Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Supplementary Summary of Cost Analysis

Aim

The aim of the economic analysis was to evaluate the hospital costs of robotic-assisted rectal cancer surgery vs. standard laparoscopic rectal cancer resection. Currently, there is only one surgical robotic system, the da Vinci™ system. To avoid any criticism of commercial bias, it is necessary that an evaluation of this robotic technology is performed independently of the manufacturer. Given wide variation in costs due to contractual arrangements for this technology, and the commercial nature of such contractual arrangements, capital and maintenance cost of the robot were excluded from the analysis.

Methods

Coding practices differ between the US and the UK. To overcome this, utilization data were obtained by local study personnel and entered into the Case Report Form (CRFs). For the initial surgery, the total time the operating room was used (not just incision to closing), the number of surgical assistants, laparoscopic and robotic tools usage, etc were recorded. Utilization information was recorded from the operative stay until 6 months post operation. Utilization outside the hospital was recorded by sending patients questionnaires at 30 days and then again at 6 months detailing any subsequent inpatient care, outpatient care, medications, and contacts with family doctors/general practitioners, nurses, and other health professionals they received. Information was collected about which resources were used rather than individual prices or costs. This avoids inconsistencies between costs and prices that differ between locations and health systems.

Data from the study CRFs were sent to the local study hub. In the US this was City of Hope and in the UK it was the Clinical Trials Research Unit, University of Leeds. Eventually all the data were sent to Leeds and incorporated into the study database.

Each resource utilization item in the database was assigned a unit cost. For example, each minute of operating room time was assigned a unit cost (£/minute) and the costs attributable to operations room utilization calculated from the total time the room was used. Unit costs were derived from several sources but wherever possible national-level reference costs were used: cost estimates were standardized for the entire country (US or UK) for each activity or resource used to ensure consistency of the analyses within each country. For example, the cost of laparoscopic surgery was assumed to be reflected in the NHS Reference Cost per case for elective, “FZ74 Complex large intestine” of £8307.78. Where reference data were not available, estimates from the literature were used, and in a very small number of cases (where no other estimates existed) unit cost data were sourced from expert opinion.

All costs were transformed to US dollars using 2015 purchasing power parities (at 0.688 GBP/USD) for reporting purposes, in accordance with *JAMA* policy. Multiple imputation methods were used for missing data. Sensitivity analysis was undertaken to account for uncertainty.

Results

The primary analysis uses imputed data for UK and US patients (n=190). Sensitivity analyses were undertaken using (1) Complete data for all patients (n=97); (2) Imputed data for UK and US patients intended to receive low anterior resection (n=135); and (3) Imputed data for all observations (n=471). The cost of initial surgery is the main cost driver in both arms (eTable 1). Data on each of the cost items are skewed, with some of the individual cost breakdowns relevant for under 25% of data (so that UQ is $0). The main drivers of the higher operative costs for the robotic surgery is duration of surgery (357 and 408 minutes respectively) and use of surgical instruments. There was little difference in the number of staff in attendance (mean number of assistants 1.7 and 1.63).

The sensitivity analyses were consistent with the primary analysis.

Conclusion

Robotic rectal cancer surgery is more expensive than conventional laparoscopic surgery, even excluding the acquisition and maintenance costs for the systems. Local costs for the surgical robot will vary, and should be considered alongside the costs presented here. A wide variation in costs is indicative of different practices between surgeons and sites.

eAppendix 2. Sensitivity Analysis of Potential Learning Effects

All participating surgeons in the Robotic versus Laparoscopic Resection for Rectal Cancer (ROLARR) trial reported the number of previous laparoscopic operations and the number of previous robotic operations that they had performed prior to randomising their first patient. Throughout the ROLARR recruitment period participating surgeons were asked at regular intervals to report how many laparoscopic and how many robotic operations they had performed – including operations performed outside of the ROLARR trial - since their last reported figure. These data were used to derive for each ROLARR patient the number of laparoscopic and number of robotic operations that their operating surgeon had performed prior to their operation. eTable 2 presents the distribution across patients of these measures.

Participating surgeons in the ROLARR trial had a wide range of previous laparoscopic and robotic experience. eTable 2 shows a clear disparity between the levels of laparoscopic and robotic experience, with the average (median) patient in ROLARR receiving an operation from a surgeon who had previous experience of around 91 laparoscopic and 50 robotic rectal cancer operations.

In order to adjust for and explore the effect of operating surgeon level of experience on the difference between the treatment groups in terms of odds of conversion to open, the primary analysis model was extended to include both number of previous laparoscopic operations performed and number of previous robotic operations performed by the operating surgeon as main effects and also as interactions with the treatment effect. eTable 3 presents the estimated odds ratios yielded by this extended model for treatment effect at different levels of operating surgeon laparoscopic and robotic experience.

It is clear from eTable 3 that the adjusted odds ratio decreases as operating surgeon robotic experience increases, and that the effect of laparoscopic experience on this pattern is negligible. This is clear as the odds ratio reduces from around 0.96 under a surgeon with 30 previous robotic operations (the lower quartile of robotic experience in ROLARR), to 0.69 under a surgeon with 91 previous robotic operations (the median robotic experience in ROLARR), to 0.30 under a surgeon with 100 previous robotic operations (the upper quartile of robotic experience in ROLARR), at all levels of laparoscopic experience.

The eFigure presents the relationship between the estimated adjusted odds ratio (robotic vs. laparoscopic) for conversion to open surgery for a patient being operated on by a surgeon with experience of 91 previous laparoscopic operations (the median in ROLARR) across the entire range of robotic experience levels of participating surgeons in ROLARR.

These findings suggest that the benefit of robotic surgery compared to laparoscopic (in terms of odds of conversion to open surgery) is greater under surgeons who have more robotic experience, regardless of their level of laparoscopic experience.

eAppendix 3. Subgroup Analyses for Conversion to Open

Results from the subgroup analyses as described in the methods section are presented here. For each subgroup, a treatment-by-subgroup interaction term was added to the primary analysis model. Odds ratios presented in eTables 4-6 are derived from the linear combination of the estimates of treatment (main effect) and treatment-by-subgroup interaction terms on the logit scale. P-values are presented for test of the treatment effect within each subgroup – this is the first column of p-values e.g. in eTable 4 the test that the treatment effect is null (odds ratio = 1) within the male subgroup is 0.0429. P-values are also presented for the test of heterogeneity of treatment effect across subgroups, the details of which are given in the footnotes of the tables.

eTable 1. Cost Breakdown and Distributions

Cost Category	Cost, $			
	Mean	**Median**	**LQ**	**UQ**
Randomized to Conventional Laparoscopic Surgery (n=95)				
Initial surgery	9726	9450	8543	10 867
Stoma reversals	676	-	-	1953
Stoma supplies	631	683	499	683
Other surgery	842	-	-	-
All other costs	681	537	289	915
Total	12 556	12 078	10 636	13 559
Randomized to Robotic-Assisted Laparoscopic Surgery (n=95)				
Initial surgery	10 979	10 987	10 084	11 926
Stoma reversals	555	-	-	1953
Stoma supplies	561	683	184	683
Other surgery	835	-	-	-
All other costs	758	655	381	966
Total	13 688	12 971	11 827	14 584

eTable 2. Number of Laparoscopic and Robotic Procedures Performed Before the Current Operation Summarized Across Patients

	Laparoscopic (n=464)	**Robotic (n=464)**
Mean (SD)	152.5 (178.38)	67.9 (48.75)
Median (Range)	91.4 (10.0, 853.0)	49.5 (10.3, 183.0)
Interquartile range	(44.9, 180.1)	(30.4, 101.3)

*n=464. 466 patients had an operation and there were 2 instances where the learning curve data for the operating surgeon were unavailable.

eTable 3. Estimated Adjusted Odds Ratios (Robotic vs Laparoscopic) for Conversion to Open Surgery vs Operating Surgeon's Level of Previous Robotic Experience

Effect	Surgeon's Laparoscopic experience level (no. of previous operations)	Surgeon's Robotic experience level (no. of previous operations)	Odds* Ratio (Robotic vs. Laparoscopic)**	95% CI for Odds Ratio	
				Lower limit	Upper limit
Treatment: robotic surgery (vs laparoscopic)*	45	30	0.961	0.336	2.747
		50	0.691	0.277	1.721
		100	0.303	0.090	1.018
	91	30	0.963	0.383	2.424
		50	0.692	0.317	1.513
		100	0.303	0.096	0.959
	180	30	0.966	0.416	2.245
		50	0.694	0.336	1.437
		100	0.304	0.094	0.988

*Adjusted for sex, BMI class, previous radio- or chemoradiotherapy, intended procedure and operating surgeon (as a random effect), as described in the methods section.
**Odds of conversion to open surgery.

eTable 4. Treatment x Sex Interaction Effects

Effect	Laparoscopic surgery (No. conversions/ No. patients (%))	Robotic surgery (No. conversions/ No. patients (%))	Risk difference and 95% CI (unadjusted)	Odds ratio and 95% CI (adjusted)*	p-value	
Treatment in males: robotic surgery (vs. laparoscopic)	25/156 (16.0)	14/161 (8.7)	7.3 (0.1, 14.6)	0.455 (0.209, 0.987)	0.0429	0.0939**
Treatment in females: robotic surgery (vs. laparoscopic)	3/74 (4.1)	5/75 (6.7)	-2.6 (-9.8, 4.6)	2.022 (0.425, 9.621)	0.3757	

*adjusted for BMI class, preoperative radiotherapy, intended procedure and operating surgeon.
**p-value for the treatment effect is referring to a test of heterogeneity of treatment effect between the subgroups.
Odds ratios derived from the Treatment term and Treatment-by-Sex interaction term.

eTable 5. Treatment x BMI Interaction Effects

Effect	Laparoscopic surgery (No. conversions/ No. patients (%))	Robotic surgery (No. conversions/ No. patients (%))	Risk difference and 95% CI (unadjusted)	Odds ratio and 95% CI (adjusted)*	p-value	
Treatment in obese patients: robotic-assisted surgery (vs. laparoscopic)	15/54 (27.8)	10/53 (18.9)	8.9 (-7.0, 24.8)	0.583 (0.212, 1.602)	0.2944	0.6862**
Treatment in overweight patients: robotic-assisted surgery (vs. laparoscopic)	6/90 (6.7)	3/90 (3.3)	3.3 (-3.0, 9.7)	0.508 (0.117, 2.213)	0.3661	0.7509**
Treatment in underweight and normal patients: robotic-assisted surgery (vs. laparoscopic)	7/86 (8.1)	6/93 (6.5)	1.7 (-6.0, 9.3)	0.751 (0.227, 2.492)	0.6396	

*adjusted for Sex, preoperative radiotherapy, intended procedure and operating surgeon.
**p-value for the treatment effect is referring to a (pairwise) test of heterogeneity of treatment effect between the subgroups. For example, the second p-value in the "Treatment in Obese patients" row refers to a test of heterogeneity of treatment effect between Obese patients and Underweight/Normal patients.

eTable 6. Treatment x Procedure Performed Interaction Effects

Effect	Laparoscopic surgery (No. conversions/ No. patients (%))	Robotic surgery (No. conversions/ No. patients (%))	Risk difference and 95% CI (unadjusted)	Odds ratio and 95% CI (adjusted)*	p-value	
Treatment (high anterior resection): robotic-assisted surgery (vs. laparoscopic)	2/19 (10.5)	2/28 (7.1)	3.4 (-13.4, 20.2)	0.771 (0.078, 7.617)	0.8234	0.7106*
Treatment (abdominoperineal resection): robotic-assisted surgery (vs. laparoscopic)	4/45 (8.9)	4/52 (7.7)	1.2 (-9.8, 12.2)	0.705 (0.144, 3.452)	0.6656	0.6833*
Treatment (low anterior resection): robotic-assisted surgery (vs. laparoscopic)	22/165 (13.3)	11/152 (7.2)	6.1 (-0.5, 12.7)	0.486 (0.210, 1.123)	0.0909	

*adjusted for Sex, BMI class, preoperative radiotherapy and operating surgeon.
**p-value for the treatment effect is referring to a (pairwise) test of heterogeneity of treatment effect between the subgroups. For example, the second p-value in the "Treatment (HAR)" row refers to a test of heterogeneity of treatment effect between patients who underwent HAR and patients who underwent LAR.
5 patients underwent a procedure other than HAR, APR or LAR – 1 in the laparoscopic treatment group (no conversion to open) and 4 in the robotic treatment group (2 conversions). These patients were excluded from this model.

eFigure. Estimated Adjusted Odds Ratios (Robotic vs Laparoscopic) for Conversion to Open Surgery vs Operating Surgeon's Level of Previous Robotic Experience