

Complete cytoreduction after five or more cycles of neo-adjuvant chemotherapy confers a survival benefit in advanced ovarian cancer

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1 **Complete cytoreduction after five or more cycles of neo-adjuvant chemotherapy confers**
2 **a survival benefit in advanced ovarian cancer.**

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28 **ABSTRACT**

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30 **Objectives**

31 To assess the impact of 5 or more cycles of neoadjuvant chemotherapy (NACT) and
32 cytoreductive outcomes on overall survival (OS) in patients undergoing interval debulking
33 surgery (IDS) for advanced ovarian cancer.

34 **Methods**

35 A retrospective review of patients receiving NACT followed by IDS between 2007-2017.
36 Patients were analysed according to number of NACT cycles received: group 1 consisted of
37 patients receiving ≤ 4 cycles and group 2 consisted of those receiving ≥ 5 cycles. Outcomes
38 were stratified by cytoreductive outcome, surgical complexity, stage and chemotherapy
39 exposure.

40 **Results**

41 231 patients in group 1 and 167 in group 2 were identified. In group 1, the OS for those
42 achieving Complete(R0), Optimal<1cm(R1) and Suboptimal(R2) was 51.1, 36.1, and 34.3
43 months respectively. Statistically significant differences in survival were seen in patients
44 achieving R0vR2($p < 0.019$) but not in R0vR1($p = 0.125$) or R1vR2($p = 0.358$). In group 2, the
45 OS for those achieving R0, R1 and R2 was 53.0, 24.7, and 22.1 months respectively.
46 Statistically significant differences were seen between R0vR1 and R0vR2 ($p < 0.00001$) but
47 not between R1vR2 ($p = 0.917$). No difference in OS was seen between groups 1 and 2. In
48 patients achieving R1, there was a trend towards decreasing OS with increasing exposure to
49 NACT from 36.1(95%CI 32.0-40.2)months with 3 cycles to 24.3(95%CI 14.4-34.2)months
50 with ≥ 6 cycles.

51 **Conclusions**

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Surgery with utilisation of cytoreductive procedures to achieve complete clearance should be offered to all patients even after ≥ 5 cycles if R0 can be achieved. R1 cytoreduction has questionable value in those receiving ≤ 4 cycles and no value in those receiving ≥ 5 cycles.

KEYWORDS

Ovarian cancer; Survival; Surgery; Chemotherapy; Patient selection; Neo-adjuvant

59 INTRODUCTION

60 Cancer of the fallopian tube, ovary or peritoneum (epithelial ovarian cancer) is the second
61 most common and the most lethal gynaecological malignancy (1). The foundation for the
62 modern management of this condition is the utilisation of surgery with the intention to
63 remove all macroscopic disease (2-4) and platinum and taxane-based chemotherapy, either as
64 treatment following surgery (adjuvant) or as treatment both before and after surgery (neo-
65 adjuvant, NACT). Since the publication of two randomised controlled trials demonstrating
66 non-inferiority of NACT over primary surgery (5, 6) the rates of NACT usage have
67 increased, in the US, overall to 22.6%(7) with some centres using NACT in up to 34% of
68 stage 3c patients and 62% of stage 4 patients (8). Suggested indications for NACT include:
69 stage 3c disease where the extent of surgery to achieve a satisfactory cytoreductive outcome
70 based on imaging or laparoscopy is considered to excessive; stage 4 disease; where the
71 patient performance status is insufficient to undertake the required debulking procedure;
72 where surgical expertise for the required surgery is unavailable; and, in some centres, in the
73 obese or elderly where extensive upper abdominal procedures appear necessary (9).

74 Although cytoreduction outcomes have repeatedly been demonstrated to be a significant
75 modifiable marker of survival (10-12), the survival gains from extensive surgery to achieve
76 complete (R0) cytoreduction after NACT is poorly quantified. Both the aforementioned
77 randomised studies into NACT demonstrate that compared to primary surgery, NACT
78 achieves elevated R0 rates but, paradoxically, delivers comparable overall survival (OS)
79 rates.

80 Previous reviews of NACT cycles and OS have offered conflicting results (13-15). However,
81 the use of four cycles does appear to be increasing in practice with such regimes being
82 utilised in recent trials (16). Although comparatively less commonly used, the safety of six
83 cycles has also been recognised (17). The impact of extended (five or more) cycles of NACT
84 on survival, especially in association with modern cytoreductive targets, remains poorly
85 described in the literature. As such there remains little information regarding the optimal
86 NACT regime to use but the joint Society of Gynecologic Oncology and American Society of
87 Clinical Oncology guidance (18) currently favours four or less cycles of platinum and taxane-
88 based chemotherapy based upon the methodology described in the EORTC (6) and CHORUS
89 (5) studies (which utilised three cycles) and the ongoing JCOG0602 (19) study (which

90 utilised four cycles). Extending NACT to 6 cycles raises theoretical biological concerns (20)
91 relating to the development of resistant clones which may or may not be removed with
92 subsequent cytoreductive surgery. Additionally, one could expect that any residual tumour
93 may not only have greater resistance to chemotherapy but is also likely to receive less
94 adjuvant chemotherapy compared to patients treated with primary surgery or less NACT.

95 The purpose of this study therefore was to assess the impact increasing numbers of cycles of
96 NACT, and the associated cytoreductive outcomes, have upon OS in patients undergoing
97 interval debulking surgery (IDS) for stage 3 or 4 epithelial ovarian, tubal or peritoneal cancer
98 (advanced ovarian cancer, AOC).

99 **MATERIALS AND METHODS**

100 We reviewed all patients diagnosed with AOC between 16th August 2007 and 16th February
101 2017. All patients were managed by subspecialty trained gynaecological oncologists at the
102 Pan-Birmingham Gynaecological Cancer Centre (PBGCC), Birmingham, United Kingdom,
103 which serves a population of 2.2 million people. All patients were discussed at the Centre
104 multi-disciplinary team (MDT) meeting and prospectively recorded in an electronic database.
105 Approval for this study was obtained from the hospital clinical effectiveness department.

106
107 All consecutive patients diagnosed with histologically proven AOC were identified from the
108 database. Women with suspected AOC underwent a standard previous described (21)
109 diagnostic pathway. Following discussion at the MDT meeting, women either underwent:
110 primary debulking surgery (PDS), 3-4 cycles carboplatin AUC 6 +/- paclitaxel 175mg/m²
111 based NACT with an intention to consider IDS, or palliation alone. NACT was used in
112 patients with: stage 4 disease; poor performance status (ECOG/WHO 3-4); obvious porta
113 hepatis involvement on scan or extensive/irresectable upper abdominal disease; small bowel
114 mesenteric or extensive serosal involvement on diagnostic laparoscopy; or large amount of
115 ascites with a serum albumin of less than 30g/l. These criteria were originally developed from
116 the EORTC trial protocol prior to August 2007 (Performance status, absence of
117 contraindications to primary surgery) and were updated following the final results to include
118 stage 4 disease patients (6). As early adopters of complete macroscopic clearance as the
119 primary surgical aim, in patients in which this would be unlikely to be achieved (due to
120 disease or patient factors) we would defer to treatment with NACT. An additional one cycle

121 was sometimes used to facilitate logistical issues around timing of surgery. An additional two
122 or three cycles of NACT were used in patients with a poor response (static disease, persistent
123 ascites) following the initial three cycles of NACT. Women not exposed to any surgery were
124 those with: progressive disease despite NACT; worsening performance status; severe
125 cardiovascular disease; and patient choice. The PBGCC was an early adopter of advanced
126 upper abdominal surgical procedures in the UK with detailed surgical outcomes previously
127 published (22, 23). All patients are offered adjuvant chemotherapy tailored to their pre-
128 operative chemotherapy exposure. All adjuvant chemotherapy was delivered via the
129 intravenous route as intraperitoneal chemotherapy is not the standard of care for AOC in the
130 United Kingdom. Definitive histology (histological sub-type and grade) is obtained following
131 review by specialist gynaecological oncology histopathologists.

132 For this study the patient cohort was divided into two groups prior to analysis. Group 1
133 included all those who underwent the standard NACT regime of up to four cycles (Three
134 standard cycles and those with an additional cycle due to scheduling issues). Group 2
135 consisted of patients who received extended treatment with NACT (five or more cycles) due
136 to patient or disease factors. Sub-group analysis by number of cycles received was
137 additionally performed.

138 *Data Collection*

139 The following data items were collected: age at initial diagnosis; body mass index (BMI);
140 FIGO stage; histological sub-type and grade; level of cytoreduction achieved (R0, R1 and R2
141 (sub-optimal)); surgical complexity score (low, intermediate and high (24)); number of cycles
142 of NACT chemotherapy; chemotherapy regime; and, adjuvant number of cycles of
143 chemotherapy.

144 *Statistical analysis*

145 Categorical variables were compared with the chi-squared test and continuous variables were
146 compared with the Kruskal-Wallis or Mann-Whitney U test depending on the distribution of
147 data. All tests were two-sided and p-values of <0.05 was regarded as being statistically
148 significant.

149 The Kaplan-Meier method was used to estimate survival with survival compared using the
150 Log rank method. Variables were selected for inclusion in the multivariate analysis model if a
151 significant ($p < 0.05$) difference was identified on univariate analysis. Multivariate analysis
152 was done using the log rank test if the proportional hazards (PH) assumption was met using
153 IBM SPSS statistics version 20.

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156 RESULTS

157 Between 16th August 2007 and 16th February 2017, 858 patients received treatment for AOC
158 at the PBGCC. Of these, 610 (71%) underwent cytoreductive surgery with 248 (29%)
159 receiving chemotherapy or palliation alone. Of the patients who underwent cytoreductive
160 surgery, 210 (35%) underwent PDS and 400 (65%) underwent IDS. Overall R0, R1 and R2
161 outcomes were achieved in 64%, 14% and 21% respectively.

162 Of the 400 patients who underwent IDS, two were excluded from the analysis due to
163 insufficient data being available, hence our study sample consisted of 398 patients. Of these,
164 231 (58.0%) patients were in group 1 (≤ 4 cycles) with 111 (48.1%) receiving standard
165 treatment with three cycles of NACT and the remaining 120 (51.9%) receiving an additional
166 cycle to facilitate timing of IDS. Group 2 (≥ 5 cycles) consisted of the remaining 167 (42.0%)
167 patients.

168 The patient characteristics are summarised in Table 1. Compared to patients in group 2,
169 patients in group 1: had a higher proportion of primary peritoneal cancer ($p = 0.03$); achieved
170 a higher rate of R0 cytoreduction ($p = 0.0003$) with a lower rate of R2 cytoreduction ($p =$
171 0.003); received more complex surgery ($p = 0.001$); were more likely to receive paclitaxel in
172 addition to carboplatin ($p = < 0.0001$); were more likely to receive bevacizumab ($p = 0.03$);
173 and received a higher median number of adjuvant chemotherapy cycles ($p = 0.0001$).

174 The median OS of all patients treated with IDS was 40.1 (95%CI 35.8 – 44.4) months with
175 OS in those achieving R0, R1 and R2 being 51.8 (95%CI 45.0 – 58.5), 29.5 (95%CI 22.2 –
176 36.7) and 28.9 (95%CI 22.0 – 35.6) months respectively. A significant difference in OS was
177 seen between those achieving R0 and R1 ($p = 0.00005$) and R0 and R2 ($p = < 0.000001$) with
178 no significant difference seen between R1 and R2 ($p = 0.52$).

179 Survival patterns differed between patients in group 1 and patients in group 2. Patients in
180 group 1 had an OS of 44.3 (95%CI 37.0 – 51.5) months. OS decreased from 51.1 (95%CI
181 42.8 – 59.3) months in those who achieved R0 to 34.3 (95%CI 30.6 – 38.0) months in those
182 who only achieved R2. Patient who achieved R1 levels of cytoreduction had an OS of 36.1
183 (95%CI 30.8 – 41.4). The difference in OS between patients achieving R0 and R2 was
184 significant ($p = 0.019$), but the differences in OS between patients achieving R0 and R1 and
185 R1 and R2 were not ($p=0.125$ and $p=0.358$ respectively) (Figure 1A).

186 Patients in group 2 had an OS of 36.5 (95%CI 28.7 – 44.2) months. OS for those achieving
187 R0, R1 and R2 was 53.0 (95%CI 40.1 – 65.8), 24.7 (95%CI 17.8 – 31.6) and 22.1 (95%CI
188 11.9 – 32.3) months respectively. The difference in OS between patients achieving R0 and
189 R1 was significant ($p= <0.00001$), as was the difference between patients achieving R0 and
190 R2 ($p= <0.00001$). There was no significant difference in OS between patients achieving R1
191 and R2 ($p=0.917$) (Figure 1B)

192 There was no significant difference in the OS between groups 1 and 2 (44.3 (95%CI 37.0 –
193 51.5) months v 36.5 (95%CI 28.7 – 44.2) months) ($p>0.05$) (Figure 2). On multivariate
194 analysis, adjusting for cytoreductive outcome, stage of disease, and chemotherapy regime, the
195 difference between R0 and R2 ($p = 0.026$) in group 1 and between R0 and R1 ($p = <0.0001$)
196 and R0 and R2 ($p = <0.00001$) in group 2 remained significant (Table 2).

197 The number of patients receiving ≤ 3 , 4, 5 or ≥ 6 cycles of NACT was 111, 120, 46 and 121
198 respectively. Subgroup analysis, looking at the actual number of cycles of NACT received,
199 demonstrated that, for patients achieving R1 ($n=55$), OS decreased from 36.1 months (95%
200 CI 32.0-40.2) in those receiving 3 cycles of NACT ($n=8$), to 24.3 months (95% CI 14.4-34.2)
201 in patients receiving six or more cycles ($n=20$) (Table 3). Although overall this was not a
202 statistically significant decrease, the OS of patients receiving three cycles of NACT was
203 significantly longer than patients receiving five cycles ($p=0.017$), as was the OS of patients
204 receiving four cycles compared to five cycles ($p=0.011$). No significant difference in OS was
205 seen in those obtaining R0 or R2 irrespective of NACT exposure.

206 In group 1, most (62.8%) patients received low complexity surgery. Only 16% of patients
207 received high complexity surgery. Although the OS in patients achieving R0 following high,
208 intermediate and low complexity surgery was 39.6 (95%CI 21.9 – 57.3) months, 56.2 (95%CI
209 40.5 – 71.9) months and 52.2 (95%CI 36.9 – 67.5) months respectively, the difference
210 between the groups was not statistically significant. (Figure 3A)

211 Only nine (5.5%) patients in group 2 underwent high complexity surgery with patients more
212 commonly receiving intermediate (23.8%) or low (70.7%) complexity surgery. No patients
213 receiving high complexity surgery achieved R2 outcomes. Although the OS in patients
214 achieving R0 was 52.9 (95%CI 34.9 – 70.9) months with low complexity surgery, 56.0
215 (95%CI 28.8 – 83.2) months with intermediate complexity surgery and 25.0 (95%CI 21.3 –
216 28.7) months with high complexity surgery, the difference between these groups was not
217 statistically significant (Figure 3B).

218

219 DISCUSSION

220 Our study finds that complete cytoreduction remains a significant independent marker of
221 survival in patients undergoing cytoreductive surgery even after 5 cycles of NACT.
222 Additionally, whether R0 is achieved with Low, Intermediate or High complexity surgery
223 makes no significant difference to overall survival. Our findings furthermore demonstrate that
224 R1 is not an acceptable cytoreductive target in patients receiving five or more cycles of
225 chemotherapy and are suggestive of decreasing overall survival in patients obtaining R1 with
226 increasing exposure to NACT. If complete cytoreduction in these patients is not possible,
227 apart from for any palliative procedures, surgery should be abandoned in favour of
228 continuation of chemotherapy alone.

229 Whilst we acknowledge that these results may be influenced by patient selection our total
230 cohort OS including PDS, IDS and non-operated cases has been shown to be comparable to
231 international peers (21). Within this cohort, in those receiving PDS 65.2% achieved R0 and
232 80.5% achieved R1 or better comparing well with other cohorts such as Chi (3) (27% and
233 80%), EORTC PDS arm (6) (19.7% and 42.2%) and CHORUS PDS arm (5) (17% and 41%).
234 NACT is used in conjunction with maximum effort cytoreductive surgery with corresponding
235 elevated cytoreduction rates, 64% R0 and 77.9% R1 or better compared to EORTC NACT
236 arm (46.9% and 73.9%) and CHORUS NACT arm (43% and 73%).

237 This is, to our knowledge, the largest study examining the use of extended cycles of NACT in
238 the treatment of AOC and It confirms previous findings that complete cytoreduction remains
239 a significant marker of survival in AOC (10). As with previous studies (13, 14) no significant
240 difference was seen in OS between those receiving four or less or five or more cycles.
241 Patients can therefore be reassured that the addition of additional cycles of NACT, if logistics

1 242 interferes with organisation of theatre scheduling, does not adversely impact survival.
2 243 Equally, patients selected for surgery after 6 cycles of NACT because of performance status
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4 244 or response rates can be reassured that surgery even at that stage confers survival benefit if
5 245 complete is achieved
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8 246 Across our entire cohort we demonstrate no benefit from R1 cytoreduction in patients
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10 247 receiving IDS although our results may be significantly influenced by the large number of
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12 248 patients receiving more than our standard three cycles of NACT. On subgroup analysis, there
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14 249 may be a benefit in R1 cytoreduction in those receiving four or less cycles of NACT although
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16 250 this requires further investigation. Surgery after 5 cycles of NACT confers survival benefit
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18 251 only when complete cytoreduction is achieved. Where surgery results in residual disease even
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20 252 at R1 this survival advantage from surgery is lost. Although relatively few patients achieved
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22 253 R1 following IDS, there is a trend in this subgroup towards decreasing OS with increasing
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24 254 exposure to NACT. Such a finding would be consistent with the argument often asserted that
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26 255 PDS inhibits the development of resistant clones (25) whereas any residual disease remaining
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28 256 after IDS will, not only have a greater proportion of resistant clones, but also be less likely to
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30 257 receive as many cycles of adjuvant chemotherapy to eradicate it. As such this study supports
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32 258 the Goldie-Coldman hypothesis (20) of the pathogenesis of AOC.

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34 259 Irrespective of biological models of resistance however our study still demonstrated no
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36 260 significant difference in OS in those patients who obtained R0 between those in group 1 and
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38 261 group 2. Our results therefore contrast with a smaller study of 24 patients by Columbo (15)
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40 262 suggesting a significantly depressed OS in their patients receiving extended NACT compared
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42 263 to those receiving a standard regime. Although this could well be due to sample size there
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44 264 appeared to be certain differences in surgical ethos between the cohort described by Columbo
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46 265 and those treated at the PBGCC, but without complete denominator descriptors any
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48 266 comparison between the two groups is impossible (21). Our study is in agreement with Da
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50 267 Costa Miranda (17) who also examined extended treatment with NACT followed by surgery
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52 268 and found that highest OS was obtained in those obtaining R0 following NACT. The OS in
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54 269 that study was 41.9 months and we postulate that the slightly lower OS may be due to that
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56 270 study not giving adjuvant chemotherapy to those patients receiving IDS after 6 cycles. (17).
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58 271 We postulate that there may be a survival benefit despite concerns about toxicity from some
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60 272 consolidation adjuvant chemotherapy (in our centre 2-3 cycles) even after extensive exposure
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62 273 to NACT. We suggest therefore that establishing the value of consolidation chemotherapy
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64 274 following IDS after extended NACT cycles is a trial worthy of consideration.
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1
2 276 One of the limitations of our study is the lack of accurate initial disease distribution data.
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4 277 However, there was no significant difference in survival amongst patients who were
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6 278 completely cytoreduced following low, intermediate or high complexity surgery after
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8 279 extended treatment with NACT. As such, even in patients with more dispersed disease
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10 280 (implied by the required surgical effort to achieve complete cytoreduction), the OS appears to
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12 281 be not significantly different from those with a presumed lower tumour burden who were also
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14 282 completely cytoreduced. However, consistent with a study by Horowitz (26), patients
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16 283 receiving high complexity surgery (with a presumed greater tumour load), did have a lower
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18 284 median OS than those who underwent low or intermediate complexity surgery. These results
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20 285 may be due to the relatively small sample size included in our study. Further research is
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22 286 needed to ensure that there remains a true benefit from high complexity surgery in patients
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24 287 with large volume disease after extensive exposure to NACT. A second limitation is the
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26 288 proportion of women receiving an extra cycle of chemotherapy to time surgery, despite this
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28 289 our NACT regime still is consistent with previous studies and remains the largest piece of
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30 290 work in this space. Finally, the PBGCC does not, at present, utilise intra-peritoneal
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32 291 chemotherapy and as such our results may not be applicable to centres who have incorporated
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34 292 this into their NACT regime.

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36 293 Despite the development of personalised medicine in gynaecological oncology our use of
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38 294 NACT or PDS remains comparatively inflexible with no sophisticated mechanisms to predict
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40 295 outcomes. Our data does however offer the potential for a more patient tailored approach to
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42 296 primary treatment strategies. It is possibly primary therapy in the form of surgery is best for
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44 297 some patients, NACT for others, with tailored NACT objectives to make surgery to RO
45
46 298 achievable or improve the patients' condition to render surgery safe. Such individualisation is
47
48 299 likely in the future, though appropriate studies are necessary.

49
50 300 The Joint Society of Gynecologic Oncology and American Society of Clinical Oncology
51
52 301 guidance (18) on the use of NACT suggests utilising either three (based upon the findings of
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54 302 CHORUS/EORTC (5, 6)) or four cycles (pending the results of JCOG0602 (19)). Our data
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56 303 raises questions about the value of R1 cytoreduction in 4 or less cycles (and no value of R1
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58 304 cytoreduction following 5 or more cycles) and suggests that prior to the matured data from
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60 305 JCOG0602, three cycles of NACT should remain standard. Indeed, the suggestion that the OS
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62 306 benefit from R1 may be impaired by four compared to three cycles of NACT questions
63
64 307 whether the use of an extra cycle of NACT to facilitate timing of surgery can be justified.
65

308 Despite concerns regarding the value of R1 cytoreduction in IDS, our data shows that if more
309 than 4 cycles are needed for patient or disease factors it can be used with no adverse effects
310 providing that R0 is achieved.

311

312 CONCLUSION

313 In conclusion, our data suggests that surgery should be offered to all patients irrespective of
314 NACT exposure and performed if R0 can be achieved. R1 cytoreduction has no value in
315 those receiving five or more cycles of NACT and thus should not be considered an acceptable
316 cytoreductive outcome in this group. In patients receiving five or more cycles of NACT if
317 complete cytoreduction in these patients is not possible, save for any palliative procedures,
318 surgery should be abandoned in favour of continuation of chemotherapy alone. Further
319 studies examining limited cycles of NACT to improve performance status and the impact of
320 high complexity surgery in those receiving five or more cycles of NACT are strongly
321 encouraged.

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Table1

	Group 1 n=231(%)	Group 2 n=167	p	Total n=398
Age	63.0 95%CI (41.1-84.9)	65.1 95%CI (44.0-86.3)	>0.05	63.9 95%CI (42.2 - 85.6)
BMI	26 IQR 23-29	25 IQR 21-29	>0.05	25 IQR 22 - 29
Site				
Ovary	142(61.5)	110(65.9)	>0.05	252(63.3)
Fallopian Tube	49(21.2)	41(24.6)	>0.05	90(22.6)
Primary Peritoneal	40(17.3)	16(9.6)	0.029	56(14.1)
Histology				
Serous	218(94.4)	152(91.0)	>0.05	370(93.0)
MMMT	6(2.6)	6(3.6)	>0.05	12(3.0)
Clear cell	1(0.4)	1(0.6)	>0.05	2(0.5)
Mixed	3(1.3)	5(3.0)	>0.05	8(2.0)
Anaplastic/Undifferentiated	0(0.0)	1(0.6)	>0.05	1(0.3)
Endometroid	1(0.4)	0(0.0)	>0.05	1(0.3)
Unknown	2(0.9)	2(1.2)	>0.05	4(1.0)
Grade				
1	7(3.0)	6(3.6)	>0.05	13(3.3)
2	1(0.4)	1(0.6)	>0.05	2(0.5)
3	219(94.8)	155(92.8)	>0.05	374(94.0)
Unknown	4(1.7)	5(3.0)	>0.05	9(2.3)
Stage				
3	153(66.2)	120(71.9)	>0.05	273(68.6)
4	78(33.8)	47(28.1)	>0.05	125(31.4)
Cytoreduction				
R0	165(71.4)	90(53.9)	0.00032	255(64.1)
R1	27(11.7)	28(16.8)	>0.05	55(13.8)
R2	39(16.9)	49(29.3)	0.0031	88(22.1)
Surgical Complexity				
LOW 0-3	145(62.8)	118(70.7)	>0.05	263(66.1)
INTER 4-7	49(21.2)	40(24.0)	>0.05	89(22.4)
HIGH 8+	37(16.0)	9(5.4)	0.0011	46(11.6)
Chemo therapy regime				
Carbo	26(11.3)	68(40.7)	<0.0001	94(23.6)
Carbo taxol	205(88.7)	99(59.3)	<0.0001	304(76.4)
Additional bevacizumab	19(8.2)	5(3.0)	0.031	24(6.0)
Adjuvant cycles	3 IQR 3-4	2 IQR 2-3	<0.0001	3 IQR 2-3

Table 1: Clinico-pathological-treatment data of all patients treated with four or less cycles of NACT and IDS (Group 1) and five or more cycles of NACT and IDS (Group 2)

Table2

		Hazard Ratio	95% CI	<i>p</i>
Group 1	Carbo taxol vrs Carbo	1.5495	0.928 - 2.588	>0.05
	R0 vrs R1	1.5723	0.928 - 2.664	>0.05
	R0 vrs R2	1.7709	1.069 - 2.933	0.0264
	R2 Vrs R1	0.8879	0.460 - 1.715	>0.05
	Stage 3 vrs Stage 4	1.6264	1.106 - 2.392	0.0134
Group 2	Carbo taxol vrs Carbo	1.1990	0.826 - 1.742	>0.05
	R0 vrs R1	2.7810	1.663 - 4.650	0.0001
	R0 vrs R2	2.6729	1.759 - 4.062	<0.00001
	R2 Vrs R1	1.0400	0.613 - 1.765	>0.05
	Stage 3 vrs Stage 4	0.7970	0.525 - 1.212	>0.05

Table 2: Multivariate analysis of the effect of cytoreduction on OS in group 1 and group 2

Table3

Cycles	n	R0		R1		R2	
		OS (months)	95% CI (months)	OS (months)	95% CI (months)	OS (months)	95% CI (months)
≤3	111	50.0	36.3 - 63.7	36.1	32.0 - 40.2	34.3	26.4 - 42.2
4	120	52.2	41.7 - 62.7	33.4	21.7 - 45.1	34.1	14.5 - 53.7
5	46	50.9	5.6 - 96.2	26.6	22.6 - 30.6	46.1	15.9 - 76.3
≥6	121	53.0	39.9 - 66.1	24.3	14.4 - 34.2	20.5	15.9 - 25.1

Table 3: Median OS of all patients analysed by cytoreductive outcomes and NACT exposure.

Tables/Figures

Table 1: Clinico-pathological-treatment data of all patients treated with four or less cycles of NACT and IDS (Group 1) and five or more cycles of NACT and IDS (Group 2)

Figures 1: Kaplan-Meier curve of OS by cytoreductive outcome in Group 1 (A) and Group 2 (B) patients undergoing treatment with NACT and IDS

Figure 2: Kaplan-Meier curve of OS for patients in Group 1 and Group 2 undergoing treatment with IDS and NACT

Table 2: Multivariate analysis of the effect of cytoreduction on OS in group 1 and group 2

Table 3: Median OS of all patients analysed by cytoreductive outcomes and NACT exposure.

Figure 3A & 3B: Kaplan-Meier curve comparing OS in patients achieving RO with Low, intermediate and high surgical complexity surgery in Group 1 (3A) and Group 2 (3B)

Figure1

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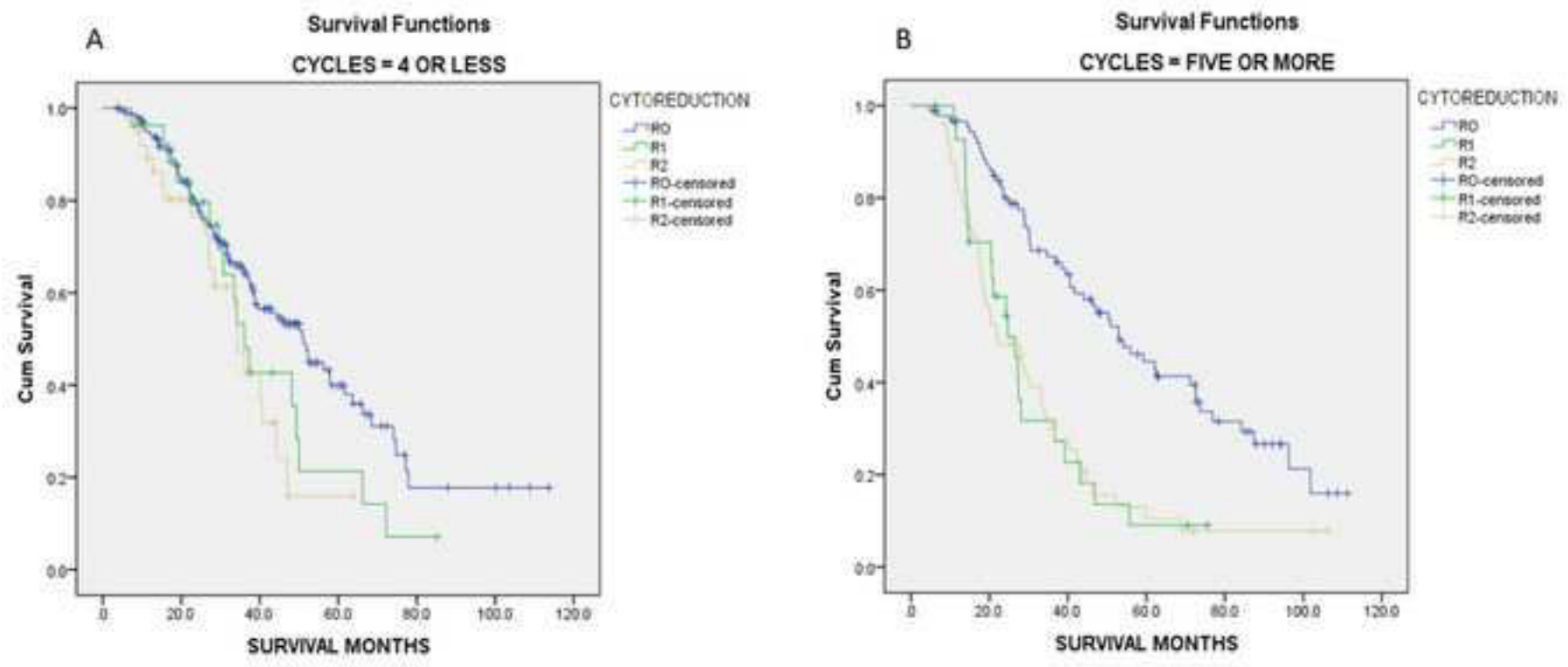


Figure2

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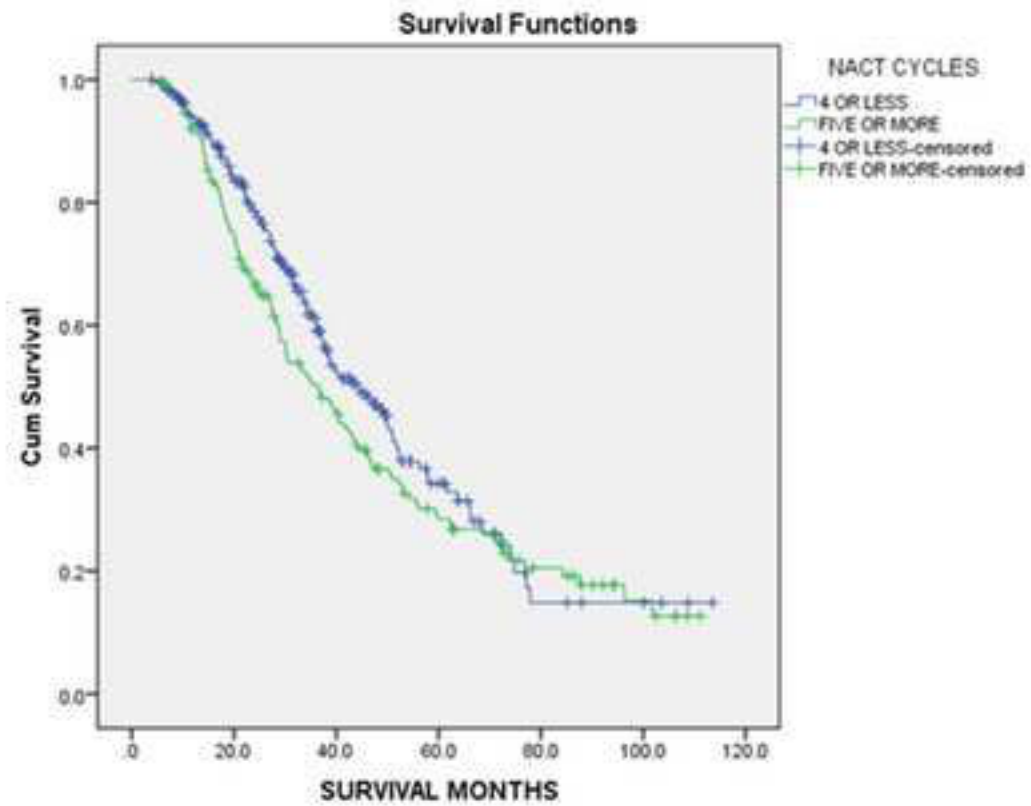


Figure3

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