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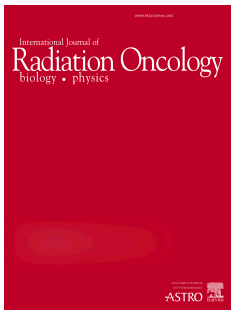

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Title

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Short title

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Conflict of interest statement

Nil

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Tolerability Of Concurrent Chemoradiotherapy With Gemcitabine (GemX), with and without prior Neoadjuvant Chemotherapy In Muscle Invasive Bladder Cancer

Summary

Chemoradiotherapy for muscle invasive bladder cancer is an accepted alternative radical treatment approach to cystectomy. This study reports tolerability and toxicity including patient reported outcomes for patients treated with hypofractionated radiotherapy and gemcitabine in this setting, comparing these outcomes in those receiving neoadjuvant chemotherapy prior to definitive treatment to those who underwent chemoradiotherapy alone. We demonstrated no increased toxicity or decline in treatment completion with the combination of chemoradiotherapy with neoadjuvant chemotherapy.

ABSTRACT

Purpose: The aim of this study is to assess the tolerability of concurrent chemoradiotherapy with gemcitabine (*GemX*) in muscle invasive bladder cancer (MIBC) following neoadjuvant chemotherapy (*neoGemX*) using patient and provider reported outcomes.

Materials and Methods:

Seventy eight patients were treated with *GemX*. Thirty-eight received prior neoadjuvant chemotherapy (NAC). Patients were prospectively assessed during treatment and at 6 weeks and 12 months post treatment completion. Radiotherapy was given to a total dose of 52.5 Gy in 20 fractions with weekly concurrent gemcitabine chemotherapy 100mg/m^2. Toxicity was assessed by care provider and using a patient reported outcome questionnaire collecting Lent Soma (LS) scores and statistically compared at baseline and 12 months and between the *neoGemX* and *GemX* groups.

Results

Median duration of follow up was 15.9 months. Radiotherapy completion rate was 95% and 96% of patients completed at least 3 cycles of gemcitabine. Bowel toxicity ≥ grade 3 was reported in 7/38 (18%) of patients in the *neoGemX* group and 5/25 (20%) in the *GemX* group. Three *GemX* and 2 *neoGemX* patients had grade ≥3 urinary toxicity.

Forty nine patients completed questionnaires and were included in the analysis. LS scores showed an expected peak by week 4 of treatment. There was no statistically significant difference between mean scores at baseline and 12 months post treatment completion, or between the *neoGemx* and *Gemx* groups.

Conclusion

This study demonstrates that *GemX*, alone or following NAC, has manageable toxicity and acceptable treatment completion rates. Allowing for small patient numbers and the non randomised nature of this study, these results do not suggest any additional toxicity from the use of NAC prior to *GemX*.

Introduction

Bladder cancer has an incidence of over 10,000 new cases per year in the UK, with nearly 25% of cases being classified as MIBC (1). Over 90% of these are histologically transitional cell carcinoma (TCC). Traditionally the gold standard of treatment for these patients has been with radical cystectomy. Bladder preservation with transurethral resection of bladder tumour (TURBT) followed by radical radiotherapy with a radiosensitiser, with salvage cystectomy in cases of recurrent disease, has become accepted in clinical practice as an alternative strategy. Recent guidance published in the UK now suggests that all patients fit for radical treatment should be offered both cystectomy and bladder preservation as equivalent options (2). There is no randomised controlled trial (RCT) data comparing these two strategies, but outcomes appear to be similar, with 5 year overall survival rates ranging from 30-60% (3-5). There is now a strong evidence base for use of platinum containing NAC in addition to definitive treatment (6,7). Radiosensitisation strategies using a variety of concurrent chemotherapy regimes or an alternative using carbogen and nicotinamide (CON) (8-24) have also demonstrated favourable outcomes. Weekly gemcitabine and moderately hypofractionated radiotherapy (*GemX*) has previously been studied in a phase II trial and demonstrated good rates of local control and tolerability (25).

The majority of patients in the pivotal trials confirming the superiority of radiosensitisation did not receive NAC prior to their definitive treatment (8,9,25). Despite this, NAC has become accepted in UK clinical practice as a standard treatment option for patients treated with bladder preservation strategies.

The aim of this prospective cohort study is to compare both provider reported toxicity and patient reported toxicity in patients receiving NAC followed by *GemX* and *GemX* alone.

Methods

Patients

All patients undergoing *GemX* between May 2010 and August 2013, treated at a single cancer centre, were eligible for the study. Patients had MIBC confirmed with TURBT and were staged (American Joint Committee on Cancer 2010) using cross sectional imaging of

thorax, abdomen and pelvis. Patients undergoing pelvic nodal irradiation and patients who were planned to receive radiotherapy alone, were excluded. Patients were selected for NAC by their performance status, comorbidities and renal function.

The study was approved by the appropriate local research committee and patients provided informed written consent for treatment as per standard practice.

Treatment: Radiotherapy was given to a total dose of 52.5 Gy in 20 fractions within 28 days with 4 cycles of weekly concurrent gemcitabine chemotherapy 100mg/m^2 given one hour before radiotherapy on days 1, 8, 15, and 22. Radiotherapy was planned using a three dimensional conformal technique, with a clinical target volume including the whole empty bladder expanded with a 1.5cm margin in all directions to form a planning target volume. NAC using a platinum doublet regime was given at physician discretion after assessment of isotope glomerular filtration rate (GFR).

Assessment of Toxicity

Toxicity was assessed at baseline, weekly during radiotherapy and at 6 weeks and 12 months post completion of treatment. Provider reported toxicity was prospectively assessed using the Radiation Therapy Oncology Group (RTOG) acute and late toxicity criteria Assessment was performed by a nurse clinician or physician before and during chemoradiotherapy and at 12 months post completion of treatment and via telephone with a nurse clinician or research nurse at 6 weeks following completion of treatment. Patients underwent 3-6 monthly cystoscopic follow up as per local policy. All cases wherein patients experienced grade 3 acute or late bowel toxicity were retrospectively reviewed to determine if any predisposing risk factors could be identified in the RT plan, on treatment imaging or pre-existing comorbidities.

Patient reported toxicity outcomes were collected using a previously validated late effects in normal tissues subjective, objective, management, and analytic scales (LENT/SOMA; subjective part) pelvic radiotherapy questionnaire. Separate male and female questionnaires were used covering domains of bowel, urinary and sexual function. Toxicity was scored from 0=no toxicity to 4= maximum level of toxicity where a score of ≥2 is considered to represent clinically significant toxicity. Questionnaires were delivered to patients at the time of attendance for radiotherapy during treatment and subsequently by post.

Statistical analysis

Male and female questionnaires were analysed separately. Mean total scores for each domain of the LS questionnaire were calculated. Patients who had not completed a questionnaire at baseline and at least one other time point were excluded from the analysis.

Wilcoxon signed rank test was used to compare baseline scores to scores at 12 months for the bowel and urinary function domains for all patients. The differences from baseline to scores at 12 months were compared between the *NeoGemX* and *GemX* group using the Wilcoxon rank sum test. Sexual scores are reported, but were not statistically compared due to the small number of responses. Baseline characteristics between groups, including age, performance status, T stage and hydronephrosis, were compared using the Wilcoxon rank sum test for age and the chi-squared test for categorical variables. Logistic regression analysis was performed to account for imbalances in confounding factors between the two groups in a model incorporating age, performance status, tumour stage and presence of hydronephrosis.

Loco-regional disease-free survival, distant metastases free survival and overall survival were compared between the two groups using Kaplan-Mier survival analysis and the log-rank test. The effect of tumour stage, performance status and age in addition to use of neoadjuvant chemotherapy was assessed in a multivariate model using the Cox proportional hazards model.

Results

Patient characteristics

Seventy eight patients, treated between 18/05/2010 and 13/08/2013, were included. Thirty eight of these patients received prior NAC. Median duration of follow up was 15.9 months (range 0.8-50.5 months), 14.1 months (range 0.8-45.4 months) in the *GemX* group and 16.1 months (range 0.8-45.4 months) in the *neoGemX* group. Patient characteristics in the *GemX* alone and *neoGemX* groups are shown in table 1. *NeoGemX* patients were significantly younger and had a trend towards better performance status than *GemX* patients. Mean GFR in patients receiving NAC was 89 ml/min.

Treatment details

Thirty four patients received cisplatin and gemcitabine doublet NAC, 4 received carboplatin rather than cisplatin due to renal impairment, 1 had small cell histology and received cisplatin and etoposide. Thirty six patients received 3 cycles of chemotherapy, the remaining 2 patients received 6 cycles. Chemoradiotherapy completion rates are shown in table 2.

Toxicity

Provider reported toxicity

Maximum acute and late RTOG bowel and urinary toxicity in the *2* groups is shown in figure 1.

Grade 1-2 acute bowel toxicity was present in 65/78 patients by week 4, with 7/78 patients experiencing grade ≥ 3 toxicity. By 6 weeks post treatment 25/78 patients had ongoing grade 1-2 toxicity and grade 3 toxicity was seen in 3/78 patients. Late bowel toxicity was assessed at 12 months or more of follow up in 58/78 patients, 41 patients reported no ongoing bowel toxicity. Two patients had late toxicity of grade ≥3. One patient developed severe colitis requiring colostomy 12 months after treatment. This patient was found to have poor bowel function at baseline with no definite underlying pathology and had declined cystectomy. The second patient had a bowel perforation, during a course of palliative chemotherapy for metastatic disease, at 9.5 months after treatment. Although two patients had increased small bowel volume within the high dose region on imaging, there was no associated toxicity and in the remaining patients, no additional risk factors were identified.

Significant urinary toxicity was less commonly observed, with grade 3 toxicity only reported in 5 patients at any time point. Late urinary toxicity was assessed in 51/78 patients. Eight patients reported ongoing urinary toxicity which was grade ≤ 2 in all cases.

Patient reported toxicity outcomes

Forty nine patients completed questionnaires at baseline and at least one other time point and were included in the questionnaire analysis. The number of patients completing questionnaires at each time point and the mean total scores for bowel, urinary and sexual functions are shown in table 3.

Figure 2 demonstrates mean LS scores for bowel and urinary function for male patients in the two groups.

In all patient groups mean LS scores peaked at 4 weeks and were returning to baseline by 12 months.

There was no statistically significant change in LS scores for bowel (p=0.48) or urinary function (p=0.19) from baseline to 12 months.
There was no statistically significant difference in LS scores between the *GemX* and *neoGemX* groups (p=0.44 for bowel and p=0.11 for urinary function), confirmed on logistic regression analysis (p=0.31 for bladder and p=0.09 for bowel) correcting for confounding factors.

Outcomes

3 month cystoscopy response

Cystoscopy results at 3 month post completion of *GemX* were available in 66/78 patients (85%). Of the patients for whom no 3 month cystoscopy result was available, 3 were from the *neoGemX* group and the remainder received *GemX* alone Two did not have cystoscopic assessment due to presence of metastatic disease, 7 due to deterioration in clinical condition, the remainder were lost to follow up. Complete response was demonstrated in 61/66 cases (92%), 30 in the *GemX* group and 31 in the *neoGemX group* (see table 4).

Disease free survival, overall survival and cystectomy rates

Local and distant recurrence and cystectomy rates and cancer related and cancer unrelated death rates are shown in table 4. Disease free survival (DFS), defined as freedom from invasive local or metastatic recurrence, and overall survival (OS) outcomes for the *neoGemX* and *GemX* groups are shown in figure 3. Two year DFS was 0.65 (95% CI, 0.48-0.87) for the *GemX* group and 0.81 (95% CI 0.68-0.96) for the *neoGemx* group, while the two year OS was 0.67 (CI 0.52 - 0.87) for the *GemX* patients and 0.69 (CI 0.51-0.92) for the *neoGemX* patients. There was no statistically significant difference in DFS (p=0.60) or OS (p=0.28) between the *neoGemX* and *GemX* groups. This remained the case after correcting for tumour stage, age and performance status in a multivariate Cox proportional hazards model (DFS p=0.59 OS p=0.61). Two year DFS was 0.65 (95% CI, 0.48-0.87) for the *GemX* group and 0.81 (95% CI 0.68-0.96) for the *neoGemx* group, while the two year OS was 0.67 (CI 0.52 - 0.87) for the *GemX* patients and 0.69 (CI 0.51-0.92) for the *neoGemX* patients.

Discussion

Traditionally, radical radiotherapy for MIBC was reserved for those patients who were considered unfit for definitive surgery. There is now an increasing role for bladder preservation, using NAC prior to radical radiotherapy with radiosensitisation, with salvage cystectomy for recurrent MIBC. The BA06 RCT demonstrated a 6% improvement in overall survival at 10 years with the addition of NAC to definitive treatment (6), which was confirmed in the ABC meta-analysis, which included results from 10 RCTs and demonstrated an improvement in 5 year overall survival of 5% (7).

Two landmark UK phase III studies have demonstrated a clear role for radiotherapy with radiosensitisation with either concurrent chemotherapy or CON. The *BC2001* RCT compared chemoradiotherapy using MMC/5FU to radiotherapy alone and demonstrated improved loco-regional disease free survival at two years, 67% compared to 54% (P = 0.03) (8). The *BCON* RCT compared radiotherapy alone to radiotherapy with CON. CON produced a small non-significant improvement in cystoscopic control at 6 months but a significant difference in overall survival (59% and 46% P = 0.04) (9). Late morbidity was similar in both trial arms in both studies. Both studies allowed the use of conventional radiotherapy fractionation with 64Gy in 32 fractions over 6.5 weeks or moderately hypofractionated fractionation with 55Gy in 20 fractions over 4 weeks. Outcomes using cisplatin containing chemoradiotherapy have also been reported in studies previously, with one RCT and other large retrospective series reporting favourable outcomes compared to others in the literature (18-24). An overview of radiotherapy vs chemoradiotherapy studies, 11 of which included patients receiving prior NAC, demonstrated a consistent improvement in tumour control for chemoradiotherapy (29). However, not all patients are suitable for these regimes. An alternative chemotherapy regime for radiosensitisation, is weekly gemcitabine. Gemicitabine is an established chemotherapy agent for use in bladder cancer and is a known radio-sensitiser. There are several phase I and II studies investigating its use in this context (10-17). A phase II trial has previously been reported, in which gemcitabine was given weekly with hypofractionated radiotherapy (25). A total of 50 patients were treated. Three year cancer-specific survival was 82%, and overall survival was 75%. Forty four patients (88%) achieved a complete endoscopic response. Four patients underwent cystectomy; three because of recurrent disease and one because of toxicity.

The results of the current study demonstrate comparable tolerability, toxicity and treatment outcomes compared to both the regimes used in the *BCON* and *BC2001* studies and the original phase II gemcitabine study, with at least 95% of patients completing all radiotherapy and over 90% completing at least 80% of prescribed radiosensitisation in all studies. This suggests that *GemX* is well-tolerated. In addition, there was no evidence of reduced completion rates in patients who received NAC. This supports the finding that NAC does not compromise ability to tolerate definitive chemoradiotherapy. In our study, only 7/20 of the patients who omitted chemotherapy did so due to G3 bowel toxicity. A small proportion of patients will develop toxicity preventing receiving full doses of scheduled radiosensitising agents, regardless of the regime used and this does not appear to compromise the overall treatment outcomes reported. Of the patients who omitted at least 1 cycle of gemcitabine in this study, only one had evidence of residual disease at the time of 3 month cystoscopy. In the total follow up period only 3 additional patients developed recurrence. Allowing for the small number of events seen, there is no obvious decline in treatment outcomes in terms of local control in the small cohort of patients who did not complete all 4 cycles of gemcitabine.

Chemoradiotherapy is recognised to cause an increased risk of acute toxicity compared to radiotherapy alone, although both the BCON and BC2001 trials did not report a significant increase in late toxicity with radiosensitisation (8,9). The *BC2001* RCT, demonstrated a rate of grade 3 or more acute bowel toxicity of 9.6% in patients receiving chemoradiotherapy. In the original phase II GemX study this figure was 8%. Late grade 3 toxicity of any type was reported at 8.3% in the radiosensitisation arm of BC2001, 7% for late bowel toxicity in BCON and 4% in the phase II GemX study.

Allowing for the shorter period of follow up and small number of events seen our results again appear comparable and the rate of late grade 3 bowel toxicity did not appear increased in the NAC group. The low rates of late toxicity were also demonstrated in the return of LS scores towards baseline at 12 months post treatment completion, with no statistically significant difference seen between scores at baseline and 12 months. Sexual toxicity is more difficult to assess, and rates of assessment were low both on provider and patient-reported outcomes.

The patient reported outcome questionnaires did not demonstrate any statistically significant difference in LS scores between the *neoGemX* and *GemX* group at any time point.

There was however, a trend towards both a higher baseline score and higher scores at each time point in the *GemX* only arm. The significance of this is uncertain given the small patient numbers and lack of randomisation between the groups. Logistic regression was used to adjust for any difference between factors in the 2 groups, but still did not suggest any significant increase in scores in the *neoGemX* group.

The rate of cystoscopic complete response at 3 months was 92% in those patients who had cystoscopy. This does not however, fully reflect local control, as patients who had developed metastatic disease did not proceed to cystoscopy at 3 months. In BCON cystoscopic response was difficult to measure accurately at a given time point due to the variation in timing of first check cystoscopy, thus making it difficult to quantify local control (9). During the follow up period of the present study, 7 patients proceeded to cystectomy, demonstrating that, in this limited follow up period, rates of bladder preservation appear comparable to those reported in the literature. Median overall survival was not reached. Second malignancy, even in this limited follow up period, reflects the burden of additional comorbidities in this group of patients.

The patient-reported outcomes and provider-reported toxicity within this study support the use of NAC prior to definitive chemoradiotherapy. However, this study is based on a limited number of patients, with relatively short follow up. The completeness of weekly provider reported toxicity assessments during treatment was very high, however it must be acknowledged that some patients were lost to follow up and that late toxicity assessment is based on follow up at 12 months post completion of treatment. Whilst the rate of questionnaire completion was sufficient to provide a useful comparison of patient reported outcomes not all patients were compliant, which may have introduced bias.

The outcomes reported are based on a heterogeneous group of patients compared to those included in RCT, including small numbers of node positive patients and those with small cell histology included in the *neoGemX* group. Although this would be expected to adversely affect the survival outcomes seen, prognostic factors such as these should not affect the toxicity data reported in this study.

This study is not a RCT, selection for NAC was based on clinical decisions by treating physicians. Given the prevalence and accepted practice of combining NAC with

chemoradiotherapy, a RCT would be difficult to perform. There was no increase in LS scores seen after adjusting for confounding factors using logistic regression. There was no statistically significant difference between the groups on baseline LS scoresAlthough there was no statistically significant difference between LS scores at any time point between the two groups, there was a trend towards increased toxicity in the *GemX* only group compared to those receiving *neoGemX*, supporting that this may be the case.

In summary, although limited by the small patient numbers and lack of randomisation and potential selection bias, our study supports the use of NAC and *GemX* for patients being treated with bladder preservation.

List of tables

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Table 1: Patient characteristics

Characteristic	NeoGemX (n=38)	GemX alone (n=40)	p value**
Median age years (range)	67.5 (53-78)	75.5 (54-82)	<0.01
Performance status *	0=25 1=12	0=17 1=20 2=2	0.06
Histology: TCC only	34	37	0.9
Histology: Other component present	SCC: 2, sarcomatoid: 1	Sarcomatoid: 2, Neuroendocrine: 1	-
Histology: non TCC	1 (small cell)	0	-
Carcinoma in situ	6	2	0.2
T stage	T2: 30 T3: 6 T4: 2	T2: 27 T3: 12 T4: 1	0.4

* not documented in 2 cases **Wilcoxon's rank sum test used for age, chi-square test used for other factors

Table 2: Treatment completion rates

Treatment	**Completion rate n=78**
Radiotherapy (20 fractions)	74 (95%)
4 cycles of gemcitabine concurrently *	58 (78%)
At least 3 cycles of gemcitabine cncurrently	75 (96%)

*due to G≥3 GI toxicity in 8 cases, G≥3 GU toxicity in 5 cases

Table 3: Rates of questionnaire completion and mean Lent Soma (LS) scores during and after treatment.

		Time Point (mean scores shown in brackets)							
		Week 1 (baseline)		Week 4 (final week of treatment)		6 weeks post treatment completion		12 months post treatment completion	
Patient Group		Bowel	Urinary	Bowel	Urinary	Bowel	Urinary	Bowel	Urinary
Male	Gemx	19 (2.6)	19 (3)	14 (11.1)	13 (8.2)	9 (7.4)	7 (5.2)	7 (1.4)	7 (3.6)
	NeoGemX	22 (1.3)	22 (1.5)	14 (8.3)	14 (5.1)	13 (5.0)	13 (3.5)	8 (1.8)	9 (2.2)
Female	Gemx	3 (0.7)	2 (5.5)	1 (22.0)	1 (1.0)	0	0	1 (1.0)	1 (1.0)
	NeoGemX	5 (1.8)	5 (7.6)	3 (2.3)	3 (4.3)	0	0	2 (0.0)	2 (8.0)

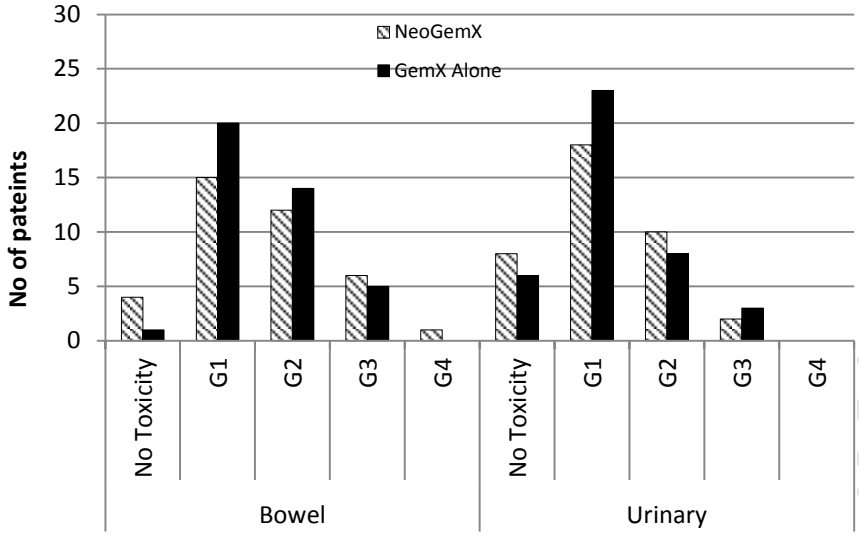
Table 4: Outcomes following treatment with GemX.

Event	**No. patients** **total n=78 assessed at 3 month cystoscopy n=66**
Residual disease at 3 month cystoscopy	Muscle invasive: 3 Superficial: 2
Recurrent superficial disease treated with intravesical therapy	5
Recurrent MIBC *	11
Cystectomy	Muscle invasive recurrence: 6 Recurrent superficial disease and CIS: 1
Metastatic disease	15
Death:cancer related	8
Death: unrelated ****	16

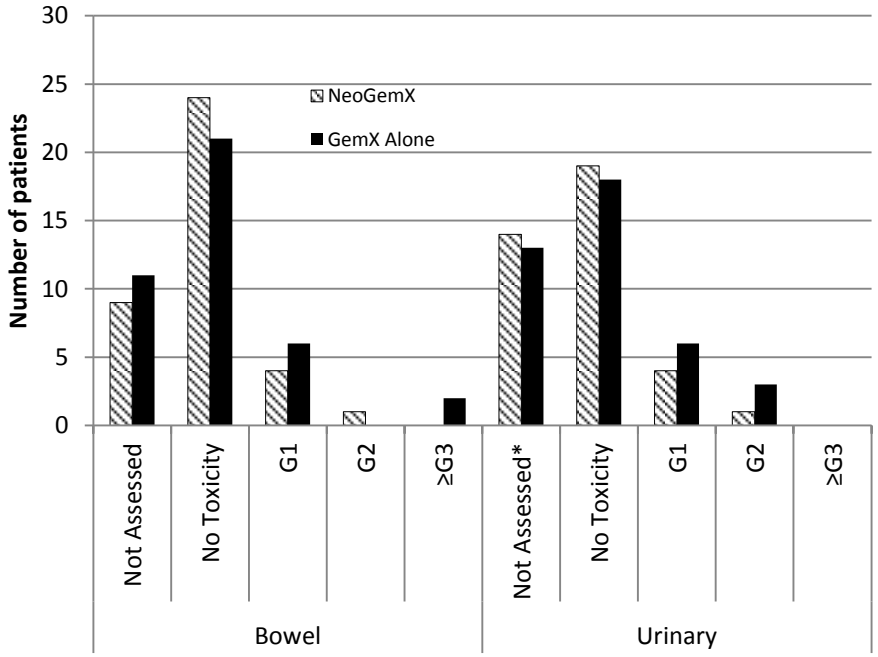
* 4 patients not suitable for cystectomy, 2 due to metastatic disease, 1 inoperable at time of attempted surgery

Figure 1.

1a: Maximum acute toxicity: weeks 1-4 and 6 weeks post treatment completion.



1b: Maximum late toxicity.



***Not assessed in 3 cases in the NeoGemX group due to cystectomy for recurrence.**

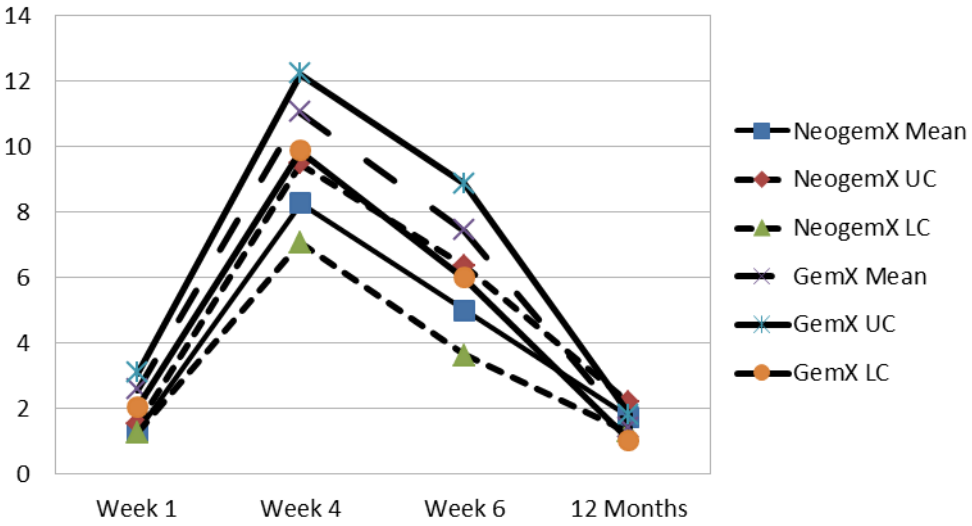


Figure 2A LENT SOMA Mean Bowel Scores for Male Patients

UC: 95% Upper confidence limit LC: 95%Lower Confidence limit

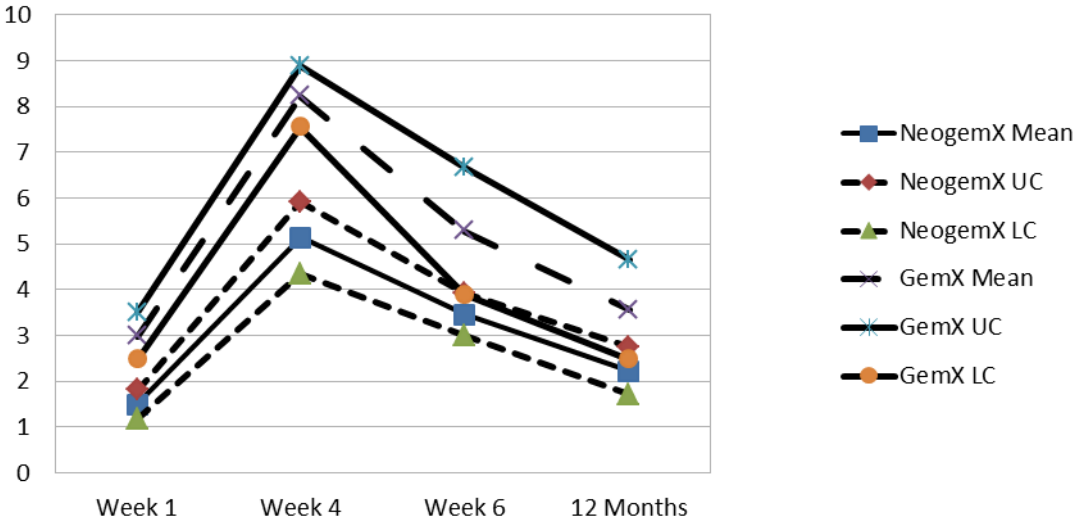


Figure 2B LENT SOMA Mean Urinary Scores for Male Patients

UC: 95% Upper confidence limit LC: 95%Lower Confidence limit

Figure 3 A) Disease Free Survival. B) Overall Survival