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Gilbert, AJ, Ziegler, L, Martland, M et al. (4 more authors) (2015) Systematic Review of Radiation Therapy Toxicity Reporting in Randomized Controlled Trials of Rectal Cancer: A Comparison of Patient-Reported Outcomes and Clinician Toxicity Reporting. International Journal of Radiation Oncology - Biology - Physics, 92 (3). 555 - 567. ISSN 0360-3016

https://doi.org/10.1016/j.ijrobp.2015.02.021

Table 1: Clinical trial demographics

Reference	Country	Years of study	Design of Toxicity measurement	Patient and/or clinician reported (P/C)	Design	Trial name	Participants in overall study (Participants in toxicity follow up)	Timing of toxicity follow up (median years)	Primary end point	Treatment arms	RT dose	Details of concurrent chemotherapy	Difference in primary outcome	Summary PRO/toxicity difference between treatment arms
Pollack et al 2006 (26)	Sweden	1980-1993	Cross sectional	P & C	Phase I&II	Stockholm trials	1406 (139)	15	Overall survival	Preop RT vs surgery alone	25Gy in 5#	Nil	Yes	Yes - Preop RT more late toxicity (mainly CVD, fecal and urinary incontinence) than surgery alone (69% vs 43%; p=0.002)
Pollack et al 2006 (27)	Sweden	1980-1993	Cross sectional	P & C	Phase I&II	Stockholm trials	1406 (64 – LAR patients only)	15	Overall survival	Preop RT vs surgery alone	25Gy in 5#	Nil	Yes	Yes - Preop RT more anorectal toxicity than surgery alone (Fecal incontinence 57% vs 26%; p=0.01; frequency of bowel movements per week 20 vs 10; p=0.02). No differences in overall HRQOL.
Dahlberg et al 1998 (28)	Sweden	1987-1990	Cross sectional	P	Phase III	Swedish Rectal Cancer Trial	1168 (171)	6.7	Local recurrence and OS	Preop RT vs surgery alone	25Gy in 5#	Nil	Yes	Yes - Preop RT more bowel toxicity than surgery alone (frequency of bowel movements per week 20 vs 10; p<0.001; fecal incontinence loose stools 50% vs 24%; p<0.001)
Bosset et al 2006 (29)	France	1993-2003	Longitudinal	C	Phase III	22921 EORTC	1011 (1011)	5.4	Overall survival	Preop CRT vs preop RT +/- postoperative chemotherapy	45Gy in 25#	5FU week 1 & 5 +/- 4 cycles of 3 weekly postoperative 5FU	No	No significant differences (fecal incontinence in 9% of patients following sphincter-sparing resection)
Tiv et al 2010 (30)	France	1993-2003	Cross sectional	P	Phase III	22921 EORTC	1011 (207)	4.6	Overall survival	Preop CRT vs preop RT +/- postoperative chemotherapy	45Gy in 25#	5FU week 1&5 +/- 4 cycles of 3 weekly postoperative 5FU	No	Yes – patients treated with addition of chemotherapy to preop or postop RT had worse diarrhea (RT 6.9 vs +chemotherapy 21.3*; p=0.001) and lower role (90 vs 83**, p=0.03) and social functioning (85 vs 75**; p=0.02) as well as worse global QOL scores (78 vs 71**; p=0.02). All patients reported low scores for sexual function (18.9**).
Taher et al 2006 (31)	Egypt	1994-1999	Longitudinal	C	Phase III	RCT	50 (50)	5.2	Local recurrence and OS	Preop RT vs post op CRT	Preop 46Gy in 23# vs post op 50Gy in 25# (5FU)	Post op CRT: Concurrent 5FU first 3 days of first and last week of RT	No	No significant differences in late radiation-related toxicity (Grade 3+ radiation-related toxicity reported in 1 patient). Acute grade 3+ radiation-related toxicity: post op CRT 34.6% vs 8.3%; p=0.039.
Sauer et al 2004 (32)	Germany	1995-2002	Longitudinal	C	Phase III	RCT	421 (421)	3.82	Overall survival	Preop CRT vs post op CRT	50.4 Gy in 28# (5FU)	Concurrent 5FU daily weeks 1 and 5	No	Yes - Worse acute and late grade 3+ toxicity in post op CRT vs preop CRT (Acute: 40% vs 27% ; p=0.001; Late: 24% vs 14%; p=0.01)
Braendengen et al 2011 (33)	Norway	1996-2003	Cross sectional	P & C	Phase III	RCT	207 (105)	6.7	Overall survival	Preop CRT vs preop RT	50Gy in 25 (+/- 5FU)	Concurrent 5FU days 1-2, 11-12 and 21-22.	No	Yes - More patients (without a stoma) in the CRT group had good anal function vs RT (using St Mark's score for fecal incontinence): 30% vs 11% (p=0.046). Severe erectile dysfunction reported in both groups (Mean 6.9 vs 10.4[1]: using IIEF)

Braendengen et al 2012 (34)	Norway	1996-2003	Longitudinal	P	Phase III	RCT	207 (105)	6.7	Overall survival	Preop CRT Vs preop RT	50Gy in 25 (+/-5FU)	Concurrent 5FU days 1-2, 11-12 and 21-22.	No	No statistically significant differences found in HRQOL. A clinically significant reduction in physical functioning found in both groups (CRT: 94 to 86*; RT: 94 to 87*)
Marijnen et al 2005 (35)	The Nether-lands	1996-1999	Longitudinal	P	Phase III	Dutch TME trial	1861 (786)	2	Local recurrence	Preop RT vs TME	25Gy in 5#	Nil	Yes	Yes - Preop RT worse sexual function than surgery alone (males: p=0.004; females: p <0.001). Preop RT slower recovery of bowel function and worse fecal incontinence (51.3% vs 36.5%; p= 0.002). No differences in overall QOL.
Peeters et al 2005 (36)	The Nether-lands	1996-2000	Cross sectional	P	Phase III	Dutch TME trial	1861 (597)	5.09	Local recurrence	Preop RT vs TME	25Gy in 5#	Nil	Yes	Yes – Preop RT worse fecal incontinence than surgery alone (62% vs 38%; p=0.001) with bowel function impacting on ADLs (34% vs 22%; p=0.01). No differences in urinary function or overall QOL.
Lange et al 2007 (37)	The Nether-lands	1996-1999	Longitudinal	P	Phase III	Dutch TME trial	1861 (399)	5	Local recurrence	Preop RT vs TME	25Gy in 5#	Nil	Yes	Yes - Preop RT worse fecal incontinence than surgery alone (61.5% vs 38.8%; p<0.001).
Lange et al 2008 (38)	The Nether-lands	1996-1999	Longitudinal	P	Phase III	Dutch TME trial	1861 (785)	5	Local recurrence	Preop RT vs TME	25Gy in 5#	Nil	Yes	No significant differences in urinary function. Incontinence reported in 38.1% of all patients (72% had normal function pre treatment).
Lange et al 2009 (39)	The Nether-lands	1996-1999	Longitudinal	P	Phase III	Dutch TME trial	1861 (526)	2	Local recurrence	Preop RT vs TME	25Gy in 5#	Nil	Yes	Yes – Preop RT was a risk factor for deterioration in male sexual function (p=0.003) and ejaculatory problems (p=0.026). Preop RT was the only risk factor for deterioration in female sexual functioning (p=0.033).
Stephens et al 2010 (40)	UK	1998-2005	Longitudinal	P	Phase III	CRO7	1350 (1208)	2	Local recurrence	Preop RT vs selective postop CRT	25Gy in 5# vs selective 45Gy in 25# (5FU)	Concurrent CVI 5FU or weekly bolus	Yes	Yes - Preop RT worse fecal incontinence than selective postop CRT (53.2% vs 37.3%; p=0.007). Deterioration in male sexual function following treatment in all groups (p<0.001).
Bujko et al 2006 (41)	Poland	1999-2002	Cross sectional	C	Phase III	RCT: phase III	316 (221)	1	Sphincter preservation of 15%	Preop CRT vs preop RT	25Gy in 5# or 50.4Gy in 28# (5FU)	Concurrent 5FU daily week 1 & 5	No	No significant differences in overall late radiation-related toxicity (CRT: 27% vs RT: 28.3%; p=0.81) or grade 3+ toxicity (CRT: 10·1% versus RT: 7·1%; P = 0·360). Acute radiation-related toxicity was higher in CRT group (18·2% vs 3·2%; p < 0·001).
Pietrzak et al 2007 (42)	Poland	1999-2002	Cross sectional	P	Phase III	RCT: phase III	316 (221)	1	Sphincter preservation of 15%	Preop CRT vs preop RT	25Gy in 5# or 50.4Gy in 28# (5FU)	Concurrent 5FU daily week 1 & 5	No	No significant differences in QOL (RT: 57* vs CRT: 61*; p=0.22) or anorectal function (estimated as good/very good RT: 41% vs CRT 37%; p=0.52) or sexual function (males: p=0.56; females: p=0.1)

Mohiuddin et al 2006 (43)	USA	2001-2003	Longitudinal	C	Phase II	RCT: Phase II	106 (106)	3	Pathologic complete response	Pre op CRT (5FU) vs preop CRT (5FU & irinotecan)	55.2 to 60Gy (5FU) in 1.2Gy bid vs 50.4 to 54Gy at 1.8Gy per day (5FU& irinotecan)	Concurrent CVI 5FU or CVI 5FU and weekly irinotecan	No	No significant differences in overall late radiation-related toxicity (CRT +irinotecan: 8% vs CRT: 4%) or acute chemotherapy or grade 3+ radiation-related toxicity (42% vs 31%).
Ngan et al 2012 (44)	Australia/NZ	2001-2006	Longitudinal	C	Phase III	RCT	326 (313)	5	Local recurrence	Preop CRT vs preop RT	25Gy in 5# and 50.4Gy in 28# (5FU)	Concurrent 5FU daily 7 days a week.	No	No significant differences in any grade 3+ toxicity late radiation-related toxicity (CRT: 8.2% vs RT: 5.8%; p=0.53) or grade 3+ small/large bowel toxicity (CRT: 5.1% vs RT 3.2%; p=0.53)
Park et al 2011 (45)	Korea	2004-2006	Longitudinal	C	Phase III	RCT: Phase III	240 (240)	4.3	OS, local control, sphincter preservation and toxicity	Preop CRT vs post op CRT	50Gy in 25# (CAP)	Capecitabine BD (without weekend breaks) daily during RT	No	No significant differences in any grade 3+ late radiation-related toxicity (preop CRT: 8% vs postop CRT: 3%; p=0.35) or acute toxicity (15% vs 16%; p=0.83).
Gerard et al 2012 (46)	France	2005-2008	Longitudinal	P & C	Phase III	ACCORD 12/0405 PRODIGE 2	598 (575)	3	Pathological complete response	Preop CRT (CAP45) vs Preop CRT (CAPOX50)	45Gy in 25# (CAP45) vs 50Gy in 25# (CAPOX50)	CAP45 - Capcitabine BD each radiation day. CAPOX50 - Capecitabine BD each radiation day. Plus oxaliplatin once a week for 5 weeks	No	No significant differences in any grade 3+ late radiation-related toxicity, over 3 year follow up (CAP45: 6.5% vs CAPOX50: 5.4%) or fecal incontinence (16% vs 20%). 71% of all patients reported erectile dysfunction following treatment (35% before).

Key 1: RCT - Randomised controlled trial; RT - radiotherapy; CRT - chemoradiotherapy; # - fraction; TME - total mesorectal excision; 5FU - 5 – flurouracil; CVI – continuous venous infusion; OS – overall survival; HRQOL – Health related quality of life; CVD – cardiovascular disease; ADL – activities of daily living. *EORTC-QLQ symptom mean scores: Scores range from 0-100 with higher scores indicating more symptoms. **EORTC-QLQ function mean scores: Scores range from 0-100 with higher scores indicating fewer functional problems. IIEF - International index of erectile function ([†]Score ranges from 1-30 with lower scores indicating more functional problems.

Table 2: Comparison between toxicity reported by clinician reported instruments and patient reported measure using QUANTEC recommendations for reporting*

	RCT PUBLICATIONS REPORTING ON TOXICITY WITH PATIENT REPORTING		RCT PUBLICATIONS REPORTING ON TOXICITY WITH CLINICIAN REPORTING	
TOTAL NUMBER OF RCT PUBLICATIONS INCLUDED (N=21)	14 (References: 26-28, 30, 33-40, 42, 46)		11 (References: 26, 27, 29, 31-33, 41, 43-46)	
Publications with both patient and clinician reporting N=4* (References: 26, 27, 33, 46)				
COCHRANE RISK OF BIAS				
Overall number of RCTs with a overall low risk of bias assessed	11		5	
TOXICITY INSTRUMENT USED				
	Modified or self created questionnaires	6	CTCAE v2	1
	ASCRS QOL questionnaire	1	CTCAE v3	1
	ASCT questionnaire	1	German Classification system	1
	EORTC QLQ C30	4	Interviews	3
	EORTC QLQ C38	2	RTOG/EORTC late radiation morbidity scoring criteria	4
	IIEF	1	St Marks score for faecal incontinence	1
	Rotterdam symptom checklist	1	WHO	1
	SF36	1	Not reported	1
	SVQ	1		
	Visual analogue scale QOL	2		
Total number of instruments used	15		7	
REPORTING OF TOXICITY				
Baseline symptom reporting	Yes	6	Yes	1
	No	8	No	10
Acute symptom reporting	Yes	6	Yes	9
	No	8	No	2
Are all grades of toxicity reported (from mild to severe symptoms)?	Yes, all grades	11	Yes, all grades	3
	No, more severe grades only (grade 3+)	1	No, more severe grades only (grade 3+)	5
	No, presence or absence of symptom	2	No, presence or absence of symptom	3
Most frequent type of toxicity reported	**Bowel**	**11**	**Bowel**	**10**
	Urinary	**5**	**Urinary**	**5**
	Sexual	**7**	Sexual	0
	HRQOL	**6**	HRQOL	0
	Skin	0	**Skin**	**5**
	Haematological	0	**Haematological**	**5**
Are various symptoms referable to a single organ grouped together (e.g. urinary frequency and incontinence grouped as 'bladder symptoms')?	Yes (grouped symptoms)	0	Yes (grouped symptoms)	5
	No (individual symptoms)	11	No (individual symptoms)	2
	Both	3	Both	2
	Unclear	0	Unclear	2

*For the four papers including data from both clinician-reporting and patient-reporting each of the different reports is considered separately.

KEY: HRQOL - Health related quality of life; ASCRS - American Society of Colon and Rectal surgeons QOL questionnaire; ASCT - Anal Sphincter-conserving treatment questionnaire; SF 36 – Short form health survey; EORTC QLQ - European Organisation for Research and Treatment of Cancer quality of life questionnaire; IIEF – International index of erectile function; SVQ – Sexual function-vaginal changes questionnaire; WHO – World Health organisation, CTCAE – Common Terminology for Common Adverse Events.

Table 3: Prevalence of toxicity reported by treatment type according to clinician or patient reports (PRO)

	RANGE OF TOXICITY REPORTED BY TREATMENT TYPE (References in brackets)				
TYPE OF TOXICITY	Surgery alone	Short course RT (25Gy in 5)	Long course RT (45-50.4Gy in 25-28)	Long course 5FU CRT (45-50.4Gy in 25-28)	Long course 5FU CRT with additional chemotherapy (45-50.4Gy in 25-28)
CLINICIAN-REPORTED					
ANY GRADE 3+ TOXICITY (%)				**1.3-14** (31, 32, 43, 45, 46[1])	**1-8** (43, 46)
BOWEL SYMPTOMS					
Grade 3+ bowel toxicity (%)		**3.2-5.1** (41, 44)		**1.4-9** (32, 41, 43, 44)	**4** (43)
Fecal incontinence (%)				**9** (29)	**9** (29)
Diarrhea (% Grade 2+)				**9.6** (29)	**9.6** (29)
URINARY SYMPTOMS					
Grade 3+ urinary toxicity (%)		**1.3-1.4** (41, 44)		**0.7-2** (32, 41, 43, 44)	**0** (43)
PATIENT-REPORTED					
BOWEL SYMPTOMS					
Fecal incontinence (%)	**24-38.8** (26, 27, 28, 35, 36, 37, 40)	**50-62** (26, 27, 28, 35, 36, 37, 40)			
Fecal incontinence (liquid stools) (%)		**72** (42)	**38** (33)	**58-66** (33, 42)	
Fecal incontinence (solid stools) (%)		**42** (42)	**13** (33)	**8-50** (33, 42)	
Frequency (median times per day)	**1.4-3** (27, 28, 36)	**2.8-4** (27, 28, 36, 42)		**5** (42)	
Urgency (unable to defer <10mins)		**60 (Very often 7%)** (42)		**64 (Very often 8%)** (42)	
Urgency (median deferral time)	**10** (28)	**5** (28)			
URINARY SYMPTOMS					
Urinary incontinence (%)	**27-38.1** (26, 36, 38)	**38.1-45** (26, 36, 38)	**18** (33)	**28** (33)	
SEXUAL DYSFUNCTION (MALES)					
Sexual function (EORTC-QLQ CR38 mean scores*)	**40.8- 57.4** (35, 40)	**47.4 - 65.7** (35, 40)			
Decline in sexual life (%)		**80** (42)		**70** (42)	
Erectile dysfunction (%)	**47.1** [(35)EORTC-QLQ CR38 mean scores]	**53.9** [(35)EORTC-QLQ CR38 mean scores]	**10.4** [(33) IIEF mean score**]	**71** (%)(42) **and 6.9** [(33) IIEF mean score**]	**71** (42)

Ejaculation dysfunction [EORTC-QLQ CR38 mean scores*]	**31.7** (35)	**42.5** (35)			
SEXUAL DYSFUNCTION (FEMALES)					
Sexual function [EORTC-QLQ CR38 mean scores*]	**29.9** (35)	**50** (35)			
Decline in sexual life (%)		**41** (42)		**52** (42)	
Vaginal dryness (%)			**100** (33)	**86** (33)	
Dyspareunia (%)			**50** (33)	**86** (33)	

Key: ł: References; *EORTC-QLQ symptom mean scores: Scores range from 0-100 with higher scores indicating more symptoms. ** IIEF - International index of erectile function: Score ranges from 1-30 with lower scores indicating more functional problems (1 to 10 – severe dysfunction).

Table 4: Overview of RCTs PRO quality of reporting

		TOTAL: n = 14 (%)
TITLE AND ABSTRACT		
The PRO should be identified in the abstract as a primary or secondary outcome (If PRO or QOL mentioned in the title/abstract this is sufficient for 'Yes')	No	2 (14)
	Yes	12 (86)
Note all included PRO studies reported on adverse events as a secondary outcome.		
INTRODUCTION, BACKGROUND AND OBJECTIVES		
Include background and rational for PRO assessment	No	1 (7)
	Yes	13 (93)
The PRO hypothesis should be stated and relevant domains identified, if applicable	No	2 (14)
	Yes	12 (86)
METHODS		
Participants: Not PRO-specific, unless the PROs were used in eligibility or stratification	No	0 (0)
	Yes	0 (0)
	N/A	14 (100)
Outcomes: Evidence of PRO instrument validity and reliability should be provided or cited if available (Both – includes a mix of validated and non validated instruments or validated instruments used methodologically in a non-validated way)	No	4 (28)
	Yes	5 (36)
	Both	5 (36)
Outcomes: States methods of data collection	Not stated	6 (43)
	Paper	5 (36)
	Paper or interview	3 (21)
	Electronic	0 (0)
Outcomes: States who completed the assessment	Patients	11 (79)
	Patient and clinician (through interviews)	3 (21)
Sample size: Not required for PRO unless it is a primary outcome	N/A	N/A
RANDOMIZATION		
Statistical methods: Statistical approaches for dealing with missing data are explicitly stated	No	10 (71)
	Yes	4 (29)
RESULTS		
Participant flow: The number of PRO outcome data at baseline and at subsequent time points should be made transparent	No	4 (29)
	Yes	10 (71)

Baseline data: Include baseline PRO data when collected	No	8 (57)
	Yes	6 (43)
Numbers analysed: Include number of participants (denominator) in each analysis and whether analysis was by original assigned group	No	0 (0)
	Yes	14 (100)
Outcomes and estimations: For multidimensional PROs provide results and effect sizes from each domain and time point	No	0 (0)
	Yes	14 (100)
Outcomes and estimations: Report estimated effect size, and it's precision	No	9 (67)
	Yes	5 (33)
DISCUSSION		
Limitations: PRO-specific limitations	No	3 (25)
	Yes	11 (75)
Limitations: Implications for generalizability and implications for clinical practice	No	0 (0)
	Yes	14 (100)
Interpretation: PRO data should be interpreted in relation to clinical outcomes including survival data, where relevant	N/A	6 (43)
	No	1 (7)
	Yes	7 (50)