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

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

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ABSTRACT

Objectives

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

Methods

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

Results

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

Conclusions

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

INTRODUCTION

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

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

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

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

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

MATERIALS AND METHODS

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

All consecutive patients diagnosed with histologically proven AOC were identified from the database. Women with suspected AOC underwent a standard previous described (21) diagnostic pathway. Following discussion at the MDT meeting, women either underwent: primary debulking surgery (PDS), 3-4 cycles carboplatin AUC 6 +/- paclitaxel 175mg/m^2 based NACT with an intention to consider IDS, or palliation alone. NACT was used in patients with: stage 4 disease; poor performance status (ECOG/WHO 3-4); obvious porta hepatis involvement on scan or extensive/irresectable upper abdominal disease; small bowel mesenteric or extensive serosal involvement on diagnostic laparoscopy; or large amount of ascites with a serum albumin of less than 30g/l. These criteria were originally developed from the EORTC trial protocol prior to August 2007 (Performance status, absence of contraindications to primary surgery) and were updated following the final results to include stage 4 disease patients (6). As early adopters of complete macroscopic clearance as the primary surgical aim, in patients in which this would be unlikely to be achieved (due to disease or patient factors) we would defer to treatment with NACT. An additional one cycle

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

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

Data Collection

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

Statistical analysis

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

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

RESULTS

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

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

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

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

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

Patients in group 2 had an OS of 36.5 (95%CI 28.7 – 44.2) months. OS for those achieving 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 11.9 – 32.3) months respectively. The difference in OS between patients achieving R0 and R1 was significant (p= <0.00001), as was the difference between patients achieving R0 and R2 (p=<0.00001). There was no significant difference in OS between patients achieving R1 and R2 (p=0.917) (Figure 1B)

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

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

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

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

DISCUSSION

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

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

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

interferes with organisation of theatre scheduling, does not adversely impact survival. Equally, patients selected for surgery after 6 cycles of NACT because of performance status or response rates can be reassured that surgery even at that stage confers survival benefit if complete is achieved

Across our entire cohort we demonstrate no benefit from R1 cytoreduction in patients receiving IDS although our results may be significantly influenced by the large number of patients receiving more than our standard three cycles of NACT. On subgroup analysis, there may be a benefit in R1 cytoreduction in those receiving four or less cycles of NACT although this requires further investigation. Surgery after 5 cycles of NACT confers survival benefit only when complete cytoreduction is achieved. Where surgery results in residual disease even at R1 this survival advantage from surgery is lost. Although relatively few patients achieved R1 following IDS, there is a trend in this subgroup towards decreasing OS with increasing exposure to NACT. Such a finding would be consistent with the argument often asserted that PDS inhibits the development of resistant clones (25) whereas any residual disease remaining after IDS will, not only have a greater proportion of resistant clones, but also be less likely to receive as many cycles of adjuvant chemotherapy to eradicate it. As such this study supports the Goldie-Coldman hypothesis (20) of the pathogenesis of AOC.

Irrespective of biological models of resistance however our study still demonstrated no significant difference in OS in those patients who obtained R0 between those in group 1 and group 2. Our results therefore contrast with a smaller study of 24 patients by Columbo (15) suggesting a significantly depressed OS in their patients receiving extended NACT compared to those receiving a standard regime. Although this could well be due to sample size there appeared to be certain differences in surgical ethos between the cohort described by Columbo and those treated at the PBGCC, but without complete denominator descriptors any comparison between the two groups is impossible (21). Our study is in agreement with Da Costa Miranda (17) who also examined extended treatment with NACT followed by surgery and found that highest OS was obtained in those obtaining R0 following NACT. The OS in that study was 41.9 months and we postulate that the slightly lower OS may be due to that study not giving adjuvant chemotherapy to those patients receiving IDS after 6 cycles. (17). We postulate that there may be a survival benefit despite concerns about toxicity from some consolidation adjuvant chemotherapy (in our centre 2-3 cycles) even after extensive exposure to NACT. We suggest therefore that establishing the value of consolidation chemotherapy following IDS after extended NACT cycles is a trial worthy of consideration.

One of the limitations of our study is the lack of accurate initial disease distribution data. However, there was no significant difference in survival amongst patients who were completely cytoreduced following low, intermediate or high complexity surgery after extended treatment with NACT. As such, even in patients with more dispersed disease (implied by the required surgical effort to achieve complete cytoreduction), the OS appears to be not significantly different from those with a presumed lower tumour burden who were also completely cytoreduced. However, consistent with a study by Horowitz (26), patients receiving high complexity surgery (with a presumed greater tumour load), did have a lower median OS than those who underwent low or intermediate complexity surgery. These results may be due to the relatively small sample size included in our study. Further research is needed to ensure that there remains a true benefit from high complexity surgery in patients with large volume disease after extensive exposure to NACT. A second limitation is the proportion of women receiving an extra cycle of chemotherapy to time surgery, despite this our NACT regime still is consistent with previous studies and remains the largest piece of work in this space. Finally, the PBGCC does not, at present, utilise intra-peritoneal chemotherapy and as such our results may not be applicable to centres who have incorporated this into their NACT regime.

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

The Joint Society of Gynecologic Oncology and American Society of Clinical Oncology guidance (18) on the use of NACT suggests utilising either three (based upon the findings of CHORUS/EORTC (5, 6)) or four cycles (pending the results of JCOG0602 (19)). Our data raises questions about the value of R1 cytoreduction in 4 or less cycles (and no value of R1 cytoreduction following 5 or more cycles) and suggests that prior to the matured data from JCOG0602, three cycles of NACT should remain standard. Indeed, the suggestion that the OS benefit from R1 may be impaired by four compared to three cycles of NACT questions whether the use of an extra cycle of NACT to facilitate timing of surgery can be justified.

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

CONCLUSION

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

Figure legend(s)

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-Meir 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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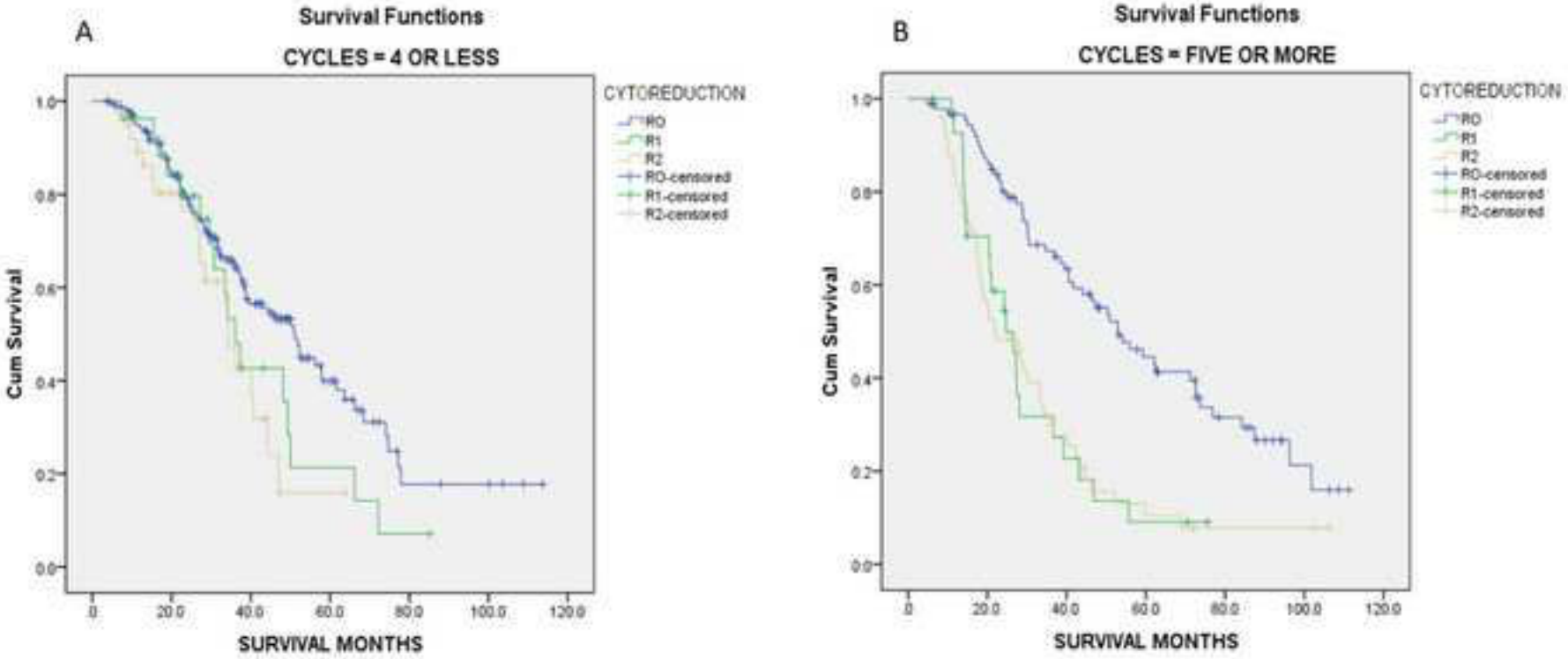

Figure2

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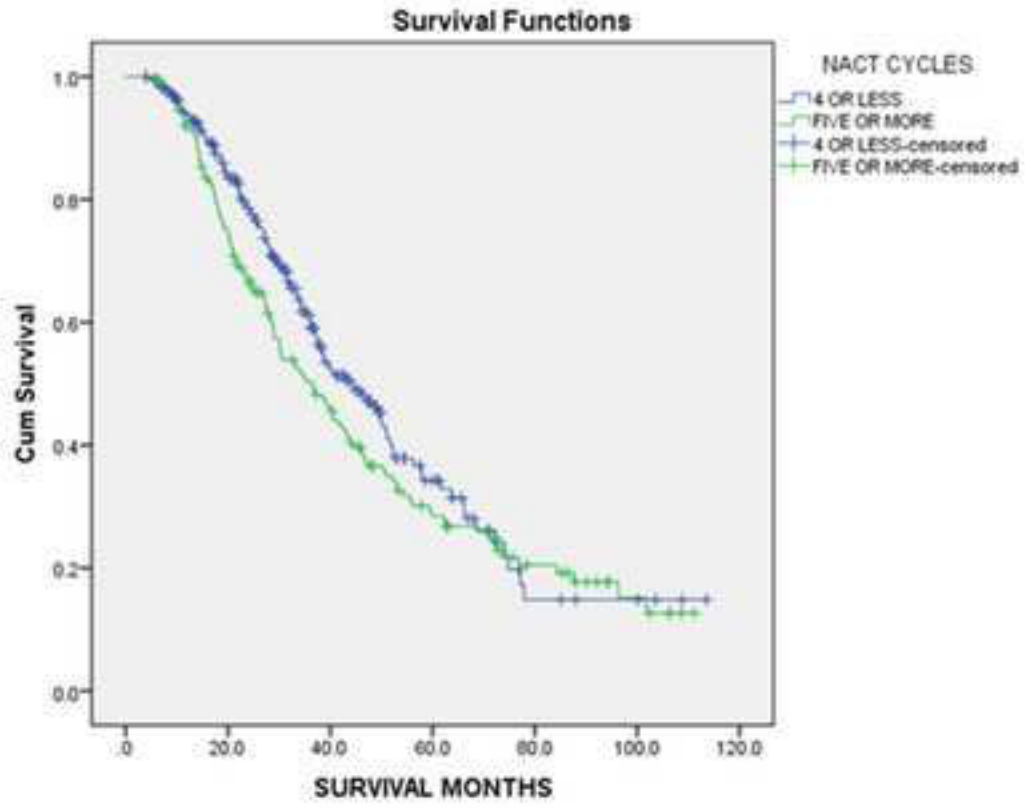

Figure3

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