Timing of severe toxicity from chemotherapy in patients with lung cancer

Running title: Timing of Toxicity from Chemotherapy in Lung Cancer

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Abstract

Background: The aim of this study was to investigate the timing of severe toxicity in lung cancer patients receiving chemotherapy.

Patients and Methods: Patients with advanced non-small cell lung cancer or limited disease small cell lung cancer included in two randomized controlled trials were analysed. Severe toxicity was defined as grade 3-5 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Results: We analysed 569 patients and 433 (76.1%) experienced severe toxicity. Of these, 249 (57.5%) experienced the first episode of severe toxicity after the first, 109 (25.2%) after the second, 54 (12.5%) after the third and 18 (4.2%) after the fourth course of chemotherapy. Performance status (PS 2 vs. 0-1; p=0.046) and treatment arm were independent predictive factors for severe toxicity.

Conclusion: Severe toxicity was most frequent after the first chemotherapy course, but some patients did not experience severe toxicity until after the fourth course. Accounting for timing might be important when studying factors predicting severe toxicity.

Severe toxicity is frequent among cancer patients who receive chemotherapy. Such toxicity causes discomfort and poor quality of life, might be life-threatening, while treatment of side-effects requires a lot of attention and resources from the health care services (1, 2).

There are several possible causes for severe toxicity. In some cases, it is caused by a very high initial dose, while toxicity occurring later may be due to exhaustion of an organ system, e.g. the bone marrow reserves (3). The different underlying reasons are not necessarily interrelated and may confound studies of risk factors, since few studies have accounted for which time point during chemotherapy severe toxicity occurs. We are only aware of one study of 4458 patients with solid tumours or lymphoma receiving four courses of chemotherapy (4). The occurrence of neutropenic fever was highest after the first course, but the study did not include information about the effect of dose-reductions or delays of subsequent courses. In addition, it provided limited data on types of toxicity and long-term outcomes and no data on predictive factors for early or late toxicity.

In this study, we aimed to investigate the timing of severe toxicity during the chemotherapy treatment period for lung cancer patients enrolled in two randomized controlled trials. We also examined whether there were differences in the type of severe toxicity at different timepoints, the associations between toxicity and baseline characteristics and associations with overall survival. Lung cancer patients have a relatively high age, a majority has significant comorbidity, and severe toxicity is common. Thus, we believe that these cohorts were suitable for this exploratory study.

Patients and Methods

Design and approvals

This study is an analysis of patients from two Norwegian randomized controlled trials (RCTs) on lung cancer patients. All patients gave written consent. Both RCTs and the present study were approved by the Regional Committee for Medical Research Ethics in Central Norway.

Patients and study treatment

The PEG trial was an open, randomized, multicentre phase III study comparing gemcitabine/carboplatin (GC) and pemetrexed/carboplatin (PC) as first-line chemotherapy in stage IIIB or IV non-small-cell lung cancer (NSCLC) (5). The study enrolled 436 patients with performance status 0-2 from April 2005 to July 2006. Patients were randomized to receive four courses of pemetrexed (500 mg/m^2) plus carboplatin (Area Under the Curve, AUC=5) on day 1 or gemcitabine (1000 mg/m^2) on day 1 and 8 and carboplatin (AUC=5) on day 1 every three weeks. There were no significant differences in health-related quality of life or overall survival, but patients on the gemcitabine-arm experienced more hematologic toxicity.

The HAST trial was an open, randomized, multicentre phase II trial comparing twice-daily thoracic radiotherapy (TRT) of 45 Gy with once-daily TRT of 42 Gy in limited disease small cell lung cancer (LD SCLC) (6). Between May 2005 and January 2011, 157 patients were enrolled. Patients were to receive four courses of cisplatin (75 mg/m^2) on day 1 and etoposide (100 mg/m^2) on day 1-3, every three weeks. There were no statistically significant differences in overall survival, but patients receiving twice-daily TRT had 6 months longer median overall survival. There were no significant differences in chemo- or radiotoxicity.

In the PEG trial, patients ≥75 years of age had a 25% dose reduction from the first chemotherapy course. In both studies, chemotherapy doses were to be reduced by 25% if haematological values on day 22 were as following: leucocytes 2.5-2.9 × 10^9/l or platelets 75-99 × 10^9/l (HAST); or absolute neutrophil count (ANC) 1.0-1.49 × 10^9/l or thrombocytes were 75-99 × 10^9/l (PEG). If the values were lower, the course was to be delayed until resolution followed by a 25% dose reduction. Furthermore, in the PEG trial, a 25% dose reduction was to be performed if nadir ANC was <0.5 × 10^9/l and platelets were ≥50 × 10^9/l, and a 50% reduction if platelets were ≤50 × 10^9/l.

In both studies dose reductions were maintained for all subsequent courses. Treatment was discontinued if a patient qualified for a third dose reduction, or if a course was postponed more than three weeks due to toxicity.

Inclusion criteria

Patients who received at least one chemotherapy course were eligible for the present study provided complete toxicity data were available.

Assessments

The Common Terminology Criteria for Adverse Effects (CTCAE) v3.0 was used for classification of toxicity in both studies (7). We defined severe toxicity as CTCAE grade 3-5, and excluded radiotoxicity (e.g. pneumonitis or esophagitis) in our analyses.

Statistical considerations

Toxicity data were compared using Pearson´s Chi-square test and logistic regression adjusting for baseline characteristics. Survival was defined as time from

randomization until death and was estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariable survival analyses were performed using the Cox proportional hazard method adjusting for baseline characteristics. The level of significance was defined as a two-sided $p<0.05$ and statistical analyses were performed using SPSS version 25 (IBM, New York, USA).

Results

Patients

All 157 patients enrolled in the HAST trial, and 412 of 436 patients (94.4%) from the PEG trial were included in the present study. Toxicity data were incomplete in three cases, and 21 patients did not complete the first course due to death (n=11), progressive disease (n=9), and deep venous thrombosis (n=1) (Figure 1).

Median age in our study cohort was 64 years, 15.3% were ≥75 years; 55.4% were men; 40.8% had stage III and 51.5% stage IV; 80.9% had PS 0-1; and 72.4% NSCLC (Table 1). Median follow up for survival was 90 months for HAST patients and 19 months for PEG patients.

Chemotherapy administered

Forty-eight (8.4%) patients received one course, 45 (7.9%) two courses, 48 (8.4%) three courses, and 428 (75.2%) four courses; 36.6% received pemetrexed/carboplatin (PC), 35.9% gemcitabine/carboplatin (GC), and 27.6% cisplatin/etoposide (PE). The mean number of courses was 3.5 for PC, 3.3 for GC and 3.8 for PE.

The total number of patients with any dose reduction after the first course was 213 (37.4%), and 142 (25.0%) patients had treatment delays. Grade 3-4 toxicity was

the most common cause for treatment delays and/or reductions (78.2%), while 14.9% were caused by grade 1-2 toxicity and 6.9% by other reasons, such as holidays.

Toxicity

In total, 433 (76.1%) experienced severe toxicity during treatment, 397 (69.8%) experienced hematologic and 176 (30.9%) non-haematological toxicity. Of the 433 patients with severe toxicity, 249 (43.8%) patients experienced grade 3-5 toxicity after the first, 237 (45.5%) after the second, 245 (51.5%) after the third, and 174 (40.7%) after the fourth course (Figure 2).

The most frequent severe haematological toxicities were neutropenia (52.7%), leukopenia (48.5%) and thrombocytopenia (37.8%) (Figure 3). Neutropenic infection (10.9%), infection without neutropenia (7.9%) and neutropenic fever (5.6%) were the most common non-haematological toxicities (Figure 3).

There were 62 deaths during the study treatment period, most commonly due to progressive disease (n=34), neutropenic infections (n=8), and infections without neutropenia (n=6). Thirty-one deaths occurred after the first course, eighteen after the second, six after the third, and seven after the fourth course.

Associations between baseline characteristics and severe toxicity

PE patients had the highest and PC patients the lowest risk of experiencing severe toxicity, both in the uni- (PE: 93.0%, GC: 85.2%, PC: 55.3%; p<0.01) and in the multivariable analysis (PE *vs.* PC; OR=9.9, 95% CI=4.5-21.7; p<0.01) (GC *vs.* PC; OR=4.7, 95% CI=2.9-7.5; p<0.01).

There was a trend towards a higher risk of severe toxicity among patients with poor PS in univariable analyses (PS 0-1: 75.1%, PS 2: 82.6%; p=0.096). In the

multivariable analyses, adjusting for baseline characteristics, poor PS was an independent predictive factor for toxicity (PS 2 *vs.* PS 0-1; OR=1.8, 95% CI=1.0-3.2; *p*=0.046). No other baseline characteristics were significantly associated with severe toxicity.

Timing of severe toxicity

Among patients experiencing severe toxicity, 249 (57.5%) first experienced severe toxicity after the first course, 109 (25.2%) after the second, 54 (12.5%) after the third, and 18 (4.2%) after the fourth course (Figure 4). Despite delays and/or dose reductions due to severe toxicity, approximately half of the patients also experienced severe toxicity after the subsequent course, and the proportions were similar independent of when they first experienced severe toxicity (51.0%, 56.0% and 42.6% respectively; *p*=0.65) (Figure 4).

Associations between baseline characteristics and timing of severe toxicity

Patients on the GC arm who experienced severe toxicity were more likely to experience their first severe toxicity after the first course (GC: 69.8% after the first course *vs.* 30.2% after course 2-4, PC: 48.7% *vs.* 51.3%, PE: 51.0% *vs.* 49.0%; *p*<0.010) (Table I).

Despite the initial dose-reduction in the PEG trial, patients at the age of ≥75 years had a higher risk of experiencing severe toxicity after the first course (≥75: 70.5%, <75: 55.8%; *p*=0.032), though this difference was not statistically significant in the multivariable analysis (≥75 *vs.* <75; OR=1.7, 95% CI=0.9–3.0; *p*=0.102). No other baseline characteristics were associated with the timing of severe toxicity.

Survival

At the time of analyses, 452 of the included patients (79.4%) were dead. Patients experiencing severe toxicity had longer median overall survival than others (14.7 *vs.* 11.3 months; *p*=0.011), mainly due to a large numerical difference among the HAST patients (23.6 *vs.* 12.8 months; *p*=0.193). Patients who first experienced severe toxicity after the second course or later had significantly longer median overall survival than those who experienced severe toxicity after the first course (16.4 *vs.* 9.6 months; *p*=0.003) (Figure 5). The difference was statistically significant for PEG patients (9.7 *vs.* 7.2 months; *p*=0.046), but not for HAST patients (24.7 *vs.* 20.4 months; *p*=0.302). However, the differences were not statistically significant in the multivariable analyses (severe toxicity *vs.* no severe toxicity; HR=0.92; *p*=0.552) (severe toxicity after the first course *vs.* later; HR=1.22; *p*=0.110).

Discussion

In this analysis of results from two randomized trials including lung cancer patients, we found that the majority (76%) of patients experienced severe toxicity from chemotherapy. Most of these patients (57.5%) first experienced toxicity after the first course, and despite dose-adjustments and delays, half of the patients also experienced severe toxicity after the subsequent course. Poor PS (PS 2) was the only independent predictive factor for severe toxicity during the treatment period, while chemotherapy regimen was the only predictor of when during the treatment period the first severe toxicity occurred; patients who received gemcitabine plus carboplatin experienced more toxicity after the first course than other patients. Interestingly, patients experiencing severe toxicity had a numerically longer median overall survival than other patients.

The rate of severe toxicity in this study was comparable to other studies of the platinum-doublets administered in our cohort (8-12), and also in another first-line study of pemetrexed-platinum, the gemcitabine-combination caused more severe toxicity (9). Furthermore, PS has also been identified as an independent predictive factor for severe toxicity in other studies (13).

All other studies investigating timing of chemotherapy toxicity also report that the first episode of severe toxicity most frequently occurred after the first course, though most studies only report haematological toxicity (4, 14-18). Only two studies investigated the frequency of severe toxicity after subsequent courses. In both of these studies, the proportion declined after the following course, and was within the same range as in our study; 46% in patients without dose-modification and 35% in patients with dose-modifications, although only 61 out of 200 patients were included in this analysis in the study by Extermann *et al.* (14). In contrast to our study, Culakova *et al.* reported that the frequency of severe toxicity declined for each course (4, 14). These studies are, however, not necessarily fully comparable due to major differences in types of cancer, treatment schedules, routines for dose modifications and classification of toxicity.

Whether both advanced NSCLC and LD SCLC patients should have been included can be debated, since treatment toxicity may be more acceptable for patients receiving potentially curative treatment. However, the results clearly indicate that the pattern of timing of toxicity varies for each chemotherapy regimen. The external validity of patients found eligible for randomized trials might be limited, since study cohorts in general are younger and more fit than many patients seen in the clinic (18, 19). On the other hand, the prospective data collection is a strength in our study, and this is one of a few studies reporting the timing of both haematological and

non-haematological toxicity. The variation in chemotherapy doses for elderly and dose adjustments are other potential limitations, though our experience and population-based studies suggest that there are also variations in clinical practice (20-22). Finally, growth factors were not recommended in Norway when the trials were conducted, and we have not adjusted for transfusion of red blood cells or platelets.

Chemotherapy-related toxicity is associated with considerable morbidity, mortality and costs for the health care system (2), and numerous studies of risk factors have been conducted. Old age, poor performance status (PS), advanced disease stage, severe comorbidity and low body skeletal muscle mass are some of the characteristics most commonly found to be associated with a higher risk of severe toxicity (13, 14, 23-26), and several models predicting chemotherapy toxicity have been suggested (15-18, 23). However, it remains unclear how these results should be implemented at the clinic. Many studies are retrospective analyses, often including participants with a wide range of patient and disease characteristics and none were designed to assess whether lowering the chemotherapy doses reduces the efficacy of the treatment. The latter is essential, since both ours and other studies indicate that patients experiencing severe chemotherapy toxicity live longer than those who do not (27, 28).

Most chemotherapy doses are calculated according to body surface area (BSA), which is estimated using the formula developed by Dubois and Dubois in 1916, based on a study of only nine subjects. This crude method does not account for differences in body composition and distribution or elimination of drugs. Several efforts have been made to develop better tools for individualizing chemotherapy

doses, but only calculation of carboplatin dose based on glomerular filtration rate (GFR) and estimated drug concentration over time (AUC) is routinely used.

Despite the introduction of targeted therapies and immunotherapy, cytotoxic chemotherapy remains an essential therapy for many cancer patients, including lung cancer patients. Thus, continued efforts aiming at individualizing chemotherapy doses in order to reduce toxicity while maintaining efficacy, are most welcome. We believe that our study shows that such efforts should include data showing on which point during a treatment period severe toxicity occurs, what kind of toxicity occurs at each timepoint, the impact of dose-reductions and delays, as well as the benefit of supportive measures. Furthermore, results of studies of some regimens are not necessarily valid for other chemotherapies.

In conclusion, we found that a large proportion of lung cancer patients experience severe treatment toxicity after the first chemotherapy course, but many patients also experience treatment toxicity for the first time after the second, third and fourth course. This pattern varied between the three chemotherapy regimens administered in our study cohort. Poor PS was the only predictor of overall severe toxicity, and there were no predictors of timing of severe toxicity. Patients who experienced severe toxicity had a longer overall survival than those who did not.

Conflicts of Interest

The Authors report no conflicts of interest.

Authors' Contributions

KS and KAJ were responsible for analysis and preparation of results for publication under supervision of TOH. BHG conceived and designed the analysis. KS, KAJ, BHG and TOH wrote the paper.

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Figure 1: 24 patients from the PEG trial were excluded from analyses

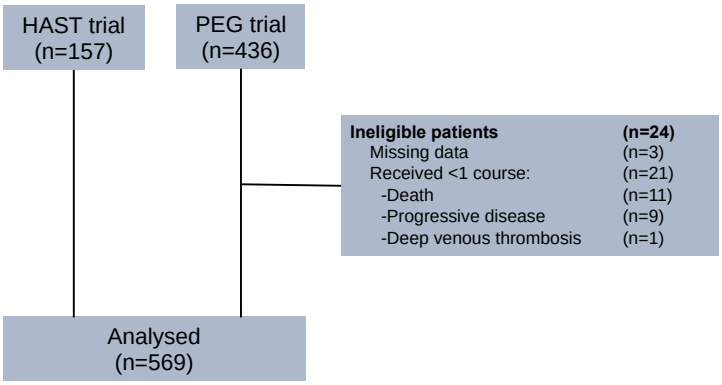


Table 1: Patient characteristics, timing of toxicity and treatment completion

		Total population n=569		First toxicity after 1st course n=249		First toxicity after 2nd—4th course n=181		No severe toxicity n=133		Received four courses n=428		Received ≤ three courses n=141		Dose reductions and/or delays of courses n=273	
Baseline characteristics		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Gender	Male	315	55.4	146	58.6	91	50.3	73	54.9	237	55.4	78	55.3	145	53.1
	Female	254	44.6	103	41.4	90	49.7	60	45.1	191	45.6	63	44.7	128	46.9
Age	≥75	87	15.3	43	17.3	18	9.9	26	19.5	64	14.9	23	16.3	35	12.8
	<75	482	84.7	206	82.7	163	90.1	107	80.5	364	85.1	118	83.7	238	87.2
	Median (range)	64 (25-90)		66 (37-84)		62 (25-85)		63 (37-90)		64 (25-85)		64 (35-90)		64 (40-85)	
Stage	1	13	2.3	6	2.4	5	2.8	2	1.5	12	2.8	1	0.7	10	3.7
	2	16	2.8	5	2.0	10	5.5	1	0.7	14	3.3	2	1.4	11	4.0
	3	232	40.8	109	43.8	80	44.2	41	30.8	188	43.9	44	31.2	132	48.4
	4	293	51.5	125	50.2	77	42.5	88	66.3	200	46.7	93	66.0	109	39.9
	Unknown	15	2.6	4	1.6	9	5.0	1	0.7	14	3.3	1	0.7	11	4.0
PS	0	141	24.8	59	23.7	44	24.3	36	27.1	115	26.9	26	18.4	68	24.9
	1	319	56.1	131	52.6	107	59.1	78	58.6	246	57.5	73	51.8	156	57.1
	2	109	19.1	59	23.7	30	16.6	19	14.3	67	15.6	42	29.8	49	18.0
Histology	Squamous	100	17.5	44	17.7	27	14.9	29	21.8	73	17.1	27	19.1	38	13.9
	Adeno	203	35.7	80	32.1	60	33.2	61	45.9	140	32.7	63	44.7	79	28.9
	Other NSCLC	109	19.2	51	20.5	23	12.7	32	24.0	79	18.4	30	21.3	39	14.3
	SCLC	157	27.6	74	29.7	71	39.2	11	8.3	136	31.8	21	14.9	117	42.9
Treatment	Pemetrexed Carboplatin	208	36.6	55	22.1	58	32.0	92	69.2	157	36.7	51	36.2	60	22.0
	Gemcitabine Carboplatin	204	35.8	120	48.2	52	28.8	30	22.5	135	31.5	69	48.9	96	35.2
	Cisplatin Etoposide	157	27.6	74	29.7	71	39.2	11	8.3	136	31.8	21	14.9	117	42.8

Figure 2: Incidence of severe toxicity after each course split for treatment arm

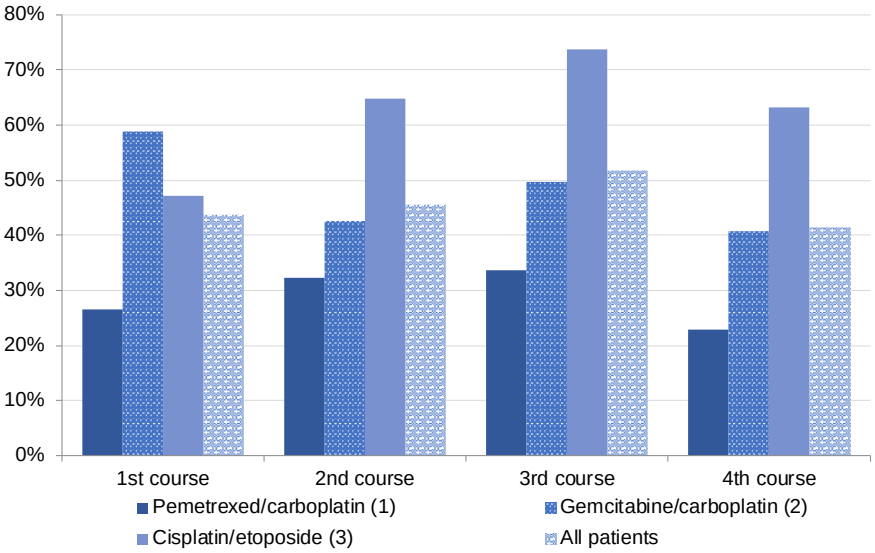


Figure 3: Types of severe toxicities after each chemotherapy course

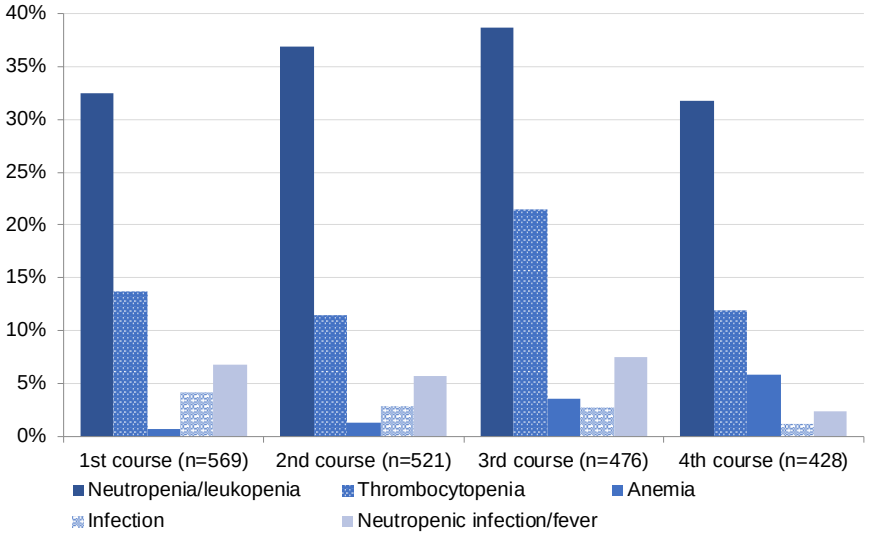
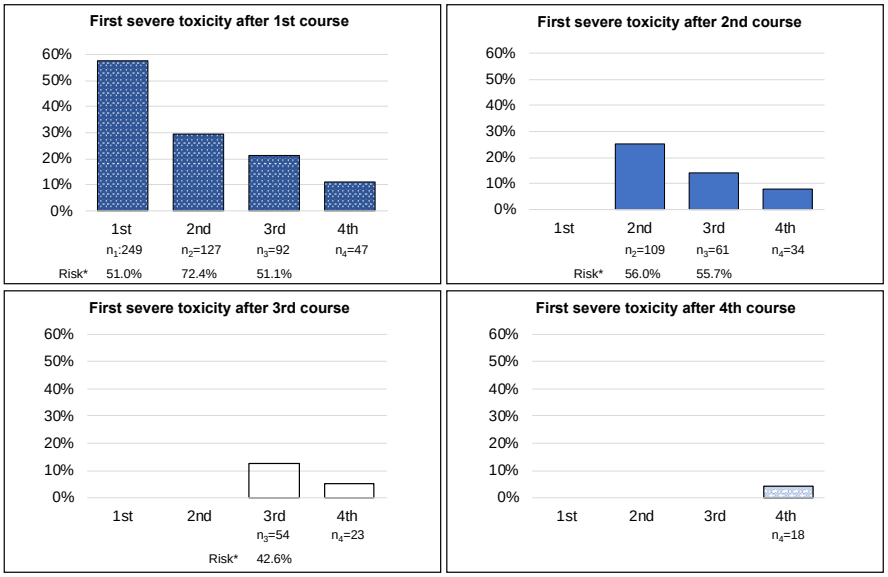


Figure 4: Severe toxicity after subsequent courses – split for when the first severe toxicity occurred



* Proportion with severe toxicity also after subsequent course (n_{+1}/n)

Figure 5: Overall survival

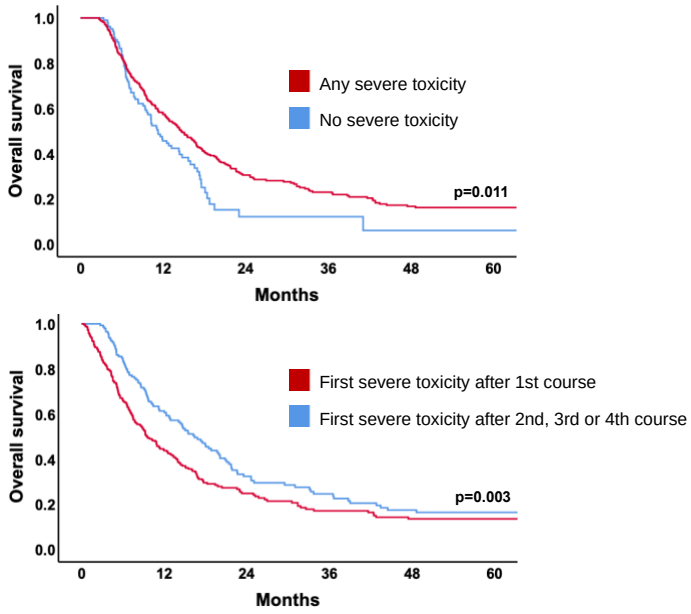


Figure legends

Figure 1: 24 patients from the PEG trial were excluded from analyses

Figure 2: Proportion of patients with severe toxicity after each course split for treatment arm

Figure 3: Types of severe toxicities after each chemotherapy course with respective frequencies

Figure 4: Proportion of patients with repeated severe toxicity after subsequent courses – split for when the first severe toxicity occurred

Figure 5: Overall survival compared using Kaplan-Meier method and logrank test