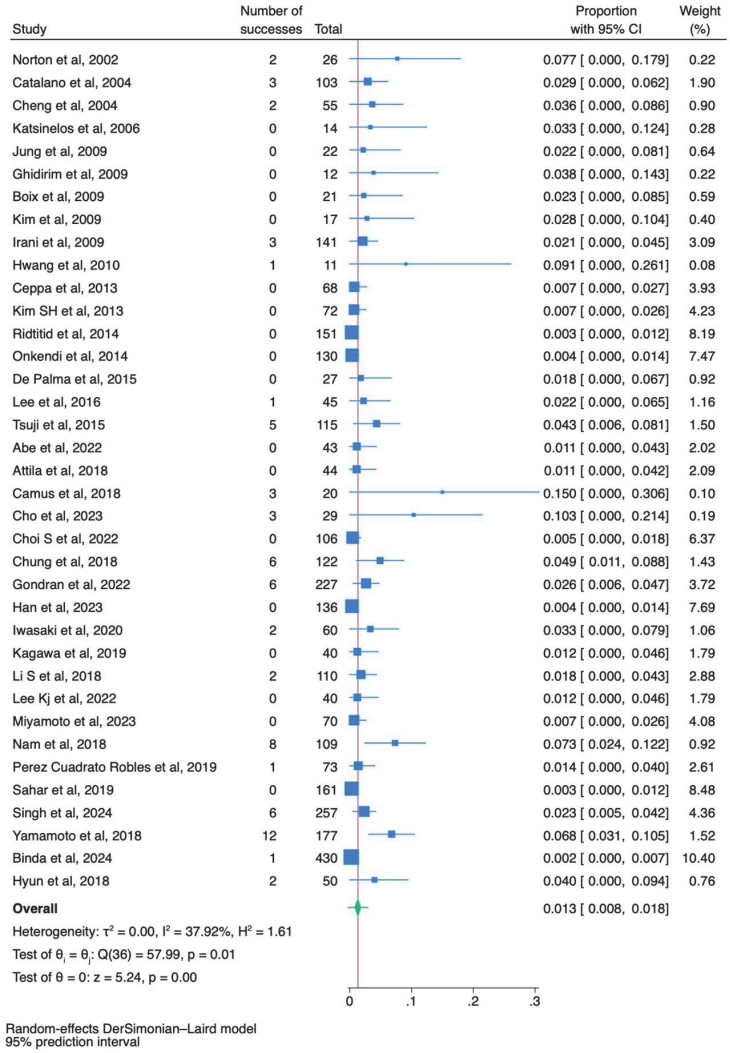
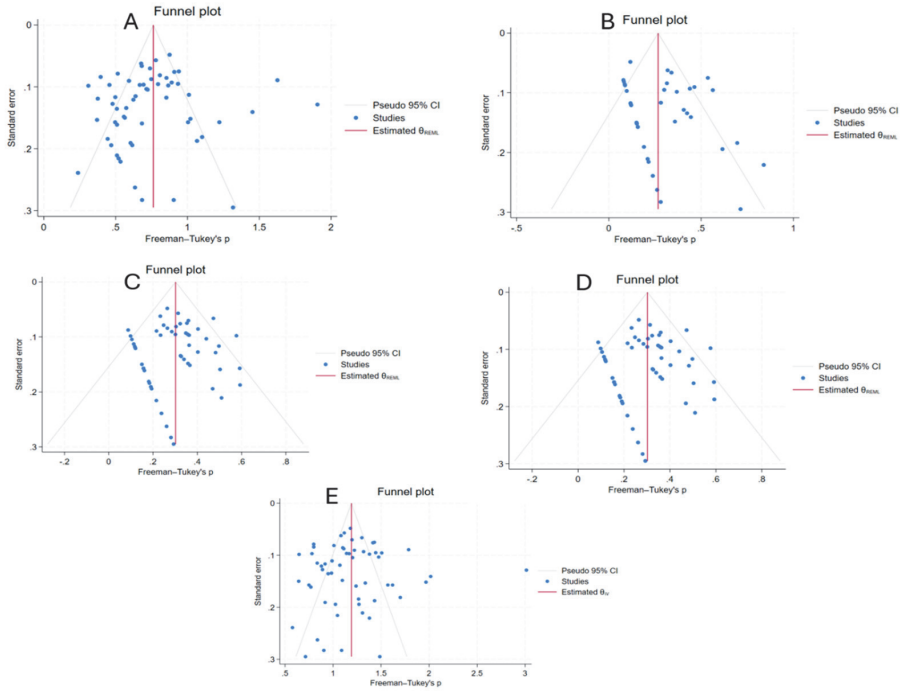



**Table 7s:** Biliary Stricture; Meta Regression analysis

| Covariate | Coefficients | Lower Bound | Upper Bound | Standard Error | P-value |
|---|---|---|---|---|---|
| Pancreatic Stent | -0.015 | -0.042 | 0.012 | 0.014 | 0.278 |
| Biliary Stent | -0.014 | -0.039 | 0.011 | 0.013 | 0.271 |
| Age | -0.001 | -0.003 | 0.000 | <0.001 | 0.084 |
| Female | -0.038 | -0.078 | 0.002 | 0.020 | 0.066 |
| Size | -0.001 | - 0.002 | 0.001 | < 0.001 | 0.420 |
| Lesions for center/year | 0.001 | - 0.000 | 0.002 | < 0.001 | 0.221 |
| **RFA** | **0.033** | **0.008** | **0.057** | **0.012** | **0.008** |

**Figure 7s:** Funnel Plot; safety outcomes, Figure A: Funnel Plot for Bleeding, B Funnel Plot for biliary stricture, C: Funnel plot for Pancreatitis, D: Funnel Plot for Perforation, E: Funnel Plot for Adverse Event Outcome Overall






Endoscopy | DOI 10.1055/a-2724-3905 | 

**Figure 8s**: En-bloc resection; Forrest Plot

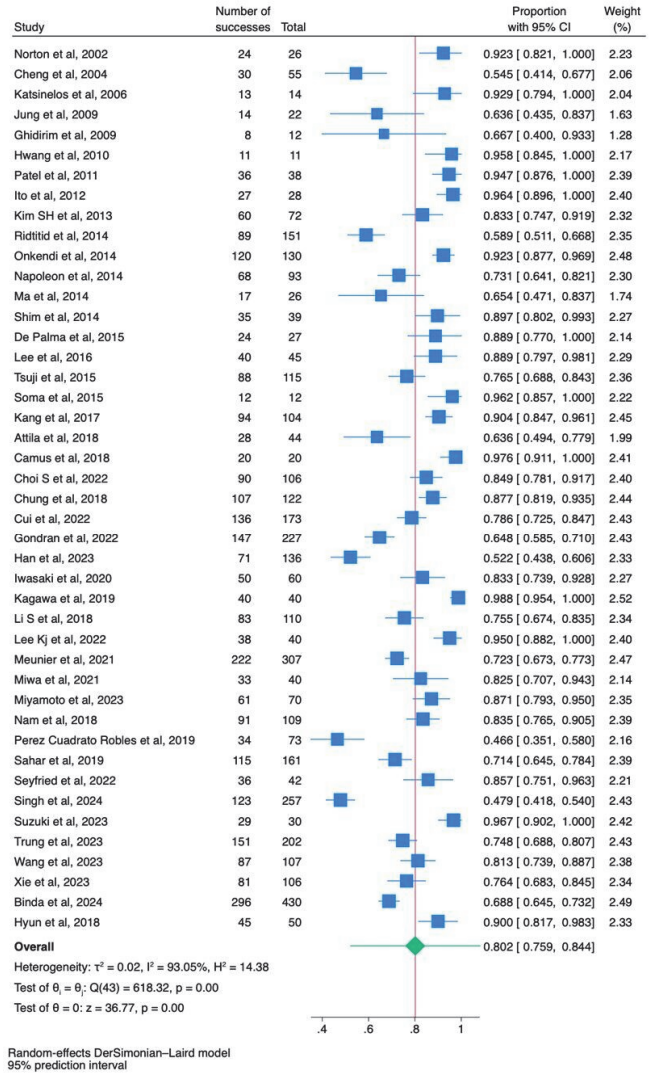


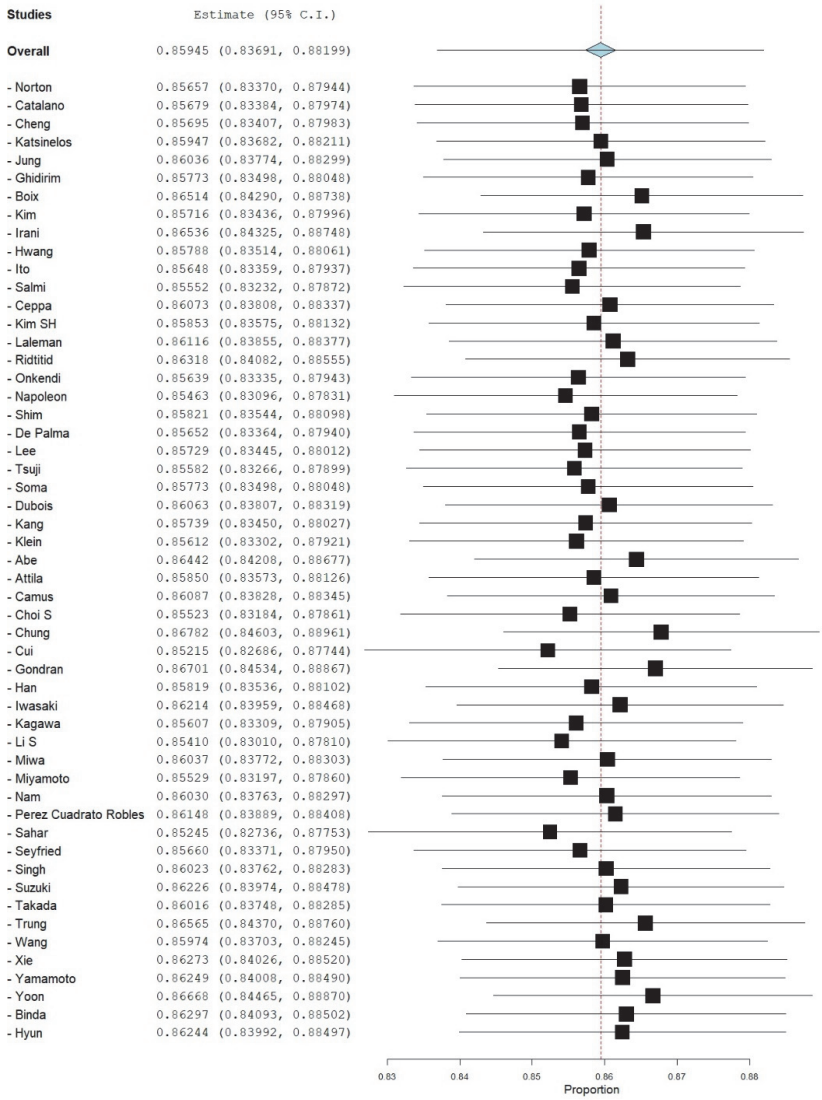

**Table 8s:** Complete Resection: Meta Regression analysis.

| Covariate | Coefficients | Lower Bound | Upper Bound | Standard Error | P-value |
|---|---|---|---|---|---|
| Lesions for center/year | 0.004 | 0.003 | 0.012 | 0.004 | 0.220 |
| Size (mm) | -0.009 | -0.023 | 0.005 | 0.007 | 0.202 |
| **Intraductal** | **-0.647** | **-1.399** | **-0.105** | **0.384** | **0.042** |

**Table 9s:** Complete resection, Recurrence; Subgroup Analysis

| Outcomes | Variables | | RR | 95%CI | $I^2$ (%) | $\tau^2$ |
|---|---|---|---|---|---|---|
| **Complete resection** | **Study design** | Prospective | 93.8 | 90.4-97.2 | 85.90 | 0.00 |
| | | Retrospective | 84.3 | 81.6-87.0 | 96.15 | 0.01 |
| | **Geographical area** | Eastern | 88.5 | 83.5-88.9 | 94.69 | 0.00 |
| | | Western | 85.1 | 81.2-89.0 | 96.34 | 0.01 |
| | **Pubblication year** | Before 2021 | 87.9 | 85.4-90.4 | 93.55 | 0.00 |
| | | 2021 and after | 81.2 | 75.6-86.8 | 97.60 | 0.01 |
| **Recurrence** | **Study design** | Prospective | 8.5 | 3.3-13.7 | 73.87 | 0.00 |
| | | Retrospective | 16.4 | 12.7-20.2 | 94.25 | 0.01 |
| | **Geographical area** | Eastern | 13.4 | 9.7-17.2 | 89.87 | 0.01 |
| | | Western | 16.8 | 11.0-22.7 | 94.10 | 0.02 |
| | **Pubblication year** | Before 2021 | 12.0 | 9.1-14.9 | 93.29 | 0.00 |
| | | 2021 and after | 21.0 | 12.2-29.8 | 93.36 | 0.02 |

**Figure 9s:** Complete resection: leave-one-out sensitivity analysis.






Endoscopy | DOI 10.1055/a-2724-3905 | 

**Figure 10s:** Recurrence after complete resection; Forrest plot.

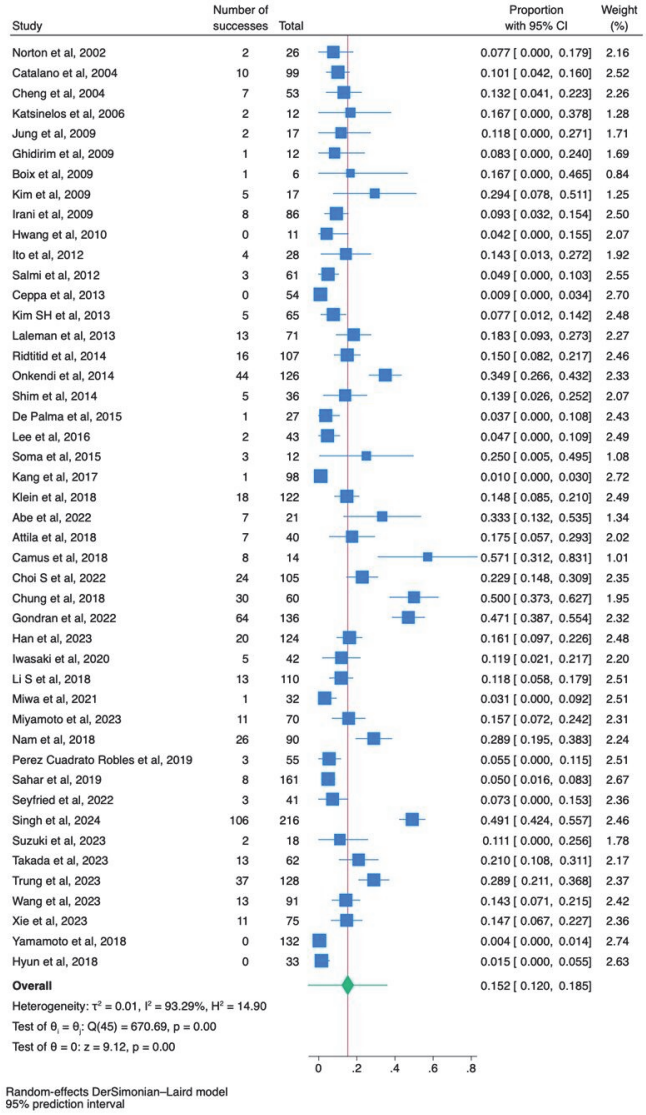



**Table 10s:** Recurrence: Meta Regression analysis.

| Covariate | Coefficients | Lower Bound | Upper Bound | Standard Error | P-value |
|---|---|---|---|---|---|
| Lesions for center/year | -0.005 | -0.012 | 0.003 | 0.004 | 0.219 |
| Size (mm) | 0.008 | -0.006 | 0.022 | 0.007 | 0.281 |
| Intraductal | -0.138 | -0.696 | 0.421 | 0.285 | 0.629 |
| AEs | -0.020 | -0.224 | 0.185 | 0.105 | 0.851 |
| HGD | -0.138 | -0.397 | 0.120 | 0.132 | 0.293 |

**Figure 11s:** Recurrence: leave-one-out sensitivity analysis.

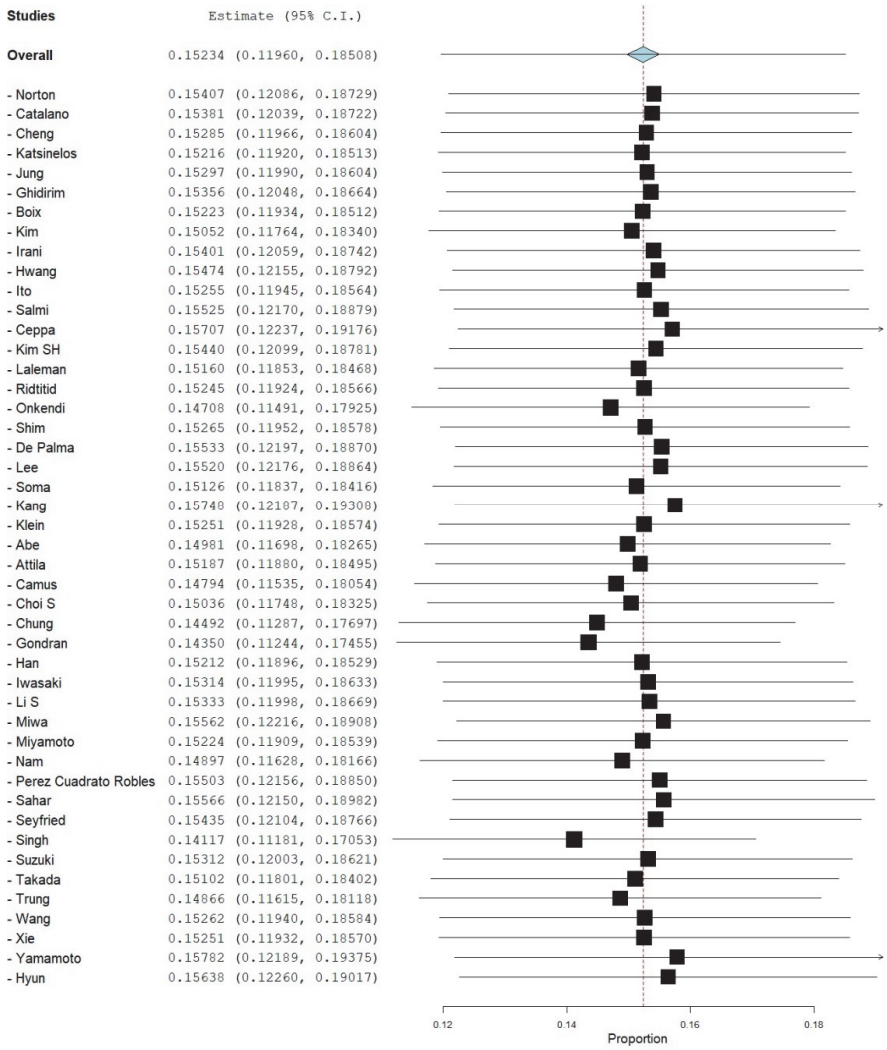
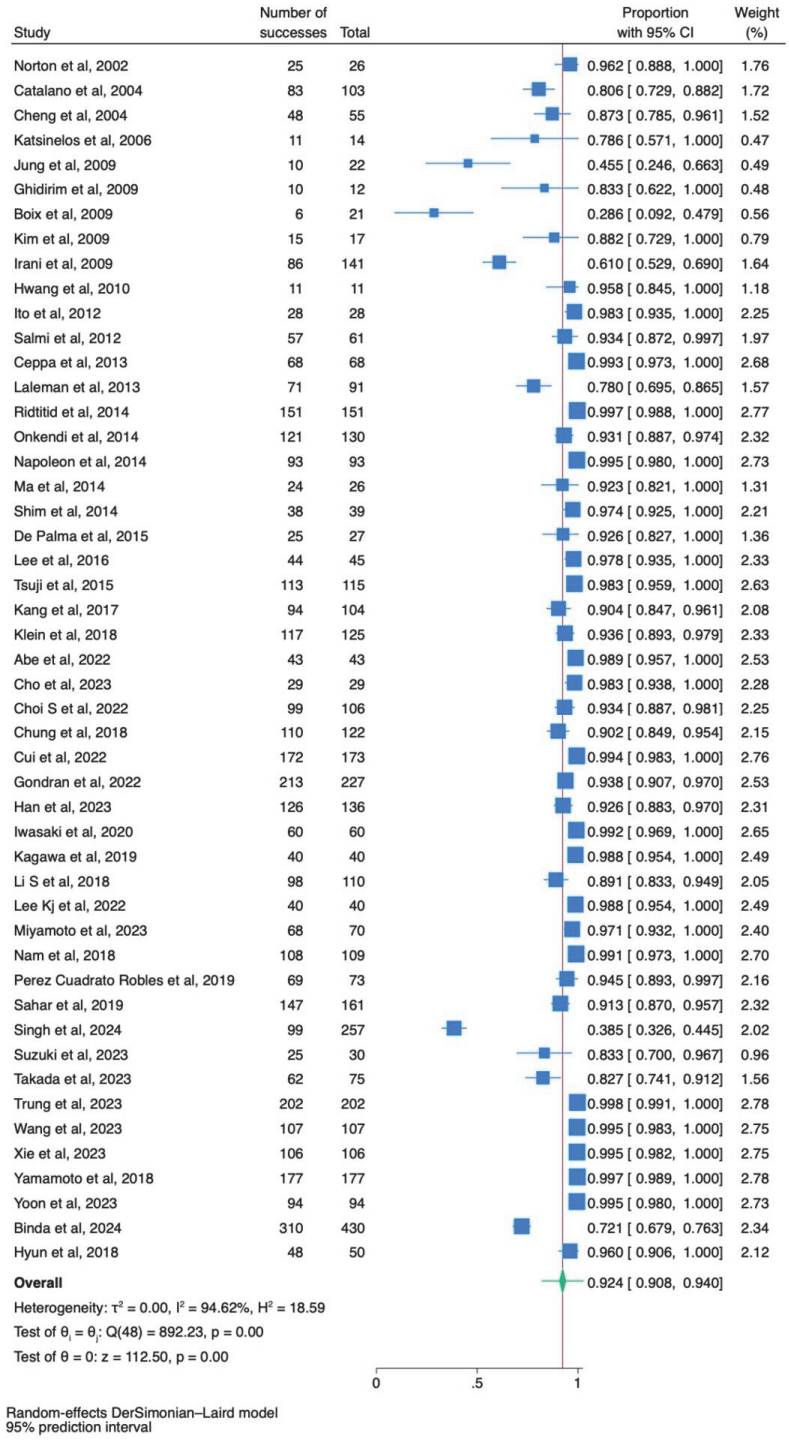


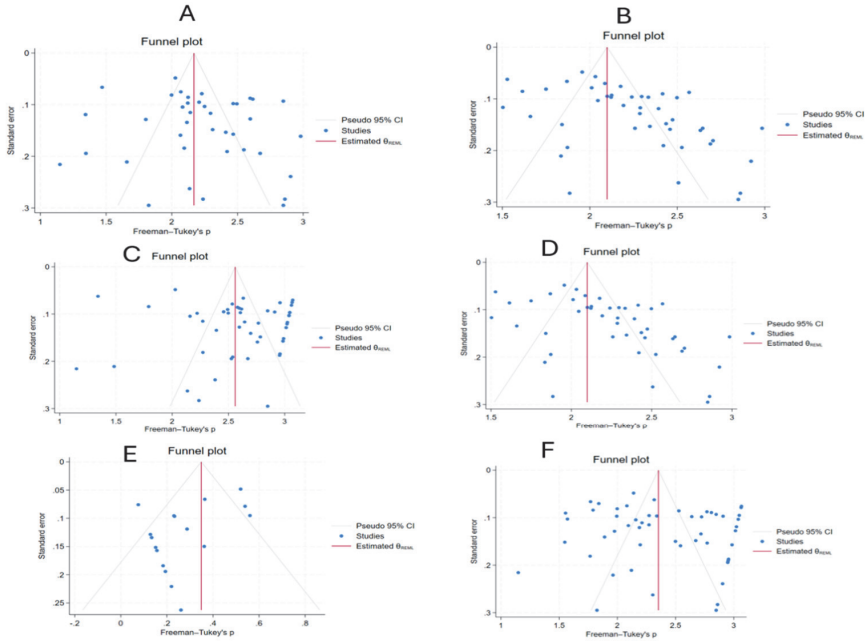
**Figure 12s:** Endoscopically managed lesions; Forrest plot.






Endoscopy | DOI 10.1055/a-2724-3905 | 

**Figure 13s.** Funnel plots. Efficacy outcomes. Figure A: Funnel Plot for Curative resection, B Funnel Plot En bloc resection, C: Funnel plot Endoscopically managed lesion, D: Funnel Plot Recurrence, E Funnel Plot Surgery for recurrence, F: Funnel Plot Complete Resection






Endoscopy | DOI 10.1055/a-2724-3905 | 