



Systematic Review

Systematic review and meta-analysis of small bowel dose–volume and acute toxicity in conventionally-fractionated rectal cancer radiotherapy



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ABSTRACT

Introduction: The limited radiation tolerance of the small-bowel causes toxicity for patients receiving conventionally-fractionated radiotherapy for rectal cancer. Safe radiotherapy dose-escalation will require a better understanding of such toxicity. We conducted a systematic review and meta-analysis using published datasets of small bowel dose–volume and outcomes to analyse the relationship with acute toxicity. **Materials and methods:** SCOPUS, EMBASE & MEDLINE were searched to identify twelve publications reporting small-bowel dose–volumes and toxicity data or analysis. Where suitable data were available (mean absolute volume with parametric error measures), fixed-effects inverse-variance meta-analysis was used to compare cohorts of patients according to Grade ≥ 3 toxicity. For other data, non-parametric examinations of irradiated small-bowel dose–volume and incidence of toxicity were conducted, and a univariate logistic regression model was fitted.

Results: On fixed-effects meta-analysis of three studies (203 patients), each of the dose–volume measures V_{5Gy} – V_{40Gy} were significantly greater ($p < 0.00001$) for patients with Grade ≥ 3 toxicity than for those without. Absolute difference was largest for the lowest dose–volume parameter; however relative difference increases with increasing dose. On logistic regression multiple small-bowel DVH parameters were predictive of toxicity risk (V_{5Gy} , V_{10Gy} , V_{30Gy} – V_{45Gy}), with V_{10Gy} the strongest ($p = 0.004$).

Conclusions: Analysis of published clinical cohort dose–volume data provides evidence for a significant dose–volume–toxicity response effect for a wide range of clinically-relevant doses in the treatment of rectal cancer. Both low dose and high dose are shown to predict toxicity risk, which has important implications for radiotherapy planning and consideration of dose escalation for these patients.

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Among patients receiving preoperative chemoradiotherapy for rectal cancer, CTC Grade ≥ 2 acute gastrointestinal toxicity is seen in 20% of patients, and Grade ≥ 3 in 10% [1]. This toxicity causes treatment to be suspended, altered, or even terminated prematurely, in up to 5% of patients [2], and failure to deliver treatment per protocol may have implications for achieving tumour control.

Much of this toxicity can be attributed to inadvertent irradiation of the small bowel, for which the dose–volume toxicity relationship was reviewed nearly a decade ago in the QUANTEC programme [3]. It is believed radiotherapy dose escalation [4] and novel radiation drug combinations may improve disease response in rectal cancer, however a better understanding of the radiation tolerance of the small-bowel will be required for these to be implemented safely. The aim of this work was to refine dose–volume toxicity relationship parameters for small-bowel radiation toxicity incorporating cohort-based datasets with

detailed dose–volume–histogram data for rectal cancer patients treated with chemoradiation.

Method and materials

Literature search

The SCOPUS, EMBASE, and MEDLINE electronic databases were searched systematically using appropriate subject headings and key words, such as *small bowel*, *ileum*, *jejunum*, *toxicity* and *radiation/radiotherapy*, for papers published in English since 2002. The PRISMA recommendations were followed where possible [5]. Publications were then identified that analysed and/or provided small bowel dose–volume histogram (DVH) values, for patients treated with conventionally fractionated radiotherapy.

Data analysis

Published DVH data were collated directly where possible. In some cases [6,7], plot digitisation was used to analyse published

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Table 1

Summary details of papers reporting dose–volume and toxicity data for small bowel and/or analyses of the dose–volume relationship for the small bowel in the treatment of rectal cancer with radiotherapy. Papers providing DVH data are highlighted in bold. Findings from DVH–toxicity analyses are summarised in the final column.

| Reference | Data | N = | Concurrent chemo | RT dose [Gy] | RT planning | Toxicity outcome | Toxicity scale | Toxicity incidence | Small bowel dose–volume parameter predictive of toxicity (with threshold if reported) |
|--|------|-----|-----------------------------|--|-------------|-------------------------------------|----------------|--------------------|--|
| Baglan 2002 [15] | R | 40 | 5-FU | 50.4 Gy in 28 # (45 Gy to pelvis) | 3D-CRT | Acute small bowel Grade ≥ 3 | CTC v2 | 25% | $V_{15\text{Gy}}$ 150 cm ³ |
| Tho 2006 [16] | P | 41 | 5-FU | 45 Gy in 25 # | 3D-CRT | Acute diarrhoea Grade ≥ 2 | CTCAE v3 | 20% | $V_{5\text{Gy}}$ to $V_{42.75\text{Gy}}$ |
| Gunnlaugsson 2007 [6] | R | 28 | Oxaliplatin & 5-FU | 50.4 Gy in 28 # (n = 15) 50 Gy in 25 # (n = 13) | 3D-CRT | Acute diarrhoea Grade ≥ 2 | CTC v2 | 29% | $V_{15\text{Gy}}$ to $V_{45\text{Gy}}$ |
| Robertson 2008 [19] | P | 96 | 5-FU | 45 Gy in 25 # | 3D-CRT | Acute diarrhoea Grade ≥ 3 | CTCAE v3 | 21% | $V_{5\text{Gy}}$ 500 cm ³ , $V_{10\text{Gy}}$ 300 cm ³ , $V_{15\text{Gy}}$ 150 cm ³ , $V_{20\text{Gy}}$ 145 cm ³ , $V_{25\text{Gy}}$ 140 cm ³ , $V_{30\text{Gy}}$ 135 cm ³ , $V_{35\text{Gy}}$ 130 cm ³ , $V_{40\text{Gy}}$ 125 cm ³ , $V_{15\text{Gy}}$ 130 cm ³ |
| Robertson 2010 [17] | Mix | 152 | 5-FU | 45 Gy in 25 # | 3D-CRT | Acute diarrhoea Grade ≥ 3 | CTCAE v3 | 21% | |
| Arbea 2012 [23] | R | 100 | Capecitabine-oxaliplatin | 47.5 Gy in 20 # | IMRT | Acute diarrhoea Grade ≥ 3 | NS | 9% | $V_{10\text{Gy}}$ 92.6 cm ³ , $V_{15\text{Gy}}$ 78.8 cm ³ , $V_{50\text{Gy}}$ 4.44 cm ³ |
| Chen 2012 [22] | P | 66 | 5-FU/capecitabine | 50.4 Gy in 28 # | 3D-CRT | Patient-reported GI | PROM | 13% | $V_{15\text{Gy}}$ |
| Van der Voort van Zyp 2012 [31] | R | 189 | NS | NS | NS | Acute small bowel Grade ≥ 3 | CTCAE v4 | 16% | |
| Banerjee 2013 [20] | R | 67 | 5-FU | 50.4 Gy in 28 # | 3D-CRT | Acute small bowel Grade ≥ 3 | RTOG | 16% | $V_{15\text{Gy}}-V_{45\text{Gy}}$; $V_{25\text{Gy}}$ 190 cm ³ (650 cm ³ for peritoneal cavity) $V_{15\text{Gy}}$ 275 cm ³ (830 cm ³ for peritoneal cavity) |
| Reis 2015 [7] | P | 45 | Cetuximab, cape, irinotecan | 50.4 Gy in 28 # | 3D-CRT | Acute diarrhoea | CTCAE v3 | 29% | $V_{5\text{Gy}} > 291.94$ cm ³ $V_{15\text{Gy}} > 125.5$ cm ³ |
| Xu 2015 [14] | R | 63 | Oxaliplatin & capecitabine | 50 Gy in 25 # | IMRT | Acute lower-GI Grade ≥ 2 | CTCAE v3 | 35% | No parameters found to be predictive |

(R = retrospective, P = prospective NS = not specified; IMRT = intensity modulated radiotherapy; GI = gastrointestinal, 5-FU = 5-fluorouracil, cape = capecitabine, CTCAE = Common Terminology Criteria for Adverse Events, RTOG = Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria, PROM = Patient-Reported Outcome Measures).

figures in order to derive numerical data values when these had not been included in the publication (Table 1 and 2 in Supplementary material). In some cases, cubic spline fitting was used to recreate a DVH from reported data points, and subsequently impute missing values (Fig. 2 and Table 6, Supplementary material). Different toxicity grading scales (CTC v2, CTCAE v3, and RTOG) were examined and aligned to enable comparisons across publications (Table 3 in Supplementary material).

Mean difference, inverse-variance, fixed-effect meta-analysis was carried out using the Cochrane Review Manager [8]. The volume of small bowel receiving a given dose (5 Gy to 40 Gy, in 5-Gy bins) was compared between cohorts of patients with Grade ≥ 3 toxicity and those without. The included studies were assessed for bias and heterogeneity using the Cochrane tools and Handbook [9]. Funnel plots were generated [10] and heterogeneity was formally evaluated using Chi-squared and I^2 .

Other methods were used to analyse the data from studies not suitable for inclusion in formal meta-analysis:

Values for observed toxicity incidence within a published clinical cohort ('toxicity incidence' column, Table 1) were compiled in a matrix according to the small-bowel dose–volume parameters reported for that clinical cohort, in a manner based on the method proposed by Jackson et al. [11]. Where data from more than one publication were entered into a cell, the resultant overall toxicity incidence was derived. The proportional toxicity risk values were then used to render a heat-map of toxicity risk according to dose and volume. The absolute values are presented in the matrix, so that the denominator is known for each data point, and thus the relative confidence in the values derived for each cell can be ascertained.

Proportional toxicity incidence was analysed against cohort values for dose–volume parameters $V_{5\text{Gy}} - V_{50\text{Gy}}$ using univariate logistic regression modelling [12,13]. For the parameters where a significant relationship was demonstrated, threshold values were derived associated with a toxicity risk of 20%.

Results

Literature review

Ten publications were identified which reported analysis of the dose–volume toxicity relationship for the small bowel (Table 1), including one study which failed to show a dose–volume–toxicity effect [14]. Four of these studies had been included in the QUANTEC review, [6,15–17], each of which reporting that all of the small bowel DVH parameters they tested ($V_{5\text{Gy}}-V_{40\text{Gy}}$) were significantly associated with risk of acute toxicity.

Data analysis

Nine studies reported small bowel DVH data that could be extracted for analysis, from a total of 659 patients (Table 1). The median rate of Grade ≥ 3 toxicity was 21% (range 4–35%). The DVH values themselves are included in the Supplementary material (Tables 5 and 6).

Formal meta-analysis

Three of the nine publications that reported data did so in a consistent manner suitable for incorporation in formal meta-analysis,

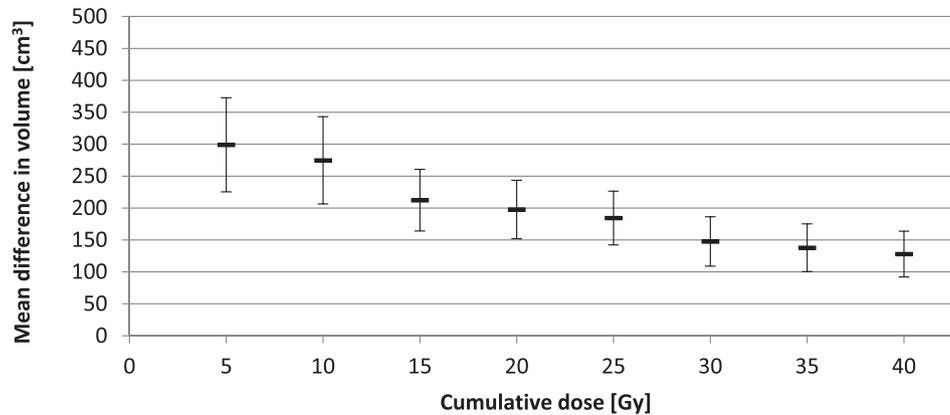


Fig. 1. Results of inverse-variance fixed-effect meta-analysis for data compiled from Baglan 2002, Banerjee 2013 and Robertson 2008 (total $n = 203$). Figure shows mean difference in volume of small bowel irradiated to specified dose levels between patients with Grade 0–2 and those with Grade ≥ 3 toxicity (error bars indicate 95% confidence intervals).

Table 2

Results of meta-analysis including absolute and relative differences in volume of small bowel irradiated to threshold dose V_xGy , between patients with Grade 0–2 and those with Grade ≥ 3 toxicity. Source data was compiled from Baglan 2002, Banerjee 2013 and Robertson 2008 (total $n = 203$).

| Participants analysed | Primary analysis | | Leave-one out analysis | | |
|-----------------------|---|---------------------|--|------------------------------|-----------------------------|
| | All studies (Baglan, Banerjee & Robertson) | | Round 1 (Banerjee & Robertson) | Round 2 (Baglan & Robertson) | Round 3 (Baglan & Banerjee) |
| | 203 | | 163 | 136 | 107 |
| | Mean absolute difference [cm ³] (95% confidence interval) | Relative difference | Absolute difference [cm ³] (95% confidence interval) | | |
| V_{5Gy} | 299 (225–373) | 81% | 285 (204–367) | 236 (133–339) | 364 (274–454) |
| V_{10Gy} | 275 (206–343) | 131% | 274 (197–351) | 197 (102–293) | 332 (250–413) |
| V_{15Gy} | 212 (164–261) | 170% | 230 (164–297) | 166 (110–223) | 245 (189–301) |
| V_{20Gy} | 198 (152–243) | 189% | 216 (153–280) | 152 (100–205) | 232 (178–285) |
| V_{25Gy} | 184 (142–227) | 219% | 198 (141–254) | 141 (91–191) | 217 (167–266) |
| V_{30Gy} | 148 (109–186) | 219% | 141 (91–190) | 121 (74–168) | 180 (134–226) |
| V_{35Gy} | 138 (100–175) | 227% | 130 (82–177) | 114 (69–159) | 169 (124–214) |
| V_{40Gy} | 128 (92–164) | 240% | 122 (76–167) | 104 (60–148) | 157 (114–200) |

namely mean volumes of small bowel irradiated according to acute small bowel or lower GI toxicity (Grade 0–2 versus Grade ≥ 3) [18–20]. For each study the data was collected from observation of patients treated with rectal cancer treated with radical conformal radiotherapy using 1.8 Gy per fraction and concomitant 5-FU. For all dose–volume parameters tested ($V_{5Gy} - V_{40Gy}$), the small bowel volume irradiated was significantly greater for patients who suffered Grade ≥ 3 toxicity, as shown in Fig. 1 (individual forest plots are included in the Supplementary material, Fig. 5). The absolute difference in irradiated volume for Grades 0–2 versus Grade ≥ 3 is largest for the lowest dose and decreases with increasing dose. However, the **relative** difference in volume **increases** with increasing dose, as shown in Table 2. On all three rounds of leave-one out sensitivity analysis, the ‘treatment effect’ (difference in small-bowel volume) lay within the 95% confidence intervals for the primary analysis, suggesting the overall result is not dependent on the inclusion of any one particular study.

Assessment of heterogeneity and bias

The analysis of bias revealed certain sources of potential high risk, including high risk of selective reporting (where not all relevant data generated in the work are reported), and confounding factors. These included patient sex (for Banerjee et al. all the patients who suffered grade ≥ 3 toxicity were female), pre- or post-operative radiotherapy (for Robertson et al. preoperatively treated patients had a lower incidence of Grade 3 acute diarrhoea than postoperatively treated patients), and extent and method of

small-bowel delineation (absolute small-bowel volumes will be dependent on the extent of the CT scan). The funnel plots show standard error in the treatment effect against the absolute treatment effect, and where the data points do not all fall within the expected triangular distribution, heterogeneity of effect size is indicated (Supplementary material, Fig. 6). The presence of heterogeneity has also been confirmed by statistically significant results for all tested dose–volume parameters on Chi-squared testing, demonstrating that the observed variability in effect size is unlikely to have arisen through chance alone ($p \leq 0.05$, Table 9, Supplementary table). Furthermore all I^2 values (a quantitative indicator of the **degree** of heterogeneity) were between 67% and 85%, lying within the range of 50–90% specified by the Cochrane Handbook that ‘may represent substantial heterogeneity’ [9].

Informal cross-trial analysis

The other papers identified in the literature search reported DVH data using a variety of measurements or criteria which meant their data could not be included in the formal meta-analysis. However, when informal analysis was undertaken using the data from these studies, there it is again shown that a significantly larger volume of small bowel has been irradiated for patients with higher grade of toxicity (Table 3). Relative change for data from Tho et al. could not be included as the irradiated volume for the patients without toxicity was zero. As shown in the formal meta-analysis, the largest absolute difference was seen for the lowest dose parameter (V_{5Gy} , 196 cm³), and the difference decreased

Table 3

Differences in cumulative (a) absolute and (b) relative volume of small bowel irradiated at each dose level between patients with or without toxicity as defined in each study. Relative change for data from Tho et al. could not be included as the irradiated volume for the patients without toxicity was zero. (c) Logistic regression model coefficients with standard error (SE) for each small bowel DVH parameter, with statistical significance of logistic regression model fit to risk of Grade ≥ 3 toxicity. *P* values <0.05 indicated in bold. *P* values < 0.005 indicated by italic typeface. 20% risk constraint denotes an irradiated volume associated with a 20% risk of acute toxicity.

| <i>(a) Absolute differences [cm³] in small bowel volume between patients with or without toxicity</i> | | | | | | | | | | | |
|--|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| | n | V _{5Gy} | V _{10Gy} | V _{15Gy} | V _{20Gy} | V _{25Gy} | V _{30Gy} | V _{35Gy} | V _{40Gy} | V _{45Gy} | V _{50Gy} |
| Tho 2006 | 41 | 252 | 228 | 190 | 94 | 70 | 64 | 54 | 23 | | |
| Gunnlaugsson 07 | 28 | 155 | 165 | 195 | 210 | 199 | 176 | 164 | 157 | 140 | 88 |
| Reis 2015 | 45 | 182 | 157 | 103 | 46 | 36 | 27 | 26 | 22 | 3 | |
| Xu 2015 | 63 | -51 | -41 | -34 | -31 | -24 | -15 | -10 | -7 | | |
| Baglan 2002 | 40 | 359 | 278 | 192 | 178 | 168 | 159 | 151 | 138 | | |
| Banerjee 2013 | 67 | 366 | 356 | 338 | 338 | 293 | 205 | 191 | 178 | 44 | |
| Robertson 2008 | 96 | 167 | 139 | 121 | 107 | 96 | 74 | 67 | 62 | | |
| Weighted mean | 380 | 196 | 176 | 152 | 131 | 116 | 92 | 86 | 77 | | |
| <i>(b) Relative differences in small bowel volume between patients with or without toxicity</i> | | | | | | | | | | | |
| | n | V _{5Gy} | V _{10Gy} | V _{15Gy} | V _{20Gy} | V _{25Gy} | V _{30Gy} | V _{35Gy} | V _{40Gy} | V _{45Gy} | V _{50Gy} |
| Gunnlaugsson 07 | 28 | 69% | 81% | 129% | 269% | 307% | 300% | 289% | 302% | 292% | 263% |
| Reis 2015 | 45 | 68% | 79% | 110% | 72% | 69% | 59% | 77% | 81% | 25% | |
| Xu 2015 | 63 | -19% | -18% | -17% | -18% | -19% | -20% | -21% | -23% | | |
| Baglan 2002 | 40 | 82% | 113% | 151% | 165% | 170% | 173% | 176% | 177% | | |
| Banerjee 2013 | 67 | 160% | 193% | 218% | 256% | 326% | 366% | 406% | 456% | 191% | |
| Robertson 2008 | 96 | 37% | 65% | 119% | 129% | 130% | 112% | 110% | 115% | | |
| Weighted mean | 339 | 63% | 84% | 117% | 135% | 152% | 153% | 162% | 175% | | |
| <i>(c) Logistic regression parameters</i> | | | | | | | | | | | |
| Parameter | V _{5Gy} | V _{10Gy} | V _{15Gy} | V _{20Gy} | V _{25Gy} | V _{30Gy} | V _{35Gy} | V _{40Gy} | V _{45Gy} | V _{50Gy} | |
| B for V _x Gy | 0.002 | 0.005 | 0.004 | 0.003 | 0.005 | 0.007 | 0.008 | 0.008 | 0.009 | 0.010 | |
| SE for B | 0.001 | 0.002 | 0.002 | 0.002 | 0.004 | 0.003 | 0.004 | 0.004 | 0.004 | 0.006 | |
| Intercept | -2.11 | -2.63 | -2.05 | -1.8 | -1.92 | -2.01 | -1.99 | -1.93 | -1.79 | -1.54 | |
| SE for intercept | 0.29 | 0.43 | 0.36 | 0.29 | 0.29 | 0.29 | 0.26 | 0.23 | 0.18 | 0.12 | |
| <i>P</i> value for V _x Gy | 0.017 | 0.004 | 0.095 | 0.227 | 0.108 | 0.046 | 0.034 | 0.026 | 0.033 | 0.143 | |
| 20% risk constraint [cm ³] | 363 | 240 | | | | 92 | 80 | 69 | 44 | | |

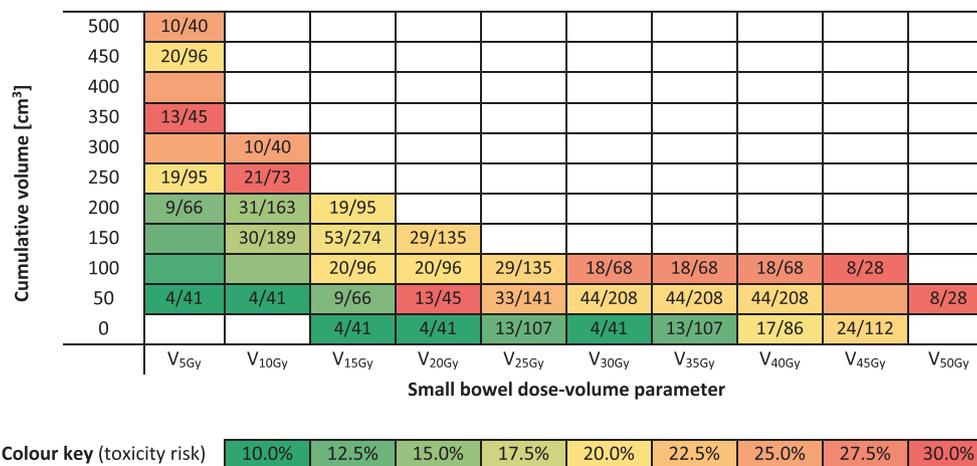


Fig. 2. Colour maps of toxicity risk associated with irradiation of small bowel to indicated dose–volumes. Values in cells indicate observed toxicity incidence for studies or cohorts whose DVH intersects in the relevant dose–volume range. Cells are colour-labelled according to risk, as per the key. Cells not containing numerical values had no data available, but for the purpose of the figure the colour has been interpolated in gaps between cells with data. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

sequentially as the dose increased. The largest **relative** difference was seen for the V_{40Gy} (175%), with the difference for the V_{5Gy} the smallest (63%).

The colour map of toxicity incidence according to small bowel dose–volume highlights that the rate of toxicity increases along both axes, i.e. there is increasing risk with increasing volume of small bowel irradiated at a given dose, and with increasing dose received by a given volume (Fig. 2). This colour map can be used as a rudimentary way to derive constraints with which to inform clinical radiotherapy planning decisions. For example, if a toxicity risk of below 20% were desired, it would appear necessary to main-

tain V_{5Gy} < 250 cm³, V_{10Gy} < 250 cm³, V_{15Gy} < 100 cm³, V_{20Gy} - V_{35Gy} < 50 cm³. It appears that maintaining V_{40Gy} < 100 cm³ and V_{45Gy} < 50 cm³ may ensure the toxicity risk is kept below 25%.

Logistic regression analysis

On logistic regression analysis of cohort toxicity risk incidence against small-bowel dose–volume, multiple small bowel cumulative dose–volume parameters were found to be significantly predictive of toxicity incidence (*p*-value of <0.05) (Table 3) demonstrating a continuous relationship between increasing risk

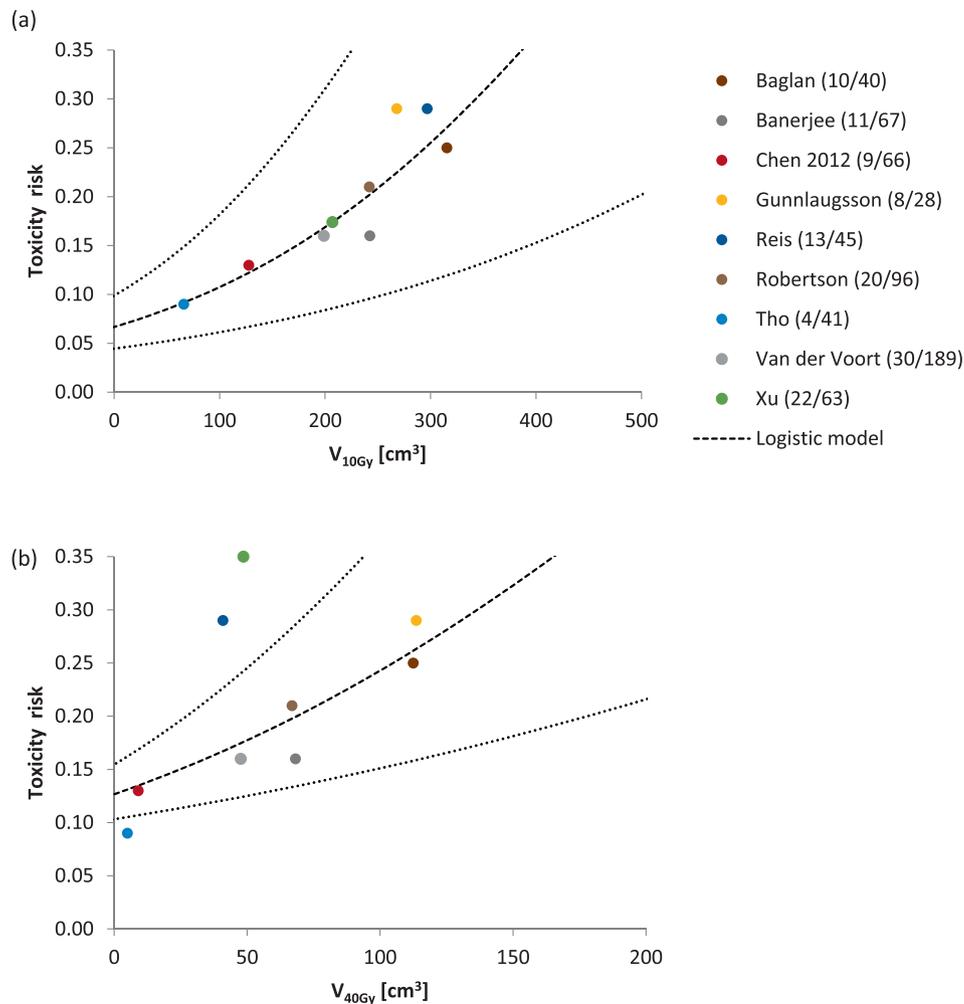


Fig. 3. Plot of reported toxicity rate against small bowel (a) V_{10Gy} [cm^3] and (b) V_{40Gy} with univariate logistic regression model (dashed line) and 69% confidence interval for model parameters (dotted lines).

of clinically-significant acute toxicity with increasing volume of small-bowel irradiated to these doses. If a Bonferroni correction were used, a p -value threshold of 0.005 would apply, and only one parameter (V_{10Gy}) would remain significant. Fig. 3 visualises the distribution of source data points for two parameters (V_{10Gy} and V_{40Gy}) with the logistic regression model overlaid.

These models can be used to derive more accurate radiotherapy planning constraints. To maintain a projected risk of acute toxicity of 20% or less, the volume of small bowel irradiated should be kept within the following thresholds: $V_{5Gy} < 363 \text{ cm}^3$, $V_{10Gy} < 240 \text{ cm}^3$, $V_{30Gy} < 92 \text{ cm}^3$, $V_{35Gy} < 80 \text{ cm}^3$, $V_{40Gy} < 69 \text{ cm}^3$, and $V_{45Gy} < 44 \text{ cm}^3$. This should not be taken to imply that the V_{50Gy} or higher have no relationship with toxicity and therefore need not be of concern, but in this analysis the data were insufficient to prove such a relationship.

Discussion

The results of the formal meta-analysis demonstrate that, for all tested dose levels, an association exists between small bowel volume and acute toxicity in which patients who suffered toxicity had larger irradiated small bowel volumes. The absolute difference in exposure is largest for the lowest doses, and the differences become smaller with increasing dose (Fig. 1). However, the relative difference in volume between the groups is actually higher as dose

increases, suggesting the volume of small bowel irradiated is increasingly important as the dose increases (Table 2). When examining the average effect size across studies, the largest relative differences in small bowel volume between the cohorts of patients with or without toxicity were for the V_{30Gy} , V_{35Gy} , and V_{40Gy} .

It is a novel finding that using population-derived small bowel data, several dose–volume parameters (V_{10Gy} , V_{30Gy} , V_{35Gy} , and V_{40Gy}) were found to be predictive of toxicity incidence, in a univariate logistic regression model. For the parameter V_{10Gy} , the p -value was sufficiently low that it would remain significant if a Bonferroni correction were applied to account for multiple testing. Use of this technique has not previously been reported for the small-bowel, although similar methods have been proposed to model toxicity in the parotid gland and lung [12].

Before the age of routine CT imaging for radiotherapy planning, Emami et al. had limited evidence with which to define dose–volume constraints for the small bowel [21]. The advent of computerised radiotherapy planning has facilitated the analysis of 3D dose distributions, and the QUANTEC review [3] considered the results of six publications, concluding that $V_{15Gy} \geq 120 \text{ cm}^3$ is a threshold above which the risk of acute toxicity escalates.

In this review we have shown how papers published since QUANTEC have mostly replicated earlier findings. In total, nine studies identified significant relationships between the risk of GI toxicity and small bowel dose–volume parameters (from the range

of V_{5Gy} to V_{50Gy}), and the most repeated finding remains the V_{15Gy} . Further work by Robertson et al. reinforced the importance of the V_{15Gy} (threshold 130 cm^3 associated with a toxicity risk of 11%) [17]. The V_{15Gy} has since been highlighted in four other studies [7,20,22,23], including one which analysed patient reported outcomes [22].

However, the previous assumption that 15 Gy is a threshold volume (above which the volume irradiated is less important) is weakened by the evidence for the importance of the higher end of the DVH, such as V_{30Gy} and V_{40Gy} , which were both found to be significant predictors in multiple studies. Alongside V_{15Gy} , Arber et al. also found that V_{10Gy} (volume threshold 92.6 cm^3) and V_{50Gy} (4.4 cm^3) [23] predicted risk of diarrhoea, while Reis et al. found V_{5Gy} (291.9 cm^3) [7]. Banerjee et al. found that among their patients, all of V_{15Gy} – V_{45Gy} were associated with a risk of small bowel toxicity [20]. Several publications have reported evidence of a volume effect for the small bowel exposed to 50 Gy. As dose escalation becomes more popular in the treatment of rectal cancer, with the intent of improving response rates [24], the importance of higher dose thresholds [23] may become even more apparent.

In the available literature the volume effect has not been tested at doses below 5 Gy, however the data have not suggested that there is a threshold below which exposure has no implications for risk of toxicity, a point which could in theory negate the intended benefit of techniques such as IMRT which can increase the volume irradiated to low dose. However, as reduced toxicity has been demonstrated when pelvic IMRT is implemented, it may be that the benefit of reduced high dose exposure outweighs the cost [25].

Study limitations

As data from randomised controlled trials were not available, this meta-analysis has used data from retrospective, observational non-randomised studies, which brings greater risk of bias and confounds. Importantly, all the studies used data from a single centre, sometimes by a single clinician. Unfortunately, not only were there few studies providing suitable data for inclusion in this work, the availability of study data also appears to have been affected by publication bias: there is reason to suspect that studies failing to show significant associations between DVH and toxicity were less likely to be published. The sparsity of source data has led us to adopt solutions such as plot digitisation and data interpolation, and we acknowledge that these may lack precision, particularly when the spline-fitting method has been used to recreate the DVH from few reported data points. The studies themselves are at risk of bias affecting their results, and this analysis has shown heterogeneity of size of treatment effect between the studies.

There is heterogeneity in the methods used to collect toxicity outcomes data and in the treatment that was delivered. Only DVH data regarding small bowel outlined as ‘individual loops’ has been analysed, but some variation persists, for example, some groups only contoured loops of bowel that contained oral contrast. While different methods and tools have been used for the collation and grading of toxicity symptoms, there are major key similarities between these, and it has been possible to translate grades between different scales. There was some inconsistency in the definition of the relevant toxicity endpoint, where many studies used terminology such as ‘lower GI toxicity’ or ‘small bowel toxicity’, but without usually specifying the toxicity events or symptoms that constitute such a description. Others reported only the rate of any non-haematological toxicity, or conversely only the incidence of a single specific symptom (‘diarrhoea’ or ‘watery stool’ were both used). All studies except for one (Chen et al. [22]) relied on

clinician-assessed toxicity, whereas potential benefits that may come from the use of patient-reported outcomes include greater breadth and sensitivity for the symptoms that trouble patients after their treatment for cancer [26]. Furthermore, the use of supportive medications such as anti-emetics and anti-diarrhoeal drugs, in a prophylactic or reactive context, was not comprehensively reported, and as such the possible interaction with the effect of dose–volume cannot be ascertained.

All the studies providing data for this analysis collected information regarding only acute toxicity. No studies could be identified in our literature search that had collected small-bowel DVH data in relation to late toxicity after radiotherapy for rectal cancer. Two studies with data from treatment of cervix cancer were found [27,28] and one from treatment of pancreatic cancer [29]. Late toxicity tends to develop gradually through a complex ongoing inflammatory process influenced by many host and treatment factors, and it is likely to be more difficult to establish a relationship with radiotherapy DVH parameters.

To benefit future work in this field would require consistent application of consensus guidelines on data acquisition, widespread prospective collection of detailed objective toxicity outcomes, wider publication of important negative findings, and increased data sharing between institutions, which can be facilitated by open-source, manufacturer-independent tools such as the Computational Environment for Radiotherapy Research (CERR) [30]. The increasing use of radiotherapy dose escalation may provide an opportunity to study the small bowel dose–volume effect at doses greater than 50 Gy, and the effect of very-low dose should also be examined, in which the use of patient-reported outcome measures may possibly improve sensitivity to lower-grade toxicity. There remains a paucity of collaborative analysis of large prospective clinical trial cohorts, and efforts to achieve this should be supported and congratulated.

In conclusion, review and analysis of published clinical cohort dose–volume data with toxicity outcomes has demonstrated the significant dose–volume–toxicity response effect for a wide range of clinically-relevant doses in the treatment of rectal cancer to refine the understanding of the parameters important in this relationship and their relationship with outcomes. We have shown how toxicity is not only associated with largest **absolute** differences in the volume of small bowel irradiated to low dose (V_{5Gy}), but also with largest **relative** differences in volume irradiated to higher doses (V_{35Gy} – V_{40Gy}). Furthermore, cohort-derived small bowel dose–volume parameters (V_{10Gy} , V_{30Gy} , V_{35Gy} and V_{40Gy}) were found to be significantly predictive of the toxicity incidence in that population in a univariate logistic regression model. These models have been used to derive radiotherapy planning constraints below which the risk of toxicity should be less than 20%: $V_{5Gy} < 363\text{ cm}^3$, $V_{10Gy} < 240\text{ cm}^3$, $V_{30Gy} < 92\text{ cm}^3$, $V_{35Gy} < 80\text{ cm}^3$, $V_{40Gy} < 69\text{ cm}^3$, and $V_{45Gy} < 44\text{ cm}^3$. However, a key point is that the relationship between irradiated volume and risk of toxicity is continuous, without a threshold below which the risk is unaltered, hence the priority of clinicians and planners should be to minimise exposure of normal tissue, regardless of such constraints.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2019.05.001>.

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