INDIVIDUAL PATIENT DATA META-ANALYSIS OF THE RANDOMISED EORTC AND CHORUS TRIALS COMPARING NEOADJUVANT CHEMOTHERAPY VERSUS UPFRONT DEBULKING SURGERY IN ADVANCED TUBO-OVARIAN CANCERS

Ignace Vergote MD [a], Corneel Coens MSc[b], Matthew Nankivell MSc [c], Gunnar B. Kristensen MD [d], Mahesh KB Parmar Dphil [e], Tom Ehlen MD [f], Gordon C. Jayson PhD [g], Nick Johnson MRCOG [h], Ann Marie Swart MB BS [i], René Verheijen MD [j], W. Glenn McCluggage FRCPath [k], Tim Perren MD [l], Pierluigi Benedetti Panici PhD [m], Gemma Kenter MD [n], Antonio Casado MD [o], Cesar Mendiola MD [p], Gavin Stuart MD [q], Nick S. Reed MB BS [r], Sean Kehoe MD [s]

[a] University Hospitals Leuven, Leuven, European Union, [b]European Organisation for Research and Treatment of Cancer, Brussels, Belgium, [c]MRC Clinical Trials Unit at UCL, London, United Kingdom, [d]Norwegian Radium Hospital and Institute for Cancer Genetics and Informatics, Oslo University Hospital, Norway, [e]MRC Clinical Trials Unit at UCL Inst of Clinical Trials &Methodology, London, United Kingdom, [f]University of British Columbia, Vancouver, Canada, [g]Christie Hospital and University of Manchester, Manchester, United Kingdom, [h]Royal United Hospitals Bath, Bath, United kingdom, iUniversity of East Anglia, Norwich, United Kingdom, , [j]Vrije Universiteit Medical Center, Amsterdam, The Netherlands, [k]Belfast Health and Social Care Trust, Belfast, United Kingdom, [l]St. James`s University Hospital, Leeds, United Kingdom, [m]University of Rome La Sapienza, Rome, Italy, [n] Center Gynaecologic Oncology Amsterdam, University of Amsterdam,The Netherlands, [o]Hospital Universitario San Carlos, Madrid, Spain, [p]Hospital Universitario Doce de Octubre, Madrid, Spain, [q]University of British Columbia, Vancouver, Canada, [r]Beatson Oncology Centre, Glasgow, United Kingdom, [s]University of Birmingham, United Kingdom

The following authors are full professor: Ignace Vergote, Gordon C Jayson, Ann Marie Swart, René Verheijen, W. Glenn McCluggage, Tim Perren,, Gemma Kenter,, Nick Reed and Gavin Stuart

Correspondence:

Ignace Vergote, MD PhD FACS FSPS

Ignace.vergote@uzleuven.be

University Hospitals Leuven,

Department of Obstetrics and Gynaecology

Division of Gynaecological Oncology

Leuven Cancer Institute

Herestraat 49

B-3000 LEUVEN

European Union

+32 16 344634

SUMMARY

Background. Two prospective randomised trials, comparing neoadjuvant chemotherapy (NACT) with upfront debulking surgery (UDS) in advanced tubo-ovarian cancer (EORTC 55971 and MRC CHORUS), were analysed with the aim to examine the long term outcomes of the patients and identify any preferable therapeutic approaches for subgroup populations.

Methods. Pre-planned individual updated patient data meta-analysis of both trials (NCT00003636 and ISRCTN74802813). , In the EORTC trial eligible women had biopsy proven stage IIIC or IV invasive epithelial tubo-ovarian carcinoma. In the CHORUS, trial the inclusion criteria were similar, but women with apparent stage IIIA and IIIB were also eligible. The main aim of the meta-analysis was to show non-inferiority in overall survival with NACT compared UDS using the "reverse Kaplan-Meier" method. Test for heterogeneity was based on the Cochran's Q heterogeneity statistic.

Findings. 1220 women were randomised. The overall median follow-up was 7.6 years (EORTC 9.2 and CHORUS 5.9 years). Median patient 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. There was no statistically significant difference for the entire population regarding the median overall survival (OS) between patients who underwent UDS and NACT (26.9 and 27.6 months; HR: 0.98, 95% CI: 0.87-1.10; p = 0.688). Median OS for EORTC and CHORUS patients was significantly different at 30.2 and 23.6 months, respectively (HR: 1.20, 95% CI:1.06-1.36;p=0.004) but not significantly heterogeneous (Cochran's Q p= 0.17). Variable outcomes were noted in some cohorts.
Interpretation. Long-term follow-up data confirm that NACT and UDS result in similar OS in advanced tubo-ovarian cancer, with preferential outcomes in some patients. This meta-analysis, with long-term follow-up, confirms that NACT is a valuable treatment option for patients with Stage IIIC-IV tubo-ovarian cancer, especially in patients with a high tumour burden at presentation and/or poor performance status.

This study was supported by grants (2U10 CA11488-28 through 2U10 CA011488-36) from the National Cancer Institute and by a donation from the "Vlaamse Liga tegen kanker (the Flemish League against Cancer)" to the EORTC Charitable Trust. Funding was provided by Cancer Research UK. Funding for a pilot phase of the trial was provided by the RCOG and supported by core MRC CTU funding. The trial sponsor was the MRC and the trial was conducted an analysed at the MRC CTU.

INTRODUCTION

Over 70% of women with carcinoma of the ovary, fallopian tube or peritoneum (hereafter referred to as tubo-ovarian cancer) present with advanced disease, and usually have a very poor prognosis (1) Since Griffiths reported In 1975 (2) the association between low residual tumour load and improved survival rates following debulking surgery, primary surgery has been embedded in clinical practice as an essential, or even mandatory therapeutic strategy.(3) However, to date, no prospective randomised controlled trials have proven that primary debulking surgery improves the prognosis of patients with advanced tubo-ovarian cancer.

An alternative approach to primary debulking surgery, is neoadjuvant chemotherapy (NACT), administered before attempting cytoreductive surgery. In 2010 the first randomised trial comparing NACT followed by interval debulking surgery (IDS) with upfront debulking surgery (UDS) was published (4). This randomised EORTC (European Organisation for Research and Treatment of Cancer) study showed a similar overall survival (OS) and progression-free survival (PFS) in women with FIGO 1988 (International Federation of Gynecology and Obstetrics) stage IIIC or IV tubo-ovarian cancer with both treatment strategies and a lower operative and postoperative morbidity with NACT. These results were later confirmed in the randomised Medical Research Council (MRC) CHORUS trial (5) and resulted in the acceptance of NACT followed by IDS as an alternative to UDS in stage IIIC and IV tubo-ovarian cancer (6). However, the selection of women with advanced ovarian cancer for NACT or UDS remained 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 analysis with the aim of analysing the long-term follow-up of both trials and to identify subgroups of women who might benefit more or less from NACT compared with UDS. Herein we report the results of this analysis.

Methods

Study design and data collection

This is a pre-planned individual updated patient data meta-analysis of the EORTC 55971 and MRC CHORUS trials. performed according to the PRISMA 2009 guidelines (Figure 1) (8) . 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 adnexal mass, and presence of extrapelvic metastases of ≥ 2 cm (measured during diagnostic laparoscopy or laparotomy, and if not done, based on CT findings) and a CA125 (KU/L)/CEA (ng/mL) ratio > 25. If any features of the triad were not present then a biopsy was mandated. If the CA125/CEA ratio was less than 25, 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. In both trials randomisation was to UDS followed by at least 6 courses of platinum-based chemotherapy, versus 3 courses of NACT (platinum-based) followed by IDS, and then at least 3 additional courses of platinum based chemotherapy. In women randomised to UDS whose surgery was completed without optimal cytoreduction, IDS was permitted and these patients were included for analyses in the UDS arm. Randomisation included stratification with a minimization technique to stratify for institution, method of biopsy (image-guided, laparoscopy, laparotomy, fine needle aspiration), stage IIIC or IV, and largest tumour size (excluding ovaries) before surgery (less than 5, 5 – 10, 10.1 - 20 cm, or more than 20 cm). Randomisation used a minimisation method with a random element, which stratified the patients according to randomising centre, largest radiological tumour size, clinical FIGO 1988 stage, and pre-specified chemotherapy regimen.

Data analysis

The analysis was designed in 2003 by the chief investigators of the two trials (IV and SK) and members of the EORTC/MRC trial managing committees. Trial databases were set up to ensure appropriate comparable information was collected in both trials to allow the planned individual patient data analysis. The women were followed until data base lock. CHORUS data were transferred to the EORTC Headquarters and analyzed in cooperation with the authors by the EORTC statistician (CC). The EORTC standard method for deriving median follow-up time using the "reverse Kaplan-Meier" method calculating time-to-event on all patients was used, while in the original CHORUS paper the median duration of follow-up of the surviving patients was used.

At the planning stage it was estimated that the pooled dataset would contain between 800 and 900 events (deaths). Assuming a median OS of 3 years, this allowed assessment of non-inferiority (9,10) 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 principal analysis was performed on the intent-to-treat policy and the primary outcome was OS. The prespecified secondary endpoint was PFS. Prespecified subgroup analyses based on the stratification factors that were common to both trials (randomising centre, largest tumour size (excluding ovaries) before surgery (less than 5, 5 – 10, 10.1 - 20 cm, or more than 20 cm), and clinical FIGO 1988 stage) were performed. The definitions applied for OS and PFS have been previously published (4). Median OS and PFS were estimated by the Kaplan-Meier method and compared via the log rank test. Hazard ratio estimates and their confidence intervals were obtained from a Cox proportional hazards model. In those subgroups where the proportional hazards assumptions was violated, restricted mean survival times were calculated to provide a more useful general measure to report the average survival times between the two treatment arms (11) Multivariable time-to-event analyses were performed using a Cox proportional hazards model, with univariate screening followed by a multivariable stepwise selection procedure (12). All baseline characteristics and results were checked for homogeneity between the two studies and stratified per trial where possible. Test for heterogeneity in PFS or OS was based on the Cochran's Q heterogeneity statistic The size of the largest metastasis before randomisation 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. All analyses were done using SAS, version 9.4.

For details on size of residual tumour, residual tumor per country, type of surgery, number of cycles and type of chemotherapy, and time to (re)initiation of chemotherapy we refer to the original papers. (4,5).

Role of funding source

The funders of the studies had no role in study design, data collection, data analysis, data interpretation, or writing of the report. CC, MN and MP had access to MRC CHORUS raw data. CC had access to the EORTC

55971 raw data. The corresponding author (IV) had full access to all the data and had final responsibility to submit for publication. All authors have seen and approved the final version and, after consultation with the collaborators, agreed to submit for publication

Results

The patient data of both trials were updated and merged into one data-base (data-base lock EORTC June 6th, 2015 and CHORUS June 3rd, 2014)that contained 1220 randomised patients. Total combined recruitment lasted almost 12 years (EORTC: 670 patients from Oct 12th, 1998 to Nov 29th 2006; MRC CHORUS: 550 patients from March 5th, 2004 to August 26th, 2010). Median follow-up was 7.6 years (IQR: 6.0-9.6 years) (EORTC 9.2 years (IQR: 7.3-10.4 years) and CHORUS 5.9 years (IQR: 4.3-7.4 years)). The characteristics of the patients by study and study arm are summarised in Tables 1 and 2, respectively. The pre-treatment characteristics were well balanced between both treatment groups.

Overall survival (OS) and progression-free survival (PFS) for the entire population were similar for NACT and UDS (median respectively for OS 27.6 (IQR: 14.1-51.3) and 26.9 (IQR: 12.7-50.1) months, HR: 0.97, 95% CI: 0.86-1.09; and for PFS respectively 11.6 (IQR: 7.9-17.7) and 11.1 (IQR: 6.4-17.5) (Figure 2). The lower 1-sided confidence of 95% confidence interval for OS and PFS hazard ratios were 0.87 and 0.89, excluding the 18% non-inferiority margin.

OS was significantly better in the EORTC trial compared with the CHORUS trial (median, respectively 30.2 (IQR: 15.7-53.7) and 23.6 (IQR: 10.5-46.9) months; HR: 1.20, 95% CI: 1.06-1.36; p = 0.004) (Figure 3), but PFS was similar (median respectively, 11.5 (IQR: 8.0-17.0) and 10.9 (IQR: 6.1-18.1) months; HR 0.96, 95% CI: 0.86-1.08; p= 0.0.531) (Supplemental file page 1).

OS and PFS according to trial and treatment arms are presented in the Supplemental file (page 2 and 3).

Cochran's Q was not significant for either OS or PFS (p=0.17 and 0.32 respectively).

Median OS was significantly different for Stage IV compared with stage III and stage II (median respectively, 23.3 (IQR: 12.4-40.8), 30.0 (IQR: 15.6-55.7) and 45.4 (IQR: 31.6-NR) months; HR 2.75 and 1.92 for Stage III and IV versus stage II, p < 0.001; see Supplemental file page 4). OS was similar for NACT and UDS in stage IIIC patients (median respectively, 30.8 (IQR: 16.5-51.3) and 28.4 (IQR: 14.1-55.7) months; HR: 1.04, 95% CI: 0.90-1.21; p = 0.569; Supplemental file page 5). PFS was similar for NACT and UDS in stage IIIC (median respectively, 12.2 (IQR: 8.4-18.3) and 11.7 (IQR: 7.5-19.9) months; HR: 1.06, 95% CI: 0.92-1.22; p = 0.429; Supplemental file page 6). However, in patients with stage IV tubo-ovarian cancer NACT resulted in significantly better OS than UDS (Figure 4) (median respectively, 24.3 (IQR: 14.1-47.6) and 21.2 (IQR: 10.0-36.4) months; HR: 0.76, 95% CI: 0.58-1.00, p = 0.048). PFS was also significantly better in stage IV disease with NACT than with UDS (median respectively, 10.6 (IQR: 7.9-15.0) and 9.7 (IQR: 5.2-13.2) months; HR: 0.77, 95% CI: 0.59-1.00, p = 0.048) (Supplemental file page 7).

OS was best in patients with a largest metastatic extrapelvic tumour size < 5 cm at the time of randomisation (Supplemental file page 8). In patients with stage IIIC disease and a largest metastatic tumour size < 5 cm, the PFS was better with UDS than with NACT (Figure 5A, respectively median 12.2 (IQR: 8.5-23.3) and 11.7 (IQR: 8.3-16.4); HR: 1.36, 95% CI: 1.06-1.75; p=0.017; hazard plots according to largest metastatic tumour size Supplemental file page 9), but the OS was not significantly different (median respectively, 33.0 (IQR: 13.5-78.7) and 30.2 (IQR: 16.5-51.3); HR: 1.26, 95% CI: 0.96-1.65; p=0.092, Figure 5B). Due to deviation from the proportional hazards assumption in this subgroup, restricted mean survival times are presented in table 3. Age and performance status were not predictive for treatment effect on survival (Supplemental file, page 10)

Discussion

This pre-planned analysis of updated data from the EORTC and CHORUS trials on NACT versus UDS in advanced tubo-ovarian cancer (stage IIIC and IV), confirms that with long-term follow-up NACT results in non-inferior OS and PFS compared with UDS. The planned non-inferiority margin, an increase of more than 18-19% in hazard ratio, was well outside the lower confidence bounds (11% and 13% for PFS and OS respectively). Hence, this meta-analysis with long-term follow-up confirmed that both UDS and NACT are 2 possible treatment options for patients with FIGO Stage IIIC or IV tubo-ovarian cancer. However, the analysis also revealed that PFS and OS was significantly better with NACT compared to UDS in patients diagnosed with stage IV disease. On the other hand, women with stage IIIC disease with a largest extrapelvic metastatic tumour mass of less than 5 cm had a significantly better PFS with UDS. For those with stage III disease and larger sized metastatic disease, either approach resulted in the same OS. In the women with stage IIIC and largest metastatic

tumours at diagnosis < 5 cm, both PFS and OS curves have crossing treatment arms indicating deviation from the proportional hazards assumptions. Therefore the restricted mean survival times (table 3) give a better indication of the treatment effect than the median times (11). These findings indicate that when deciding on a treatment strategy, not only should the risk of perioperative morbidity (6) and the possibility of debulking the patient' disease to zero residual tumour (7) be taken into account, but also FIGO 1988 stage and the extent of the metastatic disease at presentation.

Although in both studies, a cytological diagnosis of malignancy was permitted, with the evolution of our knowledge regarding tubo-ovarian cancer disease subtypes, presently only histology can reliably distinguish between high-grade and low-grade serous carcinomas (13). This is important since low grade serous carcinomas are much less sensitive to chemotherapeutic regimens and primary surgery is an important and much preferred intervention in this group (14). Thus to facilitate optimal decision making, tissue should be obtained for histological diagnosis in all cases and this should be combined with extensive radiological imaging. Obtaining tissue for histological examination is usually possible using image guided biopsy (usually of the omental cake), although a laparoscopic approach is necessary in some cases and provides additional information on disease distribution which can be included in the decision making process. (15-17)

Both trials have been investigating the timing of surgery in advanced tubo-ovarian cancer and have been criticised for their low R0 rates and low survival rates. However, it should be noted that at the time these patients were randomised, NACT was not accepted as an alternative for UDS and the majority of the patients had extensive Stage IIIC or IV disease, visible on CT. Furthermore, in addition to the EORTC 55971 and CHORUS trials, the SCORPION (15) and the JCOG0602 (18) randomised trials concluded that perioperative morbidity was more favourable with interval debulking after neoadjuvant chemotherapy than after primary debulking surgery. Currently, the TRUST trial randomising NACT versus PDS in advanced tubo-ovarian cancer has been developed and is recruiting patients in selected centres with 50% or more R0 rates. The results of this new trial are awaited with interest. A limitation of this meta-analysis might be that in the EORTC trial only patients with stage IIIC and IV were included while in the CHORUS trial also a (limited) number of patients with stage IIIA and B were included. In addition, the number of patients with Stage IIIC-IV disease without residual tumor after UDS tended to be lower in the CHORUS than in the EORTC trial.

Application of the findings of this analysis to the care of every woman with stage IIIC or IV tubo-ovarian cancer should be tempered by the patients' clinical picture. For example, women in these studies had metastatic disease with a high tumour burden at presentation, and many had a poor performance status. (19) This clinical scenario is not uncommon and improving outcomes for this population is as important (if not more so) than those who have much better prognostic factors. 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 cohorts of women with stage IV disease in phase III studies. Although some stage IV patients have a better prognosis and present with less spread and more easily resectable disease (14) than the majority of Stage IV patients, our data infer that NACT be the standard of care for most patients with stage IV tubo-ovarian cancer, and primary surgery should only be undertaken exceptionally in women selected on an individual basis.

Declaration of interests

Contributors

All authors contributed to the design and execution of this study. The draft of the paper has been written by I. V. and S. K. and all authors have been actively involved in the final drafting and approved the manuscript.

Conflict of interestM. N. reports grants from MRC CTU / CRUK, during the conduct of the study. N.J. reports that EORTC, the Royal United Hospital (his employing institution) benefited by having support for clinical trials nurse who collected and verified data from some participants in one of the trials reported in this manuscript,. C.M. reports personal fees and other (travel expenses) from Roche Farma España, other support (travel expenses) from AstraZeneca and other from Pharmamar outside the submitted work. T.P. reports personal fees and non-financial support from Astra Zeneca, non-financial support from Roche, non-financial support from IGEA Medical, outside the submitted work; and he is co-Chief Investigator for the ICON7 trial of bevacizumab in first line treatment of patients with advanced ovarian cancer. All other authors declare to have no conflicts of interest in relation to this study.

References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. *Eur J Cancer* 2013; 49: 1347-1403
2. Berek J, Tropé C, Vergote I. Surgery during chemotherapy and at relapse of ovarian cancer. *Ann Oncol* 1999; 10(1): 3-7.
3. Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *Journal of the National Cancer Institute Monographs* 1975;42:1014
4. Vergote I., Tropé C.G., Amant F. et al. European Organization for Research and Treatment of Cancer-Gynaecological Cancer Group; NCIC Clinical Trials Group. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med.* 2010;363(10):943-53
5. Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet* 2015; 386:249-57.
6. Wright AA, Bohlke K, Armstrong DK et al. Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline.; *J Clin Oncol.* 2016 Oct 1;34(28):3460-73
7. Vergote I, du Bois A, Amant F, Heitz F, Leunen K, Harter P. Neoadjuvant chemotherapy in advanced ovarian cancer: On what do we agree and disagree? *Gynecol Oncol.* 2013;128(1):6-11
8. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
9. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. CONSORT Group. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA. 2006 Mar 295(10):1152-60.
10. Mauri L, D'Agostino RB Sr. Challenges in the Design and Interpretation of Noninferiority Trials. N Engl J Med. 2017 Oct 5;377(14):1357-1367.
11. Royston P, Parmar MK. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. Stat Med. 2011 Aug 30; 30(19):2409-21
12. Collett D. Strategy for model selection. In: Collett D, editor. Modelling survival data in medical research. Florida: CRC Press, Inc.; London: Chapman and Hall; 1994. p. 78–83
13. Grabowski JP, Harter P, Heitz F et al. Operability and chemotherapy responsiveness in advanced low-grade serous ovarian cancer. An analysis of the AGO Study Group metadatabase. Gynecol Oncol. 2016 Mar;140(3):457-62
14. Gockley A, Melamed A, Bregar AJ, et al. Outcomes of Women With High-Grade and Low-Grade Advanced-Stage Serous Epithelial Ovarian Cancer. *Obstet Gynecol.* 2017 Mar;129(3):439-447.
15. Fagotti A, Ferrandina G, Vizzielli G, et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): Final analysis of perioperative outcome. *Eur J Cancer* 2016, 59:22-33
16. Rutten MJ, van Meurs HS, van de Vrie R, et al. Laparoscopy to predict the result of primary cytoreductive surgery in patients with advanced ovarian cancer: A randomized controlled trial. *J Clin Oncol* 2017, 35(6): 613-21
17. Vergote IB, Van Nieuwenhuysen E, Vanderstichele A. How to select neoadjuvant chemotherapy or primary debulking in patients with Stage IIIC or IV ovarian carcinoma. *J Clin Oncol* 2016, 34(32): 3827-8
18. Onda T, Satoh T, Saito T, et al. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for Stage III/IV ovarian, tubal, and peritoneal cancers in a phase II randomised trial : Japan Clinical Oncology Study Group Study JCOG0602. Eur J Cancer 2016; 64:22-31
19. Van Meurs HS, Tajik P, Hof MH, et.al. Which patients benefit most from primary surgery or neoadjuvant chemotherapy in stage IIIC or IV ovarian cancer? An exploratory analysis of the European Organisation for Research and Treatment of Cancer 55971 randomised trial. Eur J Cancer 2013, 49(25): 3191-201

LEGEND

TABLES

FIGURES

Table 1. Baseline characteristics by study

	EORTC (n= 670)	CHORUS (n=550)	TOTAL (n=1220)
Median Age (years) (range)	62 (25-86) IQR: 54.0 - 69.0	65 (26-88) IQR: 58.0 - 72.0	63 IQR: 56.0 - 71.0
Largest metastatic tumor size (mm) (range)	80 (0-400) IQR: 42.0 - 140.0	80 (7-500) IQR: 50.0 - 120.0	80 IQR: 48.0 - 130.0
CA125 at entry (KU/L) (range)	1161 (15-41456) IQR:	1016 (26-39323) IQR:	1089 IQR:

Table 2. Baseline characteristics by allocated treatment

	UDS (n=612)	NACT (n=608)	TOTAL (n=1220)
Median Age (years) (range)	63 (25-87) IQR: 55.0 - 71.0	64 (33-88) IQR: 57.0 - 70.0	63 IQR: 56.0 - 71.0
Largest metastatic tumor size (mm) **(range)**	80 (0-430) IQR: 49.0 - 130.0	80 (0-500) IQR: 47.0 - 125.0	80 IQR: 48.0 - 130.0
CA125 at entry (KU/L) (range)	1039 (16-39323) IQR: 409.0 - 2547.5	1137 (15-41456) IQR: 446.0 - 2606.0	1089 IQR: 431.0 - 2599.0

Table 3: restricted mean survival time (RMST) estimates in patients with FIGO Stage IIIC and largest metastatic tumour size < 5 cm at entry

		RMST	95% CI
Overall survival	UDS	47.3 months	40.4 – 54.1
	NACT	39.3 months	33.9 – 44.8
Progression free survival	UDS	27.5 months	21.2 – 33.8
	NACT	17.0 months	13.8 – 20.2

Figure 1

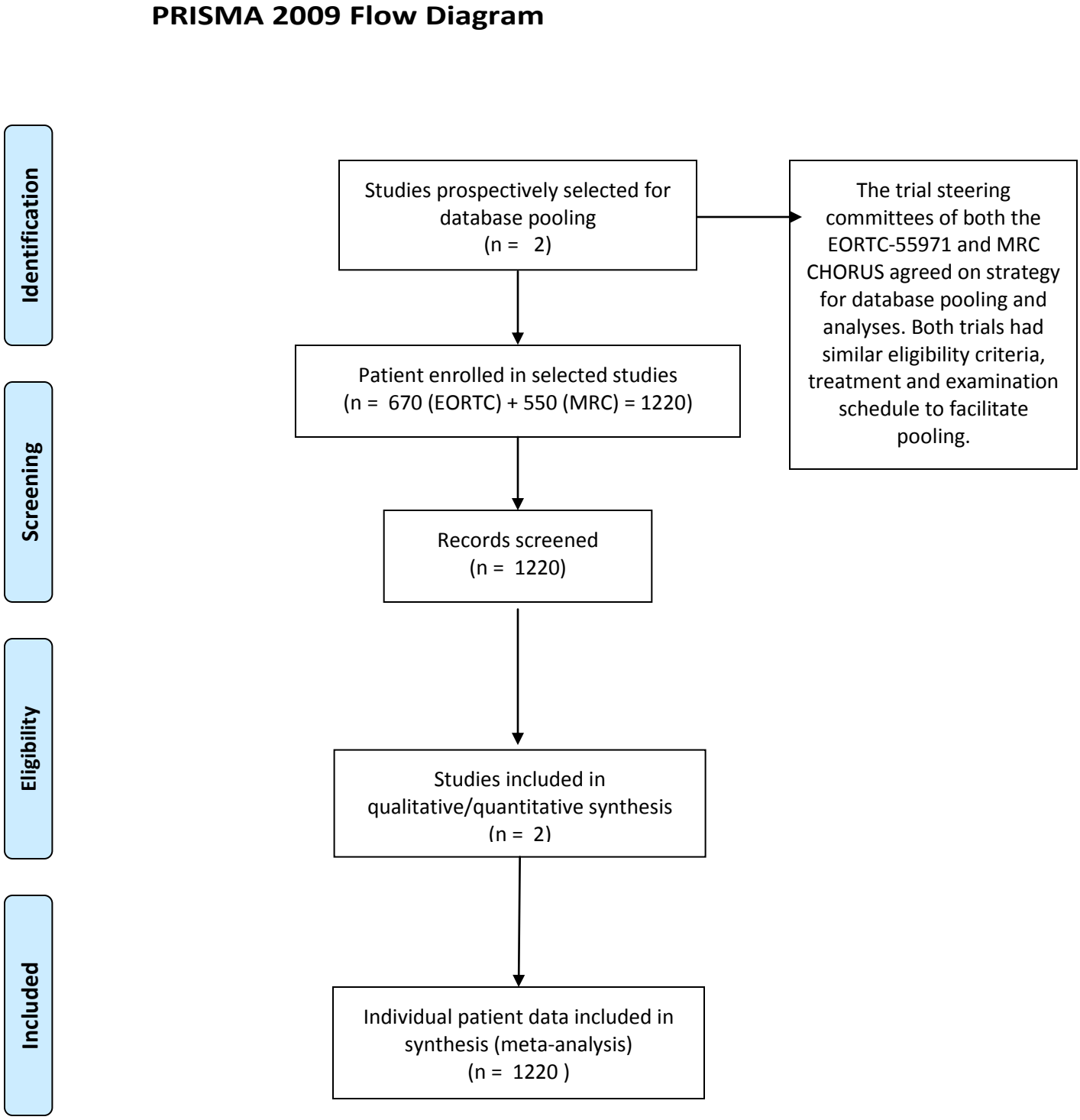
PRISMA 2009 Flow Diagram
Identification
Screening
Eligibility
Included
Studies prospectively selected for database pooling (n = 2)
The trial steering committees of both the EORTC-55971 and MRC CHORUS agreed on strategy for database pooling and analyses. Both trials had similar eligibility criteria, treatment and examination schedule to facilitate pooling.
Patient enrolled in selected studies (n = 670 (EORTC) + 550 (MRC) = 1220)
Records screened (n = 1220)
Studies included in qualitative/quantitative synthesis (n = 2)
Individual patient data included in synthesis (meta-analysis) (n = 1220)

Figure 2 Panel A

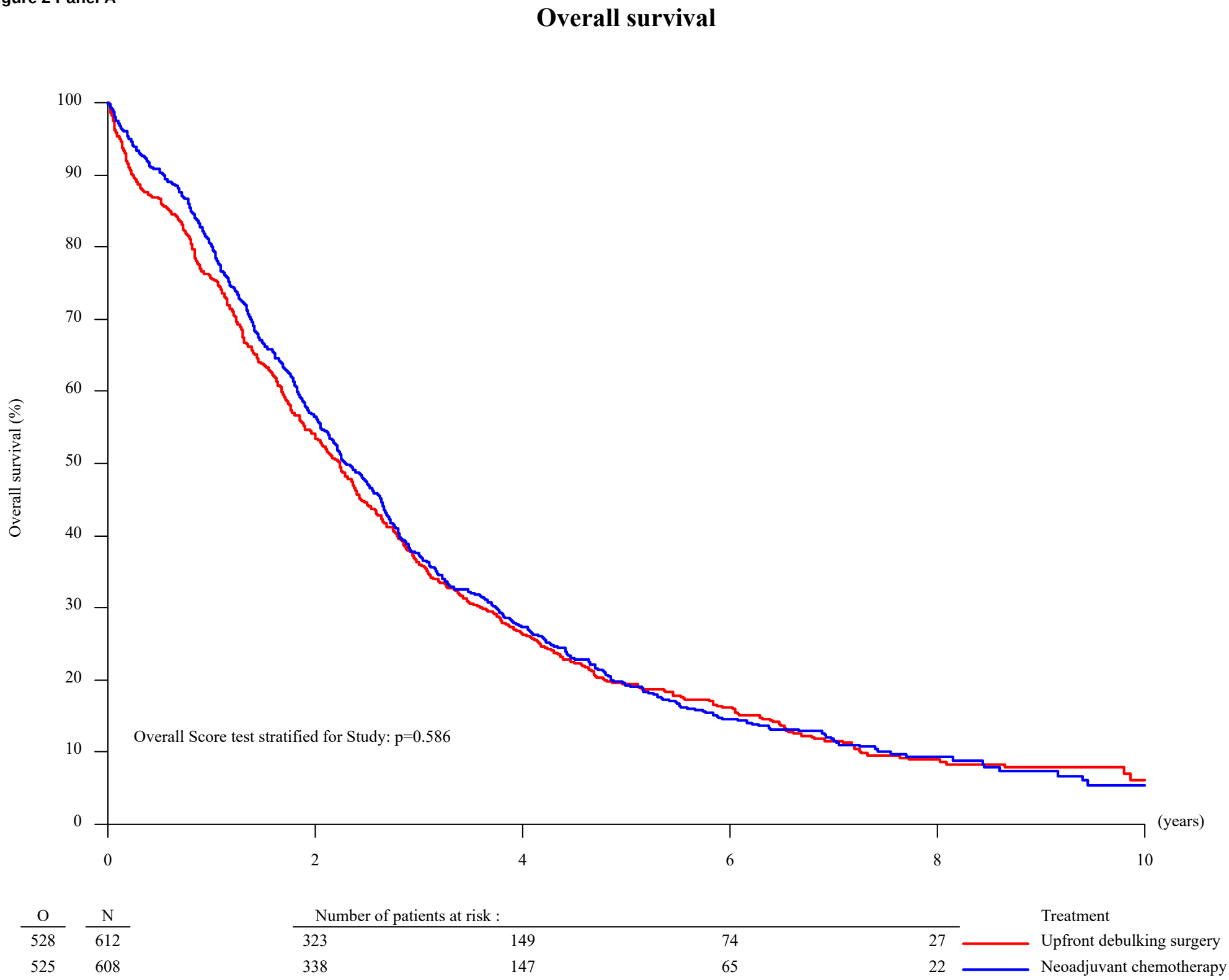

Figure 2 Panel B

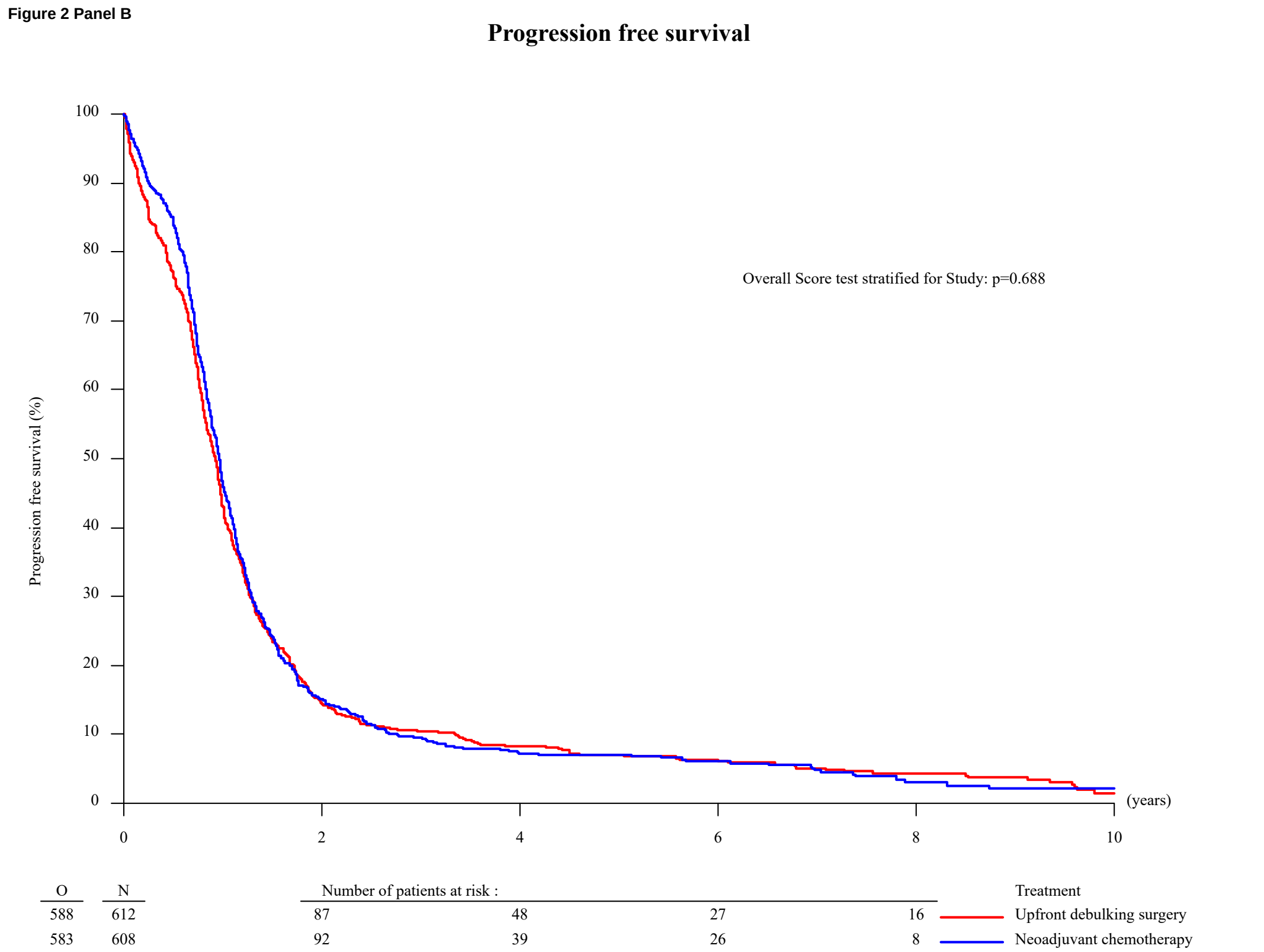

Figure 3

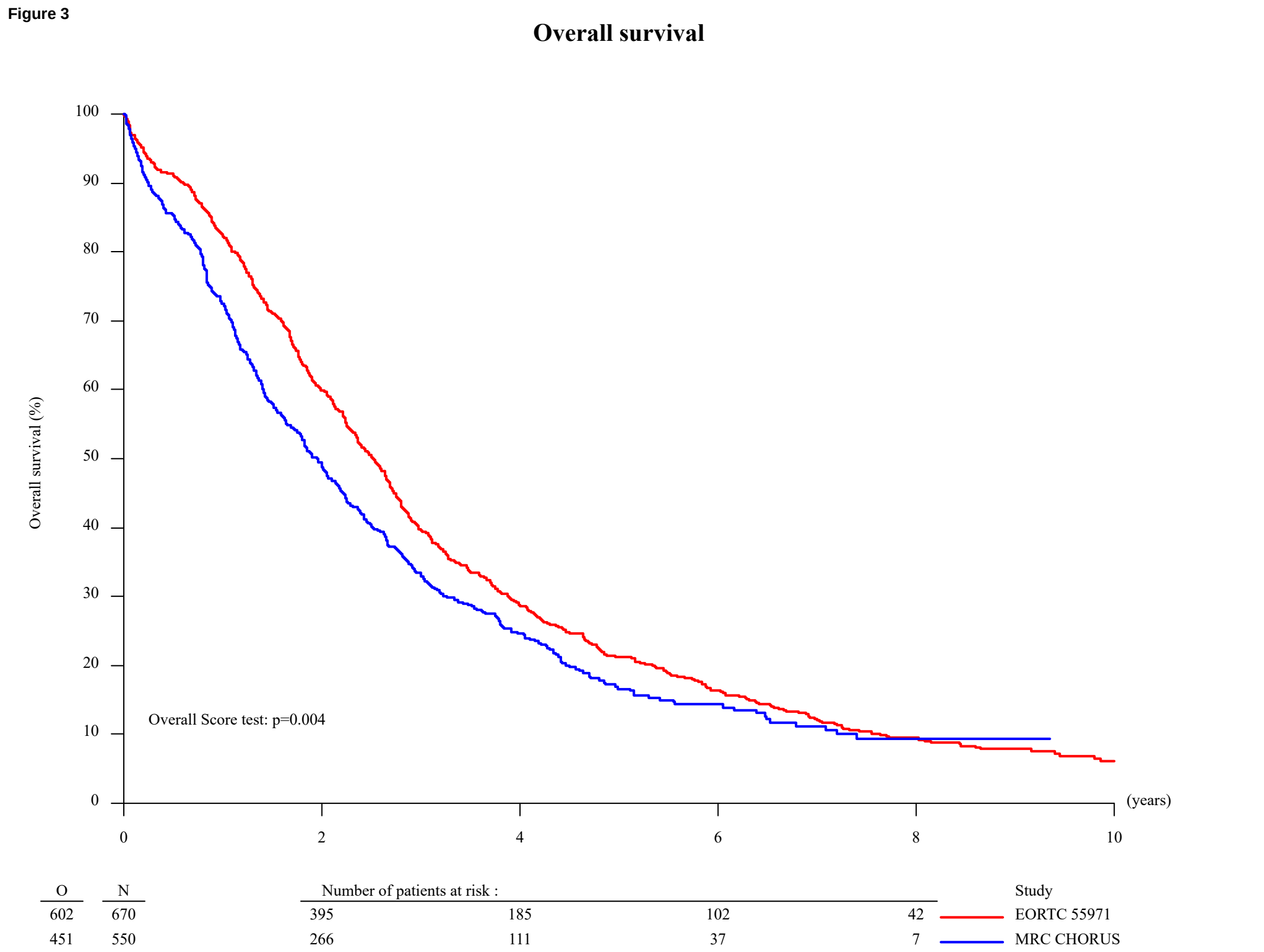
Overall survival
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
Overall Score test: p=0.004
0
2
4
6
8
10
(years)
O
N
Number of patients at risk :
602
670
395
185
102
42
451
550
266
111
37
7
Study
EORTC 55971
MRC CHORUS

Figure 4 Panel A

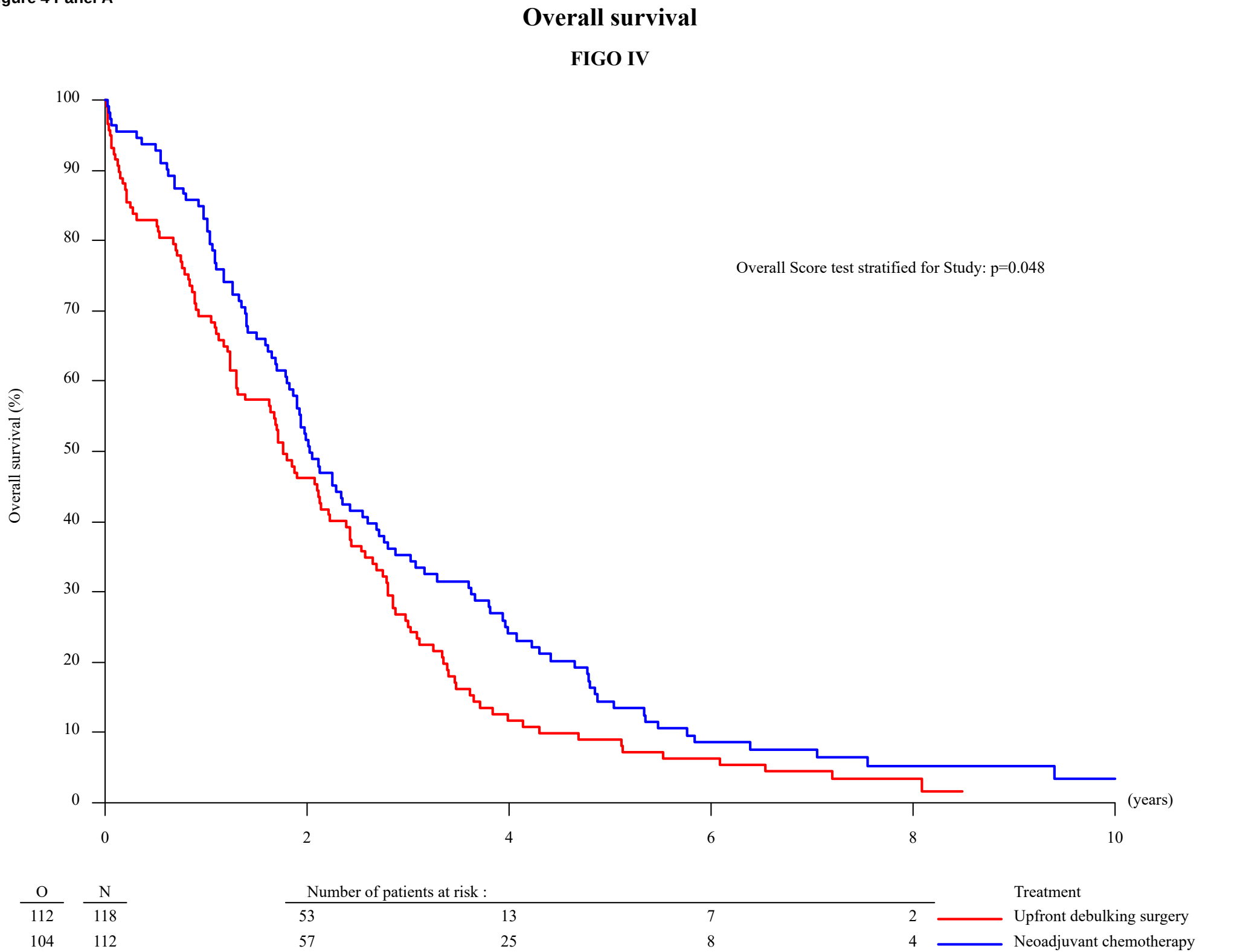

Figure 4 Panel B

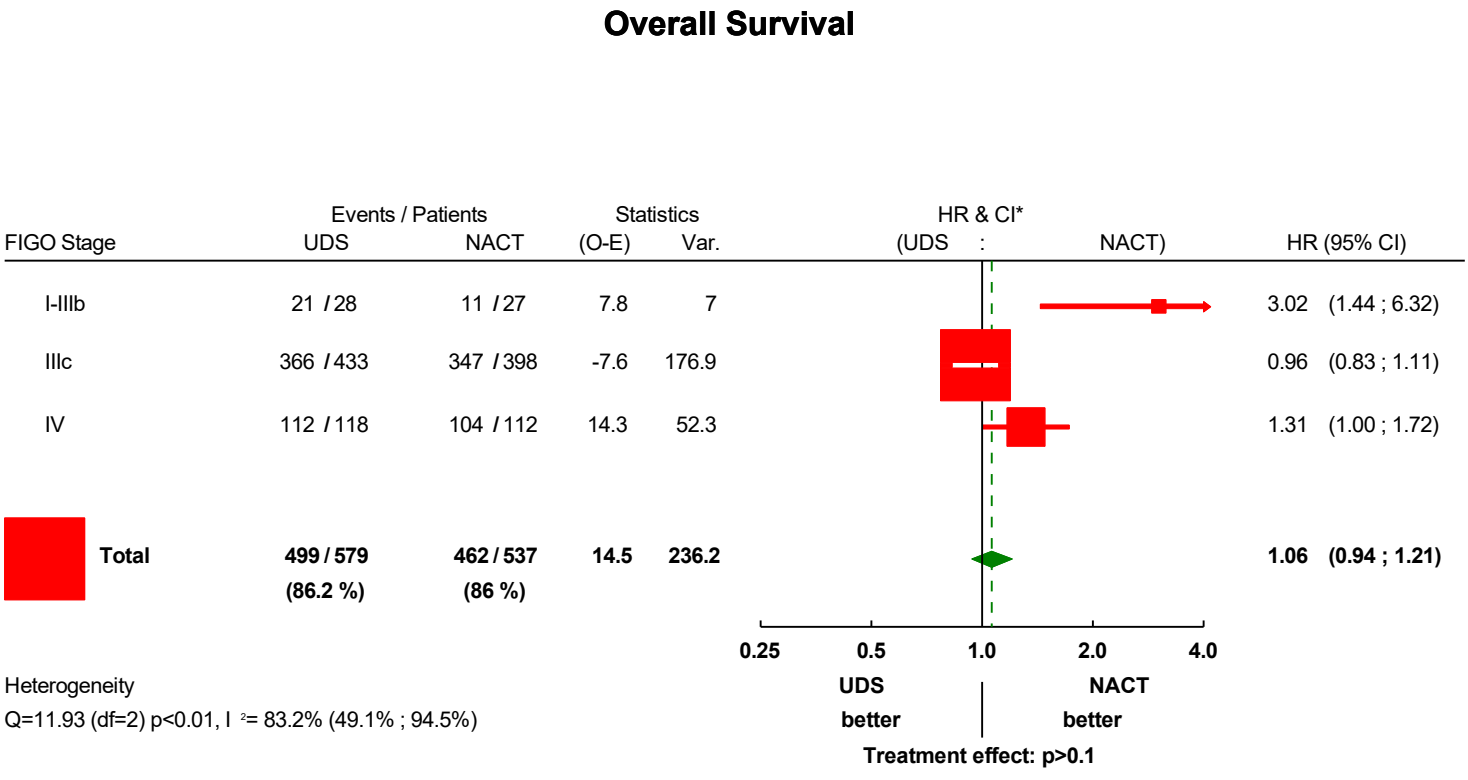

Figure 5 Panel A

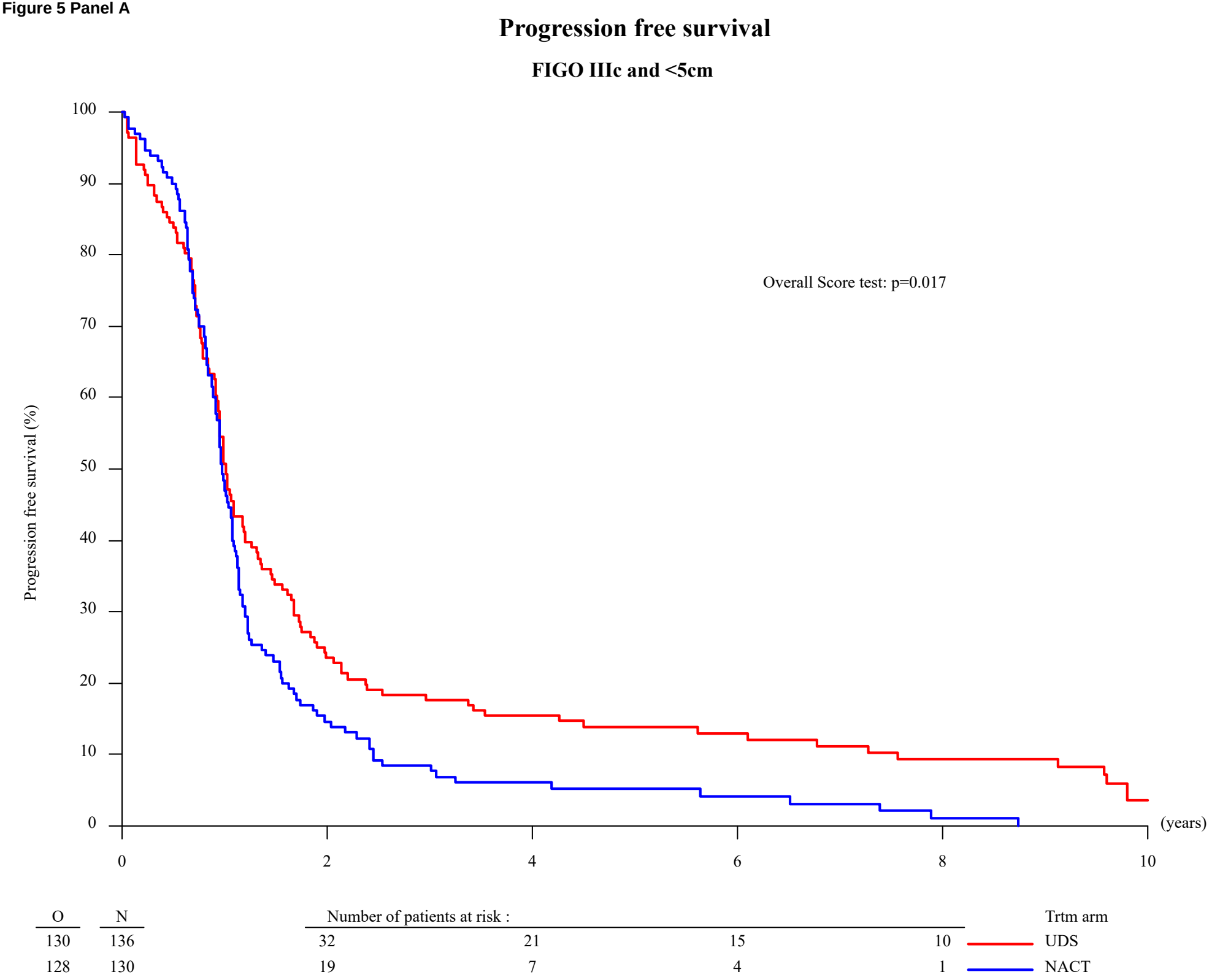

Figure 5 Panel B