

Institution: University of Birmingham		
Unit of Assessment: UoA 1, Clinical Medicine		
Title of case study: Changing the model of clinical care for advanced ovarian cancer		
Period when the underpinning research was undertaken: January 2000–December 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Sean Kehoe	Senior Lecturer in Gynaecological Cancer	1997–2002
	Lawson-Tait Professor of Gynaecological Cancer	2012–present
Period when the claimed impact occurred: 2015–December 2020		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact <p>The University of Birmingham has had global impact on clinical care for patients with advanced ovarian cancer. The CHORUS trial showed significantly reduced patient morbidity and hospital stay, without compromising survival, by administering chemotherapy before surgery rather than the conventional treatment, where chemotherapy follows surgery.</p> <p>The specific impacts are:</p> <ol style="list-style-type: none"> Improved patient health outcomes, in particular, a reduction of treatment-related morbidity, better survival rates for patients with advanced disease and improved quality of life. Global changes to national clinical guidelines and clinical practice; the use of pre-surgery chemotherapy is now routine practice following guideline changes in the UK, USA, Spain, France, Poland, Singapore and Korea. The cost of treatment has reduced, such that in the USA alone the annual saving is estimated to be \$142 million. 		
2. Underpinning research <p>Approximately 300,000 women worldwide develop ovarian cancer annually, including 7,500 in the UK, where it is estimated that numbers will increase to >10,000 over the next decade. 75% of patients present with advanced disease, defined as stage 3 or 4 (the disease is classified into four stages according to the size and spread of the tumour), and these women, who are the focus of this work, have a five-year survival rate of just 30% (CRUK 2017).</p> <p>For over 50 years, the standard intervention was primary surgery, which aimed to remove as much of the tumour as possible, followed by cytotoxic (chemo) therapy. Clearance of macroscopic tumour is associated with better survival, however about 50–60% of patients will have disease left behind after primary surgery. The concept of administering non-surgical interventions <i>before</i> definitive surgery had been explored in other cancers on the basis that administering chemotherapy first increased the likelihood of clearing all cancer at surgery. However, this approach required evaluation in advanced ovarian cancer.</p> <p>CHORUS was a multi-centre randomised trial, involving 67 centres across the UK and New Zealand, conducted to compare the efficacy of neoadjuvant chemotherapy (NACT) given prior to surgery with conventional treatment in which surgery precedes chemotherapy. Professor Kehoe (Senior Lecturer and subsequently chair in Gynaecological Cancer University of Birmingham (UoB) 1997–2021) developed the CHORUS trial with the UK Medical Research Council, identified recruitment centres and informed the national community about the trial in a series of national meetings (1999–2002). At the same time, he developed collaborations with the</p>		

European Organisation of Research and Treatment of Cancer (EORTC) to assess NACT usage in Europe, ensuring that data from the UK and European studies could be amalgamated to provide definitive international evidence of the efficacy of NACT in advanced ovarian cancer.

Between March 2004 and September 2010, 552 women with suspected stage 3 or 4 ovarian cancer were randomly assigned to treatment. Of 550 eligible women, 276 were assigned to primary surgery followed by six cycles of chemotherapy and 274 to three cycles of primary chemotherapy, then surgery and three more cycles of completion chemotherapy.

Patients were followed up until 2012 when analysis of the CHORUS outcomes started, leading to an oral presentation in 2013 at **ASCO (American Society of Clinical Oncology)** and a subsequent **Lancet** publication in 2015 (R1) reporting the results from the CHORUS trial.

Overall survival with NACT was equal to conventional therapy but there was a significant reduction in a) **severe treatment-related side-effects** (48% primary surgery Group to 40% NACT Group); b) **post-surgical complications** (24% to 14%) and c) **early post-surgical deaths** (5.6% to 0.5%) along with shortened **post-operative hospital inpatient stay (92% of NACT discharged within 14 days of surgery vs 80% in primary surgery arm).**

In 2016, Professor Kehoe was **invited to ASCO to present data concerning patients' quality of life (QOL)** assessment in the CHORUS study. This showed that neoadjuvant chemotherapy prior to surgery was associated with significantly improved QOL over the 6 months of treatment (R2).

Furthermore, amalgamation of the results of CHORUS and EORTC for a per-patient analysis was published in *Lancet Oncology* in 2018 (R3), reporting for the first time that **in stage 4 disease a statistically significant improvement in progression-free and overall survival was seen with NACT when compared with conventional therapy.**

3. References to the research

R1. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. **Kehoe S**, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, Luesley D, Perren T, Bannoo S, Mascarenhas M, Dobbs S, Essapen S, Twigg J, Herod J, McCluggage G, Parmar M, Swart AM. **Lancet.** **2015** Jul 18;386(9990):249-57. DOI: [10.1016/S0140-6736\(14\)62223-6](https://doi.org/10.1016/S0140-6736(14)62223-6)

R2. Primary Surgery or Neoadjuvant Chemotherapy in Advanced Ovarian Cancer: The Debate Continues.... Leary A, Cowan R, Chi D, **Kehoe S**, Nankivell M. **Am Soc Clin Oncol Educ Book.** **2016**;35:153-62. DOI: [10.1200/EDBK_160624](https://doi.org/10.1200/EDBK_160624) The Debate continues

R3. Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. Vergote I, Coens C, Nankivell M, Kristensen GB, Parmar MKB, Ehlen T, Jayson GC, Johnson N, Swart AM, Verheijen R, McCluggage WG, Perren T, Panici PB, Kenter G, Casado A, Mendiola C, Stuart G, Reed NS, **Kehoe S**; EORTC; MRC CHORUS study investigators. **Lancet Oncol.** **2018** Dec;19(12):1680-1687. DOI: [10.1016/S1470-2045\(18\)30566-7](https://doi.org/10.1016/S1470-2045(18)30566-7)

4. Details of the impact

The CHORUS trial has fundamentally transformed the treatment of advanced ovarian cancer globally, improving patient survival and quality of life, whilst reducing healthcare-related costs.

1. Improving patient health outcomes as a result of change in practice worldwide

Significant **patient benefits** are demonstrated by the findings that NACT **improves post-surgical mortality and morbidity leading to quicker discharge rates**.

Based on the results of the CHORUS trial, women with advanced stage 3 or 4 ovarian cancer are receiving NACT benefit from:

- **reduced post-surgical mortality** (<1% in NACT vs 6% post surgery group);
- **a reduction of grade 3 and 4 post-surgical morbidities** (including haemorrhage, the most common grade 3 or 4 adverse event, which reduced from 6% to 3%);
- **they are more likely to be discharged within 14 days** from operation (93% compared with only 80% in the primary-surgery group) (R1); and
- **they show improved survival for patients with stage 4 disease** (R3).

These improved patient outcomes are evidenced in a 2018 US study (S1) using the National Cancer Database records. This found that adoption of NACT by cancer centres resulted in a **19% reduction in mortality** within three years after diagnosis. In contrast, no improvement in mortality was observed in Centres that did not adopt the NACT protocol. Rapidly adopting centres also demonstrated a **43% reduction in 90-day surgical mortality** during this period compared to 14% in the control centres (p<0.001). These benefits to patients are now being realised through worldwide change in practice informed by CHORUS.

Evidence of patient benefit and improved outcomes is also attested to by the chief clinician at Cancer Research UK, who stated in 2015 that the CHORUS trial “is a great example of how research can help us to plan the best care for people with cancer. Thanks to this study we can say that having chemotherapy first makes the surgery safer, the stay in hospital shorter and women’s quality of life better. These are important results that will make a big difference to many women in the future” (S2).

2. National and International guidelines for the treatment of advanced ovarian cancer and clinical practices have changed as a result of CHORUS

Clinical guidelines have changed such that NACT is **recommended as the preferred treatment strategy for advanced ovarian cancer**. Our work (R1–R3) led directly to **changes in national clinical guidelines** around the world including in the UK, USA, Spain, France, Poland, Singapore and Korea (S3). This change in guidelines has translated to changes in clinical practice across the world for the treatment of patients with advanced ovarian cancer.

Citing the CHORUS study (R1, 2015) as the evidence, the following **national clinical guidelines changed** to incorporate NACT as **the preferred** treatment strategy for advanced ovarian cancer:

- The **Polish** Society of Oncological Gynaecology: recommendations on the diagnosis and treatment of epithelial ovarian cancer 2015 (S3);
- **Singapore** Cancer Network (SCAN) Guidelines for Front-Line Systemic Therapy of Newly Diagnosed Advanced Epithelial Ovarian Cancer (2015) (S3);
- The **American** Society of Clinical Oncology and the Society of Gynecological Oncologists 2016 (S3);
- Sociedad **Espanola** de Oncologia Medica (SEOM): Clinical Guidelines in ovarian cancer (2016) in Spain (S3);
- The **British** Gynaecological Cancer Society guidelines (2017) (S3);
- Practice guidelines for management of ovarian cancer in **Korea** 2018 (S3);
- **French** national college of obstetricians and gynaecologists Guidelines in oncology (2019) (S3).

Clinical practice has changed for patients with advanced ovarian cancer, such that they now routinely have chemotherapy as the preferred first line treatment. That this is the case is attested to by the ASCO Senior Vice President of Clinical Affairs and National Director for

Medical Oncology at Cancer Treatment Centres of America in Philadelphia, who stated that, “without question CHORUS should have a major Impact on community oncology practice” (S4).

A seismic change in clinical practice is illustrated by **increased usage of NACT since 2013–2015**. NACT was used in England in only 21.4% of cases between 2013–2015 (S5). In November 2020, the National Cancer Registration and Analysis Service released an audit on over 20,000 women diagnosed with ovarian cancer and treated in England during 2016–2018. Of 7,157 women with a histological diagnosis of a serous cancer, 71% were treated with NACT, representing 57% of women with stage 2/3 disease and 87% of those with stage 4 disease (S6).

3. The cost of treatment for advanced ovarian cancer has reduced

The CHORUS study reported that 92% of women treated with the NACT protocol were discharged within 14 days after surgery compared with only 74% in the primary surgery arm, providing evidence of economic savings (R1). This was corroborated by a large economic analysis by Cole *et al.* (S7, 2018) which found that, compared with primary surgery, **NACT was associated with a potential \$142 million in cost savings across the USA alone**. Comparable relative cost saving would be expected within the NHS setting.

5. Sources to corroborate the impact

Evidence of improving patient health

S1. Effect of adoption of neoadjuvant chemotherapy for advanced ovarian cancer on all cause mortality: quasi-experimental study. Melamed A, Fink G, Wright AA, Keating NL, Gockley AA, Del Carmen MG, Schorge JO, Rauh-Hain JA. *BMJ*. 2018 Jan 3;360:j5463. DOI: 10.1136/bmj.j5463

S2. [Statement, chief clinician at Cancer Research UK \(2015\).](#)

Evidence of changes to National Guidelines

S3. Changes to **National Guidelines**:

- **Poland:** Recommendation of the Polish Society of Oncological Gynaecology on the diagnosis and treatment of epithelial ovarian cancer. Antoni Basta et al. *Oncol Clin Pract* 2015; 11, 5: 233–243 – CHORUS citation (**R1**) - Reference 26, page 240. [Polish Guideline](#).
- **Singapore:** Singapore Cancer Network (SCAN) Guidelines for Front-Line Systemic Therapy of Newly Diagnosed Advanced Epithelial Ovarian Cancer; The Singapore Cancer Network (SCAN) Gynaecological Cancers Systemic Therapy Workgroup. *Ann Acad Med Singap*. 2015 Oct;44(10):421-33. PMID: 26763060. CHORUS citation (**R1**) – Reference 43, page 429. [Singapore Guideline](#).
- **USA:** Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. Wright AA, Bohlke K, Armstrong DK, et al. *J Clin Oncol*. 2016 Oct 1;34(28):3460-73. DOI: 10.1200/JCO.2016.68.6907 – CHORUS citation (**R1**) – Reference 2, page 3472.
- **Spain:** SEOM Clinical Guideline in ovarian cancer (2016) Spanish guidelines. Clinical and Translational Oncology, December 2016, Volume 18, Issue 12, pp 1206–1212. DOI: 10.1007/s12094-016-1588-8 – CHORUS citation (**R1**) - Reference 14, page 1212.
- **UK** – British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. Fotopoulou C, Hall M, Cruickshank D, Gabra H, Ganesan R, Hughes C, Kehoe S, Ledermann J, Morrison J, Naik R, Rolland P, Sundar S. *Eur J Obstet Gynecol Reprod Biol*. 2017 Jun;213:123-139. DOI: 10.1016/j.ejogrb.2017.04.016. Epub 2017 Apr 18 – CHORUS citation (**R1**) – Reference 72, page 137.
- **Korea:** Practice guidelines for management of ovarian cancer in Korea: a Korean Society of Gynecologic Oncology Consensus Statement. Suh DH, Chang SJ, Song T, Lee S, Kang WD, Lee SJ, Roh JW, Joo WD, Yoon JH, Jeong DH, Kim HS, Lee SJ, Ji YI,

Kim HJ, Lee JW, Kim JW, Bae DS. *J Gynecol Oncol*. 2018 Jul;29(4):e56. English. Published online May 10, 2018. DOI: 10.3802/jgo.2018.29.e56. CHORUS citation (R1) – Reference 7, page 16.

- **France:** Surgery for advanced stage ovarian cancer: Article drafted from the French Guidelines in oncology entitled “Initial management of patients with epithelial ovarian cancer” developed by FRANCOGYN, CNGOF, SFOG, GINECO-ARCAGY under the aegis of CNGOF and endorsed by INCa G.Ferron et al. *Gynécologie Obstétrique Fertilité & Sénologie* Volume 47, Issue 2, February 2019, Pages 197-213. DOI: 10.1016/j.gofs.2019.01.003 - CHORUS citation (R1) – Reference 103, page 212.

Evidence of change in Clinical practice

S4. [Statement ASCO Senior Vice President of Clinical Affairs](#) and National Director for Medical Oncology at Cancer Treatment Centres of America in Philadelphia.

S5. [A population registry trend analysis](#) of neoadjuvant chemotherapy and incidence of ovarian peritoneal and fallopian tube carcinomas in England 2004-15. Rebecca Elleray, Cong Chen, Sean Kehoe (2017).

S6: Geographic variation in ovarian, fallopian tube and primary peritoneal cancer treatment in England, NCRAS Nov. 2020. [published in NCIN Gynaecological Cancer site, Ovarian Cancer Audit Feasibility Pilot: Outputs, section 2]. [ncin.org.uk > gynaecological cancer > resources](http://ncin.org.uk/gynaecological_cancer/resources) (accessed 13 November 2020).

Evidence of cost savings

S7. Economic Analysis of Neoadjuvant Chemotherapy Versus Primary Debulking Surgery for Advanced Epithelial Ovarian Cancer Using an Aggressive Surgical Paradigm. Cole AL, Barber EL, Gogate A, Tran AQ, Wheeler SB. *Int J Gynecol Cancer*. 2018 Apr 21

DOI: 10.1097/igc.0000000000001271. Includes CHORUS cited papers