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LETTERS TO THE EDITOR

Capsule endoscopy in Italy: An unbalanced review of the literature

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To the Editor:

We read the recently published study by Lo Scalzo et al. (4). The study is a short version of a more extensive report published on the Italian Ministry of Health Web site (1). A careful evaluation of both documents reveals several critical issues that cast doubts on the correctness of their conclusions. Usually, decisions about clinical practice should be based on levels of evidence in literature and on the strength of recommendations issued in the guidelines of international scientific societies, many of which rely on the Oxford system (Oxford Center for Evidence based Medicine) (http://cebm.jr2.ox.ac.uk/docs/level.html). As far as diagnostic tests are concerned, the Oxford system assigns the highest level of evidence to systematic reviews supported by homogeneous results. The same system assigns the second highest level of evidence to the "independent blind comparison of an appropriate spectrum of consecutive patients all of whom have undergone both the diagnostic test and the reference standard," while the expert's opinion ranks at the lowest level. Surprisingly, the authors flatly dismissed all sequential studies that fulfill the criteria of independent blind comparison, based on the fact that they were not randomized. At the same time, they cited as source data the results of a questionnaire presented to the attendees of an Italian meeting, never published in literature, which is plainly an "expert opinion."

As early as 2006, there was a strong (and not "anecdotal" as Lo Scalzo writes) evidence of the benefits of wireless capsule endoscopy (WCE) in the diagnosis of small bowel (SB) diseases. To date, more than 1,000 studies concerning WCE have been published, homogeneously showing the diagnostic dominance of WCE over the other standard methods used before its introduction, and the comparability of its diagnostic yield with that of the most recent diagnostic techniques. Many of these studies represent reference points for the scientific community and served as a basis for Guidelines formulation (6). Even if we limit our attention to the single work (2) considered as methodologically adequate, when only SB lesions are considered, a statistically significant difference in terms of diagnostic yield emerges in favor of WCE when compared with push-enteroscopy.

Sequential comparative studies were also dismissed by the authors on the assumption that such studies might be biased because of the time interval between the performance of WCE and the comparator test. The argument is that angiodysplasias might quickly modify their morphology. According to this assumption, vascular lesions might vary, or even disappear, between procedures, and "time" might represent a relevant factor affecting the results. The authors should have provided references for this assertion. They did not, and to the best of our knowledge, there is no reference confirming this assumption in the literature. A careful evaluation of the document published on the Italian Ministry of Health Web site reveals the reason for this misunderstanding. When Lo Scalzo refers to vascular lesions, she refers to Dieulafoy's lesions (5), which constitute only a tiny minority (less than 1 percent) of all vascular lesions and have a peculiar clinical history as they bleed intermittently and are not visible in the interval between bleeds. This does not apply to other vascular malformations which remain unmodified over time or even worsen (3). Such a misconception might have influenced the elaboration of the entire report.

Another unfounded statement is that WCE has not been sufficiently compared with other comparative methods capable of exploring the entire SB mucosa. The "real" comparator should be able to explore the entire SB. Only intraoperative enteroscopy can consistently explore the entire SB. However, this procedure requires a surgical intervention, and no

ethics committee would have authorized a study comparing WCE with this procedure. Push-and-pull enteroscopy could also potentially explore the entire SB. However, a complete SB examination is not guaranteed even when a double intubation (oral and anal), is provided. Studies that compared the completion rate of WCE and push-and-pull enteroscopy consistently showed a superiority of WCE. As far as radiological tests are concerned, although these tests can visualize entirely the SB, they cannot detect flat vascular lesions and comparative studies are consistently in favor of WCE.

The intent to add context-specific data to literature review is appealing. However, the questionnaires sent to the Centers performing WCE were inaccurate: that is, definitions of technical problems and adverse events were missing. Among adverse events, only "intestinal occlusion" was mentioned. All other adverse events were listed in an entry named "Others." Furthermore, the authors considered a capsule retained when it was not expelled within 1 day, whereas retention by definition occurs when the WCE capsule is not excreted within 15 days. This might have led to misinterpretations and to an overestimation of the retention rate.

As far as costs are concerned, the authors only mention that WCE is expensive. Information about cost-effectiveness and costs of alternative procedures are not provided. A cost assessment of the diagnostic-therapeutic strategies including WCE would have been much more informative than the analysis of the single procedure.

In conclusion, we believe that the study by Lo Scalzo et al. is the result of a subjective and biased analysis of the literature. The criteria used to select and refuse published studies are arbitrary and do not comply with the accepted methodology for the evaluation of scientific evidence for diagnostic procedures. The context-specific data are hardly representative of the Italian situation because the survey was unclearly structured, reflecting a lack of clinical insight by the authors.

CONFLICT OF INTEREST

R de Franchis has received honoraria from Given Imaging and travel expenses from unidentified sources. G Costamagna has received payments for educational presentations from Given Imaging and grants or pending grants from unidentified sources. The other authors report having no potential conflicts of interest.

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Capsule endoscopy in Italy: An unbalanced review of the literature. Authors' response

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To the Editor:

The comments by Spada et al. (which are similar in style and content to the ones already made by the authors on the Italian Ministry of Health Web site) are based on misunderstandings and manipulations. The essence of systematic reviews is to sum up available knowledge and minimize bias. The latter is done by *a priori* stating study inclusion criteria both in the protocol and in the full HTA report (see Fig. 1, p. 299) and assessing methodological quality of included studies using an instrument which was specified in the protocol text and never changed (the Quality Assessment Diagnostic Accuracy Studies checklist or QUADAS). The purpose of inclusion criteria and bias minimization efforts is to ensure that what is included in a review is both relevant and contributes evidence weighted by its reliability to answer the study question (in our case the diagnostic performance of WCE in the small bowel). The high number of excluded studies is thus irrelevant, although it is a common feature of systematic reviews. What matters is what the included studies tell us.

We did not "dismiss" sequential study designs. We included them but judged them to be unreliable because of the likelihood of time bias occurring in the interval time (which was incompletely reported in a proportion of included studies) between WCE and comparator examinations. Lack of randomization makes the likelihood of systematic error in the morphology of intestinal lesions high, with a consequent impossibility to compare like with like in a fair way. To put it another way, each subject enrolled in studies comparing the diagnostic accuracy of WCE for obscure small bowel bleeding should be given an equal chance of being allocated to one or the other diagnostic procedure. If sufficient numbers are enrolled, there will be a fair chance that participants with similar looking lesions are assigned to either procedure. We disagree that the morphology of most vascular lesion morphology change slowly and the reference cited by Spada et al. does not support their statement (2). As we have shown in our report, there is substantial uncertainty on this very point. In the absence of evidence, the combined opinion of several experts is better than that of one. Because of equipoise and the need to ensure fairness of tests, a large, independent randomized controlled trial is the only way to have a definitive answer. Efforts to evaluate new devices or procedures by any other study designs (such as interrupted time series, expertise based randomized trials, or parallel group nonrandomized studies) can be affected by confounding, making the results difficult to interpret (3).

The ignorance of these basic principles of epidemiology and ethics is manifest in our survey of the first authors of the included studies, most of whom had not even taken randomization into consideration. While the "hands on" approach is understandable, unregulated introduction of untested new technology, led by a few key opinion leaders is fraught with dangers for any national health service. Our context analysis shows a high level of inappropriateness of use of the WCE, the diagnostic performance of which was and remains unknown.

As explained in our report, one of the tenets of conducting meaningful economic evaluations is the use of credible estimates of comparative effectiveness. We did not feel confident that our review had identified such estimates and decided to avoid further polluting the WCE literature with a meaningless set of ICERs.

About the national survey, this was based on a comprehensive population denominator (all the Italian centers delivering WCE) and response rate was 48 percent. We obtained data on 2,457 WCE procedures, this is one of the broadest data pools a policy maker has ever had as a basis for decisions.

Finally, we note that Spada et al. do not appear to be free of conflicts of interest. Their links to the Italian distributor of the device must be close, as the postage envelope in which their comments (to the Health Minister as well as to us) were sent bears the logo of the distributor.

Regardless of the basic points of study design and transparency, the introduction and widespread use of invasive devices should be regulated in a stricter way than at present.