

Format for ANSWERING REVIEWERS

April 22, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPSmanscript 9661-review.doc).

Title: Multidisciplinary treatment of rectal cancer in 2014: where are we going ?

Author: Andrea Vignali, Paola De Nardi

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 9661

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

Review no 1 : A comprehensive review on rectal cancer imaging and pre-operation staging. It would help the readers to understand the review if the authors includes a table summarizing the pros and cons of each imaging systems.

Answer review 1 : a table summarizing the pro and cons of each imaging system has been added.

Review no 2 : *I have the following comments: The article is timely and nicely-written except for several grammar and typographical mistakes which need to be corrected. For examples: "will not beneficiate , MERCURY study GROUP, invariable malignant, MERCURY study GROUP, muscolaris propria, the complementarity, downstaging response, the Stockholm III trial , could underwent delayed, and in a overall survival, may be not benefit, alone is indicate in, extramesorectal lymph-adenopathy, the significative response, etc." ? 2. Under PET-CT scan: rephrase this sentence for clarity as it is unclear and confusing: "Moreover , the above -mentioned limitations in the spatial resolution of PET (4-6 mm), which enables the research of lymph-nodes less than 5 mm, poses the accuracy of FDG-PET-CT in the evaluation of lymph-nodes similar to*

the one of MRI with a reported sensitivity of 72 % [35-36].”? 3. Moreover, I would have liked you to include in this review: An elaborated account on updates on the impact of chemoradiation in reducing the rate of abdominoperineal resection of low rectal cancers and increasing the rate of sphincter-sparing resections. Also in rendering non-resectable rectal cancer feasible for resection. 4. The routine vs. selective defunctioning stoma formation in case of low rectal cancer and irradiated pelvis. 5. A brief account on pelvic exenteration in locally advanced rectal cancer after chemoradiation.

Answer Review no 2:

Point 1. Grammar and typographical errors have been corrected and the whole manuscript has been reviewed by a native English speaker .

Point 2. The sentence Under PET-Ct has been rephrased .

Point 3. please include an elaborated account on updates the impact of chemoradiation in reducing the rate of abdominoperineal resection of low rectal cancers and increasing the rate of sphincter-sparing resections. Also in rendering non-resectable rectal cancer feasible for resection :

“Sphincter preservation seems to have increased over the time in the last 15 years However, the role of preoperative RCT in decreasing the rate of abdomino-perineal amputation, thus resulting in a increase in the rate of sphincter preservation is still unclear and debable. This issue has been recently addressed by Gerard and co-workers who analyzed the results of 17 trials randomizing close to 10800 patients [73]. In this elegant analysis, none of the studies tested was able to demonstrate a beneficial effect of neo-adjuvant treatment on the rate of sphincter preservation. Other factors, such as the acceptance of progressive smaller distal margins, advances in surgical technology such as staplers, improvement in surgical techniques as intersphincteric resection could be responsible of the observed increased sphincter-saving reported by the literature [7,74,75] . Another controversial issue is the role of neoadjuvant chemotherapy in the management of unresectable rectal cancer (i.e palpably fixed lesion involving adjacent organ or structures, not amenable for primary surgical resection) which represented 15 % of all

rectal cancer at presentation . Chemoradiation aims for tumor shrinkage to allow radical resection. Two RCT trials demonstrated a higher resectability rate when chemoradiation was compared to radiation alone with figures in the range of 80-85 % for CRT versus 68-75 % for RT alone^[76,77] . Moreover, the effect of boosted radiotherapy alone vs conventional neoadjuvant chemoradiation on resectability has been recently evaluated by Engineer and co-workers in another RCT trial in which 90 patients with advanced or unresectable rectal cancer were included. Escalated radiation dose was not associated to a higher resectability rate, while it resulted in a increased wound infection and delayed wound healing ^[78]. On the other hand preoperative short-course radiation could represent a valid alternative to CRT in elderly patients with primary unresectable rectal unfit for preoperative chemotherapy cancer due to severe co-morbidities. [79]. “

Point 4 and 5 : A brief account on pelvic exenteration in locally advanced rectal cancer after chemoradiation. The routine vs. selective defunctioning stoma formation in case of low rectal cancer and irradiated pelvis.3.

These two points have been addressed, however, In our opinion these are not pertinent with the scope of the present review, which aims to evaluate the role of conservative and more limited surgical approaches and probably should not be included.

Point 3 Despite improvement in surgical techniques, increasing use of intersphincteric resection and neoadjuvant chemoradiotherapy, abdominoperineal excision is still required in approximately 15% to 25% of patients diagnosed with rectal cancer. Notwithstanding, while oncological outcome for conservative operations has improved over the last years, the outcome for APE remains poor, with high local recurrence rate, in spite of aggressive adjuvant therapy. This may be explained by technical difficulties, resulting in higher rate of tumor perforation and positive circumferential margins, both factors being predictors of local recurrence. An extended abdominoperineal excision (ELAPE) has been recently proposed by Holm and Coll. The goal of the new approach is to achieve a R0 resection with a wide “cylindrical” excision without a waist, removing the levator muscle together with the recto anal muscle tube . No large series of ELAPE cases and only one randomized study have been published, and experience with this technique is still evolving, however better tumor clearance with further oncologic benefits seem to be expected with this approach

Point 4. Anastomotic leakage is one of the most serious complications after rectal cancer surgery. Low rectal anastomoses and TME appear to increase the risk of symptomatic anastomotic leakage; in addition the risk seems higher after neoadjuvant therapy. A recent Cochrane review, assessing 6 randomized trials, showed that the use of covering stoma was significantly associated with less anastomotic leakage and less urgent reoperation, even if

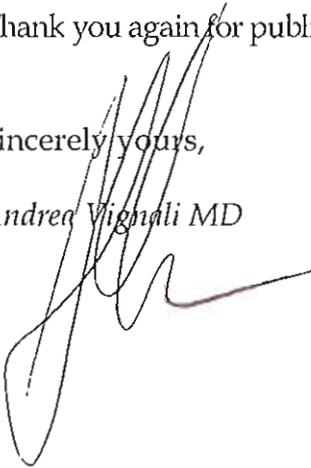
there was no difference in terms of mortality. On the other hand the dehiscence rate in high volume centers is less than 10%, therefore the vast majority of the patients appeared to have no benefit from the stoma with the risk of stoma related morbidity, and chance that “temporary” stomas may become definitive in up to 32% of cases. In our opinion selective use of a primary stoma for high-risk anastomoses seems appropriate. However there is still no consensus about which factors should be defined as high risk, being ASA 3 and 4, immunodepressive status, urgent surgery, incomplete rings, positive hydro pneumatic test, the use of steroids, major intra-operative hemorrhage and intersphincteric anastomosis the most commonly accepted determinants.

3 References have been updated and renumbered in view of new paragraph added. References have been checked by crossref.

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

Sincerely yours,

Andrea Vignali MD

A handwritten signature in black ink, appearing to read 'Andrea Vignali', with a long horizontal flourish extending to the right.