



## Duodenal toxicity

## Modelling duodenum radiotherapy toxicity using cohort dose-volume-histogram data

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## ABSTRACT

**Background and purpose:** Gastro-intestinal toxicity is dose-limiting in abdominal radiotherapy and correlated with duodenum dose-volume parameters. We aimed to derive updated NTCP model parameters using published data and prospective radiotherapy quality-assured cohort data.

**Material and methods:** A systematic search identified publications providing duodenum dose-volume histogram (DVH) statistics for clinical studies of conventionally-fractionated radiotherapy. Values for the Lyman-Kutcher-Burman (LKB) NTCP model were derived through sum-squared-error minimisation and using leave-one-out cross-validation. Data were corrected for fraction size and weighted according to patient numbers, and the model refined using individual patient DVH data for two further cohorts from prospective clinical trials.

**Results:** Six studies with published DVH data were utilised, and with individual patient data included outcomes for 531 patients in total (median follow-up 16 months). Observed gastro-intestinal toxicity rates ranged from 0% to 14% (median 8%). LKB parameter values for unconstrained fit to published data were:  $n = 0.070$ ,  $m = 0.46$ ,  $TD_{50(1)} [Gy] = 183.8$ , while the values for the model incorporating the individual patient data were  $n = 0.193$ ,  $m = 0.51$ ,  $TD_{50(1)} [Gy] = 299.1$ .

**Conclusions:** LKB parameters derived using published data are shown to be consistent to those previously obtained using individual patient data, supporting a small volume-effect and dependence on exposure to high threshold dose.

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## Introduction

Upper-gastrointestinal toxicity remains the principal factor limiting the escalation of radiotherapy dose in the treatment of upper abdominal tumours [1], and irradiation of the duodenum may result in severe, even life-threatening toxicity. Ulceration (which can be acute or late) comes with risk of bleeding or fistula formation and fibrosis (typically late) can lead to stenosis with possible gastric outlet obstruction. The duodenum was not mentioned specifically in the 1991 review of dose-volume by Emami et al. [2] and QUANTEC [3] referred to only one publication reporting specific duodenal toxicity outcomes, with no dose-volume histogram (DVH) data available [4]. Following the QUANTEC publication several studies have shown that risk of toxicity is associated with increased volume of duodenum irradiated to between 25 and 55 Gy. These use data from the treatment of pancreatic cancer

[5–8], liver tumours [9] and para-aortic lymph node irradiation for gynaecological malignancies [10] (Table 1).

Prospective estimation of risk to inform treatment planning for subsequent patients requires derivation of parameters for a normal tissue complication probability (NTCP) model, such as that of Lyman-Kutcher-Burman (LKB) [11]. One study (published as an abstract) has used individual patient data to derive parameters for the LKB model for the duodenum, using the endpoints of gastrointestinal (GI) bleeding following irradiation for liver tumours [12]. A major potential limitation of findings derived from a single cohort of patients is their external generalisability. Results derived using data from multiple institutions and treatment protocols may be more indicative of the true underlying properties of the tissue or organ of interest, and hence be more universally applicable [13]. Two papers have previously attempted to derive NTCP model parameters using published duodenum DVH and toxicity data: Prior and colleagues used published DVH data for the small intestine and duodenum [14], while Elhammali et al. derived LKB parameters for the duodenum using an assumed radiation exposure (homogenous irradiation of 5% of the duodenum by the prescription dose) [15]. Both studies used data from both standard

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**Table 1**

Published duodenum dose-volume parameters predictive of toxicity, with derived dose-volume parameters or volume thresholds (as either absolute or proportional volumes of the duodenum) and associated comparison of proportional incidence of specified toxicity between those patients whose radiotherapy plans achieved or did not achieve this threshold value.

Reference	Cancer site	Concurrent Chemotherapy	Toxicity outcome	Duodenum DVH Parameters	Risk comparison
Huang 2012 [5]	LAPC	Gemcitabine ± erlotinib	Grade ≥ 3 GI	V <sub>25Gy</sub> 45%	8% vs 48%
Nakamura 2012 [6]	LAPC	Gemcitabine	Grade ≥ 2 GI	D <sub>mean</sub> 46.1 Gy D <sub>2cm3</sub> 55.5 Gy	19% vs 57% 21% vs 58%
Cattaneo 2013 [7]	LAPC	Capecitabine or 5FU	Grade ≥ 2 GI	V <sub>40Gy</sub> 16% V <sub>45Gy</sub> 2.6%	Not specified
Kelly 2013 [8]	LAPC	Gemcitabine ± 5FU/capecitabine ± EGFRi	Grade ≥ 2 'duodenal'	V <sub>55Gy</sub> 1 cm <sup>3</sup>	9% vs 47%
Yoon 2013 [9]	HCC	None	Grade ≥ 2 'gastro-duodenal'	V <sub>35Gy</sub> 5.4%	9% vs 46%
Verma 2014 [10]	Gynae (PA nodes)	Platinum agents (55 %)	Grade ≥ 2 'duodenal'	V <sub>55Gy</sub> 13.94%	7% vs 49%

DVH: dose-volume histogram; LAPC: locally advanced pancreatic cancer; GI: gastro-intestinal; D<sub>mean</sub>: mean dose to a structure; D<sub>2cm3</sub>: dose to at least 2cm<sup>3</sup> of a structure; V<sub>xGy</sub>: volume of structure receiving at least x Gy; 5FU: 5-fluoro-uracil; EGFRi: epidermal growth factor receptor inhibitor; HCC: hepatocellular carcinoma; Gynae: gynaecological malignancies; PA: para-aortic.

and hypofractionated radiotherapy, however the radiobiology and pathology of upper-GI toxicity is poorly understood, and potentially the mechanisms for normal tissue damage and repair in standard fractionation might follow different pathways than those of extreme hypofractionation.

Our group intended to supplement the available published reports through access to individual patient data from two prospective clinical trials of chemoradiotherapy for locally-advanced pancreatic cancer: the SCALOP study (NCT 01032057, *n* = 74) in which patients were randomised to receive either gemcitabine or capecitabine [16], and the ARCII study (EudraCT 2008-006302-42, *n* = 23) in which patients received concomitant CRT with gemcitabine, cisplatin and nelfinavir (a hypoxia modifier) [17].

The aim of this work is (1) to derive an updated NTCP model for duodenal toxicity in conventional fractionated radiotherapy using available published duodenum DVH data, (2) to test model predictions in two prospective trials delivering chemo-radiation in pancreatic cancer, and (3) further revise the model incorporating prospective trial data.

## Materials and methods

### Updating current NTCP model using published standard fractionation DVH data

A comprehensive literature search was conducted using appropriate keywords and headings (including variants of duodenum, radiotherapy, toxicity, pancreas cancer) in the SCOPUS, EMBASE & MEDLINE databases, limited to reports published in English since 2002. Further suitable publications were identified through existing reviews and results were examined systematically.

### Extraction of DVH data for prospective clinical trial cohorts

For the SCALOP and ARCII datasets the computed tomography (CT) scan, contours, dose cubes and individual patients' outcomes were available. For the SCALOP cohort the GI tract normal structures had not previously been contoured and were segmented post hoc by one radiation oncologist (DH) according to the recent Radiation Therapy Oncology Group (RTOG) atlas [18], reviewed with a radiologist and a radiation oncologist with an interest in GI oncology. For ARCII the GI tract had previously been contoured but all contours were checked and revised if necessary to achieve consistency with the RTOG guidance. Median DVH statistics for the SCALOP and ARCII clinical trials were derived from the individual patient DVH data. The SCALOP trial had undertaken prospective radiotherapy quality assurance (RTQA) review during the trial including approval of pre-trial benchmark test cases of contouring

and planning required before centres were permitted to treat patients in the study [19].

### Equivalent dose calculation and LKB model fitting

To facilitate comparisons between studies the reported duodenum dose-volume parameters were converted to the equivalent dose in 25 fractions (EQD<sub>25#</sub>) (chosen as it was both median and mode among the source cohorts) using an alpha-beta ratio of 4 [20,21]. For the majority of studies all treatment was delivered in a fixed and consistent number of fractions, but there were some cohorts with mixed numbers of fractions delivered. Verma et al. report that in 7% of their patients a sequential rather than integrated boost was used, but more detail is not provided [10]. In the study by Poorvu et al. sequential dose escalation was titrated to tolerance by normal-tissue constraints, hence in conversions to EQD<sub>25#</sub> the reference number of fractions for each partial dose-volume in the study was different for each dose level [22]. All source data values are included in [Supplementary material](#) for reference.

Cubic splines were fitted to the published DVH data to recreate continuous distributions, which were sampled at 5 Gy intervals to reduce each DVH to a single effective volume *V<sub>eff</sub>* using the following expression [23]:

$$V_{\text{eff}} = \sum_j \left[ \left( \frac{D_j}{D_{\text{max}}} \right)^{\frac{1}{n}} \Delta V_j \right] \quad (1)$$

where *D<sub>j</sub>* and *V<sub>j</sub>* are the dose and volume of the *j*<sup>th</sup> element on the DVH, *D<sub>max</sub>* is the maximum dose and *n* is the LKB tissue architecture parameter.

The standard form of the LKB model was adopted [11]:

$$\text{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^u e^{-\frac{t^2}{2}} dt \quad (2)$$

where *u* is a function of the "steepness" parameter *m* [11]:

$$u = \frac{D_{\text{max}} - \text{TD}_{50}(V)}{m \text{TD}_{50}(V)} \quad (3)$$

The 50% tolerance dose to a sub-volume of the organ *TD<sub>50</sub>(V)* is found by applying a power law volume effect [11]:

$$\text{TD}_{50}(V) = \frac{\text{TD}_{50}(1)}{V_{\text{eff}}^{\frac{1}{n}}} \quad (4)$$

Values of *n*, *m*, and *TD<sub>50</sub>(1)* (the 50% tolerance dose for irradiation of the whole organ) were found by simultaneously minimising the least square error between the LKB model prediction and all

**Table 2**  
Details of publications and clinical trial cohorts with duodenum DVH data available, including those used in this analysis.

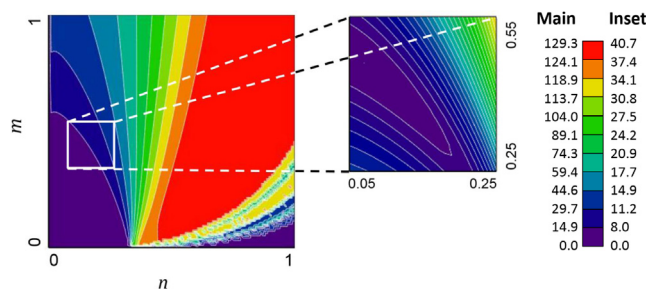
Reference	Clinical Data	Patients	mFU, [m]	Cancer site	Radiotherapy Dose-schedule (EQD <sub>25#</sub> where applicable)	Chemotherapy	Radiotherapy Technique	Toxicity Scale	Grade ≥ 3 Toxicity	Duodenum dose-volume data available
Cattaneo 2013 [7]	NS	61	19	LAPC	45 Gy ± 15 Gy boost in 15 # (EQD <sub>25#</sub> = 51.9 Gy ± 17.1 Gy)	Capecitabine or 5FU	IMRT	CTCAE v3	12%	D <sub>mean</sub> , V <sub>20Gy</sub> , V <sub>30Gy</sub> , V <sub>40Gy</sub> , V <sub>45Gy</sub>
Kelly 2013 [8]	Retro	106	12	LAPC	50.4 Gy in 28 # (EQD <sub>25#</sub> = 49.0 Gy)	Gemcitabine ± 5FU/cape ± EGFRi	3D-CRT (75) / IMRT (31)	CTCAE v4	8%	D <sub>mean</sub> , V <sub>40Gy</sub> , V <sub>45Gy</sub> , V <sub>50Gy</sub> , V <sub>55Gy</sub> , V <sub>60Gy</sub>
Xia 2013 [24]	Prosp	33	6	Pancreas	PTV: 50 Gy, GTV: 70 Gy in 20 # (EQD <sub>25#</sub> = PTV: 53.1 Gy, GTV: 75.0 Gy)	None	Tomo	NS	0%	D <sub>1cc</sub> , D <sub>5cc</sub> , D <sub>10cc</sub>
Poorvu 2013 [22]	Retro	53	17	Gynae	54 Gy in 30 # (EQD <sub>25#</sub> = 51.6 Gy)	Cisplatin	IMRT	CTCAE v4	7%	V <sub>55Gy</sub> & V <sub>60Gy</sub>
Xu 2014 [25]	Retro	76	19	Gynae (PA nodes)	45 Gy ± 10 Gy boost in 25 #	Platinum agents (86%)	IMRT	CTCAE v4	4%	D <sub>mean</sub> , D <sub>Max</sub> , V <sub>35Gy</sub> , V <sub>40Gy</sub> , V <sub>50Gy</sub> , V <sub>55Gy</sub> , D <sub>2cc</sub> , D <sub>5cc</sub>
Verma 2014 [10]	Retro	105	32	Gynae	64 Gy in 25 #	Platinum agents (55%)	IMRT	RTOG	8%	D <sub>Max</sub> , D <sub>2cc</sub> , D <sub>5cc</sub>
Mukherjee 2013 [16]	Prosp	74	12	LAPC	50.4 Gy in 28 # (EQD <sub>25#</sub> = 49.0 Gy)	Gemcitabine (51%) or capecitabine (49%)	3D-CRT	CTCAE v3	9%	Access to full individual patient DVH data
Wilson 2016 [17]	Prosp	23	14	LAPC	59.4 Gy in 33 # (EQD <sub>25#</sub> = 55.4 Gy)	Gemcitabine, cisplatin & nelfinavir	3D-CRT/IMRT	CTCAE v3	14%	Access to full individual patient DVH data
Kim 2009 [33]	Retro	73	11	HCC	36 Gy in 12 #	None	3D-CRT	CTC v2	12%	'StoDuo' D <sub>mean</sub> , D <sub>Max</sub> , V <sub>25Gy</sub> , V <sub>40Gy</sub>
Pan 2003 [12]	Retro	92	7.6	Hepatic	1.5 Gy per # BD with chemo or 1.8 – 3 Gy per # QDS without	Hepatic arterial chemotherapy	3D-CRT	N/A	16%	D <sub>mean</sub>

mFU [m] = median follow-up, months; # = radiotherapy treatment fractions; NS = not specified; Retro = retrospective; Prosp = prospective; LAPC = locally advanced pancreatic cancer; 5FU = 5-fluoro-uracil; cape = capecitabine; IMRT = intensity modulated radiotherapy; 3D-CRT = 3D conformal radiotherapy; Tomo = TomoTherapy; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; PA: para-aortic; RTOG = Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria, StoDuo = combined stomach & duodenum; EQD<sub>25#</sub> = Equivalent Dose in 25 #, using  $\alpha/\beta$  ratio = 4; BD = twice daily; QDS = four times per day.

**Table 3**  
Results of LKB model fitting. Mean values for parameters are shown with 95% confidence intervals estimated by refitting all data using the leave-one-out method (in each refitting of DuoLKB2 the optimal value for parameter  $n$  was precisely 0.09).

Model	Data source	Fitting details	$n$	$m$	TD <sub>50</sub> (1) [Gy]
DuoLKB1	Published data	Unconstrained, unweighted	0.068 (0.060–0.076)	0.36 (0.30–0.43)	125.9 (63.1–188.7)
DuoLKB2	Published data	Constraint: $n > 0.09$	0.090 (0.090–0.090)	0.39 (0.32–0.46)	141.8 (36.7–246.9)
DuoLKB3	Published data	Unconstrained, weighted	0.070 (0.061–0.079)	0.46 (0.40–0.52)	183.8 (122.1–245.5)
DuoLKB4	Published & IPD	Unconstrained, weighted	0.193 (0.147–0.239)	0.51 (0.47–0.55)	299.1 (242.1–356.1)

IPD: Individual Patient Data.



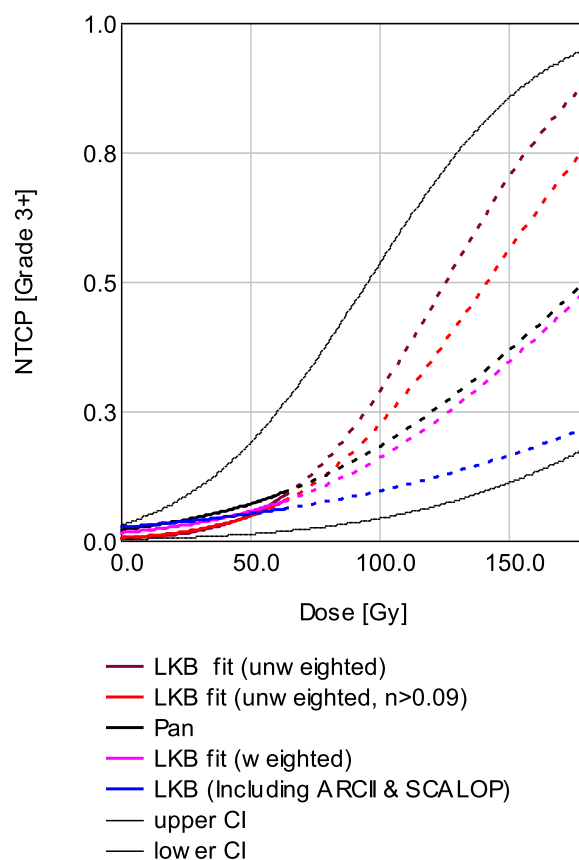
**Fig. 1.** Plot of solution space for model DuoLKB2 (TD<sub>50</sub>(1) value of 142 Gy), showing the low cost (favourable) solutions in purple and the high cost (unfavourable) solutions in red. The degeneracy in  $n$  and  $m$  is clearly visible, although the presence of a well-defined minimum valley in solution space is clear. A subset of solution space is shown (inset). The colour bar shows the value of the cost function (note a different scale for the inset plot for clarity).

observed clinical outcomes using Levenberg–Marquardt optimisation. Confidence intervals on the fit values obtained were estimated using the leave-one-out method.

The model was firstly fitted using only the published DVH data sources, initially with an unconstrained fit of all three parameters (DuoLKB1). As the resulting value for  $n$  fell slightly below the confidence intervals for the value derived by Pan et al. (0.09–0.30), the model was fitted again with  $n$  constrained to  $\geq 0.09$  (DuoLKB2). For models DuoLKB1 & DuoLKB2 each data source was treated with equal significance, while for model DuoLKB3 the contribution of each source was weighted according to the number of patients included in that treatment cohort, with an unconstrained fit. The model values were then used to predict the rate of toxicity expected in the clinical trial datasets for which individual patient data were available, and finally the model was fitted again with these data sources included (DuoLKB4).

## Results

The literature search identified 170 results, among which were six publications that reported duodenum dose-volume data and relevant toxicity outcomes and could therefore be included in our analysis [7,8,10,22,24,25] (see Table 2). Two of the studies reported data separately for separate cohorts treated using variants of the same treatment protocol and these patient cohorts were considered separately for model fitting. In the analysis by Cattaneo et al., 38 of the 61 patients were treated to a dose of 44.25 Gy in 15 fractions, while the other 23 patients also received a simultaneous integrated boost to a total dose in the range of 48–58 Gy [7]. In the report by Xu et al. 35 of the 76 patients were treated to a dose of 45 Gy in 25 fractions while the other 41 received a boost to 55 Gy in 25 fractions [25]. The SCALOP trial randomised 74 patients to receive capecitabine or gemcitabine as a sensitizer with a radiotherapy dose of 50.4 Gy in 28 fractions delivered conformally [16], whilst ARCI study patients received 50.4 Gy in 28 fractions followed by a sequential boost to 59.4 Gy with cisplatin-gemcitabine-nelfinavir chemotherapy [17].

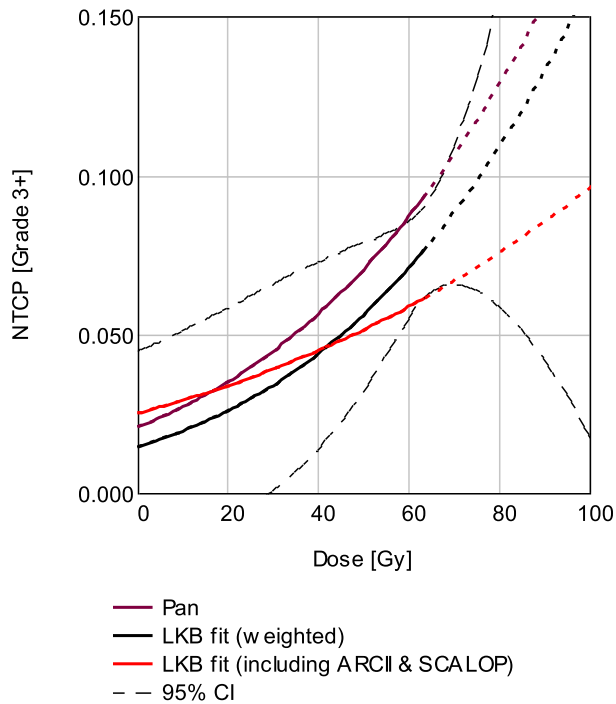


**Fig. 2.** NTCP model of grade  $\geq 3$  duodenal toxicity fitted to published data for: unconstrained fit (DuoLKB1), fit with constraint  $n \geq 0.09$  (DuoLKB2), fit weighted according to cohort size (DuoLKB3), weighted fit including ARCI and SCALOP data (DuoLKB4), and the model parameters as published by Pan et al. Confidence intervals for the fitting process show the envelope of solutions given using a leave-one-out error estimation. Curves are shown by dotted lines where the model extrapolates beyond the region supported by the data.

The analysis included treatment data for a total of 531 patients with a median of 68 patients (range 23–106) per cohort. Median follow-up duration ranged from 6 to 32 months (median 16 months) and the observed rate of grade  $\geq 3$  gastrointestinal toxicity ranged from 0 to 14% (median 8%).

The LKB model parameter values derived using the different model fits are detailed in Table 3. The solution space for DuoLKB2 (LKB function with a TD<sub>50</sub>(1) value of 142 Gy) is visualised in Fig. 1. Fig. 2 shows a plot of the four models (DuoLKB1–4) and the model derived by Pan et al. Confidence limits are shown for the unconstrained model, derived using leave-one out cross-validation.

The proportional incidence of grade 3 gastro-intestinal toxicity observed in the SCALOP trial was 8.8%, and the values predicted by the three models DuoLKB1, 2 and 3 were 7.4%, 7.6% and 7.0% respectively. For the ARCI trial, the observed toxicity incidence



**Fig. 3.** NTCP model of duodenal toxicity published by Pan, and fitted to published data either excluding (DuoLKB3) or including (DuoLKB4) the ARCI and SCALOP trials, weighted according to cohort size. 95% confidence intervals are shown for the fit excluding the ARCI and SCALOP trials.

was 14.3%, while the incidence predicted by the model fits were 8.9%, 9.1% and 7.8% respectively.

Fig. 3 shows the model derived when incorporating the clinical trial datasets (DuoLKB4), along with 95% confidence estimates for this curve, demonstrating the uncertainty that exists outside of the observed data range.

## Discussion

We have identified publications with clinical duodenum DVH data which we have used to fit the LKB model and derive parameter values that have consistency with those derived by existing publications using individual patient data. The derived values were especially similar to previous results when the sources were weighted according to the number of patients in each cohort, as highlighted in Fig. 2. We have then used these parameters to predict toxicity within two clinical trials of pancreatic cancer chemoradiotherapy, with accurate results for one study but not the other. We believe this to be the first time this iteration for developing an NTCP model has been used, and think it is likely that the particular chemotherapy combination used in the ARCI trial (concurrent gemcitabine, cisplatin and nelfinavir) explains the observed toxicity in this study being higher than is predicted by the model. When we incorporate the data from these clinical trials the model fit is less consistent with existing literature, however this comprises the largest meta-analysis of this type to have been conducted. This model (DuoLKB4) is based on the pooled data regarding treatment of over five hundred patients and is therefore the model we would suggest be adopted for clinical practice.

The values derived for the parameter  $n$  are consistent with a small volume effect for the toxicity endpoint. Low values of  $n$  increase the dependence of the outcome on the maximum dose received by the tissue and are seen for tissues (or endpoints) where

the functional subunits (FSU's) are arranged in a serial manner. An example is myelitis in the spinal cord, where the volume of the organ affected (along the axial length of the cord) is of little consequence [26]. Our results suggest a similar behaviour for the duodenum, where the maximum exposure dose is more important than the affected volume of the organ at risk.

Pan and colleagues had derived LKB model values for the duodenum using retrospective analysis of 92 patients treated with conformal radiotherapy [12]. The patients received either 1.5 Gy twice-daily with intrahepatic arterial chemotherapy or 1.8–3.0 Gy four times per day without chemotherapy, hence for analysis the authors converted these to effective doses at 2 Gy per fraction ( $EQD_{2Gy}$ ). The LKB values derived were  $n = 0.12$  (0.09–0.30),  $m = 0.49$  (0.36–0.61) and  $TD_{50}(1) = 180$  Gy (69% CI  $\approx 100$ – $>200$  Gy), suggesting a small volume effect and shallow dose-NTCP curve. When the value of  $n$  was constrained to be  $\geq 0.09$ , the other fitted values also shifted closer to those of Pan et al., but with no change in the goodness of fit, suggesting these values are equally appropriate to our data. Interestingly, the values for DuoLKB3 were even closer to those of Pan et al.

When analysing conventionally fractionated chemoradiotherapy in pancreatic cancer Murphy et al. did not identify any significant associations of toxicity with specific duodenum dose-volume parameters, though saw a trend for association with generalised equivalent uniform dose (gEUD, a DVH-reduction parameter closely related to  $V_{eff}$  in the LKB model [27–29]) [30]. They subsequently derived LKB parameters for the duodenum using a cohort of 73 patients treated with single-fraction SBRT for inoperable pancreatic cancer ( $n = 0.12$ ,  $m = 0.23$ , and  $TD_{50}(1) = 24.6$  Gy) [31]. The authors acknowledged that comparing single-fraction treatment with conventional fractionation regimens is challenging, however the  $EQD_{2Gy}$  for 24.6 Gy in a single fraction is 117.3 Gy (alpha-beta 4 Gy), a value not dissimilar to those established by other authors and ourselves.

In their meta-analysis Prior et al. incorporated published duodenum DVH and toxicity data from four studies (two using conventional fractionation, also used in this investigation, and two using hypofractionated radiotherapy) encompassing 312 patients [14]. A model was derived partly using small-bowel homogenous irradiation tolerance data from Burman et al. [32], hence they were unable to derive a value for  $n$ , and this may explain the difference between the LKB values they have fitted ( $m = 0.21 \pm 0.05$  and  $TD_{50}(1) = 60.9 \pm 7.9$  Gy) and ours.

Elhammali et al. collated toxicity data from 16 human studies (and two canine studies) involving a total of 1160 patients and used regression analysis to show that dose was the only significant predictor of toxicity among the studies they analysed [15]. The authors went on to derive LKB parameters  $n = 0.38$ – $0.63$ ,  $m = 0.48$ – $0.49$ , and  $TD_{50}(1) = 35$ – $95$  Gy, however as the majority of publications they examined did not report treatment DVH data the authors had resorted to an assumption that across all studies 1–5% of the duodenum was exposed to the prescription dose. Their values for  $n$  are higher and their values for  $TD_{50}(1)$  are considerably lower than those found in other studies (including ours). The assumption of volume made by the authors is not likely to reflect the true exposure of the duodenum in these patients, particularly when some cohorts included single-fraction intraoperative radiotherapy and others were preclinical animal studies, and these further particularities limit the applicability of these results to conventional clinical external beam irradiation.

A key limitation of our own study is the persistently small number of somewhat heterogeneous studies that provide suitable data, though our results are potentially strengthened by the addition of data derived directly from the complete DVH for the individual patients treated in the SCALOP and ARCI trials, and the coherent use of similarly fractionated studies. One publication that was



found and reviewed provided DVH data only for a combined stomach-duodenum structure [33] hence these values were not incorporated into the model fitting, while Pan et al. reported only mean dose for the duodenum [12]. While there is some degeneracy of the parameter values derived in our model fitting there is also a well-defined minimum 'valley' as shown in Fig. 1. The confidence intervals for our parameter values are broad and the proportion of each of our models that is extrapolated beyond the observed data should be interpreted with caution. We acknowledge that the spline-fitting method we have used to recreate the DVH's from reported data points may lack precision when few data are provided. We also appreciate further uncertainty exists in the conversion of the varying dose-fractionation schedules, and in the influence of the differing chemotherapy drugs and combination regimens on the behaviour of duodenal radiotherapy toxicity.

For an organ to be studied rigorously, it must be defined consistently. Detailed guidance on the delineation of the duodenum has now been published in the recent RTOG upper GI atlas, but the authors of this guideline noted that the fourth part of the duodenum was frequently missed by the contributing clinicians, meaning that existing data relating to this organ may be affected by this inconsistency in anatomical delineation [18]. While the duodenum is less mobile than other parts of the small bowel, large inter-fractional variations in volume still occur and which can lead to significant differences in delivered dosimetry compared to that which is planned [34–36]. Very few publications have investigated the delivered or accumulated dose to upper GI organs [37], and the data used here rely on planned dose as a surrogate.

The perceived benefits of the LKB model include the rational interpretation that can be made of the parameter values, relating to tissue architecture, dose–response gradient and tolerance dose. However, the LKB model originates from a time of more homogeneous dose distribution across target structures and normal-tissues, and the DVH-reduction step may be inappropriate for the modern era of highly modulated radiotherapy dose depositions as the detail of the shape of the DVH will be obscured [38]. Furthermore, in hollow organs such as the gastrointestinal tract the tissue of interest is only a thin layer surrounding a variable amount of contents and dose-surface-maps may therefore offer greater insight into the causality of toxicity in hollow or tubular organs [37,39].

Gastrointestinal toxicity outcomes and their relationships to the relevant tissues are complex, and there is subtle variation in the endpoints defined by the source publications utilised here. Many of the relevant symptoms that indicate radiation toxicity (nausea, vomiting, anorexia, abdominal pain) could arise from damage to the other tissues of the abdomen (particularly the stomach and small bowel) even if the duodenum were entirely spared, or could result from systemic therapy or the underlying disease. Some analyses have confined their study to outcomes with physical evidence of toxicity, such as ulceration or bleeding in the organ of interest, proven using endoscopy. To us this seems an oversimplification, which may overlook other features of duodenal toxicity that also cause patient morbidity and may impair outcomes if they were to impede the delivery of a prescribed course of radiotherapy.

While results of dosimetry-toxicity analysis have differed between studies the predictive value of the duodenum  $V_{55\text{Gy}}$  has been reproduced by independent investigators [8,10]. Similarly while there is variability in the values that have been derived for the LKB model by the various publications considered here, there is some consistency in the ranges of results observed, and the results of our meta-analysis are closer to those found in studies of individual patient data [12] than in the two other attempted meta-analyses [14,15]. This we attribute to the use of collated rather than assumed volume data, and the exclusion of possibly confounding hypofractionated radiotherapy data.

## Conclusions

We have successfully derived parameters for the LKB model for the duodenum using reconstructed DVH data from a set of publications reporting clinical toxicity outcomes after irradiation of upper abdominal tumours, which show some consistency with values derived using individual patient data. These parameters can be used to understand the dependence of toxicity in this organ on dose and volume and potentially predict toxicity risk in a patient cohort, but work in this field is restricted by a limited availability of source data and the complexity of the outcome of interest.

## Conflict of interest statement

The authors declare that they have no competing or conflicting interests.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2017.04.024>.

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