TOKYO criteria: Standardized reporting system for endoscopic biliary stent placement

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ABSTRACT

Placement of a plastic or metal stent via endoscopic retrograde cholangiopancreatography (ERCP) currently serves as the first-line procedure for obstructive jaundice and acute cholangitis. Dysfunction of the biliary stent causes recurrence of symptoms and often requires reinterventions and hospitalizations. Therefore, duration of stent patency is commonly used as the primary endpoint in clinical studies of biliary stents. However, owing to considerable heterogeneity between studies in reporting of biliary stent patency, it has been difficult to compare and integrate results of independent studies. There has been between-study heterogeneity in definitions of stent patency, statistics reported for survival curves of stent patency, and methods to treat censored cases. In addition to stent occlusion, stent migration is a major cause of recurrent biliary obstruction after covered metal stent placement, which further complicates the reporting of stent patency. Reporting of functional success and adverse events has been also inconsistent between the studies. From the perspective of evidence-based medicine, the variations in the definitions of outcome variables potentially hinder robust meta-analyses. To overcome the issues due to the lack of outcome reporting guidelines on the topic, the TOKYO criteria 2014 for reporting outcomes associated with endoscopic transpapillary placement of biliary stents have been proposed. Due to their comprehensiveness, the TOKYO criteria can be readily utilized to evaluate various types of biliary stent placement using ERCP, irrespective of types of stents and location of biliary stricture. In this article, we review the TOKYO criteria as a standardized reporting system for endoscopically-placed biliary stents. We also discuss potential controversial issues in the application of the TOKYO criteria. Given that endoscopic ultrasound-guided biliary drainage is increasingly utilized for cases with failed ERCP or altered gastrointestinal anatomy, we further propose a potential application of the TOKYO criteria to reporting of outcomes of this procedure.

Introduction

In clinical research, a standardized outcome reporting system is mandatory to interpret study results appropriately and to ensure comparability of different studies. The study results reported based on different reporting systems may be difficult to be compared and integrated, potentially compromising robust pooled- and meta-analyses.1 The STROBE (STrengthening the Reporting of Observational studies in Epidemiology),2 CONSORT (CONsolidated Standards Of Reporting Trials),3 and PRISMA (the Preferred Reporting Items for Systematic reviews and Meta-Analyses)4 statements have been successfully utilized for reporting results of observational cohort studies, randomized controlled trials (RCTs), and meta-analyses, respectively. However, those guidelines have focused mainly on standardization of essential and general items that should be reported in corresponding types of studies. Therefore, clear and standardized definitions of outcome variables are required for a specific research topic of interest.

Endoscopic placement of a biliary stent has remained a cornerstone of management of benign and malignant biliary strictures.5–10 In clinical studies of biliary stents, duration of stent patency is often used as the primary outcome variable and typically defined as the time between stent placement and dysfunction. The duration of stent patency directly affects patients’ quality of life and burden of health care costs: that is, longer stent patency is associated with fewer procedures, less frequent hospitalizations, and...
lower costs.\textsuperscript{11,12} In addition, the time-point of stent dysfunction is readily determined based on symptoms and/or laboratory tests.\textsuperscript{13} However, the definitions of stent patency and the statistics used for reporting of duration of stent patency have been considerably heterogeneous across the studies, such that comparisons and integrations of the results of studies conducted in different settings have been largely hindered. For example, due to the heterogeneity in reporting stent patency across the studies,\textsuperscript{14,15–36} only a fraction of RCTs comparing different types of biliary stents for nonresectable distal malignant biliary obstruction (MBO) have been used for meta-analyses.\textsuperscript{27–41} Several statistical methods are available for imputation of missing outcome data, these methods have inherent bias and are not always feasible.\textsuperscript{27,42,43} Therefore, there is a great need for specific guidelines for reporting of outcomes associated with endoscopically-placed biliary stents.

Under these circumstances, the TOKYO criteria for transpapillary biliary stenting were proposed in 2014\textsuperscript{44} and are increasingly utilized in clinical studies of endoscopic biliary stents.\textsuperscript{45–61} As illustrated in Fig. 1, these guidelines have standardized the definitions and reporting of procedure-related outcomes, stent-related outcomes, and adverse events. In this article, we review the TOKYO criteria and discuss several issues that researchers may encounter when using the criteria in clinical settings. We further propose an application of the TOKYO criteria to reporting of outcomes of endoscopic ultrasound (EUS)-guided biliary drainage that is increasingly utilized as an alternative to ERCP for cases with endoscopic transpapillary biliary access unavailable.\textsuperscript{62–68}

**Reporting of Recurrent Biliary Obstruction**

Dysfunction of plastic stents and uncovered self-expandable metal stents (SEMSs) is caused predominantly by occlusion due to tumor ingrowth/mucosal hyperplasia (for uncovered SEMSs), biliary sludge, and/or food impaction.\textsuperscript{69} Therefore, duration of stent patency served as a reasonable surrogate for clinical benefits from a specific type of biliary stent. Subsequently, covered SEMSs were developed to prevent tumor ingrowth and thereby prolong time to dysfunction in patients with nonresectable distal MBO.\textsuperscript{14} Covered SEMSs are more prone to migration after placement compared with plastic stents and uncovered SEMSs.\textsuperscript{40,41} While removability is another strength of covered SEMSs,\textsuperscript{69,70} further expanding their indication to benign biliary strictures,\textsuperscript{71,72} evaluation of stent patency is censored at the time of stent removal. Accordingly, in the current clinical practice, we often encounter various types of outcomes associated with biliary stents as well as stent occlusion. Consequently, evaluating outcomes of biliary stents has become complicated, and the terminology for stent-related outcomes has been inconsistent.

Recurrent biliary obstruction (RBO) has been defined as a composite endpoint of either occlusion or migration, and TRBO has been defined as the time from stent placement to RBO or patient death, whichever comes first.\textsuperscript{44} From the perspective of patient care, an endoscopic reintervention and additional hospitalization are usually needed both for stent occlusion and migration such that deterioration in patients’ quality of life and burden on health care costs are considered comparable between these two causes of RBO. Therefore, the composite endpoint as an indicator for stent dysfunction is considered reasonable. Another strength of the use of TRBO as an outcome variable in studies of biliary stents is that the estimation of TRBO is not sensitive to potential misclassifications of stent occlusion and migration. It is occasionally difficult to differentiate stent occlusion and migration as causes of RBO after covered SEMS placement: e.g., based on findings of complete occlusion due to biliary sludge in a migrated covered SEMS, we would speculate that the migration might be due to the intrabiliary pressure enhanced by stent occlusion. Fig. 2 summarizes the items that should be included in reporting of RBO and TRBO after biliary stent placement. Stent occlusion has been defined as presence of biochemical evidence on cholestasis (i.e., elevated liver enzymes as compared with baseline values) along with biliary dilation on imaging studies, or endoscopic findings suggesting it.\textsuperscript{44} Causes of stent occlusion are categorized as tumor ingrowth/mucosal hyperplasia, tumor overgrowth, biliary sludge with/without stones, food impaction, hemobilia, and others (kinking of the bile duct due to a SEMS, SEMS collapse, etc.). Stent migration has been defined as presence of endoscopic findings of a completely or partially migrated stent at the time of a reintervention for patients with RBO.\textsuperscript{44} It is recommended that, in cases with asymptomatic stent migration, the time-point of migration is set as the point when symptoms associated with stent migration are observed.

Non-occlusion cholangitis has been defined as a high-grade fever (> 38°C) which continues longer than 24 hours without deterioration in dilation of the drained bile duct or a definite finding of stent occlusion or migration at the time of a reintervention.\textsuperscript{44} In cases with distal MBO, this type of cholangitis is typically observed after placement of a SEMS which has a large luminal diameter and compromises the sphincter function.\textsuperscript{73–75} Non-occlusion cholangitis may require medications, interventions, and/or a hospitalization, and thus, pose similar burden to occlusion or migration as a cause of RBO. Therefore, non-occlusion cholangitis that requires interventions including stent removal may be categorized as an event in evaluation of RBO for cases with distal MBO, although this condition has not been defined as a cause of RBO in the TOKYO criteria.

Information on causes of RBO and timing of RBO due to specific causes may help us to characterize and improve clinical
outcomes of SEMSs, because structures and mechanical properties of SEMSs play a key role in determining the risk of RBO. For example, higher levels of axial force, which is defined as shape recovery force from a bending to straight position, have shown to be associated with a higher risk of covered SEMS migration. Based on the observations of premature stent occlusion due to the duodenobiliary reflux characterized by biliary sludge and food impaction, researchers were motivated to develop biliary stents with an antireflux valve.

As a substantial proportion of patients with periampullary malignancy die without RBO owing to the aggressiveness of underlying diseases, TRBO is usually estimated using the Kaplan-Meier method that takes censored cases into account, and is compared between groups using the log-rank test. TRBO is underestimated when patient’s premature death without RBO is treated as censored in the Kaplan-Meier method, and thus, data on patient survival in each study-arm are required to interpret the results of TRBO appropriately. Recently, a competing risk analysis is increasingly utilized to evaluate stent patency while mitigating a potential bias due to patient’s death as a competing risk event. A competing risk analysis treats death without RBO as informative censoring as opposed to non-informative censoring in the conventional Kaplan-Meier method. Although application of the competing risk analysis to all clinical trials of biliary stents should be further discussed, this statistical method may mitigate the bias due to unbalanced survival times between the groups that is typically observed in retrospective studies. In addition, this analysis serves as a powerful tool that provides less biased estimations of cumulative curves when cumulative incidence functions for TRBO due to specific causes (e.g., stent occlusion and migration) are examined separately. Namely, in this analytic framework, the summation of all cumulative incidence functions remains one at all time-points.

Reporting of Technical and Functional Successes

Technical and functional successes are assessed as immediate outcomes associated with biliary stent placement and are particularly important at the phase of pilot studies. Technical success has been defined as successful placement of a stent in the intended location with sufficient coverage of a target biliary stricture. The definitions of functional success have been considered different across the studies. In the TOKYO criteria, functional success has been defined as a 50% decrease or normalization of total serum bilirubin level within 14 days of stent placement. For biliary stents placed for cholangitis without obstructive jaundice (e.g., segmental cholangitis) or cholecystitis, functional success can be alternatively defined as cessation of antibiotics or a 50% decrease or normalization of levels of blood inflammatory markers within 14 days of stent placement. Failure in stent placement and thus technical failure pose a challenge for evaluations of biliary stents in RCTs. In RCTs, intention-to-treat (ITT) analyses are recommended rather than per-protocol analyses and are widely utilized. However, for cases where biliary drainage has not been carried out, clinical outcomes including RBO and TRBO cannot be evaluated. In patients who undergo an alternative modality of biliary drainage (e.g., surgical choledochojejunostomy and percutaneous biliary drainage), interpretations of causes of RBO, TRBO, and adverse events should be different from those in patients who receive biliary drainage via ERCP. Therefore, per-protocol analyses are considered acceptable for evaluations of stent-related outcome variables. Nonetheless, patient survival time can be evaluated using ITT analyses.

Reporting of Adverse Events

Fig. 3 summarizes how adverse events associated with endoscopic placement of biliary stents can be reported. Etiologies of the adverse events are generally categorized as procedure-related and stent-related, which are occasionally difficult to be differentiated. The TOKYO criteria recommend reporting types and severity of adverse events, irrespective of underlying etiologies. Reporting the timing of occurrence of adverse events (within 30 days of stent placement vs 31 days or later) may help characterize the risk of adverse events due to specific stent types. For example, pancreatitis usually occurs as post-ERCP pancreatitis within a few days of the procedure, but may develop several months later based on obstruction of the pancreatic duct orifice due to a SEMS with high axial force.

The adverse events associated with biliary stents include pancreatitis, non-obstruction cholangitis, cholecystitis, and others (e.g., bleeding, perforation of the gastrointestinal tract). The landmark consensus criteria proposed by Cotton et al. have been long utilized to define and grade adverse events associated with ERCP. In 2010, the American Society of Gastrointestinal Endoscopy lexicon guidelines were proposed as a comprehensive scheme for documenting and grading of adverse events associated with endoscopic procedures. The TOKYO criteria have integrated and customized these guidelines specifically for evaluation of adverse events associated with endoscopic placement of biliary stents. The adverse events associated with biliary stent placement have been rarely defined in articles, but can be documented consistently using the local clinical criteria at each institution. However, there are challenges in evaluation of cholangitis as an adverse event. In the TOKYO criteria, cholangitis due to RBO is not classified as occurrence of an adverse event, but as RBO due to respective causes. As described above, non-obstruction cholangitis after stent placement for distal MBO may be considered as an event in evaluation of RBO when interventions are required. However, non-obstruction cholangitis is often managed conservatively by administration of antibiotics and is difficult to be differentiated from other infectious diseases. Therefore, non-obstruction cholangitis without requirement of interventions can be documented as an adverse event so that evaluation of TRBO is not censored at the time of this adverse event. Using this definition, segmental cholangitis caused by obstruction of the biliary branch due to stent placement or cholangitis in the undrained branch can be dealt as non-obstruction cholangitis among cases with biliary obstruction. Segmental cholangitis is defined as a high-grade fever (>38°C) which continues longer than 24 hours with inhomogeneous parenchymal enhancement in an undrained segment during the hepatic arterial phase on the contrast-enhanced computed tomography or deteriorated dilatation of an undrained branch.

Figure 3. The TOKYO criteria for reporting of adverse events associated with endoscopic placement of biliary stents.
Application of the TOKYO Criteria to Reporting of Outcomes of EUS–guided Biliary Drainage

EUS-guided biliary drainage, including choledochoduodenostomy, hepatocystgastrostomy, and antegrade transpapillary stent placement, is increasingly utilized as an alternative to ERCP for cases where endoscopic approach to the biliary system is difficult or impossible. Although the TOKYO criteria were originally proposed as guidelines for evaluation of biliary stents placed via the transpapillary route, these criteria can be readily applied for evaluation of outcomes of EUS-guided biliary drainage. Using the TOKYO criteria, TRBO, causes of RBO, and functional success can be similarly assessed for EUS-guided biliary drainage. Due to the nature of the procedure, technical success can be defined as successful placement of a stent in the intended location, whether a stent covers the stricture or not. In patients receiving EUS-guided biliary drainage for segmental cholangitis or cholecystitis, stent dysfunction, which is also defined as a composite endpoint of either occlusion or migration, can be used as the primary outcome. Here, stent occlusion is defined as presence of elevated inflammatory markers as compared with baseline values along with biliary dilation on imaging studies, or endoscopic findings suggesting it. Stent migration is defined as presence of endoscopic findings of a completely or partially migrated stent at the time of a reintervention for patients with stent dysfunction. The TOKYO criteria have documented the definitions and severity of adverse events that are observed both for transpapillary and EUS-guided placement of biliary stents, including pancreatitis, cholangitis, cholecystitis, bleeding, and perforation. A potential modification to the list of adverse events is to include bile leakage as an adverse event specific for EUS-guided biliary drainage (Table 1). Bile leakage is defined as extravasation of bile suggested by contact during the procedure or abdominal bile collection demonstrated by imaging studies and/or an elevated level of bilirubin in abdominal fluids after the procedure. Pancreatitis is less commonly observed compared with biliary stent placement via ERCP. In studies of EUS-guided biliary drainage, it is also mandatory to report procedural characteristics (e.g., puncture route, use of the rendezvous technique, combined use of transpapillary and transmural stents), but this discussion is beyond the scope of this article.

Conclusions

In this review, we overviewed the TOKYO criteria as a standardized reporting system for outcomes of endoscopic biliary stents and discussed potential challenges in application of the criteria in clinical practice. The TOKYO criteria can be utilized irrespective of cause of biliary obstruction (benign vs malignant), location of biliary obstruction (distal vs hilar) and types of stents (e.g., plastic vs metal, uncovered vs covered SEMS). These guidelines can be also utilized for evaluation of biliary stents placed via ERCP assisted by a single- or double-balloon endoscope for patients with altered gastrointestinal anatomy (e.g., Billroth II, Roux-en-Y gastrojejunostomy). Therefore, if combined with the STROBE or CONSORT checklist, the TOKYO criteria would help us to report the outcomes associated with a variety of ERCP-based stent placement procedures in a standardized manner. Standardizing the terminology and methodology for reporting study results would also facilitate the design of clinical studies. More importantly, a standardized reporting system would help readers of a published study to interpret the results appropriately and compare the findings between different studies. Given growing popularity of EUS-guided biliary drainage, the application of the TOKYO criteria to evaluation of the outcomes of this endoscopic procedure may be considered. Finally, the TOKYO criteria would support recent trends in use of individual patient data and

Table 1 Severity Grading of Adverse Events Associated with Endoscopic Ultrasound–guided Biliary Drainage

| Adverse event                          | Severity                        |
|----------------------------------------|---------------------------------|
|                                        | Mild                            | Moderate                       | Severe                          |
| Bile leakage                           | Possible or only slight leak of  | Definite bile leakage treated  | Treatment for > 10 days or an   |
|                                        | bile or contrast, requiring     | for 4–10 days                   | intervention (endoscopic,        |
|                                        | treatment for ≤ 3 days          |                               | percutaneous, or surgical)       |
| Pancreatitis*                          | Hospitalization† for ≤ 3 days   | Hospitalization† for 4–10 days  | Hospitalization† for > 10 days   |
|                                        |                                 | or any of the following:       |                                 |
|                                        |                                 | requirement of stent removal,  |                                 |
|                                        |                                 | organ failure lasting ≤ 48     |                                 |
|                                        |                                 | hours, or local or systemic   |                                 |
|                                        |                                 | complications without persist-|                                 |
|                                        |                                 | ent organ failure              |                                 |
| Cholangitis*                           | Antibiotics only                | Fehrile or septic illness      | Hospitalization† for > 10 days,  |
|                                        |                                 | requiring hospitalization‡ for | septic shock, or                  |
|                                        |                                 | 4–10 days or an intervention   | organ failure                    |
|                                        |                                 | (endoscopic or percutaneous)   |                                 |
| Cholecystitis*                         | Conservative management only    | Hospitalization† for 4–10 days | Hospitalization† for > 10 days,  |
|                                        |                                 | or an intervention (endoscopic | septic shock, or                  |
|                                        |                                 | or percutaneous, or surgical)  | organ failure                    |
|                                        |                                 | including stent removal        |                                 |
| Bleeding*                              | No transfusion                  | Transfusion of ≤ 4 units       | Transfusion of ≥ 5 units or an   |
|                                        |                                 | without an angiographic or     | intervention (angiographic or    |
|                                        |                                 | surgical intervention          | surgical)                        |
| Perforation of the gastrointestinal    | Possible or only slight leak of | Definite perforation treated   | Hospitalization† for > 10 days   |
| tract*                                 | fluid or contrast, treated by   | for 4–10 days or an intervention|                                 |
|                                        | fluids and suction for ≤ 3 days | (endoscopic or percutaneous)   |                                 |
| Other                                  | Conservative management only    | Hospitalization† for 4–10 days |                                 |

†Severity of these adverse events has been defined similarly as that of adverse events associated with transpapillary placement of biliary stents in the TOKYO criteria.

‡Hospitalization or prolonged hospitalization.

§Excluding additional placement of a biliary stent or nasobiliary catheter during the same session as endoscopic ultrasound–guided biliary drainage.
data sharing for integration of the results of studies across different institutions and nations.

Conflicts of Interest
No potential conflict of interest relevant to this article was reported.

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Our Goals:

- **Multi-disciplinary Collaboration to promote world-wide Expertise**
  Establish a comprehensive GI intervention network among endoscopists, interventional radiologists and gastrointestinal surgeons for multidisciplinary collaboration and interaction

- **Sharing and advancing technological Innovations**
  Inform, promote and globalize the many outstanding technological innovations of each of the specialties

- **Foster future Specialists**
  Aid young brilliant doctors to make an early debut on the international stage through SGI

- **Become a Role Model**
  Showcasing the benefits of multi-disciplinary collaboration in science, education and clinical practice