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Geneva, the 17^h of June 2019

Prof. Subrata Ghosh
Prof. Andrzej S Tarnawski
Editors-in-Chief

Dear Professor Subrata Ghosh,

Dear Professor Andrzej S Tarnawski,

We thank both reviewers for examining our manuscript **02554808: "Lateral lymph node dissection for low rectal cancer: is it necessary?"**.

As recommended, we have followed your suggestions and we have carefully considered all comments. Corrections in the text are in red letters.

Manuscript ID : 48288

Title: " Lateral lymph node dissection for low rectal cancer: is it necessary?"

Corresponding author: Dr CHRISTOU Niki

COMMENTS TO THE AUTHOR:

Reviewer: Number ID : 02554808

Comments 1:

The authors use various definitions of rectum segments that require LLND – in some paragraphs they refer only to the low rectum, in others they talk about the mid- and low-rectum. There is therefore a confusion – only the low rectum cancers require LLND or also mid-rectum tumors situated below the peritoneal reflection. A more detailed discussion about the anatomy of the rectum in the subperitoneal region, the presence and size of lymphatics draining in the lateral pelvic nodes and the rate of metastases in these nodes correlated with the tumor T and N stage is necessary

Response 1:

We have added the following paragraph :

Lymphatic vessels of the rectum are formed from the lymphatic plexuses located in the rectal wall under the mucosa. Then, they reach the perirectal ganglia located in the mesorectum. After crossing mesorectum, they form three trunks with nodal groups : the superior trunk drains into the rectosigmoid and the inferior mesenteric nodal groups; the middle one into the internal, external and common iliac lymph nodes and sacral nodes; and the inferior one drains into the superficial inguinal and external iliac lymph nodes, but also into the pelvic, sacral and internal iliac nodal groups. In case of cancer, its level of localization correlates to the risk of lymph node metastasis with greater invasion for lower rectal cancers (1). Moreover, rates of lymph node metastasis are higher according to T stage and more precisely to the depth of invasion of cancer in each stage (2) (3).

Comments 2:

In recent Japanese publications reporting on patients who underwent LLND for advanced low rectal cancer, the prevalence of LLN metastasis has ranged from 6%(4) to 50%(5) – however in Western series in which neoadjuvant radiochemotherapy the local recurrence rate is far lower than these figures. It seems thus that neoadjuvant treatment has the potential to sterilize these metastases. Further development of this topic is advisable.

Response 2:

We have added the following sentence: after neoadjuvant radiochemotherapy, tumor regression grade is variable and disease free survival depends on the importance of tumor regression. A recent meta analysis encompassing 17 studies with 4875 patients treated with long course neoadjuvant radiochemotherapy for stages II-III rectal cancer, has shown only 15.9% of patients with a complete pathological response (6). As a result, to define and generalize neoadjuvant treatment as a treatment leading to sterilization is quite daring.

Comments 3:

The authors reported that neoadjuvant radiochemotherapy plus TME plus LLND led to a 5-year lateral local recurrence rate of 5.7% (vs 19.5% without LLND - the 19.5% local recurrence rate is unusual after RCT and TME and the results of this study should be discussed more cautiously. Furthermore, these results are not validated by the meta-analysis.

Response 3:

A sentence more nuanced has been added in red in the text.

Comments 4:

Also, the role of LLND in combination with neoadjuvant treatment could have been further explored. There are several recent (*mainly Korean – Kim TH – Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection*) studies in which patients who had neoadjuvant CRT followed by standard TME (without LLND) were analyzed to see whether they developed local recurrence in the lateral lymph node compartment. It has been suggested that CRT + TME might not be sufficient to prevent lateral recurrence in the case of obvious lateral lymph node metastases

Response 4:

A sentence more nuanced has been added in red in the text.

Comments 5:

The fact that LLND has a high morbidity is also reflected by the attempts of Japanese surgeons to reduce its indications. However limiting indications only to T3/4 tumors is somewhat difficult to understand. Some small tumors are more prone to lymphatic metastasis than large tumors. Maybe selection of patients for LLND should be based on pre-radiotherapy presence of pelvic side wall metastases diagnosed by MRI. The authors have started to head the discussion in this direction Subgroups of patients should be identified based on preoperative workup^[34, 35], to offer targeted therapies, including neoadjuvant radiochemotherapy and/or LLND, according to the risk of metastatic LLN. It is conceivable that a multistep treatment, including both of these therapeutic strategies, could be adopted consensually but I believe that further development on this issue is needed

Response 5:

A sentence more nuanced has been added in red in the text in the paragraph perspectives.

Comments 6:

An overview of the factors that make the comparison between Eastern and Western treatment approaches so difficult (different definitions of lower rectum, different pathologic techniques, different BMI of patients) could have been included in this review.

Response 6:

A sentence more nuanced has been added in red in the text in the paragraph perspectives.

Bibliography :

1. Frenkel JL, Marks JH. Predicting the risk of lymph node metastasis in early rectal cancer. *Semin Colon Rectal Surg.* 2015 Mar 1;26(1):15–9.
2. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of Lymph Node Metastasis in T1 Carcinoma of the Colon and Rectum. *Dis Colon Rectum.* 2002 Feb 1;45(2):200–6.
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5. Yano H, Saito Y, Takeshita E, Miyake O, Ishizuka N. Prediction of lateral pelvic node involvement in low rectal cancer by conventional computed tomography. *BJO.* 2007;94(8):1014–9.
6. Kong JC, Guerra GR, Warriar SK, Lynch AC, Michael M, Ngan SY, et al. Prognostic value of tumour regression grade in locally advanced rectal cancer: a systematic review and meta-analysis. *Colorectal Dis.* 2018;20(7):574–85.
7. Kim TH, Jeong S-Y, Choi DH, Kim DY, Jung KH, Moon SH, et al. Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection. *Ann Surg Oncol.* 2008 Mar;15(3):729–37.

We hope that our corrections will allow publication in your Journal.

Best regards.

Dr N. Christou

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A handwritten signature in black ink, appearing to be 'N. Christou', located below the printed name and affiliation.