

Peer Review File

Article information: <http://dx.doi.org/10.21037/dmr-20-74>.

Reviewer 1

Comments to the authors:

A very well researched summary of the current state of treatment. An area of interest is the completion rate of preop chemotherapy vs postop. Patient QOL and preferences would be an important addition to the article.

Noted. Adjustments have been made in the latter part of the manuscript to reflect this.

Reviewer 2

Comments to the authors:

Thank you for providing an interesting manuscript on a relevant topic to readership.

I would suggest a few areas for revision, might improve your manuscript

1. Lines 56-89 on preoperative assessment, a lot in the section should be removed as very general and not specific to locally advanced disease (stage 4 disease)
Agreed, it is not specific to T4 disease, has been reworded.
2. Lines 56-89, You have molded acute presentation and elective together. Most of what you say is not relevant to acute situation as you can't change much, I would suggest you might consider saying something along the lines:, that in an acute presentation, were radical resection, is not possible or is difficult, consideration should be given to defunctioning the patient and not resecting the primary. The cancer can then be approached following any relevant preoperative treatment, with the correct team.
Agreed, this has been reworded.
3. Lines 58-89, the benefit of tissue analysis should be discussed. Both in regard to the importance of IHC for MSI (as many locally advanced cancers are MSI positive) and also these days there is considerable benefit to knowing specific IHC of the cancer for specific treatment option's eg monoclonal antibody treatment such bevacizumab and VEGF etc
Acknowledged and a section has been added.
4. Lines 217 re balder resection consider reading Carne PW, Frye JN, Kennedy-Smith A, et al. Local invasion of the bladder with colorectal cancers: surgical management and patterns of local recurrence. Dis Colon Rectum. 2004;47(1):44-47. doi:10.1007/s10350-003-0011-z
Acknowledged, this article was reviewed and referenced.

Reviewer 3

Comments to the authors:

1) Colon or colorectal? Some of the wording in the abstract etc is confused. My understanding is that this is specifically a review of T4 colon cancers

Acknowledged, reworded.

3) Line 78: “usually detected intra-operatively”. This could be written more clearly. More commonly? What’s the sensitivity of CT??

Whole sentence has been removed.

4) Line 82: define LACC

Rectified.

5) Lines 88-89. Is this really the one main question? Pre-operative staging is to accurately stage the patient to determine whether treatment approach is overall curative or palliative. If palliative, is any surgery indicated? What is a palliative oncologic resection? This is not usually performed. Primary tumour resection in setting of inoperable or metastatic disease has not been shown to improve survival. If curative, what is the best sequence of chemotherapy and surgery (with or without radiation)

Acknowledged and rectified.

6) Lines 91-94. This seems a rather cursory section on surgery for locally advanced colon cancers.

Acknowledged and changed.

7) Line 103: neoadjuvant chemotherapy enhances R0 resection rates in oesophageal cancer. The reference provided is for chemoradiation. OEO2 study might be better.

Acknowledged and changed.

8) Line 101; it’s not initially obvious that you are now talking about neoadjuvant chemotherapy in general, beyond colon cancer. Reference 29 was the CR07 study and was a radiation timing study.

Acknowledged and rectified

9) Line 107: I would say that NAC in LACC has been vastly understudied to date. FOXTROT reference is old. 1000 pt randomized study has been presented several times

Acknowledged and rectified

10) Line 114: State the length on NAC used in FOXTROT. This is very important. (6 weeks)

Acknowledged and rectified

11) Line 123: “conversion rate” is a very strange endpoint in this study. Maybe elaborate more on how this was defined. I don’t understand the 94% V 63% comparison

Agreed, it was a very strange endpoint, we have further added to the section to clarifying outcomes.

12) The authors should provide a summary at the end of the NAC section describing whether the literature discussed is consistent etc (it seems to be) and what it has shown

to date. The updated FOXTROT study results are paramount and must be discussed. Also FOXTROT follow-on study designs are finalized and about to recruit.

Added.

13) Line 156: references provided 41-43 describe postoperative adjuvant radiation and are quite old.

Agreed, this reference was erroneously used.

14) Line 188: I don't agree with the conclusion as stated. There is no clear data showing that NAR improves survival in LACC. It is very rarely used, as seen from the national cancer database study. What do the authors think is the likelihood of randomized studies investigating NAR for LACC ever eventuating? NAC seems much more promising.

Agreed and deleted.

15) Line 196: can't conclude neoadjuvant chemoradiation improves R0 resection rates from single arm studies. I would just state that the rates were encouragingly high, notwithstanding bias in these types of studies.

Acknowledged and rectified

16) The surgical section seems to be confusing colon with rectal cancers. Particularly lines 221-

The authors should take care to restrict their discussion to colon cancers.

Acknowledged and rectified

17) 254 the prodige 7 study did not meet it's primary endpoint of overall survival with the addition of oxaliplatin intraperitoneal chemotherapy to surgery. This should be emphasized, not an exploratory secondary endpoint.

Acknowledged and rectified

18) 262: The results of the intergroup 0130 trial should be explained more clearly. This was an underpowered study. However, no discernable difference in OS or DFS was seen between the arms, but given the power issues, a small true benefit from radiation may have been missed?

Apologies, on re-review this section was very vague and has been rectified.

19) 270-275. This section is a little cursory regarding the complexities surrounding adjuvant chemotherapy. Both the T and N stage are important. For many patients 3 months of chemotherapy is sufficient, based on the IDEA meta-analysis.

Section has been removed.