Evidence Essential

Neoadjuvant radiochemotherapy for rectal cancer

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The Royal Australasian College of Surgeons
Neoadjuvant radiochemotherapy for rectal cancer

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ASERNIP-S Evidence Essentials

PURPOSE AND SCOPE
The ASERNIP-S Evidence Essentials document is a structured literature review on a given health technology (procedure or device). It may be produced where current published systematic review evidence is available on a procedure nominated for ASERNIP-S assessment.

The Evidence Essentials is designed to inform on the existence and findings of high-level evidence such as systematic reviews and health technology assessments. In this way it reduces duplication of endeavour and provides rapid and timely information to interested end-users, particularly those who have approached ASERNIP-S to investigate the given topic. Evidence Essentials intends to provide a summary of the high-level evidence base, including an appraisal of the quality and appropriateness of the published evidence; a commentary on the appropriateness of the data to the Australian locality (if possible); and a summary of the overall conclusions of the published evidence.

METHODOLOGY
Evidence Essentials presents summary high-level evidence arising from current, English language systematic reviews (published within two years as either a full systematic review/health technology assessment or a peer-reviewed publication). For this purpose, systematic reviews are defined as those studies that meet all the following criteria as defined by Cook et al (1997) (focused clinical question, explicit search strategy, use of explicit, reproducible and uniformly applied criteria for article selection, critical appraisal of the included studies, qualitative or quantitative data synthesis). Evidence Essentials does not encompass any new synthesis of primary data.

Evidence Essentials also provides a comment on any clinical trials in progress, to provide an indication of the current status of research, and also presents available clinical practice guidelines.

Where necessary, recent non-systematic clinical reviews are used to provide background information on the indications and technology. These papers are cited at the end of the document. Evidence Essentials provides a summary on available high-level evidence on a given topic, but does not include direct input from clinical experts as it is anticipated that the included studies have incorporated clinical input as part of their methodology.

INTRODUCTION

DEVICE/PROCEDURE

Neoadjuvant radiochemotherapy for rectal cancer.

Neoadjuvant radiochemotherapy is a pre-operative combined modality treatment where both radiotherapy and chemotherapy are administered. The aim of this treatment is to downsize tumours with the objective of enhancing surgical outcomes (Rodel and Sauer 2004). The adverse events associated with neoadjuvant radiochemotherapy include local and systemic toxicity and over-treatment of inaccurately staged patients (Celeen et al 2009).
**INDICATION**
Neoadjuvant radiochemotherapy is available for use in patients with rectal cancer. The treatment aims to downsize and downstage tumours to enhance R0 resection and sphincter preservation rate (Celeen et al 2009).

**ALTERNATIVE TREATMENTS**
The comparators to neoadjuvant radiochemotherapy include preoperative radiotherapy, postoperative radiotherapy and postoperative radiochemotherapy.

**CURRENT FUNDING STATUS IN AUSTRALIA**

<table>
<thead>
<tr>
<th>MBS item number</th>
<th>Descriptor</th>
<th>Fee</th>
<th>Benefit 75%</th>
<th>Benefit 85%</th>
</tr>
</thead>
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<tr>
<td>15100</td>
<td>RADIOTHERAPY, DEEP OR ORTHOVOLTAGE each attendance at which fractionated treatment is given at 3 or more treatments per week - 1 field</td>
<td>$43.10</td>
<td>$32.35</td>
<td>$36.65</td>
</tr>
<tr>
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<td>RADIOTHERAPY, DEEP OR ORTHOVOLTAGE each attendance at which fractionated treatment is given at 2 treatments per week or less frequently - 1 field</td>
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<td>$38.15</td>
<td>$43.25</td>
</tr>
<tr>
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<td>RADIOTHERAPY, DEEP OR ORTHOVOLTAGE attendance at which single dose technique is applied 1 field</td>
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<td>$81.45</td>
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<td>13915</td>
<td>CYTOTOXIC CHEMOTHERAPY, administration of, either by intravenous push technique (directly into a vein, or a butterfly needle, or the side-arm of an infusion) or by intravenous infusion of not more than 1 hours duration - payable once only on the same day, not being a service associated with photodynamic therapy with verteporfin or for the administration of drugs used immediately prior to, or with microwave (UHF radiowave) cancer therapy alone</td>
<td>$58.75</td>
<td>$44.10</td>
<td>$49.95</td>
</tr>
<tr>
<td>13918</td>
<td>CYTOTOXIC CHEMOTHERAPY, administration of, by intravenous infusion of more than 1 hours duration but not more than 6 hours duration - payable once only on the same day</td>
<td>$88.40</td>
<td>$66.30</td>
<td>$75.15</td>
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<td>13921</td>
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<td>$75.05</td>
<td>$85.05</td>
</tr>
<tr>
<td>13924</td>
<td>CYTOTOXIC CHEMOTHERAPY, administration of, by intravenous infusion of more than 6 hours duration - on each day subsequent to the first in the same continuous treatment episode</td>
<td>$58.95</td>
<td>$44.25</td>
<td>$50.15</td>
</tr>
<tr>
<td>13927</td>
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<td>$76.25</td>
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<td>$76.90</td>
<td>$57.70</td>
<td>$65.40</td>
</tr>
</tbody>
</table>

NOTES: MBS Medicare Benefits Schedule
AVAILABLE HIGH LEVEL EVIDENCE

A systematic search of the literature was carried out to identify available, current, English-language systematic reviews and health technology assessments. The databases searched and terminologies used are included at Appendix A.

RELEVANT UNIQUE CITATIONS IDENTIFIED

- Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer (Borschitz et al 2007)
- Chemoradiotherapy for rectal cancer: an updated analysis of factors affecting pathological response (Sanghera et al 2008)
- Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer (Ceelen et al 2009)

EVIDENCE APPRAISAL

The quality of the identified systematic reviews was assessed using key items from the QUOROM statement (Moher et al 1999).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
<td>Analyse previously published data about recurrence rates and prognostic risk factors of neoadjuvant chemoradiation and local excision.</td>
<td>To compare preoperative radiotherapy with preoperative radiochemotherapy in patients with resectable stage II or III rectal cancer.</td>
<td>Analyse the factors affecting a pathological complete response.</td>
</tr>
<tr>
<td>Selecting</td>
<td>Exclusion criteria insufficient.</td>
<td>Sufficient.</td>
<td>Sufficient.</td>
</tr>
<tr>
<td>Study flow</td>
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<td>Table of excluded studies included.</td>
<td>Not reported.</td>
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<td>Validity assessment</td>
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<td>Comprehensive.</td>
<td>Not reported.</td>
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<tr>
<td>Data abstraction</td>
<td>Not described.</td>
<td>Processes described.</td>
<td>Not described.</td>
</tr>
<tr>
<td>Study characteristics</td>
<td>Comprehensive, tabulated.</td>
<td>Comprehensive.</td>
<td>Brief, tabulated.</td>
</tr>
<tr>
<td>Data synthesis</td>
<td>Data did not permit a statistical analysis, narratively described.</td>
<td>Odds Ratio and associated 95% confidence interval.</td>
<td>No data synthesis performed on outcome of interest.</td>
</tr>
</tbody>
</table>

Borschitz et al (2007) reported upon a variety of studies, with diverse patient populations and surgical characteristics. Attempts were made to analyse the various surgical techniques, data collection methods, and follow-up periods separately. Borschitz et al (2007) and Sanghera et al (2008) did not adequately report upon their study methodology, including study selection. This made it difficult to determine if their grouping of studies was valid. Borschitz et al (2007) also reported upon a series of their own patients in addition to identified studies, and it was unclear whether this data had been previously published. Borschitz et al (2007) noted that their collective patients were
highly selected. Sanghera et al (2008) included 149 patients who received neoadjuvant radiochemotherapy together with 4583 patients who received other treatments for rectal cancer. The neoadjuvant radiochemotherapy patients were not analysed separately from the alternative treatment groups, therefore it was not possible to draw relevant conclusions from this systematic review concerning the safety and effectiveness of neoadjuvant radiochemotherapy.

**SUMMARY OF FINDINGS**

None of the identified systematic reviews assessed the effect of neoadjuvant radiochemotherapy on tumour downstaging as a primary outcome. However, they did report upon this as a secondary outcome. Measures used to quantify this outcome included pathological complete response and T and N stage downstaging.

Local excision is an established treatment for patients with T1 low-risk rectal cancer. Borschitz et al (2007) assessed whether local excision could be used to treat patients with T2 or greater rectal cancer, after receiving neoadjuvant radiochemotherapy. This review included six retrospective trials and one prospective trial. A total of 237 patients with T2-T3 carcinoma who received neoadjuvant radiochemotherapy then local excision 2-10 weeks after were studied. All patients received 5-FU chemotherapy, and between 36 to 52.5 Gy radiotherapy.

None of the reported complications were severe, and all were managed without rectal resection or extirpation. Suture dehiscence, fever, dermatitis, phlegmons and abscesses were the most frequently reported adverse events. Clinical staging of patients before surgery showed a T1-2 tumour in 37 (16%), a T2 in 81 (34%) and a T3 in 119 (50%) patients. It was unclear whether this staging was measured before or after neoadjuvant radiochemotherapy. The proportion of clinical complete response (T0) in the highly selected patients of three retrospective studies was 85% (22 of 26), 89% (23 of 26) and 27% (7 of 26). The tumour of one patient in the authors’ series of five patients showed complete response. No statistical analysis was performed.

This systematic review concluded that local excision of T2-3 rectal cancer after neoadjuvant radiochemotherapy should be considered. It concluded that local excision is not adequate in patients whose tumours exhibit no response or weak response to the neoadjuvant radiochemotherapy, and that such patients should be treated with radical surgery.

Ceelen et al (2009) assessed four randomised trials in a Cochrane systematic review. All trials used a biologically equivalent dose >30 Gy and delivered 5-FU chemotherapy, with two trials also delivering leucovorin during weeks one and five of neoadjuvant radiochemotherapy. Significantly more patients who received neoadjuvant radiochemotherapy developed grade III or IV treatment related toxicity than patients who received neoadjuvant radiotherapy only (14.9% vs. 5.1%) (OR 4.1, 95% CI 1.68-10, p=0.002). However there appeared to be between-study heterogeneity for this outcome. There were no significant differences between patients who received neoadjuvant radiochemotherapy and patients who received neoadjuvant radiotherapy regarding postoperative 30 day mortality, postoperative morbidity or anastomotic leak rate. One study used different radiation schedules and waiting periods until surgery between the study arms, hence it was unclear whether the outcomes were due to the neoadjuvant...
radiochemotherapy or to these differences. Significantly more patients who received neoadjuvant radiochemotherapy had pathological complete response than patients who received neoadjuvant radiotherapy only (11.8% vs. 3.5%) (OR 3.65, 95% CI 2.52-5.27, p<0.001). There was no significant between-study heterogeneity. Neoadjuvant radiochemotherapy led to a decrease in local recurrence rate compared with radiotherapy alone (9.4% vs. 16.5%).

This systematic review concluded that compared to preoperative radiotherapy alone, neoadjuvant radiochemotherapy enhances tumour response and improves local recurrence rates. It recommended that neoadjuvant radiochemotherapy should be considered when the tumour is located less than 2mm from the circumferential resection margin or the sphincter apparatus.

Although Sanghera et al (2008) included 149 patients from three trials who received neoadjuvant radiochemotherapy, these patients were not analysed separately from patients who received radiotherapy with 5-FU and a second drug, or varying doses or radiotherapy, so no meaningful conclusions were drawn.

OTHER CONSIDERATIONS

- Downstaging was not the outcome of interest in most systematic reviews. Rather, survival, recurrence and sphincter preservation were the outcomes of interest.

- Two of the systematic reviews reported upon patients with stage II or III rectal cancer, and it is unclear whether these outcomes may be extended to patients with other stages of cancer.

- No study of quality of life (QoL) was included in the systematic reviews. The review by Celeen et al (2009) recommended that “Patients should be informed about the possible functional and other QoL related aspects of preoperative therapy.”

- Although most of the available clinical practice guidelines were evidence-based (see Appendix B), neoadjuvant radiochemotherapy was generally not addressed in detail.

CONCLUSIONS

There is a good evidence base, including a recent Cochrane systematic review, upon which to judge the safety and effectiveness of neoadjuvant radiochemotherapy for rectal cancer. A further full systematic review is unlikely to add value.
REFERENCES

SYSTEMATIC REVIEW EVIDENCE USED TO PRODUCE THIS EVIDENCE ESSENTIALS DOCUMENT


FURTHER REFERENCES USED


### APPENDIX A

**DATABASES SEARCHED AND SEARCH TERMS USED**

<table>
<thead>
<tr>
<th>Database</th>
<th>Search terms</th>
<th>Date searched</th>
</tr>
</thead>
<tbody>
<tr>
<td>York CRD</td>
<td>'Rectal' or 'rectum' or 'colorectal'</td>
<td>22 October 2008</td>
</tr>
<tr>
<td>Entrez PubMed</td>
<td>('Rectal' or 'rectum' or 'colorectal') AND systematic [sb]</td>
<td>22 October 2008</td>
</tr>
<tr>
<td>The Cochrane Library</td>
<td>Rectal neoplasms</td>
<td>27 October 2008</td>
</tr>
<tr>
<td>Current Controlled Trials</td>
<td>'Rectal' or 'rectum' or 'colorectal'</td>
<td>27 October 2008</td>
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<tr>
<td>Clinical Trials.gov</td>
<td>'Rectal' or 'rectum' or 'colorectal'</td>
<td>28 October 2008</td>
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<tr>
<td>Australian New Zealand Clinical Trials Registry</td>
<td>'Rectal' or 'rectum' or 'colorectal'</td>
<td>28 October 2008</td>
</tr>
<tr>
<td>Trip database</td>
<td>'Rectal' or 'rectum' or 'colorectal'</td>
<td>22 October 2008</td>
</tr>
<tr>
<td>NLH National Library of Guidelines</td>
<td>'Rectal' or 'rectum' or 'colorectal'</td>
<td>22 October 2008</td>
</tr>
</tbody>
</table>

**NOTES:** CRD Centre for Reviews and Dissemination
APPENDIX B

CLINICAL PRACTICE GUIDELINES AND CURRENT CLINICAL TRIALS

CLINICAL GUIDELINES

• Guidelines for the management of colorectal cancer. (London (UK): Association of Coloproctology of Great Britain and Ireland 2007)
• Clinical practice guidelines for the prevention, early detection and management of colorectal cancer (Australia: National Health and Medical Research Council 2005)  
  This guideline was rescinded by the NHMRC in 2005.
• Preoperative or postoperative therapy for the management of patients with stage II or III rectal cancer: guideline recommendations. (Ontario: Cancer Care Ontario 2008)  
  Did not appear to be evidence-based
• Rectal cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up  
  (ESMO Guidelines Working Group, Annals of Oncology 2007)  
  Did not appear to be evidence-based

CURRENT CLINICAL TRIALS IDENTIFIED

More than 90 current clinical trials were identified. Examples of current trials include:

• Chemotherapy or no chemotherapy in clear margins after neoadjuvant chemoradiation in locally advanced rectal cancer. A randomised phase III trial of control vs capecitabine plus oxaliplatin
• Study of neoadjuvant chemotherapeutic treatment (XELOX) followed by chemoradiotherapy (XELOX/RT) and surgery versus chemoradiotherapy followed by surgery and chemotherapy in patients with high risk rectal cancer
• Radiation therapy plus chemotherapy followed by surgery in treating patients with locally advanced cancer of the rectum
• Radiation therapy plus chemotherapy before surgery with or without chemotherapy after surgery in treating patients with rectal cancer