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Long term resource consequences of a nationwide introduction of robotic surgery for women with early stage endometrial cancer

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1 **Title page**

2 Long term resource consequences of a nationwide introduction of robotic surgery for women with early stage
3 endometrial cancer

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27 **Abstract**

28 **Objective:** The majority of cost-studies related to robotic surgery has a short follow-up and primarily report
29 the costs from the index surgery. The aim of this study was to evaluate the long-term resource
30 consequences of introducing robotic surgery for early stage endometrial cancer in Denmark.

31 **Methods:** The study included all women with early stage endometrial cancer who underwent robotic,
32 laparoscopic and open access surgery from January 2008 to June 2015. Data was linked from national
33 databases to determine resource consumption and costs from hospital treatments, outpatient contacts,
34 primary health care sector visits, labor market affiliation and prescription of medication. Each patient was
35 observed in a period of 12 months before- and after surgery. The key exposure variable was women who
36 were exposed to robotic surgery compared to those who were not.

37 **Results:** A total of 4133 women underwent surgery for early stage endometrial cancer. The study found
38 additional costs of \$7309 (95% confidence interval [CI] 2100-11620, P=0.001) per patient in the group
39 exposed to robotic surgery including long-term costs post-surgery compared to the non-exposed group (non-
40 robotic group). When controlling for time trends, the introduction of robotic surgery did not reduce the
41 number of bed days (mean diff -0.42, 95% CI -3.03-2.19, P=0.752).

42 **Conclusions:** The introduction of robotic surgery for early stage endometrial cancer did not generate any
43 long-term cost savings. The additional costs of robotic surgery were primarily driven by the index surgery.
44 Any reduction in bed days could be explained by time trends.

45

46

47 **1. Introduction**

48 The robotic platform has been rapidly adopted for gynecological procedures in the US and Europe thereby
49 reducing the use of Open Access Surgery (OAS) [1]. The establishment of robotic surgical availability is
50 associated with high initial purchase costs of the platform and additional maintenance and surgical supply
51 costs [2, 3]. In a recent review, we compared the methodological design in 32 cost studies within the
52 gynecological field [2]. Most studies suffered from selection bias, as they were not able to control for data on
53 tumor stage, comorbidities and/or unobservable patient characteristics [2, 4-8], nor did they control for prior
54 levels of health care service use. The majority of these studies had a short follow-up reporting the costs from
55 the index surgery without investigating the long-term resource implications of Robotic Minimally Invasive
56 Surgery (RMIS) [2]. There is currently insufficient evidence as to whether the immediate costs of introducing
57 RMIS are offset by long term savings due to e.g. reduced need for rehabilitation services, reduced utilization
58 of primary care services, fewer outpatient visits and/or faster return to the labor market, compared to other
59 surgical procedures. Previous studies comparing RMIS with OAS for women with endometrial cancer have
60 shown shorter length of stay from the index surgery [9-11], fewer readmissions [9] and reduced risk of severe
61 complications [12].

62 The present study aims to evaluate the long-term resource consequences of introducing RMIS for early stage
63 endometrial cancer in Denmark. The evaluation strategy has three major strengths. Firstly, we took advantage
64 of the fact that RMIS was introduced in the regions of Denmark at different points in time and at different paces
65 between 2008 and 2013. This allowed assessment of exposed and non-exposed individuals simultaneously,
66 and minimization of potential patient selection bias as exposure to RMIS depended on RMIS introduction
67 patterns and not women's characteristics. Secondly, we applied an analytical approach where the patient acted
68 as her own control. We controlled for use of health care resources one year prior to surgery, which allowed us
69 to isolate the resource use associated with surgery. Thirdly, we operated with a follow-up period of one-year
70 post-surgery, and used high quality registry data to monitor the long-term resource consequences of RMIS in
71 the primary and secondary health care sector. We also measured production losses due to sickness leave or
72 earlier exit from the labor market.

73

74

75 **2. Materials and methods**

76 *Study design*

77 RMIS was gradually introduced in Denmark over a five-year period from 2008 to 2013. We included all
78 women in Denmark who underwent surgery for early stage endometrial cancer FIGO stage I-II from January
79 1st, 2008 to June 30th, 2015. Women operated before the date of the first RMIS performed in their region
80 were allocated to the non-exposed group. The non-exposed group (non-robotic group) mainly underwent
81 open access surgery and a minor proportion had conventional laparoscopy. Women in the exposed group
82 were operated after the date of the first RMIS performed in their region and were considered as *exposed* to
83 RMIS. The majority in the exposed group underwent robotic surgery and a minor proportion underwent
84 laparoscopy and open access surgery.

85

86 The treatment of endometrial cancer in Denmark is conducted in accordance with national guidelines from
87 the Danish gynecological cancer group [13] and revised every 3-4th year. The gold standard of surgery
88 consists of total hysterectomy and bilateral salpingo-oophorectomy. Women with increased risk of metastatic
89 disease undergo additional staging lymphadenectomy (pelvis +/- para-aortic) and omentectomy for certain
90 histological subtypes [14]. To estimate the resource consequences of introducing RMIS we utilized the
91 gradual phase-in of this new technology and constructed a quasi-experimental design comparing women
92 who were exposed to robotic surgery with those who were not. We assume that the time and place at which
93 a woman undergoes surgery for endometrial cancer is random and independent of patient characteristics
94 such as age, BMI and comorbidity. Our key exposure variable is the fraction of women who had RMIS out of
95 the total number of women receiving surgery for early stage endometrial cancer in a given region and at a
96 specific time. Our primary outcomes are changes in resource use and costs, as well as labor market
97 affiliation, in the first year after surgery compared to the year before surgery.

98

99 *Data sources*

100 The study population was extracted from the Danish Gynecological Cancer Database (DGCD) which covers
101 clinical, surgical, and pathology data. Data are registered mandatory by gynecologists specialized in
102 gynecological cancer surgery and pathologists [15]. The DGCD is a nationwide, clinical quality registry that
103 covers 97% of women diagnosed with endometrial cancer [15]. From this database we extracted information

104 on the surgical modality, date of surgery, location of the hospital, Body Mass Index (BMI), histological type,
105 grade, FIGO stage, and information on whether lymphadenectomy was performed.

106 All Danish residents have a unique personal identification number (CPR-number) which enables accurate
107 linkage between all national registers [16]. The study population was linked with individual-level register data
108 from the Danish National Patient Register (NPR) [17], The Danish National Health Service Register [18], and
109 The Danish Education register [19]. The NPR holds information on dates of all hospital admissions and
110 discharges, hospital in-patient treatments, and operations including re-operations, outpatient contacts, and
111 diagnoses [17]. The National Health Service Register holds data from the primary health care sector,
112 accounting for health services [18]. Any production losses due to changes in job market affiliation were
113 measured by comparing individual-level labor market data and sickness benefit data before and after surgery
114 [20]. The DREAM database includes weekly information for all Danish citizens who have received social
115 benefit or any other transfer benefit [21].

116 Costs of hospital admissions were estimated using unit costs derived from the Diagnosis Related Grouping
117 system (DRG) for somatic in-patients [22], the Danish Ambulatory Grouping System (DAGS) for ambulatory
118 patients [22], The National Health Service Register for primary health contacts [18], and The Danish National
119 Prescription Registry. The Danish National Prescription Registry provide information on the costs for
120 prescription medication handed out from pharmacies [23]. The national DRG-tariffs for surgery for
121 endometrial cancer included activities from hospital admission to discharge. Outpatient visits and
122 reoperations associated with the index hospitalization were reimbursed separately. DRG tariffs are based on
123 annual detailed costing reporting's from all public hospitals in Denmark, and reflect the national average
124 operating costs within each DRG group [22]. The DRG tariffs thus represent reimbursement fees that do not
125 reflect the precise cost of treating the individual patient. DRG-tariffs are adjusted each year and published by
126 the Danish Health Authority [22]. All costs were adjusted to price index 2015 [24] and converted into USD
127 (\$).

128

129 *Statistical methods*

130 Each patient was observed in a pre-treatment period of 12 months before the date of the index surgery and a
131 post-treatment period of 12 months after the date of the index surgery. To control for potential pre-surgery
132 differences in health care service utilization, and to isolate the costs associated with surgery, we applied a

133 Difference-in-Difference (DiD) design. In the DiD design, the patient acts as her own control and the outcome
 134 variable is *change* in resource use post-surgery versus pre-surgery [25-27]. In the analyses, the focus is to
 135 estimate whether the introduction of RMIS, measured by level of exposure (proportion of patients being
 136 treated with RMIS out of the total number of patients in a given region and calendar year), was associated
 137 with changes in the primary outcome variables measuring resource use and costs as obtained from
 138 registers. Underlying the DiD design lies the common trends assumption to ensure internal validity of the
 139 approach. For ease of presentation the exposure variable was dichotomized (exposed; non-exposed) in the
 140 descriptive analyses but modelled as a continuous variable in the regression models. The common trends
 141 assumption requires the exposed and non-exposed group to have the same parallel trends in outcomes the
 142 year before index surgery. Time series in resource use were plotted graphically for outpatient visits, primary
 143 sector visits, employment status and sickness benefit and the pattern of costs were plotted for primary sector
 144 visits, outpatient visits, and prescription of drugs per woman to evaluate whether the common trends
 145 assumption was fulfilled in the one-year period prior to surgery (Figure 1).

146 To ensure that potential differences in baseline characteristics did not drive differences in trends, a linear
 147 regression was performed. We adjusted for potential time trends by including fixed effects for calendar year,
 148 and for potential differences in resource use across regions by including fixed effects for each region.
 149 This resulted in the fully adjusted model in which our exposure variable was defined as the proportion of
 150 patients being treated with RMIS out of the total number of patients receiving surgery for early stage
 151 endometrial cancer by calendar year and region:

$$152 \quad \Delta C_i = C_{i1} - C_{i0} = c + \beta_1 p_{RMIS_i} + \sum_k \beta_k \times X_{ik} + \varepsilon_i$$

153
 154 Here ΔC_i indicates the difference in costs per patient the year after surgery (C_{i1}) relative to the year prior to
 155 surgery (C_{i0}), c denotes the model intercept, β_1 is the key result denoting the association between the
 156 outcome variable ΔC_i and our exposure variable p_{RMIS_i} , X_{ik} represents covariates (age, BMI, Charlson
 157 comorbidity index, ASA score, histopathological risk groups, lymphadenectomy, education level,
 158 socioeconomic group) including region-of-surgery and year-of-surgery fixed effects, and ε_i denotes the
 159 residuals in the linear regression model. To investigate any possible over adjustment in time trends a
 160 sensitivity analysis was performed in which we analyzed data for a short time period only (2011-2012).

161

162 We performed a further sensitivity analysis excluding patients who underwent surgery in the region of
163 Southern Denmark due to potentially confounding research projects related to the postoperative follow-up
164 visits taking place in the region during the time of observation.

165

166 Results are reported as mean differences with 95% confidence intervals (CI) based on bootstrapping with
167 5000 replicates to take into account the skewed nature of cost and resource use data. The difference-in-
168 difference mean estimates for resource use and costs one year post-operatively (contacts/costs per patient)
169 are reported in three models, 1) an unadjusted model, 2) a model adjusted for patient characteristics and
170 region of surgery and 3) a model that is further adjusted for surgical year. Resource use and costs are
171 compared between 12 months before and 12 months after the index surgery. Resource use and costs of bed
172 days were analyzed both including and excluding the index surgery stay to investigate if potential differences
173 were driven by the index surgery stay. Resource use and costs are reported as year totals, while
174 employment status and sickness benefit are reported as number of weeks per year.

175

176 A two-sided p-value below 0.05 was considered statistically significant. All analyses were performed using
177 Stata version 15.1. Data was pseudo-anonymized and administered by Statistics Denmark.

178

179 *Ethical consideration*

180 The study was approved by the Data Protection Agency (18/43728).

181

182 **3. Results**

183 During the study period, 4133 women with early stage endometrial cancer underwent surgery in Denmark
184 (Figure 2). Before RMIS was introduced 78% of women underwent open access surgery (Figure 2). During
185 the 7.5 years of observation while robotic surgery was introduced nationwide, 72% of the women underwent
186 minimally invasive surgery (laparoscopy and RMIS). In the present study these women are nominated
187 “exposed” vs. “non-exposed” but modelled as proportions in the regression models. Figure 3 illustrates the
188 introduction of RMIS nationwide and separately for each region. Conventional laparoscopy was used in 22%
189 of the women in the exposed and the non-exposed group. As it appears, the use of conventional

190 laparoscopy increased before the introduction of RMIS and decreased slightly during the RMIS period
191 (Figure 3). Sociodemographic characteristics between the groups are given in Table 1.

192

193 *Resource use*

194 Patients assigned to the exposed group had almost four fewer bed days the year following surgery
195 compared to the non-exposed group, when adjusting for patient characteristics only (Table 2). After further
196 adjustment for surgical year no statistically significant difference was observed in bed days between the
197 exposed and non-exposed group (Table 2). This was true for both index surgery and subsequent
198 hospitalizations. Also, no statistically significant difference in resource use was observed for primary sector-
199 or outpatient visits between the exposed and the non-exposed group (Table 2).

200

201 *Costs*

202 The total costs one-year post-surgery from hospitalization, primary sector visits, outpatient visits and
203 prescription drugs were \$7309 higher per patient in the exposed group compared to the non-exposed group
204 ($p=0.001$) (Table 3). The costs related to the hospitalization including the index surgery and subsequent
205 hospitalizations were \$7434 higher per person in the exposed group vs. non-exposed group ($p=0.001$)
206 (Table 3). No statistically significant cost difference was found between the exposed and the non-exposed
207 group for the other cost categories (Table 3).

208

209 A sensitivity analysis, which included a smaller sample based on a shorter time period showed results
210 consistent with the main analysis, indicating no signs of over-adjustment for time trend. The sensitivity
211 analysis excluding patients from the Region of Southern Denmark did not change any results significantly.

212

213 **4. Discussion**

214 This study included all women with early stage endometrial cancer who underwent surgery at Danish
215 hospitals over a period of 7.5 years. Long-term resource use and costs related to their index surgery and the
216 year following surgery were evaluated. The introduction of robotic surgery did not generate any long-term
217 cost savings related to primary sector, outpatient visits, or prescription of medicine in this population of
218 gynecological cancer patients. The introduction of robotic surgery was associated with additional costs of

219 \$7309 per patient in the exposed group compared to non-exposed and the extra costs were mainly
220 attributable to the index surgery. Our findings are in line with other cost studies reporting RMIS to be more
221 costly than open and conventional laparoscopic surgery in women with endometrial cancer [4, 7, 28-31].
222 Smith et al. reported that the overall hospital charge was 40% higher with RMIS compared to laparoscopy
223 and open access surgery [31]. In contrast to our findings, Laursen et al. found that RMIS generated cost
224 savings of \$3861 per women when compared with open access surgery and increased costs of €\$3749
225 when compared with laparoscopy in Danish cancer patients [32]. Important differences between the study of
226 Laursen and the present study concern the selection of the patient population and the data source. Further,
227 our study applied an intention to treat approach thus minimizing the risk of selection bias due to non-random
228 allocation to treatment modalities. Importantly, our findings relate to the particular patient group of women
229 with early stage endometrial cancer who are comparatively unaffected by their cancer when diagnosed.
230 Hence, our results cannot be used to generalize about resource use and costs related to robotic surgery in
231 other patient groups with e.g. a greater need of longer rehabilitation or sick leave. However, the evaluation
232 method used in the present study can be applied to other patient groups for a valid non-biased evaluation of
233 resource use and costs related to the introduction of a new technology.

234

235 In a recent study, we showed that a Danish nationwide introduction of robotic surgery for early stage
236 endometrial cancer is associated with reduced risk of severe complications and improved survival
237 independent of histopathological risk group [12, 33]. However, taking time trends as well as patient
238 characteristics into account, the present study was unable to demonstrate that the introduction of RMIS was
239 associated with a significant reduction in bed days as would be expected in case of fewer re-admissions due
240 to severe complications after minimally invasive surgery. Scrutinizing the graphical presentation of the RMIS
241 introduction in the different regions in Denmark reveals different trends of robotic introduction in two regions
242 (the region of central Jutland and the Zealand region). These regions had a very slow introduction of RMIS
243 compared to the other regions while the proportion of women undergoing conventional laparoscopy
244 increased dramatically. This led to an increased use of conventional laparoscopy already before the
245 introduction of RMIS in these regions and contributed to the decrease in bed days in the non-exposed group.
246 Further, during the time period with robotic introduction another time trend arose; even women who
247 underwent open surgery had fewer bed days compared to earlier time periods. This was likely due to

248 emerging evidence regarding the importance of early mobilization and faster recovery at home. It may be
249 looked at as a paradigm shift and is likely to influence on the results when including a comparatively large
250 time period in the analyses. This emphasizes the importance of adjusting for potential time trends when
251 including patients over several years. In the present study, length of stay was driven by time trends rather
252 than surgical modality.

253

254 Using the Danish DRG-tariffs, all gynecological procedures were listed as more expensive when involving
255 robotic surgery i.e. a simple hysterectomy with bilateral salpingo-oophorectomy without lymph node
256 dissection is valued at \$11259 using robotic surgery versus \$7722 without the robotic assistance for the
257 same procedure. The in-hospital costs of RMIS is likely to decrease in the years to come due to increased
258 surgeon experience and hence reduction in procedure- and operating room time. This prediction is
259 supported by Avondstondt et al. who found a reduction in total costs attributable to a decrease in the
260 operating room costs and costs of anesthesia after five years of experience with RMIS [34]. In addition,
261 present patents related to the robotic platform will expire in the near future. The lack of market competition is
262 highly related to the high costs of robotic instrument supplies. Same-day discharge may be another cost-
263 saving procedure for RMIS. Several studies have found this safe and feasible for the majority of women
264 undergoing minimally invasive surgery [35-38]. According to the literature, Enhanced Recovery After Surgery
265 (ERAS) protocols decreased length of stay by 30% to 50% thereby lowering hospital costs [39]. ERAS, a
266 comprehensive program with multimodal approaches of perioperative pathways, has resulted in early
267 recovery after surgery and has shown to improve outcomes in almost all major surgical specialties [39-41]. A
268 recent study reported that ERAS was feasible and safe in older patients undergoing gynecologic oncological
269 surgery as in younger patients [42]. ERAS protocols have not been implemented systematically in this
270 population. However, Fast-Track principle has been used to optimizing patient outcomes in Denmark
271 outlined in the national guidelines from the Danish gynecological cancer group. This is likely to influence on
272 the observed effect of time-trend adjustment.

273

274 To our knowledge, this is the first detailed investigation of job market affiliation related to treatment of
275 endometrial cancer. No statistically significant effect was observed regarding women's return to the labor
276 market and their use of sickness benefits. A plausible explanation for this is that we included a population

277 with a median age of 67 years at the time of surgery which meant that the majority of the women received
278 pension both before and after the index surgery. Only 40.2% of the women were working at least one week
279 the year before surgery. Further, endometrial cancer is often diagnosed in an early stage and the operation
280 therefore often leads to a rather short sick leave. Since only periods of leave longer than 14 days are
281 observable in the Danish registries, our estimate of total days of leave may be underestimated.

282

283 An important strength of our study is the use of the gradual implementation of RMIS as the basis of a quasi-
284 experimental design, thus minimizing patient selection bias. We also controlled for differences in baseline
285 characteristics, time trends and differences in resource consumption across regions. Another strength of this
286 study relates to the large population and the DiD design evaluating differences in resource use and cost
287 patterns one-year pre- versus one-year post-surgery. A further advantage is the use of high-quality national
288 databases, thereby allowing for systematic and objective measurement of resource use at an individual
289 patient level.

290 An inherent limitation in the study design is the use of retrospective data and a comparatively long time
291 period. Using registry data some clinical details are not routinely recorded e.g. surgeon experience and we
292 cannot completely preclude some institutional selection bias. A further limitation is the use of DRG-tariffs as
293 an approximation of the costs of hospital admissions. The Danish DRG-tariffs do not include the purchase or
294 the maintenance cost of the robot. Another Danish study reported costs for instruments and disposals to be
295 \$2500 for each procedure and the purchase cost of the robotic platform was estimated to cost \$2.4 million
296 which amounts to \$800 per operation with an amortization over 10 years [10].

297

298 **5. Conclusion**

299 The introduction of robotic surgery in Denmark did not generate any long-term cost savings in women with
300 early stage endometrial cancer. The additional costs of robotic surgery are primarily driven by the index
301 surgery. The introduction of robotic surgery decreased the number of bed days but adjusting for time trends
302 outweighed any difference between the group exposed to robotic surgery and those who were not.

303

304

305 **Conflict of interest**

306 The authors have no conflicts of interest to disclose.

307

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318

319 **Author contribution**

320 MK, DGH, SM, PTJ: Contributed to the conception and design, processing of data, statistical analysis and
321 interpretation of data; drafting the article, revising it critically for important intellectual content and final
322 approval of the version to be published.

323 OM, SLJ, LS: Contributed to the conception and design, processing of data, interpretation of data; drafting
324 the article, revising it critically for important intellectual content and final approval of the version to be
325 published.

326

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441 **Legends of included figures and tables**

442

443 Figure 1: Resource use and costs one year before and after the index hospitalization

444 Figure 2: Flowchart of included patients

445 Figure 3: The introduction to robotic surgery in DK and each region Jan. 2008- July 2015

446

447 **Legends of included figures and tables**

448

449 Table 1: Demographic characteristics of included women

450 Table 2: Resource use associated with the introduction of robotic minimally invasive surgery for women with

451 early stage endometrial cancer

452 Table 3: Costs associated with the introduction of robotic minimally invasive surgery for women with early

453 stage endometrial cancer

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