Title: Meta-analysis of the effect of extending the interval after long-course chemoradiotherapy before surgery in locally advanced rectal cancer

Authors: É. J. Ryan, D. P. O'Sullivan, M. E. Kelly, A. Z. Syed, P. C. Neary, P. R. O'Connell, D. O. Kavanagh, D. C. Winter and J. M. O'Riordan

Institution: Department of Surgery, Tallaght University Hospital, Surgical Professorial Unit, St Vincent's University Hospital, School of Medicine, Trinity College Dublin, University of Dublin, and School of Medicine, University College Dublin, Dublin, Ireland

Published: *BJS* 2019; **106**: 1298–1310

What is known about this subject?

Neoadjuvant chemoradiotherapy (nCRT) is widely accepted as one of the principal modalities in the treatment of locally advanced rectal cancer. Achievement of a complete pathological response (pCR) is associated with improved local control and improved oncological outcomes. The traditional interval between the completion of nCRT and TME surgery is accepted to be around 6-8 weeks. Prolonging this interval may improve pCR rates and thus local control, but concern still remains that it may also make surgery technically more difficult due to increased fibrosis, and expose patients to a greater risk of systemic disease due to the delay in undergoing systemic chemotherapy. The aim of this review was to review all studies that have compared standard (<8 week) interval to extended interval (>8 weeks)

What this study adds?

Design

This meta-analysis examined the results from 26 studies (including 4 RCT's) in order to determine the effect of extending the interval (8 weeks or more) between nCRT and TME surgery.

Primary endpoints

The primary outcome measure was pCR rate, defined as complete absence of tumour cells in the resected specimen and lymph nodes (ypT0N).

Secondary endpoints

Rates of downstaging and upstaging, length of stay, R0 resection rates, margin involvement, TME completeness, sphincter preservation and stoma rates, morbidity, 30-day mortality, disease free and overall survival rates

Results

26 papers were selected from 2728 papers which included 4 RCT's and 22 650 patients. 24/26 studies reported pCR rate and were included in the quantitative analysis. pCR rate in the standard group was 11.3% and in the extended group was 15.9% (OR 1.41). The extended group was also significantly associated with T and overall downstaging (OR 1.33 and 1.18) and a trend to N downstaging (OR 1.34). There was no difference in upstaging, R0 rates or TME completeness. Extended interval was associate with increased duration of surgery and blood loss, but stoma rates, complications rates and 30-day mortality were similar in both groups.

Extended interval was associated with a reduction in distant metastasis (OR 0.71) but not local recurrence. Data for OS and DFS were available from 10 and 12 studies only, with a suggestion that the extended interval is associated with improved DFS (OR 0.74)

Conclusions

This meta-analysis has found that extending the interval between nCRT and TME surgery is associated with an increased pCR rate, with no difference in morbidity or quality of surgery and an improved DFS. The finding of this study would support the routine adoption of an 8 week minimum interval between nCRT and TME surgery

Implications for colorectal practice ?

The publication of this study is very timely and of great relevance to the current treatment of locally advanced rectal cancer. The data reported certainly provide some reassurances that delaying the interval between nCRT and surgery does not appear to be detrimental. The observation of increased pCR rates is also of great interest and this strategy may be more palatable to patients that other strategies such as radiotherapy dose escalation, which may be associated with greater levels of toxicity or poor functional outcomes. The increased pCR rate also raises the thorny issues of what to do with those patients who will presumably display a complete clinical response (cCR), and we will need to await more data regarding the management of patients who will naturally enter a “watch and wait” strategy.

This analysis only included data from 4 RCT’s, with the majority of the other studies being retrospective observational in nature. There are therefore a number of confounding variables that may have influenced overall oncological outcomes and thus a meaningful conclusion cannot be necessarily be drawn regarding this outcome. It would be of particular interest if future prospective studies could perhaps identify the upper limit of the interval following which further increases in pCR rates are not seen.