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Table 4: Incidence and prevalence of acute clinician reported toxicity in RCTs (emboldened text indicates studies where a significant difference in primary outcome was demonstrated).

Type of Toxicity & how reported		% of toxicity		Treatment type	
ACUTE EFFECTS-clinician reported					
Genitourinary symptoms					
Detail not specified					
Grade 1	RTOG	37%(70.2Gy); 29% (79.2Gy)	[72]	Conventional 3D conformal RT	
Grade 2		54%(70.2Gy); 60% (79.2Gy)			
≥ Grade 2		40%	[49]		
		47%		Hypofractionated 3D conformal RT & 9 mth prior TAD	
	CTCAE V 2.0 & RTOG	15.1	[64]	Conventional 3D conformal RT	
		9.7%		CIMRT	
Grade 3	RTOG	0%(70.2Gy); 1% (79.2Gy)	[72]	Conventional 3D conformal RT	
		2%	[63]		
		2%			
Bladder					
≤ Grade 2 Recorded at 18 weeks	RTOG	7.0% (74Gy)	[58]	CIMRT	3-6 mth AS before and during RT
		7.6% (60Gy)		HIMRT	
		7.0% (57Gy)			
Retention					
Catheterised		7.9% (day 0 MXM) 6.2% (7 days prior MXM)	[55]	EBRT with BT & meloxicam	
Prostate Oedema					
Calculated as a ratio of MRI-determined prostate volume at 1 month to baseline determined prostate volume		1.01% (day 0 MXM) 1.05% (MXM)7 days before)	[55]	EBRT with BT & meloxicam	
Dysurea					
Measured as change from baseline at 1mth and 3mth	IPSS	1 mth: 8.4% day 0 (MXM); 8.8% (MXM 7 days before) 3mth 7.9% (day 0 MXM) 6.2% (MXM 7 days before)	[55]	EBRT with BT & meloxicam	

Type of Toxicity & how reported		% of toxicity		Treatment type	
Gastrointestinal symptoms					
Detail not specified					
Grade 1	RTOG	39%(70.2Gy); 26% (79.2Gy)	[72]	Conventional 3D conformal RT	
Grade 2		44%(70.2Gy); 60% (79.2Gy)			
		21%	[49]	Hypofractionated 3D conformal RT	
		35%			
	CTCAE V 2.0 RTOG	15.1%	[64]	Conventional 3D conformal RT	
		9.7%		CIMRT	
	NCI-CTC V3.0 RTOG	10%	[60]	3D Conformal RT with HT & EMP	
≤ Grade 2 Recorded at 18 weeks	RTOG	2.3% (74Gy)	[58]	CIMRT	Short-course androgen suppression for 3–6 months before & during RT
		2.3% (57Gy); 0.8% (60Gy)		HIMRT	
Grade 3	RTOG	1% ≥3 J	[63]	Conventional 3D conformal RT	
		1% ≥3 J		Conventional 3D conformal RT with HT	
		3%(70.2Gy); 2% (79.2Gy)	[72]	Conventional 3D conformal RT	
Hepatic toxicity					
Grade 1	RTOG	1%	[63]	Conventional 3D conformal RT	
		20%		Conventional 3D conformal RT with HT	
Grade 2		5%			
Grade 3		5%			
Grade 4		1 %			

Key: 3D-Three dimensional; EMP-estramustine phosphate;BT- Brachytherapy; HT-Hormone therapy ; CIMRT- Conventional intensity modulated radiotherapy; HIMRT- Hypofractionated intensity modulated radiotherapy; MXM-Meloxicam; TAD-Total androgen deprivation; TRUS (transrectal ultrasound); AS-Androgen Suppression; Mth=Month; Yr =year; NCI-CTC-National Cancer Institute Common Toxicity Criteria; Radiation Therapy Oncology group –RTOG; IPSS-International prostate symptom score; MRI-magnetic resonance imaging; ≥ greater than and equal to; ≤- less than or equal to; Mth-Month; Yr-Year. **NB table only includes papers reporting figures for incidence, prevalence and proportion of toxicity.**

Table 5: Incidence and prevalence of late clinician reported toxicity in RCTs (emboldened text indicates studies where a significant difference in primary outcome was demonstrated).

Type of Toxicity, how & when reported		% of toxicity		Treatment type
LATE EFFECTS-clinician reported				
Genitourinary symptoms				
Not specified				
Grade 1	10yrs	42%(70.2Gy) ; 45% (79.2Gy)	[72]	Conventional 3D conformal RT
		22%(70.2Gy) ; 27 %(79.2Gy)		
Grade 1-2	3 yrs NCI-CTC v3.0	42%	[69]	HT
		43%		Conventional 3D conformal RT with HT
Grade 2	7yrs	16 % (4mth HT) 17 % (8mth HT)	[56]	Conventional 3D conformal RT with HT
≥ Grade 2	3yrs LENT-SOMA	11 %	[49]	Conventional 3D conformal RT
		16 %		Hypofractionated 3D conformal RT
	5 yrs prevalence RTOG	14.6%	[67]	CIMRT
		15.3%		HIMRT
7yrs Cumulative Incidence RTOG	16% (4mth HT) (7yrs)	[56]	Conventional 3D conformal RT with HT	
	17% (8mth HT)(7yrs)			
Grade 3	10 yrs	2%(70.2Gy); 2% (79.2Gy)	[72]	Conventional 3D conformal RT
	3 yrs NCI-CTC v3.0	2%	[69]	HT
	2%	Conventional 3D conformal RT with HT		
≥Grade 3	2yrs	6 %	[63]	Conventional 3D conformal RT
	5yrs	9 %	[62]	
	7yrs	4 %		
	2yrs	8 %	[63]	Conventional 3D conformal RT with HT
	5yrs	0 %	[62]	
	7yrs	2 %		
Urinary toxicity				
Grade 1	Cumulative rate at 5 years RTOG	18.9 % (70Gy); 20.9% (80Gy)	[53]	Conventional 3D conformal RT
		22 % (70Gy); 25% (80Gy)		
Grade 2		7.1 % (70Gy); 15.6% (80Gy)		

	LENT-SOMA	13.7 % (70Gy); 20.9% (80Gy)			
	2yrs	74 %		[60]	Conventional 3D conformal RT with HT
		90 %			Conventional 3D Conformal RT with HT & EMP
≥Grade 2	5yrs RTOG	10 % (70Gy); 17.5% (80Gy)		[53]	Conventional 3D conformal RT
	5 yrs RTOG	14.6%		[67]	CIMRT
		15.3			HIMRT
Grade 3	2yrs	26%		[60]	3D conformal RT with HT
		10%			3D Conformal RT with HT & EMP
1 patient had grade 4 toxicity (RTOG)	Cumulative rate at 5 years RTOG LENT-SOMA	2.6% (70Gy); 1.9% (80Gy) 3.2% (70Gy); 5.4% (80Gy)		[53]	Conventional 3D conformal RT
Grade 4	LENT-SOMA	0.4% (70Gy); 0.6% (80Gy)			
Decreased stream					
Grade1	LENT-SOMA% change in score from baseline (93) to 5yrs	5%	64 & 74Gy	[51]	Conventional 3D conformal RT with HT
Grade 2		1%			
Incontinence					
Grade 1	LENT-SOMA% change in score from baseline (93) to 5yrs	6%	64 & 74Gy	[51]	Conventional 3D conformal RT with HT
Grade2		1%			
Urinary frequency					
Grade 1	LENT-SOMA% change in score from baseline (85) to 5yrs	10%	64 & 74Gy	[51]	Conventional 3D conformal RT with HT
Grade2		4%			
Nocturnal frequency					
Grade 1	MH change in score from baseline (88) to 5yrs	12%	64 & 74Gy	[51]	Conventional 3D conformal RT with HT
Grade2		2%			
Grade 3		1%			
Cystitis					
≥ Grade 2	5 yrs RTOG	15% (70Gy); 19% (80Gy)		[53]	Conventional 3D conformal RT
Haematuria					
Grade 1	LENT-SOMA% change in score from baseline to 5yrs	2%	64 & 74Gy	[51]	Conventional 3D conformal RT with HT
≥ Grade 2	5 yrs RTOG	10% (70Gy); 14% (80Gy)		[53]	Conventional 3D conformal RT
Urinary obstruction					
≥ Grade 2	5 yrs RTOG	6% (70Gy); 9% (80Gy)		[53]	Conventional 3D conformal RT

Bladder					
Grade 1	Prevalence at 2 yrs RMH LENT-SOMA	43.9 (74Gy)	[58]	CIMRT	3-6 mth AS before and during RT
		20.4 (74Gy)		HIMRT	
≥Grade 2		28.3% (60Gy) ; 35.0%(57Gy)		CIMRT	
		18.2% (60Gy) ; 19.7%(57Gy)		HIMRT	
Grade 3		10.8%(74Gy) 15.3% (74Gy)		CIMRT	
		6.5% (60Gy); 6.3% (57Gy)		HIMRT	
		12.3% (60Gy);12.0% (57Gy)		CIMRT	
		4.4%(74Gy)		HIMRT	
		5.8% (60Gy);3.5% (57Gy)			
Gastrointestinal symptoms					
Not specified					
Grade 1	2 yr prevalence RMH LENT-SOMA	28.9% (74Gy)	[58]	CIMRT	3-6 mth AS before and during RT
		22.% (74Gy)		HIMRT	
		18.1% (60Gy); 20.3% (57Gy)			
		16.8% (60Gy); 15.5% (57Gy)			
	10 yrs	35%(70.2Gy); 41% (79.2Gy)	[72]	Conventional 3D conformal RT	
Grade 2	1yr RTOG	13%(70.2Gy); 24% (79.2Gy)	[56]	Conventional 3D conformal RT	
		12%(4 mth HT)		Conventional 3D conformal RT	
		12% (8 mth HT)		Conventional 3D conformal RT	
≥Grade 2	2 yr prevalence RMH LENT-SOMA	22%	[64]	Conventional 3D conformal RT	
		15.1%		CIMRT	3-6 mth AS before and during RT
		5.8% (74Gy)	[58]	CIMRT	3-6 mth AS before and during RT
		9.4% (74Gy)		HIMRT	
		2.9% (60gy); 0.7% ≥2 (57Gy)			
		5.1% (60gy); 4.2% ≥2 (57Gy)			
	7yrs Cumulative Incidence RTOG	12% (4mth HT)	[56]	Conventional 3D conformal RT with HT	
		17% (8mth HT)			
Grade 3	2 yrs RTOG	3%	[63]	Conventional 3D conformal RT	
		3%		Conventional 3D conformal RT with HT	
≥Grade 3	5 yrs* 7yrs	1.4% (74Gy)	[58]	CIMRT	3-6 mth AS before and during RT
		0.7%(60Gy); 0.7%(57Gy)		HIMRT	
		9% *	[62]	Conventional 3D conformal RT	
		4%			
		0% *		Conventional 3D conformal RT with HT	
		2%			

Rectal toxicity					
Grade 1	Cumulative rate at 5 years	19% (70Gy); 22% (80Gy)		[53]	Conventional 3D conformal RT
		18.3% (70Gy); 15% (80Gy)			
Grade 2	RTOG	12.4% (70Gy); 13.7% (80Gy)			
	LENT-SOMA	18.3% (70Gy); 20.2% (80Gy)			
≥ Grade 2	3yrs	11%		[49]	Conventional 3D conformal RT
	LENT-SOMA	14%			Conventional 3D conformal RT with HT
	5yrs	14% (70Gy); 19.5% (80Gy)		[53]	Conventional 3D conformal RT
	RTOG				
Grade 3	Cumulative rate at 5 years	1.9% (70Gy); 5.9% (80Gy)			
	RTOG	1.9% (70Gy); 6.5% (80Gy)			
	LENT-SOMA				
Diarrhoea/stool frequency					
Grade 1	LENT-SOMA% Change form Baseline (89) at 5 yrs	10%	64 & 74Gy	[51]	Conventional 3D conformal RT with HT
Grade 1	Cumulative incidence RTOG, LENT-SOMA 5 yrs	33% (64Gy); 34%(74Gy) 44% (64Gy); 46%(74Gy)		[68]	Conventional 3D conformal RT with HT
Grade 1-2	3 yrs NCI-CTC v 3.0	8%		[69]	HT
		13%			Conventional 3D conformal RT with HT
Grade 2	LENT-SOMA% Change form Baseline (89) at 5 yrs	2%	64 & 74Gy	[51]	Conventional 3D conformal RT with HT
Grade 2	5 yrs Cumulative incidence RTOG	10% (64Gy); 15%(74Gy) 6% (64Gy); 12%(74Gy)		[68]	Conventional 3D conformal RT with HT
Grade 3	RMH LENT-SOMA	1% (64Gy); 4%(74Gy) 0% (64Gy); 2%(74Gy)			
≥Grade 3	3 yrs NCI-CTC v3.0	< 1% 1%		[69]	Conventional 3D conformal RT
					Conventional 3D conformal RT with HT
Bowel frequency					
Mild	5 yrs	9% (64Gy); 14%(74Gy)		[68]	Conventional 3D conformal RT with HT
Moderate	Cumulative incidence	2% (64Gy); 6%(74Gy)			
Stool frequency	RMH				
	LENT-SOMA				
≥ Grade 1		44% (64Gy); 46% (74Gy)			
≥ Grade 2		6% (64Gy); 12% (74Gy)			

≥ Grade 3		0% (64Gy); 2% (74Gy)			
Rectal bleeding					
Mild		43 % (64gy); 53 %(74Gy)			
Moderate		11% (64Gy);21% (74Gy)			
Severe		1% (64Gy);1% (74Gy)			
≥ Grade 2		22% (64Gy); 32%(74Gy)			
≥ Grade 3		3% (64Gy); 10%(74Gy)			
≥ Grade 4		1% (64Gy); 1%(74Gy)			
Grade 1	RTOG % Change form Baseline (82) at 5 yrs	16%	64 & 74Gy	[51]	Conventional 3D conformal RT with HT
Grade 1-2	3 yrs NCI-CTC v3.0	5%		[69]	HT
		12%			Conventional 3D conformal RT with HT
Grade 2	RTOG % Change form Baseline (82) at 5 yrs	3%	64 & 74Gy	[51]	Conventional 3D conformal RT with HT
≥Grade 2	5yrs RTOG	19% (70Gy)		[53]	Conventional 3D conformal RT
		28% (80Gy)			
Grade 3	3 yrs NCI-CTC v 3.0	1%		[69]	Conventional 3D conformal RT
		< 1%			Conventional 3D conformal RT with HT
≥Grade 3	5 yrs Cumulative incidence	3% (64Gy); 10%(74Gy)		[68]	Conventional 3D conformal RT with HT
≥Grade 4	LENT-SOMA	1% (64Gy); 1%(74Gy)			
Sphincter control					
Grade 1	LENT-SOMA% Change form Baseline (95) at 5 yrs	2%	64 & 74Gy	[51]	Conventional 3D conformal RT with HT
Grade 2		1%			
Proctitis					
Grade 1	5yrs cumulative incidence RTOG	42% (64Gy);50 %(74Gy)		[68]	Conventional 3D conformal RT with HT
Grade 2		15 % (64Gy);25% (74Gy)			
Grade 3		7% (70Gy); 8% (80Gys)			
		4% (64Gy);7%(74Gy)			
Rectal pain					
Grade 2	5yrs cumulative incidence RTOG	5% (64Gy);8%(74Gy)		[68]	Conventional 3D conformal RT with HT
Grade 3		0% (64Gy);2%(74Gy)			
Anorexia					

Grade 1	2 years	11%	[60]	Conventional 3D conformal RT with HT		
Grade 2		25%		3D Conformal RT with HT & EMP		
		5%				
Nausea						
Grade 1	2 years	15%	[60]	Conventional 3D Conformal RT with HT & EMP		
Grade 2		5%				
Erectile dysfunction						
Grade 1	2 yr prevalence LENT-SOMA	74Gy 95.0%	[58]	CIMRT	3-6 mth AS before and during RT	
		60Gy 94% ; 57Gy 90.5%		HIMRT		
	7 yrs	18%(4mth); 21%(8mth)	[57]	3D Conformal RT with HT		
Grade 2	2 yr prevalence LENT-SOMA	91% (74Gy)	[58]	CIMRT	3-6 mth AS before and during RT	
		90.9% (60 Gy) ; 89.3% (57Gy)		HIMRT		
	7 yrs	5%(4mth); 3%(8mth)	[57]	3D Conformal RT with HT		
Grade 3	2 yr prevalence LENT-SOMA	80% (74Gy)	[57]	CIMRT	3-6 mth AS before and during RT	
		79.8% (60Gy) ; 81.8% (57Gy)		HIMRT		
	7 yrs	10%(4mth) ; 17%(8mth)	[57]	3D Conformal RT with HT		
Grade 4	2 yr prevalence LENT-SOMA	64.6% (74Gy)	[58]	CIMRT	3-6 mth AS before and during RT	
		70.1 (60Gy); 64.6 (57Gy)		HIMRT		
	7 yrs	47%(4mth); 42%(8mth)	[57]	3D Conformal RT with HT		
Cardiac effects						
Grade 1	2 yrs	1%	[63]	Conventional 3D conformal RT		
Gynaecomastia						
Grade 1	2yrs NCI-CTC V 3.0 RTOG	45%	[60]	3D Conformal RT with HT & EMP		
Anaemia						
Grade 1		65%			3D Conformal RT with HT & EMP	
		74%			3D Conformal RT with HT	
Grade 2		10%			3D Conformal RT with HT & EMP	
		26%		3D Conformal RT with HT		

Key: Three dimensional-3D; EMP-estramustine phosphate;BT- Brachytherapy; HT-Hormone therapy ; CIMRT- Conventional intensity modulated radiotherapy;HIMRT- Hypofractionated intensity modulated radiotherapy; TAD-Total androgen deprivation; AS-Androgen suppression; NCI-CTC- Canadian National Cancer Institute Common Toxicity Criteria; RTOG- Radiation Therapy Oncology Group; LENT-SOMA -Late Effect in Normal Tissue-Subjective Objective Management Analytic – Scales; RMH-Royal Marsden Hospital Scale; Mth=Month; Yr =year, ≥ greater than and equal to; ≤- less than or equal to. **NB table only includes papers reporting figures of incidence, prevalence and proportion of toxicity.**

Table 6: Incidence of late patient reported toxicity and Quality of life (QOL) scores in RCTs (emboldened text indicates studies where a significant difference in primary outcome was demonstrated).

Type of Toxicity or QOL how & when reported		% of toxicity or QOL score			Treatment type		
LATE EFFECTS-patient reported							
Genitourinary symptoms							
Mean score change from baseline ↑ score =↑ QOL * 6mth 3yrs	FACT-P	-6.1*		[69]	HT		
		-5.2					
		0.1*					
		-5.5					
		-1.4*					
Increase from 13 at baseline	QLQC-30 PR25	Mean score 17		[53]	Conventional 3D conformal RT		
		70 & 80Gy					
		-0.6					
		0.1*					
		-0.4					
Gastrointestinal symptoms							
Bowel problems							
Composite bowel score: 0 (min dysfunction) to 100 (max dysfunction)	7 yr MGH	7.3 (70.2 Gy); 9.1 (79.2)			[65]	Conventional 3D conformal RT	
Mean score change from baseline * 6mth 3yrs	EORTC	-1.3*		[69]	HT		
		-0.3					
		3.4*					
		1.7					
Faecal/rectal urgency							
Grade 1	UCLA-PCI % change in score from baseline (84) to 5yrs	7%		[51] *	Conventional 3D conformal RT with HT		
Grade 2		5%					
Grade 3		3%					
Grade 4		2%					
Mild	UCLA-PCI Cumulative incidence at 5yrs	64Gy	61%	74Gy	[68]	Conventional 3D conformal RT with HT	
Moderate							32%
Severe							
Bowel distress							
Mild	UCLA-PCI Cumulative incidence at 5yrs	64Gy	61%	74Gy	[68]	Conventional 3D conformal RT with HT	
Moderate							29%
Severe							

Bowel problems							
Mild	UCLA-PCI Cumulative incidence at 5yrs	46%	64Gy	46%	74Gy	[68]	Conventional 3D conformal RT with HT
Moderate		26%		29%			
Severe		6%		8%			
Trouble moving bowels							
Mild	FACT-P Cumulative incidence at 5yrs	57%	64Gy	56%	74Gy	[68]	Conventional 3D conformal RT with HT
Moderate		12%		17%			
Severe		5%		9%			
Loose stools							
Grade 1	UCLA-PCI % change in score from baseline (70) to 5 yrs	24%	64 & 74Gy		[51]	Conventional 3D conformal RT	
Grade 2		6 %					
Grade 3		1%					
Bowel disorders							
Point increase from baseline	QLQC-30 PR25	Mean score 8	70 & 80Gy		[53]	Conventional 3D conformal RT	
Treatment related symptoms							
Increase from 5 at baseline	QLQC-30 PR25	8 score	70 & 80Gy		[53]	Conventional 3D conformal RT	
Quality of life							
Global QOI score							
Mean score change form baseline ↑ score = ↑ symptoms * 6mth 3yrs	FACT-P	4.3*	[69]		HT		
		2.5					
		-3.0*				Conventional 3D conformal RT with HT	
	-1.1						
	EORTC-PR13	-1.74*			HT		
		-9.4					
8.98*		Conventional 3D conformal RT with HT					
-11.4							
QOL subscales							
Physical Health Summary	SF-36 (summary scores) *6 mths 3 yrs	68Gy	78Gy	[46]		Conventional 3D conformal RT	
		75.4*	75.5*				
Mental health Summary		73.2	71.8				
		78.1*	77.6*				
Physical functioning		76.7	76.1				
		79.0*	76.0*				
Role -physical		81.1	75.0				
		68.4*	71.9*				
General health		69.1	66.4				
		67.2*	61.1*				

Vitality		65.2	62.4		
		68.2*	67.5*		
		68.2	64.7		
Social functioning		68.5*	85.3*		
		84.0	83.0		
Role-emotional		80.3*	79.8*		
		80.0	80.1		
Mental health		79.0*	75.9*		
		79.0	76.9		
Physical function					
Mean score change from baseline ↑ score = ↑ symptoms * 6mth 3yrs	FACT-P	-4.1*		[69]	HT
		-6.1			Conventional 3D conformal RT with HT
	-7.6*-		HT		
	-5.5		Conventional 3D conformal RT with HT		
EORTC-PR13		-3.5*			
		-9.2			
		-3.8			
		-10.2			
Mean score *Grade 2≥ GU toxicity No toxicity	FACT G 10yrs	91.0		[62]	EBRT & EBRT with HTR Brachytherapy Conventional 3D conformal RT
		85.5*			
	FACT-P 1yr	127.4			
	FACT-P TOI	85.4			
Mean score *Grade 3≥ GU toxicity No toxicity	FACT- G	89.7			
		81.7*			
	FACT -P	124.6			
		110.1*			
FACT-P TOI	83.1				
	71.0*				
Erectile dysfunction					
Always/almost always able to have an erection	SAQ	21%		[63]	Conventional 3D conformal RT
		31%			Conventional 3D conformal RT & HT
Sexual functioning point decrease from baseline 5yrs	QLQC-30 PR25	↓19 points 70Gy & 80Gy		[53]	Conventional 3D conformal RT
Patients reporting a degree of sexual functioning 5yrs		38 70Gy & 80Gy			

Key: 3D-Three dimensional; EMP-estramustine phosphate;BT- Brachytherapy; HT-Hormone therapy; CIMRT- Conventional intensity modulated radiotherapy; HIMRT- Hypofractionated intensity modulated radiotherapy; MXM-Meloxicam; TAD-Total androgen deprivation; AS-Androgen suppression; UCLA-PCI-University of California, Los Angeles, Prostate Cancer Index; EORTC QLQ-C30-European Organisation for Research and Treatment of Cancer-30 (30 questions) -PR13-prostate-specific module (13 questions); FACT-G –Functional Assessment of Cancer Therapy (General); FACT-P- Functional Assessment of Cancer Therapy (Prostate); TOI-Trial Outcome Index; SAQ- Sexual adjustment questionnaire; SF-36- Short Form (36) Health Survey (SF-36); MGH- Massachusetts General Hospital –MGH; Mth=Month; Yr =year; ≥ greater than and equal to; ≤- less than or equal to. **NB table only includes papers reporting figures for incidence, prevalence and proportion of toxicity & mean PRO scores.**