Healthcare Improvement Scotland | SHTG Advice on health technologies

Evidence Note
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In response to enquiry from NHS Greater Glasgow and Clyde

What is the clinical and cost-effectiveness of robot-assisted surgery compared with laparoscopic resection for the treatment of rectal cancer?

What is an evidence note?

Evidence notes are rapid reviews of the evidence surrounding health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6-month period and the process of peer review and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The evidence notes are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all evidence reviews.

This evidence note includes a patient group submission from Bowel Cancer UK.

Key points

- In a meta-analysis of five RCTs (n=681) there were no statistically significant differences between robot-assisted surgery and laparoscopic surgery for 30-day mortality, positive circumferential resection margins (CRM), completeness of total mesorectal excision (TME), mean number of lymph nodes harvested, length of hospital stay, or perioperative complications (which did not include urinary or sexual dysfunction).
- The same meta-analysis of RCTs reported that patients with rectal cancer randomised to robot-assisted surgery had a lower risk of conversion to open surgery compared with

patients randomised to laparoscopic surgery: relative risk (RR) 0.58, 95% confidence interval (CI) 0.35 to 0.97, 4 studies, n=544, p=0.04.

- Two meta-analyses of observational studies reported no statistically significant difference in 3-year overall survival, and one meta-analysis reported no statistically significant difference in 3-year local disease recurrence, in comparisons of robot-assisted surgery with laparoscopic surgery in patients with rectal cancer.
- A survey by Bowel Cancer UK reported that patients (n=29) considered reducing side effects, such as urinary, bowel or sexual dysfunction, the most important outcome for robot-assisted rectal cancer surgery as these had a substantial impact on long-term quality of life. Only one survey respondent had experience of robot-assisted rectal cancer surgery. Evidence from published studies was inconsistent on whether robot-assisted surgery improved these outcomes compared with laparoscopic surgery.
- A systematic review of nine observational studies (n=917) calculated that the mean number of robot-assisted rectal cancer surgeries required for a surgeon to be considered an expert was 39 procedures.
- In a cost analysis within the ROLARR RCT (n=190) robot-assisted surgery had a statistically significant higher total healthcare cost, not including capital or maintenance costs of the robotic surgical device, compared with laparoscopic surgery: mean difference £980, 95% CI £165 to £1,795, p=0.02.

Definitions

Total mesorectal excision (TME): rectal cancer surgery where the surgeon removes the section of rectum containing the cancer, some healthy bowel on either side of the tumour and the mesorectum (a fatty tissue containing blood vessels and lymph nodes that surrounds the rectum)[1].

Abdomino-perineal resection (APR): a type of total mesorectal excision surgery for rectal cancer where the entire rectum and anus are removed. Mainly used when the cancer is situated low in the rectum (near the anus). Patients will generally have a permanent stoma after this operation[1].

Anterior/low anterior resection (AR/LAR): a type of total mesorectal excision surgery for rectal cancer where the surgeon removes the rectum, or section of rectum containing the tumour, and then rejoins the two ends of the bowel[1]. Mainly performed when the cancer is in the upper two-thirds of the rectum.

Anastomosis: surgical connection between two structures; in the current context two ends of the bowel[2].

Circumferential resection margin (CRM)/radial margin: margin between the deepest penetration of the tumour and the edge of the resected soft tissue around the rectum. The CRM has been shown to be a strong predictor of both local recurrence and overall survival[3].

Rectosigmoid junction: where the end section of the colon (sigmoid colon) and the top section of the rectum meet[4].

Stoma: temporary or permanent opening in the skin of the abdomen to allow faecal matter to exit the body following rectal cancer surgery. Faecal matter passes from the bowel, out through this opening and into a disposable bag worn over the stoma (colostomy or ileostomy bag)[1].

Anal verge and anal margin: the anal verge is where the anal canal connects to the external skin at the anus. The skin around the anal verge is referred to as the anal margin[5].

A complete list of abbreviations used in the evidence note is provided in appendix 1.

Literature search

A systematic search of the secondary literature was carried out between 23 April 2018 and 02 May 2018 to identify systematic reviews, health technology assessments and other evidence-based reports. Medline, Embase, Cinahl and Web of Science databases were searched for systematic reviews and meta-analyses.

A primary literature search was conducted to identify randomised controlled trials (RCTs) published after the inclusion period of the most recent meta-analysis of RCTs, volume-outcome studies, learning curve studies, and economic studies. The primary literature was systematically searched between 23 April 2018 and 02 May 2018 using the following databases: Medline, Embase, Cinahl and Web of Science.

Key websites were searched for guidelines, policy documents, clinical summaries and economic studies.

All search results were limited to English language; no date limits were applied.

Concepts used in all searches included: cancer of the rectum, rectal neoplasms, robot-assisted surgery, da Vinci robot. A full list of resources searched and terms used is available on request.

Introduction

Rectal cancer develops in the part of the large bowel that connects the colon with the anal canal – the rectum[6]. Rectal cancer can be defined anatomically as malignant tumours that have a lower edge ≤15cm from the anal margin[7].

The primary treatment option for patients diagnosed with rectal cancer is surgical removal of the tumour[8]. Patients may require chemoradiotherapy prior to surgery in order to reduce the size of the tumour and some patients will have a temporary or permanent stoma created during the operation (figure 1). After recovering from surgery approximately half of all patients with rectal cancer will require chemotherapy (Mr R Molloy, Consultant Surgeon, NHS Greater Glasgow and Clyde. Personal communication, 7 March 2018).

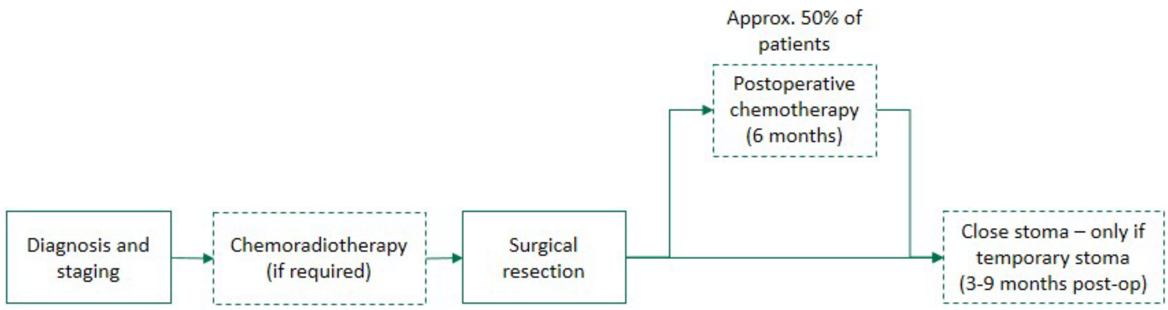

Figure 1: diagnosis and treatment pathway for patients with rectal cancer (Mr R Molloy, Consultant Surgeon, NHS Greater Glasgow and Clyde. Personal communication, 7 March 2018)

Very early stage rectal cancers that are situated very low in the rectum (near the anus) can sometimes be removed using transanal surgery, where the surgeon inserts instruments into the rectum through the anus to remove the malignant tissue[1]. Other surgeries for rectal cancer involve removing the affected segment of the rectum along with surrounding fatty tissues that contain lymph nodes and blood vessels (mesorectum)[9]. This total mesorectal excision (TME) is currently considered the most appropriate procedure for high quality rectal cancer surgery. Total mesorectal excision can be performed as an anterior resection or an abdomino-perineal resection depending on the stage, size and location of the tumour.

Laparoscopic surgery is the preferred surgical approach for many Scottish surgeons performing rectal cancer resection (Mr R Molloy, Consultant Surgeon, NHS Greater Glasgow and Clyde. Personal communication, 23 July 2018). However an estimated 9% to 16% of laparoscopic procedures for rectal cancer will be converted to open surgery during the operation, which is associated with poorer outcomes for the patient[10, 11]. Robot-assisted rectal cancer surgery is a potential alternative to laparoscopic surgery for patients with rectal cancer. This review therefore addresses the question:

- What is the clinical and cost-effectiveness of robot-assisted surgery compared with laparoscopic resection for the treatment of rectal cancer?

Health technology description

The technology for robot-assisted rectal cancer surgery comprises a surgeon console, computerised control system, and patient-side cart that houses robotic arms which hold a dual telescope and surgical instruments. The surgeon operates the robotic arms by remote control from the console while viewing the magnified 3D surgical field on the monitor. The da Vinci® System (Intuitive Surgical Inc., California) is available with three or with four robotic arms. Products include the da Vinci® X, da Vinci® Xi, da Vinci® Si and da Vinci® Si-e.

Da Vinci® robotic systems are installed in four centres in Scotland – the Western General Hospital (Edinburgh), Queen Elizabeth University Hospital (Glasgow), Golden Jubilee National Hospital (Clydebank) and Aberdeen Royal Infirmary. These devices are not currently used for robot-assisted rectal cancer surgery.

Epidemiology

An estimated 28% to 35% of colorectal cancers are located in the rectum[11].

Age is the biggest risk factor for developing rectal cancer, with approximately 95% of cases occurring in adults aged over 50 years[12]. However incidence and mortality rates for cancer of the rectum or rectosigmoid junction at any age are higher for men than women (table 1). ISD Scotland have estimated that the lifetime risk of developing cancer of the rectum or rectosigmoid junction is 1 in 45 for men compared with 1 in 74 for women[12].

Table 1: incidence and mortality data for cancer of the rectum or rectosigmoid junction in Scotland 2016[12]

	Incidence (n)	European age standardised incidence rate (per 100,000)	Mortality (n)	European age standardised mortality rate (per 100,000)
Male	727	30.7	393	17.9
Female	454	16.1	268	9.2
All persons	1,181	23.4	661	13.5

Clinical effectiveness

The type of robotic surgical system used to perform rectal cancer surgery was not reported in any of the included studies.

A systematic review with meta-analysis of randomised controlled trials (RCTs) was selected as the highest quality evidence available on the clinical effectiveness of robot-assisted rectal cancer surgery compared with laparoscopic surgery[11]. RCTs published after the literature search inclusion period of the meta-analysis were included to ensure the most recent randomised evidence was considered and to address methodological concerns relating to some analyses within the meta-analysis[10, 13, 14]. Recent meta-analyses of observational studies were included if they reported additional relevant outcomes to those reported in the meta-analysis of RCTs[15, 16]. A meta-analysis of observational studies that compared robot-assisted surgery with open surgery was included for completeness, as some rectal cancer surgeries in Scotland are still performed as open laparotomies[17].

Robot-assisted surgery versus laparoscopic surgery

Meta-analysis of RCTs

The systematic review with meta-analysis of five RCTs (n=681) compared robot-assisted surgery with laparoscopic surgery for the treatment of rectal adenocarcinoma situated ≤15cm from the anal verge[11]. Data from a subset of trial participants – rectal cancer patients extracted from a colorectal cancer patient sample – were used for two included studies, which may have affected statistical power in these studies. Three RCTs were judged by the review authors to have high or unclear risk of selection and/or detection bias based on the Cochrane risk of bias tool. This judgment was based on lack of reporting of allocation concealment in two RCTs and lack of clarity around blinding of outcome assessors in three studies. It is uncertain how great an effect these biases had on the meta-analysis results, however it may be minimal given the results of the analysis were generally not statistically significant. One high quality included study (ROLARR, n=471) was only available as conference abstracts.

There were no statistically significant differences between robot-assisted and laparoscopic rectal cancer surgery for the outcomes of 30-day mortality, positive circumferential resection margin (CRM), complete total mesorectal excision (TME), mean number of lymph nodes harvested, length of hospital stay, overall perioperative complications, anastomosis leakage, wound infection, urinary complications or respiratory complications (table 2). In the analyses for 30-day mortality and positive CRM, the authors stated the analyses were based on five studies and two studies respectively. However only a single study in each analysis (ROLARR) reported any events for these outcomes and therefore the results from these 'meta-analyses' reflect the results from the ROLARR trial.

Patients randomised to robot-assisted surgery were at lower risk of conversion to open surgery compared with patients randomised to laparoscopic surgery: relative risk (RR) 0.58, 95% confidence interval (CI) 0.35 to 0.97, 4 studies, 544 patients, p=0.04, I^2=0%. This result should be treated with some caution as all four RCTs included in the meta-analysis reported no statistically significant difference in rate of conversion to open surgery and the upper limit of the 95% confidence interval approaches an RR of one (0.97). Subgroup analyses within the meta-analysis explored the effect of factors such as gender (males have a narrower pelvic bone making surgery more difficult), age, comorbidities, stage of disease, preoperative neoadjuvant therapy and type of procedure, on clinical outcomes. The subgroup analysis restricted to male patients found a statistically significant lower risk of conversion to open surgery in men undergoing robot-assisted surgery compared with men undergoing laparoscopic surgery: RR 0.49, 95% CI 0.28 to 0.88, 3 studies, 342 patients, p=0.02, I^2=0%. The most common reasons for converting to open surgery included a difficult pelvic dissection, patient obesity and intraoperative haemorrhage. Robot-assisted surgery was also associated with a statistically significant difference in time to return of bowel function: mean difference (MD) -0.59, 95% CI -0.95 to -0.23, 2 studies, 173 patients, p=0.001, I^2=0%.

To determine the impact of conversion to open surgery on patient outcomes an additional literature search was conducted. A meta-analysis of thirteen observational studies (n=10,781) compared outcomes for patients who had laparoscopic surgery for rectal cancer converted to open surgery with outcomes for patients who had completed laparoscopic surgery or completed open surgery[18]. In comparisons of complete laparoscopic surgery with laparoscopic surgery converted to open surgery, patients who converted to open surgery had statistically significant longer operating time, longer stays in hospital, higher wound infection rates and greater odds of tumour recurrence. When comparing complete open surgery with laparoscopic surgery converted to open surgery, there were no statistically significant differences in outcomes with the exception of a longer operating time. This suggests that patients who have laparoscopic surgery converted to open surgery experience similar outcomes to those who are initially allocated to open surgery.

Two studies in the meta-analysis of RCTs reported on postoperative erectile dysfunction: in one study (n=9) erectile dysfunction was more common in the robot-assisted surgery group and in the other (n=137) it was more common in the laparoscopic surgery group[11]. This difference in direction of effect may be a consequence of measuring erectile dysfunction at a different follow-up point (median 32.5 months versus 12 months post-surgery), the small sample size in one study, or between-study differences in measures of erectile dysfunction. One RCT (n=137) using validated quality of life scoring tools reported statistically significant differences in urinary function that favoured robot-assisted surgery and male sexual function that favoured laparoscopic surgery. Four RCTs within the systematic review reported estimated blood loss but used different definitions and measures (perioperative haemoglobin concentration, mean estimated blood loss, transfusions needed, overall range of estimated blood loss) which prevented meta-analysis for this outcome. None of the four RCTs reported a statistically significant difference in estimated blood loss for robot-assisted surgery compared with laparoscopic surgery.

Table 2: results from a meta-analysis of RCTs comparing robot-assisted surgery with laparoscopic surgery for rectal adenocarcinoma[11]

Outcome	N studies (n patients)	Findings (95% CI) RR = relative risk MD = mean difference OR = odds ratio	p-value**	I^2
Primary outcomes				
30-day mortality*	5 (681)	RR 0.97 (0.14 to 6.86)	0.90	–
Positive CRM*	2 (489)	RR 0.82 (0.39 to 1.73)	0.60	–
Complete TME	2 (505)	RR 0.92 (0.68 to 1.25)	0.60	10%
Harvested lymph nodes (n)	5 (674)	MD -0.35 (-1.83 to 1.12)	0.54	0%
Conversion to open surgery	4 (544)	RR 0.58 (0.35 to 0.97)	0.04	0%
Conversion to open surgery (males only)	3 (342)	RR 0.49 (0.28 to 0.88)	0.02	0%
Perioperative complications	5 (681)	RR 1.02 (0.80 to 1.31)	0.85	0%
Anastomosis leakage	3 (174)	RR 1.26 (0.39 to 4.10)	0.70	0%
Secondary outcomes				
Length of hospital stay (days)	4 (552)	MD -0.61 (-2.23 to 1.02)	0.46	66%
Time to return of bowel function (days)	2 (173)	MD -0.59 (-0.95 to -0.23)	0.001	0%
Wound infection	5 (681)	OR 0.97 (0.52 to 1.71)	0.05	0%
Urinary complications	5 (681)	OR 0.97 (0.54 to 1.71)	0.91	0%
Respiratory complications	5 (681)	OR 0.40 (0.22 to 1.63)	0.32	0%

**Although multiple RCTs were included in the meta-analysis, only a single study (ROLARR, n=471) reported one or more events for this outcome.*

***Some p-values are estimated due to the poor print quality of the forest plots in the published meta-analysis.*

Randomised controlled trials (RCTs)

The RObotic versus LAparoscopic Resection for Rectal cancer (ROLARR) RCT, which was included in the meta-analysis of RCTs as conference abstracts, has since published full short-term study results[13]. Due to the large size of this RCT compared to other relevant trials, the low risk of bias, and the involvement of multiple UK centres in the study, the ROLARR RCT is described separately from the meta-analysis and results are reported in tables 3 and 4.

The ROLARR trial was at low risk of bias based on the Cochrane risk of bias tool: randomisation was performed centrally using a computer-generated randomisation sequence and although the RCT was not blinded, some outcomes were assessed by experts blinded to treatment allocation. Surgeons participating in the trial had to have performed at least 30 minimally invasive rectal cancer resections, including at least ten conventional laparoscopic procedures and at least ten robot-assisted procedures. Study participants had rectal cancer located ≤15cm from the anal verge. Approximately one quarter of participants were obese and 46% had preoperative chemoradiotherapy.

The results reported in the published ROLARR study (table 3) were consistent with the findings of the meta-analysis of RCTs for the outcomes of positive CRM, perioperative complications and 30-day mortality[11, 13]. In the published trial (n=471) there was no statistically significant difference in rate of conversion to open surgery between study groups: OR 0.61, 95% CI 0.31 to 1.21, p=0.16. This difference in the statistical significance of results for conversion to open surgery between the published RCT and the meta-analysis of RCTs may be a consequence of combining data from three small RCTs with large effect estimates and wide confidence intervals with data from the ROLARR study.

Table 3: results from the ROLARR RCT (n=471) comparing robot-assisted surgery with laparoscopic surgery for rectal cancer[13]

Outcome	Unadjusted risk difference (95% CI)	Adjusted OR (95% CI)	Laparoscopic: n/total N	Robot-assisted: n/total N
Primary outcome				
Conversion to open surgery	4.1 (-1.4 to 9.6)	0.61 (0.31 to 1.21) p=0.16	28/230	19/236
Secondary outcomes				
30-day mortality	0.02 (-1.7 to 1.7)	–	2/230	2/236
Positive CRM	1.2 (-3.1 to 5.4)	0.78 (0.35 to 1.76) p=0.56	14/224	12/235
Intraoperative complications	-0.5 (-6.0 to 7.0)	1.02 (0.60 to 1.74) p=0.94	34/230	36/236

Postoperative complications: ≤30 days	-1.3 (-9.8 to 7.2)	1.04 (0.69 to 1.58) p=0.84	73/230	78/236
Postoperative complications: >30 days and ≤6 months	2.1 (-4.5 to 8.7)	0.72 (0.41 to 1.26) p=0.25	38/230	34/236

There were no statistically significant differences in self-reported urinary function, male sexual function or female sexual function in the ROLARR trial. The study authors used multivariate logistic regression to explore the odds of conversion to open surgery for pre-specified subgroups of patients. There was a statistically significant increase in the odds of converting to open surgery for obese patients compared with underweight or normal weight patients and for males compared with females (table 4).

Table 4: multivariable logistic regression for odds of conversion to open surgery from the ROLARR RCT[13]

Variable		Unadjusted risk difference (95% CI)	Adjusted OR (95% CI)	n/total N
Gender	Male	6.9 (1.8 to 12.1)	Reference	39/317
	Female		2.44 (1.05 to 5.71) p=0.04	8/149
BMI: overweight vs underweight or normal weight	Underweight or normal weight	2.3 (-2.7 to 7.2)	Reference	13/179
	Overweight		0.54 (0.21 to 1.37) p=0.19	9/180
BMI: obese vs underweight or normal weight	Underweight or normal weight	-16.1 (-25.0 to -7.2)	Reference	13/179
	Obese		4.69 (2.08 to 10.58) p<0.001	25/107

BMI=body mass index

One of the centres involved in the ROLARR trial conducted a small sub-study (n=51) to measure perioperative pain in patients at their centre who were randomised to robot-assisted or laparoscopic surgery as part of the ROLARR trial[14]. Postoperative pain was measured using a numerical rating scale (0 = no pain, 10 = maximum pain) at hourly intervals in the postoperative care unit and then approximately three times per day in the general recovery ward. Intraoperative analgesic use was recorded and converted to the equivalent in morphine. There were no statistically significant differences in postoperative morphine consumption or pain scores between the robot-assisted and laparoscopic surgery groups. There was however a statistically significant difference in mean opioid use during surgery which was lower in the robot-assisted surgery group: 0.17 (standard deviation (SD) 0.11) mcg/kg/min versus 0.24 (SD 0.05) mcg/kg/min, p=0.0001.

A second RCT not included in the meta-analysis of RCTs compared robot-assisted surgery with laparoscopic surgery for treatment of patients with mid- to low-lying (≤9cm from the anal verge) rectal cancer at a specialist centre in South Korea[10]. Study participants had a mean BMI of 24 and approximately 78% had received preoperative chemoradiotherapy. Participants were randomised 1:1 using computer-generated random numbers communicated by telephone to the surgeons by a trial coordinator. There was no blinding of surgeons or participants, however pathologists assessing the primary outcome of TME completeness – which was used as a surrogate endpoint for local recurrence – were blinded to treatment allocation. Surgeons performing the procedures had prior experience of over 100 laparoscopic rectal cancer surgeries and approximately 30 robot-assisted procedures.

Of 163 patients randomised, 139 were available for the analysis: 14 withdrew consent, seven had newly discovered distant metastases, two had T4 tumours, and one was referred to another hospital. Only one procedure, in the robot-assisted surgery group, was converted to open surgery. Results for the primary and secondary outcomes of the trial are reported in table 5. There were no statistically significant differences in TME completeness, postoperative pain or quality of life scores, with the exception of insomnia and sexual function scores at 12 months follow-up (table 5).

Table 5: results from an RCT (n=139) comparing robot-assisted surgery with laparoscopic surgery in patients with mid- to low-lying rectal adenocarcinoma[10]

Outcome	Robot-assisted	Laparoscopic	p-value
Primary outcome			
Complete TME, n (%)	53 (80.3)	57 (78.1)	0.599
Secondary outcomes			
Positive CRM, n (%)	4 (6.1)	4 (5.5)	0.999
Length of hospital stay (days) Mean (SD)	10.3 (3.4)	10.8 (7.4)	0.621
Time (days) to first defecation Median (range)	2 (0 to 6)	2 (0 to 8)	0.418
Intraoperative adverse events (bleeding or perforation of rectum) n (%)	5 (7.6)	3 (4.1)	0.647
Postoperative complications, n (%)	23 (34.8)	17 (23.3)	0.133
Insomnia score at 12 months Mean (95% CI)	28.3 (19.6 to 37.0)	15.7 (8.1 to 23.3)	0.035
Sexual function score at 12 months Mean (95% CI)	35.2 (26.9 to 43.5)	23.0 (15.7 to 30.2)	0.032

Meta-analyses of observational studies

Two of the most recent systematic reviews of observational studies, incorporating mainly retrospective comparative studies of moderate methodological quality, reported outcomes not included in the meta-analysis of RCTs[15, 16]. Outcomes reported only in systematic reviews of observational studies are summarised in table 6. The results of these reviews are likely to be at higher risk of bias than the meta-analysis of RCTs due to the retrospective, non-randomised study designs included.

Table 6: results from two systematic reviews with meta-analysis of observational studies comparing robot-assisted surgery with laparoscopic surgery in patients with rectal cancer[15, 16]

Outcome	Ohtani (2018) OR (95% CI)	Li (2017) OR (95% CI)
3-year overall survival	0.92 (0.58 to 1.46) p=0.71	0.71 (0.44 to 1.12) p=1.14
3-year local disease recurrence	–	0.68 (0.36 to 1.26) p=0.22
Overall disease recurrence	1.08 (0.84 to 1.38) p=0.55	–
Re-operation within 30 days	–	0.66 (0.41 to 1.05) p=0.80

Robot-assisted surgery versus open surgery

Meta-analysis of observational studies

Although the focus of this evidence note is the comparison of robot-assisted surgery with laparoscopic surgery for rectal cancer, a proportion of rectal cancer surgery in Scotland is still performed as open surgery (laparotomy). A meta-analysis of seven observational studies (n=1,074) was identified that compared robot-assisted surgery with open surgery for treatment of rectal cancer and is included here for completeness[17]. The included studies comprised four retrospective, and three prospective, non-randomised comparative studies. The definition of rectal cancer used is not reported. Quality of included studies was assessed by the review authors using the modified Newcastle-Ottawa Scale (NOS). The studies scored between 6 and 9 on the NOS, suggesting they were of moderate quality.

Outcomes were reported in the meta-analysis as intraoperative, postoperative, pathological and long-term (table 7). Statistically significant differences, all favouring robot-assisted surgery, were reported for estimated blood loss, length of hospital stay, time to passage of flatus and time to return of normal diet. No statistically significant differences were reported for any of the pathological outcomes or for disease-free survival. There were no statistically significant differences between robot-assisted and open surgery for intraoperative transfusion requirements, postoperative mortality, overall complication rate, anastomosis leakage, wound infection, postoperative bleeding or urinary retention.

Table 7: results from a meta-analysis of observational studies comparing robot-assisted surgery with open surgery for rectal cancer[17]

Outcome	N studies (n patients)	Findings (95% CI) HR = hazard ratio MD = mean difference OR = odds ratio	p-value	I^2
Intraoperative outcomes				
Estimated blood loss (ml)	5 (712)	MD -139.98 (-159.11 to -120.86)	<0.00001	33%
Intraoperative transfusion	3 (692)	OR 0.52 (0.28 to 0.99)	0.05	21%
Postoperative outcomes				
Postoperative mortality	2 (222)	OR 0.87 (0.11 to 6.86)	0.90	0%
Length of hospital stay (days)	7 (1,074)	MD -2.10 (-3.47 to -0.73)	0.003	92%
Time to flatus passage (days)	6 (992)	MD -0.97 (-1.06 to -0.88)	<0.00001	0%
Time to normal diet resumption (days)	5 (770)	MD -1.71 (-3.31 to -0.12)	0.04	97%
Overall postoperative complications	7 (1,074)	OR 1.00 (0.75 to 1.32)	0.97	0%
Anastomosis leakage	7 (1,074)	OR 1.54 (0.90 to 2.66)	0.12	0%
Wound infection	4 (638)	OR 0.37 (0.05 to 2.50)	0.31	63%
Bleeding	3 (510)	OR 2.05 (0.52 to 8.13)	0.31	0%
Urinary retention	3 (262)	OR 0.52 (0.10 to 2.77)	0.44	0%
Pathological outcomes				
Harvested lymph nodes (n)	7 (1,074)	MD 1.49 (-0.82 to 3.79)	0.21	79%
Positive CRM	2 (180)	MD -0.22 (-1.82 to 1.38)	0.79	35%
Positive proximal margins	2 (470)	MD 2.23 (-1.19 to 5.65)	0.20	88%
Positive distal margins	6 (992)	MD 0.17 (-0.14 to 0.48)	0.27	79%
Long-term outcomes				
Disease-free survival	2 (314)	HR 0.84 (0.53 to 1.35)	0.47	0%

Ongoing studies

Five ongoing RCTs comparing robot-assisted surgery with laparoscopic surgery for rectal cancer were identified (table 8). The COLRAR trial was not included as an ongoing study as it was discontinued due to funding difficulties (Mr G Choi, Kyungpook National University. Personal communication, 02 October 2018).

Table 8: ongoing RCTs comparing robot-assisted surgery with laparoscopic surgery for rectal cancer

Trial ID	Title	Estimated completion date
NCT02673177	Trial of robotic versus laparoscopic-assisted radical resection for rectal cancer (TRVL)	May 2019
NCT01985698	A trial of robotic-assisted versus laparoscopic versus open abdomino-perineal resection for treating low rectal cancer (RLOAPR)	Oct 2019
NCT03209076	Robotic versus laparoscopic low anterior resection for rectal cancer (RAR)	Dec 2020
NCT03574493	Rectal surgery evaluation trial (RESET)	June 2022
NCT02817126	Robot-assisted versus laparoscopic surgery for mid/low rectal cancer (REAL)	Oct 2023

Device safety

Complications and adverse events relating to robot-assisted surgical procedures for rectal cancer have been discussed in the clinical effectiveness section. In this section adverse events relating specifically to the robotic surgical device (da Vinci® system) are discussed. Three sources provided data on adverse events relating to da Vinci® robotic surgical devices.

In the ROLARR RCT 'surgical equipment failure' – of laparoscopic equipment or the robotic system including hardware and software – was reported as an intraoperative complication during surgery for rectal cancer[13]. Eight equipment failure events (3.4%) were reported in the robot-assisted surgery group and six events (2.6%) in the laparoscopic surgery group.

A total of 10,624 (0.6%) adverse events associated with any da Vinci® robot-assisted surgery (n=1,745,000) were recorded as medical device reports in the US Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) database between 2000 and 2013[19]. Three-hundred and one (2.8%) of these adverse events related to robot-assisted colorectal surgeries; 44 (0.4%) occurred during low anterior resection surgery. There were 11 deaths, 58 injuries and 209 device malfunctions during robot-assisted colorectal surgeries. Device malfunctions encompassed system errors, video and imaging problems, broken instruments falling into the patient's body, electrical arcing, sparking or charring of instruments, and uncontrolled movements or spontaneous powering on/off of the system. Due to the voluntary reporting system used to populate the MAUDE database, adverse events may have been underreported or incorrectly attributed to the medical device (da Vinci® robot).

The NHS England National Reporting and Learning System (NRLS) recorded 104 incidents relating to the da Vinci® robotic device/equipment (any surgery) between 2007 and 2017. Of these incidents, 95 were categorised as no harm, eight as low harm and one as moderate harm (P Salter, Oversight and Business Support Officer, NRLS. Personal communication, 10 October 2017).

Patient and social aspects

A patient submission received from Bowel Cancer UK described patient experiences of living with colorectal cancer and their views on robot-assisted surgery. Information provided in the submission came from the Bowel Cancer UK website, case studies and a small survey of patients that was conducted by the charity. The full submission is available from the Healthcare Improvement Scotland website.

Patients who had undergone surgery for the treatment of rectal cancer reported experiencing post-surgery changes in bowel, urinary and sexual function that had a substantial impact on their daily life. Patients also described difficulty in adjusting to having a stoma and feeling fatigued following the surgery. These experiences affected patients' mental health, self-esteem, relationships and quality of life.

In the Bowel Cancer UK survey of patients (n=29), participants were asked to rank factors they felt were most important to them when considering the potential benefits of robot-assisted rectal cancer surgery. The most important factor for respondents was a reduction in treatment-related side effects, such as urinary, sexual and bowel dysfunction, as these can have a substantial impact on long-term quality of life. The second most important factor was a faster recovery time followed by smaller scars and a quicker return to work. Patients felt that improved precision was important and that robot-assisted surgery should be able to access difficult tumours that may not be suitable for conventional laparoscopic surgery. A single survey respondent had experienced robot-assisted rectal cancer surgery and stated that they would choose it again if offered, as there was a quick recovery time and little scarring.

Survey respondents highlighted concerns about what would happen if there was a mechanical failure with the robot during surgery and the need for reassurance that surgeons had adequate training and experience with using the robotic surgical device.

Learning curve

The learning curve for any procedure can be conceptualised as the number of procedures required for an individual to reach a defined measure of adequacy or competence. Two moderate quality systematic reviews with overlap of included studies assessed the learning curve for robot-assisted rectal cancer surgery[20, 21].

One systematic review included nine studies (n=917) and the other 12 studies (n=1,256); seven studies were common to both reviews. The majority of studies in both reviews were single-arm case series and approximately half were retrospective. Neither systematic review reported the location of rectal tumours or other baseline patient characteristics that may have affected complexity of the surgery, for example obesity. In both reviews the authors identified heterogeneity between studies, possibly due to variation in surgical procedures, level of surgical complexity and surgeon experience. One review expressed concerns about potential selection and reporting bias due to case series being reported by proponents of robot-assisted surgery[20].

The authors of the first systematic review calculated that the mean number of robot-assisted rectal cancer surgeries required for a surgeon to be considered an expert was 39 procedures[20]. This calculation was based on analysis of intraoperative data, such as operating time, lymph nodes harvested, blood loss and complications, and perioperative outcomes, such as postoperative complications, return to surgery, disease recurrence and length of hospital stay, recorded in included studies across a three phase learning curve. The second systematic review reported the learning curve calculated in each included study which ranged from 15 to 44 procedures[21]. The learning curve was defined in this review as the number of procedures required to reach stability of operating time, complication rates and patient outcomes.

Volume-outcome

No relevant studies were identified that considered the volume-outcome relationship for robot-assisted rectal cancer surgery.

Cost effectiveness

Four studies provided information about comparative costs relating to robot-assisted and laparoscopic surgery for rectal cancer[13, 22-24].

The ROLARR RCT incorporated a cost analysis based on resource utilisation data from 190 study participants from the UK and USA[13]. The analysis took an NHS perspective and excluded both capital and maintenance costs of the robotic surgical device on the basis that these vary depending on local arrangements. Total healthcare cost estimates therefore included the initial surgery, stoma supplies and stoma reversal costs, additional surgeries and miscellaneous costs. There was a statistically significant difference in total healthcare costs which were higher for robot-assisted surgery compared with laparoscopic surgery for rectal cancer: mean difference £980, 95% CI £165 to £1,795, p=0.02. The higher cost for robot-assisted surgery was attributed by the study authors to longer mean operating theatre time and higher mean cost of instruments.

Two observational studies compared costs and clinical outcomes for robot-assisted and laparoscopic surgery for rectal cancer[22, 23]. The first study was a retrospective analysis based on the Nationwide Inpatient Sample database which contains data from 20% of all inpatient discharges from hospitals in the USA[22]. The study identified 113,180 patients who had undergone surgery for rectal cancer between 2008 and 2012: 5,578 (4.9%) laparoscopic surgery and 4,474 (4.2%) robot-assisted surgery. After propensity score matching using 48 potential predictors of being assigned to a particular surgery, there were 551 matched patients in each of the robot-assisted and laparoscopic surgery groups. Details of the matching criteria used were not provided in the paper and baseline patient characteristics, such as BMI or tumour location within the rectum, are not reported. There were statistically significant differences in hospitalisation cost (£15,679 versus £13,431) and length of hospital stay (5 days versus 6 days) in the robot-assisted surgery group compared with the laparoscopic surgery group, with comparable morbidity and mortality. Despite propensity matching, selection bias may have exaggerated the study results as patients in the robot-assisted surgery group appeared to have fewer comorbidities than the laparoscopic surgery patients.

The second study was conducted at a high-volume surgical centre in South Korea (n=502)[23]. Participants who underwent robot-assisted or laparoscopic surgery for rectal cancer ≤15cm from the anal verge were propensity score matched using ten variables including age, BMI, year of operation and cancer stage. The only statistically significant difference in perioperative outcomes between matched cohorts was operating time, which was longer for robot-assisted surgery (353.1±86.9min versus 266.6±81.8min, p<0.001). Total hospital charges, operation fees and anaesthesia fees were all statistically significantly higher in the robot-assisted group compared with the laparoscopic surgery group (p<0.001) with no statistically significant differences in short-term patient outcomes.

The final study was a retrospective analysis of costs associated with robot-assisted and laparoscopic surgery for rectal cancer performed by a single surgeon with experience of laparoscopic surgery[24]. Seventy-five patients were included in the study; 50 received robot-assisted surgery and 25 laparoscopic surgery. Patient characteristics, such as the location of the rectal tumour, were not reported in the study. Costs were calculated from a hospital-based HTA and included both fixed costs (amortized costs of instruments, robot maintenance and purchase of the robotic device) and variable costs (disposable instruments, operating theatre staff costs, length of hospital stay). All costs were converted from Euros (€) to pounds sterling (GBP) using the XE currency converter on 2 July 2018. There was a statistically significant decrease in median overall cost, not including fixed costs, for robot-assisted surgery between phase one (1–19 patients, median cost £9,862) and phase three (41–50 patients, median cost £8,584) of the surgeon's learning curve, p=0.009. Median overall costs were statistically significantly higher for the robot-assisted surgery group compared with the laparoscopic surgery group (table 9). When fixed costs were excluded from the analysis, there was no statistically significant difference in median overall cost between experienced (phase 3, 41-50 patients) robot-assisted surgery and laparoscopic surgery performed by an experienced surgeon.

Table 9: comparison of costs for robot-assisted and laparoscopic surgery (multivariate analysis)[24]

Comparison	Median cost difference (95% CI)	p-value
Overall costs *Robotic vs laparoscopic*	£3,516 (£2,553 to £4,479)	<0.001
Overall costs excluding fixed costs *Robotic vs laparoscopic*	£2,108 (£1,142 to £3,075)	<0.001
Overall costs excluding fixed costs *Robotic phase 1 vs laparoscopic*	£2,833 (£1,658 to £4,009)	<0.001
Overall costs excluding fixed costs *Robotic phase 2 vs laparoscopic*	£1,818 (£641 to £2,995)	0.002
Overall costs excluding fixed costs *Robotic phase 3 vs laparoscopic*	£1,279 (-£170 to £2,731)	0.084

Conclusion

Based on the best quality evidence available (a meta-analysis of RCTs and a high quality RCT) there appear to be no statistically significant differences in most perioperative outcomes between robot-assisted and laparoscopic surgery for rectal cancer. The meta-analysis of RCTs suggests that patients receiving robot-assisted surgery are at lower risk of conversion to open surgery, however this result should be treated with some caution as the RCTs underpinning the result all reported no statistically significant difference in conversion rate.

Long-term oncological outcomes for patients undergoing robot-assisted surgery for rectal cancer were not reported in the randomised studies identified. In two meta-analyses of observational studies there was no statistically significant difference in 3-year overall survival, and in one meta-analysis there was no statistically significant difference in 3-year local disease recurrence, in comparisons of robot-assisted surgery and laparoscopic surgery.

For some patients with rectal cancer the most important outcome following surgery is a reduction in postoperative urinary, bowel and sexual dysfunction as these side-effects have a substantial negative impact on long-term quality of life. Evidence from identified studies was inconsistent on whether robot-assisted surgery improved these outcomes compared with laparoscopic surgery.

Robot-assisted surgery for rectal cancer was associated with significantly higher costs (£165 to £1,795) per procedure than laparoscopic surgery. However, few statistically significant differences in clinical outcomes suggest it is unlikely that robot-assisted surgery for rectal cancer is cost-effective.

Identified research gaps

Robot-assisted surgery for rectal cancer appears to be at the assessment stage of the IDEAL framework for surgical innovation.

- Prospective, randomised studies are needed that report long-term patient and oncological outcomes for robot-assisted surgery compared with laparoscopic surgery in patients with rectal cancer.
- Cost-effectiveness analyses applicable to the UK setting are needed to compare robot-assisted surgery with laparoscopic surgery in patients with rectal cancer.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

About evidence notes

Evidence Notes are produced to inform a decision at a particular point in time and are therefore not routinely updated. They will however be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the advice given. For further information about the evidence note process see:

www.healthcareimprovementscotland.org/our_work/clinical__cost_effectiveness/shtg/standard_operating_procedures.aspx

To propose a topic for an evidence note, email shtg.hcis@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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Healthcare Improvement Scotland development team

- Jenny Harbour, Lead Author/Health Services Researcher
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- Members of the SHTG evidence review committee

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Appendix 1: abbreviations

APR	abdomino-perineal resection
BMI	body mass index
CI	confidence interval
CRM	circumferential resection margin
GBP	Great Britain pounds
HR	hazard ratio
LAR	low anterior resection
MAUDE	Manufacturer and User Facility Device Experience database
MD/WMD	mean difference/weighted mean difference
NRLS	National Reporting and Learning System
OR	odds ratio
RCT	randomised controlled trial
RD	risk difference
ROLARR	RObotic versus LAparoscopic Resection for Rectal cancer
RR	risk ratio/relative risk
SD	standard deviation
TME	total mesorectal excision