Ultra-radical surgery compared to standard surgical treatment for women with advanced ovarian cancer: a cost-effectiveness analysis

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Shortened title: *Cost-effectiveness of ultra-radical surgery for ovarian cancer*

Objective To compare current surgical practice for women with AOC to ultra-radical surgery; to assess whether the new approach would be cost-effective under NICE guidelines of approximately £20,000/QALY.

Design Cost-effectiveness analysis.

Setting NHS, using data from a variety of sources.

Population Patients with advanced ovarian cancer (FIGO stages IIIC-IV).

Methods A decision analytic model (microsimulation model) was built to examine the Objective; deterministic and probabilistic sensitivity analyses were used to test the susceptibilities of the baseline model and its assumptions.

Main Outcome Measures ICER (incremental cost-effectiveness ratio).

Results The standard model yielded an ICER of £5325.06; this is in spite of an associated overall decrease in utility due to predicted increase in surgical mortality. The parameters with the most significant impact on the ICER are the cost of ultra-radical surgery, the utility associated with progression-free survival, and the probability of death from ultra-radical surgery.

Conclusions Ultra-radical surgery is cost-effective under NICE willingness-to-pay thresholds of £20000; the costs of ultra-radical surgery are bound to decrease as centres

specialise further, and its effectiveness is also likely due to increase with development of newer techniques and more surgical training.

Tweetable abstract Ultra-radical surgery for advanced ovarian cancer is cost-effective under NICE willingness-to-pay threshold.

Introduction

Overview and prevalence

Ovarian cancer is the sixth most common type of cancer affecting women in the UK.[1] Over 7400 cases of ovarian cancer are diagnosed in the UK each year, 53% of them in women over 65. About 50% of these patients are confirmed to have advanced ovarian cancer (AOC), FIGO stages IIIC-IV.[2]

Ovarian cancer is the deadliest of gynaecological malignancies (10-year survival: 35%). In 2017, ovarian cancer led to over 4116 deaths in the UK.[3] High mortality is due to multiple factors, including late diagnosis,[4] but also incomplete surgical cytoreduction, which is an independent predictor of survival.[5, 6, 7, 8]

Treatment options

The mainstay of treatment for AOC consists of cytoreductive surgery, platinum-based chemotherapy (carboplatin/paclitaxel) and novel chemotherapeutic agents such as angiogenesis inhibitors (Bevacizumab) and PARP inhibitors (Olaparib, for BRCA-positive patients). Traditionally, surgical treatment was focused on pelvic disease, including total abdominal hysterectomy with bilateral salpingo-oopherectomy (TAHBSO), omentectomy and nodal resections.[9] However, following emerging data in the US and Europe, the National Institute for Heath and Care Excellence (NICE) gave guidance in 2013 for more extensive “ultra-radical (cytoreductive) surgery” to be introduced into gynaecological cancer centres, with the requirement of special arrangements for clinical governance, consent and audit of patients undergoing such extensive surgery. The definition of what constitutes ultra-radical surgery is unclear in NICE guidance[10]; in this analysis, it includes diaphragmatic and peritoneal stripping, multiple resections of the bowel (excluding localised colonic resection), liver resections, partial gastrectomy, cholecystectomy or splenectomy.

Despite the introduction of a framework to introduce ultra-radical surgery, uptake across the UK is variable[11]. NICE guidance expressed caution regarding ultra-radical surgery due to perceived increased risk of morbidity/mortality. Subsequent reviews have found that the NICE definition poorly predicts morbidity/mortality compared to other measures of surgical extent.[10] However, with increasing surgical extent one would expect, *ceteris paribus*, a greater rate of postoperative morbidity and mortality. Therefore, there is a balance between the benefits of achieving complete cytoreduction, which improves survival, and the mortality risk of ultra-radical surgery. Because ultra-radical surgery is associated with higher costs, the purpose of this study is to determine whether offering ultra-radical surgery to all women with AOC would be cost-effective under NICE economic evaluation guidelines.

Aim

To conduct a cost-effectiveness analysis comparing standard surgery to ultra-radical surgery for AOC patients by using a decision-analytic model; to assess whether the new approach would be cost-effective under NICE guidelines of approximately £20,000/QALY.

Methods

Economic evaluation

Current practice in gynaecological oncology is rapidly evolving: the use of economic evaluation methods plays an important role in providing an evidence base for the adoption of new practices within the NHS. Economic evaluation allows policy-makers to decide between two alternatives in systematic, explicit and accountable manner[12]. Cost-effectiveness analysis using QALYs (quality-adjusted life-years) is the ideal method of economic evaluation to evaluate health interventions, allowing for the comparison between different types of interventions and different disease areas, and weighting any increase in survival by the quality of life experiences by patients.[13]

Model overview

A patient-level microsimulation model was developed in TreeAge Pro 2019 (v 19.2.1) software (TreeAge Software, Inc., Williamstown, MA). Microsimulation models simulate the experience of individuals, allowing for the analysis of a cohort with heterogeneous risk characteristics, and of problems where risk is dependent on time and on previous health states.[14]

The model assumes the perspective of the UK National Health Service; discounting of both costs and outcomes is 3.5%, in accordance with NICE guidelines.[15] Interestingly, because some methods used to determine utilities already factor in time (e.g. time trade-offs), discounting outcomes at the same rate as costs tends to underestimate the benefits of a new intervention[16]. NICE's required measure of effect is the

QALY, which represents increases in the length of survival adjusted by utility values attributed to different health states. Utility values vary between 0 (death) to 1 (full health).

The model reflects the pathways taken by an ovarian cancer patient entering the health service, including the costs of diagnosis, treatment and follow-up. Every cycle in the model represents one year; during any given cycle, the patient can either survive (in which case they would accrue additional treatment costs until death or remission), or die from their ovarian cancer.

The model takes on a lifetime time horizon, to best reflect the downstream costs and outcomes accrued by individual patients. A half-cycle correction was applied both during the first and during the final cycle of the simulation to take into account the fact that most transitions from one health state to the next occur anytime during the year-cycle, not precisely at its end[17].

Cost-effectiveness measure

The primary measure of cost-effectiveness produced by the model is an incremental cost-effectiveness ratio (ICER). The ICER is calculated with the formula:

$$ICER = \frac{C_1 - C_0}{E_1 - E_0}$$

where C_1 represents the cost of the alternative treatment (ultra-radical surgery), and C_0 is the cost of the control treatment (standard surgery). The difference between the costs is divided by the difference between E1 (the effect of the alternative) and E0 (the effect of the control). The ICER represents the average incremental cost per one unit of effect (for example, per QALY) gained[13].

Probabilities

The ovarian cancer yearly mortality rate from recurrence (0.1732) was derived from Office of National Statistics data (5-year survival rates)[3]. All-cause mortality for all age groups was estimated from Office of National Statistics tables.[18]

Cost data

Costs were compiled from UK-based reference guidelines;[25] they were complemented and validated using Royal Derby Hospital data. They are reported in British pounds and were not subject to currency conversion.

Utility values

Utility values range between 0 (death) and 1 (full health). They were compiled from preliminary results from the Surgery in Ovarian Cancer - Quality of Life Evaluation Research (SOCQER 2) study, which aims to evaluate QoL in the short, medium and long-term after OC surgery.[27]

Other assumptions

- The average age of AOC diagnosis at Royal Derby Hospital is 63; to reflect this, the distribution of age at diagnosis for the model starts at 60 years of age. The distribution was derived from Cancer Research UK data tables.
- The time horizon for the model is 30 years; this goes well over UK life expectancy for women (82.9 years)[19] so as to more fully reflect lifetime costs and benefits.
- The rate of ultra-radical surgery in the non-intervention branch of the model is held at zero.[29]
- Ascertaining mortality rates for "ultra-radical surgery" is a complex task, as these are poorly described in the literature. NICE guidance on ultra-radical surgery suggests death rates of less than 1%;[21] however, the data is based on low-quality evidence with significant limitations. Retrospective review of patients undergoing extensive surgery have wide variations in mortality rates and all have their own inherent biases; some of the values reported in the literature include 0.7%[24], 1.2%[10, 21], 1.7%[30], 3.1%[31], and 3.6%[32]. For the purpose of this study the mortality rate in the ultra-radical arm of the model was set at 3.0% - consistent with local data,[22] and comparable to other published cohort studies.
- BRCA mutation-related treatment and associated costs were modeled, but any BRCA-related breast cancer and associated morbidity/mortality were not included.
- Some studies have found BRCA mutations to have an effect on 5-year survival for patients with ovarian cancer, with BRCA2 in particular leading to a better prognosis; the use of PARP inhibitors in this cohort has the potential to significantly decrease the risk of disease progression or death (by up to 70%)[33]. However, other evidence seems to indicate that long-term survival is not affected by BRCA mutations[34]. As such, the model makes a simplifying assumption that ovarian cancer survival is the same for all AOC patients, regardless of genetic mutations.
- The 5-year mortality for AOC is held to be constant over the 5-year period.

Sensitivity analyses

To test the robustness of the model, a one-way deterministic sensitivity analysis was carried out on key parameters of interest, such as mortality from surgery, costs, and utility scores, by varying one parameter at a time, all else held constant.

A Monte Carlo probabilistic sensitivity analysis (PSA) was then carried out to test parameter uncertainty by varying all parameters simultaneously, as recommended by NICE.[35] The distributions for the parameters included in the PSA were assigned as follows;[36]

- Beta distribution for transition probabilities, as these can only take values of between 0 and 1. The uncertainty in this type of distribution is defined by the parameters α and β, where:

  $\alpha = mean - \left(\frac{mean(1-mean)}{SE^2} - 1\right)$ and $\beta = \frac{alpha(1-mean)}{mean}$
- The beta distribution was also applied to utility values; this is appropriate as the values under consideration are far from 0, but it also implies that there are no states worse than death (i.e. below 0).
- Costs were taken to follow a gamma distribution, considering the skewness of the data and constraining them not to be negative. The parameters of α and β, in this case, are $\alpha = \frac{(mean)^2}{SE^2}$ and $\beta = \frac{SE^2}{mean}$
- All-cause mortality parameters were not varied in the PSA as they are based on very large studies, leading to less uncertainty; their deterministic values were used instead.

Results

Baseline model

The result of the microsimulation over 100,000 first-order trials yielded a mean ICER of 5325.06 per QALY gained, indicating that the new strategy of ultra-radical surgery for 50.4% of women with an AOC diagnosis is cost-effective under NICE guidelines. There were 8189 fewer deaths from OC associated with this strategy (25,031 vs. 16,842). The expected values for costs and QALYs associated with the two strategies are reported in Table 1.

Deterministic sensitivity analysis

A one-way sensitivity analysis was carried out running microsimulations (100000 trials) on key parameters of interest one at a time and recording their impact on the ICER. Costs were varied by ±30%, utilities by ±25% (upper values were capped at 1); probabilities and risks were varied by ±25% or according to their 95% confidence interval.

Figure 1 shows how the cost of ultra-radical surgery is one of the variables with the largest impact on the ICER, both negatively and positively. The utility associated with progression-free survival also has a sizeable impact; a lower utility is associated with a much higher ICER in this analysis. The probability of death from ultra-radical surgery also has a large impact on the ICER, with a lower death rate bringing about a negative ICER (cost-saving).

Because one-way sensitivity analyses only take into account one variable at a time, they are unable to estimate any uncertainty due to the fact that variables are likely to co-vary and have a downstream effect on one another, thus underestimating the amount of uncertainty. To overcome these limitations, a PSA is more appropriate.

Probabilistic sensitivity analysis

The PSA is used to measure the uncertainty of multiple parameter distributions, sampled at random, which are then combined and varied simultaneously.[36] It was carried out using a Monte Carlo simulation with 100 second-order parameter samples and 100,000 first order simulation trials. The total number of iterations is equal to the number of samples times the number of trials; so, in this case, the PSA ran for 10,000,000 iterations. The benefit of this PSA method is that the results of each iteration come from a set of individual microsimulations, rather than just the simple combination of weighted averages for each strategy.[36]

The cost-effectiveness scatterplot (Figure 2) plotting all iterations of the PSA on the cost-effectiveness plane shows extensive overlap in the "probability clouds" of the two strategies; this indicates that, in most iterations, ultra-radical surgery is only moderately more costly than the standard surgery, while the associated utility is either the same or marginally diminished.

The incremental cost-effectiveness scatterplot (Figure 3) shows that a majority of PSA iterations fall within the southern half of the plot, illustrating the potential for ultra-radical surgery to be cost-saving; because a majority of these iterations fall in the south-western corner, it is also more likely that the utility associated with this strategy would be lower.

Discussion

Main findings

The ICER for the intervention arm of this model, which raises the proportion of OC patients eligible for ultra-radical surgery, is fairly low (£5325.06, well under the NICE £20,000 threshold), in spite of the decreased utility associated with the ultra-radical surgery strategy. This is particularly interesting for two reasons. First, utility values in particular are currently not well-validated with larger studies (in the UK and abroad). More surveys of peri-surgical outcomes and perceptions surrounding fear of recurrence are needed. Secondly, the decreased utility can be mostly attributed to the extra mortality due to surgery itself. Mortality from AOC is diminished in the intervention strategy (8149 fewer ovarian cancer deaths over the course of the model), but this does not compensate for the extra surgical mortality associated with ultra-radical surgery (0.03% vs. 0.01% in standard surgery).

Strengths and limitations

Whether the extra mortality is due to patient characteristics or surgical technique should be a matter of study, as it will be particularly relevant in guiding policy. For ultra-radical surgery to be cost effective we suggest that mortality rate from surgery should be <2.7%. This analysis only included patients aged 60 and above to best represent the patient population at Royal Derby Hospital: data on mortality is taken from a single centre and rates elsewhere may be lower or higher. This should be further investigated, given that the model is highly sensitive to this parameter. Outcomes in younger patients might differ radically, assuming lower rates of comorbidities and higher levels of fitness. It is also worth mentioning that the data sources are mixed between patients who undergo primary debulking surgery (more common in the US literature) and patients who undergo neoadjuvant chemotherapy (UK data) first. We did not differentiate between the two patient cohorts because survival rates are similar, however morbidity tends to be lower for the neoadjuvant chemotherapy patients.

Interpretation

The utility of progression-free survival is one of the variables with the highest single impact on the ICER; this is because, if we accept the empirical evidence that complete cytoreduction is the best predictor of progression-free survival,[5, 6, 7] it follows that patients who have undergone ultra-radical surgery and achieved a complete resection (R0) will spend most time in this state, compared to patients with similar disease who have standard surgery and who therefore will not have R0, accruing more utility every year. The increased availability of maintenance treatment that could benefit R0 resection patients would also allow more patients to spend more time in this state.

From the financial perspective, there is scope for ultra-radical surgery costs to come down. With increased technical standardisation and increasing operating volumes, it is plausible that costs, operative times and mortality would all decrease over time, bringing about a lower (if not cost-saving) cost-effectiveness value. Newer techniques and more training could also lead to decreased ICU stays, which certainly make up a large proportion of the cost component. Using reference costs might not accurately distinguish between more and less intensive OC surgery. While the reference costs data in this model was validated with Royal Derby Hospital administrators, it might not reflect costs in other centres.

Finally, data were heterogeneous. The assumptions outlined in the Methods section are specific to the UK reality or to the University Hospitals of Derby and Burton NHS Foundation Trust; however, the data were gathered from numerous sources. Whilst UK data were used and validated with local hospital departments where possible, some data points were unavailable and were obtained from the literature. Data about recurrence rates, for example, have been drawn from the American context. The majority of American OC patients receiving treatment would need to have private insurance cover (or Medicare if they are over 65 or disabled) to afford the costs of surgery and ancillary treatment; this patient selection is likely to be different from the general population – wealthier, possibly healthier. Considering the differences in healthcare system and patient mix, recurrence rates are likely to be higher in the UK. High-quality, UK-based data is required to best reflect the local population, especially where patients' preferences are concerned, as these may vary due to personal, societal and cultural differences, and may thus not be accurately represented in studies carried out abroad. There is also a need for more data to define the risk of early mortality in ultra-radical surgery, to enable surgeons to more meaningfully counsel patients in regards to their individual risk of surgical mortality.

Since the data sources for parameter values are based on observational studies, outcomes are likely to reflect some residual confounding. The model implicitly assumes that the characteristics of patients undergoing standard and ultra-radical surgery are comparable. This is unlikely to be the case in reality, as some patients undergoing standard surgery may have extensive disease, but by definition patients who have late stage but less extensive disease not requiring extensive surgical procedures will not undergo ultra-radical surgery. To confirm model results, more information on parameter values on women with comparable disease undergoing standard or ultra-radical surgery is needed, but still may be subject to residual confounding.

Conclusion

Offering ultra-radical surgery to more women with AOC would be cost-effective under NICE willingness-to-pay thresholds. More research should be carried out to gather good quality data about progression-free survival, patients' preferences for different health states, as well as peri- and post-operative morbidity and mortality rates. Decreasing costs associated with economies of scale due to surgical centre specialisation, as well as improved surgical training and the introduction of safer techniques, have the potential to further reduce the ICER for this intervention.

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References

1. About ovarian cancer. Available online: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/about (accessed on Jul 13, 2018)
2. Bhatla, N.; Denny, L. FIGO Cancer Report 2018. *International Journal of Gynecology & Obstetrics* 2018, *143*, 2–3, doi:https://doi.org/10.1002/ijgo.12608.
3. Office for National Statistics. Cancer survival in England - adults diagnosed. Available online: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed (accessed on Nov 18, 2019).
4. Bankhead, C.; Collins, C.; Stokes-Lampard, H.; Rose, P.; Wilson, S.; Clements, A.; Mant, D.; Kehoe, S.; Austoker, J. Identifying symptoms of ovarian cancer: a qualitative and quantitative study. *BJOG* 2008, *115*, 1008–1014, doi:10.1111/j.1471-0528.2008.01772.x.
5. Polterauer, S.; Vergote, I.; Concin, N.; Braicu, I.; Chekerov, R.; Mahner, S.; Woelber, L.; Cadron, I.; Gorp, T.V.; Zeillinger, R.; et al. Prognostic Value of Residual Tumor Size in Patients With Epithelial Ovarian Cancer FIGO Stages IIA–IV: Analysis of the OVCAD Data. *International Journal of Gynecologic Cancer* 2012, *22*, doi:10.1097/IGC.0b013e31823de6ae.

6. Aletti, G.D.; Dowdy, S.C.; Gostout, B.S.; Jones, M.B.; Stanhope, C.R.; Wilson, T.O.; Podratz, K.C.; Cliby, W.A. Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. *Obstetrics and Gynecology* 2006, *107*, 77–85, doi:10.1097/01.AOG.0000192407.04428.bb.
7. Chang, S.-J.; Hodeib, M.; Chang, J.; Bristow, R.E. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: A meta-analysis. *Gynecologic Oncology* 2013, *130*, 493–498, doi:10.1016/j.ygyno.2013.05.040.
8. Rutten, M.J.; Sonke, G.S.; Westermann, A.M.; van Driel, W.J.; Trum, J.W.; Kenter, G.G.; Buist, M.R. Prognostic Value of Residual Disease after Interval Debulking Surgery for FIGO Stage IIIC and IV Epithelial Ovarian Cancer. *Obstetrics and Gynecology International* 2015, doi:10.1155/2015/464123.
9. Desai, A.; Xu, J.; Aysola, K.; Qin, Y.; Okoli, C.; Hariprasad, R.; Chinemerem, U.; Gates, C.; Reddy, A.; Danner, O.; et al. Epithelial ovarian cancer: An overview. *World J Transl Med* 2014, *3*, 1–8, doi:10.5528/wjtm.v3.i1.1.
10. Phillips, A.; Sundar, S.; Singh, K.; Pounds, R.; Nevin, J. The NICE classification for 'Ultra–radical (extensive) surgery for advanced ovarian cancer' guidance does not meaningfully predict postoperative complications: a cohort study. *BJOG* 2019, *126*, 96–104.
11. Barton, D.P.J.; Adib, T.; Butler, J. Surgical practice of UK gynaecological oncologists in the treatment of primary advanced epithelial ovarian cancer (PAEOC): A questionnaire survey. *Gynecologic Oncology* **2013**, *131*, 347–351.
12. Drummond, M.F. *Methods for the Economic Evaluation of Health Care Programmes*; 4th ed.; Oxford University Press: Oxford, 2015; ISBN 0198529457.
13. *Economic evaluation*; Fox-Rushby, J., Cairns, J., Eds.; Understanding Public Health; Open University Press: Maidenhead, 2005.
14. Wright, D. Micro-Simulation. *York Health Economics Consortium* 2016.
15. NICE. Guide to the methods of technology appraisal. Available online: https://www.nice.org.uk/process/pmg9 (accessed on Jul 11, 2018).
16. Severens, J.; Milne, R. Discounting Health Outcomes in Economic Evaluation: The Ongoing Debate. *Value in Health* **2004**, *7*.
17. Sonnenberg, F.A.; Beck, J.R. Markov Models in Medical Decision Making: A Practical Guide. *Medical Decision Making* **1993**, *13*, 322–338.

18. Office of National Statistics. Life expectancies. Available online: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies (accessed on Apr 22, 2020).
19. Cancer Research UK. Ovarian Cancer - Proportion of Cases Diagnosed at Each Stage. Available online: https://www.cancerresearchuk.org/sites/default/files/cstream-node/inc_by_stage_ovarian.pdf (accessed on Apr 11, 2020).
20. Barclay, M.; Gildea, C.; Poole, J.; Hirschowitz, L.; Menon, U.; Nordin, A. Factors Affecting Short-term Mortality in Women With Ovarian, Tubal, or Primary Peritoneal Cancer: Population-Based Cohort Analysis of English National Cancer Registration Data. *International Journal of Gynecological Cancer* **2016**, *26*, 56–65, doi:doi: 10.1097/IGC.0000000000000562.
21. NICE. Ultra-radical (extensive) surgery for advanced ovarian cancer - Interventional procedures guidance. Available online: https://www.nice.org.uk/guidance/ipg470/resources/ultraradical-extensive-surgery-for-advanced-ovarian-cancer-pdf-1899869924690629 (accessed on Apr 11, 2020).
22. Phillips, A. Database of surgical morbidity and mortality trends for advanced ovarian cancer, Royal Derby Hospital 2017-2019. (Unpublished)
23. NHS England. Clinical Commissioning Policy: Genetic Testing for BRCA1 and BRCA2 Mutations. Available online: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/e01pb-brca-ovarian-cancer-oct15.pdf (accessed on Apr 11, 2020).
24. Turnbull, H.; Akrivos, N.; Wemyss-Holden, S.; Maiya, B.; Duncan, T.; Nieto, J.; Burbos, N. The impact of ultra-radical surgery in the management of patients with stage IIIC and IV epithelial ovarian, fallopian tube, and peritoneal cancer. *Archives of Gynecology and Obstetrics* **2016**, *295*, 681–687, doi:10.1007/s00404-016-4265-9.
25. NHS Improvement. Archived Reference Costs 2017-18. Available online: https://improvement.nhs.uk/resources/reference-costs/ (accessed on Apr 11, 2020).
26. NICE. BNF: British National Formulary Available online: https://bnf.nice.org.uk/drug/olaparib.html (accessed on Apr 22, 2020).
27. Sundar, S. The SOCQER-2 Study Surgery in Ovarian Cancer - Quality of Life Evaluation Research Available online: https://clinicaltrials.gov/ct2/show/NCT02569983 (accessed on Apr 11, 2020).

28. Havrilesky, L.J.; Broadwater, G.; Davis, D.M.; Nolte, K.C.; Barnett, J.C.; Myers, E.R.; Kulasingam, S. Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. *Gynecologic Oncology* **2009**, *113*, 216–220, doi:10.1016/j.ygyno.2008.12.026.
29. NICE. Information for the public | Ultra-radical (extensive) surgery for advanced ovarian cancer. Available online: https://www.nice.org.uk/guidance/ipg470/ifp/chapter/What-has-NICE-said (accessed on Apr 24, 2020).
30. Fotopoulou, C.; Jones, B.P.; Savvatis, K.; Campbell, J.; Kyrgiou, M.; Farthing, A.; Brett, S.; Roux, R.; Hall, M.; Rustin, G.; et al. Maximal effort cytoreductive surgery for disseminated ovarian cancer in a UK setting: challenges and possibilities. *Arch Gynecol Obstet* **2016**, *294*, 607–614, doi:10.1007/s00404-016-4080-3.
31. Harter, P.; Sehouli, J.; Lorusso, D.; Reuss, A.; Vergote, I.; Marth, C.; Kim, J. A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms. NEJM 2019, 822–832, doi:10.1056/NEJMoa1808424.
32. Fagotti, A.; Ferrandina, M.; Vizzielli, G.; Pasciuto, T. Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850). *International Journal of Gynecologic Cancer* **2020**, doi:10.1136/ijgc-2020-001640.
33. Moore, K.; Colombo, N.; Scambia, G.; Kim, B.-G.; Oaknin, A.; Friedlander, M.; Lisyanskaya, A.; Floquet, A.; Leary, A.; Sonke, G.S.; et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *NEJM* **2018**, 379, 2495–2505, doi:10.1056/NEJMoa1810858.
34. McLaughlin, J.R.; Rosen, B.; Moody, J.; Pal, T.; Fan, I.; Shaw, P.A.; Risch, H.A.; Sellers, T.A.; Sun, P.; Narod, S.A. Long-Term Ovarian Cancer Survival Associated With Mutation in BRCA1 or BRCA2. *J Natl Cancer Inst* **2013**, *105*, 141–148, doi:10.1093/jnci/djs494.
35. Briggs, A. Probabilistic Analysis of Cost-Effectiveness Models: Statistical Representation of Parameter Uncertainty. *Value in Health 8*, 1–2, doi:10.1111/j.1524-4733.2005.08101.x.
36. TreeAge Software Inc. A Guide to Reviewing TreeAge Pro Models. Available online: https://www.treeage.com/wp-content/uploads/2014/06/TreeAge-Pro-Reviewer-Guide.pdf.
37. TreeAge Software Inc. TreeAge Pro 2-Day Healthcare Training - Using TreeAge Pro for Health Economic Modeling **2016**.

Table 1. Results from the baseline microsimulation model (100,000 trial runs)

Strategy	Cost	Increase in cost	Eff (QALY)	Increased effectiveness	ICER	Net Monetary Benefits	C/E
Standard	63071.27	-1783.19	8.67	-0.34	5325.06	110,388.38	7272.15
Ultra-radical	61288.08		8.33			105,474.21	7350.35
Standard (undiscounted)	72040.08	-4239.60	12.23	-0.71	5983.47	172,557.97	5890.49
Ultra-radical (undiscounted)	67800.47		11.52			162,626.51	5884.77