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Complete List of Authors:	Moss, Esther; University of Leicester College of Medicine Biological Sciences and Psychology, Leicester Cancer Research Centre Morgan, George; HCD economics, Martin, Antony; HCD economics, Sarhanis, Panos; North West London Hospitals NHS Trust Ind, Thomas; Royal Marsden Hospital NHS Trust
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Economic evaluation of different routes of surgery for the management of endometrial cancer: A retrospective cohort study.

[1]Moss EL (PhD), [2]Morgan G, [2]Martin A, [3]Sarhanis P (FRCOG), [4,5]Ind T (FRCOG)

[1]Leicester Cancer Research Centre, University of Leicester, Leicester, LE1 7RH

[2]HCD Economics

[3]North West London NHS Trust

[4]Royal Marsden Hospital

[5]St George's University of London, London, SW17 0RE

Corresponding Author

Dr Esther Moss

Leicester Cancer Research Centre, University of Leicester, Leicester, LE1 7RH, UK

Tel: +44 (0)116 252 3170

Fax: +44 116 258 8210

Email: em321@le.ac.uk

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ABSTRACT

Objectives: The benefits of minimally invasive surgery (MIS) for endometrial carcinoma (EC) are well established although the financial impact of robotic-assisted hysterectomy (RH) compared to laparoscopic hysterectomy (LH) is disputed.

Design: Retrospective cohort study.

Setting: English NHS hospitals 2011-2017/8.

Population: 35,304 women having a hysterectomy for EC identified from Hospital Episode Statistics (HES).

Methods: Analysis of Hospital Episode Statistics (HES) for England 2011-2017/18 for all women undergoing an open (OH) or MIS (LH/RH) for EC. Costing data was analysed by each surgical approach by age, Charlson Comorbidity Index (CCI) and hospital MIS rate classification. The average marginal effect (AME) was calculated to compare RH vs OH/RH vs LH which adjusted for any differences in the characteristics of the surgical approaches.

Main outcome measures: The association between route of surgery on cost at intervention, 30, 90 and 365 days.

Results: A total of 35,304 procedures were performed, 20,405 (57.8%) were MIS (LH 18,604 and RH 1,801), 14,291 (40.5%) OH. Mean cost for LH was significantly less than RH, whereas RH was significantly less than OH at intervention, 30, 90 and 365 days ($p<0.001$). Overtime patients who underwent RH became increasingly complex and by the 2015/16 year had a higher average CCI than LH. Comparing the cost of LH and RH against CCI score identified that the costs closely reflected the patients' CCI. There was also increasing disparity between the MIS and OH costs with rising age. When exploring the association between provider volume, MIS rate and surgical costs there was an association with the higher the MIS rate the lower the average cost.

Conclusions: The cost of surgery was influenced by the level of patients' co-morbidities rather than the route of surgery alone. Further research is needed to investigate costs in matched populations to determine optimum surgical modality in different populations.

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Key words: Endometrial cancer; minimally invasive surgery; laparoscopic hysterectomy; open hysterectomy; robotic-assisted hysterectomy; cost

Tweetable abstract: Analysis of financial cost of laparoscopic, robotic and open hysterectomy for the treatment of endometrial cancer in England.

Strengths and limitations

- The findings from the study are based on a population-based database which is a key strength as it is representative of all procedures via the NHS in England.
- The reliability of the coding might have changed over time although there was no evidence of changes in treatment coding or significant changes in the underlying study population.
- HES database reliably captures extensive amount of demographic, diagnosis and procedure outcomes however there is a lack of cancer stage information therefore it is not possible to split out the cost outcomes into more specific groups of patients.
- The capital and maintenance costs of RH have also not been included since these costs vary dramatically across different healthcare settings and often utilised by a wide group of specialities in a hospital setting.
- As the analysis was undertaken over a number of years of the HES database, we were able to accurately follow hospital activity for at least a year after intervention.

INTRODUCTION

The introduction of minimally invasive surgery (MIS) for endometrial cancer (EC) has had a dramatic impact on patients' surgical outcomes with reduced morbidity, hospital stay and improved short-term quality of life[1]. Translating these patient benefits into cost benefits to the healthcare economy has been challenging because although MIS requires significantly less bed days than open surgery, it does require more costly consumable equipment, for example single-use vessel sealing devices. This has been demonstrated in several studies including the multi-centre randomised LACE trial where the surgery costs were greater for laparoscopic hysterectomy (LH) compared to open hysterectomy (OH), but the overall costs of treatment were lower[2].

MIS is the preferred surgical route for EC[3]. RH is accepted as an alternative to LH, supported by evidence from a randomised controlled trial[4] and RH has been shown to have a lower conversion rate to laparotomy and shorter operating time[5–7]. Wide spread adoption of RH is limited in England, although the number of EC cases having RH increasing year on year[8]. In light of the capital and consumable costs of RH, as compared to OH or LH, the use of RH in EC is therefore being called into question[6]. Reports from institutions with well-established robotic programmes however have contested this view with no significant difference[9], or cost improvements reported as compared to LH[10]. What is clear is that focusing solely on in-hospital costs does not give the full picture of the economic costs of a surgical procedure, since many costs are accrued following discharge or attributed to the economy as a whole as a result of delayed return to employment.

We therefore investigated the HES data for England in order to look at the financial impact of RH as compared to LH and OH. We also investigated the patient characteristics that contributed

to cost and examined the top 5% of procedures to identify factors that may have contributed to the costs.

METHODS

Data Source and cohort selection

Data was sourced from the Hospital Episode Statistics (HES) database from 2011-2017/8[11]. HES database captures demographic, diagnosis and procedure outcomes data however does not include cancer stage or histology information. No ethical approval was required for this study. Patients or the public were not involved in the design, or conduct, or reporting of our research. The inclusion criteria for patients was a diagnosis of endometrial cancer (EC) or endometrial cancer in situ/complex atypical hyperplasia (ECIS) undergoing a hysterectomy between October 2011 to December 2017. The surgical approach was classified by intention-to-treat as open hysterectomy (OH), vaginal hysterectomy (VH), laparoscopic hysterectomy (LH), robotic hysterectomy (RH) and minimally invasive surgery (MIS) which was the combination of LH and RH. Due to the low numbers the VH cases were not included in any of the subsequent analyses. The cohort selection for the study has been described in more detail previously[8] and the list of specific diagnosis (ICD-10) and procedure (OPCS-4.7) codes can be found in the Appendix Table A1.

Patient Characteristics

Patient age was divided by 10-year intervals from the age of 50 into six groups. Ethnicity was classified into Asian, Black, Other and White. The Index of Multiple Deprivation (IMD) was split into statistical quartiles and indicated whether the sociodemographic status was high (>25083), intermediate (17475-25083), low (9618-17474) or very low (<9618) for each patient. Comorbidities were examined using the Charlson Comorbidity Index (CCI), an additional list of other co-morbidities were also assessed using specific ICD-10 codes (Appendix Table A2).

Hospital characteristics were assessed by region (East, East Midlands, Greater London, Home Counties, North East, North West, South East, South West, West Midlands, Yorkshire) and volume, which was based on the annual mean of hysterectomies performed for EC/ECIS grouped by statistical quartiles (High (>220), Intermediate (71-220), Low (70-21) and Very Low (0-20)). MIS rates of hospitals for EC/ECIS hysterectomy procedures were classified into four groups based on percentage of hysterectomies performed by MIS approach (High (76-100%), Intermediate (51-75%), Low (26-50%) and Very Low (0-25%)).

Outcomes

For each patient episode, in the HES database, a cost is assigned based on the health resource group (HRG) which is diagnosis/procedure-based grouping and the length of stay. These costs are based on reference costs provided by each hospitals and are estimated based upon recorded inpatient, outpatient, and A&E episode activity in the HES database using NHS Payment by Results Health Resource Group (HRG) tariffs[12]. Costs were then summarised, by each procedure approach, at intervention, 30 days, 90 days and 365 days. Further to this, the cost of each approach was assessed by the subgroups of age, CCI groups and MIS rate classification. A list of non-surgical cancer related treatments was collated (See Appendix Table A3 for specific OPCS-4.7 procedure codes) and these costs were excluded in the analysis. Peri-operative outcomes included mortality, conversion to open hysterectomy and length of stay. The 90-day outcomes included the mortality, total and specific inpatient, outpatient and emergency readmissions. Subgroup analyses were performed, firstly to assess high cost (top 5% of costs at intervention by approach) and low-cost patients (lowest 50% of costs at intervention by approach) in the cohort to assess what was driving high costs patients. In addition, provider level analysis was conducted to assess hospital characteristics and costs to further understand the impact of differing MIS rates and volume sizes.

Statistical Analyses

A descriptive analysis of patient characteristics and data on costs and other health resource was performed. The different approaches (LH, RH, OH, MIS) were then compared by using t-test (for independent samples) and Wilcoxon rank-sum test (Mann-Whitney U test) for continuous variable and for categorical variables by using the chi-squared tests. The average marginal effect (AME)[13] was used to compare RH vs OH and RH vs LH on costing outcomes at intervention, 30 days, 90 days and 365 days. This approach adjusted for patient age, ethnicity, IMD rank, Charlson Comorbidity Index, year of procedure and whether a patient received cancer treatment following the intervention (for further details see Appendix Table A3) by fitting Generalised Linear Models (GLMS). The Modified Park Test & Pregibon's Link Test[14] were used to ensure the most efficient model structure was used to model the costs. All statistical analyses were performed using Stata 15®.

Patient and Public Involvement

There was no patient or public involvement in the study planning or design.

RESULTS

A total of 35,304 procedures were performed, 18,604 (52.7%) LH, 1,801 (5.1%) RH, 14,291 (40.5%) OH and 608 (1.7%) VH. The proportion of MIS cases increased significantly overtime each year from 46.6% in 2012/13 to 68.7% in 2016/17 ($p<0.001$). This was primarily due to an increase in LH of 15.8% (44.7% to 60.5%), but there was also a 6.2% increase (2.0% to 8.2%) in the number of RH performed when comparing 2012/13 to 2016/17 as a proportion of all surgeries performed each year. Consequently, the number OH cases decreased significantly overtime ($p<0.001$) from 53.4% in 2012/13 to 31.3% in 2016/17 of cases in that year.

Table 1 presents the patient characteristics of the surgical approaches LH, RH and OH. Most cases were performed at high volume providers (>220 cases/year) with 72.4% for RH, 62.1%

for LH and 60.9% for OH being undertaken at these providers (Table 1). As previously described, there was a significant difference in the social/racial characteristics of the women undergoing MIS as compared to OH within this cohort of patients[8]. The characteristics of the RH population differed to women undergoing LH; with a significantly higher percentage of RH patients having any co-morbidity from our defined list than LH (68.2% vs 64.0%, $p<0.001$), more specifically the comorbidities of diabetes, hypertension and obesity all being higher proportion in RH cohort than LH cohort.

Short-term costs by approach

The short-term costs of intervention, 30 days, 90 days and 365 days by surgical approach are presented in Table 2. LH was associated with the lowest mean cost at the intervention (£3069), 30 (£3083), 90 (£3111) and 365 (£3169) days following the procedure. The mean cost for RH was significantly less than OH at all the time points ($p<0.001$ for all). The average marginal effect (AME) for RH versus OH, controlling for patient characteristics, also showed a significant difference for RH over OH with the difference in cost increasing when comparing the unadjusted and AME value ($p<0.001$ for all). Comparing RH and LH short-term costs, LH costs were significantly lower for the unadjusted and AME differences ($p<0.001$ for all). The AME differences in cost between RH and LH were lower compared to the unadjusted differences (e.g., AME difference of £108 vs. unadjusted difference of £260 at intervention.

High-Cost and Low-Cost Patient Comparison

Assessing the top 5% highest cost (HC) patients of each approach (LH: n=336; OH: n=593, RH: n=27) and comparing to the low-cost (LC) cohort, which was set at less than or equal to the median cost of the surgery (LH: n=12,913; OH: n=9,021, RH: n=812). The patients in the HC group were significantly older in all the routes of surgery (LH: 69.0 vs 65.7 years, OH: 68.8 vs 65.1 years, RH: 67.5 vs 65.5 years: $p<0.001$ for all). The HC cohort contained a higher percentage of women from the lower socioeconomic groups (IMD Rank: 16637 vs 17287, p<0.001) and women of non-white ethnicity (29.6% vs 19.2%, p<0.001) as compared to the LC cohort. Women in the HC cohort also had significantly greater number of co-morbidities compared to the LC cohort (CCI 1.82 vs 1.41 and any comorbidity 71.0% versus 63.9% p<0.001 for all). The length of hospital stay was significantly longer in the HC cases compared to the LC group (RH: 11.22 vs 1.84 days; LH: 11.42 vs 2.03 days; OH: 20.82 vs 3.71days; p<0.001 for all). Although the rate of complications was greater in the HC compared to the LC cohort (RH: 55.6% vs 14.0%; LH: 61.0% vs 16.2%; OH: 71.5% vs 19.1%; p<0.001 for all), the rate was significantly lower with RH as compared to OH in both the HC and LC groups (HC: 55.6% vs 71.5%, p= 0.075; LC: 14.0% vs 19.1%, p<0.001).

Patient Characteristics and Costs

Patient characteristics, age and CCI, were associated with increasing costs for almost all routes of surgery at intervention, and 365 days following the procedure (Table 3). Assessing the age categories showed the costs at intervention were very similar for the <50 years, 50-59 years and 60-69 years groups but gradually increased for each of the higher age groups. There was an increasing difference between the MIS and OH costs with rising age with the difference between MIS and OH for Age <50 being £258 increasing to a difference of £653 for Age >90 years population. RH costs were significantly lower (p<0.001) than OH in all age categories except 60-69 years. Comparing CCI showed that CCI group >=3 was associated with the greatest difference in costs with the difference at 365 days between CCI group 1 and CCI group >3= being £130 for RH, £174 for LH and £759 for OH (Table 3).

Overtime patients who underwent RH became increasingly complex, when using the CCI score, and have in recent years had a higher average CCI than LH in 2015/16-2016/17 (Figure 1). Comparing the cost of LH and RH against CCI score, identified that the costs closely reflected the patients' CCI. In 2012/13 when the RH population had a lower CCI then the costs were less, however, since 2014/15 the patient population undergoing RH higher CCI score and this was associated with a rise in the costs of RH above that of LH (Figure 1).

Hospital Characteristics and Costs

When exploring the association between provider volume, MIS rate and surgical costs there was an association with the MIS rate and cost, i.e. the greater the MIS rate the lower the cost (Figure 2). Many of the highest volume providers had higher average costs than providers with less volume, however the patient population undergoing surgery at the high volume providers were significantly older and had a higher CCI compared to the lower volume providers (Age: 66.2 vs 65.6 years, p<0.001; CCI: 1.47 vs 1.43, p<0.001). The majority of the highest volume providers had MIS rates between 50% to 90% and the relationship held for high volume providers with average costs decreasing as MIS rates increased for the year 2016/17.

DISCUSSION

Main findings

In this study, we have performed an in-depth analysis of real-world data and have identified financial benefits for MIS as compared to OH for EC. We have demonstrated that LH has the lowest mean cost at intervention and that costs increased with increasing patient age. In keeping with other studies, we have also shown that OH, although attracting the lowest operative consumable costs, had the greatest overall financial cost, even significantly higher than RH. We have also identified that patients undergoing RH have different characteristics compared to women having LH in recent years, and that cost of surgery appears to be influenced by level of patients' co-morbidities rather than the route of surgery alone.

There will always be a proportion of cases that have to be performed OH due to contra-indications/complications with MIS, which will inevitably attract higher costs due to their complexity, but this can be reduced to low levels[15]. The longer recovery time and significantly higher complication/re-admission rate with OH may impact on patient and employment costs, with greater loss of earnings and longer return to work or contribution to society activities as compared to MIS. Korsholm et al.[16], reported no significant difference in return to the labour market or use of sickness benefits in a study from Denmark however, in their study robotic surgery was associated with greater cost than both laparoscopic and open hysterectomy, unlike this UK analysis. Allowing for a number of OH cases, the disparity in MIS uptake across England[8] does indicate that there is room for improvement in increasing the proportion of MIS cases and thereby benefitting both the patient and the healthcare economy.

The primary argument used against the widespread use of RH, rather than LH, for EC is an economic one[6,17], since the clinical outcomes are comparable although, there is a lack of randomised control trial data, particular for high BMI patients[18]. The HES data does confirm a cost advantage for LH over RH however, the two patient populations are not directly comparable since there is a significant difference in the CCIs between the groups. During 2012/13, when RH was only performed in a few selected centres, the majority of UK robotic surgeons would still have been within the learning phase, and therefore likely to select patients with less co-morbidities for RH. We have shown that during this time period the cost of RH was less than LH. Increasing robotics experience appears to have led to the positive selection of co-morbid patients, especially obesity, for RH, and this is associated with rising costs. Class III obesity and rising number of patient co-morbidities are reported to attract increased inpatient care costs due to increased medical rather than surgical complications associated with undergoing surgery[19,20]. The selection of high-BMI cases for RH is not unexpected given the reported ergonomic benefits for surgeons as compared to straight-stick laparoscopy[21], with less movements and muscle activity required to perform tasks[22]. RH is not without issues due to the fixed console position[23], however more extreme muscle movements are required for laparoscopic procedures increase with rising BMI[22], which is not reported with robotics. The cost to the healthcare service of work-related musculoskeletal symptoms in surgeons is of growing concern[24] and not considered in economic analyses such as this study, however it is an additional cost that needs to be considered when calculating service delivery costs.

What is clear the data is that OH is the most costly route of surgery, a finding reported in other healthcare settings[25], not only in financial terms but more importantly for patient complications and post-operative mortality[8]. The key focus therefore, rather than being between LH or RH, should instead be on reducing the OH rate to a minimum. Although there are only a few absolute contra-indications for OH, the number of cases that are performed through open surgery is still high in some institutions and there has been much discussion how this could be reduced through greater surgical training[26] or centralisation of cases to hospitals and surgeons with high MIS rates[27]. A reduction in OH can also be achieved through reducing the number of conversions from LH/RH to a minimum. A meta-analysis of observational studies did show that the conversion rate of LH increased with BMI >40kg/m^2 more than for RH, 6.5% (95% CI 4.3-9.9) versus 5.5% (95% CI 3.3-9.1), as compared to >30kg/m^2, 7.0% (95% CI 3.2-14.5) versus 3.8% (95% CI 1.4-99) respectively[18]. One reason for this may be the lower intra-abdominal insufflation pressure used with RH, typically 8mmHg, which has been shown to be associated with lower post-operative pain and shorter hospital stay as compared to standard pressure (15mmHg)[28]. Inability to tolerate Trendelenburg position was reported to be the indication for 31% of LH conversions but only 6% of RH conversions[18]. This therefore raises the possibility as to whether cases should be selected for RH where there is high risk of conversion due to severe obesity or inability tolerate the pneumoperitoneum.

Strengths and limitations

The key strength of the study is in the number of patients in which can be analysed by using the HES database. This gives strength to the study's findings as it is representative of all procedures via the NHS in England. Due to RH being a newer surgery approach the number of patients is much lower compared to the other surgery approaches. In addition, we must consider the impact of a learning curve of RH and that in the earlier years it may not been used to full efficiency. As we had a number of years of the HES database we could analyse any potential trends across surgical approaches and the year.

As we have previously described[8], HES data does have limitations primarily it only covered NHS-funded care, the reliability of coding and lacks oncological details of stage/histology. There will be a proportion of patients with advanced disease that require open surgery due to requiring a more extensive cytoreductive procedure and HES data is not able to differentiate these cases from early stage disease that is being treated through open surgery. The analysis comparing LH and RH should however not be impacted by stage of disease.

The capital and maintenance costs of RH have also not been included since these costs vary dramatically across different healthcare settings and there would be a need to also included similar costs for laparoscopic and open surgery. In addition, the robotic surgery equipment is often utilised by a wide group of specialities in a hospital setting and it would be infeasible to apply capital and maintenance costs to one surgery modality[13].

Interpretation

In conclusion, LH was associated with the lowest and OH the greatest mean cost per procedure. Patient factors have an impact on the cost of MIS procedures and further research is needed to compare the costs in matched populations of women undergoing LH and RH, since there appears to be selection bias in the choice of procedure being performed.

Ethical approval: The HES database is managed by the NHS Digital and is available for research without ethical approval.

All the authors consent to publication

Data availability: Data analysed in this study is available through Hospital Episode Statistics (HES)

Conflicts of Interest: EM and TI perform Da'Vinci robotic gynaecological surgery (Intuitive Surgical) and are members of the British and Irish Association of Robotic Surgeons (BIARGS), which is supported by Intuitive Surgical and other robotics/laparoscopic companies to hold education/training events. EM has been awarded research grants from Intuitive Surgical and Hope Against Cancer for unrelated studies. TI has done two days paid consultancy work for Medtronic. GM and AM from HCD Economics were funded by Intuitive Surgical. None of the clinicians (EM, PS, TI) received funding from Intuitive Surgical for this study. Intuitive Surgical did not have any involvement with the study design, data analysis and writing of the manuscript. The authors declare no other potential conflict of interest.

Contributors: EM, TI, GM and AM contributed to the conceptualisation and study design. Data analysis and interpretation was performed by EM, TI, GM, AM and PS. Figures and tables creation was performed by EM, GM and AM. All authors were involved in the writing or review of the manuscript and approved the final version.

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Figure 1: Intervention Cost & CCI Over Time

The average cost and CCI of RH & LH over time.

(CCI = Charlson Comorbidity Index, LH = laparoscopic hysterectomy, RH = robotic hysterectomy, NHS = National Health Service)

Figure 2: Average Provider Cost of Hysterectomy per Provider by MIS rate in 2016/17

The association between provider volume, MIS rate and surgical cost at intervention. Provider volume is represented by the size of the bubble with a larger bubble representing a higher provider volume.

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Table 1. Clinical and Demographic Characteristics by the cohorts of hysterectomy approach

	Unadjusted Results							
	Laparoscopic Hysterectomy (N=18604)		Robotic Hysterectomy (N=1801)		MIS Hysterectomy (N=20405)		Open Hysterectomy (N=14291)	
Characteristics	No.	(%)	No.	(%)	No.	(%)	No.	(%)
NHS Year of surgery								
2011/12*	1,108	6%	19	1%	1,127	6%	1,671	12%
2012/13	2,367	13%	104	6%	2,471	12%	2,829	20%
2013/14	2,824	15%	147	8%	2,971	15%	2,614	18%
2014/15	3,134	17%	253	14%	3,387	17%	2,361	17%
2015/16	3,118	17%	382	21%	3,500	17%	1,948	14%
2016/17	3,577	19%	483	27%	4,060	20%	1,852	13%
2017/18*	2,476	13%	413	23%	2,889	14%	1,016	7%
Age, years								
<50	1,033	6%	120	7%	1,153	6%	1,082	8%
50-59	3,937	21%	380	21%	4,317	21%	3,098	22%
60-69	6,522	35%	589	33%	7,111	35%	4,672	33%
70-79	5,160	28%	533	30%	5,693	28%	3,779	26%
80-89	1,846	10%	174	10%	2,020	10%	1,540	11%
90>	106	1%	5	0%	111	1%	120	1%
Ethnicity								
White	15,033	81%	1,420	79%	16453	81%	11117	78%
Asian	583	3%	66	4%	649	3%	499	3%
Black	231	1%	20	1%	251	1%	365	3%
Other	2,757	15%	295	16%	3052	15%	2310	16%
Socio-Economic Group (IMD)								

High	4,506	25%	643	37%	5,149	25%	3,291	23%
Intermediate	4,612	25%	403	23%	5,015	25%	3,387	24%
Low	4,548	25%	376	21%	4,924	24%	3,489	24%
Very Low	4,435	25%	333	19%	4,768	23%	3,703	26%
Charlson Comorbidity Group								
0	22	0%	1	0%	23	0%	13	0%
1	12,432	67%	1,159	64%	13,591	67%	8,405	59%
2	4,915	26%	514	29%	5,429	27%	4,535	32%
>=3	1,235	7%	127	7%	1,362	7%	1,338	9%
Region								
Greater London	2,529	14%	319	18%	2,848	14%	2,184	15%
Yorkshire	1,501	8%	270	15%	1,771	9%	1,220	9%
West Midlands	1,747	9%	154	9%	1,901	9%	1,672	12%
South West	2,676	14%	75	4%	2,751	13%	1,348	9%
South East	1,746	9%	339	19%	2,085	10%	1,451	10%
North West	2,628	14%	281	16%	2,909	14%	2,550	18%
North East	1,264	7%	138	8%	1,402	7%	432	3%
Home Counties	1,095	6%	31	2%	1,126	6%	912	6%
East Midlands	1,485	8%	165	9%	1,650	8%	1,003	7%
East	1,922	10%	4	0%	1,926	9%	1,497	10%
Missing	11	0%	25	1%	36	0%	22	0%
Provider Volume								
High	11,423	62%	1,302	72%	12,725	62%	8,703	61%
Intermediate	6,653	36%	487	27%	7,140	35%	5,102	36%
Low	279	2%	9	1%	288	1%	191	1%
Very Low	36	0%	0	0%	36	0%	58	0%
Missing	213	1%	3	0%	216	1%	237	2%

* *NHS Year 2011/12 & 2017/18 not full year

468 **Table 2. Short-term costs of intervention, 30 days, 90 days and 365 days by surgical approach**

	Mean Cost in £ (SD)			Difference RH vs OH				Difference RH vs LH			
	RH (N =1353)	OH (N=12379)	LH (N=15666)	Unadjusted Difference (£)	P Value	AME (£) *	P Value	Unadjusted Difference (£)	P Value	AME (£) *	P Value
At Intervention	3329 (713)	3349 (1318)	3069 (676)	-20	<0.001	-197	<0.001	260	<0.001	108	<0.001
At 30 days	3334 (722)	3379 (1395)	3083 (721)	-45	<0.001	-220	<0.001	251	<0.001	98	<0.001
At 90 days	3357 (761)	3424 (1468)	3111 (826)	-67	<0.001	-241	<0.001	246	<0.001	89	<0.001
At 365 days	3417 (906)	3533 (1687)	3169 (984)	-116	<0.001	-273	<0.001	248	<0.001	94	<0.001

469 *AME adjusted for Year, Age, Socioeconomic Status (IMD Rank), Charlson Comorbidity, Ethnicity, Cancer Tx

470 Notes:

471 RH vs OH: We see that the average marginal effect is greater than the actual difference between RH and OH when we control for covariates

472 RH vs LH: We see the average marginal effect is less than the actual difference between RH and LH when we control for covariates

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Table 3. Mean Cost at intervention and 365 days by CCI/Age for each approach

	LH		RH		MIS		OH	
	N	Cost	N	Cost	N	Cost	N	Cost
Intervention								
Age Groups								
<50	860	£ 3,031.89	90	£ 3,283.71	950	£ 3,055.74	921	£ 3,313.62
50-59	3336	£ 3,024.86	293	£ 3,257.56	3629	£ 3,043.65	2687	£ 3,259.23
60-69	5522	£ 3,052.62	436	£ 3,356.87	5958	£ 3,074.89	4077	£ 3,283.08
70-79	4328	£ 3,101.11	398	£ 3,343.10	4726	£ 3,121.49	3255	£ 3,418.83
80-89	1533	£ 3,148.51	134	£ 3,385.03	1667	£ 3,167.52	1338	£ 3,546.07
90>	87	£ 3,214.70	<10	£ 3,453.50	89	£ 3,220.07	101	£ 3,855.14
CCI Groups								
0	21	£ 3,060.48	<10	£ 3,939.00	22	£ 3,100.41	12	£ 2,968.00
1	10526	£ 3,038.06	887	£ 3,319.27	11413	£ 3,059.92	7369	£ 3,246.57
2	4126	£ 3,125.58	377	£ 3,337.09	4503	£ 3,143.29	3875	£ 3,411.77
>=3	993	£ 3,166.00	88	£ 3,391.30	1081	£ 3,184.30	1123	£ 3,808.20
365 days								
Age Groups								
<50	860	£ 3,136.11	90	£ 3,286.98	950	£ 3,150.40	921	£ 3,614.82
50-59	3336	£ 3,111.41	293	£ 3,273.97	3629	£ 3,124.53	2687	£ 3,398.50
60-69	5522	£ 3,144.29	436	£ 3,475.53	5958	£ 3,168.53	4077	£ 3,448.76
70-79	4328	£ 3,219.07	398	£ 3,467.83	4726	£ 3,240.02	3255	£ 3,606.54
80-89	1533	£ 3,256.01	134	£ 3,476.81	1667	£ 3,273.76	1338	£ 3,776.23
90>	87	£ 3,252.47	<10	£ 3,453.50	89	£ 3,256.99	101	£ 4,174.64
CCI Groups								
0	21	£ 3,074.48	<10	£ 3,939.00	22	£ 3,113.77	12	£ 2,968.00
1	10526	£ 3,125.62	887	£ 3,358.03	11413	£ 3,143.68	7369	£ 3,389.67
2	4126	£ 3,248.94	377	£ 3,538.35	4503	£ 3,273.17	3875	£ 3,629.09
>=3	993	£ 3,299.13	88	£ 3,488.25	1081	£ 3,314.52	1123	£ 4,148.06

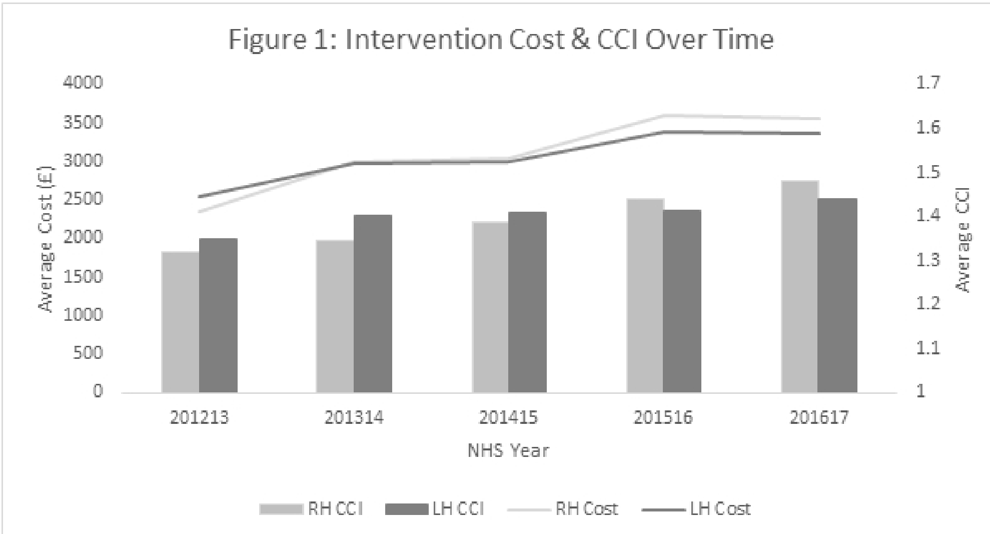

Figure 1: Intervention Cost & CCI Over Time
The average cost and CCI of RH & LH over time.
(CCI = Charlson Comorbidity Index, LH = laparoscopic hysterectomy, RH = robotic hysterectomy, NHS = National Health Service)

127x68mm (120 x 120 DPI)

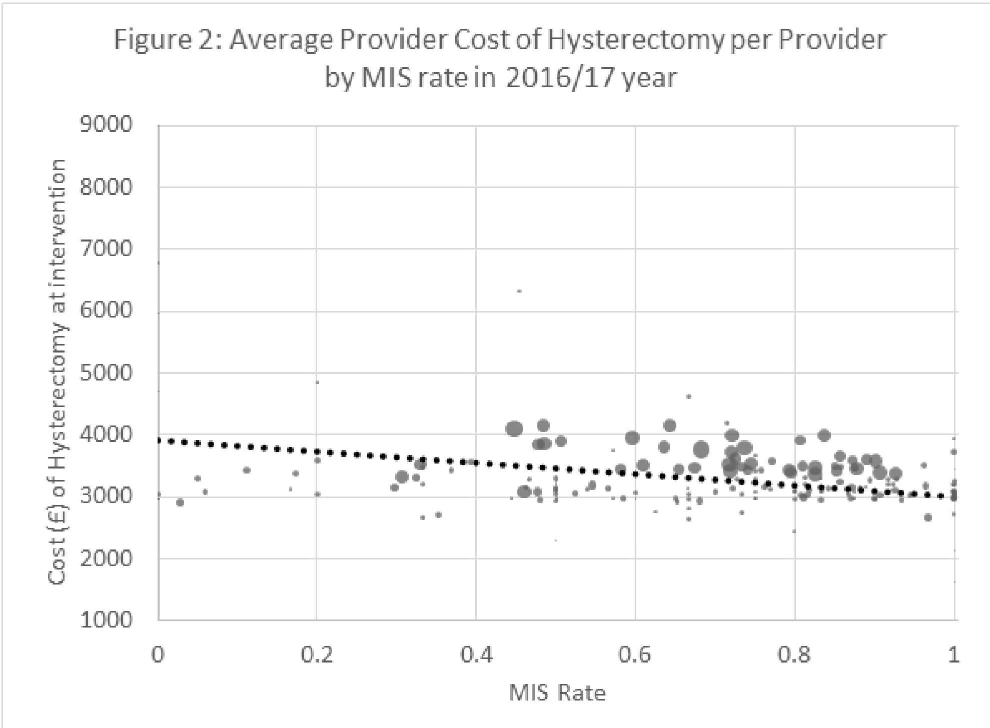

Figure 2: Average Provider Cost of Hysterectomy per Provider by MIS rate in 2016/17
The association between provider volume, MIS rate and surgical cost at intervention. Provider volume is represented by the size of the bubble with a larger bubble representing a higher provider volume.

127x93mm (120 x 120 DPI)

Appendix Tables:

Table A1- Cohort Selection ICD-10 & OPCS-4.7 Codes

Table A1: Cohort Selection

Category	ICD-10 / OPCS-4.7
Hysterectomies	Procedures with: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9, Q08.1, Q08.2, Q08.3, Q08.8, Q08.9
Endometrial/uterine carcinoma or endometrial carcinoma in situ	Patients must have as primary diagnosis: C540, C541, C542, C543, C548, C549, C55X, D070
Laparoscopic hysterectomy	Any procedures with one of: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9, Q08.1, Q08.2, Q08.3, Q08.8, Q08.9 And with one of: Y75.1, Y75.2, Y75.5, Y75.8, Y75.9, T43.9
Robotic hysterectomy	Any procedures with one of: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9, Q08.1, Q08.2, Q08.3, Q08.8, Q08.9 And with one of: Y75.3
Open hysterectomy	Any procedures with one of: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9 And without any: Y75.1, Y75.2, Y75.5, Y75.8, Y75.9, T43.9 Y75.3
Vaginal hysterectomy	Any procedures with one of: Q08.1, Q08.2, Q08.3, Q08.8, Q08.9 And without any: Y75.1, Y75.2, Y75.5, Y75.8, Y75.9, T43.9 Y75.3
Minimally Invasive Surgery	Any procedures with one of: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9, Q08.1, Q08.2, Q08.3, Q08.8, Q08.9 And with one of: Y75.1, Y75.2, Y75.5, Y75.8, Y75.9, T43.9, Y75.3

Table A2 – Other complications OPCS-4.7 codes assessed

Table A2: Complication classification[a]

Category	ICD-10 / OPCS-4.7
Gastrointestinal complications	A090 I898 K228 K250 K252 K254 K256 K260 K261 K262 K264 K265 K266 K270 K272 K274 K276 K280 K282 K284 K286 K290 K450 K560 K565 K566 K567 K625 K631 K638 K660 K720 K729 K85 K913 K918 K919 K92 S360 K61 N824
Wounds	D649 K603 K604 K605 K632 K829 K832 L89 T813 T815 T343 T453 T793
Infections	A40 A41 A49 B95 B96 K630 K65 L03 L04 N10 N12 N151 N159 N300 N309 N390 R788 T793 T802 T814 T816 T827 T836 T857
Uteric Injury Complication	N133 N139 N17 N19 N280 N312 N990 N991 N998 N999 R32 R33 S360 N12 N151 N159 N300 N309 N390 N360 S371 N131 N821
Haemorrhage	T810 S35 D65
Cardiovascular disorders	I21 I46 I48 I49 I50 I74 I80 I81 I82 I950 I952 I959 I978 I979 R57 T801 T811 T817 T827
Pulmonary complications	J80 J81 J90 J91 J93 J955 J958 J959 J960 J969 J981 R060 R09 I26 J100 J110 J12 J13 J14 J15 J16 J17 J18 J690 J85 J86
Neurological disorders	F05 F13 F15 F19 G45 G46 G569 G81 G82 G83 G931 G936 G970 G971 G978 G979 I63 I65
Other	T882 T790 T800 E15 E272 E86 E87 R798 T812 T818 T888 T792

[a] Adapted from Ma C, et al. Postoperative complications following colectomy for ulcerative colitis: A validation study. BMC Gastroenterol 2012; 12:39.

Table A3: Cancer Treatment OPCS 4.7 Codes excluded for cost analysis

Category	Specific Code	Sub Category
Chemotherapy	X70.1	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 1
	X70.2	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 2
	X70.3	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 3
	X70.4	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 4
	X70.5	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 5
	X70.8	Other specified procurement of drugs for chemotherapy for neoplasm in Bands 1-5
	X70.9	Unspecified procurement of drugs for chemotherapy for neoplasm in Bands 1-5
	X71.1	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 6
	X71.2	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 7
	X71.3	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 8
	X71.4	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 9
	X71.5	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 10
	X71.8	Other specified procurement of drugs for chemotherapy for neoplasm in Bands 6-10
	X71.9	Unspecified procurement of drugs for chemotherapy for neoplasm in Bands 6-10
	X72.1	Delivery of complex chemotherapy for neoplasm including prolonged infusional treatment at first attendance
	X72.2	Delivery of complex parenteral chemotherapy for neoplasm at first attendance
	X72.3	Delivery of simple parenteral chemotherapy for neoplasm at first attendance
	X72.4	Delivery of subsequent element of cycle of chemotherapy for neoplasm
	X72.8	Other specified delivery of chemotherapy for neoplasm
	X72.9	Unspecified delivery of chemotherapy for neoplasm
	X73.1	Delivery of exclusively oral chemotherapy for neoplasm
	X73.8	Other specified delivery of oral chemotherapy for neoplasm
	X73.9	Unspecified delivery of oral chemotherapy for neoplasm
	X74.1	Cancer hormonal treatment drugs Band 1
	X74.2	Cancer supportive drugs Band 1
	X74.8	Other specified other chemotherapy drugs
	X74.9	Unspecified other chemotherapy drugs
Radiotherapy	X65.1	Delivery of a fraction of total body irradiation
	X65.2	Delivery of a fraction of intracavitary radiotherapy
	X65.3	Delivery of a fraction of interstitial radiotherapy
	X65.4	Delivery of a fraction of external beam radiotherapy NEC
	X65.5	Oral delivery of radiotherapy for thyroid ablation
	X65.6	Delivery of a fraction of intraluminal brachytherapy
	X65.7	Delivery of radionuclide therapy NEC
	X65.8	Other specified radiotherapy delivery
	X65.9	Unspecified radiotherapy delivery
	X67.1	Preparation for intensity modulated radiation therapy
	X67.2	Preparation for total body irradiation
	X67.3	Preparation for hemi body irradiation
	X67.4	Preparation for simple radiotherapy with imaging and dosimetry
	X67.5	Preparation for simple radiotherapy with imaging and simple calculation
	X67.6	Preparation for superficial radiotherapy with simple calculation
	X67.7	Preparation for complex conformal radiotherapy
	X67.8	Other specified preparation for external beam radiotherapy

	X67.9	Unspecified preparation for external beam radiotherapy
	Y92.1	Technical support for preparation for radiotherapy
	Y92.2	Other specified support for preparation for radiotherapy
	Y92.3	Unspecified support for preparation for radiotherapy
Brachytherapy	X68.1	Preparation for intraluminal brachytherapy
	X68.2	Preparation for intracavitary brachytherapy
	X68.3	Preparation for interstitial brachytherapy
	X68.8	Other specified preparation for brachytherapy
	X68.9	Unspecified preparation for brachytherapy
	Y35.4	Introduction of radioactive substance into organ for brachytherapy NOC
	Y36.4	Introduction of non-removable radioactive substance into organ for brachytherapy NOC
	Y89.1	High dose rate brachytherapy treatment
	Y89.2	Pulsed dose rate brachytherapy treatment
	Y89.8	Other specified brachytherapy
	Y89.9	Unspecified brachytherapy

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Economic evaluation of different routes of surgery for the management of endometrial cancer: A retrospective cohort study.

[1]Moss EL (PhD), [2]Morgan G, [2]Martin A, [3]Sarhanis P (FRCOG), [4,5]Ind T (FRCOG)

[1]Leicester Cancer Research Centre, University of Leicester, Leicester, LE1 7RH

[2]HCD Economics

[3]North West London NHS Trust

[4]Royal Marsden Hospital

[5]St George's University of London, London, SW17 0RE

Corresponding Author

Dr Esther Moss

Leicester Cancer Research Centre, University of Leicester, Leicester, LE1 7RH, UK

Tel: +44 (0)116 252 3170

Fax: +44 116 258 8210

Email: em321@le.ac.uk

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ABSTRACT

Objectives: The benefits of minimally invasive surgery (MIS) for endometrial carcinoma (EC) are well established although the financial impact of robotic-assisted hysterectomy (RH) compared to laparoscopic hysterectomy (LH) is disputed.

Design: Retrospective cohort study.

Setting: English NHS hospitals 2011-2017/8.

Participants: 35,304 women having a hysterectomy for EC identified from Hospital Episode Statistics (HES).

Primary and secondary outcome measures: The primary outcome was the association between route of surgery on cost at intervention, 30, 90 and 365 days for women undergoing an open (OH) or MIS (LH/RH) for EC in England. The average marginal effect (AME) was calculated to compare RH vs OH/RH vs LH which adjusted for any differences in the characteristics of the surgical approaches. Secondary outcomes were to analyse costing data for each surgical approach by age, Charlson Comorbidity Index (CCI) and hospital MIS rate classification.

Results: A total of 35,304 procedures were performed, 20,405 (57.8%) were MIS (LH 18,604 and RH 1,801), 14,291 (40.5%) OH. Mean cost for LH was significantly less than RH, whereas RH was significantly less than OH at intervention, 30, 90 and 365 days ($p<0.001$). Overtime patients who underwent RH had increasing CCI scores and by the 2015/16 year had a higher average CCI than LH. Comparing the cost of LH and RH against CCI score identified that the costs closely reflected the patients' CCI. Increasing disparity was also seen between the MIS and OH costs with rising age. When exploring the association between provider volume, MIS rate and surgical costs there was an association with the higher the MIS rate the lower the average cost.

Conclusions: Further research is needed to investigate costs in matched populations to determine optimum surgical modality in different populations.

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Key words: Endometrial cancer; minimally invasive surgery; laparoscopic hysterectomy; open hysterectomy; robotic-assisted hysterectomy; patient stratification; healthcare economy

Tweetable abstract: Analysis of financial cost of laparoscopic, robotic and open hysterectomy for the treatment of endometrial cancer in England.

Strengths and limitations

- The findings from the study are based on a population-based database which is a key strength as it is representative of all procedures via the NHS in England.
- The reliability of the coding might have changed over time although there was no evidence of changes in treatment coding or significant changes in the underlying study population.
- HES database reliably captures extensive amount of demographic, diagnosis and procedure outcomes however there is a lack of cancer stage information therefore it is not possible to split out the cost outcomes into more specific groups of patients.
- The capital and maintenance costs of RH have also not been included since these costs vary dramatically across different healthcare settings and often utilised by a wide group of specialities in a hospital setting.
- As the analysis was undertaken over a number of years of the HES database, we were able to accurately follow hospital activity for at least a year after intervention.

INTRODUCTION

The introduction of minimally invasive surgery (MIS) for endometrial cancer (EC) has had a dramatic impact on patients' surgical outcomes with reduced morbidity, hospital stay and improved short-term quality of life[1]. Translating these patient benefits into cost benefits to the healthcare economy has been challenging because although MIS requires significantly less bed days than open surgery, it does require more costly consumable equipment, for example single-use vessel sealing devices. This has been demonstrated in several studies including the multi-centre randomised LACE trial where the surgery costs were greater for laparoscopic hysterectomy (LH) compared to open hysterectomy (OH), but the overall costs of treatment were lower[2].

MIS is the preferred surgical route for EC[3]. RH is accepted as an alternative to LH, supported by evidence from a randomised controlled trial[4] and RH has been shown to have a lower conversion rate to laparotomy and shorter operating time[5–7]. Wide spread adoption of RH is limited in England, although the number of EC cases having RH is increasing year on year[8]. In light of the capital and consumable costs of RH, as compared to OH or LH, the use of RH in EC is therefore being called into question[6]. Reports from institutions with well-established robotic programmes however have contested this view with no significant difference[9], or cost improvements reported as compared to LH[10]. What is clear is that focusing solely on in-hospital costs does not give the full picture of the economic costs of a surgical procedure, since many costs are accrued following discharge or attributed to the economy as a whole as a result of delayed return to employment.

We therefore investigated the HES data for England in order to look at the financial impact of RH as compared to LH and OH. We also investigated the patient characteristics that contributed

to cost and examined the top 5% of procedures to identify factors that may have contributed to the costs.

METHODS

Data Source and cohort selection

Data was sourced from the Hospital Episode Statistics (HES) database from 2011-2017/8[11]. HES database captures demographic, diagnosis and procedure outcomes data however does not include cancer stage or histology information. No ethical approval was required for this study. Patients or the public were not involved in the design, or conduct, or reporting of our research. The inclusion criteria for patients was a diagnosis of endometrial cancer (EC) or endometrial cancer in situ/complex atypical hyperplasia (ECIS) undergoing a hysterectomy between October 2011 to December 2017. The surgical approach was classified by intention-to-treat as open hysterectomy (OH), vaginal hysterectomy (VH), laparoscopic hysterectomy (LH), robotic hysterectomy (RH) and minimally invasive surgery (MIS) which was the combination of LH and RH. Due to the low numbers the VH cases were not included in any of the subsequent analyses. The cohort selection for the study has been described in more detail previously[8] and the list of specific diagnosis (ICD-10) and procedure (OPCS-4.7) codes can be found in the Appendix Table A1.

Patient Characteristics

Demographic data was captured in the hospital admission data for each patient and included age, ethnicity, postcode, comorbidities. Patient age was divided by 10-year intervals from the age of 50 into six groups. Ethnicity was classified into Asian, Black, Other and White. Based on postcode of residence, each patient who received EC surgery was mapped to the English Index of Multiple Deprivation rank. The IMD indicates the socioeconomic deprivation of patients which combines seven indicators (income, employment, health deprivation and disability, education, skills and training, barriers to housing and services, crime, and living environment), into a single deprivation index where a higher rank indicated a less deprived group and a lower rank indicated a more deprived group[12]. The Index of Multiple Deprivation (IMD) was split into statistical quartiles and indicated whether the sociodemographic status was high (>25083), intermediate (17475-25083), low (9618-17474) or very low (<9618) for each patient. Comorbidities were examined 12 months prior to intervention using the Charlson Comorbidity Index (CCI)[13], an additional list of other co-morbidities were also assessed using specific ICD-10 codes (Appendix Table A2).

Hospital characteristics were assessed by region (East, East Midlands, Greater London, Home Counties, North East, North West, South East, South West, West Midlands, Yorkshire) and volume, which was based on the annual mean of hysterectomies performed for EC/ECIS grouped by statistical quartiles (High (>220), Intermediate (71-220), Low (70-21) and Very Low (0-20)). MIS rates of hospitals for EC/ECIS hysterectomy procedures were classified into four groups based on percentage of hysterectomies performed by MIS approach (High (76-100%), Intermediate (51-75%), Low (26-50%) and Very Low (0-25%)).

Outcomes

For each patient episode, in the HES database, a cost is assigned based on the health resource group (HRG) which is diagnosis/procedure-based grouping and the length of stay. These costs are based on reference costs provided by each hospitals and are estimated based upon recorded inpatient, outpatient, and A&E episode activity in the HES database using NHS Payment by Results Health Resource Group (HRG) tariffs[14]. Costs at intervention and short-term costs were calculated based upon the reported hospital admission costs over the time period of 30-, 90- and 365-days following intervention, these were all summarised by procedure approach. Further to this, the cost of each approach was assessed by the subgroups of age, CCI groups

161 and MIS rate classification. A list of non-surgical cancer related treatments was collated (See Appendix Table A3 for specific OPCS-4.7 procedure codes) and these costs were excluded in the analysis. Peri-operative outcomes included mortality, conversion to open hysterectomy and length of stay. The 90-day outcomes included the mortality, total and specific inpatient, outpatient and emergency readmissions. Subgroup analyses were performed, firstly to assess high cost (top 5% of costs at intervention by approach) and low-cost patients (lowest 50% of costs at intervention by approach) in the cohort to assess what was driving high costs patients. In addition, provider level analysis was conducted to assess hospital characteristics and costs to further understand the impact of differing MIS rates and volume sizes.

170 ***Statistical Analyses***

171 A descriptive analysis of patient characteristics and data on costs and other health resource was performed. The different approaches (LH, RH, OH, MIS) were then compared by using t-test (for independent samples) and Wilcoxon rank-sum test (Mann-Whitney U test) for continuous variable and for categorical variables by using the chi-squared tests. The average marginal effect (AME)[15] was used to compare RH vs OH and RH vs LH on costing outcomes at intervention, 30 days, 90 days and 365 days. This approach adjusted for patient age, ethnicity, IMD rank, Charlson Comorbidity Index, year of procedure and whether a patient received cancer treatment following the intervention (for further details see Appendix Table A3) by fitting Generalised Linear Models (GLMS). The Modified Park Test & Pregibon's Link Test[16] were used to ensure the most efficient model structure was used to model the costs. All statistical analyses were performed using Stata 15®.

182 ***Patient and Public Involvement***

183 There was no patient or public involvement in the study planning or design.

184

RESULTS

A total of 35,304 procedures were performed, 18,604 (52.7%) LH, 1,801 (5.1%) RH, 14,291 (40.5%) OH and 608 (1.7%) VH. The proportion of MIS cases increased significantly overtime each year from 46.6% in 2012/13 to 68.7% in 2016/17 (p<0.001). This was primarily due to an increase in LH of 15.8% (44.7% to 60.5%), but there was also a 6.2% increase (2.0% to 8.2%) in the number of RH performed when comparing 2012/13 to 2016/17 as a proportion of all surgeries performed each year. Consequently, the number of OH cases decreased significantly overtime (p<0.001) from 53.4% in 2012/13 to 31.3% in 2016/17 of cases in that year.

Table 1 presents the patient characteristics of the surgical approaches LH, RH and OH. Most cases were performed at high volume providers (>220 cases/year) with 72.4% for RH, 62.1% for LH and 60.9% for OH being undertaken at these providers (Table 1). As previously described, there was a significant difference in the social/racial characteristics of the patients undergoing MIS as compared to OH within this cohort of patients[8]. The characteristics of the RH population differed to patients undergoing LH; with a significantly higher percentage of RH patients having any co-morbidity from our defined list than LH (68.2% vs 64.0%, p<0.001), more specifically the comorbidities of diabetes, hypertension and obesity all being higher proportion in RH cohort than LH cohort.

Short-term costs by approach

The short-term costs of intervention, 30 days, 90 days and 365 days by surgical approach are presented in Table 2. LH was associated with the lowest mean cost at the intervention (£3069), 30 (£3083), 90 (£3111) and 365 (£3169) days following the procedure. The mean cost for RH was significantly less than OH at all the time points (p<0.001 for all). The average marginal effect (AME) for RH versus OH, controlling for patient characteristics, also showed a significant difference for RH over OH with the difference in cost increasing when comparing the unadjusted and AME value (p<0.001 for all). Comparing RH and LH short-term costs, LH costs were significantly lower for the unadjusted and AME differences (p<0.001 for all). The AME differences in cost between RH and LH were lower compared to the unadjusted differences (e.g., AME difference of £108 vs. unadjusted difference of £260 at intervention.

High-Cost and Low-Cost Patient Comparison

Assessing the top 5% highest cost (HC) patients of each approach (LH: n=336; OH: n=593, RH: n=27) and comparing to the low-cost (LC) cohort, which was set at less than or equal to the median cost of the surgery (LH: n=12,913; OH: n=9,021, RH: n=812). The patients in the HC group were significantly older in all the routes of surgery (LH: 69.0 vs 65.7 years, OH: 68.8 vs 65.1 years, RH: 67.5 vs 65.5 years: p<0.001 for all). The HC cohort contained a higher percentage of patients from the lower socioeconomic groups (IMD Rank: 16637 vs 17287, p<0.001) and patients of non-white ethnicity (29.6% vs 19.2%, p<0.001) as compared to the LC cohort. Patients in the HC cohort also had significantly greater number of co-morbidities compared to the LC cohort (CCI 1.82 vs 1.41 and any comorbidity 71.0% versus 63.9% p<0.001 for all). The length of hospital stay was significantly longer in the HC cases compared to the LC group (RH: 11.22 vs 1.84 days; LH: 11.42 vs 2.03 days; OH: 20.82 vs 3.71days; p<0.001 for all). Although the rate of complications was greater in the HC compared to the LC cohort (RH: 55.6% vs 14.0%; LH: 61.0% vs 16.2%; OH: 71.5% vs 19.1%; p<0.001 for all), the rate was significantly lower with RH as compared to OH in both the HC and LC groups (HC: 55.6% vs 71.5%, p= 0.075; LC: 14.0% vs 19.1%, p<0.001).

Patient Characteristics and Costs

Patient characteristics, age and CCI, were associated with increasing costs for almost all routes of surgery at intervention, and 365 days following the procedure (Table 3). Assessing the age categories showed the costs at intervention were very similar for the <50 years, 50-59 years and 60-69 years groups but gradually increased for each of the higher age groups. There was an increasing difference between the MIS and OH costs with rising age with the difference between MIS and OH for Age <50 being £258 increasing to a difference of £653 for Age >90 years population. RH 365-day costs were significantly lower (p<0.01) than OH in all age categories except 60-69 & 90> years. Comparing CCI showed that CCI group >=3 was associated with the greatest difference in costs with the difference at 365 days between CCI group 1 and CCI group >3= being £130 for RH, £174 for LH and £759 for OH (Table 3).

Overtime patients who underwent RH had increasing levels of co-morbidities, when using the CCI score, and have in recent years had a higher average CCI than LH in 2015/16-2016/17 (Figure 1). Comparing the cost of LH and RH against CCI score, identified that the costs closely reflected the patients' CCI. In 2012/13 when the RH population had a lower CCI then the costs were less, however, since 2014/15 the patient population undergoing RH higher CCI score and this was associated with a rise in the costs of RH above that of LH (Figure 1).

Hospital Characteristics and Costs

When exploring the association between provider volume, MIS rate and surgical costs there was an association with the MIS rate and cost, i.e. the greater the MIS rate the lower the cost (Figure 2). Many of the highest volume providers had higher average costs than providers with less volume, however the patient population undergoing surgery at the high volume providers were significantly older and had a higher CCI compared to the lower volume providers (Age: 66.2 vs 65.6 years, p<0.001; CCI: 1.47 vs 1.43, p<0.001). The majority of the highest volume providers had MIS rates between 50% to 90% and the relationship held for high volume providers with average costs decreasing as MIS rates increased for the year 2016/17.

DISCUSSION

Main findings

In this study, we have performed an in-depth analysis of real-world data and have identified financial benefits for MIS as compared to OH for EC. We have demonstrated that LH has the lowest mean cost at intervention and that costs increased with increasing patient age. In keeping with other studies, we have also shown that OH, although attracting the lowest operative consumable costs, had the greatest overall financial cost, even significantly higher than RH. We have also identified that although the cost of RH is greater than LH, patients undergoing RH have different characteristics compared to women having LH in recent years, and that cost of surgery appears to be influenced by level of patients' co-morbidities and not the route of surgery alone.

There will always be a proportion of cases that have to be performed OH due to contra-indications/complications with MIS, which will inevitably attract higher costs due to their complexity, but this can be reduced to low levels[17]. The significantly higher complication/re-admission rate with OH have been reported previously[8] and in this study we have shown that even in the HC groups, the complication rate was higher with OH (71.5%) as compared to RH (55.6%) and LH (61.0%). A longer recovery time may impact on patient and employment costs, with greater loss of earnings and longer return to work or contribution to society activities as compared to MIS. Korsholm et al.[18], reported no significant difference in return to the labour market or use of sickness benefits in a study from Denmark however, in their study robotic surgery was associated with greater cost than both laparoscopic and open hysterectomy, unlike this UK analysis. Allowing for a number of OH cases, the disparity in MIS uptake across England[8] does indicate that there is room for improvement in increasing the proportion of MIS cases and thereby benefitting both the patient and the healthcare economy.

The primary argument used against the widespread use of RH, rather than LH, for EC is an economic one[6,19], since the clinical outcomes are reported to be comparable although, there is a lack of randomised control trial data, particular in patients with a high BMI[20]. The HES data does confirm a cost advantage for LH over RH however, the two patient populations are not directly comparable since there is a significant difference in the CCIs between the groups. During 2012/13, when RH was only performed in a few selected centres, the majority of UK robotic surgeons would still have been within the learning phase, and therefore likely to select patients with less co-morbidities for RH. We have shown that during this time period the cost of RH was less than LH. Increasing robotics experience appears to have led to the positive selection of co-morbid patients, especially obesity, for RH, and this is associated with rising costs. Class III obesity and a rising number of patient co-morbidities are reported to attract increased inpatient care costs due to increased medical rather than surgical complications associated with undergoing surgery[21,22]. The selection of patients with a high-BMI for RH is not unexpected given the reported ergonomic benefits for surgeons as compared to straight-stick laparoscopy[23], with less movements and muscle activity required to perform tasks[24]. RH is not without issues due to the fixed console position[25], however more extreme muscle movements are required for laparoscopic procedures increase with rising BMI[24], which is not reported with robotics. The cost to the healthcare service of work-related musculoskeletal symptoms in surgeons is of growing concern[26] and not considered in economic analyses such as this study, however it is an additional cost that needs to be considered when calculating service delivery costs.

What is clear from the data is that OH is the most costly route of surgery, a finding reported in other healthcare settings[27], not only in financial terms but more importantly for patient complications and post-operative mortality[8]. The key focus therefore, rather than being between LH or RH, should instead be on reducing the OH rate to a minimum. Although there are only a few absolute contra-indications for OH, the number of cases that are performed through open surgery is still high in some institutions and there has been much discussion how this could be reduced through greater surgical training[28] or centralisation of cases to hospitals and surgeons with high MIS rates[29]. A reduction in OH can also be achieved through reducing the number of conversions from LH/RH to a minimum. A meta-analysis of observational studies did show that the conversion rate of LH increased with BMI >40kg/m^2 more than for RH, 6.5% (95% CI 4.3-9.9) versus 5.5% (95% CI 3.3-9.1), as compared to >30kg/m^2, 7.0% (95% CI 3.2-14.5) versus 3.8% (95% CI 1.4-99) respectively[20]. One reason for this may be the lower intra-abdominal insufflation pressure used with RH, typically 8mmHg, which has been shown to be associated with lower post-operative pain and shorter hospital stay as compared to a pressure 15mmHg[30]. Inability to tolerate Trendelenburg position was also reported to be the indication for 31% of LH conversions but only 6% of RH conversions[20]. This therefore raises the possibility as to whether cases should be selected for RH where there is high risk of conversion due to Class III obesity or inability tolerate the pneumoperitoneum. Further research is needed to compare the clinical outcomes and costs of LH and RH in matched populations, for example BMI >40kg/m^2 or previous abdominal surgery, to investigate whether differences reported in retrospective case series are confirmed. Such trials would determine whether certain patient characteristics could be used to personalise the route of surgery in order to maximise the potential benefit from MIS and reduce the rate of OH. Prospective randomised controlled trials (RCT) are the gold standard study design however can be challenging to perform and may be subject to many biases, including patient selection, if a surgeon has a greater preference for one surgical modality over another. Also, RCTs can take many years to complete accrual, for example LACC[31], by which time the current robotic/laparoscopic platforms may be obsolete. Instead, the use of real-world data in a propensity score matching study may enable matching of key patient characteristics to give results in a more timely manner[32].

Strengths and limitations

The key strength of the study is in the number of patients in which can be analysed by using the HES database. This gives strength to the study’s findings as it is representative of all

332 procedures via the NHS in England. Due to RH being a newer surgery approach the number of
333 patients is much lower compared to the other surgery approaches. In addition, we must consider
334 the impact of a learning curve of RH and that in the earlier years it may not been used to full
335 efficiency. As we had a number of years of the HES database we could analyse any potential
336 trends across surgical approaches and the year.

337 As we have previously described[8], HES data does have limitations, primarily it only covers
338 NHS-funded care, the reliability of coding and lacks oncological details of stage/histology.
339 There will be a proportion of patients with advanced disease that require open surgery due to
340 requiring a more extensive cytoreductive procedure and HES data is not able to differentiate
341 these cases from early stage disease that is being treated through open surgery. The analysis
342 comparing LH and RH should however not be impacted by stage of disease. In addition, there
343 are limitations with the HES data with the recording of magnitude of patient co-morbidities, in
344 particular obesity since a numerical value for BMI is not included and therefore the obesity
345 classification could be applied to any patient with a BMI >30kg/m^2.

346 The capital and maintenance costs of RH have also not been included since these costs vary
347 dramatically across different healthcare settings and there would be a need to also included
348 similar costs for laparoscopic and open surgery. In addition, the robotic surgery equipment is
349 often utilised by a wide group of specialities in a hospital setting and it would be infeasible to
350 apply capital and maintenance costs to one surgery modality[15].

351 ***Interpretation***

352 In conclusion, LH was associated with the lowest and OH the greatest mean cost per procedure.
353 Patient factors have an impact on the cost of MIS procedures and further research is needed to
354 compare the costs in matched populations of women undergoing LH and RH, since there
355 appears to be selection bias in the choice of procedure being performed.

Ethical approval: The HES database is managed by the NHS Digital and is available for research without ethical approval.

All the authors consent to publication

Data availability: Data analysed in this study is available through Hospital Episode Statistics (HES)

Conflicts of Interest: EM and TI perform Da'Vinci robotic gynaecological surgery (Intuitive Surgical) and are members of the British and Irish Association of Robotic Surgeons (BIARGS), which is supported by Intuitive Surgical and other robotics/laparoscopic companies to hold education/training events. EM has been awarded research grants from Intuitive Surgical and Hope Against Cancer for unrelated studies, serves on advisory boards for Inivata and GlaxoSmithKline and has received speaker fees from GlaxoSmithKline. TI has done two days paid consultancy work for Medtronic. GM and AM from HCD Economics were funded by Intuitive Surgical. None of the clinicians (EM, PS, TI) received funding from Intuitive Surgical for this study. Intuitive Surgical did not have any involvement with the study design, data analysis and writing of the manuscript. The authors declare no other potential conflict of interest.

Contributors: EM, TI, GM and AM contributed to the conceptualisation and study design. Data analysis and interpretation was performed by EM, TI, GM, AM and PS. Figures and tables creation was performed by EM, GM and AM. All authors were involved in the writing or review of the manuscript and approved the final version.

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Figure 1: Intervention Cost & CCI Over Time

The average cost and CCI of RH & LH over time.

(CCI = Charlson Comorbidity Index, LH = laparoscopic hysterectomy, RH = robotic hysterectomy, NHS = National Health Service)

Figure 2: Average Provider Cost of Hysterectomy per Provider by MIS rate in 2016/17

The association between provider volume, MIS rate and surgical cost at intervention. Provider volume is represented by the size of the bubble with a larger bubble representing a higher provider volume.

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Table 1. Clinical and Demographic Characteristics by the cohorts of hysterectomy approach

	Unadjusted Results							
	Laparoscopic Hysterectomy (N=18604)		Robotic Hysterectomy (N=1801)		MIS Hysterectomy (N=20405)		Open Hysterectomy (N=14291)	
Characteristics	No.	(%)	No.	(%)	No.	(%)	No.	(%)
NHS Year of surgery								
2011/12*	1,108	6%	19	1%	1,127	6%	1,671	12%
2012/13	2,367	13%	104	6%	2,471	12%	2,829	20%
2013/14	2,824	15%	147	8%	2,971	15%	2,614	18%
2014/15	3,134	17%	253	14%	3,387	17%	2,361	17%
2015/16	3,118	17%	382	21%	3,500	17%	1,948	14%
2016/17	3,577	19%	483	27%	4,060	20%	1,852	13%
2017/18*	2,476	13%	413	23%	2,889	14%	1,016	7%
Age, years								
<50	1,033	6%	120	7%	1,153	6%	1,082	8%
50-59	3,937	21%	380	21%	4,317	21%	3,098	22%
60-69	6,522	35%	589	33%	7,111	35%	4,672	33%
70-79	5,160	28%	533	30%	5,693	28%	3,779	26%
80-89	1,846	10%	174	10%	2,020	10%	1,540	11%
90>	106	1%	5	0%	111	1%	120	1%
Ethnicity								
White	15,033	81%	1,420	79%	16453	81%	11117	78%
Asian	583	3%	66	4%	649	3%	499	3%
Black	231	1%	20	1%	251	1%	365	3%
Other	2,757	15%	295	16%	3052	15%	2310	16%
Socio-Economic Group (IMD)								

High	4,506	25%	643	37%	5,149	25%	3,291	23%
Intermediate	4,612	25%	403	23%	5,015	25%	3,387	24%
Low	4,548	25%	376	21%	4,924	24%	3,489	24%
Very Low	4,435	25%	333	19%	4,768	23%	3,703	26%
Charlson Comorbidity Group								
0	22	0%	1	0%	23	0%	13	0%
1	12,432	67%	1,159	64%	13,591	67%	8,405	59%
2	4,915	26%	514	29%	5,429	27%	4,535	32%
>=3	1,235	7%	127	7%	1,362	7%	1,338	9%
Region								
Greater London	2,529	14%	319	18%	2,848	14%	2,184	15%
Yorkshire	1,501	8%	270	15%	1,771	9%	1,220	9%
West Midlands	1,747	9%	154	9%	1,901	9%	1,672	12%
South West	2,676	14%	75	4%	2,751	13%	1,348	9%
South East	1,746	9%	339	19%	2,085	10%	1,451	10%
North West	2,628	14%	281	16%	2,909	14%	2,550	18%
North East	1,264	7%	138	8%	1,402	7%	432	3%
Home Counties	1,095	6%	31	2%	1,126	6%	912	6%
East Midlands	1,485	8%	165	9%	1,650	8%	1,003	7%
East	1,922	10%	4	0%	1,926	9%	1,497	10%
Missing	11	0%	25	1%	36	0%	22	0%
Provider Volume								
High	11,423	62%	1,302	72%	12,725	62%	8,703	61%
Intermediate	6,653	36%	487	27%	7,140	35%	5,102	36%
Low	279	2%	9	1%	288	1%	191	1%
Very Low	36	0%	0	0%	36	0%	58	0%
Missing	213	1%	3	0%	216	1%	237	2%

**NHS Year 2011/12 & 2017/18 not full year

510 **Table 2. Short-term costs of intervention, 30 days, 90 days and 365 days by surgical approach**

	Mean Cost in £ (SD)			Difference RH vs OH				Difference RH vs LH			
	RH (N =1353)	OH (N=12379)	LH (N=15666)	Unadjusted Difference (£)	P Value	AME (£) *	P Value	Unadjusted Difference (£)	P Value	AME (£) *	P Value
At Intervention	3329 (713)	3349 (1318)	3069 (676)	-20	<0.001	-197	<0.001	260	<0.001	108	<0.001
At 30 days	3334 (722)	3379 (1395)	3083 (721)	-45	<0.001	-220	<0.001	251	<0.001	98	<0.001
At 90 days	3357 (761)	3424 (1468)	3111 (826)	-67	<0.001	-241	<0.001	246	<0.001	89	<0.001
At 365 days	3417 (906)	3533 (1687)	3169 (984)	-116	<0.001	-273	<0.001	248	<0.001	94	<0.001

511 *AME adjusted for Year, Age, Socioeconomic Status (IMD Rank), Charlson Comorbidity, Ethnicity, Cancer Tx

512 Notes:

513 RH vs OH: We see that the average marginal effect is greater than the actual difference between RH and OH when we control for covariates

514 RH vs LH: We see the average marginal effect is less than the actual difference between RH and LH when we control for covariates

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Table 3. Mean Cost at intervention and 365 days by CCI/Age for each approach

	LH			RH			MIS			OH	
	N	Mean (SD)	P-Value*	N	Mean (SD)	P-Value*	N	Mean (SD)	P-Value*	N	Mean (SD)
Age Groups (Costs at Intervention)											
<50	860	£3032 (616)	<0.001	90	£3284 (942)	0.783	950	£3056 (657)	<0.001	921	£3314 (1325)
50-59	3336	£3025 (558)	<0.001	293	£3258 (593)	0.967	3629	£3044 (565)	<0.001	2687	£3259 (1033)
60-69	5522	£3053 (657)	<0.001	436	£3357 (819)	0.089	5958	£3075 (675)	<0.001	4077	£3283 (1173)
70-79	4328	£3101 (732)	<0.001	398	£3343 (600)	0.052	4726	£3121 (725)	<0.001	3255	£3419 (1406)
80-89	1533	£3149 (777)	<0.001	134	£3385 (716)	0.041	1667	£3168 (774)	<0.001	1338	£3546 (1782)
90>	87	£3215 (1311)	0.023	<10	£3454 (687)	0.461	89	£3220 (1298)	0.023	101	£3855 (2425)
CCI Groups (Costs at Intervention)											
0	21	£3060 (292)	0.156	<10	£3939 (0)	-	22	£3100 (341)	0.078	12	£2968 (0)
1	10526	£3038 (616)	<0.001	887	£3319 (763)	0.010	11413	£3060 (633)	<0.001	7369	£3247 (994)
2	4126	£3126 (777)	<0.001	377	£3337 (607)	0.051	4503	£3143 (767)	<0.001	3875	£3412 (1375)
>=3	993	£3166 (806)	<0.001	88	£3391 (614)	<0.001	1081	£3184 (794)	<0.001	1123	£3808 (2421)
Age Groups (Costs at 365 days)											
<50	860	£3136 (900)	<0.001	90	£3287 (945)	0.005	950	£3150 (905)	<0.001	921	£3615 (1821)
50-59	3336	£3111 (903)	<0.001	293	£3274 (612)	0.005	3629	£3125 (884)	<0.001	2687	£3399 (1373)
60-69	5522	£3144 (922)	<0.001	436	£3476 (1091)	0.638	5958	£3169 (940)	<0.001	4077	£3449 (1503)
70-79	4328	£3219 (1103)	<0.001	398	£3468 (836)	0.008	4726	£3240 (1086)	<0.001	3255	£3607 (1806)
80-89	1533	£3256 (1017)	<0.001	134	£3477 (925)	0.003	1667	£3274 (1011)	<0.001	1338	£3776 (2169)
90>	87	£3252 (1350)	0.003	<10	£3454 (687)	0.200	89	£3257 (1337)	0.003	101	£4175 (2774)
CCI Groups (Costs at 365 days)											
0	21	£3074 (294)	0.106	<10	£3939 (0)	-	22	£3114 (341)	0.054	12	£2968 (0)
1	10526	£3126 (891)	<0.001	887	£3358 (827)	0.323	11413	£3144 (888)	<0.001	7369	£3390 (1368)
2	4126	£3249 (1160)	<0.001	377	£3538 (1088)	0.148	4503	£3273 (1157)	<0.001	3875	£3629 (1745)
>=3	993	£3299 (1097)	<0.001	88	£3488 (747)	<0.001	1081	£3315 (1073)	<0.001	1123	£4148 (2832)

*Significance test were carried out against the OH category within each age/CCI group for the approaches LH, RH and MIS

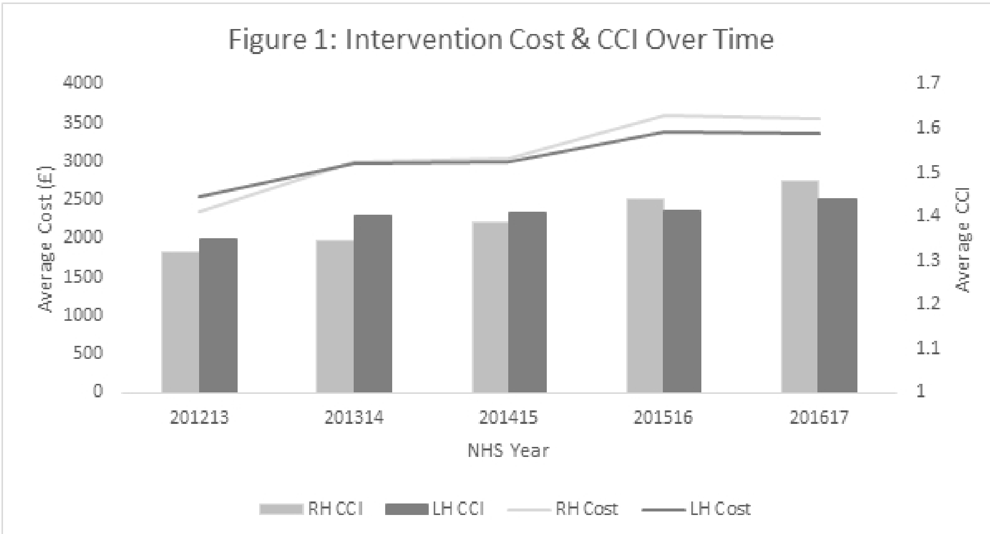

Figure 1: Intervention Cost & CCI Over Time
The average cost and CCI of RH & LH over time.
(CCI = Charlson Comorbidity Index, LH = laparoscopic hysterectomy, RH = robotic hysterectomy, NHS = National Health Service)

127x68mm (120 x 120 DPI)

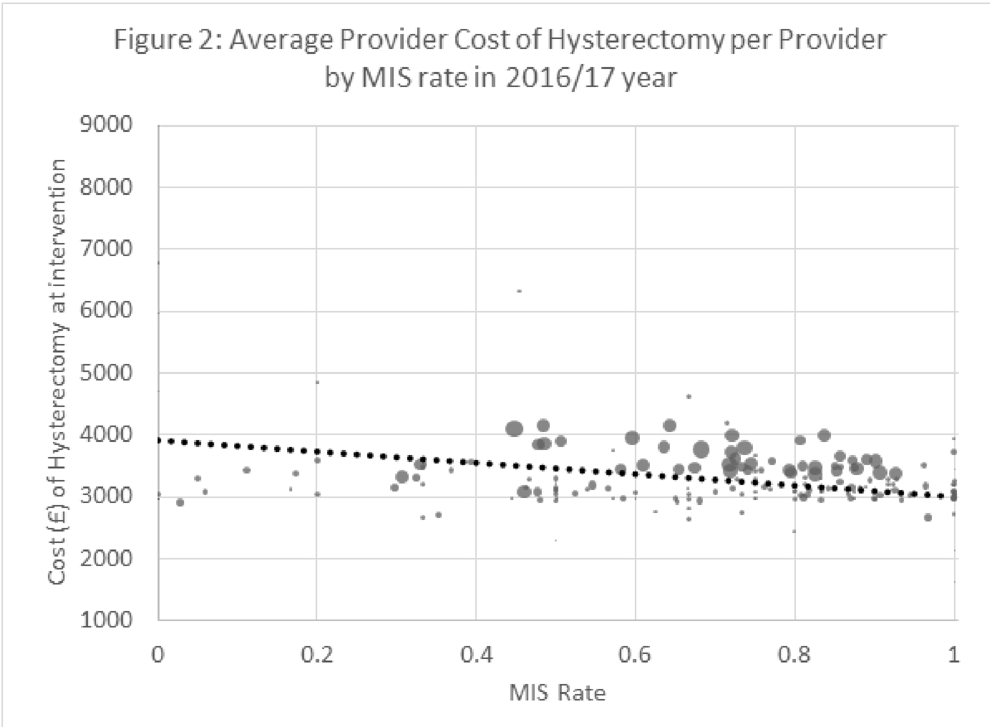

Figure 2: Average Provider Cost of Hysterectomy per Provider by MIS rate in 2016/17
The association between provider volume, MIS rate and surgical cost at intervention. Provider volume is represented by the size of the bubble with a larger bubble representing a higher provider volume.

127x93mm (120 x 120 DPI)

Appendix Tables:

Table A1- Cohort Selection ICD-10 & OPCS-4.7 Codes

Table A1: Cohort Selection

Category	ICD-10 / OPCS-4.7
Hysterectomies	Procedures with: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9, Q08.1, Q08.2, Q08.3, Q08.8, Q08.9
Endometrial/uterine carcinoma or endometrial carcinoma in situ	Patients must have as primary diagnosis: C540, C541, C542, C543, C548, C549, C55X, D070
Laparoscopic hysterectomy	Any procedures with one of: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9, Q08.1, Q08.2, Q08.3, Q08.8, Q08.9 And with one of: Y75.1, Y75.2, Y75.5, Y75.8, Y75.9, T43.9
Robotic hysterectomy	Any procedures with one of: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9, Q08.1, Q08.2, Q08.3, Q08.8, Q08.9 And with one of: Y75.3
Open hysterectomy	Any procedures with one of: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9 And without any: Y75.1, Y75.2, Y75.5, Y75.8, Y75.9, T43.9 Y75.3
Vaginal hysterectomy	Any procedures with one of: Q08.1, Q08.2, Q08.3, Q08.8, Q08.9 And without any: Y75.1, Y75.2, Y75.5, Y75.8, Y75.9, T43.9 Y75.3
Minimally Invasive Surgery	Any procedures with one of: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9, Q08.1, Q08.2, Q08.3, Q08.8, Q08.9 And with one of: Y75.1, Y75.2, Y75.5, Y75.8, Y75.9, T43.9, Y75.3

Table A2 – Other complications OPCS-4.7 codes assessed

Table A2: Complication classification[a]

Category	ICD-10 / OPCS-4.7
Gastrointestinal complications	A090 I898 K228 K250 K252 K254 K256 K260 K261 K262 K264 K265 K266 K270 K272 K274 K276 K280 K282 K284 K286 K290 K450 K560 K565 K566 K567 K625 K631 K638 K660 K720 K729 K85 K913 K918 K919 K92 S360 K61 N824
Wounds	D649 K603 K604 K605 K632 K829 K832 L89 T813 T815 T343 T453 T793
Infections	A40 A41 A49 B95 B96 K630 K65 L03 L04 N10 N12 N151 N159 N300 N309 N390 R788 T793 T802 T814 T816 T827 T836 T857
Uteric Injury Complication	N133 N139 N17 N19 N280 N312 N990 N991 N998 N999 R32 R33 S360 N12 N151 N159 N300 N309 N390 N360 S371 N131 N821
Haemorrhage	T810 S35 D65
Cardiovascular disorders	I21 I46 I48 I49 I50 I74 I80 I81 I82 I950 I952 I959 I978 I979 R57 T801 T811 T817 T827
Pulmonary complications	J80 J81 J90 J91 J93 J955 J958 J959 J960 J969 J981 R060 R09 I26 J100 J110 J12 J13 J14 J15 J16 J17 J18 J690 J85 J86
Neurological disorders	F05 F13 F15 F19 G45 G46 G569 G81 G82 G83 G931 G936 G970 G971 G978 G979 I63 I65
Other	T882 T790 T800 E15 E272 E86 E87 R798 T812 T818 T888 T792

[a] Adapted from Ma C, et al. Postoperative complications following colectomy for ulcerative colitis: A validation study. BMC Gastroenterol 2012; 12:39.

Table A3: Cancer Treatment OPCS 4.7 Codes excluded for cost analysis

Category	Specific Code	Sub Category
Chemotherapy	X70.1	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 1
	X70.2	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 2
	X70.3	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 3
	X70.4	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 4
	X70.5	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 5
	X70.8	Other specified procurement of drugs for chemotherapy for neoplasm in Bands 1-5
	X70.9	Unspecified procurement of drugs for chemotherapy for neoplasm in Bands 1-5
	X71.1	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 6
	X71.2	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 7
	X71.3	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 8
	X71.4	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 9
	X71.5	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 10
	X71.8	Other specified procurement of drugs for chemotherapy for neoplasm in Bands 6-10
	X71.9	Unspecified procurement of drugs for chemotherapy for neoplasm in Bands 6-10
	X72.1	Delivery of complex chemotherapy for neoplasm including prolonged infusional treatment at first attendance
	X72.2	Delivery of complex parenteral chemotherapy for neoplasm at first attendance
	X72.3	Delivery of simple parenteral chemotherapy for neoplasm at first attendance
	X72.4	Delivery of subsequent element of cycle of chemotherapy for neoplasm
	X72.8	Other specified delivery of chemotherapy for neoplasm
	X72.9	Unspecified delivery of chemotherapy for neoplasm
	X73.1	Delivery of exclusively oral chemotherapy for neoplasm
	X73.8	Other specified delivery of oral chemotherapy for neoplasm
	X73.9	Unspecified delivery of oral chemotherapy for neoplasm
	X74.1	Cancer hormonal treatment drugs Band 1
	X74.2	Cancer supportive drugs Band 1
	X74.8	Other specified other chemotherapy drugs
	X74.9	Unspecified other chemotherapy drugs
Radiotherapy	X65.1	Delivery of a fraction of total body irradiation
	X65.2	Delivery of a fraction of intracavitary radiotherapy
	X65.3	Delivery of a fraction of interstitial radiotherapy
	X65.4	Delivery of a fraction of external beam radiotherapy NEC
	X65.5	Oral delivery of radiotherapy for thyroid ablation
	X65.6	Delivery of a fraction of intraluminal brachytherapy
	X65.7	Delivery of radionuclide therapy NEC
	X65.8	Other specified radiotherapy delivery
	X65.9	Unspecified radiotherapy delivery
	X67.1	Preparation for intensity modulated radiation therapy
	X67.2	Preparation for total body irradiation
	X67.3	Preparation for hemi body irradiation
	X67.4	Preparation for simple radiotherapy with imaging and dosimetry
	X67.5	Preparation for simple radiotherapy with imaging and simple calculation
	X67.6	Preparation for superficial radiotherapy with simple calculation
	X67.7	Preparation for complex conformal radiotherapy
	X67.8	Other specified preparation for external beam radiotherapy

	X67.9	Unspecified preparation for external beam radiotherapy
	Y92.1	Technical support for preparation for radiotherapy
	Y92.2	Other specified support for preparation for radiotherapy
	Y92.3	Unspecified support for preparation for radiotherapy
Brachytherapy	X68.1	Preparation for intraluminal brachytherapy
	X68.2	Preparation for intracavitary brachytherapy
	X68.3	Preparation for interstitial brachytherapy
	X68.8	Other specified preparation for brachytherapy
	X68.9	Unspecified preparation for brachytherapy
	Y35.4	Introduction of radioactive substance into organ for brachytherapy NOC
	Y36.4	Introduction of non-removable radioactive substance into organ for brachytherapy NOC
	Y89.1	High dose rate brachytherapy treatment
	Y89.2	Pulsed dose rate brachytherapy treatment
	Y89.8	Other specified brachytherapy
	Y89.9	Unspecified brachytherapy

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9 (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	9 (Table 1)
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Economic evaluation of different routes of surgery for the management of endometrial cancer: A retrospective cohort study.

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Economic evaluation of different routes of surgery for the management of endometrial cancer: A retrospective cohort study.

[1]Moss EL (PhD), [2]Morgan G, [2]Martin A, [3]Sarhanis P (FRCOG), [4,5]Ind T (FRCOG)

[1]Leicester Cancer Research Centre, University of Leicester, Leicester, LE1 7RH

[2]HCD Economics

[3]North West London NHS Trust

[4]Royal Marsden Hospital

[5]St George's University of London, London, SW17 0RE

Corresponding Author

Dr Esther Moss

Leicester Cancer Research Centre, University of Leicester, Leicester, LE1 7RH, UK

Tel: +44 (0)116 252 3170

Fax: +44 116 258 8210

Email: em321@le.ac.uk

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ABSTRACT

Objectives: The benefits of minimally invasive surgery (MIS) for endometrial carcinoma (EC) are well established although the financial impact of robotic-assisted hysterectomy (RH) compared to laparoscopic hysterectomy (LH) is disputed.

Design: Retrospective cohort study.

Setting: English NHS hospitals 2011-2017/8.

Participants: 35,304 women having a hysterectomy for EC identified from Hospital Episode Statistics (HES).

Primary and secondary outcome measures: The primary outcome was the association between route of surgery on cost at intervention, 30, 90 and 365 days for women undergoing an open (OH) or MIS (LH/RH) for EC in England. The average marginal effect (AME) was calculated to compare RH vs OH/RH vs LH which adjusted for any differences in the characteristics of the surgical approaches. Secondary outcomes were to analyse costing data for each surgical approach by age, Charlson Comorbidity Index (CCI) and hospital MIS rate classification.

Results: A total of 35,304 procedures were performed, 20,405 (57.8%) were MIS (LH 18,604 and RH 1,801), 14,291 (40.5%) OH. Mean cost for LH was significantly less than RH, whereas RH was significantly less than OH at intervention, 30, 90 and 365 days ($p<0.001$). Overtime patients who underwent RH had increasing CCI scores and by the 2015/16 year had a higher average CCI than LH. Comparing the cost of LH and RH against CCI score identified that the costs closely reflected the patients' CCI. Increasing disparity was also seen between the MIS and OH costs with rising age. When exploring the association between provider volume, MIS rate and surgical costs there was an association with the higher the MIS rate the lower the average cost.

Conclusions: Further research is needed to investigate costs in matched patient cohorts to determine optimum surgical modality in different populations.

Funding: HCD economics were funded by Intuitive Surgical, Award/Grant number is not applicable. None of the clinicians involved in this study received funding from Intuitive Surgical. Intuitive Surgical did not have any involvement with the study design, data analysis or writing of the manuscript.

Key words: Endometrial cancer; minimally invasive surgery; laparoscopic hysterectomy; open hysterectomy; robotic-assisted hysterectomy; patient stratification; healthcare economy

Tweetable abstract: Analysis of financial cost of laparoscopic, robotic and open hysterectomy for the treatment of endometrial cancer in England.

Strengths and limitations

- The findings from the study are based on a population-based database which is a key strength as it is representative of all procedures via the NHS in England.
- The reliability of the coding might have changed over time although there was no evidence of changes in treatment coding or significant changes in the underlying study population.
- HES database reliably captures extensive amount of demographic, diagnosis and procedure outcomes however there is a lack of cancer stage information therefore it is not possible to split out the cost outcomes into more specific groups of patients.
- The capital and maintenance costs of RH have also not been included since these costs vary dramatically across different healthcare settings and often utilised by a wide group of specialities in a hospital setting.
- As the analysis was undertaken over a number of years of the HES database, we were able to accurately follow hospital activity for at least a year after intervention.

INTRODUCTION

The introduction of minimally invasive surgery (MIS) for endometrial cancer (EC) has had a dramatic impact on patients' surgical outcomes with reduced morbidity, hospital stay and improved short-term quality of life[1]. Translating these patient benefits into cost benefits to the healthcare economy has been challenging because although MIS requires significantly less bed days than open surgery, it does require more costly consumable equipment, for example single-use vessel sealing devices. This has been demonstrated in several studies including the multi-centre randomised LACE trial where the surgery costs were greater for laparoscopic hysterectomy (LH) compared to open hysterectomy (OH), but the overall costs of treatment were lower[2].

MIS is the preferred surgical route for EC[3]. RH is accepted as an alternative to LH, supported by evidence from a randomised controlled trial[4] and RH has been shown to have a lower conversion rate to laparotomy and shorter operating time[5–7]. Wide spread adoption of RH is limited in England, although the number of EC cases having RH is increasing year on year[8]. In light of the capital and consumable costs of RH, as compared to OH or LH, the use of RH in EC is therefore being called into question[6]. Reports from institutions with well-established robotic programmes however have contested this view with no significant difference[9], or cost improvements reported as compared to LH[10]. What is clear is that focusing solely on in-hospital costs does not give the full picture of the economic costs of a surgical procedure, since many costs are accrued following discharge or attributed to the economy as a whole as a result of delayed return to employment.

We therefore investigated the HES data for England in order to look at the financial impact of RH as compared to LH and OH. We also investigated the patient characteristics that contributed

to cost and examined the top 5% of procedures to identify factors that may have contributed to the costs.

METHODS

Data Source and cohort selection

Data was sourced from the Hospital Episode Statistics (HES) database from 2011-2017/8[11]. HES database captures demographic, diagnosis and procedure outcomes data however does not include cancer stage or histology information. No ethical approval was required for this study. Patients or the public were not involved in the design, or conduct, or reporting of our research. The inclusion criteria for patients was a diagnosis of endometrial cancer (EC) or endometrial cancer in situ/complex atypical hyperplasia (ECIS) undergoing a hysterectomy between October 2011 to December 2017. The surgical approach was classified by intention-to-treat as open hysterectomy (OH), vaginal hysterectomy (VH), laparoscopic hysterectomy (LH), robotic hysterectomy (RH) and minimally invasive surgery (MIS) which was the combination of LH and RH. Due to the low numbers the VH cases were not included in any of the subsequent analyses. The cohort selection for the study has been described in more detail previously[8] and the list of specific diagnosis (ICD-10) and procedure (OPCS-4.7) codes can be found in the Appendix Table A1.

Patient Characteristics

Demographic data was captured in the hospital admission data for each patient and included age, ethnicity, postcode, comorbidities. Patient age was divided by 10-year intervals from the age of 50 into six groups. Ethnicity was classified into Asian, Black, Other and White ethnicity. Based on postcode of residence, each patient who received EC surgery was mapped to the English Index of Multiple Deprivation rank. The IMD indicates the socioeconomic deprivation of patients which combines seven indicators (income, employment, health deprivation and disability, education, skills and training, barriers to housing and services, crime, and living environment), into a single deprivation index where a higher rank indicated a less deprived group and a lower rank indicated a more deprived group[12]. The Index of Multiple Deprivation (IMD) was split into statistical quartiles and indicated whether the sociodemographic status was high (>25083), intermediate (17475-25083), low (9618-17474) or very low (<9618) for each patient. Comorbidities were examined 12 months prior to intervention using the Charlson Comorbidity Index (CCI)[13], an additional list of other co-morbidities were also assessed using specific ICD-10 codes (Appendix Table A2).

Hospital characteristics were assessed by region (East, East Midlands, Greater London, Home Counties, North East, North West, South East, South West, West Midlands, Yorkshire) and volume, which was based on the annual mean of hysterectomies performed for EC/ECIS grouped by statistical quartiles (High (>220), Intermediate (71-220), Low (70-21) and Very Low (0-20)). MIS rates of hospitals for EC/ECIS hysterectomy procedures were classified into four groups based on percentage of hysterectomies performed by MIS approach (High (76-100%), Intermediate (51-75%), Low (26-50%) and Very Low (0-25%)).

Outcomes

For each patient episode, in the HES database, a cost is assigned based on the health resource group (HRG) which is diagnosis/procedure-based grouping and the length of stay. These costs are based on reference costs provided by each hospitals and are estimated based upon recorded inpatient, outpatient, and A&E episode activity in the HES database using NHS Payment by Results Health Resource Group (HRG) tariffs[14]. Costs at intervention and short-term costs were calculated based upon the reported hospital admission costs over the time period of 30-, 90- and 365-days following intervention, these were all summarised by procedure approach. Further to this, the cost of each approach was assessed by the subgroups of age, CCI groups and MIS rate classification. A list of non-surgical cancer related treatments was collated (See Appendix Table A3 for specific OPCS-4.7 procedure codes) and these costs were excluded in the analysis. Peri-operative outcomes included mortality, conversion to open hysterectomy and length of stay. The 90-day outcomes included the mortality, total and specific inpatient, outpatient and emergency readmissions. Subgroup analyses were performed, firstly to assess high cost (top 5% of costs at intervention by approach) and low-cost patients (lowest 50% of costs at intervention by approach) in the cohort to assess what was driving high costs patients. In addition, provider level analysis was conducted to assess hospital characteristics and costs to further understand the impact of differing MIS rates and volume sizes.

Statistical Analyses

A descriptive analysis of patient characteristics and data on costs and other health resource was performed. The different approaches (LH, RH, OH, MIS) were then compared by using t-test (for independent samples) and Wilcoxon rank-sum test (Mann-Whitney U test) for continuous variable and for categorical variables by using the chi-squared tests. The average marginal effect (AME)[15] was used to compare RH vs OH and RH vs LH on costing outcomes at intervention, 30 days, 90 days and 365 days. This approach adjusted for patient age, ethnicity, IMD rank, Charlson Comorbidity Index, year of procedure and whether a patient received cancer treatment following the intervention (for further details see Appendix Table A3) by fitting Generalised Linear Models (GLMS). The Modified Park Test & Pregibon's Link Test[16] were used to ensure the most efficient model structure was used to model the costs. All statistical analyses were performed using Stata 15®.

Patient and Public Involvement

There was no patient or public involvement in the study planning or design.

RESULTS

A total of 35,304 procedures were performed, 18,604 (52.7%) LH, 1,801 (5.1%) RH, 14,291 (40.5%) OH and 608 (1.7%) VH. The proportion of MIS cases increased significantly overtime each year from 46.6% in 2012/13 to 68.7% in 2016/17 ($p<0.001$). This was primarily due to an increase in LH of 15.8% (44.7% to 60.5%), but there was also a 6.2% increase (2.0% to 8.2%) in the number of RH performed when comparing 2012/13 to 2016/17 as a proportion of all surgeries performed each year. Consequently, the number of OH cases decreased significantly overtime ($p<0.001$) from 53.4% in 2012/13 to 31.3% in 2016/17 of cases in that year.

Table 1 presents the patient characteristics of the surgical approaches LH, RH and OH. Most cases were performed at high volume providers (>220 cases/year) with 72.4% for RH, 62.1% for LH and 60.9% for OH being undertaken at these providers (Table 1). As previously described, there was a significant difference in the social/ethnic characteristics of the patients undergoing MIS as compared to OH within this cohort of patients[8]. The characteristics of the RH population differed to patients undergoing LH; with a significantly higher percentage of RH patients having any co-morbidity from our defined list than LH (68.2% vs 64.0%, $p<0.001$), more specifically the comorbidities of diabetes, hypertension and obesity all being higher proportion in RH cohort than LH cohort.

Short-term costs by approach

The short-term costs of intervention, 30 days, 90 days and 365 days by surgical approach are presented in Table 2. LH was associated with the lowest mean cost at the intervention (£3069), 30 (£3083), 90 (£3111) and 365 (£3169) days following the procedure. The mean cost for RH was significantly less than OH at all the time points ($p<0.001$ for all). The average marginal effect (AME) for RH versus OH, controlling for patient characteristics, also showed a significant difference for RH over OH with the difference in cost increasing when comparing the unadjusted and AME value (p<0.001 for all). Comparing RH and LH short-term costs, LH costs were significantly lower for the unadjusted and AME differences (p<0.001 for all). The AME differences in cost between RH and LH were lower compared to the unadjusted differences (e.g., AME difference of £108 vs. unadjusted difference of £260 at intervention).

High-Cost and Low-Cost Patient Comparison

Assessing the top 5% highest cost (HC) patients of each approach (LH: n=336; OH: n=593, RH: n=27) and comparing to the low-cost (LC) cohort, which was set at less than or equal to the median cost of the surgery (LH: n=12,913; OH: n=9,021, RH: n=812). The patients in the HC group were significantly older in all the routes of surgery (LH: 69.0 vs 65.7 years, OH: 68.8 vs 65.1 years, RH: 67.5 vs 65.5 years: p<0.001 for all). The HC cohort contained a higher percentage of patients from the lower socioeconomic groups (IMD Rank: 16637 vs 17287, p<0.001) and patients from ethnic minority groups (29.6% vs 19.2%, p<0.001) as compared to the LC cohort. Patients in the HC cohort also had significantly greater number of co-morbidities compared to the LC cohort (CCI 1.82 vs 1.41 and any comorbidity 71.0% versus 63.9% p<0.001 for all). The length of hospital stay was significantly longer in the HC cases compared to the LC group (RH: 11.22 vs 1.84 days; LH: 11.42 vs 2.03 days; OH: 20.82 vs 3.71days; p<0.001 for all). Although the rate of complications was greater in the HC compared to the LC cohort (RH: 55.6% vs 14.0%; LH: 61.0% vs 16.2%; OH: 71.5% vs 19.1%; p<0.001 for all), the rate was significantly lower with RH as compared to OH in both the HC and LC groups (HC: 55.6% vs 71.5%, p= 0.075; LC: 14.0% vs 19.1%, p<0.001).

Patient Characteristics and Costs

Patient characteristics, age and CCI, were associated with increasing costs for almost all routes of surgery at intervention, and 365 days following the procedure (Table 3). Assessing the age categories showed the costs at intervention were very similar for the <50 years, 50-59 years and 60-69 years groups but gradually increased for each of the higher age groups. There was an increasing difference between the MIS and OH costs with rising age with the difference between MIS and OH for Age <50 being £258 increasing to a difference of £653 for Age >90 years population. RH 365-day costs were significantly lower (p<0.01) than OH in all age categories except 60-69 & 90> years. Comparing CCI showed that CCI group >=3 was associated with the greatest difference in costs with the difference at 365 days between CCI group 1 and CCI group >3= being £130 for RH, £174 for LH and £759 for OH (Table 3).

Overtime patients who underwent RH had increasing levels of co-morbidities, when using the CCI score, and have in recent years had a higher average CCI than LH in 2015/16-2016/17 (Figure 1). Comparing the cost of LH and RH against CCI score, identified that the costs closely reflected the patients' CCI. In 2012/13 when the RH population had a lower CCI then the costs were less, however, since 2014/15 the patient population undergoing RH higher CCI score and this was associated with a rise in the costs of RH above that of LH (Figure 1).

Hospital Characteristics and Costs

When exploring the association between provider volume, MIS rate and surgical costs there was an association with the MIS rate and cost, i.e. the greater the MIS rate the lower the cost (Figure 2). Many of the highest volume providers had higher average costs than providers with less volume, however the patient population undergoing surgery at the high volume providers were significantly older and had a higher CCI compared to the lower volume providers (Age: 66.2 vs 65.6 years, p<0.001; CCI: 1.47 vs 1.43, p<0.001). The majority of the highest volume providers had MIS rates between 50% to 90% and the relationship held for high volume providers with average costs decreasing as MIS rates increased for the year 2016/17.

DISCUSSION

Main findings

In this study, we have performed an in-depth analysis of real-world data and have identified financial benefits for MIS as compared to OH for EC. We have demonstrated that LH has the lowest mean cost at intervention and that costs increased with increasing patient age. In keeping with other studies, we have also shown that OH, although attracting the lowest operative consumable costs, had the greatest overall financial cost, even significantly higher than RH. We have also identified that although the cost of RH is greater than LH, patients undergoing RH have different characteristics compared to women having LH in recent years, and that cost of surgery appears to be influenced by level of patients' co-morbidities and not the route of surgery alone.

There will always be a proportion of cases that have to be performed OH due to contra-indications/complications with MIS, which will inevitably attract higher costs due to their complexity, but this can be reduced to low levels[17]. The significantly higher complication/re-admission rate with OH have been reported previously[8] and in this study we have shown that even in the HC groups, the complication rate was higher with OH (71.5%) as compared to RH (55.6%) and LH (61.0%). A longer recovery time may impact on patient and employment costs, with greater loss of earnings and longer return to work or contribution to society activities as compared to MIS. Korsholm et al.[18], reported no significant difference in return to the labour market or use of sickness benefits in a study from Denmark however, in their study robotic surgery was associated with greater cost than both laparoscopic and open hysterectomy, unlike this UK analysis. Allowing for a number of OH cases, the disparity in MIS uptake across England[8] does indicate that there is room for improvement in increasing the proportion of MIS cases and thereby benefitting both the patient and the healthcare economy.

The primary argument used against the widespread use of RH, rather than LH, for EC is an economic one[6,19], since the clinical outcomes are reported to be comparable although, there is a lack of randomised control trial data, particular in patients with a high BMI[20]. The HES data does confirm a cost advantage for LH over RH however, the two patient populations are not directly comparable since there is a significant difference in the CCIs between the groups. During 2012/13, when RH was only performed in a few selected centres, the majority of UK robotic surgeons would still have been within the learning phase, and therefore likely to select patients with less co-morbidities for RH. We have shown that during this time period the cost of RH was less than LH. Increasing robotics experience appears to have led to the positive selection of co-morbid patients, especially high BMI, for RH, and this is associated with rising costs. Class III obesity and a rising number of patient co-morbidities are reported to attract increased inpatient care costs due to increased medical rather than surgical complications associated with undergoing surgery[21,22]. The selection of patients with a high-BMI for RH is not unexpected given the reported ergonomic benefits for surgeons as compared to straight-stick laparoscopy[23], with less movements and muscle activity required to perform tasks[24]. RH is not without issues due to the fixed console position[25], however more extreme muscle movements are required for laparoscopic procedures increase with rising BMI[24], which is not reported with robotics. The cost to the healthcare service of work-related musculoskeletal symptoms in surgeons is of growing concern[26] and not considered in economic analyses such as this study, however it is an additional cost that needs to be considered when calculating service delivery costs.

What is clear from the data is that OH is the most costly route of surgery, a finding reported in other healthcare settings[27], not only in financial terms but more importantly for patient complications and post-operative mortality[8]. The key focus therefore, rather than being between LH or RH, should instead be on reducing the OH rate to a minimum. Although there are only a few absolute contra-indications for OH, the number of cases that are performed through open surgery is still high in some institutions and there has been much discussion how this could be reduced through greater surgical training[28] or centralisation of cases to hospitals and surgeons with high MIS rates[29]. A reduction in OH can also be achieved through reducing the number of conversions from LH/RH to a minimum. A meta-analysis of observational studies did show that the conversion rate of LH increased with BMI >40kg/m^2 more than for RH, 6.5% (95% CI 4.3-9.9) versus 5.5% (95% CI 3.3-9.1), as compared to >30kg/m^2, 7.0% (95% CI 3.2-14.5) versus 3.8% (95% CI 1.4-99) respectively[20]. One reason for this may be the lower intra-abdominal insufflation pressure often used with RH, typically 8mmHg, which has been shown to be associated with lower post-operative pain and shorter hospital stay as compared to a pressure 15mmHg[30]. Inability to tolerate Trendelenburg position was also reported to be the indication for 31% of LH conversions but only 6% of RH conversions[20]. This therefore raises the possibility as to whether cases should be selected for RH where there is high risk of conversion due to Class III obesity or inability tolerate the pneumoperitoneum. Further research is needed to compare the clinical outcomes and costs of LH and RH in matched populations, for example BMI >40kg/m^2 or previous abdominal surgery, to investigate whether differences reported in retrospective case series are confirmed. Such trials would determine whether certain patient characteristics could be used to personalise the route of surgery in order to maximise the potential benefit from MIS and reduce the rate of OH. Prospective randomised controlled trials (RCT) are the gold standard study design however can be challenging to perform and may be subject to many biases, including patient selection, if a surgeon has a greater preference for one surgical modality over another. Also, RCTs can take many years to complete accrual, for example LACC[31], by which time the current robotic/laparoscopic platforms may be obsolete. Instead, the use of real-world data in a propensity score matching study may enable matching of key patient characteristics to give results in a more timely manner[32]. The development and adoption of prognostic and risk-stratifying biomarkers in the future may also inform decisions on the optimum route of surgery thereby enabling more personalised management[33–35].

Strengths and limitations

The key strength of the study is in the number of patients in which can be analysed by using the HES database. This gives strength to the study's findings as it is representative of all procedures via the NHS in England. Due to RH being a newer surgery approach the number of patients is much lower compared to the other surgery approaches. In addition, we must consider the impact of a learning curve of RH and that in the earlier years it may not been used to full efficiency. As we had a number of years of the HES database we could analyse any potential trends across surgical approaches and the year.

As we have previously described[8], HES data does have limitations, primarily it only covers NHS-funded care, the reliability of coding and lacks oncological details of stage/histology. A limitation of the CCI calculated using the HES data is that people with no hospital attendance 12 months prior to intervention are classified as having no comorbidities instead of missing, but as the NHS is free at the point of contact the HES database is extensive at capturing all hospital reported comorbidities in England. There will be a proportion of patients with advanced disease that require open surgery due to requiring a more extensive cytoreductive procedure and HES data is not able to differentiate these cases from early-stage disease that is being treated through open surgery. The analysis comparing LH and RH should however not be impacted by stage of disease. In addition, there are limitations with the HES data with the recording of magnitude of patient co-morbidities, in particular obesity since a numerical value for BMI is not included and therefore the obesity classification could be applied to any patient with a BMI >30kg/m^2.

The capital and maintenance costs of RH have also not been included since these costs vary dramatically across different healthcare settings and there would be a need to also included similar costs for laparoscopic and open surgery. In addition, the robotic surgery equipment is often utilised by a wide group of specialities in a hospital setting and it would be infeasible to apply capital and maintenance costs to one surgery modality[15].

Interpretation

In conclusion, LH was associated with the lowest and OH the greatest mean cost per procedure. Patient factors have an impact on the cost of MIS procedures and further research is needed to compare the costs in matched populations of women undergoing LH and RH, since there appears to be selection bias in the choice of procedure being performed.

Ethical approval: The HES database is managed by the NHS Digital and is available for research without ethical approval.

All the authors consent to publication

Data availability: Data analysed in this study is available through Hospital Episode Statistics (HES)

Conflicts of Interest: EM and TI perform Da'Vinci robotic gynaecological surgery (Intuitive Surgical) and are members of the British and Irish Association of Robotic Surgeons (BIARGS), which is supported by Intuitive Surgical and other robotics/laparoscopic companies to hold education/training events. EM has been awarded research grants from Intuitive Surgical and Hope Against Cancer for unrelated studies, serves on advisory boards for Inivata and GlaxoSmithKline and has received speaker fees from GlaxoSmithKline. TI has done two days paid consultancy work for Medtronic. GM and AM from HCD Economics were funded by Intuitive Surgical. None of the clinicians (EM, PS, TI) received funding from Intuitive Surgical for this study. Intuitive Surgical did not have any involvement with the study design, data analysis and writing of the manuscript. The authors declare no other potential conflict of interest.

Contributors: EM, TI, GM and AM contributed to the conceptualisation and study design. Data analysis and interpretation was performed by EM, TI, GM, AM and PS. Figures and tables creation was performed by EM, GM and AM. All authors were involved in the writing or review of the manuscript and approved the final version.

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Figure 1: Intervention Cost & CCI Over Time

The average cost and CCI of RH & LH over time.

(CCI = Charlson Comorbidity Index, LH = laparoscopic hysterectomy, RH = robotic hysterectomy, NHS = National Health Service)

Figure 2: Average Provider Cost of Hysterectomy per Provider by MIS rate in 2016/17

The association between provider volume, MIS rate and surgical cost at intervention. Provider volume is represented by the size of the bubble with a larger bubble representing a higher provider volume.

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523 **Table 1. Clinical and Demographic Characteristics by the cohorts of hysterectomy approach**

	Unadjusted Results							
	Laparoscopic Hysterectomy (N=18604)		Robotic Hysterectomy (N=1801)		MIS Hysterectomy (N=20405)		Open Hysterectomy (N=14291)	
Characteristics	No.	(%)	No.	(%)	No.	(%)	No.	(%)
NHS Year of surgery								
2011/12*	1,108	6%	19	1%	1,127	6%	1,671	12%
2012/13	2,367	13%	104	6%	2,471	12%	2,829	20%
2013/14	2,824	15%	147	8%	2,971	15%	2,614	18%
2014/15	3,134	17%	253	14%	3,387	17%	2,361	17%
2015/16	3,118	17%	382	21%	3,500	17%	1,948	14%
2016/17	3,577	19%	483	27%	4,060	20%	1,852	13%
2017/18*	2,476	13%	413	23%	2,889	14%	1,016	7%
Age, years								
<50	1,033	6%	120	7%	1,153	6%	1,082	8%
50-59	3,937	21%	380	21%	4,317	21%	3,098	22%
60-69	6,522	35%	589	33%	7,111	35%	4,672	33%
70-79	5,160	28%	533	30%	5,693	28%	3,779	26%
80-89	1,846	10%	174	10%	2,020	10%	1,540	11%
90>	106	1%	5	0%	111	1%	120	1%
Ethnicity								
White	15,033	81%	1,420	79%	16453	81%	11117	78%
Asian	583	3%	66	4%	649	3%	499	3%
Black	231	1%	20	1%	251	1%	365	3%
Other	2,757	15%	295	16%	3052	15%	2310	16%
Socio-Economic Group (IMD)								

High	4,506	25%	643	37%	5,149	25%	3,291	23%
Intermediate	4,612	25%	403	23%	5,015	25%	3,387	24%
Low	4,548	25%	376	21%	4,924	24%	3,489	24%
Very Low	4,435	25%	333	19%	4,768	23%	3,703	26%
Charlson Comorbidity Group								
0	22	0%	1	0%	23	0%	13	0%
1	12,432	67%	1,159	64%	13,591	67%	8,405	59%
2	4,915	26%	514	29%	5,429	27%	4,535	32%
>=3	1,235	7%	127	7%	1,362	7%	1,338	9%
Region								
Greater London	2,529	14%	319	18%	2,848	14%	2,184	15%
Yorkshire	1,501	8%	270	15%	1,771	9%	1,220	9%
West Midlands	1,747	9%	154	9%	1,901	9%	1,672	12%
South West	2,676	14%	75	4%	2,751	13%	1,348	9%
South East	1,746	9%	339	19%	2,085	10%	1,451	10%
North West	2,628	14%	281	16%	2,909	14%	2,550	18%
North East	1,264	7%	138	8%	1,402	7%	432	3%
Home Counties	1,095	6%	31	2%	1,126	6%	912	6%
East Midlands	1,485	8%	165	9%	1,650	8%	1,003	7%
East	1,922	10%	4	0%	1,926	9%	1,497	10%
Missing	11	0%	25	1%	36	0%	22	0%
Provider Volume								
High	11,423	62%	1,302	72%	12,725	62%	8,703	61%
Intermediate	6,653	36%	487	27%	7,140	35%	5,102	36%
Low	279	2%	9	1%	288	1%	191	1%
Very Low	36	0%	0	0%	36	0%	58	0%
Missing	213	1%	3	0%	216	1%	237	2%

524 **NHS Year 2011/12 & 2017/18 not full year

525

Table 2. Short-term costs of intervention, 30 days, 90 days and 365 days by surgical approach

	Mean Cost in £ (SD)			Difference RH vs OH				Difference RH vs LH			
	RH (N =1353)	OH (N=12379)	LH (N=15666)	Unadjusted Difference (£)	P Value	AME (£) *	P Value	Unadjusted Difference (£)	P Value	AME (£) *	P Value
At Intervention	3329 (713)	3349 (1318)	3069 (676)	-20	<0.001	-197	<0.001	260	<0.001	108	<0.001
At 30 days	3334 (722)	3379 (1395)	3083 (721)	-45	<0.001	-220	<0.001	251	<0.001	98	<0.001
At 90 days	3357 (761)	3424 (1468)	3111 (826)	-67	<0.001	-241	<0.001	246	<0.001	89	<0.001
At 365 days	3417 (906)	3533 (1687)	3169 (984)	-116	<0.001	-273	<0.001	248	<0.001	94	<0.001

*AME adjusted for Year, Age, Socioeconomic Status (IMD Rank), Charlson Comorbidity, Ethnicity, Cancer Tx

Notes:

RH vs OH: We see that the average marginal effect is greater than the actual difference between RH and OH when we control for covariates

RH vs LH: We see the average marginal effect is less than the actual difference between RH and LH when we control for covariates

Table 3. Mean Cost at intervention and 365 days by CCI/Age for each approach

	LH			RH			MIS			OH	
	N	Mean (SD)	P-Value*	N	Mean (SD)	P-Value*	N	Mean (SD)	P-Value*	N	Mean (SD)
Age Groups (Costs at Intervention)											
<50	860	£3032 (616)	<0.001	90	£3284 (942)	0.783	950	£3056 (657)	<0.001	921	£3314 (1325)
50-59	3336	£3025 (558)	<0.001	293	£3258 (593)	0.967	3629	£3044 (565)	<0.001	2687	£3259 (1033)
60-69	5522	£3053 (657)	<0.001	436	£3357 (819)	0.089	5958	£3075 (675)	<0.001	4077	£3283 (1173)
70-79	4328	£3101 (732)	<0.001	398	£3343 (600)	0.052	4726	£3121 (725)	<0.001	3255	£3419 (1406)
80-89	1533	£3149 (777)	<0.001	134	£3385 (716)	0.041	1667	£3168 (774)	<0.001	1338	£3546 (1782)
90>	87	£3215 (1311)	0.023	<10	£3454 (687)	0.461	89	£3220 (1298)	0.023	101	£3855 (2425)
CCI Groups (Costs at Intervention)											
0	21	£3060 (292)	0.156	<10	£3939 (0)	-	22	£3100 (341)	0.078	12	£2968 (0)
1	10526	£3038 (616)	<0.001	887	£3319 (763)	0.010	11413	£3060 (633)	<0.001	7369	£3247 (994)
2	4126	£3126 (777)	<0.001	377	£3337 (607)	0.051	4503	£3143 (767)	<0.001	3875	£3412 (1375)
>=3	993	£3166 (806)	<0.001	88	£3391 (614)	<0.001	1081	£3184 (794)	<0.001	1123	£3808 (2421)
Age Groups (Costs at 365 days)											
<50	860	£3136 (900)	<0.001	90	£3287 (945)	0.005	950	£3150 (905)	<0.001	921	£3615 (1821)
50-59	3336	£3111 (903)	<0.001	293	£3274 (612)	0.005	3629	£3125 (884)	<0.001	2687	£3399 (1373)
60-69	5522	£3144 (922)	<0.001	436	£3476 (1091)	0.638	5958	£3169 (940)	<0.001	4077	£3449 (1503)
70-79	4328	£3219 (1103)	<0.001	398	£3468 (836)	0.008	4726	£3240 (1086)	<0.001	3255	£3607 (1806)
80-89	1533	£3256 (1017)	<0.001	134	£3477 (925)	0.003	1667	£3274 (1011)	<0.001	1338	£3776 (2169)
90>	87	£3252 (1350)	0.003	<10	£3454 (687)	0.200	89	£3257 (1337)	0.003	101	£4175 (2774)
CCI Groups (Costs at 365 days)											
0	21	£3074 (294)	0.106	<10	£3939 (0)	-	22	£3114 (341)	0.054	12	£2968 (0)
1	10526	£3126 (891)	<0.001	887	£3358 (827)	0.323	11413	£3144 (888)	<0.001	7369	£3390 (1368)
2	4126	£3249 (1160)	<0.001	377	£3538 (1088)	0.148	4503	£3273 (1157)	<0.001	3875	£3629 (1745)
>=3	993	£3299 (1097)	<0.001	88	£3488 (747)	<0.001	1081	£3315 (1073)	<0.001	1123	£4148 (2832)

*Significance test were carried out against the OH category within each age/CCI group for the approaches LH, RH and MIS

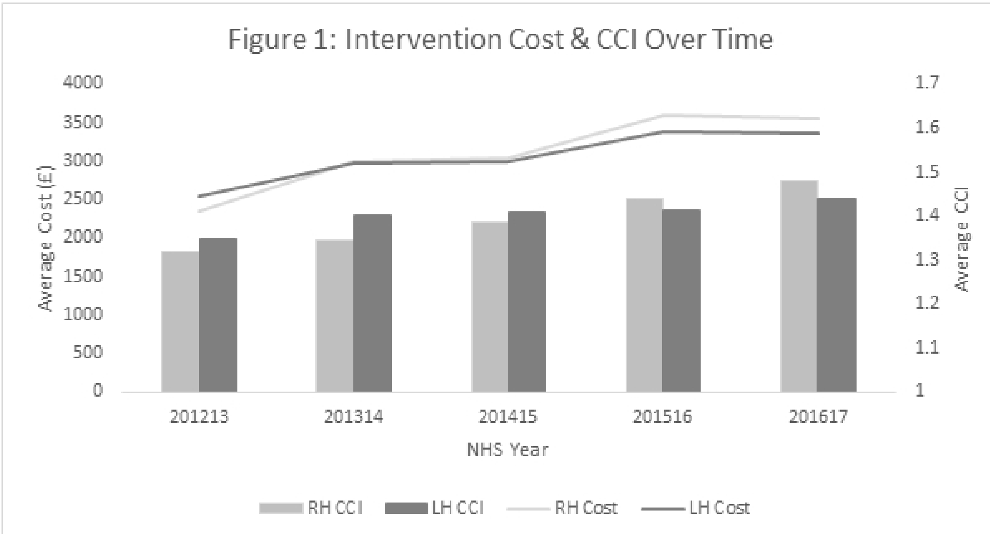

Figure 1: Intervention Cost & CCI Over Time
The average cost and CCI of RH & LH over time.
(CCI = Charlson Comorbidity Index, LH = laparoscopic hysterectomy, RH = robotic hysterectomy, NHS = National Health Service)

127x68mm (120 x 120 DPI)

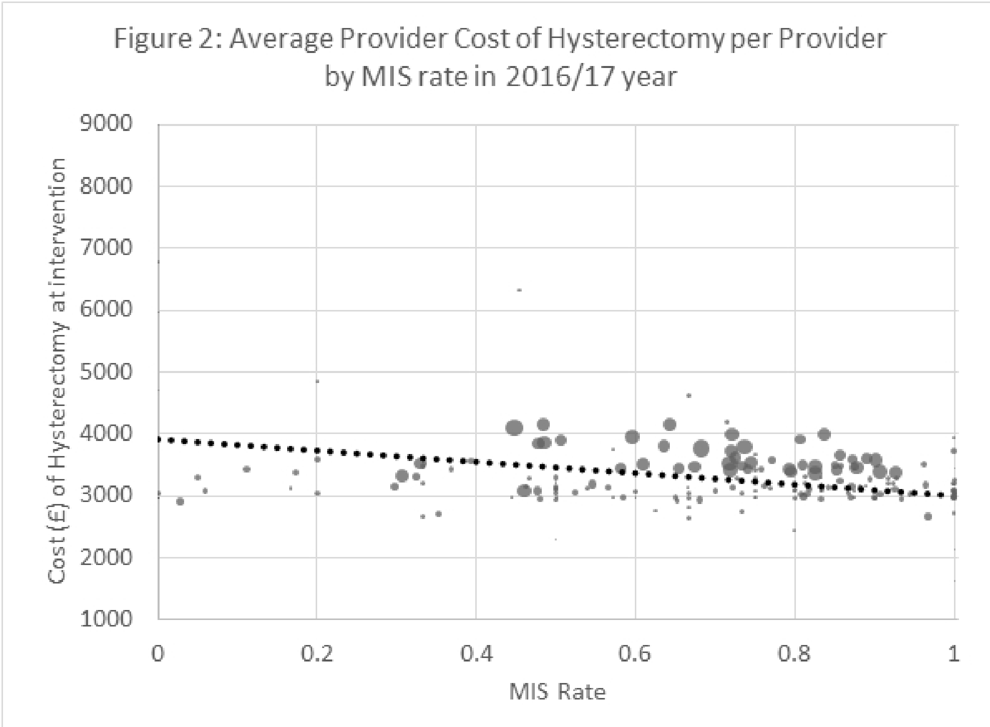

Figure 2: Average Provider Cost of Hysterectomy per Provider by MIS rate in 2016/17
The association between provider volume, MIS rate and surgical cost at intervention. Provider volume is represented by the size of the bubble with a larger bubble representing a higher provider volume.

127x93mm (120 x 120 DPI)

Appendix Tables:

Table A1- Cohort Selection ICD-10 & OPCS-4.7 Codes

Table A1: Cohort Selection

Category	ICD-10 / OPCS-4.7
Hysterectomies	Procedures with: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9, Q08.1, Q08.2, Q08.3, Q08.8, Q08.9
Endometrial/uterine carcinoma or endometrial carcinoma in situ	Patients must have as primary diagnosis: C540, C541, C542, C543, C548, C549, C55X, D070
Laparoscopic hysterectomy	Any procedures with one of: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9, Q08.1, Q08.2, Q08.3, Q08.8, Q08.9 And with one of: Y75.1, Y75.2, Y75.5, Y75.8, Y75.9, T43.9
Robotic hysterectomy	Any procedures with one of: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9, Q08.1, Q08.2, Q08.3, Q08.8, Q08.9 And with one of: Y75.3
Open hysterectomy	Any procedures with one of: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9 And without any: Y75.1, Y75.2, Y75.5, Y75.8, Y75.9, T43.9 Y75.3
Vaginal hysterectomy	Any procedures with one of: Q08.1, Q08.2, Q08.3, Q08.8, Q08.9 And without any: Y75.1, Y75.2, Y75.5, Y75.8, Y75.9, T43.9 Y75.3
Minimally Invasive Surgery	Any procedures with one of: Q07.1, Q07.2, Q07.3, Q07.4, Q07.5, Q07.8, Q07.9, Q08.1, Q08.2, Q08.3, Q08.8, Q08.9 And with one of: Y75.1, Y75.2, Y75.5, Y75.8, Y75.9, T43.9, Y75.3

Table A2 – Other complications OPCS-4.7 codes assessed

Table A2: Complication classification[a]

Category	ICD-10 / OPCS-4.7
Gastrointestinal complications	A090 I898 K228 K250 K252 K254 K256 K260 K261 K262 K264 K265 K266 K270 K272 K274 K276 K280 K282 K284 K286 K290 K450 K560 K565 K566 K567 K625 K631 K638 K660 K720 K729 K85 K913 K918 K919 K92 S360 K61 N824
Wounds	D649 K603 K604 K605 K632 K829 K832 L89 T813 T815 T343 T453 T793
Infections	A40 A41 A49 B95 B96 K630 K65 L03 L04 N10 N12 N151 N159 N300 N309 N390 R788 T793 T802 T814 T816 T827 T836 T857
Uteric Injury Complication	N133 N139 N17 N19 N280 N312 N990 N991 N998 N999 R32 R33 S360 N12 N151 N159 N300 N309 N390 N360 S371 N131 N821
Haemorrhage	T810 S35 D65
Cardiovascular disorders	I21 I46 I48 I49 I50 I74 I80 I81 I82 I950 I952 I959 I978 I979 R57 T801 T811 T817 T827
Pulmonary complications	J80 J81 J90 J91 J93 J955 J958 J959 J960 J969 J981 R060 R09 I26 J100 J110 J12 J13 J14 J15 J16 J17 J18 J690 J85 J86
Neurological disorders	F05 F13 F15 F19 G45 G46 G569 G81 G82 G83 G931 G936 G970 G971 G978 G979 I63 I65
Other	T882 T790 T800 E15 E272 E86 E87 R798 T812 T818 T888 T792

[a] Adapted from Ma C, et al. Postoperative complications following colectomy for ulcerative colitis: A validation study. BMC Gastroenterol 2012; 12:39.

Table A3: Cancer Treatment OPCS 4.7 Codes excluded for cost analysis

Category	Specific Code	Sub Category
Chemotherapy	X70.1	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 1
	X70.2	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 2
	X70.3	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 3
	X70.4	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 4
	X70.5	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 5
	X70.8	Other specified procurement of drugs for chemotherapy for neoplasm in Bands 1-5
	X70.9	Unspecified procurement of drugs for chemotherapy for neoplasm in Bands 1-5
	X71.1	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 6
	X71.2	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 7
	X71.3	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 8
	X71.4	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 9
	X71.5	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 10
	X71.8	Other specified procurement of drugs for chemotherapy for neoplasm in Bands 6-10
	X71.9	Unspecified procurement of drugs for chemotherapy for neoplasm in Bands 6-10
	X72.1	Delivery of complex chemotherapy for neoplasm including prolonged infusional treatment at first attendance
	X72.2	Delivery of complex parenteral chemotherapy for neoplasm at first attendance
	X72.3	Delivery of simple parenteral chemotherapy for neoplasm at first attendance
	X72.4	Delivery of subsequent element of cycle of chemotherapy for neoplasm
	X72.8	Other specified delivery of chemotherapy for neoplasm
	X72.9	Unspecified delivery of chemotherapy for neoplasm
	X73.1	Delivery of exclusively oral chemotherapy for neoplasm
	X73.8	Other specified delivery of oral chemotherapy for neoplasm
	X73.9	Unspecified delivery of oral chemotherapy for neoplasm
	X74.1	Cancer hormonal treatment drugs Band 1
	X74.2	Cancer supportive drugs Band 1
	X74.8	Other specified other chemotherapy drugs
	X74.9	Unspecified other chemotherapy drugs
Radiotherapy	X65.1	Delivery of a fraction of total body irradiation
	X65.2	Delivery of a fraction of intracavitary radiotherapy
	X65.3	Delivery of a fraction of interstitial radiotherapy
	X65.4	Delivery of a fraction of external beam radiotherapy NEC
	X65.5	Oral delivery of radiotherapy for thyroid ablation
	X65.6	Delivery of a fraction of intraluminal brachytherapy
	X65.7	Delivery of radionuclide therapy NEC
	X65.8	Other specified radiotherapy delivery
	X65.9	Unspecified radiotherapy delivery
	X67.1	Preparation for intensity modulated radiation therapy
	X67.2	Preparation for total body irradiation
	X67.3	Preparation for hemi body irradiation
	X67.4	Preparation for simple radiotherapy with imaging and dosimetry
	X67.5	Preparation for simple radiotherapy with imaging and simple calculation
	X67.6	Preparation for superficial radiotherapy with simple calculation
	X67.7	Preparation for complex conformal radiotherapy
	X67.8	Other specified preparation for external beam radiotherapy

	X67.9	Unspecified preparation for external beam radiotherapy
	Y92.1	Technical support for preparation for radiotherapy
	Y92.2	Other specified support for preparation for radiotherapy
	Y92.3	Unspecified support for preparation for radiotherapy
Brachytherapy	X68.1	Preparation for intraluminal brachytherapy
	X68.2	Preparation for intracavitary brachytherapy
	X68.3	Preparation for interstitial brachytherapy
	X68.8	Other specified preparation for brachytherapy
	X68.9	Unspecified preparation for brachytherapy
	Y35.4	Introduction of radioactive substance into organ for brachytherapy NOC
	Y36.4	Introduction of non-removable radioactive substance into organ for brachytherapy NOC
	Y89.1	High dose rate brachytherapy treatment
	Y89.2	Pulsed dose rate brachytherapy treatment
	Y89.8	Other specified brachytherapy
	Y89.9	Unspecified brachytherapy

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9 (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	9 (Table 1)
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.