



# The quest for optimal and reliable guidelines based on robust evidence for the treatment of cholangiocarcinoma

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*Comment on:* Gavriilidis P, Askari A, Roberts KJ, *et al.* Appraisal of the current guidelines for management of cholangiocarcinoma-using the Appraisal of Guidelines Research and Evaluation II (AGREE II) Instrument. *Hepatobiliary Surg Nutr* 2020;9:126-35.

Submitted Mar 16, 2021. Accepted for publication Apr 15, 2021.

doi: 10.21037/hbsn-21-117

**View this article at:** <https://dx.doi.org/10.21037/hbsn-21-117>

In 1991, Gordon H. Guyatt described the evidence-based medicine (EBM) as “a focus on educating front-line clinicians in assessing the credibility of research evidence, understanding the results of clinical studies, and determining how best to apply the results to their everyday practice” (1).

In 2010, Graham *et al.* defined clinical guidelines as “statements that include recommendations intended to optimize patient care that are informed by a systematic review of the evidence and an assessment of the benefits and harms of alternative care options” (2). Since 2010, the number of clinical guidelines increased exponentially, and the query on PubMed with the term “new guidelines” produces 59,773 results.

In the field of oncology, the systematic review of the evidence has specific and formal rules (3).

Traditional hierarchies place systematic reviews and meta-analyses followed by randomized trials at the top of the evidence pyramid and are used for developing clinical guidelines. The development of guidelines is a tremendous endeavor: the National Institute for Health and Care Excellence (NICE framework) guide manual (199 pages, available online) to develop guidelines counts no less than 48 steps and mandates a guideline update every 3 years.

Notwithstanding, the validity of the recommendations of clinical practice guidelines depends upon the quality of the methodology used to create them.

The Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument is acknowledged as the most adapted tool (out of more than available 40 tools) to appraise clinical practice guidelines (4). The AGREE II tool includes 23 items divided into six domains: scope and purpose, stakeholder involvement, the rigor of development, clarity of presentation, applicability and editorial independence. Each domain score is calculated according to an adapted formula (<https://www.agreetrust.org>) and a guideline with a score >80%, upon overall appraisal, can be considered applicable without modifications. The polychotomous nature of the AGREE checklist giving equal importance to all of its domains is the main weakness of this tool: whether all items and domains contribute equally to the quality of a guideline remains unclear.

Recently in this journal, Gavriilidis *et al.* (5), using the AGREE II instrument, reported the first appraisal of the current guidelines for the management of cholangiocarcinoma (CC). The main results of their research are as follows:

- (I) Thirteen such guidelines are available;
- (II) The guidelines scored poorly for applicability (13%), the rigor of development (30%), and stakeholder involvement (39%);
- (III) None of the 13 guidelines was recommended universally for use without modification;
- (IV) The conclusion of the authors is unambiguous

and without appeal: “Overall, the methodological quality of guidelines on the surgical management of cholangiocarcinoma is poor”.

This type of conclusion of guidelines appraisal is common: the quality scores as measured with the AGREE Instrument have remained moderate to low over the last two decades in general (6) and specifically in the field of liver tumors (7-9). In brief, most often, “guidelines do not fulfill the guidelines to build them”.

So far, well-conducted randomized controlled trials (RCTs) remain the gold standard of objective clinical research and have the highest level of evidence in the GRADE system (10).

Only 11 RCTs are available in the field of CC because the recruitment of a sufficient number of patients within a reasonable period of time is difficult due to the rarity of the disease and, further, to palliate the latter, these studies often mix patients with three genuinely different diseases (intrahepatic CC, peri-hilar cancer and CC of the main bile duct). In this journal, Horesh *et al.* (11) tackle the robustness of RCTs in the field of CC using three main tools: (I) the survival-inferred fragility index (SIFI, the minimum number of reassignments of the best survivors between arms that would overturn the statistical outcomes); (II) the restricted mean survival time (RMST) difference to evaluate the gain in survival; (III) the level of spin in inconclusive studies to assess distorted reporting strategies. Here also, the conclusion of the authors is unambiguous and without appeal: “RCTs regarding the treatment of CC showed a low degree of robustness with a frequent proportion of associated spin”.

In conclusion, the quest for developing guidelines based on robust evidence via well-conducted RCTs and applicable in real-life remains ongoing in the field of CC management. We hope that our community will succeed in running the two hares simultaneously for the best of our patients.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

*Conflicts of Interest:* All authors have completed the ICMJE

uniform disclosure form (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-117/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Cite this article as:** Azoulay D, Bomze D, Meirson T. The quest for optimal and reliable guidelines based on robust evidence for the treatment of cholangiocarcinoma. *HepatoBiliary Surg Nutr* 2021;10(6):913-915. doi: 10.21037/hbsn-21-117