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Editorial Comment

# Radio-chemotherapy in rectal cancer

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The benefit of adjuvant chemotherapy in colon cancer has now been demonstrated in several trials. In fact, at least in stage III disease there is a consensus that it is now no longer considered acceptable to perform trials of chemotherapy *versus* none. In earlier stage disease it is more controversial. The absolute margin of benefit shown in each individual trial in this setting is small. In the MOSAIC trial[1] using oxaliplatin in combination with 5-fluorouracil and folinic acid, a 6% improvement in disease-free survival at 3 years was demonstrated. It is also very likely that any benefits in adjuvant therapy of rectal cancer would be of the same sort of magnitude as in colon cancer.

Attempts to define benefits for post-operative chemotherapy in rectal cancer have been even more difficult. This partly reflects the natural history of the disease with local relapse being (at least historically) a much more important problem in rectal cancer than in colonic cancer. But a number of other variables make it more complex to design and complete trials in this setting.

Firstly, the surgical approach to rectal cancer has changed very dramatically in the last decade or so with more widespread adoption of the principles of total mesorectal excision as popularised by Heald et al.[2] This has led to a marked reduction in local relapse rates in most literature reported series.

Secondly, the potential influence of radiotherapy on local control and perhaps also in the eradication of disease may be important. There is also the question of pre- *versus* post-operative application of radiotherapy. As if that was not enough we also have different schedules of radiotherapy – so-called short course *versus* long course and variations in dose and schedule between similar institutions even within one country.

Thirdly, and maybe not least there is the potential influence of drugs given in sequence or concomitantly with radiotherapy. This is also more complex to define as a variety of commonly used regimens are in use throughout the World. It is also very likely that some of the drugs act at least in part as radio-sensitizers, so the exact schedule of drug and radiation may be a crucial (but empirical) variable.

If one considers all these possible variables it is not a surprise that we have struggled to reach any consensus on how best to treat rectal cancer. In an ideal World we would do adequately powered randomised controlled trials in which only one variable was altered between arms to refine and define the treatment parameters that really did have influence using a solid outcome such as overall survival. Instead we have witnessed a series of trials which when taken together over the last 2 decades or so have led to a current standard. This evolution was very well reviewed by Rodel at the recent ASCO meeting in Chicago[3] and has led us to conclude that some form of pre-operative chemoradiotherapy followed by adjuvant 5-FU based chemotherapy in the post-operative phase could be considered as 'standard'.

In this issue of EJC Kalofonos et al. present their Hellenic Co-operative Oncology Group study of adjuvant radiochemo-

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therapy in rectal cancer patients. This study illustrates very nicely some of the issues raised above.

The title is somewhat misleading since the therapy administered spanned both pre- and post-operative time windows.

TME was not mandatory but was recommended.

Staging is poorly defined and did not appear to include pelvic MRI which many would contend is a mandatory investigation to show 'margin threatening disease' and then select for pre-operative chemoradiotherapy.

The study was powered to detect a 15% difference in 3-year OS rate. Put another way they expected the addition of irinotecan to **halve** the death rate. This is an unreasonable assumption on which to base power and recruitment targets. No drugs have ever shown such a large benefit in this context in the past. As it happens the irinotecan arm actually had a worse observed survival, and the 95% confidence intervals rules out a maximum of 13% reduction in the death rate with irinotecan. So whilst underpowered the study is informative, and when taken in the context of existing literature helps us to conclude that irinotecan is not beneficial. So the authors 'got lucky' this time round with an underpowered trial.

So does this particular trial add to our knowledge? I guess the answer is that it does and that is why it appears in the journal.

Rectal cancer is a common disease and we should be able to conduct well designed randomised controlled trials which address the complexities of this disease. I would argue very strongly that we are now in an era where we have to accept that larger-scale trials are required with sufficient power to have confidence in the results, based on more realistic (and evidence based when possible) assumptions about margins of benefit.

## Conflict of interest statement

None declared.

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