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Christodoulou, M, Reeves, KJ, Hodgson, C et al. (6 more authors) (2018) Outcomes of radiosensitisation in elderly patients with advanced bladder cancer. Radiotherapy and Oncology, 129 (3). pp. 499-506. ISSN 0167-8140

https://doi.org/10.1016/j.radonc.2018.05.022

Title: Outcomes of radiosensitisation in elderly patients with advanced bladder cancer

Short title: Radical radiotherapy for bladder cancer in the elderly

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Keywords: Muscle invasive bladder cancer, radiotherapy, elderly, radiosensitisation

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Total number of pages: 16 pages including references

Total number of tables: 2

Total number of figures: 3

Abstract

Introduction: There is little evidence to guide treatment in elderly patients with muscle invasive bladder cancer (MIBC). We evaluated the efficacy and tolerability of concurrent radical radiotherapy with gemcitabine radiosensitisation (GemX) in elderly patients with MIBC and compared outcomes to those from the bladder carbogen and nicotinamide (BCON) phase III trial.

Materials and Methods: Data was retrospectively analysed for patients who received GemX from two oncology centres in the UK. Elderly was defined as aged ≥75 at the start of GemX. Following transurethral resection of bladder tumour, patients received neo-adjuvant platinum-based chemotherapy followed by radiotherapy concurrently with weekly gemcitabine. A separate, age-specific analysis was performed in the BCON cohort. Overall survival (OS), disease specific survival (DSS) and local progression free survival (LPFS) were evaluated using Kaplan-Meier methodology and Cox proportional hazards regression.

Results: Out of 167 patients who received GemX, 61 were elderly (36.5%) with a median age of 78 years. Elderly patients had worse performance status (p=0.020) and co-morbidities (p=0.030). A similar proportion of patients received planned dose radiotherapy in both groups (p=0.260), although fewer elderly patients received all four cycles of concurrent chemotherapy (p=0.017) due to toxicity. For OS, age had some prognostic power; HR 1.04 (95% CI 1.00-1.08; p=0.068). Overall survival and LPFS in elderly patients were comparable between CON and GemX (HR 1.13, 95% CI 0.69-1.85; p=0.616 and HR 0.85, 95% CI 0.41-1.74; p=0.659 respectively).

Discussion: Radiosensitisation is safe and effective and should be considered for fit elderly patients with MIBC.

Introduction

Bladder cancer is more common in the elderly, with a median age of over 73 years at diagnosis [1]. There are over 10,000 cases diagnosed in the UK each year, 54% are in patients aged 75 years old or over [2]. In the last two decades, the proportion of newly diagnosed patients over 80 years has increased from 13% to 20% [1]. This trend is likely to continue given advances in healthcare and increasing life expectancy, with projections of a rise in octogenarians from 125 million in 2015 to 434 million by 2050 worldwide [3].

Muscle invasive bladder cancer (MIBC) comprises a third of bladder cancer diagnoses and is associated with a poor prognosis despite optimal treatment [4,5]. Definitive treatment is either radical cystectomy with pelvic node dissection [6] or tri-modality bladder preservation combining transurethral resection of bladder tumour (TURBT), radiotherapy and radiosensitisation with comparable outcomes to cystectomy [7]. Consequently, national and international guidelines recommend bladder preservation as an excellent option for the definitive management of locally advanced disease in older, less fit patients [8,9]. Radiosensitisation with systemic chemotherapy (fluorouracil/mitomycin C, gemcitabine or cisplatin) [10-12] or hypoxia modification (bladder carbogen nicotinamide protocol, BCON) [13,14], has shown favourable outcomes compared to radiotherapy alone and has been introduced as standard of care in the UK [9].

Despite advances in the management of MIBC, there is little evidence to guide treatment strategies for the elderly, with concerns raised about potential under-treatment. Noon et al. demonstrated that elderly patients with bladder cancer are significantly less likely to receive radical treatment compared to their younger counterparts (52% vs. 12% respectively) and suffer from higher cancer-specific mortality [15]. Decision making on optimal treatment strategies for elderly patients can be challenging due to multiple factors. There is a lack of consensus in the literature on the definition of “elderly”, which can refer to chronological age, change in social role or functional status [16]. In addition, elderly patients are under-represented in clinical trials resulting in poor prospective evidence on treatment efficacy and safety [17,18]. Clinicians’ fear of increased treatment-related complications due to co-morbidities, poor physiological reserve and polypharmacy adds further challenge.

In this analysis, we compare the outcomes of elderly patients with MIBC who received concurrent radiotherapy with gemcitabine radiosensitisation (GemX protocol) against those of their younger counterparts. In a separate analysis, we compare the results with the outcomes of elderly patients in the BCON phase III clinical trial.

Materials and Patients

Patient population

Data was retrospectively analysed for patients with histologically confirmed MIBC treated with GemX at two different NHS Trusts in the UK after obtaining local ethical approval. The eligibility criterion has previously been described by Choudhury et al. 2011 [11]. The age cut-off of 75 years at the start of treatment was selected to be well above the median age of patients traditionally included in clinical trials. All patients underwent TURBT prior to chemo-radiotherapy. Co-morbidity was assessed using the Adult Co-morbidity Evaluation (ACE-27) score.

A separate analysis compared the outcomes of young and elderly patients in the CON arm of the BCON trial. Details of the trial methodology have been described previously [13,14,19].

Treatment

Both GemX and BCON protocols have previously been published [13,19,20]. After discussion in a multi-disciplinary team meeting, 3-6 cycles of platinum-based chemotherapy was given for patients with Eastern Co-operative Group performance status 0 or 1 with organ-confined MIBC where neoadjuvant chemotherapy is indicated, prior to receiving GemX, however, none of the patients in the BCON trial received neo-adjuvant chemotherapy since it was completed before neoadjuvant chemotherapy became a standard of care.

Toxicity

Grade ≥3 late genitourinary (GU) or gastrointestinal (GI) toxicity in the GemX cohort was assessed at 12 months following treatment completion according to the Radiation Therapy Oncology Group (RTOG)/ European Organization for Research and Treatment of Cancer (EORTC) Late Radiation Morbidity Scoring Schema [21]. In the BCON trial, late GU/GI adverse events were reported as per the Late Effects Normal Tissues (LENT)/Subjective, Objective, Management, Analytic (SOMA) scales [22].

Statistical analysis

Patient age was calculated at the start of the GemX protocol. The geometric mean was calculated for haemoglobin and glomerular filtration rate (GFR) values. Overall survival (OS), disease specific survival (DSS), progression free survival (PFS) and local progression free survival (LPFS) were calculated from the start date of GemX to the date of death from any cause. Kaplan-Meier curves and univariate and multivariate Cox proportional hazards regression were used to evaluate these survival outcomes for patient age, T stage,

Eastern Cooperative Oncology Group (ECOG) performance status (PS), ACE-27 score, carcinoma in situ and hydronephrosis. Comparisons of patient characteristics between elderly and young patients were performed using Fisher's exact tests, trend tests and t-tests. A p value of ≤0.05 was considered statistically significant. Data from the BCON trial was used to perform an age-specific analysis. Of interest were the outcomes of OS and LPFS. The statistical considerations used in the BCON trial are described previously [13]. Statistical analysis was performed using Stata version 13.

Results

Patient characteristics

Between May 2010 to December 2014, one-hundred and sixty-seven patients received GemX of which, sixty-one (36.5%) were 75 years or over with a median age of 78 years (range 75-89), compared to 68 years in the younger group (range 45-74) (Table 1). All patients had grade 3 disease and the commonest histological subtype was transitional cell carcinoma. Characteristics were well balanced apart from worse ECOG PS (p=0.020), ACE27 score (p=0.030) and GFR (p<0.001) in the elderly with more smokers in the younger group (p=0.017). These differences are expected since the elderly are generally less fit with more co-morbidities compared to their younger counterparts. Hydronephrosis was evident in 23% vs. 17% of elderly and younger patients respectively (p=0.412).

In the BCON cohort three-hundred and thirty-three patients were randomised between November 2000 and April 2006. Out of the one-hundred and sixty-four patients receiving CON, seventy-three (44.5%) were elderly with a median age of 79 years (range 75-89) compared to 68 years in the younger group (range 51-74). The baseline characteristics of the patients included in the BCON trial have been described previously [13]. In the CON arm of the trial, eight elderly patients had grade 2 disease compared to none in the GemX cohort (p=0.029). Gender, T stage, presence of carcinoma in situ at diagnosis and haemoglobin values differed slightly between elderly patients that received GemX and CON, although any differences did not reach statistical significance.

Treatment delivered

Neo-adjuvant chemotherapy

Ninety (53.9%) patients received between 1 and 6 cycles of platinum based neo-adjuvant chemotherapy. From the ninety patients, the majority of patients (86.5%) received 3 cycles of chemotherapy. Four patients

received less than 3 cycles of chemotherapy; 1 patient received 1 cycle due to hepatic and GI toxicity and 3 patients received 2 cycles due to GI toxicity, ototoxicity and patient's choice. Patients with T4 or N1/x disease received up to 6 cycles of neoadjuvant chemotherapy (1 patient received 4 cycles and 4 patients received 6 cycles). The most frequently used chemotherapy regimen was cisplatin/gemcitabine (87.8%) followed by carboplatin/gemcitabine (8.9%), MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) (2.2%) and cisplatin/etoposide (1.1%). Significantly fewer elderly patients were offered neo-adjuvant chemotherapy compared to their younger counterparts (21.3% vs. 72.6%, p<0.001). Of the patients who received neo-adjuvant chemotherapy, a similar proportion completed at least 3 cycles in both age groups (p=1.000). No patients received neo-adjuvant chemotherapy as part of the BCON trial.

GemX

Radiotherapy compliance was comparable in both groups (93.4% vs. 97.2% received planned dose radiotherapy in the elderly and younger groups respectively, p=0.260). There was a significant difference in the proportion of patients who received less than four compared to four doses of gemcitabine in the two groups (36.1% elderly vs. 18.9% younger, p=0.017). Out of the patients who received less than 4 cycles of gemcitabine in the elderly and younger groups respectively; 15 (24.6%) vs. 14 (13.2%) patients received 3 cycles, 5 (8.2%) vs. 3 (2.8%) patients received 2 cycles and 2 patients out of each group (3.3% vs, 1.9%) received 1 cycle of gemcitabine. Most patients did not complete planned treatment due to GU or GI toxicity. In the younger group, three patients did not complete chemotherapy; one due to a cardiac event, one due to a combination of toxicity and disease progression and one due to deep vein thrombosis. However, all three patients completed planned radiotherapy.

Survival

Median follow up for OS was 38.0 months in the GemX cohort; three-year OS was 63.3% (95% CI 47.6-75.5) vs.73.1% (95% CI 62.7-81.0) for the elderly and younger groups.

For OS, age was close to statistical significance in univariate Cox regression (HR 1.04, 95% CI 1.00-1.08; p=0.068) (Figure 1A),

There was no difference in OS between the two groups in a multivariate model including hydronephrosis, carcinoma in situ and PS. Five patients were excluded from DSS (three elderly and two young) due to lack of data. DSS rates were similar in both groups (Figure 1B).

There were no significant differences between elderly and young for PFS or LPFS; HR 1.00 (95% CI 0.96-1.04; p=0.989) and HR 0.55 (95% CI 0.30-1.03; p=0.063), respectively (Figure 1C and 1D).

Age was not significant in multivariate analysis for DSS, PFS or LPFS. Table 2 summarises 3-year survival estimates and hazard ratios using univariate analyses. A comparison of LPFS between the 2 age groups was not significant (HR1.26; 95% CI 0.68-2.3; p=0.463).

Local recurrence, muscle-invasive or non-muscle invasive, was reported in forty-five patients; fourteen elderly and thirty-one younger patients. Two elderly patients and 15 young patients underwent cystectomy/cystoprostatectomy including four patients planned for cystectomy at the time of their last follow-up). Eleven patients were treated with either bacille Calmette-Guerin immunotherapy or mitomycin C instillations for non-muscle invasive recurrence. Thirty-one patients had metastatic disease, nine elderly (14.8%) and twenty-two young (20.8%) patients.

In the CON arm of the BCON trial, elderly patients demonstrated similar LPFS (HR 1.03, 95% CI 0.99-1.06; p=0.145), but worse OS (HR 1.05, 95% CI 1.02-1.08; p=0.002) compared to their younger counterparts. Three-year OS estimates for CON and GemX were 54.4% and 58.5% (HR 1.13, 95% CI 0.69-1.85, p=0.616) and for LPFS 69.8% and 69.2% (HR 0.85, 95% CI 0.41-1.74, p=0.659) respectively (Figure 2).

Late toxicity

In the GemX cohort, Grade 3 or 4 GU toxicity at 12 months following treatment completion was available for thirty-two elderly and seventy-six younger patients; 52.5% v 71.7% respectively. GI toxicity was available for thirty-one elderly and seventy-seven younger patients; 50.8% vs 72.6% respectively. Twenty-three patients died prior to their 12-month follow-up, toxicities were not known for thirty-six patients, and for two patients only one of GU/GI toxicity was known. There were 3 grade 3 treatment related toxicities reported in the younger group (urinary incontinence and recurrent urinary tract infections, colitis and diarrhoea) compared to none in the elderly group. There were no treatment related deaths. In the CON arm of the BCON trial, Grade 3 or 4 LENT/SOMA GU/GI toxicity at 12 months was available for sixty-four (GU) and sixty-three (GI) patients in the younger group and for both toxicities for thirty-seven patients in the elderly group. Toxicity (GU/GI) was reported in eleven (17.2%) and two (3.2%) patients in the younger group respectively. The corresponding figures for the elderly group were eight (21.6%) and three (8.1%) patients. All cases of GI toxicity were reported as Grade 3.

Co-morbidity

Median follow up for OS was 36.3 months in the GemX cohort. A higher ACE 27 score was associated with worse OS at 3 years (0; 95% CI 0.62-0.89, 1; 95% CI 0.53-0.80, 2/3; 95% CI 0.36-0.71). DSS, PFS and LPFS were similar in both groups (Figure 3).

Discussion

The results of this study are particularly relevant in view of evidence supporting similar outcomes between radical cystectomy and bladder preservation strategies [23-26]. Cystectomy in patient's ≥75 years old is associated with high inpatient mortality, 90-day mortality and post-operative complication rates [27, 28]. These risks, in addition to the potential significant impact on quality of life, means that radical radiotherapy is often the treatment option of choice for octogenarians in the UK and the US [29-31]. A large UK study of 4639 patients demonstrated that radiotherapy was used preferentially to cystectomy in 1243 octogenarians (29.3% vs. 1.4% respectively) [30].

Although a number of different radiosensitisation schedules are in use [10, 12], this study focuses on GemX and BCON. In this retrospective, two-centre analysis and re-analysis of the BCON trial, we demonstrated comparable outcomes in elderly patients with MIBC treated with radiosensitisation, compared to their younger counterparts. Overall and DSS outcomes as well as locoregional control rates in the elderly, were similar to those reported in studies evaluating organ sparing modalities [10,11,13]. The median age of patients within these studies was at least four years lower compared to the elderly patients in our cohort.

The age-specific analysis of the BCON trial is of particular interest since outcomes of elderly patients are not commonly evaluated within phase III randomised controlled trials. The BCON trial demonstrated significantly improved OS and LPFS and lower risk of death with the addition of CON to radical radiotherapy [13]. Due to improved outcomes from combined radiotherapy and CON, we considered an age-specific analysis of the CON arm to be of greater relevance to aid clinical treatment decisions. We found that elderly patients in the CON group had similar LPFS but worse OS compared to their younger counterparts. The difference in OS could be explained by the absolute difference in median age between the two age groups. Given the higher co-morbidity burden in the elderly, worse survival outcomes are expected compared to younger patients. However, we demonstrate comparable outcomes in the two age groups which suggest that patient selection in older patients is more robust. Survival outcomes in the elderly who were treated with either GemX or BCON were similar, reflecting the feasibility and effectiveness of both radiosensitisation methods.

Our group has previously demonstrated acceptable acute and late toxicity with GemX using patient and clinician-reported outcomes [32]. In this study, there is no evidence of increased toxicity in the elderly group. Similarly, the BCON trial results showed excellent compliance in the radiotherapy plus CON arm by all age groups. A direct comparison of toxicity between GemX and BCON was not possible due to the use of different scoring systems.

In the BCON trial, none of the patients received chemotherapy prior to radical treatment, whereas a small number of elderly patients received neo-adjuvant chemotherapy in the GemX cohort. The limited use of neo-adjuvant chemotherapy in the elderly could be as a result of the co-morbid state of elderly patients who had worse baseline PS, ACE27 scores and renal function compared to the younger group. However, a similar proportion of patients completed a minimum of three treatment cycles in the elderly compared to the younger group, reflecting the importance of appropriate patient selection. A recent case series by Chau et al., compared the outcomes of MIBC patients above and below 70 years following cisplatin-based neo-adjuvant chemotherapy with comparable survival and local control rates in the two groups [33]. However, the median age of the patients in this study was 68 years which is significantly lower than this study. In addition, more elderly patients proceeded to have cystectomy as definitive treatment rather than radical radiotherapy (48.5% vs 39.4%) and therefore the results might not be directly relevant to this patient cohort. The value of neo-adjuvant chemotherapy with modern bladder preservation has been challenged since the underlying evidence predates radiosensitisation [34]. Concerns exist of prolonged treatment time, delay of radical treatment and increased risk of toxicity impacting delivery of definitive treatment [34]. It is interesting that outcomes in this study were similar regardless of age despite the limited use of neo-adjuvant chemotherapy in the elderly.

Radiotherapy compliance was excellent, although fewer elderly patients completed all four cycles of gemcitabine chemotherapy mainly due to toxicity. The rates of chemotherapy compliance in this cohort were expectedly lower compared to those described in the phase II trial evaluating the GemX protocol (92%), which reflects the higher co-morbidity burden amongst older patients.

There are a number of limitations of the GemX component of this study. Firstly, the retrospective nature of the study limits the strength of the results. Secondly, lack of completed data for some patients included in the study could have biased results. For example, cause of death was not known for eight patients who were subsequently excluded from the DSS analysis, potentially leading to inaccuracy in estimation of the difference in DSS between the two age groups. It could also be the case that LPFS was slightly overestimated for a small number of patients due to missing periods of follow up. In addition, direct comparison between GemX and BCON should be carefully interpreted given the different mechanisms involved in the radiosensitisation process and toxicity.

There is a drive to consider physiological or functional rather than chronological age for treatment decisions as this is thought to better reflect disease processes [16,35,36]. A variety of tools, such as the Comprehensive Geriatric Assessment (CGA), have been developed to offer a multidisciplinary, holistic

approach to the management of elderly patients and have shown to predict mortality and morbidity in cancer [37] However, lack of evidence on the feasibility and effectiveness of these tools in clinical practice is currently restricting their routine use [37,38]. One of the few phase III clinical trials which evaluated treatment allocation for lung cancer based on CGA, showed no difference in treatment failure free and OS but a small improvement in toxicity in the CGA arm [39]. Further work needs to be undertaken to assess the utility of the CGA, particularly in bladder cancer.

Conclusions

In conclusion, survival and toxicity outcomes of elderly patients treated with radiosensitisation with GemX or BCON are similar to their younger counterparts, indicating that radiosensitisation is an appropriate treatment for fit elderly patients with MIBC. Further research is warranted to bladder preservation in the elderly.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

The authors would like to thank Dr Richard Walshaw for his advice on data collection.

Funding source

BCON received funding from Cancer Research United Kingdom.

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List of tables

Figure Captions

Figure 1. Kaplan-Meier curves for overall survival (A), disease specific survival (B), progression free survival (C) and local progression free survival (D) for elderly (grey) and younger (black) groups in the GemX cohort. Hazard ratios, 95% confidence intervals, p values and number of patients at risk against yearly intervals are shown.

Figure 2. Kaplan-Meier curves for overall survival and local progression free survival for elderly patients who received radiosensitisation with CON (grey) or GemX (black). Hazard ratios, 95% confidence intervals, p values and number of patients at risk against yearly intervals are shown.

Figure 3. Kaplan-Meier curves for overall survival (A), disease specific survival (B), progression free survival (C) and local progression free survival (D) by ACE 27 score. Hazard ratios, 95% confidence intervals, p values and number of patients at risk against yearly intervals are shown.

Table 1. Baseline characteristics of the patients in the GemX cohort.

	Age (years)		p value
	<75 n (%)	**≥75 n (%)**	
	n=106	n=61	
Cancer centre			
xxxxxx	92 (86.8)	48 (78.7)	
xxxxxx	14 (31.2)	13 (21.3)	
Gender			p=0.128
Male	86 (81.1)	43 (70.5)	
Female	20 (18.9)	18 (29.5)	
T stage			p=0.573
T1	2 (1.9)	1 (1.6)	
T2	74 (69.8)	44 (72.1)	
T3	23 (21.7)	15 (24.6)	
T4	6 (5.7)	1 (1.6)	
Not known	1 (0.9)	0 (0)	
Histology			
TCC	98 (92.5)	54 (88.5)	
TCC, sarcomatoid differentiation	1 (0.9)	2 (3.3)	
TCC, squamous cell differentiation	2 (1.9)	0 (0)	
TCC, neuroendocrine differentiation	0 (0)	2 (3.3)	
Small cell	1 (0.9)	0 (0)	
Squamous cell	1 (0.9)	0 (0)	
Carcinoma	1 (0.9)	1 (1.6)	
Adenocarcinoma, sarcomatoid differentiation	1 (0.9)	0 (0)	
Not known	1 (0.9)	2 (3.3)	
Presence of preceding carcinoma in situ (CIS)			p=1.000
No	87 (82.1)	46 (75.4)	
Yes	13 (12.3)	6 (9.8)	
Not known	6 (5.7)	9 (14.8)	
Hydronephrosis			p=0.413
No	88 (83.0)	46 (75.4)	
Yes	18 (17.0)	14 (23.0)	
Not known	0 (0)	1 (1.6)	
ECOG PS			p=0.020
0	63 (59.4)	18 (29.5)	
1	30 (28.3)	33 (54.1)	
2	6 (5.7)	2 (3.3)	
3	1 (0.9)	0 (0)	
Not known	6 (5.7)	8 (13.1)	
ACE27 score*			p=0.030
0	35 (33.0)	10 (16.4)	
1	36 (34.0)	24 (39.3)	
2	16 (15.1)	16 (26.2)	
3	5 (4.7)	3 (4.9)	
Not known	14 (13.2)	8 (13.1)	
Smoking history†			p=0.017
Never	23 (21.7)	19 (31.1)	
Former smoker	39 (36.8)	21 (34.4)	
Current smoker	29 (27.4)	7 (11.5)	
Not known	15 (14.2)	14 (23.0)	
Haemoglobin, g/L			p=0.900
Geometric mean	131	131	
Range	91-178	96-180	
Not known	1 (0.9)	2 (3.3)	
GFR, ‡ ml/minute			p<0.001
Geometric mean	81	65	
Range	38-149	32-121	
Not known	16 (15.1)	29 (47.5)	
Neo-adjuvant chemotherapy (cycles completed)	n=76	n=13	
<3	5 (6.6)	1 (7.7)	p=1.000
≥3	71 (93.4)	12 (92.3)	

Abbreviations (in alphabetical order):

ACE, Adult Co-morbidity Evaluation; CIS, Carcinoma in Situ; ECOG, Eastern Cooperative Oncology Group; GFR, Glomerular Filtration Rate; PS, Performance Status; TCC, Transitional Cell Carcinoma.

*Where ACE27 scores[38] were not available, they were calculated based on the patient's co-morbidities as recorded on the electronic patient records.

†Never Smokers – Adults who have never smoked a cigarette or who smoked fewer than 100 cigarettes in their entire lifetime.
Former Smokers – Adults who have smoked at least 100 cigarettes in their lifetime, but say they currently do not smoke.
Current Smokers – Adults who have smoked 100 cigarettes in their lifetime and currently smoke cigarettes every day (daily) or some days (non-daily).

‡Isotopic measurements. Where these were not available, estimated GFR values were used.

Table 2. Kaplan-Meier Estimates and 95% Confidence intervals for overall survival, progression free survival, local progression free survival and disease specific survival at 3 years from the start of GemX, HRUV and 95% CIs for risk of death/relapse/local relapse/risk of death due to bladder cancer are presented. Due to patient numbers, it was not possible to calculate survival at 3 years for some groups (shown as '.').

	Overall Survival			Disease Specific Survival			Progression Free Survival			Local Progression Free Survival		
	3-year survival % (95% CI)	**HR_{UV} (95% CI)**	**p**	**3-year survival % (95% CI)**	**HR_{UV} (95% CI)**	**p**	**3-year survival % (95% CI)**	**HR_{UV} (95% CI)**	**p**	**3-year survival % (95% CI)**	**HR_{UV} (95% CI)**	**p**
Age		1.04 (1.00-1.08)	0.068		1.00 (0.95-1.04)	0.916		1.00 (0.96-1.04)	0.989		1.00 (0.95-1.04)	0.899
Young	73.1 (62.7-81.0)			79.0 (68.6-86.3)			57.0 (44.2-67.9)			70.0 (56.3-80.1)		
Elderly	63.3 (47.6-75.5)			77.8 (61.5-87.8)			59.7 (41.4-74.0)			68.0 (48.3-81.5)		
T stage		1.35 (0.86-2.11)	0.198		1.67 (0.96-2.88)	0.068		1.70 (1.12-2.57)	0.012		1.47 (0.84-2.57)	0.176
T1	100	.		100	.		66.7 (5.4-94.5)			66.7 (5.4-94.5)		
T2	71.0 (60.8-79.1)			80.0 (69.6-87.1)			67.8 (55.7-77.2)			77.4 (65.4-85.6)		
T3	65.7 (46.1-79.7)			78.0 (59.1-89.0)			31.7 (13.2-52.1)			42.9 (19.1-65.0)		
T4	57.1 (17.2-83.7)			57.1 (17.2-83.7)			.			.		
ECOG PS		1.60 (1.07-2.40)			1.27 (0.72-2.24)	0.406		1.70 (1.08-2.68)	0.022		1.99 (1.14-3.49)	0.016
0	77.6 (66.4-85.5)			81.9 (70.7-89.1)			68.1 (54.4-78.4)			80.4 (67.1-88.8)		
1	59.8 (45.4-71.5)			75.1 (60.2-85.1)			45.9 (30.0-60.5)			55.5 (36.9-70.5)		
2	62.5 (22.9-86.1)			.			.			.		
3	.			.			.			.		
CIS		2.39 (1.15-4.97)	0.019		3.67 (1.62-8.36)	0.002		2.47 (1.19-5.11)	0.015		2.26 (0.87-5.92)	0.096
No	73.1 (64.3-80.2)			82.9 (74.4-88.8)			60.8 (49.6-70.2)			71.3 (59.8-80.0)		
Yes	43.1 (18.7-65.6)			46.5 (20.3-69.2)			38.9 (15.3-62.2)			53.0 (20.9-77.3)		
Hydronephrosis		2.43 (1.32-4.47)	0.004					2.37 (1.27-4.42)	0.007		1.86 (0.80-4.32)	0.150
No	74.3 (65.2-81.3)			80.3 (71.2-86.7)	2.01 (0.85-4.74)	0.110	64.9 (53.5-74.1)			73.9 (62.7-82.2)		
Yes	49.1 (28.0-67.2)			70.0 (44.9-85.3)			30.1 (12.3-50.2)			45.9 (18.0-70.3)		

Abbreviations (in alphabetical order):

CIS, carcinoma in situ; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PS, performance status; UV, univariate.

Figure 1. Kaplan-Meier curves for overall survival (A), disease specific survival (B), progression free survival (C) and local progression free survival (D) for elderly (light) and younger (dark) groups in the GemX cohort. Hazard ratios, 95% confidence intervals, p values and number of patients at risk against yearly intervals are shown.

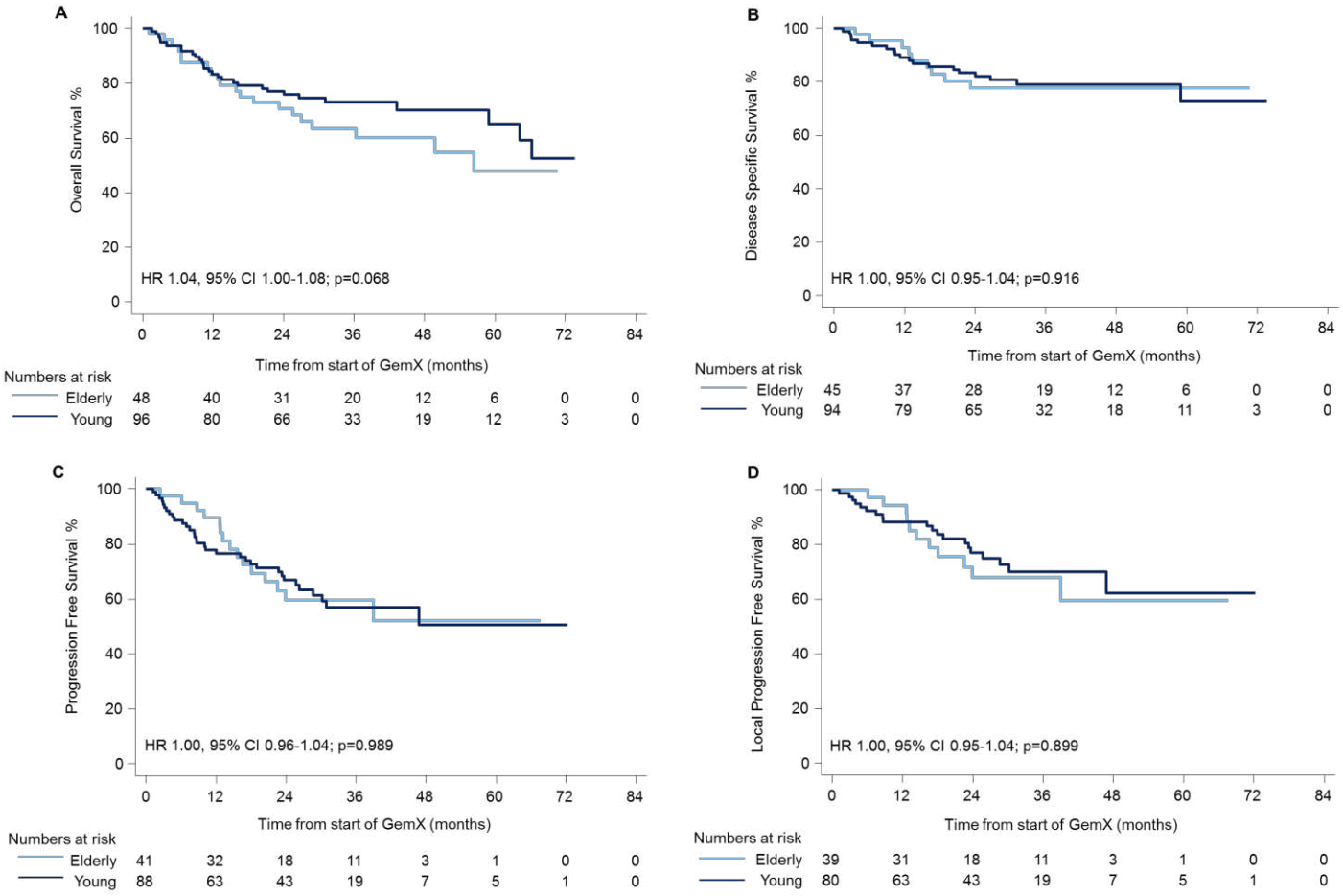

Figure 2. Kaplan-Meier curves for overall survival and local progression free survival for elderly patients who received radiosensitisation with CON (light) or GemX (dark). Hazard ratios, 95% confidence intervals, p values and number of patients at risk against yearly intervals are shown.

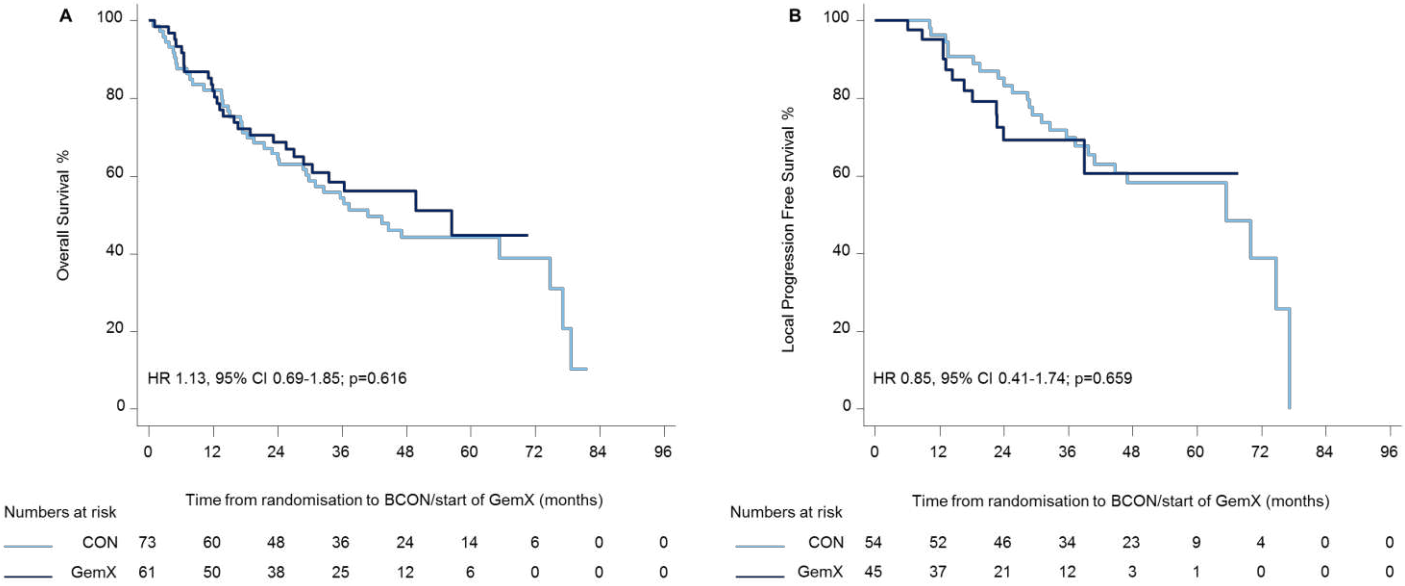

Figure 3. Kaplan-Meier curves for overall survival (A), disease specific survival (B), progression free survival (C) and local progression free survival (D) by ACE 27 score. Hazard ratios, 95% confidence intervals, p values and number of patients at risk against yearly intervals are shown.