

Reply to reviewer's comments

Reviewer 1

1. This study seems to be on the pathological factors that predict distant metastasis alone. The title may be adjusted to indicate this.

- Thank you for your comments.

This study aimed to evaluate the predictive factors for early distant metastasis before surgery, so predictive factors were based on clinical factors, such as images or biopsy.

2. The 10 treated with intensity modulated radiation cannot translate to 10% of the population

- Ten patients who received IMRT were elderly or expected to have large radiotherapy field. The type of radiotherapy has no prognostic significance, we didn't include on analysis.

3. What is the preferred adjuvant chemotherapy for the patients that received systemic therapy?

- The most common regimen was FOLFOX, followed by FL and capecitabine.

4. Your stated first follow up at 6-8wks clashes with the time of surgery

- The first follow up was done before surgery. Patient received surgery after the first follow-up evaluation

5. Was the survival duration calculated from date of surgery or chemo-radiation?

- Survival durations were calculated from the start date of chemoradiotherapy.

6. What categories of differentiation were the tumors in the population studied? Mention was made of only the 3 that were poorly differentiated MRI was not done for all patients. This would affect the conclusions from the study if applied to the general population.

- The pathologic report was reference to the report with reference to the College of American Pathologists (CAP) protocol, American Joint Committee on Cancer (AJCC) 8th edition, World Health Organization (WHO) classification of tumors of the digestive system, and International Classification of Diseases for Oncology (ICD-O).

Although only three patients (2.4%) had poorly differentiated adenocarcinoma in this study, poorly differentiated adenocarcinoma constitutes approximately 2-25% of colorectal carcinoma.

7. Surgical treatment also varied. Therefore not all patients studied had standard treatment

- The type of surgical treatment depends on surgeon's discretion and the location of tumor.

8. Duration of follow up should be more detailed

- The first follow-up was 6–8 weeks after the last day of preoperative chemoradiotherapy. After then, regular follow-up evaluations were scheduled at 3-month intervals for the first 2 years and then at 6-month intervals thereafter.

I edited surveillance and statistical analyses part.

7. Your discussion should be more specific to the topic and your literature search on similar studies
This has made it difficult to relate your conclusion with your study

- I agree with your comments. I modified the discussion part to clarify my findings.

Reviewer 2

1. what are the original findings of this manuscript?

- Thank you for your comments.

Some patients who received neoadjuvant chemoradiotherapy show early distant metastasis before surgery. I would like to know the predictive factors for such patients. I modified the discussion part to clarify my findings.

Reviewer 3

1. Please indicate the distance from the anal verge of the rectal tumours. In Table 1 – please define the tumour location i.e. distal, mid and proximal rectum based upon distance from anal verge.

- Thank you for your comments.

I modified as your comments (Table 1).

2. Please indicate the reason for the limited MRI and FDG PET assessment at baseline with regard to local and distant staging? "Magnetic resonance (MR) imaging of the rectum was taken in 91 patients (71.1%) and whole-body 18F-fluorodeoxyglucose positron emission tomography with CT (PET-CT) was taken in 90 patients (70.3%)".

- As I described in the discussion part, the low rates of MRI and PET CT assessment are the limitation of this study. The pretreatment evaluation was made by surgeon or gastroenterologist in my institution and in the past, MRI was not a routine evaluation. Now, MRI is the routine evaluation for rectal cancer. Most of the patients (29/36, 75%) who didn't receive MRI or PET CT were treated in 2015-2016.

3. The reason for approx. 50% of patients not receiving post-operative adjuvant chemotherapy:

- Among 58 patients who didn't receive adjuvant chemotherapy, 34 patients didn't receive surgery and three patients received local excision only.

Rest of 21 patients didn't receive adjuvant chemotherapy due to following reasons;

Two patients received chemotherapy before surgery due to early distant metastasis

Four patients didn't receive scheduled surgery due to endoscopic complete remission after preoperative chemoradiotherapy or patient's refusal.

Two patients refuse to receive adjuvant chemotherapy.

Two patients couldn't receive adjuvant chemotherapy due to poor performance status after surgery.

Six patients showed ypT2N0 after surgery and four patients showed ypT3N0, so surgeon didn't recommend adjuvant chemotherapy.

One patient received adjuvant chemotherapy after follow-up.

4. Had the five patients that showed distant metastasis at their first evaluation after NACRT- had they undergone FDG PET at baseline?

- Four patients undergone PET CT at baseline. One patient who didn't receive PET CT at baseline showed distant metastasis in the lung scanned with abdominopelvic CT.

5. Approximately 25% of patients did not proceed with surgery- how does compare to the literature?

- As I described in the discussion part, another limitation of this study is the low rate of surgical resection compared to other literature. Due to this weakness, studies of treatment outcome such as overall survival, distant metastasis free survival, or disease free survival may not appropriate. This study, however, would like to know the predictive factors for early distant metastasis which occur before surgery in patients who received preoperative chemoradiotherapy.

6. Table 5 would be best updated with the recent phase III trials reported at ASCO 2020 in this regard.

- Thank you for your comments. I updated the Table.

There were two phase III trials of neoadjuvant chemotherapy and chemoradiotherapy for rectal cancer, RAPIDO trial and PRODIGE 23/UNICANCER trial.

The treatment arm in RAPIDO trial was short-course radiotherapy followed by chemotherapy, so I didn't include this study in Table 5 (neoadjuvant chemotherapy followed by chemoradiotherapy or radiotherapy).