Supplementary materials

Robust dose planning objectives for mesorectal radiotherapy of early stage rectal cancer – a multicentre dose planning study

Appendix A: Selected studies of dose-volume effect for bowel toxicity

Reference	Endpoint	Type	Patient #	Patient population	Treatment technique	OAR definition	Main findings
Baglan et al (1)	Acute bowel toxicity	Retrospective	40	Rectal cancer, LCRT	3D-CRT	Bowel loops	Correlation with volume at each dose level at 5-40 Gy. Suggestion of "threshold effect" at ~15-25 Gy. Suggested volume-response for V_{15Gy}.
Tho et al (2)	Acute bowel toxicity	Retrospective	41	Rectal cancer, LCRT	3D-CRT	"Small bowel" (loops?)	Correlation with volume at each dose level at 5-40 Gy. Strongest correlations for V_{5Gy} -V_{30Gy}
Gunnlaugsson et al (3)	Acute bowel toxicity	Retrospective	28	Rectal cancer, LCRT + oxaliplatin	3D-CRT	Small bowel loops, large bowel, whole abdomen	Only correlation for volume of small bowel irradiated. Correlation with all dose levels 5-50 Gy, strongest for V_{15Gy}.
Kavanagh et al (4)	Acute & late bowel toxicity	**Review** (QUANTEC)	NA	Various pelvic cancers	Primarily 3D-CRT	NA	Six studies of small bowel complication identified for review of acute toxicity; one study for late toxicity. Conclusion: Outlining of bowel loops - minimise V_{15Gy}. Outlining peritoneal space - minimise V_{45Gy}. This will also likely reduce late toxicity risk.
Robertson et al (5)	Acute bowel toxicity	Retrospective	152	Rectal cancer, LCRT pre- & post-op	3D-CRT	Small bowel loops	Absolute V_{15Gy}, V_{20Gy} and V_{25Gy} correlated with acute toxicity; similar findings for pre- and post-operative patients.
Chen et al (6)	Patient-reported acute GI symptoms	Prospective PRO collection, explorative analysis	66	Rectal cancer, LCRT	3D-CRT	Small bowel loops	Absolute V_{15Gy} correlated with overall patient-reported GI symptoms.
Banerjee et al (7)	Acute bowel toxicity	Retrospective	67	Rectal cancer, LCRT	3D-CRT	Small bowel loops, peritoneal space	Absolute V_{15Gy} and V_{25Gy} correlated with acute toxicity for both small bowel loops and peritoneal space.

Yang et al (8)	Acute bowel toxicity	Retrospective	177	Rectal cancer, LCRT	IMRT & 3D-CRT	Bowel loops	Relative V_{45Gy} best predictor for acute toxicity in multivariate modelling.
Devisetty et al (9)	Acute bowel toxicity	Retrospective	48	Anal cancer, CRT	IMRT	Outer contour of bowel	Absolute V_{30Gy} correlated with clinically significant acute toxicity.
DeFoe et al (10)	Acute bowel toxicity	Retrospective	58	Anal cancer, CRT	IMRT	Intestinal cavity	Absolute V_{30Gy} and V_{40Gy} correlated with acute toxicity.
Han et al (11)	Acute bowel toxicity	Prospective	42	Anal cancer, CRT	IMRT	Small and large bowel loops	Relative V_{30Gy} for small bowel showed moderate correlation with acute toxicity; no correlation for large bowel.
Julie et al (12)	Acute bowel toxicity	Retrospective	108	Anal cancer, CRT	IMRT	Bowel loops	Model combining absolute bowel V_{45Gy} and mean dose to hottest 5% of bowel best predictor for acute toxicity.
Olsen et al (13)	Acute & late bowel toxicity	Prospective	52	Anal cancer, CRT	IMRT	Small bowel loops, intestinal cavity	Absolute V_{25Gy}-V_{35Gy} for small bowel correlated with acute toxicity (and absolute V_{5Gy}-V_{25Gy} for intestinal cavity with high grade acute toxicity). Absolute V_{60Gy} for intestinal cavity correlated with late toxicity.
Ng et al (14)	Acute bowel toxicity	Retrospective	55	Anal cancer, CRT	IMRT	Small and large bowel loops, intestinal cavity	Absolute volume of intestinal cavity correlated with acute toxicity for all dose levels 5-50 Gy; strongest correlation for V_{10Gy}-V_{35Gy}.
Sanguineti et al (15)	Acute bowel toxicity	Retrospective	149	Prostate cancer	3D-CRT & IMRT	Intestinal cavity	Absolute V_{15Gy} and V_{30Gy} cavity correlated with acute toxicity.
Perna et al (16)	Acute bowel toxicity	Retrospective	96	Prostate cancer, post-op	IMRT	Intestinal cavity outside PTV, bowel loops	Relative V_{50Gy} for bowel loops correlated with acute toxicity.
Sina et al (17)	Patient-reported acute GI symptoms	Prospective	206	Prostate cancer, some post-op	IMRT	Small and large bowel loops	Best multivariate model for change in loose stools from baseline to RT mid-point included absolute V_{42Gy} for small bowel.
Chi et al (18)	Acute bowel toxicity	Retrospective	32	Endometrial cancer, post-op	IMRT	Small bowel loops, limited bowel space, intestinal cavity	Relative V_{45Gy} for intestinal cavity correlated with acute toxicity, no correlation for alternative outlining.
Isohashi et al (19)	Acute & late bowel toxicity	Retrospective	62	Cervical cancer, post-op	3D-CRT & IMRT	Small bowel loops, bowel bag	Higher values of absolute V_{40Gy} and V_{45Gy} for both small bowel and bowel bag for patients with acute toxicity,

							higher values of absolute V_{15Gy}-V_{45Gy} for patients with chronic toxicity.
Chopra et al (20)	Acute & late bowel toxicity	Retrospective	103	Cervical cancer, post-op	3D-CRT & IMRT	Small and large bowel loops, intestinal cavity	Absolute V_{30Gy} for intestinal cavity correlated with acute toxicity. Absolute V_{30Gy}-V_{40Gy} for small and large bowel and intestinal cavity correlated with late toxicity in univariate, but not multivariate, analysis.

Pubmed search string

((((chemoradiation) OR radiation therapy) OR radiochemotherapy)) AND ((((Toxicity intestines) OR (((Gastrointestinal toxicity) OR Gastrointestinal side effects)))) OR Side effects intestines) AND ((dose-response) OR dose-volume)

Abstracts were screened by hand, and relevant papers selected for full text review, with additional studies identified from reference lists.

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Appendix B: Calculation of SCRT optimisation dose levels

All short course radiotherapy (SCRT) optimisation dose levels were based on dose levels from long course radiotherapy (LCRT), recalculated to 5-fraction treatment schedules, using:

$$D_{SCRT} = \frac{n_{SCRT}}{2}\left(\sqrt{\left(\alpha/\beta\right)^2 + 4\frac{D_{LCRT}}{n_{SCRT}}\left(\frac{D_{LCRT}}{n_{LCRT}} + \alpha/\beta\right)} - \alpha/\beta\right)$$

where D_{SCRT} / n_{SCRT} and D_{SCRT} / n_{SCRT} are total dose and number of fractions for the SCRT and LCRT treatment schedules, respectively. This equation follows directly from the linear-quadratic equation for effective dose.

Dose levels were recalculated using α/β = 10 Gy (generic value for acute complications) and α/β = 3 Gy (generic value for late complications), and with n_{SCRT} set to 25-30 fractions (to represent the range of LCRT schedules used in clinical practice).

Results can be found in Table B1.

	α/β = 10 Gy	α/β = 3 Gy
15 Gy		
Originally in 25 fractions	12.7 Gy	10.6 Gy
Originally in 30 fractions	12.6 Gy	10.4 Gy
30 Gy		
Originally in 25 fractions	23.0 Gy	18.7 Gy
Originally in 30 fractions	22.7 Gy	18.1 Gy
35 Gy		
Originally in 25 fractions	26.2 Gy	21.2 Gy
Originally in 30 fractions	25.8 Gy	20.5 Gy

Table B1: Recalculation of dose levels from long course (25-30 fractions) to short course (5 fractions) schedules.

Appendix C: Detailed dose planning results

Planning results long-course radiotherapy			
	Centre 1	**Centre 2**	**Centre 3**
CTV			
$V_{47.5Gy}$ [%]	100.0 (100.0 -100.0)	100.0 (100.0 - 100.0)	100.0 (100.0 - 100.0)
PTV			
$V_{47.5Gy}$ [%]	99.4 (99.1 - 99.4)	99.1 (99.1 - 99.2)	99.8 (99.7 - 99.9)
V_{45Gy} [%]	100.0 (100.0 - 100.0)	100.0 (100.0 - 100.0)	100.0 (100.0 - 100.0)
$V_{52.5Gy}$ [%]	0.1 (0.1 - 0.3)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)
$D_{50\%}$ [Gy]	50.5 (50.4 - 50.5)	49.8 (49.7 - 49.9)	50.0 (50.0 - 50.0)
Bowel cavity			
V_{15Gy} [cm^3]	169 (162 – 201)	137 (123 – 158)	144 (121 – 185)
V_{20Gy} [cm^3]	128 (111 – 156)	113 (98 – 136)	118 (89 – 153)
V_{30Gy} [cm^3]	92 (74 – 111)	87 (72 – 109)	81 (63 – 108)
V_{45Gy} [cm^3]	62 (47 – 73)	58 (45 – 75)	53 (41 – 68)
Small bowel loops			
V_{15Gy} [cm^3]	22 (0 – 68)	10 (0 – 45)	20 (0 – 57)
V_{20Gy} [cm^3]	9 (0 – 47)	5 (0 – 37)	9 (0 – 45)
V_{30Gy} [cm^3]	1 (0 – 30)	1 (0 – 28)	1 (0 – 27)
V_{45Gy} [cm^3]	0 (0 – 18)	0 (0 – 19)	0 (0 – 17)
Bladder			
V_{15Gy} [%]	53.1 (39.4 - 58.4)	33.1 (22.7 - 50.6)	36.5 (25.3 - 43.1)
V_{35Gy} [%]	12.6 (6.4 - 15.3)	13.0 (5.5 - 15.8)	11.2 (4.5 - 13.6)
V_{50Gy} [%]	1.5 (0.5 - 3.5)	0.5 (0.1 - 1.4)	1.5 (0.8 - 3.0)
Right femoral head			
V_{25Gy} [%]	3.0 (0.3 - 7.4)	6.2 (5.4 - 9.1)	0.0 (0.0 - 0.2)
V_{50Gy} [%]	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)
Left femoral head			
V_{25Gy} [%]	2.9 (0.9 - 5.7)	7.4 (4.3 - 8.6)	0.0 (0.0 - 0.1)
V_{50Gy} [%]	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 – 0.0)
CI1	0.89 (0.87 - 0.90)	0.96 (0.95 - 0.97)	0.93 (0.93 - 0.94)
CI2	3.27 (3.11 - 3.37)	4.83 (4.53 - 5.02)	3.43 (3.34 - 3.50)

Table C1: Planning results for long-course radiotherapy (LCRT) divided by centre. All numbers are medians with interquartile ranges (IQR) in brackets. CTV: Clinical target volume. PTV: Planning target volume. CI: Conformity index.

Planning results short-course radiotherapy			
	Centre 1	**Centre 2**	**Centre 3**
CTV			
$V_{23.75Gy}$ [%]	100.0 (100.0 - 100.0)	100.0 (100.0 - 100.0)	100.0 (100.0 - 100.0)
PTV			
$V_{23.75Gy}$ [%]	99.4 (99.3 - 99.5)	99.1 (99.0 - 99.1)	99.8 (99.5 - 99.8)
$V_{22.5Gy}$ [%]	100.0 (99.9 - 100.0)	100.0 (100.0 - 100.0)	100.0 (100.0 - 100.0)
$V_{26.25Gy}$ [%]	0.2 (0.1 - 0.3)	0.0 (0.0 - 0.0)	0.7 (0.4 - 0.8)
D_{50} [Gy]	25.3 (25.2 - 25.3)	24.9 (24.9 - 24.9)	25.0 (25.0 - 25.0)
Bowel cavity			
V_{10Gy} [cm^3]	135 (128 – 168)	114 (102 – 142)	110 (92 – 155)
$V_{12.5Gy}$ [cm^3]	109 (96 – 138)	98 (84 – 125)	91 (75 – 126)
V_{18Gy} [cm^3]	79 (65 – 101)	76 (63 – 99)	67 (53 – 88)
V_{23Gy} [cm^3]	59 (46 – 74)	55 (43 - 70)	51 (38 – 64)
Small bowel loops			
V_{10Gy} [cm^3]	15 (0 – 51)	7 (0 – 39)	9 (0 – 40)
$V_{12.5Gy}$ [cm^3]	6 (0 – 38)	3 (0 – 32)	4 (0 – 32)
V_{18Gy} [cm^3]	0 (0 – 25)	0 (0 – 24)	0 (0 – 22)
V_{23Gy} [cm^3]	0 (0 – 17)	0 (0 – 17)	0 (0 – 16)
Bladder			
$V_{12.5Gy}$ [%]	24.7 (14.3 - 33.1)	20.9 (9.4 - 28.9)	21.9 (9.7 - 25.5)
V_{21Gy} [%]	8.4 (3.9 - 10.6)	8.2 (3.6 - 9.8)	7.2 (3.1 - 8.1)
V_{25Gy} [%]	1.6 (0.6 - 3.0)	0.9 (0.3 - 1.8)	1.6 (0.6 - 2.8)
Right femoral head			
$V_{12.5Gy}$ [%]	3.9 (0.7 - 7.9)	7.2 (3.1 - 8.8)	0.0 (0.0 - 0.0)
V_{25Gy} [%]	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)
Left femoral head			
$V_{12.5Gy}$ [%]	2.2 (1.1 - 3.9)	5.6 (4.4 - 8.2)	0.0 (0.0 – 0.0)
V_{25Gy} [%]	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)
CI1	0.87 (0.86 - 0.89)	0.95 (0.95 - 0.96)	0.94 (0.93 - 0.95)
CI2	3.31 (3.20 - 3.45)	4.57 (4.45 - 5.17)	3.48 (3.44 - 3.56)

Table 2: Planning results for short-course radiotherapy (SCRT) divided by centre. All numbers are medians with interquartile ranges (IQR) in brackets. CTV: Clinical target volume. PTV: Planning target volume. CI: Conformity index.