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Health-Related Quality of Life After Cytoreductive Surgery/ HIPEC for Mucinous Appendiceal Cancer: Results of a Multicenter Randomized Trial Comparing Oxaliplatin and Mitomycin

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Abstract

Background.—This study evaluated health-related quality of life (HRQOL) using patient-reported outcomes in subjects with mucinous appendiceal neoplasms who underwent cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) as part of a randomized trial comparing mitomycin with oxaliplatin.

Methods.—In this prospective multicenter study, 121 mucinous appendiceal cancer patients, with evidence of peritoneal dissemination who underwent CRS, were randomized to receive mitomycin (divided 40 mg) or oxaliplatin (200 mg/m²) for HIPEC. The Functional Assessment of Cancer Therapy Neurotoxicity (FACT-G/NTX) questionnaire was utilized to assess HRQOL. The Trial Outcome Index (TOI) is a summary index responsive to changes in physical/functional outcomes. Repeated measures mixed models with an unstructured variance matrix were applied to assess changes in HRQOL longitudinally.

Results.—Baseline questionnaire compliance was 95.9%. Baseline physical well-being (PWB) was independently associated with overall survival (hazard ratio 0.79, 95% confidence interval 0.66–0.96; $p = 0.017$). The TOI was significantly lower in the mitomycin group compared with the oxaliplatin arm at 12 weeks ($p = 0.044$; score difference 6.35) and 24 weeks after surgery ($p =$

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0.049; score difference 5.61). At 12 weeks after surgery, declines from baseline were significant in the TOI ($p = 0.004$; score decline 8.99), PWB ($p < 0.001$; score decline 2.83), and FWB ($p < 0.001$; score decline 3.42) in the mitomycin group but not the oxaliplatin group.

Conclusions.—Compared with mitomycin, HIPEC perfusion with oxaliplatin results in significantly better physical and functional outcomes. With similar survival outcomes and complication rates, oxaliplatin should be considered as the chemoperfusion agent of choice in mucinous appendiceal cancer patients undergoing CRS/HIPEC.

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is now widely accepted as an effective treatment that potentially confers long-term survival for appendiceal cancer with peritoneal dissemination.^{1–3} CRS/HIPEC is a potentially morbid procedure and may adversely impact quality of life.⁴ There is a growing interest in assessment of health-related quality of life (HRQOL) as an important outcome in cancer research, particularly in prospective clinical trials.^{5–7} The American Society of Clinical Oncology has recognized HRQOL as an essential therapeutic outcome,⁸ and it has been considered as a primary or secondary endpoint in various clinical trials.⁹ Integration of HRQOL data with clinical findings can provide additional prognostic value in cancer patients.^{10,11} Moreover, evaluation of HRQOL, particularly in randomized clinical trials, could provide valuable information that can assist clinical decision making in the management of cancer patients.

Mitomycin and oxaliplatin are the two agents commonly utilized for intraperitoneal perfusion in CRS/HIPEC for appendiceal and colorectal cancers with peritoneal dissemination. We have recently reported the results of the first completed randomized clinical trial for appendiceal cancer, comparing mitomycin versus oxaliplatin delivered via HIPEC.¹² While some variations were observed in hematologic toxicities, there were no differences in overall or disease-free survival. However, in addition to survival benefits, the impact of the chemotherapeutic agent used during HIPEC on HRQOL should also be evaluated. We assessed HRQOL using the validated Functional Assessment of Cancer Therapy-Gynecologic Oncology Group Neurotoxicity scale (FACT/GOG-NTX) questionnaire. In this study, we report a comparative analysis of the longitudinal impact of mitomycin versus oxaliplatin perfusion via HIPEC on patient-reported outcomes in a multicenter randomized trial.

METHODS

Trial Design

The study was approved by the Institutional Review Board and all participants provided written consent. The trial was registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (identifier: [NCT01580410](https://clinicaltrials.gov/ct2/show/study?term=NCT01580410)), and an investigational drug approval was obtained for oxaliplatin (NCI-2009-00947). The details of the trial design have been published previously.¹² Briefly, this study was a multicenter, open-label, randomized clinical trial that was carried out with the primary objective of comparing the toxicity profiles of oxaliplatin and mitomycin delivered via HIPEC in patients with peritoneal surface malignancies from primary appendiceal tumors. The secondary objective of this study was to compare the quality of life, complications,

survival, and time to progression of disease. Eligible patients had a histologic confirmation of peritoneal surface malignancies from primary appendiceal tumors, and were at least 18 years of age with no history of prior HIPEC, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , and with adequate organ and marrow function who have recovered from both the acute and late effects of any prior surgery, radiotherapy, or other antineoplastic therapy. We excluded patients with carcinoid histology, extra-abdominal disease, known hypersensitivity to any of the components of oxaliplatin or mitomycin, active infection, previous radiation, investigational therapy, pregnancy, peripheral neuropathy Grade 2 or higher, and HIV, hepatitis or tuberculosis infection. Patients with a history of prior malignancy within the past 5 years were also excluded from the study (except for curatively treated basal cell carcinoma of the skin, cervical intraepithelial neoplasia, or localized prostate cancer with a current PSA of < 1.0 mg/dL on two successive evaluations, at least 3 months apart, with the most recent evaluation no more than 4 weeks prior to entry).

Patients were randomly assigned to treatment with either mitomycin or oxaliplatin upon registration. They received a mechanical and antibiotic bowel preparation, and CRS/HIPEC was performed using a closed technique, as previously described in detail.¹² A complete cytoreduction was attempted before HIPEC. Intraperitoneal catheters were placed and the perfusion circuit was established as per standard institutional practice. The chemotherapy agent was added to the perfusate once outflow temperatures exceed 39°C . In the oxaliplatin group, the drug was administered at a dose of 200 mg/m^2 , and, in the mitomycin arm, 30 mg of the drug was perfused with an additional 10 mg after 60 min . The target outflow temperature was 40°C and the maximum tolerated inflow temperature during the perfusion was 42.5°C , with a total perfusion time of 120 min .

Health-Related Quality of Life Measurement

To evaluate HRQOL, the FACT/GOG-NTX questionnaire was utilized. This validated instrument is composed of the general version of the Functional Assessment of Cancer Therapy (FACT-G), a 27-item self-report questionnaire that measures QOL in cancer patients, plus the Neurotoxicity (NTX) subscale, an 11-item subscale that is designed to evaluate symptoms associated with chemotherapy-induced neuropathy.^{13,14} FACT-G is comprised of four separate subscales: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). The Trial Outcome Index (TOI) representing $\text{PWB} + \text{FWB} + \text{NTX}$ was used as a measure of treatment impact on physical symptoms and functional outcomes. The FACT-G provides subscale scores and a total QOL score. A higher FACT-G score indicates a better QOL.

The questionnaire was either self-administered or completed in an interview format. Patients were asked to rate themselves on how they felt that day, and over the past 7 days, on a Likert scale from 0 (not at all) to 4 (very much). It was completed at baseline and on follow-up visits at 3, 6, 12, 18, 24, 30, and 36 months.

Score differences were considered clinically significant and meaningful when a minimally important difference (MID) was achieved.¹⁵ The MID was 8 for FACT-G, 5 for TOI, and 2 for subscales, including PWB, FWB, SWB, EWB and NTX.¹⁶

Statistical Analysis

Means and standard error of the mean, ranges for continuous measures, and frequencies and proportions for categorical variables were calculated for descriptive analysis of the quality-of-life measures, including FACT-G, its subscales, and TOI. Mixed models for repeated measures (MMRM) with an unstructured variance matrix were applied to assess longitudinal changes in HRQOL measures (FACT-G, TOI, NTX, FACT-G subscales, and individual measures of each subscale). For each follow-up visit, least squares mean differences were compared between the treatment arms, with the differences evaluated via a pair-wise comparison. Least square mean estimates from MMRM models were also used for post hoc analysis of changes from baseline or between different follow-up visits within each treatment group, as well as the whole cohort. Overall survival was calculated as the interval between surgery and the date of death or last contact; survival estimates were created using the Kaplan-Meier method. Log-rank tests were used to test for group differences in unadjusted survival models, while Cox proportional hazards regression modeling was used in models with adjustments for patient demographics and clinicopathological features and quality-of-life measures in univariate and multivariable regression analysis. *p* values < 0.05 were considered to be statistically significant. SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used for analyses.

RESULTS

Patient Population

From July 2009 to October 2015, 121 patients were enrolled and randomized in three different institutions (Wake Forest University [WFU], University of Pittsburgh Medical Center [UPMC] and MD Anderson Cancer Center [MDACC]). Patients were randomized intraoperatively to HIPEC perfusion with oxaliplatin or mitomycin. Ninety-eight patients (81%) were accrued at WFU, 13 (10.7%) patients were accrued at MDACC, and 10 (8.3%) patients were accrued at UPMC. Mean age at diagnosis was 54.1 ± 13.0 years (range 22.0–81.8) and 69/121 (57%) patients were female. Patients had predominantly low-grade appendiceal tumors (82/121, 68%). Administration of preoperative chemotherapy was not significantly different between the two arms, with 20% of patients in the oxaliplatin group receiving preoperative chemotherapy compared with 10% of patients in the mitomycin group (*p* = 0.26). Patient demographics, clinicopathologic features, and outcomes were balanced across both treatment groups (electronic supplementary Table 1).

Among the 121 patients enrolled in the trial, 116 patients completed one or more questionnaires (Fig. 1). There were no significant differences in the baseline quality-of-life measures between the two arms (Fig. 3).

Compliance

The completion rate of one or more questionnaires in the cohort was 95.9% (116/121), while the average response rate at various time points was similar in both groups, with 76.2% (60–98%) compliance in the mitomycin group and 80.5% (68–93%) compliance in the oxaliplatin group (Fig. 1).

Quality of Life and Survival

To investigate any association between baseline quality of life and overall survival, we performed a univariate analysis of various quality-of-life measures and subscales and overall survival as the clinical outcome (Table 1). There was no association between baseline FACT-G and TOI with overall survival. Among the subscales, PWB was associated with overall survival (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.75–97; $p = 0.013$), indicating higher PWB had increased survival. This association was independent of clinicopathologic characteristics of patients in multivariable analysis (per 1 unit: HR 0.79, 95% CI 0.66–0.96; $p = 0.017$). Other factors independently associated with improved overall survival include tumor histologic grade (low), resection status (R0/1), and age (Table 2). Survival rate was similar in both arms (electronic supplementary Fig. 1), and there was no association between perfusion agent and overall survival (electronic supplementary Table 1, and Table 2).

Impact of Hyperthermic Intraperitoneal Chemotherapy on Quality of Life

Figure 2 illustrates changes in quality-of-life measures (FACT-G, TOI, PWB, FWB, EWB, SWB, and NTX). FACT-G decreases at 12 weeks and increases back to baseline afterwards. This decrease is statistically significant ($p = 0.030$), but not clinically significant (score decline < 8 points) (Fig. 2a). TOI also decreased at 12 weeks and increased back to baseline afterwards (Fig. 2b). The decline in TOI was both statistically ($p = 0.002$) and clinically significant (TOI score decline 5.36). Among the components of TOI, PWB (Fig. 2c) and FWB (Fig. 2d) declined at 12 weeks and increased back to baseline afterwards at a statistically and clinically significant level ($p = 0.001$, and score declined by 2.03 for PWB; $p = 0.003$, and score declined by 2.27 for FWB). The changes in NTX were neither statistically nor clinically significant (Fig. 2e). To evaluate the social aspects, we assessed SWB subscale, and no significant changes from baseline were observed after HIPEC (Fig. 2f). However, EWB steadily improved during the first year after HIPEC (Fig. 2g). Compared with baseline, this was statistically significant at 12 and 24 weeks and reached a clinical significance at 1 year ($p < 0.001$; EWB score increased by 2.10).

Impact of Perfusion Chemotherapy Agent on Quality of Life

We compared the impact of HIPEC perfusion agents (oxaliplatin vs. mitomycin) on various quality-of-life measures (Fig. 3). At 12 weeks after surgery, FACT-G had a more significant decline, in the mitomycin group compared with the oxaliplatin group, with a trend toward statistical significance ($p = 0.050$), but the MID was not met. There was a significant difference between the arms in TOI scores (Fig. 3b). TOI was significantly lower in the mitomycin group at 12 and 24 weeks ($p = 0.044$ and 0.049 , respectively) after surgery. At both time points, the differences were more significant than MID, and also reached clinical significance (TOI score differences were 6.35 at 12 weeks, and 5.61 at 24 weeks). Moreover, the decline from baseline was statistically significant, and MID was achieved in the mitomycin group (score decline 8.99; $p = 0.004$), while there was no significant decline in TOI in the oxaliplatin group at 12 weeks.

Differences in PWB and FWB drove between-the-arms differences in TOI. At 12 weeks after surgery, PWB was significantly lower in the mitomycin group ($p = 0.025$; score decline

2.58) (Fig. 3c). Similar differences were observed in FWB at 12 weeks ($p = 0.049$; score decline 2.63), but also extended to 24 weeks after surgery ($p = 0.023$; score decline 2.76) [Fig. 3d]. NTX was not significantly different between the two study arms (Fig. 3e). At 12 weeks, PWB had a statistically and clinically significant decline from baseline in the mitomycin group ($p < 0.001$; score decline 2.83), while changes from baseline were not significant in the oxaliplatin group. Similar declines were observed in FWB and NTX at 12 weeks after surgery ($p < 0.001$ and score decline 3.42 for FWB; $p = 0.003$ and score decline 2.87 for NTX) in the mitomycin group, while changes were not significant in the oxaliplatin group.

SWB changes were similar and non-significant in both arms (Fig. 3f). There was no significant difference in EWB between the oxaliplatin and mitomycin groups (Fig. 3g).

Symptoms Driving Differences in Physical and Functional Aspects of Quality of Life

Individual measures that were responsible for differences in physical and functional aspects of quality of life (PWB and FWB) are shown in Fig. 4. Lack of energy was significantly higher in the mitomycin group compared with the oxaliplatin arm ($p = 0.034$) [Fig. 4a], and was also significantly higher from baseline in the mitomycin group ($p = 0.007$). There was a trend toward statistical significance in the oxaliplatin group ($p = 0.053$). Patients in the mitomycin group reported higher pain score compared with the oxaliplatin group at postoperative week 12 ($p = 0.007$) [Fig. 4b]. Differences from baseline at 12 weeks after surgery were significant in the mitomycin group ($p < 0.001$), but not the oxaliplatin group ($p = 0.24$). Patients' ability to work were reported to be significantly lower in the mitomycin group at 12 and 24 weeks ($p = 0.006$ and 0.022 , respectively) after surgery (Fig. 4c). Compared with baseline, patients' reported ability to work was significantly lower at 12 weeks after surgery ($p < 0.001$) in the mitomycin group, while differences were not significant in the oxaliplatin group ($p = 0.32$). Feeling weak all over was another symptom reported to be significantly higher in the mitomycin arm at 12 and 24 weeks after surgery ($p = 0.040$ and 0.003 , respectively) [Fig. 4d]. Compared with baseline, weakness significantly increased in the mitomycin group 12 weeks after surgery ($p = 0.020$), while changes were not significant from baseline in the oxaliplatin group ($p = 0.23$).

DISCUSSION

CRS/HIPEC is a substantial operation with the significant possibility of both extending life and impacting the quality of life. We have previously reported the prognostic value of preoperative HRQOL measures in a retrospective analysis.¹⁷ In this randomized, prospective study, we show baseline patient-reported PWB is a prognostic factor independent from established clinicopathologic characteristics. This finding emphasizes the significance of careful patient selection and special attention to physical status and functional capacity as a critical consideration to improve outcomes and maximize the potential benefits of CRS/HIPEC.

Consistent with previous reports, we demonstrate that, in the whole cohort, physical and functional aspects of quality of life (TOI) decline in the early postoperative phase but recover back to baseline afterwards.¹⁸ The overall decline in quality of life was not clinically

significant, in part due to a steady improvement of emotional well-being that offsets the impact of the decline in PWB and FWB on global quality of life. We have previously reported that emotional well-being improves with CRS/HIPEC,⁴ corroborating with other published studies demonstrating postoperative improvement of emotional well-being (either steadily or after a brief decline in the immediate postoperative period).¹⁹ This outcome might be a result of optimism developed after CRS and HIPEC that refines patients' perspective towards what is otherwise perceived as a 'terminal disease'.

The results of comparative analysis of the impact of HIPEC perfusion with oxaliplatin versus mitomycin on various aspects of quality of life are the key findings of this study. Our results demonstrate that physical and functional outcomes are worse with mitomycin, compared with oxaliplatin 3 and 6 months after surgery. The differences are diminished and clinically insignificant 1 year after surgery. TOI represents a measure of treatment impact on physical/functional status. Among the components of TOI, PWB and FWB were the drivers of these differences, while neurotoxicity scores were similar between the two groups. One surprising finding was the change observed during postoperative follow-up, as opposed to baseline. In the mitomycin group, the decline from baseline was significant, while such decline was not observed in the oxaliplatin group. These results show that physical and functional aspects of quality of life are better maintained with oxaliplatin after CRS/HIPEC. Social and emotional aspects of quality of life were similar in both treatment arms. While there was a trend toward statistical significance, there were no clinically meaningful differences in overall quality of life (FACT-G) between the two arms, which is again driven by the dilutional impact of similar SWB and EWB scores.

Many clinical trials with HRQOL as an endpoint have not reported their findings based on MIDs, notwithstanding that MIDs have been determined for various HRQOL instruments.¹⁶ Putting statistical findings in a clinical context is crucial. The between-group differences we observed in this study are both statistically significant and clinically meaningful based on validated tools.

To better understand the differences in physical/functional outcomes, we looked into the reported symptoms. Patients in the mitomycin group reported a significantly higher pain, more noticeable lack of energy, and generalized weakness. Their ability to work was also significantly lower than patients in the oxaliplatin arm. When compared with baseline, the postoperative changes were significant in the mitomycin arm only. Overall, patients in the oxaliplatin arm recovered better from the procedure, with no significant impact on their functional/physical status. On the other hand, patients in the mitomycin group had significantly worse physical/functional outcomes and also a significant drop from their baseline preoperative state. Thus, HIPEC perfusion with oxaliplatin has superior physical/functional outcomes compared with mitomycin.

The low incidence of appendiceal cancer and the clinical challenges of CRS and HIPEC have impacted efforts to design and complete randomized clinical trials. This is the first completed randomized clinical trial for appendiceal cancer, and the first HIPEC trial completed in the Western hemisphere. The purpose of this trial was to identify the better agent for intraperitoneal chemoperfusion. Previously published retrospective studies have

reported inconsistent results comparing the efficacy of mitomycin versus oxaliplatin for HIPEC perfusion. One study reported a survival benefit for HIPEC perfusion with oxaliplatin in colorectal cancer patients.²⁰ In contrast, a report from the American Society of Peritoneal Surface Malignancies suggested that mitomycin might be a superior chemoperfusion agent for a subset of colorectal cancer patients with favorable histologies and low disease burden.²¹ Other studies, including a report from our group, showed no survival benefit for either agent.^{22–25} Complication profiles of the two drugs have also been compared retrospectively. Most of the studies have reported similar morbidity and complication rates,^{20,23,24} while one small study ($N = 21$) reported higher complication rates with oxaliplatin (460 mg/m^2 for 30 min). In addition to small sample size, we believe the utilized protocol is suboptimal (high dose and short perfusion time).

In the randomized prospective setting, we report no significant differences in survival or complication rates between oxaliplatin and mitomycin. With similar oncologic outcomes, HRQOL measures become crucial in the assessment of clinical benefits in cancer trials.²⁷ With superior physical/functional outcomes, our data suggest that oxaliplatin (200 mg/m^2 for 120 min) should be the chemoperfusion agent of choice for CRS/HIPEC in patients with mucinous appendiceal cancer.

CONCLUSIONS

This is the first randomized, prospective, patient-reported outcome data study in patients with mucinous appendiceal cancer who underwent CRS/HIPEC. The results demonstrate that HIPEC perfusion with oxaliplatin has better physical/functional outcomes in the early postoperative period compared with mitomycin. We also showed that baseline PWB is an independent prognostic factor and should be considered in patient selection to achieve optimal clinical outcomes. Our findings demonstrate that, while emotional well-being steadily improves, HIPEC causes a deterioration in the physical and functional aspects of quality of life in the early postoperative phase, then recovers to baseline. However, this observed decline was only statistically and clinically significant with mitomycin, not oxaliplatin. With similar oncologic outcomes and better quality of life, oxaliplatin should be considered as the chemoperfusion agent of choice for appendiceal mucinous carcinoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Votanopoulos KI, Russell G, Randle RW, Shen P, Stewart JH, Levine EA. Peritoneal surface disease (PSD) from appendiceal cancer treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC): overview of 481 cases. *Ann Surg Oncol*. 2015;22(4):1274–9. [PubMed: 25319583]
2. Mogal HD, Levine EA, Russell G, Shen P, Stewart JH, Votanopoulos KI. Conditional survival after cytoreductive surgery with heated intraperitoneal chemotherapy for low- and high-grade appendiceal primaries. *Ann Surg Oncol*. 2016;23(2):534–8. [PubMed: 26289808]
3. Wagner PL, Austin F, Maduekwe U, et al. Extensive cytoreductive surgery for appendiceal carcinomatosis: morbidity, mortality, and survival. *Ann Surg Oncol*. 2013;20(4):1056–62. [PubMed: 23456385]
4. Dodson RM, McQuellon RP, Mogal HD, et al. Quality-of-life evaluation after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol*. 2016;23(Suppl 5):772–83. [PubMed: 27638671]
5. Langenhoff BS, Krabbe PF, Wobbes T, Ruers TJ. Quality of life as an outcome measure in surgical oncology. *Br J Surg*. 2001;88(5):643–52. [PubMed: 11350434]
6. Au HJ, Ringash J, Brundage M, et al. Added value of health-related quality of life measurement in cancer clinical trials: the experience of the NCIC CTG. *Exp Rev Pharmacoecon Outcomes Res*. 2010;10(2):119–28.
7. Quinten C, Coens C, Mauer M, et al. Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials. *Lancet Oncol*. 2009;10(9):865–71. [PubMed: 19695956]
8. Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. American Society of Clinical Oncology. *J Clin Oncol*. 1996;14(2):671–9. [PubMed: 8636786]
9. Osoba D Health-related quality of life and cancer clinical trials. *Ther Adv Med Oncol*. 2011;3(2):57–71. [PubMed: 21789156]
10. Bascoul-Mollevi C, Gourgou S, Galais MP, et al. Health-related quality of life results from the PRODIGE 5/ACCORD 17 randomised trial of FOLFOX versus fluorouracil-cisplatin regimen in oesophageal cancer. *Eur J Cancer*. 2017;84:239–49. [PubMed: 28829992]
11. Gotay CC, Kawamoto CT, Bottomley A, Efficace F. The prognostic significance of patient-reported outcomes in cancer clinical trials. *J Clin Oncol*. 2008;26(8):1355–63. [PubMed: 18227528]
12. Levine EA, Votanopoulos KI, Shen P, et al. A multicenter randomized trial to evaluate hematologic toxicities after hyperthermic intraperitoneal chemotherapy with oxaliplatin or mitomycin in patients with appendiceal tumors. *J Am Coll Surg*. 2018;226(4):434–43. [PubMed: 29331663]
13. Calhoun EA, Welshman EE, Chang CH, et al. Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. *Int J Gynecol Cancer*. 2003;13(6):741–8. [PubMed: 14675309]
14. Huang HQ, Brady MF, Cella D, Fleming G. Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study. *Int J Gynecol Cancer*. 2007;17(2):387–93. [PubMed: 17362317]
15. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials*. 1989;10(4):407–15. [PubMed: 2691207]
16. Trask PC, Hsu MA, McQuellon R. Other paradigms: health-related quality of life as a measure in cancer treatment: its importance and relevance. *Cancer J*. 2009;15(5):435–40. [PubMed: 19826365]
17. Ihemelandu CU, McQuellon R, Shen P, Stewart JH, Votanopoulos K, Levine EA. Predicting postoperative morbidity following cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CS + HIPEC) with preoperative FACT-C (Functional Assessment of Cancer Therapy) and patient-rated performance status. *Ann Surg Oncol*. 2013;20(11):3519–26. [PubMed: 23748607]

18. Seretis C, Youssef H. Quality of life after cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies: a systematic review. *Eur J Surg Oncol.* 2014;40(12):1605–13. [PubMed: 25242382]
19. Shan LL, Saxena A, Shan BL, Morris DL. Quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: a systematic review and meta-analysis. *Surg Oncol.* 2014;23(4):199–210. [PubMed: 25466850]
20. Leung V, Huo YR, Liauw W, Morris DL. Oxaliplatin versus Mitomycin C for HIPEC in colorectal cancer peritoneal carcinomatosis. *Eur J Surg Oncol.* 2017;43(1):144–9. [PubMed: 27780675]
21. Prada-Villaverde A, Esquivel J, Lowy AM, et al. The American Society of Peritoneal Surface Malignancies evaluation of HIPEC with Mitomycin C versus Oxaliplatin in 539 patients with colon cancer undergoing a complete cytoreductive surgery. *J Surg Oncol.* 2014;110(7):779–85. [PubMed: 25088304]
22. Glockzin G, von Breitenbuch P, Schlitt HJ, Piso P. Treatment-related morbidity and toxicity of CRS and oxaliplatin-based HIPEC compared to a mitomycin and doxorubicin-based HIPEC protocol in patients with peritoneal carcinomatosis: a matched-pair analysis. *J Surg Oncol.* 2013;107(6):574–8. [PubMed: 22833286]
23. Hompes D, D’Hoore A, Wolthuis A, et al. The use of Oxaliplatin or Mitomycin C in HIPEC treatment for peritoneal carcinomatosis from colorectal cancer: a comparative study. *J Surg Oncol.* 2014;109(6):527–32. [PubMed: 24375059]
24. van Eden WJ, Kok NFM, Woensdregt K, Huitema ADR, Boot H, Aalbers AGJ. Safety of intraperitoneal Mitomycin C versus intraperitoneal oxaliplatin in patients with peritoneal carcinomatosis of colorectal cancer undergoing cytoreductive surgery and HIPEC. *Eur J Surg Oncol.* 2018;44(2):220–7. [PubMed: 29258720]
25. Votanopoulos K, Ihemelandu C, Shen P, Stewart J, Russell G, Levine EA. A comparison of hematologic toxicity profiles after heated intraperitoneal chemotherapy with oxaliplatin and mitomycin C. *J Surg Res.* 2013;179(1):e133–9. [PubMed: 22480844]
26. Rouers A, Laurent S, Detroz B, Meurisse M. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis: higher complication rate for oxaliplatin compared to Mitomycin C. *Acta Chir Belg.* 2006;106(3):302–6. [PubMed: 16910003]
27. Bonnetain F, Fiteni F, Efficace F, Anota A. Statistical challenges in the analysis of health-related quality of life in cancer clinical trials. *J Clin Oncol.* 2016;34(16):1953–6. [PubMed: 27091712]

FIG. 1.
CONSORT diagram

FIG. 2.

Longitudinal changes in adjusted least squares mean for the FACT/GOG-NTX questionnaire in the whole cohort. **a** FACT-G; **b** TOI; **c** PWB; **d** FWB; **e** NTX; **f** SWB; **g** EWB. *p* values in the tables represent the level of significance in changes from baseline and changes from the previous visit. *FACT/COG-NTX* Functional Assessment of Cancer Therapy-Gynecologic Oncology Group Neurotoxicity scale, *TOI* Trial Outcome Index, *PWB* physical well-being, *FWB* functional well-being, *NTX* neurotoxicity, *SWB* social well-being, *EWB* emotional well-being

FIG. 3.

Longitudinal changes in adjusted least squares mean for the FACT/GOG-NTX questionnaire in both arms of the study, i.e. HIPEC perfusion with oxaliplatin, and HIPEC perfusion with mitomycin. **a** FACT-G; **b** TOI; **c** PWB; **d** FWB; **e** neurotox; **f** SWB; **g** EWB. *p* values in the tables represent the difference between the measures at each visit. *FACT/COG-NTX* Functional Assessment of Cancer Therapy-Gynecologic Oncology Group Neurotoxicity scale, *HIPEC* hyperthermic intraperitoneal chemotherapy, *MMC* mitomycin, *TOI* Trial Outcome Index, *PWB* physical well-being, *FWB* functional well-being, *NTX* neurotoxicity, *SWB* social well-being, *EWB* emotional well-being

FIG. 4.

Longitudinal changes in adjusted least squares mean for the individual items in the FACT/GOG-NTX questionnaire that were different between both arms of the study, i.e. HIPEC perfusion with oxaliplatin, and HIPEC perfusion with mitomycin. **a** Lack of energy; **b** pain; **c** ability to work; and **d** weakness. *p* values in the tables represent the difference between the measures at each visit. *FACT/GOG/NTX* Functional Assessment of Cancer Therapy-

Gynecologic Oncology Group Neurotoxicity scale, *HIPEC* hyperthermic intraperitoneal chemotherapy, *MMC* mitomycin

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TABLE 1

Association between FACT-G, its subscales, and overall survival in univariate analysis

	HR	95% CI	p value
FACT-G	0.94	0.83–1.18	NS
TOI	0.92	0.82–1.03	NS
PWB	0.85	0.75–0.97	0.013
SWB	0.98	0.82–1.18	NS
EWB	1.12	0.95–1.33	NS
FWB	0.95	0.85–1.06	NS
NTX	0.97	0.88–1.06	NS

HR hazard ratio, *CI* confidence interval, *TOI* Trial Outcome Index, *PWB* physical well-being, *SWB* social/family well-being, *EWB* emotional well-being, *FWB* functional well-being, *NTX* neurotoxicity, *NS* non-significant

TABLE 2

Multivariable analysis of clinical factors associated with overall survival

	HR	95% CI	p value
PWB (per 1 unit)	0.79	0.66–0.96	0.017
Race (non-White)	1.91	0.49–7.37	NS
Histologic grade (low)	0.21	0.09–0.50	< 0.001
Resection status (R0/1)	0.28	0.12–0.66	0.004
Sex (female)	0.44	0.17–1.14	NS
Perfusing agent (MMC)	0.65	0.28–1.48	NS
ECOG	0.69	0.35–1.34	NS
Age (per 1 year)	1.31	1.08–1.59	0.006

HR hazard ratio, *CI* confidence interval, *PWB* physical well-being, *MMC* mitomycin, *ECOG* Eastern Cooperative Oncology Group performance status, *NS* non-significant