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Citation for published version (APA):

Voogt, E. L. K., Nordkamp, S., Nieuwenhuijzen, G. A. P., Creemers, G. J., Peulen, H. M. U., Rutten, H. J. T., & Burger, J. W. A. (2021). Curative treatment of locally recurrent rectal cancer: is induction chemotherapy warranted? *British Journal of Surgery*, *108*(6), E213-E214. https://doi.org/10.1093/bjs/znab065

Document status and date:
Published: 01/06/2021

DOI:
10.1093/bjs/znab065

Document Version:
Publisher's PDF, also known as Version of record

Document license:
Taverne

Please check the document version of this publication:

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Download date: 24 Mar. 2025

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BJS, 2021, **108,** e213–e214
DOI: 10.1093/bjs/znab065
Advance Access Publication Date: 12 March 2021
Research Letter

Curative treatment of locally recurrent rectal cancer: is induction chemotherapy warranted?

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Locally recurrent rectal cancer (LRRC) is associated with severe morbidity and a poor prognosis, even after treatment with curative intent. This is caused by a high rate of locoregional recurrence and distant metastases. A resection with clear margins (R0) is the most important prognostic factor for survival[1]. To increase the R0 resection rate, downstaging of LRRC with neoadjuvant treatment is the standard of care, with full-course chemoradiotherapy considered the treatment of choice[2]. Nevertheless, R0 resection rates remain low. Moreover, previous radiotherapy for the primary tumour hinders the administration of radiotherapy, although reirradiation is considered the standard of care in some countries[3].

To improve outcomes for patients with LRRC, induction chemotherapy (ICT) is increasingly being applied; ICT may increase downstaging by itself and enhance tumour sensitivity to radiotherapy by improving tumour vascularity. Moreover, it has the potential to eradicate micrometastases.

Evidence for additional value of ICT in LRRC is lacking. In the Catharina Hospital Eindhoven, a tertiary referral centre, the current standard of care is ICT in addition to chemo(re)irradiation (CRT). Initially, ICT was offered only to patients with unresectable LRRC. Since 2014, it has been implemented gradually for all patients with LRRC, with 48 per cent of surgically treated patients receiving ICT in 2015 up to 88 per cent in 2019.

The authors recently reported the results for 132 patients with LRRC treated with ICT + CRT and surgery. The pathological complete response (pCR) rate was 17 per cent. However, the R0 resection rate was not superior to rates reported in other studies describing different treatment strategies[4].

To further explore these findings, results for patients who underwent surgery for LRRC between 2009 and 2013 (period 1; ICT not standard of care) were compared with those for patients who underwent surgery between 2014 and 2018 (period 2; ICT local standard of care). In period 1, 20 of 127 patients (15.7 per cent) received ICT compared with 113 of 171 (66.1 per cent) in period 2 ($P < 0.001$). The pCR rate was 7.9 and 15.8 per cent respectively ($P = 0.040$). However, the R0 resection rate did not differ significantly (59.1 *versus* 68.4 per cent; $P = 0.095$). The 3-year

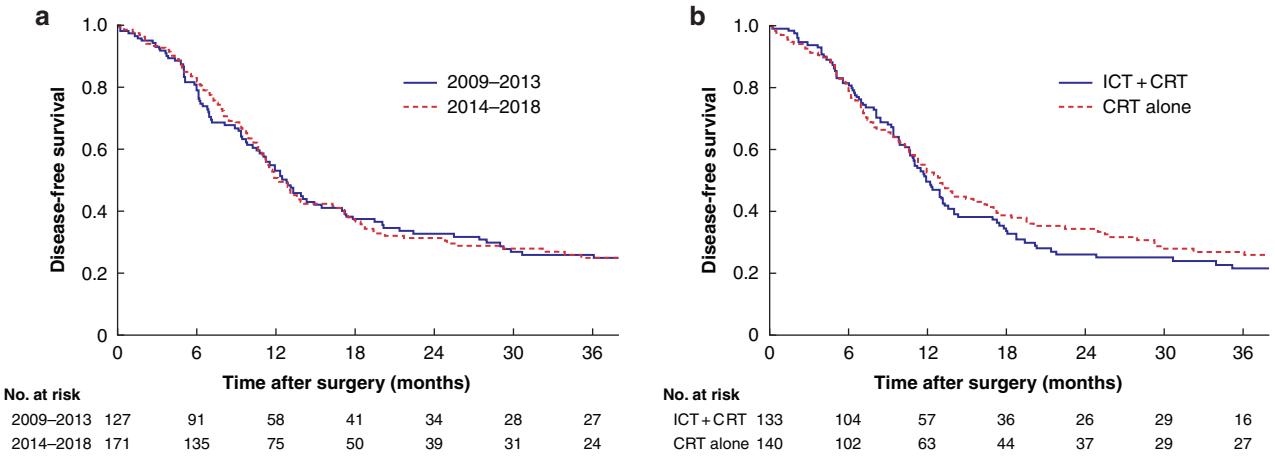

Fig. 1 Disease-free survival according to treatment period and type of neoadjuvant treatment

Disease-free survival in **a** 2009–2013 (induction chemotherapy not local standard of care) *versus* 2014–2018 (induction chemotherapy local standard of care), and **b** after treatment with induction chemotherapy, chemo(re)irradiation and surgery *versus* chemo(re)irradiation and surgery alone. **a** $P = 0.893$, **b** $P = 0.412$ (log rank test).

Received: January 26, 2021. **Accepted:** January 29, 2021
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disease-free survival (DFS) rate was also comparable: 26.2 per cent (median 12.8 months) *versus* 25.1 per cent (median 12.3 months) ($P = 0.893$) (*Fig. 1a*).

In addition, patients with LRRC who received ICT + CRT (133, 48.7 per cent) were compared with those who received CRT alone (140, 51.3 per cent) between 2010 and 2018. The pCR rate was 16.5 per cent in the ICT + CRT group *versus* 8.6 per cent in the CRT group ($P = 0.046$). Again, the R0 resection rate did not differ significantly (63.2 *versus* 64.3 per cent respectively; $P = 0.846$). The 3-year DFS rate was also similar: 21.3 per cent (median 11.9 months) *versus* 26.7 per cent (median 12.9 months) ($P = 0.412$) (*Fig. 1b*).

Many confounding factors may explain why the R0 resection rate and DFS did not seem to benefit from the addition of ICT: patients receiving ICT + CRT more often received radiotherapy for the primary tumour (72.9 *versus* 48.6 per cent; $P < 0.001$); in the ICT + CRT group, more patients received reirradiation than in the CRT group (81.2 *versus* 53.6 per cent; $P < 0.001$); in both analyses, patients treated with ICT more often had synchronous metastases; escalation of treatment by adding ICT was considered justified specifically in patients with the poorest prognosis; and no data were available for patients in whom surgery was omitted owing to toxicity or progressive disease.

Although the increased pCR rate implied increased downstaging, the lack of effect on the R0 resection rate and DFS do not substantiate the efficacy of ICT in the treatment of LRRC. Additionally, data on toxicity and compliance are lacking. An RCT is warranted; the PelvEx II trial[5] will randomize patients with LRRC after previous partial or total mesorectal resection, without synchronous distant metastases, to receive either ICT followed by CRT and surgery or CRT alone and surgery.

Disclosure. The authors declare no conflict of interest.

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