Hospital costs associated with adverse events in gynecological oncology

Author list:

Srinivas KONDALSAMY-CHENNAKESAVAN, MBBS; MPH[1,2]

Louisa G GORDON, BEc, MPH; PhD[3]

Karen SANDAY, BSc; HIM [2]

Chantal BOUMAN, [4]

Suzanne DE JONG, [4]

James NICKLIN, FRANZOG; CGO [2]

Russell LAND, FRANZOG; CGO [2] and

Andreas OBERMAIR, MD; FRANZOG; CGO[1,2]

1. School of Medicine, The University of Queensland, Brisbane, Australia
2. Queensland Centre for Gynaecological Cancer, Royal Brisbane and Women's Hospital, Brisbane, Australia
3. Queensland Institute of Medical Research, Genetics and Population Health Division, Brisbane, Australia
4. Radboud University, Nijmegen, The Netherlands

Author for correspondence:

Dr. Srinivas KONDALSAMY-CHENNAKESAVAN
PO Box: 213
Royal Brisbane Hospital
Herston 4029
Australia
Ph : +61 7 3636 5486
Fax: +617 3636 8501
Email: uqskonda@uq.edu.au

Total pages: 16 (Text)
Tables: 6
Figures: 0
Word count: 2,699

Abstract

Background and objective: Treatment for gynaecological malignancies is complex and may cause unintended or accidental adverse events (AE). We evaluated the costs of hospitalization associated with those AEs among patients who had an abdominal or laparoscopic procedure for proven or suspected gynaecological cancer at a tertiary gynaecological cancer center in Australia.

Methods: Data on AEs were prospectively collected and matched with cost data (AU$ 2008) from the hospital's clinical costing unit and linked to demographical, clinical and histopathological data. Total costs were adjusted for various clinical factors and estimated using log-transformed ordinary least squared regression. Back-transformation was achieved using smearing factors. From epidemiological data, we also estimated the costs of AEs Australia-wide and undertook scenario and probabilistic sensitivity analyses to investigate the potential cost impact of reducing AEs.

Results: A total of 369 patients had surgical procedures of which 95 patients (26%) had at least one AE. Patients with AEs incurred an extra AU$ 12,780 on average, adjusted for age, co-morbidities, ovarian cancer, major or minor complications, surgical complexity, presence of malignancy and abdominal surgery. Mean adjusted costs (95% CI) for patients with intra-operative, minor post-operative and major post-operative AEs were AU$ 40,746 (11,582-71,859) AU$ 18,459 (17,270-19,713) and AU$ 67,656 (5,324-131,761), respectively. Up to an estimated AU$ 20.6 million/year could be saved if the AEs were reduced by 40%.

Conclusion: Adverse events are associated with significantly increased hospitalization costs and appropriate evidence-based interventions are justified to minimize AEs.

70

73
74
75

Introduction

A landmark Australian study, the Quality of Australian Health Care Study (QAHCS), reviewed the quality of delivered health care and concluded that 16.6% of admissions were associated with adverse events (AEs) each year [1]. More than 50% of the AEs reported were associated with surgery and up to 48% of these AEs were considered preventable. The estimated costs associated with these AEs are exorbitant, at AU$ 1-2 billion dollars [2]. Recent studies based on 2003-2004 data have shown that the cost of AEs in Australia could exceed AU$ 2 billion per year [3].

In recent decades there has been a worldwide development towards reporting and analyzing the quality of delivered healthcare in specialized centers and, more specifically, in the field of surgery. This is arguably a direct consequence of 'variations' in outcomes noticed among different institutions for similar procedures. The shift in clinical attitudes towards greater transparency in performance regarding the quality of care to improve outcomes has led to a number of studies focusing on post-operative morbidity and mortality and the formation of adequate and validated models of risk assessment [4]. Such studies have had a positive influence on the quality of surgical practice and contributed to reduced AE rates[5].

The occurrences of AEs during or following a surgical procedure are not uncommon, especially in high-risk specialties such as surgical oncology. Surgeons in these sub-specialties utilize state-of-the-art procedures, innovative minimally-invasive techniques, combined with chemotherapy and or radiotherapy to improve patient outcomes. However, these procedures and management approaches are associated with serious risks of AEs, along with patient related and environmental factors, and are estimated to vary from 34% in head and neck cancers to as high as 69% in esophageal cancers [6]. The published incidence of AEs among

101   patients with gynaecological cancer varies from 26% to 54%[6, 7]. As there is potential scope

102   for reducing AEs among these women, it is important to have a sound understanding of the

103   current clinical outcomes as well as the economic costs so that future intervention studies can

104   be adequately planned for and assessed for their effectiveness and cost-effectiveness.

105   Therefore, the aim of our study was to quantify the nature and extent of AEs in the

106   subspecialty of gynaecological oncology and estimate their associated hospital costs.

107

108   **Methods**

109   All patients who underwent a laparoscopic procedure or laparotomy for suspected or proven

110   gynaecological malignancies were enrolled from a major tertiary referral hospital in the state

111   of Queensland, Australia. All the AEs were recorded prospectively between 1st January 2007

112   and 20th August 2008 by a dedicated patient safety officer. We reviewed all the medical

113   records for potential risk factors for AEs. The methods have been previously reported [7] but

114   briefly, all patients who underwent surgery between 1st January 2007 and 30th June 2008 were

115   included. We reviewed electronic and paper-based medical records and extracted information

116   related to: (1) patient-related risk factors (e.g., BMI, age); (2) clinical characteristics from pre-

117   operative lab results (e.g., serum albumin and liver function tests); (3) surgical procedures

118   (type and complexity of procedure, approach, duration of surgery, conversions, surgeon's

119   experience (trainee/consultant)); (4) type of AEs classified as intra-operative or post-

120   operative; and (5) other outcomes such as length of hospital stay and death within 30 days)

121   [7]. Intra-operative AEs included injuries to the bladder, bowel, ureter, blood vessels, nerves

122   and the need for intra-operative blood transfusions and post-operative AEs included wound

123   infection, wound dehiscence, wound hematoma, secondary hematoma, pneumonia, pulmonary

124   embolism, urinary tract infections, renal complication, stroke/cerebrovascular accidents,

125   pelvic abscess, subphrenic abscess, other abscesses, septicemia, deep venous thrombosis,

126 gastric ileus, urinary fistula, gastro-intestinal fistula, cardiac complications and other post-

127 operative events. These post-operative events were further classified into minor and major

128 events based on the nature of the treatment used to manage these events.

129 To permit comparison of AE rates over time and across studies, post-operative AEs were

130 classified using a standardized grading system [8]. This grading system is based on the

131 interventions used to manage AEs. For example, grades I and II do not require surgical,

132 endoscopic and radiological intervention whereas grade III does. Grade IV events are life-

133 threatening requiring either intermediate care or intensive care unit management. Death of a

134 patient is considered an AE of grade V. Patients in this study with grade III or above events

135 were considered to have had a 'major' AE whereas those who had an AE below grade three

136 were considered 'minor'.

137

138 AEs were prospectively collected and matched with cost data from the hospital's clinical

139 costing and casemix unit and linked to demographical, clinical and histopathological data.

140 Data linkage was achieved using a hospital identification number. The cost information was

141 retrieved from the hospital's detailed costing system (Transition Systems Inc) which tracks all

142 the resources used in caring for the patient. The total cost for the aggregated hospital

143 resources used by each patient was provided to the research team and no further breakdown of

144 the types of hospital resources were provided. As specific resource quantities were not

145 separated from costs, here we used the aggregated cost figure and assumed that excess costs

146 for the group of patients with AEs were fully attributed to the AEs.

147

148 **Statistical analyses**

149 Descriptive statistics were used to show baseline characteristics of patients. Multivariate

150 modeling was used to quantify costs attributed to AEs adjusted for various clinical factors.

151 As health cost data is commonly skewed to reflect that some patients accrue very high costs,

152 total patient costs for patients were log-transformed before using multivariate ordinary least

153 squared regression. Re-transforming costs back to the raw cost scale were achieved with

154 Duan's smearing factors [9]. We tested the model assumptions by examining the normality

155 and heteroskedasticity of residuals while goodness-of-fit and model specification was

156 assessed with the adjusted R^2, Pregibon's link test, Ramsey's reset test and the v-fold cross-

157 validation Copas test for over-fitting [10]. Stratification by patients receiving a laparoscopy or

158 laparotomy was also performed.

159

160 To extrapolate the costs of AEs attributed to gynecological oncology Australia-wide, we

161 multiplied the cost figures to all new cases (ICD10, C51-C58) from the latest national

162 incidence report [11] after inflating the number of cases to account for suspected cases of

163 cancer later found to be benign (n=5736). One-way sensitivity analyses were performed to

164 test if changing the probabilities of intra-operative, minor and major post-operative AEs by

165 ±10% and ±20%, substantially varied the overall results. To account for multiple parameter

166 uncertainty, probabilistic sensitivity analysis was performed where beta distributions were

167 assigned to probabilities and gamma distributions to costs. Monte Carlo simulations were

168 performed (5736 times) and total costs generated under different scenarios where the

169 proportions of AEs were altered. STATA SE (version 11.0, StataCorp, Tx) and TreeAge Pro

170 (2009) was used for statistical analyses. Costs are reported in 2008 (the year of data

171 collection) Australian dollars.

172
173
174 **Results**
175
176 Overall the 369 women in the study ranged in age from 13 to 91 years with a mean (SD) age

177 at the time of surgery of 56.3 (14.4) years with 63 patients (17.1%) aged≥ 70 years (Table 1).

178   The mean (SD) BMI was 30.3 (8.2) kg/m² with 44.7% of patients classified as obese (BMI ≥

179   30).

180

181   The most common surgical procedures were hysterectomy and salpingo-oophorectomy

182   followed by pelvic, para-aortic and groin lymph node dissection (Table 1). Nearly 73% of the

183   patients underwent at least one procedure with a complexity grade 1. There was a significant

184   difference in the distribution of surgical complexity (p=0.003) among AE categories with

185   very complex procedures associated with major AEs. One hundred and forty five (39.4%)

186   patients had a laparoscopic procedure. The proportions of patients who underwent

187   laparoscopic procedures differed significantly between the AE categories (p=0.027) with

188   lower rates of post-operative AEs noticed among patients who underwent a laparoscopic

189   procedure. Nine patients (2.4%) required a conversion from a laparoscopic procedure to an

190   abdominal procedure mostly due to dense adhesions and/or intra-operative complications.

191   Two thirds (65%) of the patients required surgery for a malignant condition and 92% of the

192   pathology was related to the ovaries or uterus.

193

194   Of the 369 patients, 95 (26%) developed at least one AE (Table 2) and 16 (4.3%) developed

195   two or more AEs. Eighteen patients (4.9%) had at least one intra-operative AE without any

196   post-operative AE. Sixty-three patients (17%) had at least one minor post-operative AE

197   (either grade I or II). Fourteen patients (3.8%) had major AEs and included one patient who

198   developed multi-organ dysfunction and died post-operatively (grade V). The most common

199   intra-operative AE was injury to the bowel (2.7%) followed by injuries to the bladder and

200   blood vessels (both 1.6%). Wound-related issues were the most common post-operative AEs

201   with 33 (9%) women developing at least one wound infection and/or wound dehiscence

202   and/or hematoma.

203

204   Hospital length of stay was 6.4 days (SD 11.1) on average for all women and ranged from 0.4

205   to 196 (Table 3). Women with major post-operative AEs had the longest average stay of 32.8

206   days (95% CI: 4.2 to 61.5) compared with those with minor AEs (8.0 days, 95% CI: 7.2 to

207   8.8), intra-operative AEs (18.1 days, 95% CI: 4.2 to 32.0) and no AEs (4.8 days, 95% CI: 4.5

208   to 5.1).

209

210   In the log-transformed regression model, the residuals were heteroskedastic with respect to

211   presence of AEs and therefore costs were re-transformed to the raw cost scale with separate

212   Duan's smearing estimators for patients with or without AEs (Table 3). Adjusted mean

213   hospital costs were AU$12,872 for patients with no AEs compared with AU$25,652 for

214   patients with AEs (Table 3). Patients with AEs incurred an extra AU$12,780 on average,

215   adjusted for age, comorbidities, ovarian cancer, weighted activity unit (a measure of the

216   relative value of care and resource utilization provided to patients), major or minor AEs,

217   surgical complexity, presence of malignancy and abdominal surgery. Adjusted mean costs

218   were significantly higher for patients with intra-operative AEs (AU$40,746), minor post-

219   operative AEs (AU$18,459), major post-operative AEs (AU$67,656), those who received

220   abdominal surgery (AU$17,644), complex surgery (AU$16,706), very complex surgery

221   (AU$30,328) and patients with malignant tumors (AU$16,857) compared to patients with no

222   AEs (AU$12,872). Overall, the log-transformed model exhibited good fit and performance as

223   indicated by the adjusted R^2=0.63 (354 degrees of freedom), the link test (p=0.29), the Copas

224   test (β=0.97, p= 0.46) but the model failed the Ramsey reset test (p=0.03).

225

226   Stratified analyses by patients receiving either laparoscopy (n=145) or laparotomy (n=224),

227   indicated that the adjusted mean costs were higher, overall, for laparotomy AU$ 17,657 (95%

228 CI $16,187, $19,127) than laparoscopy AU$ 13,612 (95% CI $8,642, $18,582)(Table 4).

229 Adjusted LOS was also higher overall for laparotomy 7.9 days (95% CI 7.2, 8.5 days) than

230 laparoscopy 4.7 days (95% CI 1.2, 8.2 days). Adjusted mean costs were AU $4,000 to $5,000

231 higher for patients receiving laparotomy compared with laparoscopy when there were no

232 complications or no major postoperative complications. When laparoscopy was used to treat

233 patients with confirmed malignancy, adjusted costs were substantially lower, AU$ 12,300

234 (95%CI: $11,525, $13,075) versus laparotomy AU$19,168 (95%CI: 17,159, $21,176). For

235 patients receiving either laparoscopic or laparotomy surgery, adjusted costs were higher for

236 patients with ovarian cancer, compared with patients with other gynecological cancers but

237 tumor site was not a strong predictor of patient costs (Table 4).

238

239 When our adjusted cost predictions for AEs were extrapolated to all gynecological cancers

240 Australia wide, based on 4243 new cases of gynecological cancer in 2006[11], average

241 hospitalization costs for patients with adverse events were an estimated AU$51.2 million

242 annually. This comprises patients with intra-operative complications of AU$18.4 million

243 (17%), minor post-operative complications of AU$18.1 million (17%) and major post-

244 operative complications AU$14.7 million (14%). Sensitivity analyses indicated that when the

245 proportion of intra-operative and minor or major post-operative complications varied by ±

246 10% or ±20%, relatively small changes to our base estimates occurred (Table 5). In

247 multivariate sensitivity analyses, cost-savings per year could vary from AU$5.02 million

248 (assuming 10% reduction in all AEs) to AU$20.62 million (assuming 40% reduction in all

249 AEs) (Table 6). Reductions in minor post-operative AEs had the greatest potential for

250 generating cost-efficiencies.

251
252 **Discussion**
253

254   A quarter of all patients requiring surgery for proven or suspected gynaecological cancer

255   develop at least one adverse event (AE) and incur higher hospitalization costs and longer

256   hospital stays. This study highlights that even when relevant risk factors are controlled for, the

257   costs remain significantly high in comparison with those who did not experience any AEs.

258   Our findings also confirm that patients receiving laparoscopic surgery in this sub-specialty

259   have shorter hospital stays and incur overall lower costs than those receiving more traditional

260   open surgical techniques.

261

262   Most of the information currently available on the incidence of surgical AEs has been

263   obtained from surgery for benign gynecological conditions. The incidence rates of bladder

264   and ureteral injury are 1.6% and 0.5%, respectively, in this series which compares well with

265   3.6% and 1.7% in the current literature [12, 13]. The incidence of post-operative wound-

266   related issues varies from 3% to 10% in the literature [14] whereas in our study it was 9%.

267   Post-operative cardiac complications are also within expectations in our study (1.9%)

268   compared to the published literature (3%) [15]. In general, the rates of AEs in our series are

269   comparable to the rates published for patients treated for benign gynecological conditions.

270   Sixty-five percent of patients in our series had a malignant condition and our study shows that

271   AEs are more common among patients with a malignant condition (30%) compared to

272   patients who underwent surgery for prophylaxis or a benign condition (p=0.009). However,

273   our study also shows that AE rates associated with procedures performed by trainees were not

274   significantly different to those of certified gynecologic oncologists (p=0.522).

275

276   A major strength of our study is that the AEs were collected prospectively on a consecutive

277   real-world sample of gynecological patients with minimal missing data. This avoids the

278   criticism of under-reporting associated with retrospective studies on selected patients.

279 Furthermore, surgeons and other staff were blinded to study participation and therefore were

280 unlikely to bias patient selection and subsequent management or change their routine use of

281 hospital resources. However, our patients were recruited from a single, high-volume tertiary

282 referral center and therefore omit the potential variation in outcomes that may exist among

283 patients across multiple health care facilities, and treated by a range of physicians. Patients

284 treated in private health care facilities may have different AE rates and associated costs than

285 those treated in public hospitals. However, we have addressed this uncertainty using

286 probabilistic sensitivity analysis and found results ~~to be robust~~were stable to plausible

287 variations in incidence of AEs. The regression modeling that we used may underestimate the

288 actual costs associated with AEs, as our analyses were limited to events identified during the

289 episode of care and up to a maximum of 30 days. Also, indirect costs such as patient and

290 family travel and out-of-pocket expenses, time spent caring for the patient, and community

291 health resources utilized, have not been taken into account. Therefore the true burden of AEs

292 on patients and society will be higher.

293

294 We performed a sensitivity analysis with the incidence rates of intra-operative and post-

295 operative AEs varying by ± 10% and ± 20% (Table 5). Evidence suggests that certain

296 interventions may reduce the incidence of surgical complications [16]. Assuming a

297 conservative 20% reduction across all complications, the savings Australia-wide will be at

298 least AU$3.8 million from intra-op AEs, AU$3.6 million from minor AEs and another

299 AU$2.9 million from major AEs. Our prior work on surgical risk prediction can help identify

300 those who are at a higher risk for AEs and appropriate precautions can be taken to minimize

301 such events [7]. This risk scoring system has attracted attention among specialists in the field

302 of gynecologic oncology [17-19].

303

304   Innovative medical technologies, improvements in overall survival, greater emphasis on the

305   quality of delivered care and increasing disease burden all contribute to escalating health care

306   costs and straining health care budgets in most developed countries. Even though we used

307   conservative estimates of 10% and 20% reduction in AE rates, some researchers estimate that

308   40% of AEs are preventable [20]. If reductions in AE of this magnitude can be achieved, it

309   will significantly reduce patient suffering, enable a speedier recovery, improve their hospital

310   experience and ultimately, reduce excess hospital costs.

311

312   In conclusion, AEs in gynaecological oncology may occur in 26% of patients with 4%

313   considered to be of major severity. Hospital costs attributed to AEs are in the order of

314   AU$12,780 per patient in our sample, on average, but are significantly higher for those with

315   major complications and receiving laparotomies after accounting for baseline risk factors.

316   There is considerable scope for hospital cost-savings if evidence-based mechanisms to reduce

317   the incidence of adverse events are adopted.

318

319

320 **Conflict of interest statement:**
321
322 Prof. Andreas Obermair runs a subscription based website (www.surgicalperformance.com)
323 which can be used as a tool by the surgeons to audit their performance.
324
325 All the other authors have declared that there are no conflicts of interest.
326
327

332

333 **References:**

334 [1]   Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The

335 Quality in Australian Health Care Study. Med J Aust l1995;163: 458-71.

336 [2]   Runciman WB, Moller J. Iatrogenic injury in Australia. Adelaide: Australian Patient

337 Safety Foundation 2001.

338 [3]   Ehsani JP, Jackson T, Duckett SJ. The incidence and cost of adverse events in

339 Victorian hospitals 2003-04. Med J Aust l2006;184: 551-5.

340 [4]   Khuri S, Daley J, Henderson W. The department of veterans affairs' NSQIP: the first

341 national, validated, outcome-based, risk-adjusted, and peer-controlled program for the

342 measurement and enhancement of the quality of surgical care. Annals of surgery l1998;228:

343 491-507.

344 [5]   Khuri SF, Daley J, Henderson WG. The comparative assessment and improvement of

345 quality of surgical care in the Department of Veterans Affairs. Arch Surg l2002;137: 20-7.

346 [6]   Friese CR, Aiken LH. Failure to rescue in the surgical oncology population:

347 implications for nursing and quality improvement. Oncol Nurs Forum l2008;35: 779-85.

348 [7]   Kondalsamy-Chennakesavan S, Bouman C, De Jong S, Sanday K, Nicklin J, Land R,

349 Obermair A. Clinical audit in gynecological cancer surgery: development of a risk scoring

350 system to predict adverse events. Gynecol Oncol l2009;115: 329-33.

351 [8]   Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new

352 proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg

353 l2004;240: 205-13.

354 [9]   Jones AM. Models for health care. HEDG Working Paper 10/01. In: Health

355 Econometrics and Data Group. Heslington, York, UK: The University of York; 2010.

356 [10]   Cameron A, Trivedi P. Microeconometrics Using Stata. Revised Ed. Revised Ed ed.

357 Texas, USA: StataCorp LP; 2009.

358 [11] Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and
359 Mortality (ACIM) books. In. Canberra: Australian Institute of Health and Welfare (AIHW);
360 2009.

361 [12] Bai SW, Huh EH, Jung da J, Park JH, Rha KH, Kim SK, Park KH. Urinary tract
362 injuries during pelvic surgery: incidence rates and predisposing factors. Int Urogynecol J
363 Pelvic Floor Dysfunct l2006;17: 360-4.

364 [13] Vakili B, Chesson RR, Kyle BL, Shobeiri SA, Echols KT, Gist R, Zheng YT, Nolan
365 TE. The incidence of urinary tract injury during hysterectomy: a prospective analysis based
366 on universal cystoscopy. Am J Obstet Gynecol l2005;192: 1599-604.

367 [14] Wechter ME, Pearlman MD, Hartmann KE. Reclosure of the disrupted laparotomy
368 wound: a systematic review. Obstet Gynecol l2005;106: 376-83.

369 [15] Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH. Surveillance
370 and prevention of major perioperative ischemic cardiac events in patients undergoing
371 noncardiac surgery: a review. CMAJ l2005;173: 779-88.

372 [16] Kable A, Gibberd R, Spigelman A. Adverse events in surgical patients in Australia.
373 International journal for quality in health care l2002;14: 269-276.

374 [17] Li AJ. Application of a risk scoring system to predict surgical adverse events in the
375 management of epithelial ovarian cancers. Gynecol Oncol l2009;115: 323-4.

376 [18] Zighelboim I, Kizer N, Taylor NP, Case AS, Gao F, Thaker PH, Rader JS, Massad
377 LS, Mutch DG, Powell MA. "Surgical Apgar Score" predicts postoperative complications
378 after cytoreduction for advanced ovarian cancer. Gynecol Oncol l2010;116: 370-3.

379 [19] Jones III JW. Editorial comment: Operative gynecology. Obstetrical & Gynecological
380 Survey l2010;65: 93-94.

381 [20] Neale G, Woloshynowych M. Retrospective case record review: a blunt instrument
382 that needs sharpening. Qual Saf Health Care l2003;12: 2-3.

Table 1. Patient characteristics and surgical factors by broad type of adverse event

Characteristics	No AE (n=274)	Intra-op AE (n=18)	Minor post-op AE (n=63)	Major post-op AE (n=14)	Total (n=369)
Demographics					
Age, years, mean (SD)	55.2 (14.5)	57.2 (13.4)	59.0 (14.1)	65.1 (10.9)	56.3 (14.4)
Risk factors					
Hypertension, n (%)	88 (32.1)	8 (44.4)	23 (36.5)	6 (42.9)	125 (33.9)
Diabetes, n (%)	25 (9.1)	2 (11.1)	10 (15.9)	4 (28.6)	41 (11.1)
Cardiac, n (%)	24 (8.8)	2 (11.1)	5 (7.9)	2 (14.3)	33 (8.9)
Respiratory, n (%)[1]	9 (3.3)	3 (16.7)	1 (1.6)	3 (21.4)	16 (4.3)
Neurologic, n (%)	16 (5.8)	1 (1 5.6)	3 (4.8)	3 (21.4)	23 (6.2)
Chronic kidney disease, n (%)	5 (1.8)	0 (0.0)	0 (0.0)	1 (7.1)	6 (1.6)
Psychological, n (%)	30 (11.0)	4 (22.2)	7 (11.1)	2 (14.3)	43 (11.7)
Prior surgery, n (%)[1]	57 (20.8)	8 (44.4)	9 (14.3)	5 (35.7)	79 (21.4)
Disseminated cancer, n (%)	21 (7.7)	2 (11.1)	6 (9.5)	2 (14.3)	31 (8.4)
Clinical characteristics					
Height (cm), mean (SD)[2]	160.5 (6.6)	158.6 (7.2)	158.4 (6.8)	158.3 (6.1)	159.9 (6.7)
Weight (Kg), mean (SD)	76.1 (20.9)	83.5 (30.9)	80.5 (18.9)	77.2 (20.2)	77.2 (21.2)
BMI (Kg/m^2), mean (SD)[2]	29.6 (8.0)	33.0 (11.5)	32.1 (7.9)	30.7 (7.2)	30.3 (8.2)
Systolic BP (mmHg), mean (SD)	122.7 (19.0)	121.4 (14.1)	127.1 (17.2)	126.7 (28.0)	123.6 (18.9)
Diastolic BP (mmHg), mean (SD)[1]	71.6 (11.0)	66.0 (9.2)	73.3 (10.6)	66.4 (14.4)	71.4 (11.1)
Surgical complexity[1,3]					
Complex procedures, category 0	84 (30.7)	3 (16.7)	11 (17.5)	2 (14.3)	100 (27.1)
Complex procedures, category 1	174 (63.5)	12 (66.7)	48 (76.2)	7 (50.0)	241 (65.3)
Complex procedures, category 2	16 (5.8)	3 (16.7)	4 (6.4)	5 (35.7)	28 (7.6)
Laparoscopy[1]	118 (43.1)	8 (44.4)	15 (23.8)	4 (28.6)	145 (39.3)
Surgical procedure by a trainee	54 (19.7)	6 (33.3)	13 (20.6)	3 (21.4)	76 (20.6)
Diagnosis					
Benign	95 (34.7)	3 (16.7)	14 (22.2)	2 (14.3)	114 (30.9)
Malignant	167 (61.0)	13 (72.2)	47 (74.6)	12 (85.7)	239 (64.8)
Prophylactic	12 (4.4)	2 (11.1)	2 (3.2)	0 (0.0)	16 (4.3)
Primary pathology					
Cervical	15 (5.5)	3 (16.7)	6 (9.5)	0 (0.0)	24 (6.5)
Ovarian	138 (50.4)	10 (55.6)	30 (47.6)	8 (57.1)	186 (50.4)
Uterine	119 (43.4)	4 (22.2)	26 (41.3)	5 (35.7)	154 (41.7)
Vulval/vaginal	2 (0.7)	1 (5.6)	1 (1.6)	1 (7.1)	5 (1.4)

384 AE: Adverse Event; BMI: Body Mass Index; BP: Blood Pressure; SD: Standard Deviation;
385   1. Significant difference in the distribution (P<0.05);
386   2. Four patients had missing information
387   3. Complex procedures in category 1 include any of the following: Radical hysterectomy, pelvic
388   lymphadenectomy, para-aortic lymphadenectomy, omentectomy, adhesiolysis and ureterolysis;
389   Complex procedures in category 2 include any of the following: anterior rectal resection, colonic
390   resection, small bowel resection, exenteration, urinary conduit, splenectomy, (sub) total peritonectomy
391   and resection of the diaphragm. All other procedures were considered category 0.

Table 2. Incidence of adverse events

	N	*%*
Total number of patients operated	369	
Patients with at least one adverse event	95	25.7
Patients with 2 or more events	16	4.3
Intra-operative adverse events	29	7.9
Bowel injury	10	2.7
Bladder injury	6	1.6
Vascular injury	6	1.6
Intra-operative blood transfusion	6	1.6
Nerve, ureteric and or other injuries	4	1.1
Post-operative adverse events	77	20.9
Wound related	33	8.9
UTI	8	2.2
Renal	5	1.4
Gastric ileus	7	1.9
Pneumonia	9	2.4
Cardiac	7	1.9
Pelvic abscess/secondary hematoma	4	1.1
Septicemia	2	0.5
DVT	3	0.8
Lymphoedema	3	0.8
Other*	13	3.5

UTI=Urinary tract infection, DVT= Deep vein thrombosis
*Other= multi organ failure, abscess, stroke, neuropathy, encephalopathy and psychological.

395 **Table 3. Median and adjusted average hospital costs (2008 AUD) and length of stay**
396

Hospital costs	N (%)	Total cost (AU$)	% of total cost	Median cost, AU$ (IQR)	Average cost per patient*	95% CI*		Excess cost
No AE	274 (74.3)	$3,533,965	53%	$11,842 ($9,791-15,120)	$12,872	$12,460	$13,277	Ref
Intra-op AE	29 (7.9)	$1,093,510	16%	$18,069 ($12,131-33,259)	$40,746	$11,582	$71,859	$27,874
Minor post-op AE	63 (17.1)	$1,192,691	18%	$15,903 ($12,196-21,355)	$18,459	$17,270	$19,713	$5,587
Major post-op AE	14 (3.8)	$813,737	12%	$27,769 ($16,484-50,899)	$67,656	$5,324	$131,761	$54,784
	Total	$6,633,903						

Length of stay (LOS)	N (%)	Total LOS	% of total LOS	Median LOS, Days (IQR)	Average LOS*	95% CI		Excess LOS
No AE	274 (74.3)	1331.9	49%	4.91 (2.2-6.2)	4.8	4.5	5.1	Ref
Intra-op AE	29 (7.9)	462.6	17%	7.1 (5.3-13.0)	18.1	4.2	32	13.3
Minor post-op AE	63 (17.1)	526.9	20%	7.0 (5.1-9.4)	8	7.2	8.8	3.2
Major post-op AE	14 (3.8)	372.9	14%	11.5 (8.3-20.9)	32.8	4.2	61.5	28
	Total	2694.3						

397
398 *Log transformed regression with back-transformation on raw cost scale using smearing factors, costs are adjusted for types of AEs, weighted activity unit, age, presence of malignancy, surgical
399 complexity, laparotomy, tumor type and multiple comorbidities;
400
401 Abbrevs: IQR: Inter Quartile Range; AE: Adverse Event; LOS: Length of Stay
402

Table 4. Subgroups of adjusted mean costs stratified by laparoscopy versus laparotomy

		\multicolumn{4}{c}{Laparoscopy[2]}				\multicolumn{4}{c}{Laparotomy[3]}			
		n	mean	\multicolumn{2}{c}{95% CI}		n	mean	\multicolumn{2}{c}{95% CI}	
Overall		145	$ 13,612	$ 8,642	$ 18,582	224	$ 17,657	$ 16,187	$ 19,127
Any complications	yes	27	$ 28,780	$ 1,450	$ 56,109	68	$ 23,796	$ 19,367	$ 28,225
	no	118	$ 10,141	$ 9,861	$ 10,422	156	$ 14,981	$ 14,461	$ 15,502
Major postop complications	yes	4	$ 107,760	-$ 174,385	$ 389,906	10	$ 47,422	$ 19,073	$ 75,772
	no	141	$ 10,941	$ 10,450	$ 11,433	214	$ 16,266	$ 15,655	$ 16,877
Minor postop complications	yes	15	$ 16,701	$ 14,050	$ 19,352	48	$ 18,930	$ 17,789	$ 20,072
	no	130	$ 13,256	$ 7,715	$ 18,796	176	$ 17,310	$ 15,463	$ 19,157
Ovarian cancer	yes	56	$ 16,053	$ 3,425	$ 28,681	130	$ 18,362	$ 16,014	$ 20,710
	no	89	$ 11,972	$ 11,235	$ 12,709	94	$ 16,660	$ 15,393	$ 17,927
Complex surgery	yes	66	$ 17,728	$ 6,751	$ 28,705	175	$ 16,186	$ 15,581	$ 16,792
	no	79	$ 10,173	$ 9,701	$ 10,646	49	$ 22,910	$ 16,596	$ 29,224
Very complex surgery	yes	0	-	-	-	28	$ 29,967	$ 19,574	$ 40,360
	no	145	-	-	-	196	$ 15,899	$ 15,298	$ 16,499
Malignant tumor	yes	80	$ 12,300	$ 11,525	$ 13,075	159	$ 19,168	$ 17,159	$ 21,176
	no	65	$ 15,227	$ 4,027	$ 26,426	65	$ 13,963	$ 13,228	$ 14,698

405
406
407
408
409
410
411

1. Adjusted for age, any complications, minor postop complications, major postop complications, weighted activity unit, malignant, ovarian cancer, complex surgery, very complex surgery.
2. Laparoscopy model performance: Adj R square=0.65, link test p=0.26, Ramsey reset test=0.54 and Copas test beta=0.72 p=0.09
3. Laparotomy model performance: Adj R square=0.49, link test p=0.52, Ramsey reset test=0.00(failed) and Copas test beta=0.84 p=0.05

412 Table 5. Summary of extrapolation to all Australian patients with suspected and confirmed gynecological cancers and one-way sensitivity
413 analyses (n=5736*)
414

	AU$ 2008 in million	% total costs
Total costs all cases	105.99	100%
Total costs of cases with AE	51.17	48%
Total costs of cases with intra-op AEs	18.37	17%
Total costs of cases with minor post-op AEs	18.08	17%
Total costs of cases with major post-op AEs	14.72	14%
Baseline total costs	105.99	
	+ 10%	-10%
Change in % no AEs	100.51	111.47
Change in % intra-operative cases	107.84	104.17
Change in % minor post-operative cases	107.80	104.18
Change in % major post-operative cases	107.44	104.53
	+20%	-20%
Change in % no AEs	95.02	116.96
Change in % intra-operative cases	109.67	102.34
Change in % minor post-operative cases	106.61	102.37
Change in % major post-operative cases	108.93	103.04

415
416 *n=5736 calculated based on 4243 new cases of gynaecological cancer inflated to include benign and prophylactic cases (by factor 1.352).
417

418 Table 6. Estimated total hospital costs for all Australian gynecology oncology patients under different scenarios in the proportion of AEs (n=5736*)
419

Scenario	Cost-savings (AU$ 2008) in million	Australia-wide (AU$ 2008) in million
Baseline case (no reduction)	-	103.73**
Intra-operative AEs		
10% reduction	1.75	101.98
20% reduction	3.79	99.94
40% reduction	7.38	96.35
Minor post-operative AEs		
10% reduction	1.81	101.92
20% reduction	3.62	100.11
40% reduction	7.25	96.48
Major post-operative AEs		
10% reduction	1.46	102.27
20% reduction	2.86	100.87
40% reduction	5.99	97.74

420
421 *Results based on 5736 simulations in probabilistic sensitivity analyses. N has been calculated based on 4243 new cases of gynaecological cancer inflated to include benign and prophylactic
422 cases (by factor 1.352). AE: Adverse Event, AUD Australian Dollar
423 **This baseline estimate is slightly different than in Table 5 ($105.99) because it is based on probabilistic sensitivity results.
424
425