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Bevacizumab for advanced cervical cancer: patient-reported outcomes of a randomised, phase 3 trial (NRG Oncology–Gynecologic Oncology Group protocol 240)

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Summary

Background GOG 240 was a practice-changing randomised phase 3 trial that concluded that chemotherapy plus bevacizumab for advanced cervical cancer significantly improves overall and progression-free survival, and the proportion of patients achieving an overall objective response, compared with chemotherapy alone. In this study, we aimed to analyse patient-reported outcomes in GOG 240.

Methods Eligible adult participants (aged ≥18 years) had primary stage IVB or recurrent or persistent carcinoma of the cervix with measurable disease and GOG performance status of 0–1. Participants were randomly assigned by web-based permuted block randomisation (block size 4) in a 1:1:1:1 ratio to the four treatment groups: cisplatin (50 mg/m² intravenously on day 1 or 2 of the treatment cycle) and paclitaxel (135 mg/m² intravenously over 24 h or 175 mg/m² intravenously over 3 h on day 1), with or without bevacizumab (15 mg/kg intravenously on day 1 or 2), or paclitaxel (175 mg/m² over 3 h on day 1) and topotecan (0·75 mg/m² for 30 min on days 1–3) with or without bevacizumab (15 mg/kg intravenously on day 1). Treatment assignment was concealed at randomisation (everyone was masked to treatment assignment, achieved by the use of a computer encrypted numbering system at the National Cancer Institute) and became open-label when each patient was registered to the trial. Treatment cycles were repeated every 21 days until disease progression or unacceptable toxicity, whichever occurred first. The coprimary endpoints of the trial were overall survival and safety; the primary quality-of-life endpoint was the score on the Functional Assessment of Cancer Therapy-Cervix Trial Outcome Index (FACT-Cx TOI). For our analysis of patient-reported outcomes, participants were assessed before treatment cycles 1, 2, and 5, and at 6 and 9 months after the start of cycle 1, with the FACT-Cx TOI, items from the FACT-GOG-Neurotoxicity subscale, and a worst pain item from the Brief Pain Inventory. All patients who completed baseline quality-of-life assessments and at least one further follow-up assessment were evaluable for quality-of-life outcomes. This study is registered with ClinicalTrials.gov, number NCT00803062.

Findings Between April 6, 2009, and Jan 3, 2012, a total of 452 patients were enrolled in the trial, of whom 390 completed baseline quality-of-life assessment and at least one further assessment and were therefore evaluable for quality-of-life outcomes. In these patients, patient-reported outcome completion declined from 426 (94%) of 452 (at baseline) to 193 (63%) of 307 (9 months post-cycle 1), but completion rates did not differ significantly between treatment regimens (p=0·78). The baseline FACT-Cx TOI scores did not differ significantly between patients who received bevacizumab versus those who did not (p=0·27). Compared with patients who received chemotherapy alone, patients who received chemotherapy plus bevacizumab reported FACT-Cx TOI scores that were an average of 1·2 points lower (98·75% CI −4·1 to 1·7; p=0·30).

Interpretation Improvements in overall survival and progression-free survival attributed to the incorporation of bevacizumab into the treatment of advanced cervical cancer were not accompanied by any significant deterioration in health-related quality of life. Patients responding to anti-angiogenesis therapy who maintain an acceptable quality of life could be suitable at progression for treatment with other novel therapies that might confer additional benefit.

Funding National Institutes of Health.

Introduction

Around 500 000 new cases of cervical cancer and 250 000 cervical cancer-related deaths occur worldwide every year.[1] Although screening with cytology and high-risk human papillomavirus DNA testing have reduced the incidence and mortality of this disease, women who do not have access to health care and those living in resource-poor areas remain at high risk of death from cervical cancer. Prophylactic human papillomavirus vaccination is an important preventive approach, but also one that needs access to health care. Although early-stage disease can be cured by radical surgery and locally advanced disease by chemoradiotherapy, women with metastatic and non-operable recurrent disease have previously had few treatment options.[1] Platinum-based chemotherapy in this setting is palliative and is associated with median overall survival of 8–12 months.[2–4]

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Vascular endothelial growth factor (VEGF) has emerged as an important therapeutic target in many solid tumours.[5] Gynecologic Oncology Group (GOG) protocol 240 (GOG 240) was a randomised phase 3 clinical trial that showed that, compared with chemotherapy alone, chemotherapy plus bevacizumab (a monoclonal antibody that binds VEGF) significantly increased overall survival from 13·3 months to 17·0 months (hazard ratio [HR] 0·71 [98% CI 0·54–0·95], p=0·004) in patients with advanced cervical cancer.[6] The triplet regimens used in the study (cisplatin, paclitaxel and bevacizumab, and topotecan, paclitaxel and bevacizumab) were quite well tolerated but were both associated with a 6% incidence of fistula and 8% incidence of thromboembolism (compared with fistula <1% and thromboembolism 1% for either chemotherapy regimen alone without bevacizumab). On Aug 14, 2014, under the US Food and Drug Administration's (FDA) Priority Review programme (which makes promising therapies rapidly available to patients), both of these bevacizumab-containing triplet regimens were approved for the treatment of advanced cervical cancer.

In the advanced cervical cancer setting, quality of life must be measured to balance potential toxicities with treatment efficacy; it is important to simultaneously assess quality of life while measuring progression-free and overall survival. Before GOG 240, progression-free and overall survival increases in cervical cancer treatments were modest, with little benefit or difference in health-related quality of life.[7–10] In view of the poor prognosis for patients with advanced cervical cancer, we should strive to identify treatments that prolong life but do not create additional toxicities that would further compromise quality of life. With the typically marginal benefit provided by the addition of new agents to combination chemotherapy, it was anticipated that short of an overall survival benefit, clinical benefit would have to be demonstrated by the additional benefit of patient-reported outcomes to a progression-free survival advantage. Therefore, a major aim of GOG 240 was to establish whether or not the addition of bevacizumab to chemotherapy affected health-related quality of life. To establish whether or not baseline health-related quality of life in this population was associated with survival was an exploratory endpoint, since earlier published studies have indicated that quality of life at study entry is a prognostic indicator for survival.

Methods

Study design and participants
Entry criteria for this international, phase 3, multicentre, randomised controlled trial have been described previously.[6] Briefly, eligible adult participants (≥18 years of age) were enrolled from participating National Cancer Institute GOG institutions in the USA and the Spanish cooperative group, Grupo Español de Investigation en Cancer de Ovario (GEICO) participating institutions in Spain. All participants had primary stage IVB or metastatic, recurrent or persistent carcinoma of the cervix with measurable disease and GOG performance status of 0–1 (where 0 indicates that the person is fully active, and 1 indicates that the person is ambulatory but restricted in physically strenuous activities). No previous chemotherapy for recurrence was allowed, and no previous paclitaxel or topotecan with prior radiation was permitted. Patients had to have adequate renal, hepatic, and bone marrow function. Patients treated with chemotherapy for recurrence, and those with nonhealing wounds, active bleeding conditions, or inadequately anticoagulated thromboembolism were ineligible. Patients with recurrent tumours that could be salvaged by pelvic exenteration were also not allowed to enroll in this study.

The trial was done through the GOG and GEICO, with funding from the National Institutes of Health and bevacizumab (Genentech, San Francisco, CA, USA/ Roche, Basel, Switzerland) supplied by the National Cancer Institute (NSC number 704865, Investigational New Drug number 113912), with central institutional review board approval and registration. All patients provided written informed consent before enrolment.

Randomisation and masking
Web-based permuted block randomisation, with a block size of 4, was done by the GOG Statistical and Data Center, with use of a 2×2 factorial design. The randomisation ratio was 1:1 for each level of each factor (subsitution of cisplatin with topotecan [ie, non-platinum chemotherapy doublet] and use of anti-angiogenesis therapy [bevacizumab]) or 1:1:1:1 for each treatment group. Random assignment to one of the four groups was balanced within disease status (recurrent or persistent vs stage IVB primary), GOG performance status (0 vs 1), and previous platinum therapy as a radiation sensitiser (eg, no previous cisplatin-based chemoradiotherapy vs previous cisplatin-based chemoradiotherapy). Treatment assignment was concealed to everyone at randomisation and became open-label when each patient was registered to the trial (which was immediately upon web-based registration with the National Cancer Institute and before the administration of any treatment).

Procedures
Briefly, patients were randomly assigned to paclitaxel (135 mg/m² intravenously over 24 h or 175 mg/m² intravenously over 3 h on day 1) plus cisplatin 50 mg/m² intravenously on days 1 or 2, with or without bevacizumab 15 mg/kg intravenously on days 1 or 2; or paclitaxel 175 mg/m² over 3 h on day 1 with topotecan 0·75 mg/m² for 30 min on days 1–3, with or without bevacizumab 15 mg/kg intravenously on day 1. Treatment cycles were repeated every 21 days until disease progression or unacceptable toxicity, whichever occurred first. To reduce the risk of neurotoxicity, paclitaxel infusions could also be given on non-platinum days. Disease was assessed by

physical examination and chest radiography, and by abdomen and pelvic CT or MRI within 28 days before the study treatment was initiated. In patients without disease progression, imaging was repeated every other cycle. Tumour measurements according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1), were made within 1 week before the next planned cycle. After discontinuation of treatment, disease was assessed every 3 months for 2 years, followed by assessment every 6 months for 3 years until disease progression was documented. Safety, as assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, was monitored during each cycle. Patient-reported outcomes, including health-related quality of life, were assessed for all treatment regimens at five timepoints: at baseline (before randomisation), before cycles 2 and 5, and at 6 and 9 months since the start date of treatment cycle 1.

Outcomes

The primary endpoints of the GOG 240 trial were overall survival and the frequency and severity of toxicity, with progression-free survival and tumour response as secondary endpoints. Health-related quality of life and patient-reported outcomes were tertiary (exploratory) endpoints.

The health-related quality-of-life measures used in this trial were the Functional Assessment of Cancer Therapy-Cervix (FACT-Cx) Trial Outcome Index (TOI), on which a higher score indicates better health-related quality of life; the FACT/GOG-Neurotoxicity four-item subscale (FACT/GOG-Ntx-4), on which a higher score indicates less neurotoxicity; and the Brief Pain Inventory (BPI) single item assessing worst pain in the past 24 h, for which a higher score indicates more pain. These previously validated, self-reported measures were selected on the basis of previous justification that quality of life, neurotoxicity, and pain are all sensitive to change in randomised clinical trials of advanced cervical cancer. All scales are available in English and Spanish; both language versions were used in this trial.[11,12]

The FACT-Cx is the FACT-G plus a cervical cancer-specific subscale.[11] The FACT-G is a 27-item self-reported quality-of-life measure that includes four subscales (physical wellbeing, social wellbeing, functional wellbeing, and emotional wellbeing). Each scale produces a score, and the scores can be summed to produce a total quality-of-life score. The FACT-Cx endpoint for this trial focuses on aspects of health-related quality of life that are most sensitive and responsive in clinical trials. This FACT-Cx TOI is the summation of the physical wellbeing, functional wellbeing, and cervical cancer subscales.

FACT-Cx TOI was selected as the primary quality-of-life endpoint and consists of two subscales from the FACT-G: physical wellbeing (seven items) and functional wellbeing (seven items), plus the cervix cancer-specific subscale (15 items).[11,12]

Four items from the 11-item FACT/GOG-Neurotoxicity (FACT/GOG-Ntx) subscale were included to assess this important side-effect (neurotoxicity) that is associated with many of the chemotherapy agents in this trial. These four questions are for sensory peripheral neuropathy and include, "I have numbness/tingling in my hands"; "I have numbness/tingling in my feet"; "I have discomfort in my hands"; and "I have discomfort in my feet") also explain more than 50% of the variation in the total Ntx score.[13,14]

The BPI is a 23-item, self-reported measurement to assess pain in cancer and other diseases.[15] To limit patient burden, we selected the most frequently used endpoint

	Cisplatin and paclitaxel (n=114)	Cisplatin and paclitaxel plus bevacizumab (n=115)	Topotecan and paclitaxel (n=111)	Topotecan and paclitaxel plus bevacizumab (n=112)
Pre-cycle 1				
Received	107 (94%)	109 (95%)	106 (95%)	104 (93%)
Noncompliance				
Insufficient answer	3 (3%)	3 (3%)	2 (2%)	3 (3%)
Illness or toxicities	1 (1%)	0	1 (1%)	1 (1%)
Patient refusal	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Administrative error	2 (2%)	0	0	2 (2%)
Other	0	2 (2%)	1 (1%)	1 (1%)
Pre-cycle 2				
Deaths	1 (1%)	1 (1%)	4 (4%)	3 (3%)
Received	95 (83%)	95 (83%)	89 (80%)	93 (83%)
Noncompliance				
Insufficient answer	1 (1%)	0	0	0
Illness or toxicities	6 (5%)	5 (4%)	2 (2%)	1 (1%)
Patient refusal	1 (1%)	4 (3%)	4 (4%)	2 (2%)
Administrative error	8 (7%)	5 (4%)	11 (10%)	10 (9%)
Lost to follow-up	1 (1%)	3 (3%)	1 (1%)	0
Other	1 (1%)	2 (2%)	0	3 (3%)
Pre-cycle 5				
Deaths	11 (10%)	8 (7%)	12 (11%)	9 (8%)
Received	82 (72%)	82 (71%)	77 (69%)	81 (72%)
Noncompliance				
Illness or toxicities	7 (6%)	1 (1%)	1 (1%)	4 (4%)
Patient refusal	4 (4%)	6 (5%)	4 (4%)	5 (5%)
Administrative error	5 (4%)	9 (8%)	8 (7%)	4 (4%)
Lost to follow-up	3 (3%)	3 (3%)	4 (4%)	4 (4%)
Other	2 (2%)	6 (5%)	5 (5%)	5 (5%)
6 months post-cycle 1				
Deaths	24 (21%)	16 (14%)	25 (23%)	19 (17%)
Received	61 (54%)	66 (57%)	54 (49%)	64 (57%)
Noncompliance				
Illness or toxicities	7 (6%)	2 (2%)	6 (5%)	2 (2%)
Patient refusal	4 (4%)	9 (8%)	5 (5%)	5 (5%)
Administrative error	6 (5%)	10 (9%)	6 (5%)	9 (8%)
Lost to follow-up	7 (6%)	6 (5%)	7 (6%)	8 (7%)
Other	5 (4%)	6 (5%)	8 (7%)	5 (5%)

(Table 1 continues on next page)

	Cisplatin and paclitaxel (n=114)	Cisplatin and paclitaxel plus bevacizumab (n=115)	Topotecan and paclitaxel (n=111)	Topotecan and paclitaxel plus bevacizumab (n=112)
(Continued from previous page)				
9 months post-cycle 1				
Deaths	39 (34%)	30 (26%)	43 (39%)	33 (29%)
Received	48 (42%)	49 (43%)	43 (39%)	53 (47%)
Noncompliance				
Illness or toxicities	7 (6%)	2 (2%)	3 (3%)	5 (5%)
Patient refusal	4 (4%)	9 (8%)	5 (5%)	4 (4%)
Administrative error	6 (5%)	9 (8%)	4 (4%)	5 (5%)
Lost to follow-up	4 (4%)	8 (7%)	6 (5%)	6 (5%)
Other	6 (5%)	8 (7%)	7 (6%)	6 (5%)
Number of patients evaluable for patient-reported outcomes	99 (89%)	98 (85%)	95 (86%)	98 (88%)
Number of patients non-evaluable for patient-reported outcomes				
Baseline incomplete	7 (6%)	6 (5%)	5 (5%)	8 (7%)
Follow-ups incomplete	8 (7%)	11 (10%)	11 (10%)	6 (5%)

Data are n (%).

Table 1: Status of quality-of-life assessment completion

	Chemotherapy (n=194)	Chemotherapy plus bevacizumab (n=196)	Cisplatin and paclitaxel with or without bevacizumab (n=197)	Topotecan and paclitaxel with or without bevacizumab (n=193)
Age group (years)				
≤39	20 (10%)	24 (12%)	21 (11%)	23 (12%)
40–49	67 (35%)	54 (28%)	65 (33%)	56 (29%)
50–59	49 (25%)	67 (34%)	53 (27%)	63 (33%)
60–69	41 (21%)	35 (18%)	35 (18%)	41 (21%)
≥70	17 (9%)	16 (8%)	23 (12%)	10 (5%)
Race				
Asian	5 (3%)	12 (6%)	10 (5%)	7 (4%)
Black	21 (11%)	31 (16%)	26 (13%)	26 (13%)
Other	12 (6%)	8 (4%)	8 (4%)	12 (6%)
White	156 (80%)	145 (74%)	153 (78%)	148 (77%)
Ethnic origin				
Hispanic	25 (13%)	22 (11%)	27 (14%)	20 (10%)
Non-Hispanic	161 (83%)	165 (84%)	159 (81%)	167 (87%)
Other/unspecified	8 (4%)	9 (5%)	11 (5%)	6 (3%)
Performance status				
0	121 (62%)	116 (59%)	119 (60%)	118 (61%)
1	73 (38%)	80 (41%)	78 (40%)	75 (39%)
Disease status				
Advanced	36 (18%)	32 (16%)	35 (18%)	33 (17%)
Persistent	17 (9%)	26 (13%)	17 (9%)	26 (14%)
Recurrent	141 (73%)	138 (70%)	145 (74%)	134 (69%)
Previous platinum-containing therapy				
Yes	139 (72%)	147 (75%)	144 (73%)	142 (74%)
No	55 (28%)	49 (25%)	53 (27%)	51 (26%)

Data are n (%).

Table 2: Baseline characteristics

from the BPI, which is the single item assessing "worst pain" in the past 24 h, on a 0–10 scale.

Each item in the FACT-Cx TOI and FACT/GOG-Ntx4 subscale is scored on a five-point scale (0=not at all; 1=a little bit; 2=somewhat; 3=quite a bit; 4=very much). The range of possible scores is 0–116 for the FACT-Cx TOI and 0–16 for the FACT/GOG-Ntx4 subscale. For all Functional Assessment of Chronic Illness Therapy (FACIT) patient-reported outcome scales, a higher score indicates better quality of life or fewer symptoms or toxicity. Collection of the later patient-reported outcome data, at 6 and 9 months after the first cycle, was needed irrespective of whether or not participants had experienced progressive disease, and participants had to fill out responses on their own (they were not allowed to be helped). Validation of the prognostic significance of patient-reported outcomes in this trial was an exploratory endpoint.

Statistical analysis

Patients who completed baseline assessment and at least one follow-up self-reported outcome assessment were judged eligible for evaluation in this final analysis. The association between baseline FACT-Cx TOI score and overall survival and progression-free survival was analysed with a proportional hazards model stratified by prognostic factors, assignment of bevacizumab, and treatment with cisplatin or topotecan.[16] The median follow-up for survival was 20·8 months (IQR 14·0–27·4 months).[6]

The presence of neurotoxic symptoms was defined as an Ntx score lower than 16. The severity of reported neurotoxic symptoms was established as the mean Ntx score that was less than 16. The distribution of the Ntx subscale score tended to show clumping at 16 (no neurotoxicity) and was skewed to the left. The distribution of BPI score tended to cluster at 0 (no pain) and was skewed to the right. To analyse these data, we used a mixed-effects mixed-distribution model. This model contains two components: the first is a logistical model to estimate the odds of reporting a non-zero value (<16 for Ntx scores) and the second component models the possibly truncated distribution of the non-zero scores (again, <16 for Ntx scores). Random effects are used to account for the correlation of repeating measures within an individual. This model also allows for a correlation of the random effects from the two components of the model.[17] We did all analyses on the whole intention-to-treat population using SAS/STAT software version 9.4. We assessed the difference in FACT-Cx TOI using the linear mixed model, adjusting for patient's pretreatment score, performance status, assignment of bevacizumab, treatment with cisplatin or topotecan, and age at enrolment. We treated the assessment timepoints as categorical since they are not equally spaced. We assumed the covariance matrix to be unstructured. To represent the observed covariance pattern of the TOI scores, the empirical variance was used to estimate the precision of parameter estimates. The denominator degrees of

freedom were approximated as described by Kenward and Roger.[14] The independence effect of two factors on quality of life (interaction between bevacizumab and topotecan or cisplatin) was tested first, and the interactions between assessment timepoints and treatment assignments were then tested first for differential effects of treatments on TOI scores over time. If the interaction effect was significant, we estimated the treatment differences for each assessment timepoint. Otherwise, we estimated the overall treatment effect using a weighted average of estimates from each timepoint.

The sample size was ascertained by the primary clinical objective.[6] Because the original study design tested two independent hypotheses (effect of bevacizumab, and substitution of topotecan for cisplatin), to control the overall type 1 error at 5%, the significance level was set to 0·0125 for the FACT-Cx TOI and the FACT/GOG-Ntx subscale, and 0·05 for the BPI worst pain score for exploratory purposes. According to previous studies, the correlation between repeated measures made on the same participant ranged from 0·3 to 0·8. With the assumption that at least 80% of eligible patients were evaluable for the analysis (ie, they completed baseline and at least one follow-up assessment), the study was expected to have at least 86% power to detect an effect size of 0·35 in FACT-Cx TOI scores between treatment groups. Treatment effect size was calculated as the ratio of the treatment difference to the baseline standard deviation in the control group. The minimum clinically important difference (ie, that perceived by patients as important, and by clinicians to require a change in the patients' management) for FACT-Cx TOI is believed to range from 5·8 to 8·7 points.[13]

Every effort was made to avoid missing data and the reasons for missing assessments were collected at each assessment timepoint and documented in the analysis. The assessment compliances were compared across assigned groups with a generalised estimating equation. Additionally, multiple imputation for missing values was done using data from those patients who were still alive at assessment time. The results from multiple imputation were consistent with the original analysis. This study is registered with ClincialTrials.gov, number NCT00803062.

Role of the funding source

The funders had no role in the study design, conduct, analysis, interpretation of the data, or writing of the report. Only the statistician (HQH) had access to the raw data, according to GOG policy. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between April 6, 2009, and Jan 3, 2012, a total of 452 patients were enrolled in the trial and assigned to the four treatment groups: 114 (25%) to cisplatin plus paclitaxel; 115 (25%) to cisplatin, paclitaxel, and bevacizumab; 111 (25%) to topotecan plus paclitaxel; and 112 (25%) to topotecan, paclitaxel, and bevacizumab. 426 (94%) of 452 patients completed the baseline quality-of-life assessment (table 1). Compliance to quality-of-life analysis (including in those who had progressive disease, since patients were followed for survival) dropped to 372 (84%) of 443 patients at pre-cycle 2 assessment, 322 (78%) of 412 at pre-cycle 5 assessment, 245 (67%) of 368 at 6 months post-cycle 1, and 193 (63%) of 307 at 9 months post-cycle 1 follow-up. Compliance did not differ significantly between treatment regimens (p=0·78; data not shown) and reasons for noncompliance were similar in the four treatment groups (table 1). 426 (96%) of the entire study population completed the questionnaires pre-cycle 1, and 193 (63%) of 307 completed the questionaires 9 months post-cycle 1. Although nearly a third (143/452 [32%]) of enrolled patients completed all five scheduled patient-reported
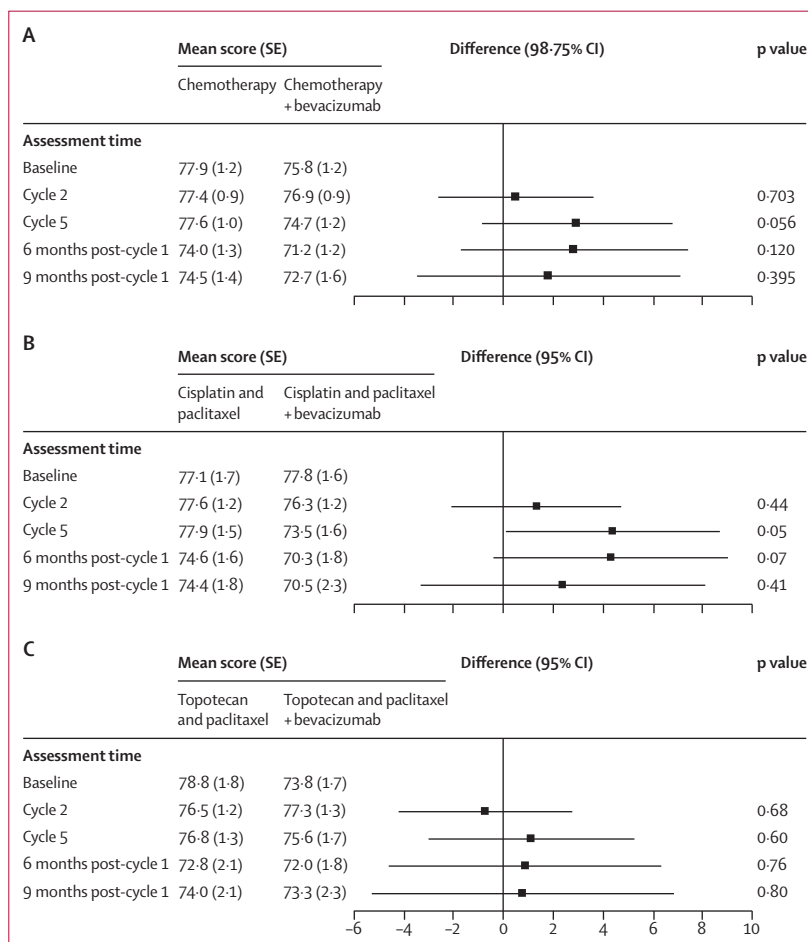

Figure 1: Patient-reported outcomes on the FACT-Cx TOI by treatment group
Mean FACT-Cx TOI scores for comparisons between patients in the chemotherapy group alone (both backbones) *vs* chemotherapy (both backbones) with bevacizumab (A); cisplatin and paclitaxel with *vs* without bevacizumab (B); and topotecan and paclitaxel with *vs* without bevacizumab (C). Means at baseline are raw means. Means at follow-ups are least-squared means estimated from the fitted linear mixed models. FACT-Cx TOI=Functional Assessment of Cancer Therapy-Cervix Trial Outcome Index.
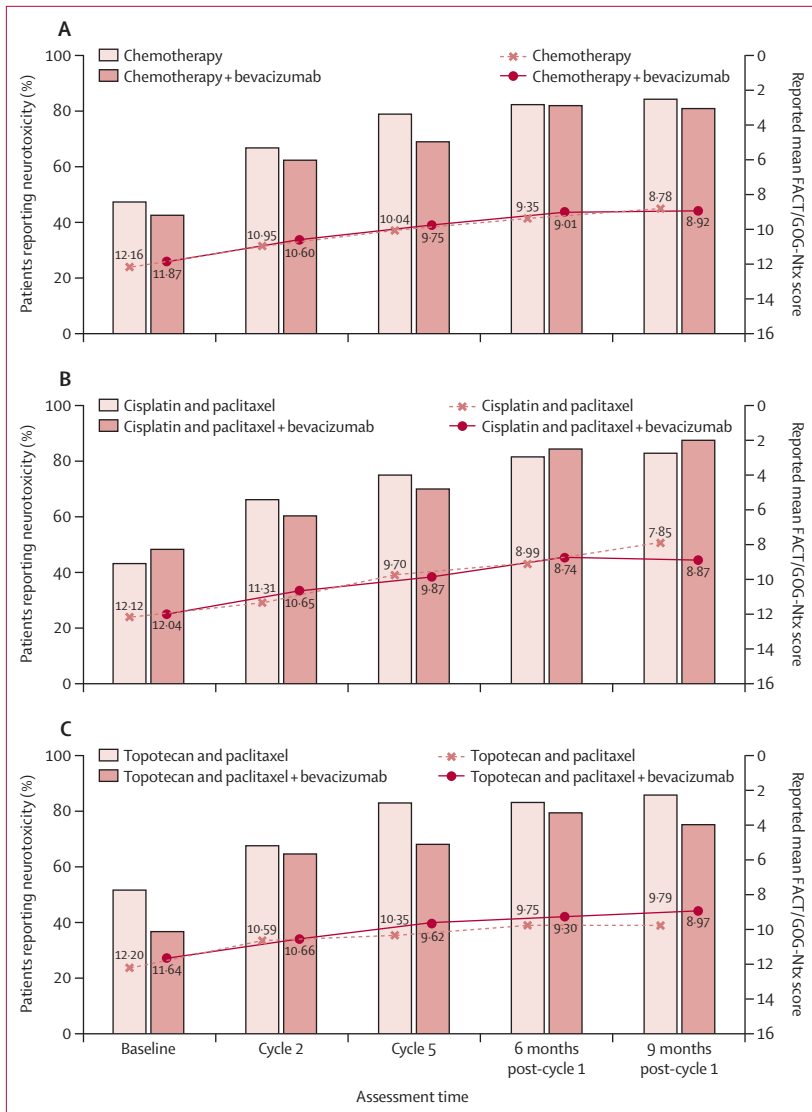
Figure 2: Patient-reported outcomes (PROs) using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group (FACT/GOG-Ntx) subscale

Comparisons of neurotoxicity severity—in patients who reported neurotoxicity—between patients in the chemotherapy group alone (both backbones) vs chemotherapy (both backbones) with bevacizumab (A); cisplatin and paclitaxel with vs without bevacizumab (B); and topotecan and paclitaxel with vs without bevacizumab (C). FACT/GOG-Ntx=Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-neurotoxicity subscale.

See **Online** for appendix

outcome assessments (33 in the cisplatin and paclitaxel group, 36 in the cisplatin and paclitaxel plus bevacizumab group, 36 in the topotecan and paclitaxel group, and 38 in the topotecan and paclitaxel plus bevacizumab group), 14 patients (three in the cisplatin and paclitaxel group, three in the cisplatin and paclitaxel plus bevacizumab group, three in the topotecan and paclitaxel group, and five in the topotecan and paclitaxel plus bevacizumab group) completed none. Additionally, 12 patients did not complete baseline quality-of-life assessments and 36 patients did not complete any follow-up assessments. These 62 patients were not evaluable for patient-reported

outcomes and were therefore not included in the final analysis. 390 patients completed baseline quality-of-life assessment and at least one further assessment and were therefore evaluable for quality-of-life outcomes.

Clinical features of the 390 evaluable patients were similar in groups treated with chemotherapy with and without bevacizumab, and in those treated with cisplatin versus topotecan (table 2; appendix p 1). Overall, 153 (39%) of 390 had performance status 1, 322 (83%) had recurrent or persistent disease, and 286 (73%) had received previous platinum therapy. This study encouraged all patients to complete the patient-reported outcome, irrespective of their disease progression status. At 9 months, 104 (68%) of 153 of patients without disease progression and 83 (64%) of 129 with disease progression completed patient-reported outcomes (appendix p 2).

The baseline FACT-Cx TOI scores did not differ significantly between patients who received bevacizumab versus those who did not (p=0·27). Analyses of follow-up FACT-Cx TOI scores suggested no interaction between bevacizumab and topotecan (p=0·31), or between assessment time and assignment of bevacizumab (p=0·29). Patients who received bevacizumab reported, on average across all timepoints, FACT-Cx TOI scores that were 1·2 points lower (98·75% CI −4·1 to 1·7) than did those receiving chemotherapy alone (p=0·30; figure 1A). After adjustment for baseline score and patients' age, those who received cisplatin and paclitaxel plus bevacizumab reported FACT-Cx TOI scores that were 2·1 points lower (95% CI −1·2 to 5·3) on average across all timepoints than those treated with cisplatin and paclitaxel alone (p=0·20; figure 1B). Patients who received topotecan and paclitaxel plus bevacizuamb reported 0·1 points higher scores (95% CI −3·1 to 3·2) on average across all timepoints on the FACT-Cx TOI than did those who were given topotecan and paclitaxel alone (p=0·96; figure 1C).

The percentage of patients reporting neurotoxic symptoms increased consistently over time in both groups (figure 2). Patients receiving bevacizumab were less likely to report neurotoxic symptoms than were those who did not receive this drug (odds ratio [OR] 0·58 [98·75% CI 0·17–0·98], p=0·01); however, the FACT/GOG-Ntx score when neurotoxicity was present did not differ significantly (difference 0·23 [98·75% CI −1·19 to 1·64], p=0·69; figure 2A). In patients treated with the cisplatin–paclitaxel chemotherapy backbone, incorporation of bevacizumab was not associated with either the likelihood of reporting neurotoxicity (OR 0·59 [95% CI 0·1–1·09], p=0·11) or with the score on the FACT/GOG-Ntx subscale (difference 0·15 [95% CI −1·54 to 1·84], p=0·86; figure 2B). Although patients who received bevacizumab on the topotecan–paclitaxel backbone were less likely to report neurotoxicity (OR 0·51 [95% CI 0·11–0·91], p=0·02) than were those who received topotecan–paclitaxel alone, in those patients who did report neurotoxicity, the FACT/GOG-Ntx scores did not differ between the groups (difference 0·17 [95% CI −1·31 to 1·65], p=0·72; figure 2C).

After adjustment for baseline BPI scores and for assignment of topotecan, no evidence suggested that treatment differences varied significantly over time in either the odds of reporting pain or the severity of the reported worse pain score. The fitted mixed-effects mixed-distribution model estimates suggested that the patients receiving chemotherapy with or without bevacizumab had similar odds of experiencing pain (OR 0·96 [95% CI 0·39–1·52], p=0·78), and those who experienced pain reported a similar severity (difference 0·5 [95% CI −0·14 to 1·14], p=0·12; figure 3A).

Figures 3B and 3C show the effect of bevacizumab on reported BPI worse pain score in each of the chemotherapy backbones. After adjustment for baseline score, bevacizumab was not associated with the odds of patients feeling pain in either chemotherapy backbone (cisplatin–paclitaxel with and without bevacizumab: OR 1·43 [95% CI 0·03–2·82], p=0·54; topotecan–paclitaxel with and without bevacizumab: OR 0·65 [0·15–1·15], p=0·16). In patients who did experience pain, bevacizumab was not associated with the reported BPI score in either the cisplatin–paclitaxel backbone (difference 0·77 [95% CI −0·13 to 1·68], p=0·09) or the topotecan–paclitaxel backbone (0·32 [−0·61 to 1·25], p=0·51).

After adjustment for baseline score, patient age, performance status, and assignment of bevacizumab, FACT-Cx TOI did not differ significantly between treatment with either chemotherapy backbone (difference 0·5 [98·75% CI −2·4 to 3·4], p=0·66; figure 4A). Compared with the cisplatin–paclitaxel backbone, the topotecan–paclitaxel backbone was not associated with significant differences in the odds of reporting neurotoxic symptoms (OR 1·05 [98·75% CI 0·32–1·77], p=0·87) or the severity of these symptoms (difference 0·43 [98·75% CI −1·84 to 0·99], p=0·45; figure 4B). We noted no significant differences in the odds of patients complaining of pain with either chemotherapy backbone (OR 1·3 [95% CI 0·5–2·0], p=0·48). However, in those patients who experienced pain, the treatment difference in the reported BPI pain score was not constant over the assessment time (p=0·02). For example, compared with patients treated on the cisplatin-based chemotherapy, the patients on the topotecan-based chemotherapy reported a 0·71 points higher BPI score (95% CI 0·02–1·39; p=0·04) at cycle 2, but a 0·86 points lower score (−1·95 to 0·22; p=0·12) at 9 months post-cycle 1 (figure 4C).

We explored the association between baseline FACT-Cx TOI score and survival using a Cox proportional hazards model stratified by patients' performance status, disease status, previous concurrent platinum-based chemo-radiation, and treatment assignment. For the entire study population, as a continuous variable, the baseline FACT-Cx TOI was significantly associated with survival. For an increment of every ten units of FACT-Cx TOI, the HR for death was 0·80 (95% CI 0·74–0·87; p<0·0001), and for progression was 0·88 (0·83–0·95; p=0·0005). The baseline FACT-Cx TOI score was further classified into four groups
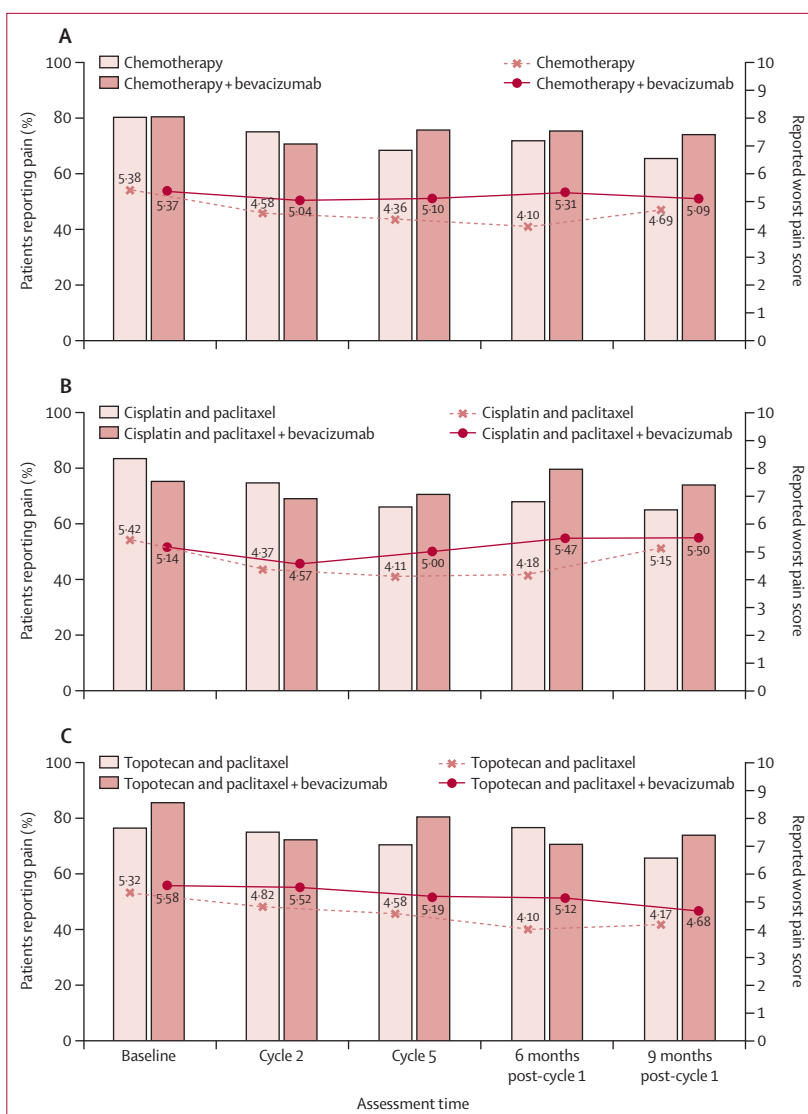

Figure 3: Patient-reported outcomes on the BPI single item scale
Comparisons of reporting of pain or the severity of pain between patients in the chemotherapy group alone (both backbones) vs chemotherapy (both backbones) with bevacizumab (A); cisplatin and paclitaxel with vs without bevacizumab (B); and topotecan and paclitaxel with vs without bevacizumab (C). BPI=Brief Pain Inventory.

(quartiles), in which the first quartile, median, and the third quartile were 63, 76, and, 89, respectively. When compared with the TOI scores lower than the first quartile, the HRs for death were 0·7 (95% CI 0·48–1·01; p=0·0533) for TOI less than the the median, 0·5 (0·35–0·74; p=0·0004) for TOI less than the the third quartile, and 0·38 (0·25–0·56; p<0·0001) for TOI higher than the third quartile, respectively (figure 5A). The HRs for disease progression relative to TOI lower than the first quartile were 0·69 (95% CI 0·50–0·97; p=0·0328) for TOI lower than the median, 0·75 (0·54–1·05; p=0·0989) for TOI lower than the third quartile, and 0·52 (0·37–0·73; p=0·0002) for TOI higher than the third quartile, respectively (figure 5B).
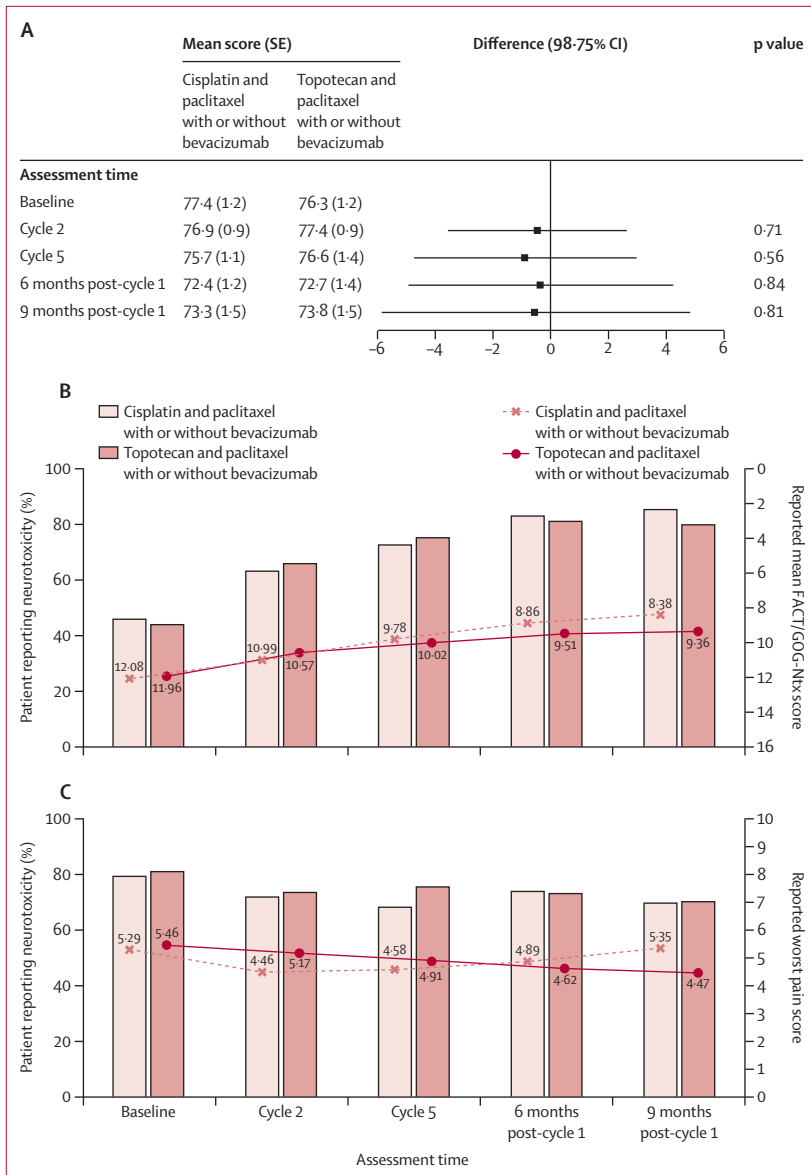
Figure 4: Effect of substitution of topotecan for cisplatin on FACT-Cx TOI, FACT/GOG-Ntx, and BPI
Comparisons of mean FACT-Cx TOI (A) scores and FACT/GOG-Ntx (B) scores during the assessment period. In patients who reported pain, the treatment difference in the reported BPI pain score was not constant throughout the assessment period (C). Means at follow-ups are least-squared means estimated from the fitted linear mixed models. FACT-Cx TOI=Functional Assessment of Cancer Therapy-Cervix Trial Outcome Index. FACT/GOG-Ntx=Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-neurotoxicity subscale. BPI=Brief Pain Inventory.

Discussion

This phase 3 study of the integration of anti-angiogenesis therapy for advanced cervical cancer showed that significant improvements in overall survival, progression-free survival, and the proportion of patients achieving an objective response conferred by the addition of bevacizumab to chemotherapy did not come at the cost of a concomitant deterioration of health-related quality of life as defined by the FACT-Cx TOI (panel). Specifically, the fitted mixed model estimates for the FACT-Cx TOI

scores shows that the addition of bevacizumab did not adversely affect quality of life. The effect of substitution of cisplatin with topotecan did not change quality of life, nor did it abrogate neurotoxic symptoms. Both triplet regimens of cisplatin–paclitaxel–bevacizumab and topotecan–paclitaxel–bevacizumab have been granted regulatory approval by the US FDA for first-line treatment of metastatic and recurrent cervical cancer and both triplets have been designated as Category 1 interventions in the National Comprehensive Cancer Network's Cervical Cancer Treatment Guidelines. This report confirms the tolerability of these new combinations.

This study showed that baseline FACT-Cx TOI as a continuous variable is associated with both overall survival and progression-free survival. Clearly, baseline health-related quality of life is strongly predictive of survival in this population.[18,19] Importantly, to further explore the effect of health-related quality of life on survival, our quartiles analysis of the FACT-Cx TOI score indicate that the estimated HR of death for patients in the highest health-related quality-of-life quartile was much lower than for patients in the lowest quartile.

Baseline predictors of overall survival and progression-free survival have clear clinical relevance, since they allow future studies to potentially pursue stratification based on baseline scores to further establish differential treatment responses and, importantly, also provide an upfront opportunity to monitor and remediate symptoms that might be contributing to the decline in quality of life.

The 2·1-points lower FACT-Cx TOI measured in the cisplatin–paclitaxel–bevacizumab group than in the cisplatin–paclitaxel alone group after adjustment for baseline score and patients' characteristics could be regarded as an improvement, although it did not reach our prespecified 5·8 points for clinically significant improvement for the FACT-Cx TOI. This could be interpreted as encouraging for the development of combination of bevacizumab with the less toxic and equally effective carboplatin–paclitaxel combination. However, carboplatin-related haematological toxicity can be substantial when patients have previously been treated with chemoradiotherapy, and this treatment approach should not yet be viewed as standard.

Several possible reasons exist for the recorded trend that patients receiving bevacizumab were less likely to report neurotoxic symptoms than were those who received chemotherapy alone, including secondary gains from increased tumour shrinkage, better health, or increased activity levels.[15,18,20] Conversely, the myalgias of bevacizumab—as perhaps documented in the BPI score—could function as a counter-irritant so-called distraction from neurotoxicity symptoms.[12] This idea is consistent with the gate theory of pain proposed by Melzack and Wall in 1965.[21] This theory suggests that physical pain is not a direct result of activation of pain receptor neurons, but rather its perception is modulated by interaction of a network of neurons and complex

central processing. In addition to inducing angiogenesis and lymphangiogenesis, VEGF is also directly involved in neuroplasticity and nerve bundle maturation, and exerts protective effects on neurons. VEGF protects dorsal root ganglion neurons against paclitaxel-induced neurotoxicity.[22] Although factors such as disease site, histology, and intrinsic and acquired drug resistance mechanisms could ultimately decide which patients respond to anti-VEGF therapy, differential expression of the VEGF transcript should also be taken into account.[23,24] In GOG 240, patients who responded and ultimately benefited from treatment on the bevacizumab-containing regimens might have comprised an enriched population who express high amounts of the target. Such patients would also be expected to experience and report less severe neurotoxicity. However, predictive factors have not yet been defined. Notably, the absence of a proven difference in neurotoxicity between cisplatin–paclitaxel and topotecan–paclitaxel suggests that we have not yet identified the appropriate methods to assess neurotoxicity with sufficient sensitivity.

In successive phase 3 randomised trials done by the GOG in patients with advanced cervical cancer, eligibility criteria have become stricter;[2–4] this is especially the case in GOG 240, in which the inclusion of an antiangiogenic agent undoubtedly contributed to a change in population demographics. The study needed patients to have better renal function than previous studies before enrolment, and excluded patients with a GOG performance status of 2. Given that this population is mostly underserved with scarce resources, it was not uncommon in previous studies to have very ill patients enrolled in trials. Median survival in the preceding phase 3 protocol (GOG 204) was 12 months for patients who received the cisplatin–paclitaxel doublet,[3] which is closer to the real-world population of patients with advanced cervical cancer, who have a likely median survival time of 7 months or shorter—closer to the GOG phase 3 experiences from the 1990s.[2,4] Therefore, the 17 months median overall survival reported in GOG 240 associated with the groups in which anti-angiogenesis therapy was administered with chemotherapy represents a new benchmark that is more than double the median survival experienced off protocol and one that represents a degree of selection bias.[6] Furthermore, investigators were required to medically optimise their patients (address nutritional needs and correct renal dysfunction) in order for them to participate in this trial, and clinicians have become proactive with nephrostomies and ureteral stents, correcting anaemia and electrolyte abnormalities, and aggressively improving nutritional status. Although it cannot be quantified, the contribution of medical optimisation to maintenance of quality of life in GOG 240 is implicit, and the generalisability of study data necessitates that improvements in supportive care be taken into account in consideration of the historical context.
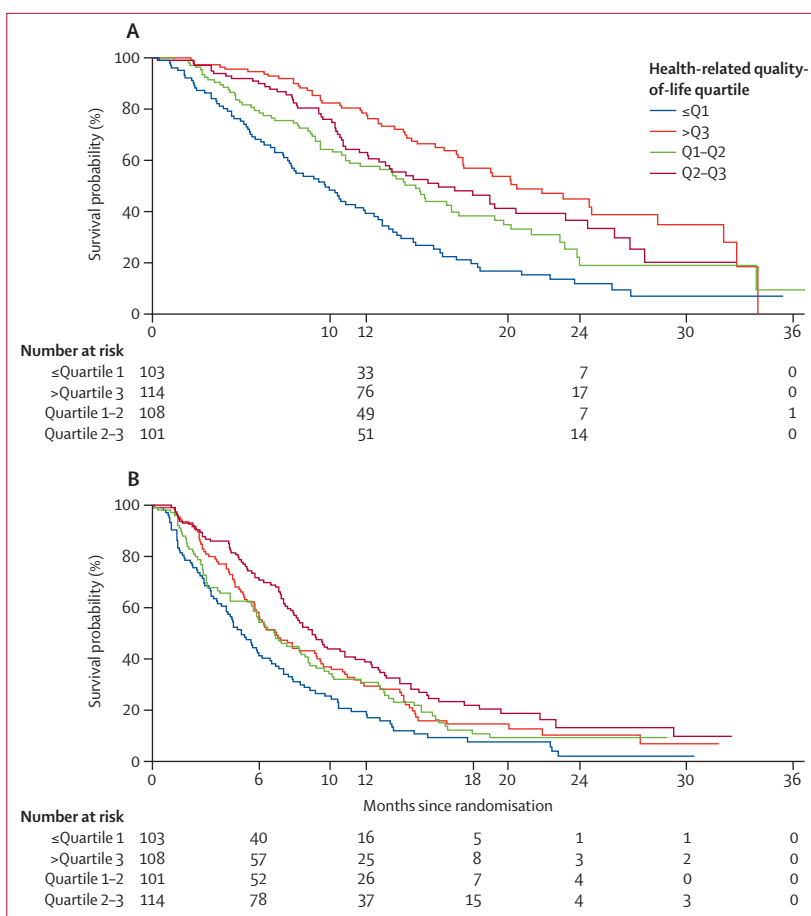

Figure 5: Quartile analysis of patient-reported outcomes on the FACT-Cx TOI
Association between baseline FACT-Cx TOI and overall survival (A) and progression-free survival (B) for the entire population. FACT-Cx TOI=Functional Assessment of Cancer Therapy-Cervix Trial Outcome Index.

Fatigue is the dominant symptom in patients with cancer.[25] Achievement of antiangiogenic blockade with tyrosine kinase inhibitors is associated with more fatigue than is reported with bevacizumab. The favourable side-effect and quality-of-life profile of bevacizumab suggests it is one of the better novel biologics to use to achieve clinical benefit,[26] which prompts the question as to whether fewer cycles of chemotherapy with maintenance bevacizumab is a good future strategy. Ongoing analyses are assessing whether or not it is possible to predict which patients are at risk of fistula or gastrointestinal perforation, and whether these adverse events can be avoided.

Patients with cervical cancer often experience quality-of-life disruptions from physical symptoms including pain; bowel, bladder, and sexual dysfunction; and lymph-oedema.[20] Additional key psychological and physical health factors have been identified, which contribute substantially to poor quality of life subsequent to definitive cancer treatment.[27] Most of these factors are amenable to supportive care interventions, and could be assessed at the time of primary treatment.

This study has the anticipated challenge of any randomised trial in that lower completion rates in the most severely ill patients create non-random bias in the evaluation of the effect of treatment. Nevertheless, the reported improvement in overall survival attributed to bevacizumab did not come at the cost of a significant deterioration in quality of life. Although patients living for 3·7 months longer might be another small incremental improvement, if this survival gain is considered in context of a sustained quality of life, the therapeutic effect becomes clinically meaningful. This patient population has very few treatment options, and, unlike many other solid tumours, several lines of chemotherapy and durable remissions are not possible for those patients with cervical cancer. The extended overall survival time provides a window of opportunity for patients who derive benefit from anti-angiogenic therapy to be treated with other classes of anti-angiogenic or targeted therapies, or immunotherapy. Through the National Cancer Institute and the Cancer Therapy Evaluation Plan mechanism, the NRG Oncology Group is studying other novel drugs for what has been anticipated will become a new population of patients with advanced cervical cancer—namely, those whose disease has progressed following treatment with anti-VEGF therapy.

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