EJGO European Journal of Gynaecological Oncology

# Has the "paradigm shift" in the management of advanced ovarian, tubal and primary peritoneal cancer altered the locations of recurrence?

**A. Phillips, S. Sundar, R. Pounds, A. Elattar, J. Nevin, S. Kehoe, J. Balega, K. Singh**

*Pan-Birmingham Gynaecological Cancer Centre, City Hospital, Birmingham (United Kingdom)*

**Summary**

*Purpose of investigation:* To determine the pattern of disease recurrence in patients treated for advanced ovarian cancer (AOC). *Materials and Methods:* A retrospective review of the locations of recurrence in all patients treated for AOC between August 16, 2007 and February 3, 2014 who underwent cytoreductive surgery and platinum based chemotherapy achieving complete (R0) or optimal (< 1cm) (R1) cytoreduction. *Results:* The study identified 254 patients. Peritoneal site relapses affected 65.4–91.1% of patients and were more common in R1 compared to R0 patients ($p = 0.01891$). Ascites at relapse was less prevalent in R0 compared to R1 patients ($p = 0.00185$) and occurred less with more complex surgery ($p = 0.00497$) and 19.2% of patients who required high complexity surgery to achieve R0 only experienced retroperitoneal recurrences. *Conclusion:* Irrespective of the surgery undertaken, the peritoneum is the commonest site of recurrence. The surgical complexity required to achieve R0 seemingly alters the relapse pattern by reducing ascites and peritoneal relapse compared to those with R1 disease, and increasing retroperitoneal relapse.

*Key words:* Ovarian cancer; Fallopian tube cancer; Peritoneal neoplasms; Recurrence; Surgery.

## Introduction

The survival prospects for women with no or low (< 1 cm) residual disease following surgery has been recognised for decades. Though based on retrospective studies, there has been a trend to increase surgical efforts – in particular resection of upper abdominal disease to achieve optimum debulking – now defined as no macroscopic residual disease. [1-4] The debate as to patient selection and the impact of this, along with inherent tumour biology remains, though it is possible that properly constructed randomised trials could enhance our understanding of these influences. With modern facilities and better surgical skills, it has been shown that more extensive surgery can be performed with good outcomes and survival rates [2, 5]. Improved optimum rates can also be achieved with neoadjuvant chemotherapy in those deemed unresectable at presentation [6].

Published outcome data on complete cytoreduction (R0) has focused mainly on progression free (PFS) and overall (OS) survival. The nature of recurrence patterns in patients having extensive surgery has only been reported in one smaller study of 73 patients. Such information is useful when considering secondary debulking as the relapse locations may be different from the traditional surgery – with potential implications for care [7-10].

This study examined the patterns of relapse in patients with advanced ovarian carcinoma (AOC) managed at the Pan-Birmingham Gynaecological Cancer Centre (PBGCC), following the introduction of more extensive surgical procedures and comparing them to historical controls. The study contains the largest cohort of women managed in the neoadjuvant setting combined with extensive surgical procedures.

## Materials and Methods

All patients treated for AOC between August 16th 2007 and February 3rd 2014 by subspecialty trained gynaecological oncologists were identified from the PBGCC database.

Patients who underwent cytoreductive surgery and received platinum based chemotherapy with optimal (R0) or < 1cm (R1) cytoreduction were included in the study. Exclusion criteria consisted of: no surgical attempt at debulking (i.e. patients treated with palliation or chemotherapy alone), large volume residual disease (> 1 cm) (R2) cytoreduction, non-epithelial histology, recurrence imaging not available, and surgery performed at a different cancer centre.

At the present Centre, the initial assessment of women with suspected AOC consists of clinical examination, transvaginal ultrasound scan, serum CA125 test, and CT scan of the thorax, abdomen and pelvis. Following discussion at the multi-disciplinary team (MDT) meeting, women either underwent: primary surgery or interval surgery after 3-4 cycles carboplatin AUC 6 ± paclitaxel 175 mg/m$^2$ based neoadjuvant chemotherapy (NACT).

Revised manuscript accepted for publication March 28, 2017

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXIX, n. 3, 2018
doi: 10.12892/ejgo4183.2018

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Typically, surgical procedures included pelvic clearance/omentectomy/lymphadenectomy though since 2008 more extensive (often termed 'ultra-radical') surgery was introduced. In appropriately selected patients, bowel resection(s); extensive peritoneal stripping, diaphragmatic stripping/resection, splenectomy, liver resection, gastric resection, and distal pancreatectomy were performed if required. Extensive stripping of the para-aortic lymph nodes was not performed routinely but enlarged para-aortic lymph nodes were resected. For this study the surgical complexity was defined as recommended by Aletti *et al.*[11]

Histological confirmation was performed by gynaecological cancer pathologists. Adjuvant chemotherapy consisted of 3–6 cycles of carboplatin AUC 6–7.5 ± paclitaxel 175 mg/m$^2$ every three weeks depending on use of NACT, patient co-morbidity, and patient choice. Bevacizumab was incorporated into the adjuvant treatment protocol for patients with Stage 4 disease in 2013.

The standard follow-up protocol after treatment was: hospital visits at three monthly intervals for the first two years, four monthly intervals the following year, and six monthly intervals for a further two years. Women were then discharged to self-initiated follow-up if no recurrence had been identified. Follow-up was shared between the gynaecological and medical/clinical oncologists. In the event of a rising CA125, clinical symptomatology or suspicion of recurrence, abdominal and pelvic imaging was performed with progression defined according to the Gynaecological Cancer Intergroup criteria. [12].

The PBGCC has referrals from four local hospitals, and data collection regarding site of relapse in those cases was derived from the local hospitals written reports, though 25% of these patients also had central radiology review at the PBGCC. All patients local to the PBGCC had central review of imaging on relapse. The written reports comprised of: number of individual recurrent lesions (up to four) or the presence of plaques, size of the largest lesion, locations of recurrence categorised into anatomical 'types' including peritoneal (P), visceral (V), retroperitoneal (R), extra-abdominal (E), ascites (A), and pleural effusions. Retroperitoneal lymphadenopathy was defined as retroperitoneal lesions greater than 10 mm in the short axis. Imaging reports were cross-referenced with the original operation note to identify whether disease had recurred in operated or non-operated sites. Biopsies were not routinely undertaken of recurrent lesions unless the clinical picture was felt to be ambiguous.

Three methods were used to analyse the data. Firstly, the authors examined the global picture of the recurrence patterns analysing recurrences by all involved anatomical "types". Secondly, they looked at the proportions of patients with disease limited to only one anatomical "type" (i.e only peritoneal recurrences, only visceral recurrences etc). Finally, they looked at the number of discrete lesions, the size of the largest lesion, and the location of that lesion in relation to previous surgery. Although both PDS and IDS patients were grouped by cytoreductive outcome or surgical complexity score for analysis, individual subgroup recurrence patterns are presented.

Women with recurrent disease were considered on case by case basis for surgical resection (secondary debulking), chemotherapy or palliation following clinical assessment, cross-sectional imaging, and discussion at the multi-disciplinary meeting.

The following data was collected: age at initial diagnosis, FIGO stage, histological sub-type and grade, type of initial surgery performed (primary or interval), degree of cytoreduction achieved (R0, R1, R2), surgical complexity score [11], time elapsed since diagnosis, serum CA125 level at diagnosis of recurrence, and the aforementioned recurrence data.

Continuous data were analysed by a Student's *t*-test or by the Mann-Whitney U-test depending on the data distribution. Categorical data were analysed using Chi-square unless more than 20% of the expected values were less than five in which case Fisher's Exact Test was used. Bonferroni corrections were applied for multiple comparisons. When $p < 0.05$, the difference was considered to be statistically significant in all statistical tests. PFS and OS survival were calculated using the Kaplan-Meier method using SPSS 22 (Statistical Package for Social Sciences).

## Results

The authors identified 276 R0 and 64 R1 cases of AOC from the MDT database. As of July 1st 2015, 53 (15.6%) had no radiological evidence of recurrent disease. Thirty-three patients (9.7%) received postoperative adjuvant treatment in peripheral hospitals and chemotherapy notes were not available for analysis. In total 254 patients were included in this analysis.

There was no significant difference in body mass index (BMI), American Society of Anaesthesiologists (ASA) grade, and performance status (PS) between those patients who achieved R0 compared to those who achieved R1. The majority (90.6%) of patients presented with stage 3C/4 disease, with serous cancers most common (89.4%) and 93.3% of the lesions were high grade. Serum CA125 at relapse was similar in both groups (Table 1).

Global locations of recurrence are summarised in Table 2. Overall, peritoneal relapses were most common affected 65.4–91.1% of patients. Peritoneal recurrence was significantly more common in those who achieved R1 following surgery compared to those who achieved R0 ($p = 0.01891$). Subgroup analysis did not reveal a statistically significant difference in peritoneal relapse even when extensive surgery was performed. Ascites at relapse was significantly less prevalent in R0 resections compared to R1 resections ($p = 0.00185$), and occurred less when R0 was achieved with more extensive surgery ($p = 0.00497$). This reduction in ascites was mirrored by a non-significant trend in the reduction of pleural effusions. Patients receiving extensive surgery recurred more commonly in the retroperitoneum than R1 patients, although these results were not significant.

When examining recurrences in lone anatomical "types" (Table 3), there was no significant difference in the presence of peritoneal disease between women who achieved R1 compared to those who achieved R, and this was not affected by the complexity of surgery performed. Almost 20% of patients who required high complexity surgery to achieve R0 only experienced retroperitoneal recurrences. This is in comparison to 2.2% of patients who achieved R1. Women who only achieved R1 had the most widespread recurrence patterns with 48.9% experiencing recurrences in three or more different anatomical "types" ($p = 0.000015$).

There was no significant difference in the size of the largest recurrent lesion between women who achieved R1 and those who achieved R0 irrespective of the surgical procedures performed. Equally recurrent disease in all groups

Table 1. — *Clinico-pathological data.*

| | R1 | R0 Complexity 0-3 | R0 Complexity 4-7 | R0 Complexity 8+ | *p* |
|---|---|---|---|---|---|
| | n = 45 n (%) | n = 121 n (%) | n = 62 n (%) | n = 26 n (%) | |
| Age (mean) | 64.8 ± 10.4 | 63.4 ± 11 .0 | 62.6 ± 10.1 | 59.7 ± 11.9 | >0.05 |
| Stage | | | | | |
| 3A | 0 (0.0) | 9 (7.4) | 1 (1.6) | 0 (0) | >0.05 |
| 3B | 1 (2.2) | 11 (9.1) | 2 (3.2) | 0 (0) | >0.05 |
| 3C | 31 (68.9) | 76 (62.8) | 46 (74.2) | 19 (73.1) | >0.05 |
| 4 | 13 (28.9) | 25 (20.7) | 13 (21.0) | 7 (26.9) | >0.05 |
| Organ of origin | | | | | |
| Ovary | 34 (75.6) | 82 (67.8) | 39 (62.9) | 19 (73.1) | >0.05 |
| Tubal | 3 (6.7) | 13 (10.7) | 10 (16.1) | 3 (11.5) | >0.05 |
| Peritoneal | 8 (17.8) | 26 (21.5) | 13 (21.0) | 4 (15.4) | >0.05 |
| Histological type | | | | | |
| Serous | 29 (86.7) | 106 (87.6) | 56 (90.3) | 26 (100) | 0.000065 |
| Endometrioid | 0 (0.0) | 0 (0.0) | 1 (1.6) | 0 (0.0) | >0.05 |
| Unknown | 1 (2.2) | 2 (1.7) | 0 (0.0) | 0 (0.0) | >0.05 |
| Clear Cell | 3 (6.7) | 5 (4.1) | 1 (1.6) | 0 (0.0) | >0.05 |
| MMMT | 2 (4.4) | 6 (5.0) | 4 (6.5) | 0 (0.0) | >0.05 |
| Undifferentiated | 0 (0.0) | 2 (1.7) | 0 (0.0) | 0 (0.0) | >0.05 |
| Second component | Endometrioid (1) Mucinous (1) Transitional (1) | Endometrioid (1) | | | |
| Grade | | | | | |
| High G3 | 44 (97.8) | 113 (93.4) | 57 (92.0) | 23 (88.5) | >0.05 |
| G2 | 0 (0.0) | 1 (0.8) | 3 (4.8) | 0 (0.0) | >0.05 |
| Low G1 | 0 (0.0) | 3 (2.5) | 2 (3.2) | 3 (11.5) | >0.05 |
| Unknown | 1 (2.2) | 4 (3.3) | 0 (0.0) | 0 (0.0) | >0.05 |
| BMI (mean) | 25.0 ± 4.3 | 26.4 ± 5.0 | 26.2 ± 5.0 | 25.4 ± 4.3 | >0.05 |
| ASA (median) (IQR) | 2 (2-2) | 2 (2-2) | 2 (2-2) | 2 (2-3) | >0.05 |
| PS (median) (IQR) | 1 (0-1) | 1 (0-1) | 1 (0-1) | 1 (0-1) | >0.05 |
| Type of surgery | | | | | |
| Primary | 11 (24.4) | 28 (23.1) | 19 (30.7) | 3 (11.5) | >0.05 |
| Interval | 34 (75.6) | 93 (76.9) | 43 (69.3) | 23 (88.5) | >0.05 |
| Surgical complexity | | | | | |
| 0-3 (low) | 33 (73.4) | 121 (100) | 0 (0.0) | 0 (0.0) | <0.00001 |
| 4-7 (intermediate) | 11 (24.4) | 0 (0.0) | 62 (100) | 0 (0.0) | <0.00001 |
| 8+ (high) | 1 (2.2) | 0 (0.0) | 0 (0.0) | 26 (100) | <0.00001 |
| CA125 at time of imaging (Median) (IQR) | 155 (61–418) | 92 (45–300) | 118 (52–227) | 97.5 (57–167) | >0.05 |
| Median PFS (months) (95% CI) | 14.9 (12.4–17.3) | 21.7 (17.5–25.9) | 18.2 (15.1 – 21.4) | 14.4 (13.2–15.6) | |
| Median OS (months) (95% CI) | 33.3 (25.1–41.6) | 52.9 (36.1–69.7) | 56.0 (44.2–67.7) | 43.0 (26.6–59.3) | |

occurred both at the site of initial surgery and at other locations (Table 4). Women in whom R0 was achieved were significantly more likely to have fewer recurrent lesions, compared to women with R1 ($p = 0.01855$). Despite cytoreductive outcome or surgical complexity, more than 50% of all patients across all groups presented with widespread plaques or deposits.

Unsurprisingly, patients with Stage IV disease demonstrated significantly more extra-abdominal recurrences than those with Stage III disease ($p \leq 0.001$), although the latter developed ascites more commonly ($p = 0.046$). The size of largest recurrent lesion, the number of recurrent lesions, and the location and distribution of recurrent disease was otherwise no different in women with Stage III disease compared to those with Stage IV disease. Similarly, there was no difference in patterns comparing those primary versus interval surgery.

A comparison was made between patients treated during 2008 when advanced procedures were first being introduced and those treated in 2013 when advanced procedures were well established (Table 5). The authors made the following assumptions: no significant change in disease distribution or stage occurred during this time period and that the profile of their patients, e.g. age and performance status, remained stable. To allow for a conservative prediction they assumed that R2 patients would reoccur in a pattern

Table 2. — *Global locations of recurrent disease.*

| | R1 | | | R0: Complexity 0-3 | | | R0: Complexity 4-7 | | | R0: Complexity 8+ | | | *p* (overall) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall n (%) n = 45 | PDS n (%) n = 11 | IDS n (%) n = 34 | Overall n (%) n = 121 | PDS n (%) n = 28 | IDS n (%) n = 93 | Overall n (%) n = 62 | PDS n (%) n = 17 | IDS n (%) n = 45 | Overall n (%) n = 26 | PDS n (%) n = 4 | IDS n (%) n = 22 | |
| Peritoneal | 41 (91.1) | 8 (72.7) | 33 (97.1) | 91 (75.2) | 22 (78.6) | 69 (74.2) | 49 (79.0) | 15 (88.2) | 34 (75.6) | 17 (65.4) | 1 (25.0) | 16 (72.7) | >0.05 |
| Visceral | 16 (35.6) | 2 (18.2) | 14 (41.2) | 30 (24.8) | 5 (17.9) | 25 (26.9) | 14 (22.6) | 6 (35.3) | 8 (17.8) | 2 (23.1) | 0 (0.0) | 2 (9.1) | >0.05 |
| Retroperitoneal | 16 (35.6) | 6 (54.5) | 10 (29.4) | 41 (33.9) | 11 (39.3) | 30 (32.3) | 27 (43.5) | 7 (41.2) | 20 (44.4) | 13 (50.0) | 3 (75.0) | 10 (45.5) | >0.05 |
| Extra-abdominal | 10 (22.2) | 1 (9.1) | 9 (26.5) | 17 (14.1) | 5 (17.9) | 12 (12.9) | 16 (25.8) | 3 (17.6) | 13 (28.9) | 7 (26.9) | 1 (25.0) | 6 (27.3) | >0.05 |
| Ascites | 20 (44.4) | 2 (18.2) | 18 (53.0) | 31 (25.6) | 6 (21.4) | 25 (26.9) | 12 (19.4) | 3 (17.6) | 9 (20.0) | 3 (11.5) | 1 (25.0) | 2 (9.1) | 0.00497 |
| Pleural effusion | 4 (8.9) | 1 (9.1) | 3 (8.8) | 5 (4.1) | 2 (7.1) | 3 (3.2) | 2 (3.2) | 1 (5.9) | 1 (2.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | >0.05 |

Table 3. — *Recurrences in single anatomical "types".*

| | R1 | | | R0: Complexity 0-3 | | | R0: Complexity 4-7 | | | R0: Complexity 8+ | | | *p* (overall) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall n (%) n = 45 | PDS n (%) n = 11 | IDS n (%) n = 34 | Overall n (%) n = 121 | PDS n (%) n = 28 | IDS n (%) n = 93 | Overall n (%) n = 62 | PDS n (%) n = 17 | IDS n (%) n = 45 | Overall n (%) n = 26 | PDS n (%) n = 4 | IDS n (%) n = 22 | |
| Peritoneal | 10 (22.2) | 4 (36.4) | 6 (17.6) | 29 (20.0) | 7 (25.0) | 22 (23.7) | 12 (19.4) | 2 (11.8) | 10 (22.2) | 5 (19.2) | 0 (0.0) | 5 (22.7) | >0.05 |
| Visceral | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (1.7) | 0 (0.0) | 2 (2.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | >0.05 |
| Retroperitoneal | 1 (2.2) | 1 (9.1) | 0 (0.0) | 12 (9.9) | 2 (7.1) | 10 (10.8) | 3 (4.5) | 1 (5.9) | 2 (4.4) | 5 (19.2) | 2 (50.0) | 3 (13.6) | >0.05 |
| Extra-abdominal | 1 (2.2) | 0 (0.0) | 1 (2.9) | 3 (2.5) | 0 (0.0) | 3 (3.2) | 5 (8.1) | 0 (0.0) (0.0) | 5 (11.1) | 2 (7.7) | 0 (0.0) (0.0) | 0 (0.0) (0.0) | >0.05 |
| Ascites | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.8) | 0 (0.0) | 1 (1.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | >0.05 |
| Pleural Effusion | 1 (2.2) | 1 (9.1) | 0 (0.0) | 1 (0.8) | 0 (0.0) | 1 (1.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | >0.05 |
| ≥ 3 recurrence anatomical "types" | 22 (48.9) | 3 (27.3) | 19 (55.9) | 16 (13.2) | 6 (21.4) | 10 (10.8) | 14 (22.6) | 2 (11.8) | 12 (26.7) | 4 (15.4) | 1 (25.0) | 3 (13.6) | 0.000015 |

similar to R1.

The median PFS in patients achieving R0 following low, intermediate, and high complexity surgery was 21.7 (17.5–25.9) months, 18.2 (15.1–21.4) months, and 14.4 (13.2–15.6) months, respectively and for R1 it was 14.9 (12.4–17.3) months. The corresponding figures for median OS were 52.9 (36.1-69.7), 56.0 (44.2-67.7), 43.0 (26.6–59.3), and 33.3 (25.1–41.6), months (Table 1). Despite the PFS being similar amongst R1 patients and those achieving R0 with high complexity surgery, the OS in the latter group was longer, although the difference between the two groups was not statistically significant.

## Discussion

This is the largest study assessing the location of recurrent disease following cytoreductive surgery for ovarian, primary peritoneal, and tubal adenocarcinoma. The findings confirm those reported in smaller series [13, 14]. Also, this study incorporates the largest reported group of women managed by neoadjuvant chemotherapy and extensive surgical effort, which may be valuable evidence in the development of relevant trials.

The different recurrence patterns observed between patients achieving R0 following high complexity surgery and patients achieving R1 are interesting and could be a surrogate for how surgery impacts the natural history of a disease. The incidence of peritoneal recurrence as well as ascites appears to reduce with advancing complexity of the

Table 4. — *Recurrence parameters.*

| | R1 | | | R0: Complexity 0-3 | | | R0: Complexity 4-7 | | | R0: Complexity 8+ | | | *p* (overall) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall n (%) n = 45 | PDS n (%) n = 11 | IDS n (%) n = 34 | Overall n (%) n = 121 | PDS n (%) n = 28 | IDS n (%) n = 93 | Overall n (%) n = 62 | PDS n (%) n = 17 | IDS n (%) n = 45 | Overall n (%) n = 26 | PDS n (%) n = 4 | IDS n (%) n = 22 | |
| Size of largest lesion (cm) (IQR) | 2.8 1.9-4.9 | 3.2 2-5.1 | 2.7 1.7–4.3 | 2 1.4-3.3 | 2 1.5–2.7 | 2 1.4 –3.7 | 2.3 1.5-3.3 | 2.8 1.9–4.3 | 2.1 1.5–2.9 | 1.8 1.2-2.5 | 1 0.9–1.6 | 2 1.3–2.7 | >0.05 |
| Disease location | | | | | | | | | | | | | |
| Operated | 2 (4.4) | 1 (9.1) | 1 (2.9) | 15 (12.4) | 5 (17.9) | 10 (10.8) | 9 (14.52) | 2 (11.8) | 7 (15.6) | 4 (15.38) | 0 (0.0) | 4 (18.2) | >0.05 |
| Not operated | 13 (28.9) | 4 (36.4) | 9 (26.5) | 44 (36.4) | 8 (28.6) | 36 (38.7) | 17 (27.42) | 2 (11.8) | 15 (33.3) | 13 (50.00) | 4 (100.0) | 9 (40.9) | >0.05 |
| Both | 30 (66.7) | 6 (54.5) | 24 (70.6) | 62 (51.2) | 14 (50.0) | 48 (51.6) | 35 (56.45) | 13 (76.5) | 22 (48.9) | 9 (34.62) | 0 (0.0) | 9 (40.9) | >0.05 |
| Data unavailable | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.00) | 0 (0.0) | 0 (0.0) | 1 (01.61) | 0 (0.0) | 1 (2.2) | 0 (0.00) | 0 (0.0) | 0 (0.0) | >0.05 |
| Lesion number | | | | | | | | | | | | | |
| 1 | 4 (8.9) | 2 (18.2) | 2 (5.9) | 16 (13.2) | 3 (10.7) | 13 (14.0) | 10 (16.1) | 1 (5.9) | 9 (20.0) | 4 (15.4) | 2 (50.00 | 2 (9.1) | >0.05 |
| 2 | 2 (4.4) | 0 (0.0) | 2 (5.9) | 20 (16.5) | 6 (21.4) | 14 (15.1) | 9 (14.5) | 2 (11.8) | 7 (15.6) | 5 (19.2) | 1 (25.0) | 4 (18.2) | >0.05 |
| 3 | 4 (8.9) | 0 (0.0) | 4 (11.8) | 12 (9.9) | 4 (14.3) | 8 (8.6) | 8 (12.9) | 1 (5.9) | 7 (15.6) | 3 (11.5) | 1 (25.0) | 2 (9.1) | >0.05 |
| 4 | 4 (8.9) | 2 (18.2) | 2 (5.9) | 4 (3.3) | 1 (3.6) | 3 (3.2) | 2 (3.2) | 1 (5.9) | 1 (2.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | >0.05 |
| Widespread | 30 (66.7) | 6 (54.5) | 24 (70.6) | 67 (55.4) | 14 (50.0) | 53 (57.0) | 32 (51.6) | 12 (70.6) | 20 (44.4) | 14 (53.8) | 0 (0.0) | 14 (63.6) | >0.05 |
| Not applicable | 1 (2.2) | 1 (9.1) | 0 (0.0) | 2 (1.7) | 0 (0.0) | 2 (2.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | >0.05 |
| Data unavailable | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.6) | 0 (0.0) | 1 (2.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | >0.05 |

initial surgery. The more complex the surgery required to achieve R0, the greater the proportion of patients presenting with retroperitoneal and extra-abdominal recurrences.

Since the introduction of advanced surgical procedures in the present unit, an increase in the R0 cytoreduction rate from 50% to 66% has been witnessed. Over the same time period, as advanced surgical procedures have become more established, the relative contribution of low, intermediate, and high complexity surgery to achieve R0 has changed dramatically (Table 5). The present authors have also seen a small increase in the number of patients receiving NACT (9.4%). The 16% increase observed in R0 is most likely in patients that previously would have been considered R1 or R2 with low complexity surgery, who are now achieving R0 due to advanced surgical procedures as well as utilisation of NACT.

The present historical analysis is a conservative estimation of the change in recurrence parameters since the introduction of advanced surgical procedures and demonstrates a decrease in peritoneal and ascites recurrences, and an increase in retroperitoneal and extra-abdominal recurrences. (Table 5). The shift in recurrence pattern distribution may have a beneficial effect on the patients' ability to receive additional lines of chemotherapy and the authors postulate that the reduction in peritoneal recurrences, and thus a reduction in gastrointestinal symptoms, may help maintain performance status. Such findings may explain the increased survival seen after implementing advanced procedures in other studies [2, 15]. Changing recurrence patterns may be a confounding variable in on-going quality of life assessments. Such impact may be detected in the ongoing prospective multicentre SOCQER-2 [16] study (NCT02569983) examining the quality of life and recurrence data in patients undergoing surgery for macroscopically metastatic ovarian cancer.

The shift from R1 to R0 at primary surgery, the reduction in ascites at recurrence and the potentially maintained performance status would greatly increase the number of patients with a positive AGO score [1) complete resection at first surgery, 2) good performance status, and 3) absence of ascites) [17], and thus increase the number that may benefit from secondary cytoreduction. The results of the DESKTOP-III RCT [7] (NCT01166737) comparing tumour debulking with chemotherapy compared to chemotherapy alone may validate secondary cytoreduction, an intervention which is increasingly becoming more relevant to our patients.

Subgroup analysis was not performed between PDS and

Table 5. — *Estimated historical changes.*

| | 2008 n (%) | 2013 n (%) | % Change |
|---|---|---|---|
| PDS | 26 (38.2) | 24 (32.4)-15.1 | |
| IDS | 42 (61.8) | 50 (67.6) | 9.4 |
| Cytoreduction rate | | | |
| R2 | 21 (30.9) | 18 (24.3) | -21.2 |
| R1 | 13 (19.1) | 7 (9.5) | -50.5 |
| R0 | 34 (50.0) | 49 (66.2) | 28.7 |
| Change in R0 surgical complexity | | | |
| R0 – low complexity | 27 (39.7) | 26 (35.1) | -11.5 |
| R0 – intermediate complexity | 5 (7.4) | 15 (20.3) | 175.7 |
| R0 – high complexity | 2 (3.0) | 8 (10.8) | 267.6 |
| Global recurrence sites | | | |
| Peritoneal | 56.3 (86.6) | 59.2 (82.2) | -5.0 |
| Visceral | 20.2 (31.1) | 20.5 (28.4) | -8.7 |
| Retroperitoneal | 24.1 (37.0) | 28 (38.9) | 4.9 |
| Extra-abdominal | 13.2 (20.3) | 15.3 (21.2) | 4.3 |
| Ascites | 23.3 (35.8) | 21.6 (30.1) | -16.1 |
| Pleural Effusion | 4.4 (6.8) | 3.9 (5.4) | -21.0 |
| Single anatomical “types” | | | |
| Peritoneal | 14.3 (22.1) | 15.2 (21.1) | -4.1 |
| Visceral | 0.4 (0.7) | 0.4 (0.6) | -13.1 |
| Retroperitoneal | 4.1 (6.3) | 5.4 (7.5) | 18.6 |
| Extra-abdominal | 2.1 (3.2) | 3.1 (4.3) | 35.7 |
| Ascites | 0.2 (0.3) | 0.2 (0.3) | -13.1 |
| Pleural Effusion | 1.0 (1.6) | 0.8 (1.1) | -29.3 |
| >3 anatomical “types” | 21.4 (32.9) | 20.1 (27.9) | -15.1 |

interval surgery patients with respect to cytoreduction or surgical complexity due to small numbers, although the data is presented for completeness. Controversy remains regarding the recurrence patterns of both treatment modalities with evidence of increased platinum sensitivity of PDS recurrences [18] being at odds with RCTs [19, 20], which demonstrated no inferiority in survival with NACT. This should be a focus of further research.

This study is retrospective and as such suffers from all the recognised limitations of such reviews. The clinical practice in the NHS is that CT imaging at relapse is triggered by a rising CA125 or symptoms, rather than a ‘routine’ evaluation at clinic visits. Though arguably, whether a routine CT as part of follow–up alters detection rate remains unproven. Indeed, small volume ascites may not be identified and peritoneal lesions may be missed [21, 22]. Additionally, differentiation between presumed visceral and peritoneal lesions may not be accurate [23]. Certain anatomical regions are less well visualised on CT meaning that small, early, and isolated recurrent disease in those areas may be missed [21, 22]. Accepting these limitations, the present study is the largest to date to focus on locations of recurrent disease, and describes a picture that is recognisable in our clinical environment: namely that the much sought after achievement of R0 is changing the nature of recurrent disease in advanced ovarian cancer.

## Conclusion

Irrespective of the surgery undertaken, the peritoneum is the commonest site of recurrence. However, the surgical approach to achieve R0 seemingly alters the incidence of ascites in relapse rates, reduces the peritoneal relapse rate, and renders retroperitoneal relapse more common, compared to those with achieving R1. Many explanatory hypotheses could be extrapolated regarding the findings of this study. However, in cases with complete resection in advanced disease after extensive surgery systematic retroperitoneal lymphadenectomy may be therapeutic – a trial that requires consideration. The first trial though must be to compare extensive primary surgery versus that in the neoadjuvant setting.

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Corresponding Author:
A. PHILLIPS, MBChB, MRCOG
Department of Obstetrics & Gynaecology
Royal Derby Hospital
Uttoxeter Road
Derby, DE22 3NE (United Kingdom)
e-mail: drandyphillips@gmail.com