# META-ANALYSIS OF THE RANDOMISED EORTC AND CHORUS TRIALS COMPARING NEOADJUVANT VERSUS UPFRONT DEBULKING SURGERY IN ADVANCED OVARIAN, FALLOPIAN OR PERITONEAL CANCERS.

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**ABSTRACT**

**Background and aims.** Two prospective randmonised trials, comparing neoadjuvant chemotherapy (NACT) with upfront debulking surgery (UDS) in advanced ovarian cancer (EORTC 55971 and MRC CHORUS) had a pre-planned meta-analysis arranged, to examine the long term outcomes of the trials, and identify any preferable therapeutic approaches for subgroup populations.

**Methods.** The data from both trials were merged with a database lock for the EORTC study on June 6th , 2015 and CHORUS May 20th, 2015. The analysis was undertaken by the EORTC statistical Team.

**Results.** 1220 women were randomised. The overall median follow-up was 7.6 years (EORTC 9.2 and CHORUS 5.9 years). Median age was 63 years (range 25-88 years) and median size of the largest metastatic tumour at diagnosis was 8 cm (range 0-50 cm ). FIGO Stage distribution was II-IIIB (4.5%), IIIC (68.1%), IV (18.9%) with 8.5% of data missing. Median overall survival (OS) for EORTC and CHORUS was significantly different at 2.5 and 2.0 years respectively, (p=0.004). When combined, there was no statistically significant difference regarding the median progression-free survival (PFS) , at 0.9 and 1 year, UDS and NACT or OS at 2.2 and 2.3 years respectively. Women with Stage IV disease had a significantly better PFS and OS with NACT compared with UDS (HR: 0.77 and 0.76; both, p=0.050 and 0.048). However, in women with stage IIIC with metastatic tumours at diagnosis ≤ 5cm, PFS was significantly prolonged with UDS (HR:1.34 and HR:1.26; p = 0.02),without significantly impacting on OS.

**Conclusion.** Long term follow-up data in this meta-analysis confirm that NACT and UDS result in similar PFS and OS in advanced ovarian cancer. However, women with stage IV

59 disease had a better OS and PFS with NACT while women with stage IIIC with metastases ≤ 5

60 cm had a better PFS with UDS.

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## INTRODUCTION

Over 70% of women with ovarian cancer present with advanced disease, and ~~In~~ usually have a very poor prognosis (1). Since Griffiths reported In 1975 (2) the association between reduced residual tumour load and improved survival rates following debulking surgery, primary surgery has been embedded in clinical practice as an essential , or even a mandatory, therapeutic strategy.(3) However, to date, there are still no prospective randomised controlled trials available proving that primary debulking surgery improves the prognosis of patients with advanced ovarian cancer.

An alternative approach to primary debulking surgery, is neoadjuvant chemotherapy, administered before attempting cytoreductive surgery. In 2010 the first randomised trial comparing neoadjuvant chemotherapy (NACT) followed by interval debulking surgery with primary debulking surgery (UDS) was published (4). This randomised EORTC study showed a similar overall and progression-free survival in women with FIGO (International Federation of Gynecology and Obstetrics) stage IIIC or IV ovarian cancer with both treatment strategies and a lower operative morbidity with NACT. These results were later confirmed in the randomised CHORUS trial (5) and resulted in the acceptance of NACT followed by IDS as an alternative for UDS in stage IIIC and IV ovarian cancer (6). However, the selection of women with advanced ovarian cancer for NACT or UDS remains controversial (7).

In 2003, while the accrual of the EORTC study was ongoing but prior to the start of the CHORUS trial, we (EORTC/MRC) planned the current meta-analysis with the aim of analysing the long-term follow-up of both trials and to identify subgroups who might benefit more or less from NACT compared with UDS.

## Materials and methods

*Eligibility and study design*

The eligibility criteria and study design of the EORTC and CHORUS trials have previously been reported (4,5). In short, in the EORTC trial eligible women had biopsy proven Stage IIIC or IV invasive epithelial ovarian, primary peritoneal, or fallopian tube carcinoma. If a biopsy was not available, fine needle aspiration showing an adenocarcinoma was acceptable under the following conditions: presence of a pelvic (ovarian) mass; and presence of metastases of ≥ 2 cm (measured during diagnostic laparoscopy or laparotomy, and if not done, based on CT findings) outside the pelvis and a CA125 (KU/L)/CEA (ng/mL) ratio > 25. If the CA125/CEA ratio was less, investigations to exclude a gastrointestinal carcinoma were necessary before entry. In the CHORUS trial the inclusion criteria were similar, but women with apparent stage IIIA and IIIB were also eligible and a histological or cytological confirmation of diagnosis was not required prior to randomization. In both trials randomization was to primary debulking surgery followed by at least 6 courses of platinum-based chemotherapy, versus three courses of neoadjuvant platinum-based chemotherapy followed by interval debulking surgery in all women showing a response or stable disease, and then at least 3 nother courses of platinum based chemotherapy. In women randomised to primary debulking whose surgery was completed without optimal cytoreduction, interval debulking surgery was permitted if stable disease or response was documented and these patients were included for analyses in the primary debulking surgery arm. Randomisation was done for the EORTC trial at the EORTC Headquarters after stratification with a minimization technique to stratify for institution, method of biopsy (imaging-guided, laparoscopy, laparotomy, or fine needle aspiration), Stage IIIC or IV, and largest tumor size

(excluding ovaries) before surgery (less than 5, 5 – 10, 10 - 20 cm, or more than 20 cm). In the CHORUS trial the random assignment was performed centrally at the MRC CTU (Medical Research Council Clinical Trials Unit) using a minimisation method with a random element, and stratified the women according to randomizing Centre, largest radiological tumour size, clinical FIGO stage, and pre-specified chemotherapy regimen.

*Statistical design of the meta-analysis*

The meta-analysis was designed in 2003 by the CIs of the two trials (IV and SK) and members of the EORTC /MRC trials committees. The databases were examined and arranged to ensure appropriate information was collected to permit merging of both for the agreed meta-analysis. The women were followed until the data base lock. The meta-analysis was done based on the individuals data, i.e. *all* data were merged instead of using only the summary data from each trial. The data were gathered at the EORTC Headquarters and analyzed in cooperation with the authors by the EORTC statistician (CC).

The pooled dataset was estimated to contain between 800 to 900 events (deaths). Assuming a median overall survival (OS) of 3 years, this allows assessment of non-inferiority with a one-sided type I error of 0.05 and a power of 80% where inferiority is considered as an increase of more than 18-19% in hazard. Similarly, it would allow a 90% power in excluding a hazard increase of 22-23%. Applying a two-sided test of superiority at 5%, the dataset would allow the detection of an 18% increase in hazard with 80% power.

The analysis was performed according to the intent to treat policy: all randomized patients are included in the principal analysis, whatever their eligibility and evaluability status. A per-protocol population served as supportive analysis. The definitions applied for

overall and progression-free survival are previously published. (4). Overall and progression-free survival were estimated by the Kaplan-Meier method and overall survival compared via the log rank test. Multivariate time-to-event analysis was performed using a Cox proportional hazards model, with univariate screening followed by a multivariate stepwise variable selection procedure (8). All results were checked for homogeneity among the two studies and stratified per trial.

The size of the largest metastases before randomization was measured in the EORTC study during diagnostic laparoscopy or laparotomy, and if not done, based on CT findings. In the CHORUS trial these measurements were based on CT radiologic imaging only. Subgroup analyses according to the stratification factors which were common in both trials (randomizing Centre, largest tumor size (excluding ovaries) before surgery (less than 5, 5 – 10, 10 - 20 cm, or more than 20 cm), and clinical FIGO stage) was planned.

## Results

*Patient characteristics*

The patient data of both trials were updated and merged in one data base (data base lock EORTC June 6, 2015 and CHORUS May 20, 2015). 1220 patients were randomised. Median follow-up was 7.6 years (EORTC 9.2 and CHORUS 5.9 years). The characteristics of the patients by study and study arm are summarised in Table 1 and 2, respectively. The baseline characteristics were well balanced between both treatment groups. For details on size of residual tumor, residual tumor per country, type of surgery, number of courses and type of chemotherapy, and time to (re)initiation of chemotherapy we refer to the original papers.

*Overall survival and progression-free survival*

Overall survival (OS) was significantly better in the EORTC trial compared with the CHORUS trial (median, respectively 2.52 and 1.95 years; Hazard ratio (HR): 1.20, 95% Confidence Intervals (CI): 1.06-1.36; p = 0.004) (Figure 1), but progression-free survival (PFS) was similar (median respectively 0.96 and 0.93 years; HR 0.94, 95% CI: 0.84-1.06; not significant) (Supplemental file page 1).

Overall survival (Figure 2) and progression-free survival (Supplemental file page 2) were similar for NACT and UDS (median respectively for OS 2.30 and 2.24 years, HR: 0.97, 95% CI: 0.88-1.09; and for PFS respectively 0.97 and 0.93 years, HR: 0.98, 95% CI: 0.87-1.09; both not significant). Overall and progression-free survival per study and treatment arm are presented in the Supplemental file (page 3 and 4).

Median overall survival was significantly different for Stage IV compared with Stage III and Stage II (median respectively, 1.94, 2.50 and 3.75 years; HR 2.75 and 1.92 for Stage III and IV versus stage II, p = 0.000; see Supplemental file page 5). Overall survival was similar for NACT and UDS in Stage IIIC patients (median respectively, 2.56 and 2.37 years; HR: 1.04, 95% CI: 0.90-1.21; not significant; Supplemental file page 6). Progression-free survival was similar or NACT and UDS in Stage IIIC (median respectively, 1.02 and 0.97 years; HR: 1.05, 95% CI: 0.92-1.21; not significant; Supplemental file page 7). However, in Stage IV NACT resulted in significantly better overall survival than UDS (Figure 3) (median respectively, 2.02 and 1.77 years; HR: 0.76, 95% CI: 0.58-1.00, p = 0.048). Also PFS was significantly better in Stage IV disease with NACT than with UDS (median respectively, 0.88 and 0.81 years; HR: 0.77, 95% CI: 0.59-1.00, p = 0.050) (Supplemental file page 8).

Overall survival was significantly worse with increasing size of the largest metastasis at the time of randomization (Supplemental file page 9). In patients with Stage IIIC disease and a largest metastatic tumour size < 5 cm the progression-free survival was better with UDS than with NACT (Figure 4, respectively median 1.02 and 1.00; HR: 1.34, 95% CI: 1.04-1.73; p=0.021), but the overall survival was not significantly different (median respectively, 2.75 and 2.51 years; HR: 1.26, 95% CI: 0.96-1.65; not significant).

## Discussion

This pre-planned meta-analysis of the updated data from the EORTC and CHORUS trials on NACT versus UDS, confirms with long-term follow-up that NACT results in a similar overall survival compared with UDS in women with advanced ovarian carcinoma FIGO Stage IIIC and IV. In addition it revealed that progression-free and overall survival was significantly better with NACT than with UDS in patients diagnosed with Stage IV disease. However, women at Stage IIIC disease with the largest metastatic tumour mass of less than 5 cm had a significantly better progression-free survival with UDS. For those with Stage III disease and larger sized metastatic disease, either approach resulted in the same overall survival. These findings indicate that when deciding on a treatment strategy, not only should the risk of perioperative morbidity (6) and the possibility to debulk the patient to zero residual tumor (7) be taken into account, but also FIGO stage and the extent of the metastatic disease at presentation.

Though in both studies, a cytological diagnoses of malignancy was permitted, with the evolution of our knowledge regarding ovarian cancer disease subtypes, presently only histology can distinguish between high and low grade serous tumours [9]. This is

important, as low grade tumours are less susceptible to chemotherapeutic regimes and primary surgery is an important and preferential intervention in this group [10]. Thus to achieve a well-informed decision, histology should be obtained, combined with extensive radiological imaging. Obtaining tissue may be by image guided biopsy, though a laparoscopic approach affords additional information on disease spread which can be included in the decision making process, besides ensuring sufficient tissue for diagnostic purposes. (11-13)

Applying the findings of this meta-analysis to the care of every woman with stage IIIC or IV ovarian cancer must always be combined with the clinical picture. For example, the women in these studies had metastatic disease with a high tumour burden at presentation, and many had a poor performance status. But this clinical scenario is not uncommon and indeed improving outcomes for this population is as important (if not more so) than those who have much better survival patterns. Accepting the caveats implicit within all clinical trials, the results regarding the clinical management of stage IV disease, are derived from one of the largest cohort of women with stage IV disease in phase III studies. With this evidence, it can be recommended that NACT becomes the standard of care for this population, and primary surgery only used for the exceptional woman with Stage IV- selected on an individual basis.

218 **Table 1. Baseline characteristics by study**

| | EORTC (n= 670) (%) | Chorus (n=550) (%) | TOTAL (n=1220) (%) |
|---|---|---|---|
| **Median Age (years)** | 62 | 65 | 63 |
| **Largest metastatic tumor size (mm)** | 80 | 80 | 80 |
| **CA125 at entry (KU/L)** | 1161 | 1016 | 1089 |
| **WHO performance** | | | |
| **0** | 300 (44.8) | 171 (31.1) | 471 (38.6) |
| **1** | 284 (42.4) | 271 (49.3) | 555 (45.5) |
| **2** | 85 (12.5) | 102 (18.5) | 186 (15.2) |
| **3** | 0 (0) | 5 (0.9) | 5 (0.4) |
| **Missing** | 2 (0.3) | 1 (0.2) | 3 (0.2) |
| **FIGO stage** | | | |
| **II** | 0 (0) | 19 (3.5) | 19 (1.6) |
| **IIIA** | 0 (0) | 14 (2.5) | 14 (1.1) |
| **IIIB** | 1 (0.1) | 21 (3.8) | 22 (1.8) |
| **IIIC** | 510 (76.1) | 321 (58.4) | 831 (68.1) |
| **IV** | 158 (23.6) | 72 (13.1) | 230 (18.9) |
| **Missing** | 1 (0.1) | 103 (18.7) | 104 (8.5) |

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222 **Table 2. Baseline characteristics by allocated treatment**

| | UDS (n=612) (%) | NACT (n=608) (%) | TOTAL (n=1220) (%) |
|---|---|---|---|
| **Median Age (years)** | 63 | 64 | 63 |
| **Largest metastatic tumor size (mm)** | 80 | 80 | 80 |
| **CA125 at entry (KU/L)** | 1039 | 1137 | 1089 |
| **WHO performance** | | | |
| **0** | 236 (38.6) | 235 (38.7) | 471 (38.6) |
| **1** | 279 (45.6) | 276 (45.4) | 555 (45.5) |
| **2** | 93 (15.2) | 93 (15.3) | 186 (15.2) |
| **3** | 1 (0.2) | 4 (0.7) | 5 (0.4) |
| **Missing** | 3 (0.5) | 0 (0) | 3 (0.2) |
| **FIGO stage** | | | |
| **II** | 12 (2.0) | 7 (1.2) | 19 (1.6) |
| **IIIA** | 7 (1.1) | 7 (1.2) | 14 (1.1) |
| **IIIB** | 9 (1.5) | 13 (2.1) | 22 (1.8) |
| **IIIC** | 433 (70.8) | 398 (65.5) | 831 (68.1) |
| **IV** | 118 (19.3) | 112 (18.4) | 230 (18.9) |
| **Missing** | 33 (5.4) | 71 (11.7) | 104 (8.5) |

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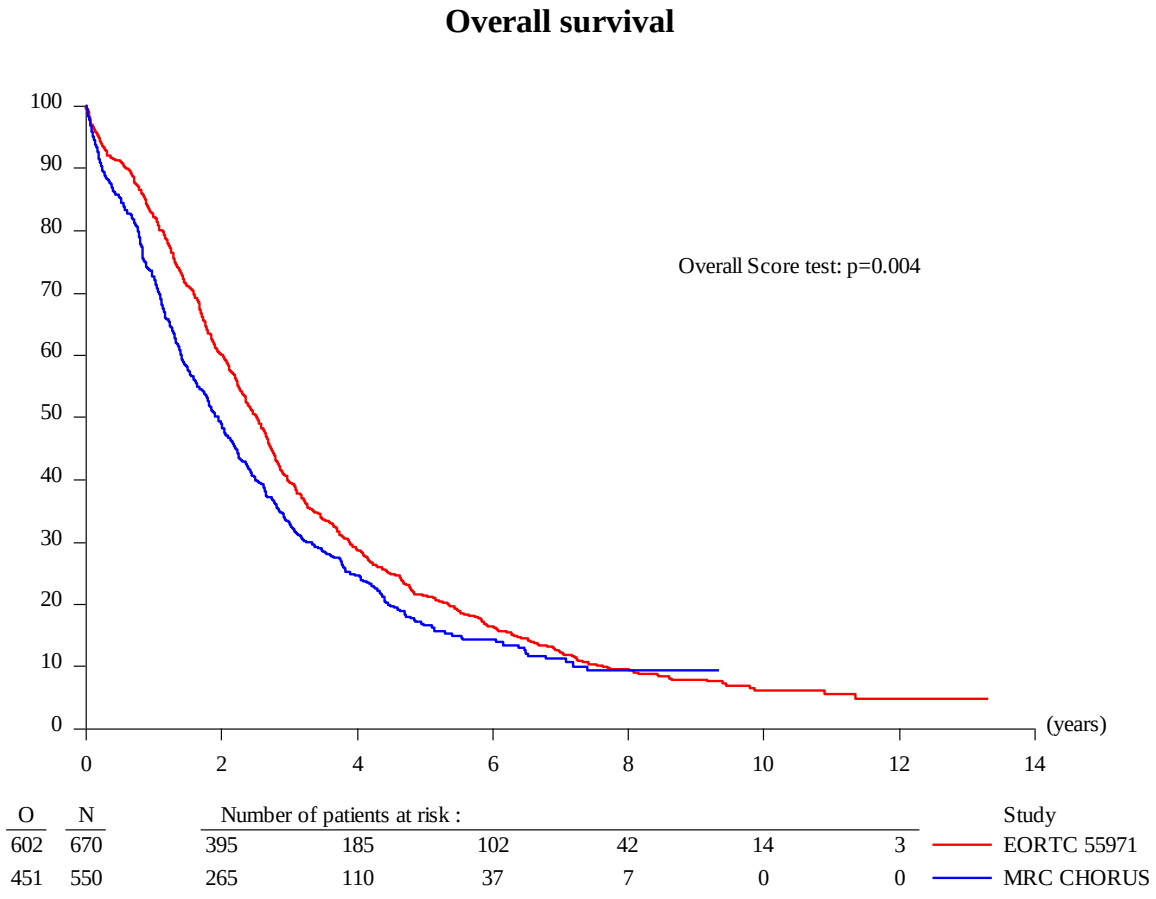
224 **Figure 1.** Overall survival according to study.

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226 **Figure 2.** Overall survival according to treatment arm.

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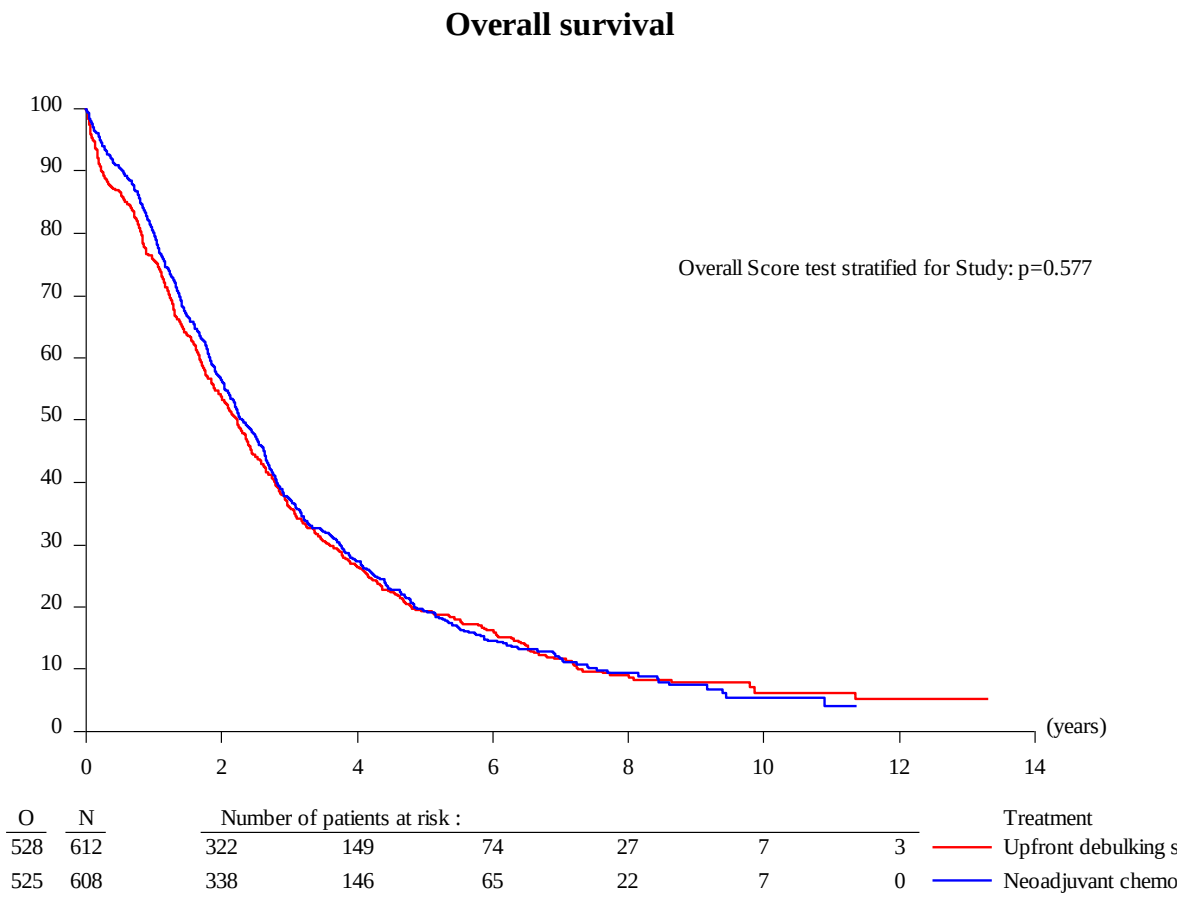


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**Figure 3.** Overall survival according to treatment arm in Stage IV patients.

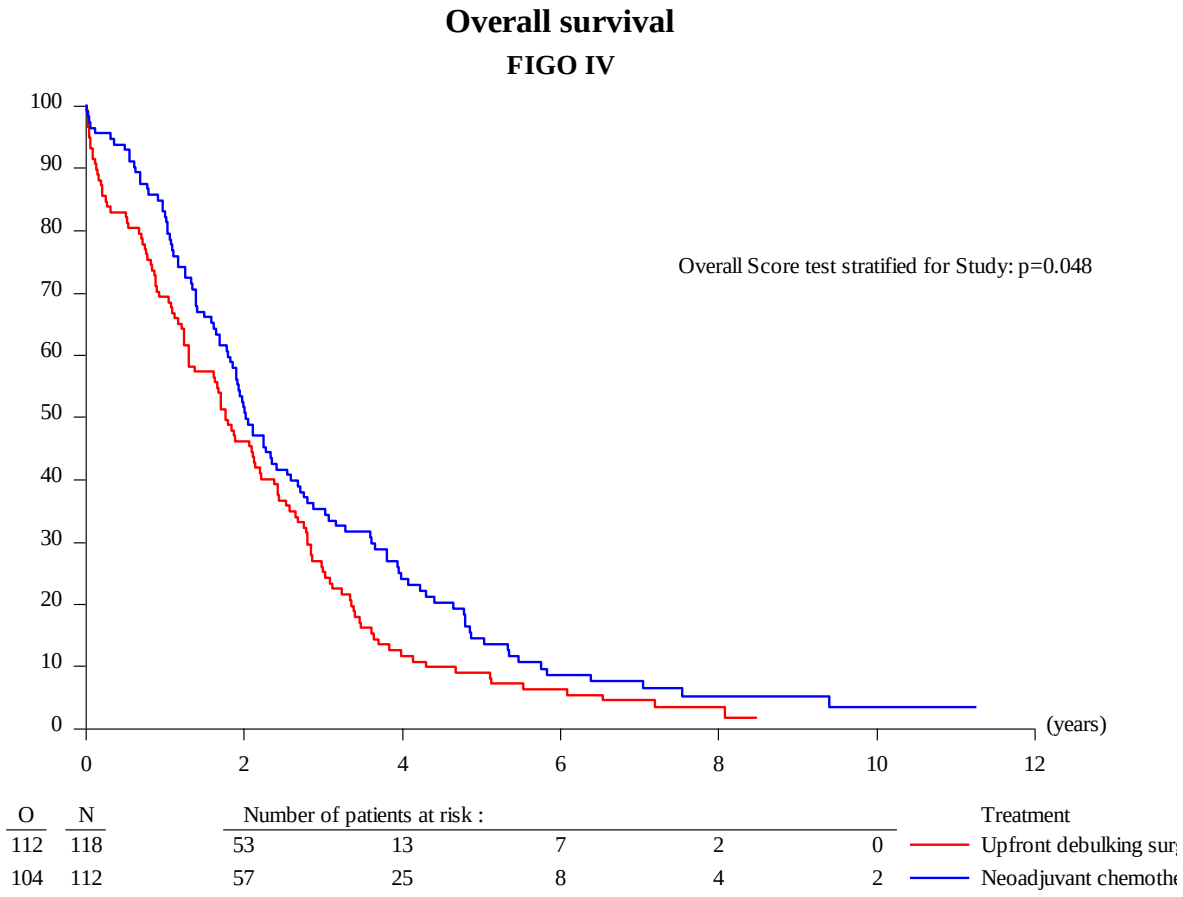
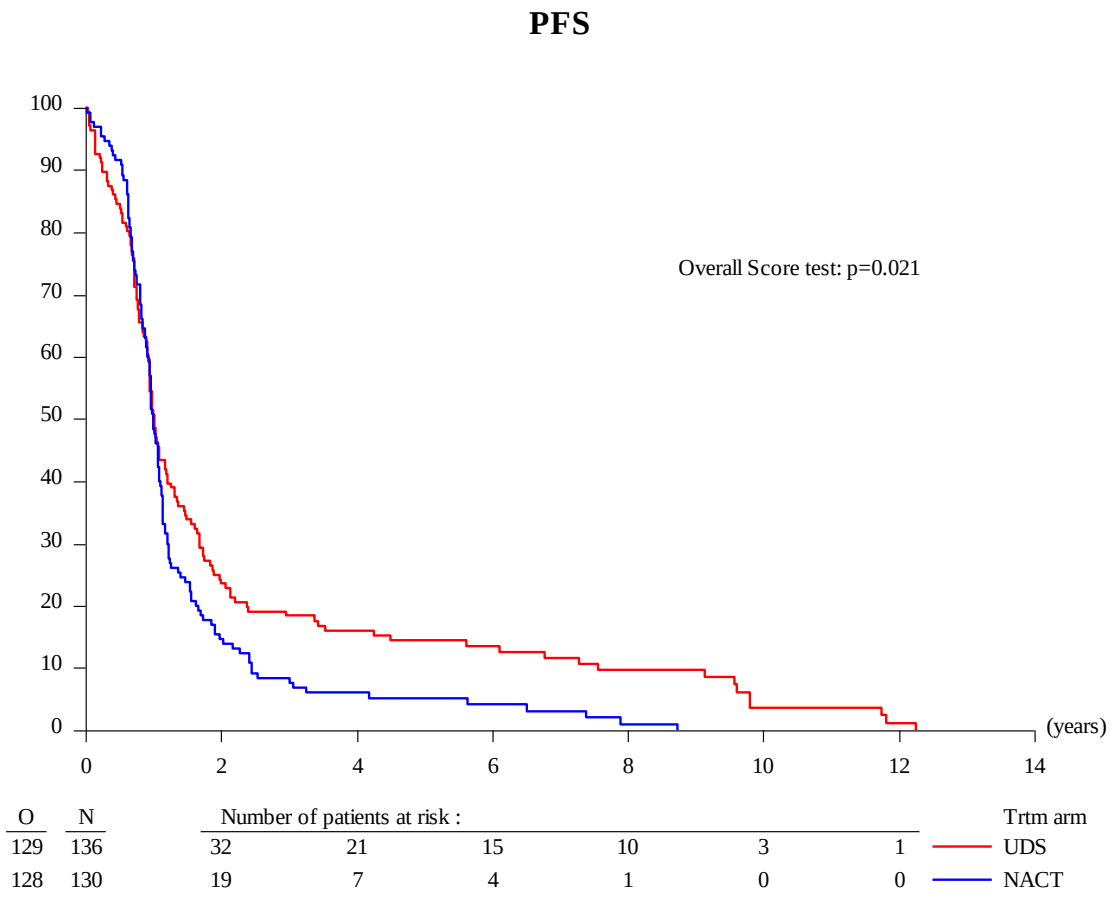


**Figure 4.** Progression-free survival in 266 patients with FIGO IIIc and largest metastatic tumour size < 5 cm at entry.



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