DOES ADDITIONAL (SEGMENTAL) COLON RESECTION YIELD BETTER OUTCOMES (PFS, OS, QOL) THAN WATCHFUL WAITING IN PATIENTS WHO ARE DIAGNOSED WITH TIS/T1 COLON CARCINOMA AND WHO HAVE UNDERGONE ENDOSCOPIC POLYPECTOMY?
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<td>EMR</td>
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<td>NHMRC</td>
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<td>NPV</td>
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<td>Clear margin of specimen</td>
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1 INTRODUCTION

1.1 PICO

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1.2 Summary Guidelines NICE, 2011 - NHMRC, 2012

Table 1 - Management of malignant adenomas after polypectomy

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<th>Level of evidence</th>
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<td>NICE 2011¹</td>
<td>February 2011</td>
<td>No recommendations could be formulated since none of the retrieved studies (non-comparative and case series of a poor quality) provided any insight to the best treatment option.</td>
<td>No evidence retrieved in the literature</td>
<td>Not applicable</td>
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| Australian NHMRC, 2011²⁴   | 31 December 2009  | Management of malignant polyps by polypectomy alone is standard practice and is acknowledged to be safe, providing that there is adherence to a strict policy of case selection and histopathological assessment recognising four key features that together identify a very low risk of lymph node metastasis:  
  - a clear margin of excision (1 to 2mm)  
  - cancer which is well- or moderately-differentiated  
  - absence of lymphatic or venous invasion  
  - complete removal as assessed endoscopically | 1 case-control study  
  5 case series  
  1 narrative review | |
| IKNL 2008³                 | February 2006     | Not covered                                                                                   | 1 systematic review (based on Medline search only; no quality appraisal; only retrospective case series retrieved)  
  1 RCT⁴  
  2 narrative reviews | |
| SIGN 2011⁴                | March 2011        | Not covered                                                                                   |                                    |                   |

Abbreviations: NHMRC: National Health and Medical Research Council  
2 SEARCH FOR EVIDENCE

2.1 Search strategy
First, guideline databases and websites of international oncology guideline developers were searched for evidence-based guidelines relevant to the subject. Evidence of the retrieved guidelines was updated with literature search from 2009 onwards. Initially, only systematic reviews and meta-analyses were searched. They were searched in the following databases: OVID Medline and PreMedline, EMBASE and Cochrane Database of Systematic Reviews. These searches were performed in November 2012. The search strategy can be found in Appendix 1 (Table 2). Additional searches for randomized controlled trials (RCTs), observational studies (case series, cohort studies and case-controlled studies) were performed to update the selected reviews. The additional information was searched in OVID Medline and PreMedline, EMBASE and CENTRAL in December 2012. The search strategy is also presented in Appendix 1 (Table 3).

2.2 Study selection
All citations retrieved were screened based on title and abstracts. Possible citations of interest were further selected based on the full text article. Study selection criteria for systematic reviews are summarized in Table 4; the criteria for the search for RCTs and observational studies were comparable, with the exception for study design.

The search for systematic reviews and meta-analyses published between 2009 and 2012 retrieved 919 citations, after removal of duplicates. After removal of studies that (based on title and abstract) did not fulfill the selection criteria, 11 citations were left for full text evaluation (Figure 1).

The update with randomized controlled trials and observational studies published in 2011 and 2012 yielded 3793 publications, after removal of duplicates. After removal of studies that (based on title and abstract) did not fulfill the selection criteria, 33 citations were left for full text evaluation (Figure 2).

Comparative cohort studies were included when at least the known risk factors (i.e. histopathological characteristics such as grade of differentiation, tumour involvement of resection margins, lymphovascular involvement) were taken into account and when statistical adjustment was performed for known confounders to measure survival or recurrence. Case series were considered eligible when uniform interventions were performed amongst well defined groups.

2.3 Critical appraisal
The one selected (systematic) review was critically appraised using the AMSTAR checklist (see Table 5). The observed shortcomings are enumerated in the last column of Table 6.
2.4 Table 8 Statistical analysis

Since no RCTs were found and the observational studies were very heterogeneous, no meta-analysis was performed. When data were available, sensitivity, specificity, positive and negative predictive values and RR for recurrence were calculated.
3 SUMMARY OF THE EVIDENCE

3.1 Management of malignant adenomas after polypectomy – guidelines, systematic reviews, RCTs and non-randomized controlled studies

Four evidence-based guidelines that included treatment of early-stage colon cancer were identified in the literature. Only two of them formulated recommendations on the preferred treatment for Tis/T1 cancer found colorectal polyps. Recommendations are summarized in Table 1.

In the NICE Clinical Guideline on colorectal Cancer, one of the research questions resembled research question 3 very closely: “For patients diagnosed with stage I colorectal cancer, including/or polyp cancer, what are the prognostic factors for determining the most effective curative treatment?”. Extensive search strategy for RCTs and observational studies was applied in Medline, Premedline, EMBASE, Cochrane Library, Cinahl, BNI, Psychinfo, Web of Science (SCI & SSCI) and ISI Proceedings and Biomed Central. The authors concluded that there was no evidence with which to answer this question as much of the literature concentrates on identifying the unfavourable prognostic features rather than focusing on the long term outcomes related to such features or which type of treatment is best for patients with specific unfavourable characteristics.

The recommendations cited in the Australian NHMRC Guideline concentrate on the clinical (tumour site and general health status), histopathological (tumour-free margin, differentiation grade, lymphatic and/or venous invasion and completeness of removal) and patient-related (age and wishes) prognostic factors for patients with malignant polyps. The recommendations are based on one systematic review of retrospective case series, 1 RCT (comparing laparoscopy-assisted colectomy versus laparotomy) 3 narrative reviews and 5 case series. The systematic review (based on 31 English papers published between 1980 and 2003 and obtained solely through a Medline search) concluded that a positive resection margin is largely predictive of residual local disease, the presence of poorly differentiated carcinoma is mainly associated with a higher cancer-related mortality and vascular invasion with a higher risk of lymph node metastasis.

An additional search was performed for RCT’s and observational studies published in 2011-2012 (i.e. after the search date of the NICE Clinical Guideline on colorectal Cancer). No study design filters were employed. The additional search did not yield any (randomized or non-randomized) comparative study that reported the primary outcomes of interest (Overall survival, PFS, QoL) for polypectomy followed by surveillance versus polypectomy followed by surgery.

Conclusions

There is no evidence to compare the effect of polypectomy followed by surveillance with polypectomy followed by (segmental) colon resection in patients who were diagnosed with Tis/T1 colorectal cancer after endoscopic polypectomy, in terms of overall survival, progression-free survival or quality of life.

3.2 Management of malignant adenomas after polypectomy – case series

There are some observational studies that suggest that polypectomy followed by surveillance maybe safe for low-risk Tis/T1 CRC but not in high risk cancer.
The results of one review of observational studies and five observational studies (all with methodological limitations) are listed below. All studies are considered of very low quality as no appropriate eligibility criteria for the different treatment groups were applied, confounding was not appropriately controlled and there were no data on the completeness of follow-up.

In 2012 Di Gregorio and co-workers\textsuperscript{9} performed a review on the available literature on the outcome of low- and high-risk malignant colorectal polyps. No quality assessment of the included observational studies was performed. High risk polyps were defined by the presence of at least one of the following histological features: positive resection margin, poorly differentiated adenocarcinoma, lymphatic/vascular invasion or tumour budding. If none of those features were present, polyps were classified as low risk. Overall, there were 345 patients with a low risk polyp reported, of whom 53 underwent surgery after polypectomy. In one of the 53 surgical specimens, residual disease was reported. One of the 345 low risk cancer patients died due to cancer. There were in total 471 patients with a high risk polyp included, 335 of them underwent surgery. In 49 of the 335 (14.6%) surgical specimens, residual cancer was seen; 23/471 (4.9%) patients died due to cancer. Results for the separate risk factors (present vs. absent) are summarized in Table 7. These results should be interpreted with great caution as it is not clear which patients underwent surgery and there is no correction for the other risk factors.

Benizri et al.\textsuperscript{10} summarized a retrospective case series of 64 patients with T1 CRC in whom resection (either by laparotomy or laparoscopy) and regional lymphadenectomy was performed after analysis of the polypectomy specimen had revealed at least one of the following adverse criteria: inadequate excision with cancer free distance of the resection margin \(\leq 1\) mm, lymphovascular invasion, poorly differentiated carcinoma (grade III), submucosal SM 2-3 involvement, tumour budding, sessile morphology or piecemeal resection (see Table 8). The rate of residual adenocarcinoma and/or lymph node metastasis was 7/64 (11%). Post-operative complications were observed in 16/64 (25%) patients.

Butte and co-workers\textsuperscript{11} reported on a retrospective case series of 143 consecutive patients with T1 CRC undergoing polypectomy followed by colectomy (see Table 8). At colectomy, invasive residual disease was observed in 16 (11%) patients, non-invasive in 3 (2.1%) and lymph node metastasis in 10 (7%). Collectively, in 13% of patients residual disease was diagnosed at the moment of surgery. In case of positive or unknown resection margin, the rate of residual invasive disease in the colonic wall was 16% vs. 0% in case of a negative resection margin. After a median follow-up period of 63 months, no recurrences were identified; 122 patients were still alive, 15 died of unknown causes and 6 died of other causes.

Kim and co-workers\textsuperscript{12} followed retrospectively a case series of 64 patients with intramucosal CRC and 65 patients with submucosal CRC who all had either EMR (Endoscopic mucosal resection) or ESD (Endoscopic submucosal resection) performed (see Table 8). After a mean FU period of 19 months 62 patients with intramucosal CRC were still alive; 2 died of unrelated diseases. The survival rate for patients who had submucosal CRC was not reported. Seven patients with submucosal cancer had colectomy performed during the FU period, five because of positive resection margin or lymphovascular involvement, one because of bowel perforation and one patient requested surgery (see Table 8). The recurrence rate (i.e. local recurrence and/or distant recurrence) was 6/64 in the intramucosal group and 7/65 in the submucosal group (3/7 underwent colectomy and 4/7 only had polypectomy). Of the seven patients who suffered from recurrence, five had a high risk polyp and two a low risk polyp. The total number of high risk and low risk polyps included in the study is unclear.

Meining et al.\textsuperscript{13} documented on 390 patients with T1 CRC: 141 patients had polypectomy and surgical removal of T1 CRC (group A) and 249 only had polypectomy (group B)(see Table 8). Decision in favour or against surgery was based on risk patterns, patients’ personal wishes and patients’ fitness. Both low-risk and high-risk polyps were included in both groups. An unfavourable outcome was defined as locoregional cancer relapse, distant metastasis, lymph
node metastasis or death related to CRC. In the polypectomy only group, an unfavourable outcome was observed in 17/249 (6.8%) patients. In this polypectomy only group, the rate of unfavourable outcome was 20% in case of incomplete resection versus 4% in case of complete resection; poorly differentiated tumours had an unfavourable outcome in 43% of cases versus 6% in other tumours and 44% of tumours with lymphovascular infiltration had an unfavourable outcome versus 5% in other cases.

Oka et al. 14 reported on retrospective case series of 792 patients with submucosal CRC who only had surveillance after endoscopic resection (see Table 8). The data were collected from 15 centres in Japan. The recurrence rate was 18/792 (2.3%) (local recurrence: 11 cases and metastatic recurrence in 13 cases). The association between histopathological characteristics at polypectomy and recurrence was evaluated by means of a multivariate logistic regression analysis: lymphatic invasion was significantly associated with recurrence after ER in patients with submucosal CRC (OR: 6.36, 95% C.I. 1.46-27.79. It has to be mentioned though that this analysis was only based on 387 cases as the histopathological data were missing for 49% of the sample. The mean interval between ER and recurrence was 19.7 (+/- 9.2) months.
## APPENDIX 1. SEARCH FOR EVIDENCE

### Appendix 1.1. Search strategy

**Table 2 - Search strategies for systematic reviews and meta-analyses**

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<tr>
<td>48</td>
<td>placebo.ab. (5581)</td>
</tr>
<tr>
<td>49</td>
<td>randomly.ab. (13885)</td>
</tr>
<tr>
<td>50</td>
<td>trial.ab. (15159)</td>
</tr>
<tr>
<td>51</td>
<td>groups.ab. (79716)</td>
</tr>
<tr>
<td>52</td>
<td>45 or 46 or 47 or 48 or 49 or 50 or 51 (105211)</td>
</tr>
<tr>
<td>53</td>
<td>44 or 52 (110852)</td>
</tr>
<tr>
<td>54</td>
<td>37 and 53 (21)</td>
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</table>

Note: The search for systematic reviews, meta-analyses and randomized controlled trials (RCTs) was performed simultaneously in PreMedline.

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</tr>
<tr>
<td>Date</td>
<td>November 19, 2012</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------</td>
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**Search Strategy**

<p>| | |</p>
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<thead>
<tr>
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<tbody>
<tr>
<td>#1</td>
<td>MeSH descriptor: [Colorectal Neoplasms] explode all trees</td>
</tr>
<tr>
<td>#2</td>
<td>MeSH descriptor: [Intestinal Polyps] explode all trees</td>
</tr>
<tr>
<td>#3</td>
<td>#1 or #2</td>
</tr>
<tr>
<td>#4</td>
<td>MeSH descriptor: [Endoscopy, Gastrointestinal] explode all trees</td>
</tr>
<tr>
<td>#5</td>
<td>endoscop*</td>
</tr>
<tr>
<td>#6</td>
<td>colonoscop*</td>
</tr>
<tr>
<td>#7</td>
<td>sigmoidoscop*</td>
</tr>
<tr>
<td>#8</td>
<td>polypectomy</td>
</tr>
<tr>
<td>#9</td>
<td>(colo* adj5 polyp*) adj5 (surg* or excis* or remov* or resect*)</td>
</tr>
<tr>
<td>#10</td>
<td>#4 or #5 or #6 or #7 or #8 or #9</td>
</tr>
<tr>
<td>#11</td>
<td>#3 and #10</td>
</tr>
<tr>
<td>#12</td>
<td>MeSH descriptor: [Colectomy] explode all trees</td>
</tr>
<tr>
<td>#13</td>
<td>MeSH descriptor: [Laparotomy] explode all trees</td>
</tr>
<tr>
<td>#14</td>
<td>MeSH descriptor: [Laparoscopy] explode all trees</td>
</tr>
<tr>
<td>#15</td>
<td>colectomy</td>
</tr>
<tr>
<td>#16</td>
<td>MeSH descriptor: [Colon] explode all trees and with qualifiers: [Surgery - SU]</td>
</tr>
<tr>
<td>#17</td>
<td>MeSH descriptor: [Rectum] explode all trees and with qualifiers: [Surgery - SU]</td>
</tr>
<tr>
<td>#18</td>
<td>MeSH descriptor: [Colonic Polyps] explode all trees and with qualifiers: [Surgery - SU]</td>
</tr>
<tr>
<td>#19</td>
<td>MeSH descriptor: [Colorectal Neoplasms] explode all trees and with qualifiers: [Surgery - SU]</td>
</tr>
<tr>
<td>#20</td>
<td>(colo* or rect*) adj5 (surg* or excis* or remov* or resect*)</td>
</tr>
<tr>
<td>#21</td>
<td>surg* adj5 manag*</td>
</tr>
<tr>
<td>#22</td>
<td>#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21</td>
</tr>
<tr>
<td>#23</td>
<td>MeSH descriptor: [Watchful Waiting] explode all trees</td>
</tr>
</tbody>
</table>
#24  #22 or #23
#25  #11 and #24 from 2009 to 2012

Note  Search to be repeated for RCTs on from 2011 to 2012

**Table 3 - Search strategies for RCT’s and observational studies**

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<thead>
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</tr>
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<td>Database</td>
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</tr>
<tr>
<td>1</td>
<td>exp Colorectal Neoplasms/ (136731)</td>
</tr>
<tr>
<td>2</td>
<td>exp colonic polyps/ (5748)</td>
</tr>
<tr>
<td>3</td>
<td>(colo$ adj5 polyp$).tw. (9725)</td>
</tr>
<tr>
<td>4</td>
<td>(colo$ adj5 cancer$).tw. (80453)</td>
</tr>
<tr>
<td>5</td>
<td>(colo$ adj5 carcin$).tw. (33026)</td>
</tr>
<tr>
<td>6</td>
<td>(colo$ adj5 neoplas$).tw. (5406)</td>
</tr>
<tr>
<td>7</td>
<td>(colo$ adj5 tumo$).tw. (22794)</td>
</tr>
<tr>
<td>8</td>
<td>(colo$ adj5 metasta$).tw. (15751)</td>
</tr>
<tr>
<td>9</td>
<td>(colo$ adj5 malig$).tw. (4661)</td>
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<td>10</td>
<td>1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (173076)</td>
</tr>
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<td>11</td>
<td>exp Endoscopy, Gastrointestinal/ (61323)</td>
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<td>12</td>
<td>endoscop$.mp. (147390)</td>
</tr>
<tr>
<td>13</td>
<td>colonoscop$.mp. (23047)</td>
</tr>
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<td>14</td>
<td>sigmoidoscop$.mp. (5955)</td>
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<tr>
<td>15</td>
<td>(colo$ adj5 polyp$ adj5 resect$).mp. (302)</td>
</tr>
<tr>
<td>16</td>
<td>(colo$ adj5 polyp$ adj5 surg$).mp. (226)</td>
</tr>
<tr>
<td>17</td>
<td>(colo$ adj5 polyp$ adj5 excis$).mp. (66)</td>
</tr>
<tr>
<td>18</td>
<td>polypectomy.mp. (2946)</td>
</tr>
<tr>
<td>19</td>
<td>colonic polyps/su (1762)</td>
</tr>
<tr>
<td>20</td>
<td>11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (178291)</td>
</tr>
</tbody>
</table>
18

21 10 and 20 (19499)
22 exp animals/ not humans.sh. (3812817)
23 21 not 22 (19344)
24 limit 23 to yr="2011 -Current" (2131)
25 limit 24 to dutch (6)
26 limit 24 to english (1922)
27 limit 24 to french (10)
28 limit 24 to german (30)
29 25 or 26 or 27 or 28 (1968)
30 exp Colorectal Neoplasms/ (136731)
31 exp colonic polyps/ (5748)
32 (colo$ adj5 polyp$).tw. (9725)
33 (colo$ adj5 cancer$).tw. (80453)
34 (colo$ adj5 carcin$).tw. (33026)
35 (colo$ adj5 neoplas$).tw. (5406)
36 (colo$ adj5 tumo$).tw. (22794)
37 (colo$ adj5 metasta$).tw. (15751)
38 (colo$ adj5 malig$).tw. (4661)
39 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 (173076)
40 *Endoscopy, Gastrointestinal/ (6780)
41 endoscop$.mp. (147390)
42 colonoscop$.mp. (23047)
43 sigmoidoscop$.mp. (5955)
44 (colo$ adj5 polyp$ adj5 resect$).mp. (302)
45 (colo$ adj5 polyp$ adj5 surg$).mp. (226)
46 (colo$ adj5 polyp$ adj5 excis$).mp. (66)
47 polypectomy.mp. (2946)
48 colonic polyps/su (1762)
49 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 (166610)
Note: The search for systematic reviews, meta-analyses and randomized controlled trials (RCTs) was performed simultaneously in PreMedline.

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<thead>
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'control group'/de OR 'controlled study'/de OR 'cross-sectional study'/de OR 'diagnostic test accuracy study'/de OR 'intermethod comparison'/de OR 'major clinical study'/de OR 'medical record review'/de OR 'practice guideline'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'retrospective study'/de OR 'systematic review'/de)

Results: 2733

<table>
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<td>MeSH descriptor: [Colorectal Neoplasms] explode all trees</td>
</tr>
<tr>
<td>#2</td>
<td>MeSH descriptor: [Intestinal Polyps] explode all trees</td>
</tr>
<tr>
<td>#3</td>
<td>#1 or #2</td>
</tr>
<tr>
<td>#4</td>
<td>MeSH descriptor: [Endoscopy, Gastrointestinal] explode all trees</td>
</tr>
<tr>
<td>#5</td>
<td>endoscop*</td>
</tr>
<tr>
<td>#6</td>
<td>colonoscop*</td>
</tr>
<tr>
<td>#7</td>
<td>sigmoidoscop*</td>
</tr>
<tr>
<td>#8</td>
<td>polypectomy</td>
</tr>
<tr>
<td>#9</td>
<td>colonic polyps, surgery</td>
</tr>
<tr>
<td>#10</td>
<td>(colo* adj5 polyp*) adj5 (surg* or excis* or remov* or resect*)</td>
</tr>
<tr>
<td>#11</td>
<td>#4 or #5 or #6 or #7 or #8 or #9 or #10</td>
</tr>
<tr>
<td>#12</td>
<td>#3 and #11 from 2011 to 2012</td>
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</table>
### Appendix 1.2. Study selection

**Table 4 - Study selection criteria for systematic reviews and meta-analyses**

<table>
<thead>
<tr>
<th>Review question:</th>
<th>Does additional segmental colon resection yield better outcomes (i.e. PFS, OS, QoL) than watchful waiting in patients who were diagnosed with Tis/T1 colon carcinoma and who had undergone endoscopic polypectomy?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selection criteria</strong></td>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td>Population</td>
<td>Patients with Tis/T1 colon carcinoma after endoscopic treatment</td>
</tr>
<tr>
<td>Intervention</td>
<td>Segmental colon resection vs. watchful waiting Cave: was only introduced as Mesh term in 2011</td>
</tr>
<tr>
<td>Outcome</td>
<td>PFS, OS, QoL, adverse events</td>
</tr>
<tr>
<td>Design</td>
<td>SR, MA &amp; RCT (only in premedline)</td>
</tr>
<tr>
<td>Language</td>
<td>English, French, Dutch and German</td>
</tr>
<tr>
<td>Full text available</td>
<td>Yes</td>
</tr>
<tr>
<td>Duplicate</td>
<td>No</td>
</tr>
</tbody>
</table>
Figure 1 – Selection of systematic reviews: flow chart

Potentially relevant citations identified: 919

Based on title and abstract evaluation, citations excluded: 908

Studies retrieved for more detailed evaluation: 12

Based on full text evaluation, studies excluded: 11
Reasons:
- Population 2
- Intervention 0
- Outcome 6
- Design 3
- Language 0
- Full text available 0

Relevant studies: 1

Golden hit: 1
Potentially relevant citations identified: **3793**

Based on title and abstract evaluation, citations excluded: **3760**

Studies retrieved for more detailed evaluation: **33**

Based on full text evaluation, studies excluded: **28**

Reasons:
- Population: 10
- Intervention: 0
- Outcome: 6
- Design: 11
- Language: 0
- Full text available: 1

Relevant studies: **5**
Appendix 1.1. Critical appraisal

Appendix 1.1.1. AMSTAR checklist

Table 5 – AMSTAR checklist

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was an ‘a priori’ design provided?</td>
<td>□ Yes</td>
</tr>
<tr>
<td>The research question and inclusion criteria should be established before the conduct of the review.</td>
<td>□ No</td>
</tr>
<tr>
<td></td>
<td>□ Can’t answer</td>
</tr>
<tr>
<td></td>
<td>□ Not applicable</td>
</tr>
<tr>
<td>2. Was there duplicate study selection and data extraction?</td>
<td>□ Yes</td>
</tr>
<tr>
<td>There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.</td>
<td>□ No</td>
</tr>
<tr>
<td></td>
<td>□ Can’t answer</td>
</tr>
<tr>
<td></td>
<td>□ Not applicable</td>
</tr>
<tr>
<td>3. Was a comprehensive literature search performed?</td>
<td>□ Yes</td>
</tr>
<tr>
<td>At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.</td>
<td>□ No</td>
</tr>
<tr>
<td></td>
<td>□ Can’t answer</td>
</tr>
<tr>
<td></td>
<td>□ Not applicable</td>
</tr>
<tr>
<td>4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?</td>
<td>□ Yes</td>
</tr>
<tr>
<td>The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.</td>
<td>□ No</td>
</tr>
<tr>
<td></td>
<td>□ Can’t answer</td>
</tr>
<tr>
<td></td>
<td>□ Not applicable</td>
</tr>
<tr>
<td>5. Was a list of studies (included and excluded) provided?</td>
<td>□ Yes</td>
</tr>
<tr>
<td>A list of included and excluded studies should be provided.</td>
<td>□ No</td>
</tr>
<tr>
<td></td>
<td>□ Can’t answer</td>
</tr>
<tr>
<td></td>
<td>□ Not applicable</td>
</tr>
<tr>
<td>6. Were the characteristics of the included studies provided?</td>
<td>□ Yes</td>
</tr>
<tr>
<td>In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration,</td>
<td>□ No</td>
</tr>
<tr>
<td></td>
<td>□ Can’t answer</td>
</tr>
<tr>
<td></td>
<td>□ Not applicable</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>severity, or other diseases should be reported.</td>
<td>Can't answer</td>
</tr>
<tr>
<td>7. Was the scientific quality of the included studies assessed and documented?</td>
<td>Yes</td>
</tr>
<tr>
<td>‘A priori’ methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.</td>
<td>No</td>
</tr>
<tr>
<td>8. Was the scientific quality of the included studies used appropriately in formulating conclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.</td>
<td>No</td>
</tr>
<tr>
<td>9. Were the methods used to combine the findings of studies appropriate?</td>
<td>Yes</td>
</tr>
<tr>
<td>For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?)</td>
<td>No</td>
</tr>
<tr>
<td>10. Was the likelihood of publication bias assessed?</td>
<td>Yes</td>
</tr>
<tr>
<td>An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).</td>
<td>No</td>
</tr>
<tr>
<td>11. Was the conflict of interest stated?</td>
<td>Yes</td>
</tr>
<tr>
<td>Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.</td>
<td>No</td>
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Appendix 1.1.2. Critical appraisal of systematic reviews

Table 6 – Critical appraisal systematic reviews: results

<table>
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<tr>
<th>AMSTAR question$</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Gregorio et al. 2012</td>
<td>Can’t answer</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>(Yes)</td>
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</table>

$ as listed in Table 5
### Appendix 1.2. Evidence tables

#### Table 7 - Management of malignant adenomas after polypectomy - literature review

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Method</th>
<th>Patient characteristics</th>
<th>Intervention(s)</th>
<th>Results primary outcome</th>
<th>Results secondary and other outcome(s)</th>
<th>Critical appraisal of review quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Gregorio, 2012²</td>
<td>Design: Clinical study and literature overview&lt;br&gt;Sources of funding: Non reported&lt;br&gt;Search date: Not reported&lt;br&gt;Searched databases: Not reported&lt;br&gt;Included study designs: Not reported&lt;br&gt;Number of included studies: 13 (incl. present study)&lt;br&gt;Includes studies: Cranley 1986&lt;br&gt;Coverlizza 1987&lt;br&gt;Muller 1989&lt;br&gt;Sughiara 1989&lt;br&gt;Geraght 1991&lt;br&gt;Kyzer 1992&lt;br&gt;Whitlow 1996&lt;br&gt;Netzer 1998&lt;br&gt;Seize 2004&lt;br&gt;Choi 2009&lt;br&gt;Pizzaro 2009&lt;br&gt;Boinike 2010</td>
<td>- Eligibility criteria: Patients with malignant polyps&lt;br&gt;- Patients characteristics: M/F: 380/259; mean age: 64.3 y.o.&lt;br&gt;- Median FU: Not reported</td>
<td>- Intervention: endoscopic polypectomy&lt;br&gt;- Comparator: endoscopic polypectomy followed by surgery&lt;br&gt;- High risk polyps were defined by the presence of at least one of the following histological features: positive resection margin, poorly differentiated adenocarcinoma, lymphatic/vascular invasion or tumour budding.&lt;br&gt;- Adverse outcome was defined as a local recurrence of adenocarcinoma or metastatic neoplasia detected during follow-up.</td>
<td>Low risk polyps&lt;br&gt;- Di Gregorio 2012: 10/105 underwent surgery: no residual disease. 0/105 patients adverse outcome due to bowel cancer&lt;br&gt;- Pooled analysis: 53/345 were treated surgically. 1/53 residual cancer reported. 1/345 death due to cancer</td>
<td>High risk polyps:&lt;br&gt;- Di Gregorio 2012: 23/50 underwent surgery. 5/23 residual tumour. 3/50 died of disease progression. 2/3 underwent polypectomy only.&lt;br&gt;- Pooled analysis: 335/471 underwent surgery; 49/335 (14.6%) residual tumour. 23/471 (4.9%) death due to cancer</td>
<td>Pooled analysis:&lt;br&gt;- Positive vs negative resection margins&lt;br&gt;- Residual disease: 22.7% vs 1.7%&lt;br&gt;- Recurrent disease: 5.1% vs 0.6%&lt;br&gt;- LN metastasis: 9.04% vs 4.85%&lt;br&gt;- Death due to cancer: 6.53% vs 1.16%&lt;br&gt;Low poorly differentiated vs well/moderately differentiated:&lt;br&gt;- Residual disease: 10.6% vs 4.0%&lt;br&gt;- Recurrent disease: 9.1% vs 0%&lt;br&gt;- LN metastasis: 4.17% vs 5.17%&lt;br&gt;- Death due to cancer: 21.87% vs 0.78%&lt;br&gt;Vascular invasion vs no vascular invasion:&lt;br&gt;- Residual disease: 15.2% vs 5.5%&lt;br&gt;- Recurrent disease:</td>
</tr>
<tr>
<td>Study ID</td>
<td>Method</td>
<td>Patient characteristics</td>
<td>Intervention(s)</td>
<td>Results primary outcome</td>
<td>Results secondary and other outcome(s)</td>
<td>Critical appraisal of review quality</td>
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</tr>
<tr>
<td>Di Gregorio 2012</td>
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<td>5.8% vs 0.9%</td>
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</tr>
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<td></td>
<td></td>
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<td></td>
<td>LN metastasis:</td>
<td>21.83% vs 2.48%</td>
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<td></td>
<td>Death due to cancer:</td>
<td>10.38% vs 0.6%</td>
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</tr>
</tbody>
</table>

**Notes:** Di Gregorio et al., 2012 was not retrieved through the literature search as the publication was not available through Ovid Medline, Embase nor Cochrane Library at the time of the search; the article was suggested as “Golden Hit” for Research Question 3 by IKNL experts. An e-mail was sent to the first author in order to get some more details on the applied methodology of the literature search and review process.

Fitzgerald et al., 2011 ("Golden Hit") is a summary of the New Zealand Guideline on the management of early colorectal cancer (2011), which was based on the Australian NHMRC guideline of 2005 (with regard to Research Question 3, no adaptations were adopted in the New Zealand Guideline).

Seitz et al., 2004 ("Golden Hit") is a clinical study and literature overview, but the review was not systematically performed, there was no critical appraisal of the literature.
### Table 8 – Management of malignant adenomas after polypectomy - observational studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Method</th>
<th>Patient characteristics</th>
<th>Intervention(s)</th>
<th>Results primary outcome</th>
<th>Results secondary and other outcome(s)</th>
<th>Critical appraisal of review quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benizri et al., 2012&lt;sup&gt;10&lt;/sup&gt;</td>
<td>• Design: Retrospective case series                                            • Sources of funding: None reported                                           • Setting: University Hospital Nice                                      • Sample size: 64                                                • Period: 2000 - 2010</td>
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<td></td>
<td>• Eligibility criteria: Patients with T1 CRC that had been removed during endoscopic polypectomy, all polyps had at least 1 of the following adverse criteria (1) inadequate excision with cancer free distance ≤ 1 mm, (2) lymphovascular invasion, (3) poorly differentiated carcinoma (grade III), (4) SM 2-3 involvement, (5) tumour budding, (6) sessile morphology, (7) piecemeal resection</td>
<td>• Comparator(s): /</td>
<td>• Intervention(s): resection (either by laparotomy or laparoscopy) and regional lymphadenectomy</td>
<td>• Survival rate: 100% (immediately after colectomy)           • Rate of lymph node metastasis and/or residual adenocarcinoma at resection: 7/64 (11%) (residual adenocarcinoma: 2, lymph node metastasis: 5) (rectum: 2, colon: 5);</td>
<td>• postoperative complications: 16/64 (25%); • benefit-risk balance = 0 when only 1 criterion indicated surgery and = 2.3 when at least two criteria indicated additional surgery (grade 3-4 complications considered as serious as the long-term risk measured by the presence by of residual carcinoma at the time of surgery. Surgery is considered beneficial if the ratio is greater than 1)</td>
<td>• Results critical appraisal: retrospective study; also rectal cancer included; sessile morphology and piecemeal resection also considered risk factor; no data reported on the number of lymph node metastasis and/or residual adenocarcinoma in patients with negative histological features; no correction for multiple testing; no long time outcome data; small sample size</td>
</tr>
</tbody>
</table>

**Notes:**
- FU: Follow-up
- SM: Submucosal
<table>
<thead>
<tr>
<th>Butte et al., 2012&lt;sup&gt;11&lt;/sup&gt;</th>
<th>Design: Retrospective case series</th>
<th>Eligibility criteria: patients with T1 CRC undergoing polypectomy followed by colectomy</th>
<th>Intervention(s): polypectomy followed by colectomy</th>
<th>Survival without evidence of disease: 122/143 (15 died of unknown causes and 6 died of other causes).</th>
<th>Rate of residual invasive disease diagnosed at colectomy: in case of positive or unknown margin at polypectomy 16% vs. 0% in case of R0;</th>
<th>Dropout: not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sources of funding: None reported</td>
<td>Setting: Tertiary teaching centre, USA</td>
<td>Patients characteristics: 73 (51%) female; mean age 60.4 +/- 12 y.o.</td>
<td>Comparator(s):</td>
<td>At colectomy: residual disease in the colonic wall in 19 (13%) pts (invasive in 16 (11%) and noninvasive in 3 (2.1%)) and lymph node metastasis in 10 (7%) pts (combination of residual disease in the colonic wall and lymph node metastasis in 2 (1.4%) pts.</td>
<td>Residual disease in the colonic wall associated with older age (p=0.03) and lymphovascular invasion (p=0.018), but after Bonferroni correction none remain significant.</td>
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<tr>
<td>Sample size: 143</td>
<td>Period: 1990-2007</td>
<td>Median FU: 63 months</td>
<td></td>
<td>Lymph node metastasis associated with young age (0.03) and lymphovascular invasion (p=0.018), but after Bonferroni correction none remain significant.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Kim et al., 2011&lt;sup&gt;12&lt;/sup&gt;</th>
<th>Design: Retrospective case series</th>
<th>Eligibility criteria: pts with early CRC (i.e. limited to mucosa or submucosa) who</th>
<th>Intervention(s): EMR or ESD (not the aim to compare results)</th>
<th>Survival rate: Intramucosal CRC: 62/64 (2 pts died of unrelated diseases)</th>
<th>Recurrence (i.e. local recurrence and distant metastasis) rate: Intramucosal CRC:</th>
<th>Dropout: unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sources of funding:</td>
<td>Setting:</td>
<td></td>
<td></td>
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<td></td>
<td>Results critical appraisal: retrospective study; pts who did not get colectomy were also excluded (low risk pts and pts with severe comorbidity); submucosal invasion could not be reliably evaluated in the study; most polypectomies were performed in other clinics; no measure of treatment effect estimation (e.g. OR), only X² and Wilcoxon tests were performed; no multivariable analyses performed; no correction for multiple testing</td>
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<tr>
<td>Sample size:</td>
<td>Period:</td>
<td></td>
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<tr>
<td>Funding:</td>
<td>None reported</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Setting:</td>
<td>University hospital, Korea</td>
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<tr>
<td>Sample size:</td>
<td>129 (64 with intramucosal CRC and 65 with submucosal CRC)</td>
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</tbody>
</table>

**Patients characteristics:**
- Mean age: 63.23 +/- 9.78 y.o.; male: 89 (69%) |
- Mean FU: 19 months of both) |

**Comparator(s):**
- Adverse outcome defined as residual cancer or lymph node metastasis at the post-surgical pathologic evaluation or the local recurrence or distant metastasis. |
- Cave: 7 pts with submucosal cancer underwent subsequent surgical resection: 5 had lymphovascular involvement or positive margin, one perforation and one requested resection |

**Adverse outcomes:**
- 7/129 patients of which 5 high risk and 2 low risk. 3 |
- 3/5 high risk pts underwent surgical resection after EMR. Two of them had no recurrence during FU |
- 2/5 high risk patients had a positive margin and had no further surgery. Both showed local recurrence |
- 2/7 low risk patients had local recurrence and liver metastasis respectively |

**Submucosal CRC:**
- Not reported. |

**Design:**
- Prospective cohort study |
**Eligibility criteria:**
- pT1 CRC |
**Patients characteristics:**
- Mean age of all patients: 63.8 +/- of both) |
**Group A:**
- Polypectomy and surgical removal of T1 CRC. |
**Intervention B:**
- Polypectomy of |
**No survival data reported** |
**Unfavourable outcome:**
- 2.8% in intervention group A and 6.8% in B |
**Rate of unfavourable outcome when tumour was not removed:**
- 2.8% in intervention group A and 6.8% in B |
**Dropouts:**
- Complete FU data available for 390/474 (83%) patients |
**Results critical:**
- Retrospective study; also rectal cancer included; no correction for two different methods (EMR and ESD) used; short FU (mean: 19 months); definition and total number of high risk and low risk patients unclear. |

Meining et al., 2011
- Setting: 1 hospital in Germany
- Sample size: n=141 (polypectomy and surgical removal of T1 CRC) and n=249 (polypectomy of T1 CRC)
- Period: 1974-2002

10.74 y.o.; 54% men

Mean FU: 87.2 +/- 50.77 months.

T1 CRC

- Decision in favour of or against surgery based on risk patterns, patients’ personal wishes and patients’ fitness.

- **Unfavourable outcome** was defined if 1 or more of the following occurred: locoregional relapse, distant M+, lymph node M+, death related to colorectal cancer or disease detected during surgery in incompletely resected: 20% (vs. 4% in case of R0), resulting in a RR of 6, Sens: 0.59, Spec: 0.82, npv: 0.96;

- Rate of unfavourable outcome when tumour was poorly differentiated: 43% (vs. 6% in other cases) resulting in a RR of 7, Sens: 0.18, Spec: 0.98, NPV: 0.94;

- Rate of unfavourable outcome in case of lymphovascular infiltration: 44% (vs. 5% in other cases) resulting in a RR of 8, Sens: 0.24, Spec: 0.98, NPV: 0.95.

Oka et al., 2011

- **Design:** Retrospective case series (questionnaire survey)
- **Eligibility criteria:** Patients with submucosal CRC with surveillance after endoscopic resection
- **Patients characteristics:**
- **Intervention(s):** endoscopic resection (en bloc resection (n=569), piecemeal resection (n=114), ER
- **Survival data not reported. Survival rate in recurrence group: 10/18 (56%)**
- **Recurrence rate: 18/792 (2.3%)**
- **local recurrence in 11 cases and metastatic recurrence in 13 cases**
- **Recurrence rate after en bloc resection: 14/569 (2.5%), after**

- **Dropouts:** not reported.
- **Results critical appraisal:** retrospective study; non-response to questionnaire
Setting: Multicentre (n=15), Japan
Sample size: 792
Period: not reported

Tumour characteristics:

- female: 236 (30%); mean age: 72.9 +/- 12.3 y.o.;
- Mean FU: 38.7 +/- 83.0 months

- 588/792 colon; 204/792 rectum
- Average size 16.2mm (range 3-60mm)
- Lateral positive margin 50/792, 238 cases not mentioned
- Vertical margin positive 34/792; 195 cases not mentioned
- Well or moderately differentiated: 787 cases, 2 poorly differentiated, 3 not reported
- Submucosal invasion less than 1000µm 324/792 cases, deeper than 1000µm 315/792, not reported 153/792 cases
- Comparator(s): /

piecemeal resection: 4/114 (3.5%)

- multivariate logistic regression analysis for recurrence after ER for submucosal CRC (n=387): lymphatic invasion OR: 6.36 (95% C.I. 1.46-27.79); mean interval between ER and recurrence: 19.7 +/- 9.2 months

survey was high (13/28 invited institutions); histopathological data only available for 387/792 (49%) cases; histopathological data come from different institutions; short FU
References

6. SIGN. SIGN 126 Diagnosis and management of colorectal cancer. 2011.