Background

‘Locoregional recurrences’ refers to anastomotic recurrences, recurrences in the surgical bed or regional nodal recurrences.
Local failure after colonic resection is relatively uncommon and is reported to occur in less than 5% of patients. Rates of local recurrences following rectal cancer surgery were previously as high as 33%, but this has diminished dramatically over the past three decades to 5–10%. This reduction in local recurrence has been achieved mainly through improved surgical techniques and pre-operative imaging which has improved patient selection for neoadjuvant treatment. These include:

- total mesorectal excision (see Elective and emergency surgery for colon and rectal cancer REC3 and COL1-2b)
- improved preoperative staging with pelvic magnetic resonance imaging (MRI) (see Imaging rectal cancer)
- the judicious use of preoperative radiotherapy with or without chemotherapy (see Neoadjuvant and adjuvant therapy for rectal cancer).

Notwithstanding the improvements in surgical techniques, there remain disease factors that predispose to local recurrence. These factors include nodal involvement, vascular invasion, grade of tumour, as well as surgical complications such as anastomotic leaks.

**The role of surgical treatment**

Re-resection for locally recurrent colorectal cancer should be undertaken where possible with a clear resection margin and with curative intent.

While multi-visceral en bloc resection of locally recurrent colon cancer has long been accepted by the wider surgical community as the standard of care, the uptake of pelvic exenteration for locally recurrent rectal cancers has been much slower because of the lack of evidence from randomised controlled trials (RCTs), the high rates of surgical morbidity and the potential quality of life implications following such radical resections. The past two-to-three decades, however, have seen increasing acceptance of pelvic exenteration for patients with isolated locally recurrent rectal cancer because of the number of studies demonstrating reduced operative mortality and improved overall survival in large case series, as well as quality-of-life outcomes particularly in selected Australian centres. In an early cross sectional quality of life study in patients with locally recurrent rectal cancers, long-term survivors after pelvic exenteration for local recurrence were found to have comparable quality of life to patients who had primary rectal cancer. Subsequently, a much larger prospective and longitudinal comparative quality of life study in these patients found that quality of life in pelvic exenteration patients was preserved compared to patients who underwent palliative treatment. As part of the quality of life study, a cost-effectiveness analysis was also undertaken which found pelvic exenteration to be cost-effective when compared to palliative treatment.

**The role of radiation treatment**

The role of neoadjuvant chemoradiation is well established for locally advanced rectal cancer (see Neoadjuvant therapy for rectal cancer).
Radiotherapy-naive patients with locally recurrent rectal cancer should receive neoadjuvant chemoradiation prior to curative surgery. In patients who have previously undergone radiation for their primary rectal cancer, the role of re-irradiation is less clear. The concerns of re-irradiation are tissue tolerance and the risk of cumulative toxicity to all pelvic viscera - in particular, to adherent pelvic small bowel loops after previous surgery and the bony pelvis.

Re-irradiation using external beam radiotherapy through hyperfractionated doses has been described by several large centres with an interest in locally recurrent rectal cancer:

- A team from the US MD Anderson Cancer Center recently described their treatment algorithm for patients with locally recurrent rectal cancer, which entailed pre-operative long-course chemoradiation for patients who are radiotherapy naïve, and re-irradiation of patients who have previously received radiotherapy using a hyperfractionated dose of 39 Gy over 26 fractions (1.5 Gy twice daily). The authors reported improved survival among patients with locally recurrent rectal cancer over their 24-year experience, and attributed this to increased use of pre-operative treatment including rate of re-irradiation (increased from 63% to 89%). Radiotherapy-related toxicities were not reported, although the authors also published a separate study using a smaller subset of the original cohort, which reported the rate of grade 3-4 toxicity as 34% over 3 years.

- A US retrospective case series study from Duke Cancer Center reported on the outcomes of re-irradiation from 33 patients with locally recurrent rectal cancer. Early and late grade 3 toxicities were reported in 6% and 21% of their cohort, respectively. However, neither re-irradiation nor other pre-operative regimes were found to be associated with improved survival or local progression-free survival.

- An Italian multicentre phase II study described a re-irradiation protocol using a twice daily hyperfractionated regime of 1.2 Gy each session for a total of 30 Gy. Radiotherapy was administered with concurrent chemotherapy using 5-flourouracil. Of the 59 enrolled patients, 10% had temporary treatment interruption because of toxicity or compliance issues. Only 3.4% of patients had treatment terminated prematurely because of toxicity. Grade 3 lower gastrointestinal toxicity developed in 5.1% of patients and there were no grade 4 toxicities. Late toxicity was reported in 7 patients, of which the most significant events were urinary outflow tract obstruction needing nephrostomy (2 patients) and small bowel fistula (1 patient). Of 24 patients who had pain pre-treatment, 20 (83%) reported reduced pain. Response rate (partial and complete responders) was 44.1% on repeat imaging. Overall median survival was 42 months. The authors concluded that re-irradiation was safe, well tolerated and associated with symptomatic improvement.

- A Chinese cohort study included 72 patients with LRRC who received re-irradiation using a 1.2 Gy twice daily hyperfractionated regimen for a total of 36 Gy over 30 fractions. Non-responders after 36 Gy continued with re-irradiation to a total of 51 to 56 Gy. Seventy patients completed the intended treatment and two patients interrupted treatment because of grade 4 toxicity. The overall response rate was 59.7%. The authors described clinical benefit in 93% of patients from improved symptom control. Early grade 3-4 toxicity with diarrhoea or neutropaenia was reported in 9.7% and 8.3% of patients, respectively. Late toxicity with small bowel obstruction was seen in 1.4% of patients. The authors also concluded that re-irradiation was safe and effective in reducing symptoms.
Clinical question: Management recurrent, resectable CRC

When interpreting the safety and efficacy findings reported in these re-irradiation studies, it should be acknowledged that most were single-institution small case series with highly selected patients and no comparative arms.\(^{[15]}\)

Despite the limited experience with re-irradiation, this is offered in some centres and forms part of their treatment algorithms for patients with locally recurrent rectal cancer. This highlights the importance of institutional experience and also the importance of discussion within an expert multidisciplinary team. Before recommending re-irradiation, it is vital that the team takes into consideration what can be achieved surgically by the surgical team (likelihood of R0 resection).

Concerns about the possibility of collateral injury to other pelvic viscera have led to the development of intra-operative radiotherapy (IORT) specifically to target the recurrence while shielding other radiosensitive tissues. While the biological rationale of this practice makes sense, the evidence behind this is somewhat limited. A Dutch group\(^{[16]}\) recently published the largest multi-centre series on IORT in patients with locally recurrent rectal cancer. The authors concluded that radicality of resection (R0 resection margins) remained the key factor that determined long-term outcome. Although pre-operative treatment improved the likelihood of R0 resection, what IORT offered was reduced risk of further local recurrence when used in combination with re-irradiation.\(^{[16]}\)

Similar findings were reported in a study by the German Cancer Research Center\(^{[17]}\), in which 97 patients with locally recurrent rectal cancer underwent radical resection and IORT. Although the combination of external beam radiotherapy and IORT (≥ 15 Gy) seemed to improve local control, once margin status was corrected for on multivariate analysis, no other factors remained significant.\(^{[17]}\) Therefore, overall, it would seem that a complete resection (R0 resection margin) remains the linchpin in achieving long-term local control and survival.

**Systematic review evidence**

*In patients with locally recurrent colon or rectal cancer, what are the outcomes of curative surgery (+/- chemotherapy, +/- radiotherapy) when compared with surgical palliation +/- palliative chemotherapy +/- palliative radiotherapy or other palliative interventions (overall survival, disease free survival, quality of life and complications)? (MNG13)*

A systematic review was undertaken to determine the outcomes of curative resection (with or without radiation or chemotherapy) in the management of locally recurrent colorectal cancer, compared with palliative treatment options including palliative surgery (with or without palliative chemoradiation) or other palliative interventions for locally recurrent colorectal cancer.

One prospective observational cohort study\(^{[18]}\) and three retrospective observational cohort studies\(^{[19],[20],[21]}\) were identified that reported outcomes for patients with locally recurrent rectal cancer who underwent different management strategies:

- A US prospective cohort study\(^{[18]}\) reported the outcomes of 105 patients with locally recurrent rectal cancer, of whom 62 (59%) underwent curative surgery and 43 (41%) underwent non-curative treatment. Of the 43 patients in the non-curative treatment group, 13 (12%) underwent non-curative surgery where an exploratory laparotomy was undertaken in conjunction with biopsies, intestinal bypass or diversion, and 30 (29%) underwent non-surgical treatment with chemoradiation, brachytherapy or supportive care. Duration of follow-up was not reported.\(^{[18]}\)
Clinical question: Management recurrent, resectable CRC

- A UK retrospective cohort study\(^{[19]}\) included 127 patients with locally recurrent rectal cancers, of whom 22 (16%) had both synchronous local and systemic recurrence. The type of primary resection varied and included prior anterior resection (69%), abdominoperineal excision (15%), Hartmann’s procedure (5%), pelvic exenteration (5%), proctocolectomy (4%), and local excision (2%). Seventy (55%) patients were offered curative surgery. Patients who were radiotherapy-naïve were also offered preoperative long-course chemoradiation. Patients with node-positive disease on imaging and patients with a threatened margin were also offered neoadjuvant chemotherapy prior to surgery. Of 70 patients who underwent curative surgery, 45 (64%) had a clear resection margin (R0), 14 (20%) had a microscopically involved margin (R1) and 11 (16%) had macroscopic residual disease (R2). Of the 57 (45%) patients who did not undergo surgery, 26 had non-resectable disease, 15 had extensive metastatic disease that precluded curative resection, 6 were unfit for surgery, 3 declined further surgery and a further 7 patients were awaiting further assessments. Mean follow-up was 3 years.\(^{[19]}\)

- A Korean retrospective cohort study\(^{[20]}\) included 67 patients with locally recurrent rectal cancer of whom 45 underwent curative resection and 22 underwent chemoradiation alone. Three of the 45 patients who underwent curative surgery also received pre-operative chemoradiation, while the remaining 42 received postoperative chemoradiation. For the 45 patients who underwent curative surgery, resection margins were R0 in 19 (42%) patients, R1 in 24 (53%) and R2 in 2 (4%). Regardless of the treatment intent, following completion of treatment, 59 of 67 patients also received maintenance chemotherapy with fluoropyrimidine, irinotecan or oxaliplatin. Median follow up was 41 months (range 16–108 months).\(^{[20]}\)

- Another Korean retrospective cohort study\(^{[21]}\) reported on the outcomes of 62 patients who had locally recurrent rectal cancer following some form of total mesorectal excision, whether sphincter sparing or not. Of these patients, 23 (37%) underwent curative resection with or without preoperative chemoradiation, while 39 (63%) underwent palliative treatment: 15 (38%) had palliative resection, 20, (51%) had palliative chemoradiation, and 4 (10%) had supportive care. Preoperative chemoradiation for the curative resection group was administered for patients who were radiotherapy naïve. In patients who previously received radiation for their primary rectal cancer, radiotherapy was restricted to the recurrence alone using 3-dimensional conformal techniques. Median follow-up was 49 months, with a range of 8–120 months.\(^{[21]}\)

All studies were at high risk of bias. No studies comparing management strategies for locally recurrent colon cancer were identified.

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Perioperative mortality, morbidity and adverse events

Treatment-associated mortality, morbidity and adverse events outcomes were reported only by the two Korean studies.\(^{[20][21]}\)

The study comparing curative resection with chemoradiation alone\(^{[20]}\) reported no severe grade I to grade III complications associated with chemoradiation. Surgical adverse events were not reported.

The other study\(^{[21]}\) reported no perioperative mortality. Of the 38 patients who underwent either curative or palliative surgery, 12 (31.6%) experienced postoperative complications: wound complications (6), intestinal obstruction (2), anastomotic leakage (1), enterocutaneous fistula (1), and pelvic abscess (1).\(^{[21]}\)
Survival outcomes

Three studies\textsuperscript{[19][20][21]} reported overall survival, while two studies\textsuperscript{[18][19]} reported median survival and two\textsuperscript{[20]} reported locoregional relapse-free survival.

**Overall survival**

The UK retrospective cohort study\textsuperscript{[19]} reported 3-year overall survival rates of 69%, 56% and 20% for patients who had R0, R1 and R2 resections respectively. This difference between the three groups was statistically significant (p=0.011).\textsuperscript{[19]}

Both Korean studies\textsuperscript{[20][21]} reported 5-year overall survival rates. One study reported no survival difference between surgically treated patients and patients who received chemoradiation alone (53% versus 41%; p = 0.181).\textsuperscript{[20]} The other study reported a significantly higher 5-year survival among surgically treated patients than among those who did not undergo curative resection (35% versus 0%; p = 0.0002).\textsuperscript{[21]}

**Median survival**

In the UK retrospective cohort study, median survival has not been reached by the end of 3-year follow-up but was 24 months amongst patients who underwent a R2 resection.\textsuperscript{[19]}

Median survival in the US prospective cohort study\textsuperscript{[18]} was 7.1 years (85.2 months) in patients within the curative surgery group, compared with 1.4 years (16.8 months) among patients treated non-curatively and 1.9 years (22.8 months) among patients treated non-surgically.\textsuperscript{[18]}

**Locoregional relapse-free survival**

The UK retrospective cohort study\textsuperscript{[19]} reported a non-significant increase 3-year locoregional relapse-free survival in the curative surgery group compared with the non-curative group (80% versus 60%; p = 0.824).\textsuperscript{[19]}

The Korean study comparing curative resection with chemoradiation alone\textsuperscript{[20]} reported no significant difference in 5-year locoregional relapse-free survival rates between the curative surgery group and the non-curative group (16% versus 5%; p = 0.113).\textsuperscript{[20]}

**Quality-of-life outcomes**

The US prospective cohort study\textsuperscript{[18]} was the only study that reported quality-of-life outcomes, measured using the Brief Pain Inventory (BPI) and FACT-C, a colorectal cancer specific quality of life measure.\textsuperscript{[18]} The only domain that demonstrated statistically significant differences between treatment groups was ‘physical well-being’, which was largely preserved among curative surgery patients but declined rapidly in patients who received non-curative or non-surgical treatments (p = 0.049).\textsuperscript{[18]}
Pain scores did not differ between treatment groups and did not adversely affect the use of restricted narcotic medications.\[18\]

### Evidence summary and recommendations

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<th>Evidence summary</th>
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<tr>
<td>In observational studies in patients with recurrent rectal cancer, curative surgery resulted in significantly better overall survival, relapse-free survival and distant metastasis-free survival than other management strategies.</td>
<td>III-2</td>
<td>[18], [19], [21]</td>
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<td>In an observational study of patients with recurrent rectal cancer, overall quality-of-life score was not different between patients undergoing curative surgery and non-curative treatments, with the exception that better physical well-being was seen amongst patients who underwent curative surgery.</td>
<td>III-2</td>
<td>[18]</td>
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<td>In an observational study, pain intensity and interference in daily life were not significantly different between patients undergoing curative surgery and non-curative treatments for recurrent rectal cancer.</td>
<td>III-2</td>
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<td>In an observational study of patients with recurrent rectal cancer, curative surgery was associated with significant treatment morbidity.</td>
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**Evidence-based recommendation**

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For patients with isolated local recurrence of rectal cancer, consider referral to a centre with the necessary expertise to perform curative surgery (also known as pelvic exenteration).

**Evidence-based recommendation**

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Re-operative surgery for locally recurrent rectal cancer should only be offered after due consideration of, and discussion with the patient about, the potential survival advantage, quality-of-life outcomes, and potential treatment-related morbidity.
Clinical question: Management recurrent, resectable CRC

- **Consensus-based recommendation**

  Patients who have not previously received radiotherapy should be considered for neoadjuvant chemoradiation prior to re-operative surgery.

- **Practice point**

  Patients with locally recurrent colorectal cancer should be referred to a centre with the expertise in the management of these cancers.

- **Practice point**

  All patients with locally recurrent colorectal cancer should be discussed at a multi-disciplinary team meeting with clinicians who have the expertise in the management of such malignancies. These meetings should review the patient’s previous histology and relevant imaging prior to making an appropriate clinical recommendation.

- **Practice point**

  Re-operative surgery for locally recurrent colorectal cancer can be associated with significant morbidity. As such, all re-resections should only be offered when cure is considered possible.

- **Practice point**

  The key factor in achieving long-term survival in patients with locally recurrent colorectal cancer is a complete resection with clear resection margins (R0 margins), which is an important consideration when making clinical decision about disease resectability.

**Considerations in making these recommendations**

The UK study by Bhangu et al\(^{[19]}\) was included as the study population had patients with systemic recurrence as well as synchronous local recurrence; this study did not alter survival outcomes.
Clinical question: Management recurrent, resectable CRC

Limitations of the body of evidence

The systematic review did not identify any randomised controlled trials (RCTs) that compared curative surgery with palliative treatments in either colon or rectal cancer. This lack reflects the difficulties of conducting RCTs in these patients because of the relative rarity of the condition and institutional differences in the management of these patients.

Considering the available evidence for re-operative surgery for locally recurrent colorectal cancers, it is unlikely that large randomised controlled trials will ever be performed in these patients.

Anecdotally, locally recurrent rectal cancers are associated with a 0% 5-year survival and a median survival of 6–9 months. Chemotherapy with or without radiation can result in a modest improvement in survival, with a median survival of 12–18 months, but this is rarely curative when used in isolation. Radical re-resection is the only curative option, provided that R0 resection margins can be achieved. Contemporary large case series have reported 5-year survival rates of over 40% (median survival of over 40 months). Even in the absence of randomised trials, this represents a large and significant survival benefit over non-curative treatment options. In view of this, RCTs to establish the role of radical resection in the future are neither ethical nor necessary.

Additional evidence from case series in rectal cancer

In addition to the included observational cohort studies, several large uncontrolled, non-comparative case series have recently been published by internationally renowned centres at the forefront of locally recurrent rectal cancer treatment and research.

Experienced centres with an interest in locally recurrent rectal cancer in Australia have also published on pelvic side wall resection and en bloc sacrectomy, with R0 rates in excess of 66%. This is an excellent R0 result, considering the technical challenges with these dissections and the published R0 rates for more centrally based recurrences (and therefore simpler resections) from other centres.

These radical surgical approaches have previously been controversial in the surgical literature, but are no longer controversial in view of the strong and overwhelming evidence that suggests that R0 resection margin is the main predictor of long-term survival.

Post-operative complications and quality of life

Although surgical mortality with radical re-resection has improved, post-operative complication rates following such procedures remain high. Depending on the reporting methodology and classification, complication rates can range from 27% and 82%.

Quality-of-life outcomes have been assessed by a handful of studies including two larger Australian studies. The first of these studies was a cross-sectional quality of life study comparing quality of life between patients with locally recurrent rectal cancers and that of patients with primary rectal cancer. Long-term survivors of locally recurrent rectal cancer were found to have quality of life comparable to that of patients who had primary rectal cancer.
A subsequent and much larger prospective and longitudinal comparative quality-of-life study in these patients found that quality of life was preserved in patients who underwent pelvic exenteration, compared with patients who underwent palliative treatment.[8]

**Cost effectiveness**

A cost-effectiveness analysis was also undertaken as part of the large Australian quality-of-life study. It found pelvic exenteration to be cost-effective when compared with palliative treatment.[9]

**Application of the evidence to colon cancer**

Although the systematic review did not identify any suitable studies that compared curative surgery (with or without radiation and with or without chemotherapy) with non-curative treatments for locally recurrent colon cancer, the same treatment principles that apply to patients with recurrent rectal cancer are likely to be applicable to patients with locally recurrent colon cancer.

**Health system implications**

**Clinical practice**

The management of patients with locally recurrent colorectal cancer requires a multidisciplinary approach. The expertise needed is not restricted to surgeons alone. Expert radiologists to review the relevant pre-operative imaging so as to allow clinicians to arrive at the appropriate recommendation is important. The peri-operative management requires an experienced multi-disciplinary team comprised not just of clinicians but also allied health members and senior nurses to manage the complex peri-operative complications that may arise. Demonstration of improved survival outcomes without any compromise to long-term patient quality of life may result in an increased interest in these complex resections. This in turn may lead to increased referrals to centres with the necessary expertise and an increase in workload. This may also require establishment of more expert centres to ensure equity of care and services to patients in regional areas.

**Resourcing**

The recommendation to refer patients with locally recurrent colorectal cancer to a centre with the necessary expertise to perform curative surgery may necessitate the establishment of more expert centres. These expert centres will require more experienced surgeons and other members of the multidisciplinary team. These expert centres are also likely to be located in metropolitan cities where the large tertiary referral centres are located, which necessarily means that patients are still having to travel long distances for treatment.

**Barriers to implementation**

No barriers to the implementation of these recommendations are envisaged.
Discussion

Unresolved issues

One of the unresolved issues in locally recurrent colorectal cancer remains patient selection for surgery. Because a clear resection margin is the key determinant of long term survival, it is currently the most important criteria that most surgeons rely on when determining disease resectability and patient suitability for surgery. Whether or not there are other disease factors that play an important role in patient selection remains unclear. Furthermore, the role of palliative resections in selected patients with intractable symptoms remains unclear.

The role of adjuvant therapy following curative surgery is also unclear. Because of the long recovery times associated with most re-operative procedures, it is not uncommon that many patients remain unwell for consideration of adjuvant therapy after surgery within conventional time frames for chemotherapy. Whether or not these patients benefit from adjuvant therapy is not clear and warrant further evaluation.

Quality-of-life outcomes and other functional outcomes have not been well studied in patients with locally recurrent colorectal cancers. These outcomes need to be evaluated as part of a prospective study.

Studies currently underway

We are not aware of any large randomised trials currently underway comparing curative surgery to non-curative treatment options. There are, however, studies currently underway to examine the role of adjuvant therapy in patients with recurrent colorectal cancer and also vaccine trials in these patients to determine its utility.

Prospective quality-of-life studies are continuing drawing on patients with locally advanced and locally recurrent malignancies of the pelvis.

Studies evaluating prognostic factors (such as CEA, time to recurrence and other disease factors) are also underway and should facilitate future decision making about patient selection.

Future research priorities

Future research should look to facilitate patient selection and refine patient treatment (e.g. adjuvant therapy), rather than defining the role of curative surgery which, within the confines of existing literature, has demonstrated improved survival relative to non-curative treatment options.

Next section: management of metastatic resectable colorectal cancer

References

Clinical question: Management of recurrent, resectable CRC


Clinical question: Management of recurrent, resectable CRC


