Format for ANSWERING REVIEWERS

January 13, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6865_unmarked.doc and 6865_marked, the latter showing changes).

Title: Problems faced by Evidence-Based Medicine in gastric cancer surgery

Author: Giuseppe Verlato, Simone Giacopuzzi, Maria Bencivenga, Paolo Morgagni, Giovanni de Manzoni

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6865

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
(1)
(2)

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Giuseppe Verlato, MD, PhD
Unit of Epidemiology and Medical Statistics
Dept. of Public Health and Community Medicine - University of Verona
Istituti Biologici 2 B, Strada Le Grazie 8, 37134 Verona, Italy
Telephone: +39-45-8027628
Fax: +39-45-8027154
e-mail: giuseppe.verlato@univr.it

FIRST REVIEWER

The authors performed a review of literature and national guidelines for gastric cancer management particularly with regard to extension of lymphadenectomy. They discuss the fact that even if D2 lymphadenectomy is the standard of surgical treatment with curative intent in most European guidelines for gastric cancer evidence based-medicine is lagging behind. They conclude EBM should value to a larger extent Eastern Asian literature to eliminate this lag.

Reply: *We also maintain that the quality of surgical procedure should be taken into account.*

The authors address an important issue with their review. But overall, what is new? In the last two years there already are many published reviews that address the importance of lymphadenectomy in gastric cancer and the lag of EBM (i.e. Schmidt et al., 2012 . J Surg Oncol; Brar et al., J Am Coll Surg 2013; de Steur et al., Dig Surg 2013).

Reply: *We enclose these reviews among the references of the revised manuscript, according to your remarks. However, our main interest was not to replicate such reviews for several reasons.*
First of all, the Japanese had achieved the same conclusions 30 years before, as acknowledged by de Steur et al (2013) in their abstract: "In 1981, the Japanese Research Society for the Study of Gastric Cancer provided guidelines for the standardization of surgical treatment and pathological evaluation of gastric cancer. Since then, D2 lymph node dissections have become the standard of care in Japan".
Second, we had already written statements supporting the Eastern approach to gastric cancer surgery 4-8 years ago. In 2005 we criticized a Cochrane review, first published in 2003 and withdrawn in January 2012, for not taking into account the Japanese literature [De Manzoni, Brit J Surg 2005, letter]. In 2009, we proposed new indexes of surgical quality for gastric cancer surgery, pointing out that we cannot "ask Japanese surgeons, in whose series postoperative mortality is only 1–2%, to believe in randomized clinical trials where postoperative mortality peaks to 10–14%, irrespectively of methodological quality of those studies" [Verlato, Ann Surg Oncol 2009].
Indeed, nowadays several papers supporting extended (D2) lymphadenectomy are being published by Western Authors. These papers are often the results of a deep rigorous reflection on personal series: for instance, the Dutch surgeons re-interpreted the results of their trial by considering gastric cancer-related death and by focusing on patients without pancreatico-splenectomy [Songun, Lancet Oncology 2010]. Anyway, rather than simply joining the bandwagon, we tried to understand why EBM, which was "voted in January 2007 as one of the 15 most important medical advances in the last 166 years" [Merchant 2007], has not supported D2 for such a long period of time.

To eliminate the lag of EBM we should not only value to a larger extent Eastern Asian literature but perform our own randomized controlled studies in specialized high volume centers and with experienced surgeons. Therefore, I would recommend to not accept this paper for publication

Reply: *Indeed we are awaiting the final results of an Italian trial comparing D1 and D2 [Degiuli, Brit J Surg 2010]. However, at present in most European countries, including Italy, it is not longer possible to perform de novo randomized trials comparing D1 and D2, as the two procedures are not anymore considered in equipoise. As a matter of fact, D2 is the procedure of choice according to most European national guidelines [Allum, Gut 2011; Meyer, Chirurg 2012; Moenig,*

Viszeralchirurgie 2005; Okines Ann Oncol 2010; Waddell, Ann Oncol 2013].

References

Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R, On behalf of the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. Gut 2011;60: 1449-72 doi: 10.1136/gut.2010.228254

Degiuli M, Sasako M, Ponti A, for the Italian Gastric Cancer Study Group. Morbidity and mortality in the Italian Gastric Cancer Study Group randomized clinical trial of D1 versus D2 resection for gastric cancer. Brit J Surg 2010; 97(5):643-649 doi:10.1002/bjs.6936 PMID:20186890

De Manzoni G, Verlato G. Gastrectomy with extended lymphadenectomy for primary treatment of gastric cancer (letter). Brit J Surg 2005; 92(6): 784 doi: 10.1002/bjs.5088 PMID:15912487

de Steur WO, Dikken JL, Hartgrink HH. Lymph node dissection in resectable advanced gastric cancer. Dig Surg 2013;30(2):96-103. doi: 10.1159/000350873

Merchant AT, Pitiphat W. Researching periodontitis: challenges and opportunities. J Clin Periodontol 2007; 34(12): 1007-15.

Meyer HJ, Hölscher AH, Lordick F, Messmann H, Mönig S, Schumacher C, Stahl M, Wilke H, Möhler M. Current S3 guidelines on surgical treatment of gastric carcinoma. Chirurg 2012; 83(1): 31-37 doi: 10.1007/s00104-011-2149-x PMID:22127381

Moenig S, Baldus S, Bollschweiler E, Ho¨lscher A. Surgery of gastric cancer—quality assurance. Viszeralchirurgie. 2005;42:42–8.

Okines A, Verheij M, Allum W, Cunningham D, Cervantes A. On behalf of the ESMO Guidelines Working Group. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2010; 21 (Supplement 5): v50–v54 doi:10.1093/annonc/mdq164 PMID:20555102

Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010; 11: 439–49 doi:10.1016/S1470-2045(10)70070-X PMID:20409751

Verlato G, Roviello F, Marchet A, Giacopuzzi S, Marrelli D, Nitti D, de Manzoni G. Indexes of surgical quality in gastric cancer surgery: experience of an Italian network. Ann Surg Oncol 2009;16(3):594-602 doi:10.1245/s10434-008-0271-x PMID:19118437

Waddell T, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24 Suppl 6: vi57-vi63 doi:10.1093/annonc/mdt344 PMID:24078663

SECOND REVIEWER

The manuscript deals with an actual topic of modern surgical oncology. The huge amount of scientific publications worldwide obviously necessitates a more critical appraisal of the research and publication activity that represents the true essence of evidence-based medicine. The authors attempted to apply a very specific methodology including scientometrics and webometrics, on the one hand, and social epidemiology, on the other hand, in terms of a preliminarily defined narrow-profile field of applied surgical oncology.
However, they remain far from the scientific foundations of applied quantitative-qualitative research.
Let us point out some crucial disadvantages of the manuscript only.
The title is promising and, in the same time, of general nature although the main emphasis is put on a specific surgical procedure, i.e. the attitude to extended and limited lymphadenectomy in different regions of the world, defined as Eastern Asia (illustrated by two countries such as Japan and South Korea only) and some countries in the Western world such as the USA, European Union, some member states, etc.

Let us give a single example of incorrect quotation to a foreign publication:
On page 4, lines 11-12 from below, the authors state that
Indeed the Western surgical approach to advanced gastric cancer was supported by Evidence-Based Medicine, in particular by a Cochrane review published in 2005[6],
while P. McCulloch et al. (2005) mentioned that
Medline, Embase, the Cochrane register and other databases were searched for studies reporting node dissection technique, 5 year survival and mortality after gastrectomy.
In fact, this specific Cochrane review was not included in the reference list. A lot of more recent pertinent publications, even by Italian authors, are omitted, too.

Reply: *Indeed we mentioned just the last version of the Cochrane review, which was published in short on the British Journal of Surgery in 2005. In the new version of the manuscript we also cited the expanded version published on the Cochrane Collaboration website [McCulloch 2003]. Of note, that particular Cochrane review was withdrawn in January 2012.*

McCulloch P, Niita ME, Kazi H, Gama-Rodrigues J. Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach (Cochrane Review). In: The Cochrane Library, 2003; Issue 4. Chichester, UK: JohnWiley & Sons, Ltd.

McCulloch P, Nita M, Kazi H, Gama-Rodrigues J. Extended versus limited lymph node dissection technique for adenocarcinoma of the stomach. Cochrane Database Syst Rev. 2004;(4).

McCulloch P, Nita ME, Kazi H, Gama-Rodrigues JJ. WITHDRAWN: Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach. Cochrane Database Syst Rev. 2012 Jan 18;1:CD001964. doi: 10.1002/14651858.CD001964.pub3. Reason for withdrawal from publication: The review was withdrawn in January 2012 as the authors were unable to contribute to the updating process due to time constraints.

There are no standardized epidemiological data in the manuscript. Data from 2008 should be actualized.

Reply: *According to your suggestion, we used the most recent estimates provided by IARC (GLOBOCAN 2012).*

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F (2013). GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from http://globocan.iarc.fr

There is no new scientific information in authors' statement that gastric cancer is much more common in Eastern Asia than in Europe and in the USA. The explanations of the better expertise of the representatives of oncologic surgery in Eastern Asia does not sound convincingly enough and should be well-grounded by a much more comprehensive set of objective measurements.

Reply: *In Japan and South Korea the volume of interventions is higher, and post-operative mortality is lower than in Europe or the United States.*

The attempts to provide scientometric argumentations (e.g. on page 4, lines 12-15 from below) failed.
As a whole, the manuscript represents an essay rather than a conventional original paper. There is no well-grounded and clearly described research methodology at all. Single-year and cumulative impact factors are listed in *Journal Citation Reports* (this term is omitted).
On page 7, line 9 from below, the authors declare that *"We searched the Web of Science for papers using the phrase "surgical trial" since 2008".* This sounds far from scientific terminology.

Reply: *According to the reviewer's suggestion, we adopted more centred keywords for the literature search: "(Lymphadenectomy or D1 or D2) and Gastric Cancer" rather than "Surgical trial", in order to perform a more exhaustive review.*

It is not allowed to include the publication year "2013" (see Figure 2), as into every database, the primarily published scientific documents are embedded with a certain delay, i. e. the number of papers published in 2013 and indexed until October 2013 (the manuscript was submitted on October 29, 2013) is smaller than that of the papers which will be indexed by the end of 2014, etc.
Web of Science should not be used alone for such ambitious analyses.

Reply: *According to your suggestion we used PubMed database, which is more inclusive than Web of Science, and we excluded the year "2013" from the systematic review.*

For instance, the authors should carefully read the following paper published by authors from Greece and Germany already in 1995 prior to claim the more insufficient experience of European surgeons in comparison with that of their colleagues in Eastern Asia:
Roukos D, Schmidt-Mathiesen A, Encke A. Adenocarcinoma of the gastric antrum: does D2 total gastrectomy with splenectomy improve prognosis compared to D1 subtotal gastrectomy? A long-term survival analysis with emphasis on Lauren classification.- Surgical Oncology, vol. 4, 1995, No 6, 323-332.

Reply: *In this study the indexes of surgical quality were rather good when compared to other European series, although far from the indexes of the Japanese surgeons. For instance in the above-mentioned Greek series "postoperative 30-day mortality rate was 7% in the TG group and 3.2% in the SG group". For a comparison, postoperative mortality after extended lymphadenectomy (D2) was 0.8% or even absent in randomized trials from East Asia [Sano, J Clin Oncol 2004; Yonemura, Hepato-gastroenterology 2006; Wu, Brit J Surg 2004;], and less than 2% in the Japanese nationwide registry [Fujii, Gastric Cancer 1999]. We could not use this paper (cited 6 times on the Web of Science by December 2013) in the present manuscript as it does not disentangle the comparison total/subtotal gastrectomy from the comparison D1/D2.*

Fujii M, Sasaki J, Nakajima T. State of the art in the treatment of gastric cancer: From the 71st Japanese Gastric Cancer Congress. Gastric Cancer. 1999;2:151–7.

Sano T, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, et al. Gastric Cancer Surgery: Morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy – Japan Clinical Oncology Group Study 9501. J Clin Oncol. 2004;22:2767–73.

Yonemura Y, Wu CC, Fukushima N, Honda I, Bandou E, Kawamura T, et al. for the East Asia Surgical Oncology Group Operative morbidity and mortality after D2 and D4 extended dissection for advanced gastric cancer: a prospective Randomized trial conducted by Asian surgeons. Hepato-gastroenterology. 2006;53:389–94.

Wu CW, Hsiung CA, Lo SS, Hsieh MC, Shia LT, Whang-Peng J. Randomized clinical trial of morbidity after D1 and D3 surgery for gastric cancer. Br J Surg. 2004;91:283–7.

There is no sufficient explanation of the results illustrated in the tables and figures. There is no conclusion at all. Among the series of punctuation, orthographic and stylistic errors, one mistake should obligatorily be mentioned: On page 9, line 2, "an happy end".

Reply: *We carefully revised the English style and we expanded the legends of Table 2 and Figure 2.*

THIRD REVIEWER

In the review, authors recommended literature from different countries to seek reasonable operation mode for gastric cancer. There is significance of this paper to guide clinical treatment for patients with gastric cancer. However, I consider that the title "Problems faced by Evidence-Based Medicine in gastric cancer surgery" is not appropriate, for there are many problems in gastric cancer surgery, and the authors only compared 2 kinds of operation mode(D1 and D2) in this review. I suggest authors to revise it.

Reply: *According to your suggestion, we changed the title as follows: "Problems faced by Evidence-Based Medicine in evaluating lymphadenectomy for gastric cancer"*

FOURTH REVIEWER

In this manuscript, the authors reviewed the problems of EBM in gastric cancer surgery. The contents were interesting as to gastric cancer surgery including comparison of extension of lymphadenectomy.
However, the style of description was not suitable to 'review style'. The authors should correctly show the search methods including key words, and source of data bases, especially in the former parts.

Reply: *As reported in the previous version of the manuscript, page 10, "We searched PubMed for papers using the key words "lymphadenectomy or D1 or D2" AND "gastric cancer", published in English language between 2008 and 2012"*

Minor revises 1. Conclusion part was so long. The authors should describe concisely.

Reply: *According to your suggestion, we removed the following sentence from the Conclusion section, sub-section "Problems of EBM in gastric cancer surgery and possible solutions", page 13: "EBM should be applied taking into account all relevant aspects of a health issue, such as the quality of the surgical procedure. The debate on gastric cancer surgery is probably affected also by the difficulty in implementing innovation in the surgical field: adopting new complex surgical techniques usually require intensive prolonged training abroad; in addition,"*

2. Fig. 1 was not needed.

Reply: *We think that Fig.1 is useful as it highlights the huge difference in gastric cancer incidence between Eastern and Western countries. In our opinion, this is one of the main reasons for the long-lasting debate on the optimal extension of lymphadenectomy for gastric cancer. Indeed, adequate surgical experience and training in D2 lymphadenectomy can be achieved only in high volume centres, mainly located in Eastern countries, i.e. outside the Western world.*