Stomach dose-volume predicts acute gastro-intestinal toxicity in chemoradiotherapy for locally-advanced pancreatic cancer

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Introduction

Patients with locally-advanced pancreatic cancer who do not progress on initial treatment with chemotherapy may achieve improved local control with chemoradiotherapy [1]. There is evidence for a dose-response relationship in pancreatic cancer [2], hence increased dose could achieve better tumour control. However, the radiotherapy dose that can be delivered is limited by gastro-intestinal (GI) toxicity [3-5], the risk of which also increases with dose [6].

Clinical data on the radiotherapy tolerances for the stomach and duodenum remain sparse, but some studies have confirmed the association between organ-at-risk (OAR) radiotherapy parameters and subsequent risk of toxicity [5, 7-12].

We analysed toxicity outcomes in patients with local-advanced pancreatic cancer treated in two prospective phase-II clinical trials. Patients in the SCALOP study (NCT 01032057, n=74) with stable or responding disease after 12 weeks of induction gemcitabine and capecitabine chemotherapy were randomised to receive either gemcitabine or capecitabine alongside 50.4 Gy in 28 fractions [13]. Patients in the single-arm open-label ARCII study (EudraCT 2008-006302-42, n=23) received 59.4 Gy in 33 fractions during concomitant chemoradiotherapy with gemcitabine, cisplatin, and nelfinavir (a hypoxia modifier) [14].

This analysis aimed to: 1) identify normal-tissue dose-volume histogram (DVH) parameters associated with increased risk of toxicity; 2) develop and validate predictive multivariable models for personalised estimation of risk that might be utilised in the clinic; 3) investigate possible associations of toxicity and survival outcomes.

Material and Methods

Patient data

The trial eligibility criteria, treatment details and outcomes have been reported previously [13, 14]. Toxicity events were prospectively recorded according to Common Terminology Criteria of Adverse Events (CTCAE), version 3.0 [15] in SCALOP and version 4.0 [16] in ARCII and both studies recorded baseline symptoms. In ARCII, clinical assessments were weekly during radiotherapy, 6–8 weeks after radiotherapy and 3-monthly until 12 months. In SCALOP, assessments were monthly during induction chemotherapy, weekly during radiotherapy, 2 weeks following radiotherapy, and 3 months and 6 months later. In both studies, patients were prescribed prophylactic anti-emetics and acid-suppressant medication.

Symptoms of acute toxicity (nausea, vomiting, abdominal pain, GI bleeding/perforation, bowel obstruction, anorexia ± weight loss) were pooled to generate a single endpoint of 'upper GI toxicity' (UGIT) [17]. The maximal grade of any of these symptoms suffered by each patient during three months (90 days) from the onset of radiotherapy was collated. The toxicity outcome was dichotomised according to a threshold of grade ≥2, chosen because this indicates requirement for medical intervention.

Two patients from ARCII were excluded as they received only one radiotherapy fraction. For one patient this was due to disease progression and the other due to unrelated medical comorbidity. One patient from SCALOP was excluded due to gastric outlet obstruction on planning CT causing abnormal stomach dilatation (measured stomach volume was 2954 cm^3. Median stomach volume was 361 cm^3 (interquartile range 255 cm^3 – 541 cm^3). Radiotherapy dose data was not available for three patients from the SCALOP study. In total 91 patients (70 from SCALOP, 21 from ARCII) were included in the final analysis.

Disease and patient characteristics collected included age, sex, performance status, Body Mass Index (BMI), tumour volume and tumour location as indicated by centre of mass (head, neck or other). In ARCII the Karnofsky Performance Status had been recorded and values were converted to equivalent ECOG grade [18]. For SCALOP patients, weight-loss during induction chemotherapy was calculated in kilograms.

Radiotherapy data

The details of radiotherapy delivery in the two studies, including radiotherapy trials quality assurance, have been described elsewhere [13, 14, 19, 20]. In SCALOP the Gross Tumour Volume (GTV) was defined as tumour visualised on CT scan with lymph nodes >1 cm diameter, and Planning Target Volume (PTV) was defined as GTV plus 20 mm margin in craniocaudal direction and 15 mm margin otherwise. All patients were prescribed 50.4 Gy in 28 daily fractions in a single phase with three-dimensional conformal radiotherapy. In ARCII radiotherapy was delivered in two phases: 50.4 Gy in 28 daily fractions was prescribed to the primary tumour and draining lymph node regions followed by a sequential boost of 9 Gy in 5 fractions to the primary tumour PTV (also defined as GTV plus 20mm in the craniocaudal direction and 15mm in other directions). Phase 1 was delivered using IMRT and phase 2 using conformal planning. No dose-volume constraints for the stomach or duodenum were set in either study. The use of intravenous contrast and oral water contrast (100-200ml) for treatment-planning imaging was specified in both studies. For ARCII, patients were fasted for two hours prior to planning and treatment. Two patients in ARCII underwent re-planning due to weight-loss during radiotherapy. The two partial courses were summed using deformable registration in Mirada RTx (Mirada Medical, Oxford, UK). Doses were recalculated to reflect the delivered dose if patients did not complete their prescribed treatment (four patients in SCALOP and two in ARCII discontinued radiotherapy early due to toxicity, while overall 95% of planned fractions were delivered in SCALOP and 99% in ARCII). For both trials the prophylactic use of a proton-pump inhibitor or histamine receptor blocker and appropriate anti-emetics during radiotherapy were mandatory, unless contra-indicated.

The stomach and duodenum were contoured retrospectively according the Radiation Therapy Oncology Group (RTOG) atlas and guidance [21], with specialist radiologist support. Where these structures had been previously contoured by treating clinicians (in all ARCII patients, and in nine SCALOP patients) they were modified as necessary.

Radiotherapy planning CT and dose data were anonymised and imported into the CERR (Computational Environment for Radiotherapy Research) software package [22] and cumulative absolute dose-volume data was exported in 5-Gy bins (i.e. $V_{5Gy,}$ V_{10Gy} etc.).

Statistics

Radiotherapy dose-volume data was not normally distributed hence non-parametric tests were used for assessment of associations and correlation. Differences in continuous variables between groups were assessed using the Mann-Whitney-Wilcoxon test and differences in categorical frequencies using Chi-squared. Tests for correlations used Kendall tau-b for dichotomous variables and Spearman's rank for continuous variables. Binary logistic regression was used to test relationships of predictive variables with risk of dichotomised outcomes and ordinal regression for grade of toxicity. Optimal risk thresholds for division of patients into groups according to continuous variables were derived using ROC analysis and Youden's index [23]. Factors showing significant associations on univariate analysis and those with sound clinical rationale for relationships with toxicity were incorporated into multivariate logistic regression, which utilised backwards stepwise selection with criterion for retention in final model $p < 0.1$. Optimal models were selected by maximal classification accuracy and AUC, with minimum Akaike Information Criterion (AIC), and five-fold internal cross-

validation was used to estimate generalisability. Overall and progression-free survival were compared between groups using log-rank (Mantel-Cox).

Results

CTCAE grade ≥2 UGIT symptoms occurred in 38 patients (42%) – grade 1 in 36 (39.6%), grade 2 in 26 (28.6%), and grade 3 in 12 (13.2%). No grade 4 or 5 toxicity occurred. Risk of grade ≥2 UGIT was higher among the ARCII cohort than among the SCALOP patients, but not significantly so (χ^2=1.267, p=0.260), as were proportion of patients with performance status ≥1 (χ^2=2.837, p=0.092) and with tumour centre of mass in the neck or body of the pancreas, rather than the head (χ^2=6.773, p=0.335). Other clinical and treatment parameters were equivalent across the two cohorts (Table 1).

On univariate analysis the stomach cumulative V_{35Gy} (volume receiving 35 Gy or more) was significantly higher for patients with toxicity: median for patients with grade 0-1 UGIT=30.9 cm^3 (IQR 12.0-62.0), compared with median for patients with grade ≥2=39.4 cm^3 (24.8-101.7), p=0.036. For the differential DVH parameter V_{35Gy} (volume receiving between 35 Gy and 40 Gy) the statistical significance of the difference between these groups was greater (median 6.36 cm^3 (IQR 1.89-18.4) vs 10.2 cm^3 (5.24-18.4), p=0.035), and the strongest association with toxicity risk was seen for differential DVH region $V_{35-45Gy}$ (median 12.9 cm^3 (IQR 3.56-23.4) vs 16.4 cm^3 (9.75-32.0), p=0.033). On univariate logistic regression the stomach $V_{35-45Gy}$ was predictive of risk of UGIT grade ≥2 (odds ratio 1.035, 95% CI 1.007-1.063, p=0.014). Median stomach $V_{35-45Gy}$ for patients increased sequentially with toxicity grade (see Table 2 and Figure 1) and on univariate ordinal regression was predictive of UGIT grade (odds ratio 1.023, 1.003-1.044, p=0.022). As a predictor of the risk of UGIT grade ≥2, the AUC was 0.632 (0.516-0.747). Toxicity incidence was 33/66 (50%) for patients with $V_{35-45Gy}$ above the optimal discriminatory threshold of 7.1 cm^3, and 5/25 (20%) below, with sensitivity of 0.868 and specificity 0.377. Using an alternative threshold of 30 cm^3 (the volume threshold with second-highest Youden index), the risk was 13/20 (65%) above and 25/71 (35%) below. Duodenum dose-volume parameters did not predict toxicity risk or severity in any cohort.

Table 3 shows the results of univariate logistic regression for risk of UGIT grade ≥2 for clinical factors. Risk was higher in patients with ECOG performance status 1 or higher, but the difference was not significant (odds ratio 1.661, 95% CI 0.717-3.852, p=0.235). For patients in the SCALOP study the amount of weight loss during induction chemotherapy, and concomitant chemotherapy (risk was highest for patients receiving gemcitabine), were significant predictors of risk and severity of UGIT – odds ratio with 95% CI 1.199 (1.040-1.382) and 3.632 (1.300-10.151) respectively. Increasing age was a significant predictor of toxicity risk and severity only for the ARCII cohort, odds ratio 1.344 (95% CI 1.015-1.780).

The optimal multivariate model incorporated patient sex, chemotherapy regimen (gemcitabine vs capecitabine vs ARCII regimen) and stomach $V_{35-45Gy}$ as a continuous variable. This achieved overall predictive accuracy of 71.4% and AUC of 0.745, and the ROC curve is shown in Figure 2. Model coefficients are included in supplementary material. Age, performance status, tumour volume and tumour location were not retained in the model. Figure 3 shows the observed against predicted incidence of toxicity for three evenly-sized groups divided by predicted risk. On five-fold internal cross-validation the mean AUC on the training set was 0.736 (standard deviation 0.035) but on an unseen test cohort was 0.598 (SD 0.188). The predictive factor most frequently retained in the model was chemotherapy group (retained in four models), followed by stomach $V_{35-45Gy}$ (three models), sex, and GTV volume (two models each). Tumour volume and stomach $V_{35-45Gy}$ were significantly correlated with each other (Spearman's correlation coefficient 0.211, p=0.044). Stomach $V_{35-45Gy}$ was highest in ARCII, (median 21.0, IQR 10.6-30.1) next highest in the gemcitabine

arm (14.5, 7.9-28.7) and lowest in the capecitabine arm (9.8, 2.9-22.3), and significantly different between these groups (Kruskal-Wallis test, χ^2=7.197, p=0.027).

Overall survival was significantly worse in patients who experienced grade ≥2 UGIT: median 10.8 months (95% CI 11.9-17.7) vs 14.8 months (8.5-13.1), log-rank 5.637, *p*=0.018, and this association persisted when patients who went on to suffer progressive disease within 90 days of starting radiotherapy were excluded from the analysis (this was the case for three patients from ARCII and three from SCALOP). Patients with acute grade ≥2 UGIT were not less likely to complete radiotherapy: 41/53 patients (71.1%) received all fractions compared to 27/38 (77.4%), χ^2=0.466, *p*=0.495. Progression-free survival was also worse for patients with acute UGI toxicity, but the difference was not significant: 6.1 months (95% CI 4.1-8.2) compared with 8.2 (6.6-9), *p*=0.052.

Discussion

We have analysed data from two prospective trials of chemoradiotherapy for locally-advanced pancreatic cancer and demonstrated dose-volume and patient-related factors influencing risk and severity of acute GI toxicity, which itself was associated with worse overall survival.

We found stomach dose-volume was predictive of toxicity risk, and have derived thresholds that could be used to inform radiotherapy planning: for our patients, if $V_{35\text{-}45Gy}$ was kept below 30 cm^3, the risk of grade ≥2 toxicity was 35% or less, and if kept below 7.1 cm^3, the risk was 20% or less. Similar findings have previously been reported (Table 4), however we believe our study is the first using pancreatic cancer chemoradiotherapy data to show with ordinal regression that increasing volume of stomach irradiated predicts increasing severity of toxicity. This result emphasises the fact that the stomach should always be accurately contoured for patients receiving this treatment, and suggests that the more effort is made to minimise stomach dose-volume, the greater the benefit to the patient in terms of both reduced risk and severity of toxicity. While tumour volume (as indicated by GTV volume) and stomach $V_{35\text{-}45Gy}$ were significantly correlated with each other, as would be expected, the evidence indicates that the stomach dose-volume is associated with increased risk of toxicity independently of tumour size. As shown in Table 3, GTV volume was not itself associated with increased toxicity on univariate analysis, and while it did get retained in two of the five multivariable models generated using the internal cross-validation, it was not mutually-exclusive for retention with the stomach $V_{35\text{-}45Gy}$, which would be expected if the two parameters were simply surrogates for each other.

We note the slightly higher predictive performance of a differential DVH parameter rather than a conventional cumulative DVH and suggest that a more specific measurement has shown a clearer association with outcomes. Relative (proportional) volume parameters were also investigated, however due to very small differences in values between patients, these parameters led to unstable results in regression modelling.

The incidence of toxicity was somewhat different between these two clinical trials, though the causal relationship for this is difficult to elucidate, due to possible confounding differences in the treatments delivered. Not only was the concomitant chemotherapy different, but in ARCII the radiotherapy field was larger in order to irradiate draining lymph nodes, and the dose to the tumour was higher, while the SCALOP patients had received induction chemotherapy. Despite this heterogeneity, we were able to show that patient sex and the stomach dose-volume remained significant contributors to overall risk in the multivariable model for the pooled cohort. It is not clear why, in both studies, females were at greater risk of toxicity than men, and there were no significant associations between sex and other factors such as age, PS, tumour size/location, or presence of baseline symptoms (included in supplementary data). In the SCALOP cohort, weight loss during

induction chemotherapy was associated with increasing risk of acute toxicity following concomitant radiotherapy, and the risk of both acute and late GI toxicity after pelvic radiotherapy has previously been shown to be higher in women with low body weight [24, 25].

Predictive modelling of radiotherapy toxicity can be prone to overfitting, with disappointing results on external validation [26]. We believe our work is the first in this clinical treatment paradigm to undertake internal cross-validation to assess generalisability and restrain potentially over-optimistic estimates of prospective model performance. Our results indicate a degree of overfitting may have occurred, with model performance on unseen data weaker than on training cohorts. This has been recognised to be a possible drawback of using stepwise predictor selection methods [27].

The association between toxicity and survival does not appear to be explained by any single factor, such as failure to complete radiotherapy, and instead may represent a combination of effects that are not individually significant. For multiple clinical factors (tumour size, age, BMI, PS, recent weight loss, symptoms at baseline) the direction of effect associated with risk of toxicity would also be expected to be associated with worse outcomes overall (Table 2).

Several publications have analysed GI OAR dose-volumes in chemoradiotherapy for pancreatic cancer (Table 3) and a number have identified stomach dose-volume as predictive of toxicity. These include Nakamura et al. who found the best predictors of grade ≥2 acute GI toxicity were stomach V_{50Gy} and D_{2cm3} (highest dose to ≥2 cm^3) [10]. Cattaneo et al. analysed outcomes for patients treated with relatively hypofractionated chemo-radiotherapy (prescribed dose 44.25 Gy in 15 #) [11] and found stomach V_{20Gy} was the best predictor of acute toxicity, while duodenum V_{40Gy} and V_{45Gy} were correlated specifically with 'anatomical' damage. Recently Shinoto et al. have published analysis of carbon-ion chemoradiotherapy dose-volume parameters, though the values themselves may not be directly comparable with those from photon radiotherapy [28]. It is worth noting that in our analysis we failed to show associations of GI toxicity with duodenum dose-volume, despite other studies having shown evidence of a relationship [29]. Murphy et al. showed a trend for association of increased duodenal dose-volume with grade ≥3 GI toxicity in patients treated with concomitant gemcitabine [7], but Huang et al. found the best predictor of toxicity in similar patients was the duodenum V_{35Gy} (V_{25Gy} when including patients who received concomitant erlotinib) [9]. Kelly et al. have examined the largest cohort in this group, and found duodenum V_{55Gy} the best predictor of risk [5]. Stomach dose-volume parameters have also been shown to predict toxicity risk in radiotherapy for hepatic tumours [30]: the combined 'Gastroduodenum' V_{35Gy} [8] and the stomach V_{25Gy} [12] have been shown to predict 'gastroduodenal' toxicity, and stomach D_{max} has shown association with gastric bleeding [31].

The stomach is where ingested food bathes in acidic secretions before passing into the duodenum. Irradiation of the stomach can cause loss of appetite, nausea and vomiting within hours. The mechanism is thought to involve 5-HT_3 secretion by enterochromaffin cells and vagal neural impulses to the brainstem vomiting centre, which stimulates expulsion of the stomach contents [32]. Gastric mucosal inflammation develops over subsequent days, with denudation of the gastric mucosa leading to painful superficial ulceration with possible GI bleeding [33]. We have added to the growing evidence-base for the importance of stomach dose-volume in predicting toxicity in chemoradiotherapy for LAPC, though with limitations. Due to the number of parameters that are tested in DVH analysis, there is a risk of type I error (a "false positive", in which the null hypothesis is rejected despite it being true). Conversely, when analysing observational data, negative results may be due to insufficient cases or insufficient variation in the independent factors, however, neither trial protocol enforced radiotherapy planning constraints for the stomach or duodenum, potentially allowing dose-volume to vary between patients. Though this dataset comprises the largest prospective pancreas radiotherapy trial cohort analysed to date, the sample size remains relatively

small and the method of pooling data from two trials increases risk heterogeneity and of confounds. True external validation of these findings is required and is intended to be conducted using data from an ongoing randomised study investigating chemoradiotherapy in LAPC.

Analysis of toxicity is hindered by the complex relationship of symptoms with the effects of treatment and disease. Conflating multiple symptoms to derive a single endpoint will obscure causes of specific symptoms, but while endpoints such as ulceration on endoscopy are highly objective, these severe events represent only a proportion of all relevant morbidity. Patient-reported outcomes may represent an improvement over conventional methods but are not established in upper-abdominal radiotherapy toxicity assessment. Spatial parameters describing dose to the structure wall could be more appropriate than dose-volume parameters [34], but due to interfractional motion and deformation the delivered dose to the stomach may significantly differ from planned dose even if breath-hold methods are implemented [35], and ideally outcomes would be analysed against delivered dose.

Conclusions

In chemoradiotherapy for locally-advanced pancreatic cancer, the volume of stomach irradiated to moderately high dose (35-45 Gy) predicts incidence and severity of acute toxicity, while other factors predictive of risk include sex and concomitant chemotherapy agents. Reducing the volume of stomach irradiated to doses in this range may reduce the risk and severity of toxicity for these patients.

Acknowledgements

DW is funded by CRUK, grant C5255/A15935. MA is funded by CRUK, grant no C8225/A21133. MP is funded by CRUK, grant C5255/A15935. SM is part-funded by Oxford Biomedical Research Centre. MAH is funded by MRC, grant number MC_PC_12001/2. SCALOP data was supplied by Cardiff University South East Wales Trials Unit. ARCII data was supplied by Oxford University Clinical Trials Research Unit.

References

[1] Hammel P, Huguet F, van Laethem JL, Goldstein D, Glimelius B, Artru P, et al. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. JAMA. 2016;315:1844-53.
[2] Moraru IC, Tai A, Erickson B, Li XA. Radiation dose responses for chemoradiation therapy of pancreatic cancer: an analysis of compiled clinical data using biophysical models. Practical radiation oncology. 2014;4:13-9.
[3] McGinn CJ, Zalupski MM, Shureiqi I, Robertson JM, Eckhauser FE, Smith DC, et al. Phase I trial of radiation dose escalation with concurrent weekly full-dose gemcitabine in patients with advanced pancreatic cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2001;19:4202-8.
[4] Crane CH, Antolak JA, Rosen, II, Forster KM, Evans DB, Janjan NA, et al. Phase I study of concomitant gemcitabine and IMRT for patients with unresectable adenocarcinoma of the pancreatic head. Int J Gastrointest Cancer. 2001;30:123-32.
[5] Kelly P, Das P, Pinnix CC, Beddar S, Briere T, Pham M, et al. Duodenal toxicity after fractionated chemoradiation for unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 2013;85:e143-9.
[6] Elhammali A, Patel M, Weinberg B, Verma V, Liu J, Olsen JR, et al. Late gastrointestinal tissue effects after hypofractionated radiation therapy of the pancreas. Radiat Oncol. 2015;10:186.
[7] Murphy JD, Adusumilli S, Griffith KA, Ray ME, Zalupski MM, Lawrence TS, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 2007;68:801-8.
[8] Kim H, Lim DH, Paik SW, Yoo BC, Koh KG, Lee JH, et al. Predictive factors of gastroduodenal toxicity in cirrhotic patients after three-dimensional conformal radiotherapy for hepatocellular carcinoma. Radiother Oncol. 2009;93:302-6.
[9] Huang J, Robertson JM, Ye H, Margolis J, Nadeau L, Yan D. Dose-volume analysis of predictors for gastrointestinal toxicity after concurrent full-dose gemcitabine and radiotherapy for locally advanced pancreatic adenocarcinoma. Int J Radiat Oncol Biol Phys. 2012;83:1120-5.
[10] Nakamura A, Shibuya K, Matsuo Y, Nakamura M, Shiinoki T, Mizowaki T, et al. Analysis of dosimetric parameters associated with acute gastrointestinal toxicity and upper gastrointestinal bleeding in locally advanced pancreatic cancer patients treated with gemcitabine-based concurrent chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2012;84:369-75.
[11] Cattaneo GM, Passoni P, Longobardi B, Slim N, Reni M, Cereda S, et al. Dosimetric and clinical predictors of toxicity following combined chemotherapy and moderately hypofractionated rotational radiotherapy of locally advanced pancreatic adenocarcinoma. Radiother Oncol. 2013;108:66-71.
[12] Yoon H, Oh D, Park HC, Kang SW, Han Y, Lim DH, et al. Predictive factors for gastroduodenal toxicity based on endoscopy following radiotherapy in patients with hepatocellular carcinoma. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]. 2013;189:541-6.
[13] Mukherjee S, Hurt CN, Bridgewater J, Falk S, Cummins S, Wasan H, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. Lancet Oncol. 2013;14:317-26.
[14] Wilson JM, Fokas E, Dutton SJ, Patel N, Hawkins MA, Eccles C, et al. ARCII: A phase II trial of the HIV protease inhibitor Nelfinavir in combination with chemoradiation for locally advanced inoperable pancreatic cancer. Radiother Oncol. 2016;119:306-11.
[15] National Cancer Institute. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). In: National Cancer Institute, editor.2006.
[16] National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). May 29, 2009 ed2009.

[17] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31:1341-6.
[18] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.
[19] Fokas E, Clifford C, Spezi E, Joseph G, Branagan J, Hurt C, et al. Comparison of investigator-delineated gross tumor volumes and quality assurance in pancreatic cancer: Analysis of the pretrial benchmark case for the SCALOP trial. Radiother Oncol. 2015;117:432-7.
[20] Fokas E, Spezi E, Patel N, Hurt C, Nixon L, Chu KY, et al. Comparison of investigator-delineated gross tumour volumes and quality assurance in pancreatic cancer: Analysis of the on-trial cases for the SCALOP trial. Radiother Oncol. 2016;120:212-6.
[21] Jabbour SK, Hashem SA, Bosch W, Kim TK, Finkelstein SE, Anderson BM, et al. Upper abdominal normal organ contouring guidelines and atlas: a Radiation Therapy Oncology Group consensus. Practical radiation oncology. 2014;4:82-9.
[22] Deasy JO, Blanco AI, Clark VH. CERR: a computational environment for radiotherapy research. Medical physics. 2003;30:979-85.
[23] Youden WJ. Index for rating diagnostic tests. Cancer. 1950;3:32-5.
[24] Eifel PJ, Jhingran A, Bodurka DC, Levenback C, Thames H. Correlation of smoking history and other patient characteristics with major complications of pelvic radiation therapy for cervical cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002;20:3651-7.
[25] Huang EY, Sung CC, Ko SF, Wang CJ, Yang KD. The different volume effects of small-bowel toxicity during pelvic irradiation between gynecologic patients with and without abdominal surgery: a prospective study with computed tomography-based dosimetry. Int J Radiat Oncol Biol Phys. 2007;69:732-9.
[26] Mbah C, Thierens H, Thas O, De Neve J, Chang-Claude J, Seibold P, et al. Pitfalls in Prediction Modeling for Normal Tissue Toxicity in Radiation Therapy: An Illustration With the Individual Radiation Sensitivity and Mammary Carcinoma Risk Factor Investigation Cohorts. Int J Radiat Oncol Biol Phys. 2016;95:1466-76.
[27] Xu CJ, van der Schaaf A, Schilstra C, Langendijk JA, van't Veld AA. Impact of statistical learning methods on the predictive power of multivariate normal tissue complication probability models. Int J Radiat Oncol Biol Phys. 2012;82:e677-84.
[28] Shinoto M, Shioyama Y, Matsunobu A, Okamoto K, Suefuji H, Toyama S, et al. Dosimetric analysis of upper gastrointestinal ulcer after carbon-ion radiotherapy for pancreatic cancer. Radiother Oncol. 2016;120:140-4.
[29] Holyoake DLP, Aznar M, Mukherjee S, Partridge M, Hawkins MA. Modelling duodenum radiotherapy toxicity using cohort dose-volume-histogram data. Radiother Oncol. 2017;123:431-7.
[30] Pan CC, Dawson LA, McGinn CJ, Lawrence TS, Ten Haken RK. Analysis of radiation-induced gastric and duodenal bleeds using the Lyman-Kutcher-Burman model. Int J Radiat Oncol Biol Phys. 2003;57:S217-S8.
[31] Feng M, Normolle D, Pan CC, Dawson LA, Amarnath S, Ensminger WD, et al. Dosimetric analysis of radiation-induced gastric bleeding. Int J Radiat Oncol Biol Phys. 2012;84:e1-6.
[32] Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10 ed. Philadelphia, PA: Elsevier; 2015.
[33] Hall EJ, Giaccia AJ. Radiobiology for the Radiologist. 6th ed. London: Lippincott Williams & Wilkins; 2006.
[34] Witztum A, George B, Warren S, Partridge M, Hawkins MA. Unwrapping 3D complex hollow organs for spatial dose surface analysis. Medical physics. 2016;43:6009.
[35] Nakamura A, Shibuya K, Nakamura M, Matsuo Y, Shiinoki T, Nakata M, et al. Interfractional dose variations in the stomach and the bowels during breathhold intensity-modulated radiotherapy for pancreatic cancer: Implications for a dose-escalation strategy. Medical physics. 2013;40:021701.

Figures

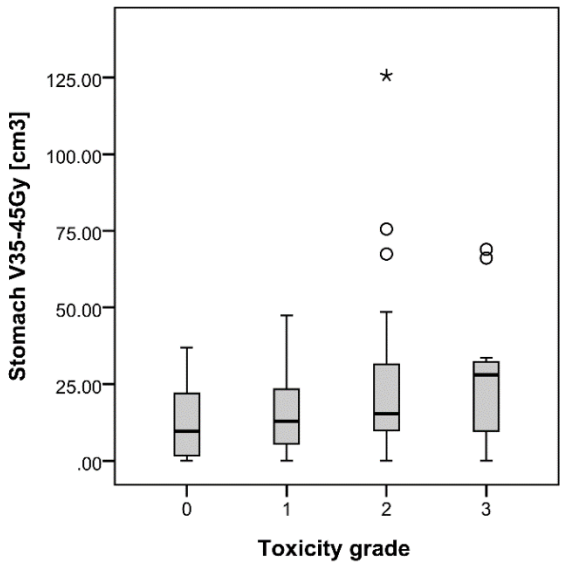

Figure 1. Box & whisker plot of stomach $V_{35\text{-}45Gy}$ against maximal acute upper-GI toxicity grade.

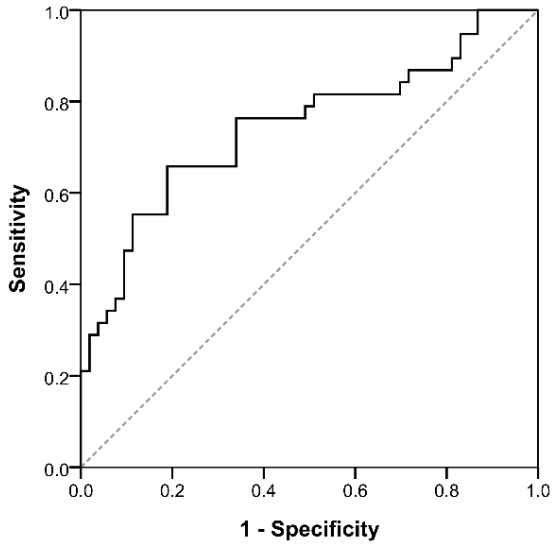

Figure 2. ROC curve for multivariable logistic regression model incorporating patient sex, chemotherapy treatment arm and stomach $V_{35\text{-}45Gy}$.

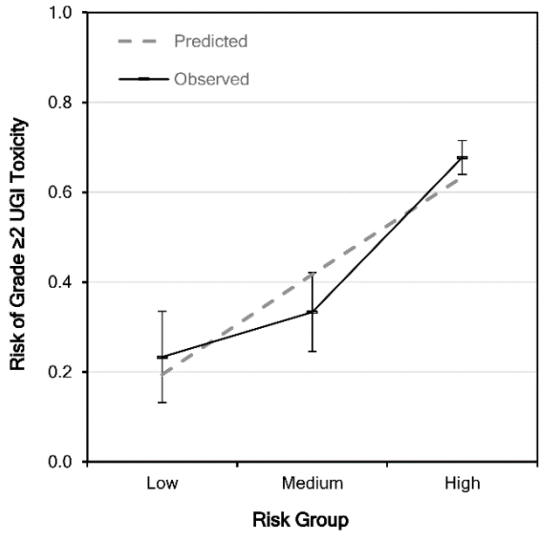

Figure 3. Plot of observed proportional incidence of acute UGI toxicity grade ≥2 among three evenly-sized cohorts divided according to risk (low, medium, high) as predicted by multivariable logistic regression model incorporating patient sex, chemotherapy treatment arm and stomach $V_{35\text{-}45Gy}$.

Figure legends

Figure 1. Box & whisker plot of stomach $V_{35\text{-}45Gy}$ against maximal acute upper-GI toxicity grade.

Figure 2. ROC curve for multivariable logistic regression model incorporating patient sex, chemotherapy treatment arm and stomach $V_{35\text{-}45Gy.}$

Figure 3. Plot of observed proportional incidence of acute UGI toxicity grade ≥2 among three evenly-sized cohorts divided according to risk (low, medium, high) as predicted by multivariable logistic regression model incorporating patient sex, chemotherapy treatment arm and stomach $V_{35\text{-}45Gy}$.

Tables

Table 1. Collated patient characteristics and acute toxicity incidence

		Combined cohort	ARCII	SCALOP
N		91	21	70
Age, mean (range)		64.0 (43.4–78.8)	64.5 (43.4-78.8)	63.8 (45.9-77.9)
Sex	Male	50 (54.9%)	11 (52.4%)	39 (55.7%)
	Female	41 (45.1%)	10 (47.6%)	31 (44.3%)
BMI, mean (range)		23.9 (16.4-44.4)	23.6 (17.4-34.2)	24.0 (16.4-44.4)
ECOG Performance status	0	45 (49.5%)	7 (33%)	38 (54.3%)
	1	39 (42.9%)	10 (47.6%)	29 (41.4%)
	2	7 (7.7%)	4 (19.0%)	3 (4.3%)
Tumour volume [cm³], mean (range)		35.9 (1.4-114.2)	29.8 (6.6 – 74.0)	37.7 (1.4-114.2)
Tumour location	Body	8 (8.8%)	4 (19.0%)	4 (5.7%)
	Head	64 (70.3%)	13 (61.9%)	51 (72.9%)
	Neck	19 (20.9%)	4 (19.0%)	45 (21.4%)
Concomitant chemotherapy			Gem, Cisplatin & Nelfinavir (100%)	Gem 36 (51.4%) Cape 34 (48.6%)
Grade 0 Upper GI Toxicity		17 (18.7%)	3 (14.3%)	14 (20.0%)
Grade 1 Upper GI Toxicity		36 (39.6%)	7 (33.3%)	29 (41.4%)
Grade 2 Upper GI Toxicity		26 (28.6%)	8 (38.1%)	18 (25.7%)
Grade 3 Upper GI Toxicity		12 (13.2%)	3 (14.3%)	9 (12.9%)
Grade ≥2 Upper GI Toxicity		38 (41.8%)	11 (52.4%)	27 (38.6%)
Grade ≥2 Nausea or Vomiting		27 (29.7%)	12 (57.1%)	15 (21.4%)
Grade ≥2 Anorexia		13 (14.3%)	3 (14.3%)	10 (14.3%)
Grade ≥2 Abdominal Pain		13 (14.3%)	3 (14.3%)	10 (14.3%)
Grade ≥2 Weight Loss		8 (8.8%)	1 (4.8%)	7 (10%)
Grade ≥2 GI Bleeding		9 (9.9%)	0 (0%)	9 (12.9%)
Baseline Grade ≥2 Upper GI toxicity		10 (11.0%)	1 (4.8%)	9 (12.9%)
Baseline Grade ≥2 Nausea or Vomiting		2 (2.2%)	1 (4.8%)	1 (1.4%)
Baseline Grade ≥2 Abdominal Pain		5 (5.5%)	0	5 (7.1%)
Baseline Grade ≥2 Weight Loss		3 (3.3%)	0	3 (4.3%)

Table 2. Stomach $V_{35\text{-}45Gy}$ according to grade of acute upper-GI toxicity, for the pooled cohort (n=91)

Toxicity Grade		**0**	**1**	**2**	**3**
Stomach	Median	9.70	12.93	15.31	28.02
$V_{35\text{-}45Gy}$ [cm^3]	IQR	1.72-22.00	5.54-23.37	9.95-31.51	9.74-32.26

Table 3. Collated results of univariate logistic regression of clinical factors against risk of Grade ≥ 2 UGIT, showing odds ratio (with 95% CI)

	Combined cohort	ARCII	SCALOP
Age	1.007 (0.955-1.060)	1.344 (1.015-1.780) *	0.969 (0.913-1.027)
BMI	0.970 (0.881-1.068)	1.082 (0.861-1.359)	0.945 (0.843-1.060)
Tumour volume	1.014 (0.995-1.033)	1.007 (0.962-1.055)	1.007 (0.989-1.026)
ECOG PS (0-1 vs 2)	1.961 (0.412 - 9.322)	3.375 (0.290 - 39.322)	0.788 (0.068 - 9.139)
Patient sex[#]	0.591 (0.255-1.370	0.556 (0.098-3.148)	0.607 (0.230-1.604)
Tumour location (head vs other)	1.795 (0.723-4.454)	4.800 (0.682-33.798)	1.225 (0.419-3.582)
Baseline UGIT (any grade)	1.540 (0.649-3.656)	1.500 (0.195-11.536)	0.800 (0.155-4.123)
Weight loss during induction chemo			1.199 (1.040-1.382) *
Concomitant chemotherapy [+]			3.632 (1.300-10.151) *

*Indicates significance at $p < 0.05$ level; [#] Risk is higher for females, in both studies, [+] Gemcitabine vs capecitabine, risk is highest for gemcitabine arm. BMI=Body Mass Index; ECOG=Eastern Cooperative Oncology Group; PS=Performance Status.

Table 4. Findings of published analyses of the dose-volume relationships of gastrointestinal organs at risk in pancreatic cancer radiotherapy, or of treatment of other conditions in which relationships with stomach DVH are identified. Risk comparison, where reported, indicates proportional incidence of specified toxicity for patients whose radiotherapy plans achieved or did not achieve the specified threshold value

Reference	Cancer site	N	Concurrent Chemotherapy	RT Dose-Schedule	RT technique	Toxicity Outcome	Predictive dose-volume parameter and threshold values (with risk comparison) where reported
Murphy 2007 [7]	LAPC	74	Gemcitabine	36 Gy in 15 #	3D	'Duodenal'	Duodenum gEUD
Huang 2012 [9]	LAPC	46	Gemcitabine ± erlotinib	36 Gy in 15 #	3D (40)/ IMRT (6)	Grade ≥3 GI	All patients: Duodenum V_{25Gy} 45% (8% vs 48%) Non-erlotinib: Duodenum V_{35Gy} 20% (0% vs 41%)
Nakamura 2012 [10]	LAPC	40	Gemcitabine	54 Gy in 30 #	3D + IMRT boost	Acute GI & Upper GI Bleed	Stomach V_{50Gy} 16 cm^3 (9% vs 61%) Stomach D_{2cm3} 53.6 Gy Gy (0% vs 57%) StoDuo V_{50Gy} 33 cm^3 (0% vs 44%)
Kelly 2013 [5]	LAPC	106	Gemcitabine ± 5FU/cape ± EGFRi	50.4 Gy in 28 #	3D (75)/ IMRT (31)	Grade ≥ 2 'Duodenal'	Duodenum V_{55Gy} 1 cm^3
Cattaneo 2013 [11]	LAPC	61	Capecitabine or 5FU	44±15 Gy boost, in 15 #	IMRT	Grade ≥2 GI	Stomach V_{20Gy} 31% Duodenum V_{40Gy} 16% Duodenum V_{45Gy} 2.6%
Kim 2009 [8]	HCC	73	None	36 Gy in 12 #	3D	Grade ≥ 3 'gastroduodenal'	Gastroduodenum V_{35Gy} 5% (4% vs 48%)
Yoon 2013 [12]	HCC	90	None	33 Gy in 11 #	3D	Grade ≥ 2 'gastroduodenal'	Stomach V_{25Gy} 6.3% (2.9% vs 57.1%) Duodenum V_{35Gy} 5.4% (9.4% vs 45.9%)
Pan 2003 [30]	Hepatic tumours	92	Hepatic arterial chemotherapy	1.5 Gy per # BD with chemo or 1.8 – 3 Gy per # QDS without	3D	Upper GI bleed	Stomach TD_{50} 62 Gy Duodenum TD_{50} 180 Gy
Feng 2012 [31]	Hepatic tumours	116	IV 5FU or Hepatic FUDR	54 Gy in 28 # or 1.5 Gy per # BD regimen with FUDR	3D	Gastric bleeding	Stomach D_{max}

(N=number of patients analysed; RT=radiotherapy; #=fractions; LAPC=locally advanced pancreatic cancer; Gy=Gray; 3D=3-dimensional conformal radiotherapy; gEUD=generalised Equivalent Uniform Dose; IMRT= intensity modulated radiotherapy; 5FU=5-fluoro-uracil; cape=capecitabine; EGFRi=epithelial growth factor receptor inhibitor; HCC=hepato-cellular carcinoma; GI=gastrointestinal; StoDuo=combined stomach & duodenum volume; IV=Intravenous; Hepatic FUDR=intrahepatic infusion of 5-fluorodeoxyuridine; NS=not specified; D_{max} =maximum dose; D_{mean}=mean dose)

Stomach dose-volume predicts acute gastro-intestinal toxicity in chemoradiotherapy for locally-advanced pancreatic cancer

Supplementary data tables

		Odds ratio	95% CI	*p*
Pooled cohort	Stomach $V_{35\text{-}45Gy}$ [cm^3]	1.023	1.003-1.044	0.022
ARCII	Age [years]	1.159	1.019-1.318	0.024
SCALOP	Concomitant Chemotherapy +	3.56	1.43-8.85	0.006
	Weight loss [kg]	1.172	1.046-1.314	0.006

Table 2. Statistically significant results for univariate ordinal regression. + Gemcitabine vs capecitabine, severity grade is higher for gemcitabine. 95% CI = 95% confidence intervals; V35-45Gy = volume of organ receiving between 35 & 45 Gy.

	Coefficient	SE	*p*	Odds Ratio	95% CI
Chemo = Gemcitabine	1.350	0.559	0.016	3.859	1.291-11.533
Chemo = ARCII	1.022	0.636	0.108	2.779	0.799-9.665
Sex = Female	0.782	0.481	0.104	2.185	0.851-5.613
Stomach $V_{35\text{-}45Gy}$ [cm^3]	0.033	0.015	0.025	1.034	1.004-1.064
Constant	-2.163	0.603	0.000	0.115	

Table 3. Multivariate logistic regression model coefficients. SE = standard error; 95% CI = 95% confidence intervals; $V_{35\text{-}45Gy}$ = volume of organ receiving between 35 & 45 Gy.

	N	Age	GTV Volume	Stomach $V_{35\text{-}45Gy}$
Male	40	64.9 (57.0-70.3)	31.7 (19.2-47.8)	18.3 (5.2-26.7)
Female	51	65.5 (57.7-69.5)	27.9 (19.9-42.7)	13.1 (6.7-26.0)
M-W U		992.5	960.0	1002.0
***p*-value**		0.795	0.604	0.854

Table 4. Continuous variables according to patient sex. Median values with inter-quartile range are reported. P-value indicates result of Mann-Whitney U test. N = number of patients; GTV = Gross Tumour Volume; $V_{35\text{-}45Gy}$ = volume of organ receiving between 35 & 45 Gy.

	ECOG PS		Tumour location		Baseline toxicity		Trial / Chemotherapy		
	0	≥1	Head	Neck/body	None	Present	ARCII	Cape	Gem
Male	25	25	40	10	33	11	11	17	22
Female	20	21	34	7	25	12	10	17	14
Chi-squared	0.013		0.127		0.663		0.945		
p-value	0.908		0.722		0.718		0.624		

Table 5. Categorical variables according to patient sex. P-value indicates result of chi-squared testing. +Trial/chemotherapy = concomitant chemotherapy regimen, considered as three categories – 1) ARCII 2) SCALOP capecitabine 3) SCALOP gemcitabine.