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Original Article

Stomach Dose–Volume Predicts Acute Gastrointestinal Toxicity in Chemoradiotherapy for Locally Advanced Pancreatic Cancer

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Abstract

Aims: Gastrointestinal toxicity impedes dose escalation in chemoradiotherapy for hepatobiliary malignancies. Toxicity risk depends on clinical and radiotherapy metrics. We aimed to identify predictive factors using data from two prospective phase II clinical trials of locally advanced pancreatic cancer (LAPC).
Materials and methods: Ninety-one patients with available data from the ARCII (59.4 Gy in 33 fractions with gemcitabine, cisplatin and nelfinavir, $n = 23$) and SCALOP (50.4 Gy in 28 fractions with capecitabine or gemcitabine, $n = 74$) trials were studied. The independent variables analysed comprised age, sex, performance status, baseline symptoms, tumour size, weight loss, chemotherapy regimen and dose–volume histogram of stomach and duodenum in 5 Gy bins. The outcome measures used were Common Terminology Criteria of Adverse Events (CTCAE) grade and risk of CTCAE grade ≥2 acute upper gastrointestinal toxicity (anorexia, pain, nausea and/or vomiting). The risk of CTCAE grade ≥2 events was modelled using multivariable logistic regression and prediction of severity grade using ordinal regression.
Results: CTCAE grade ≥2 symptoms occurred in 38 patients (42%). On univariate analysis, stomach $V_{35–45Gy}$ was predictive of risk (odds ratio 1.035, 95% confidence interval 1.007–1.063) and grade (1.023, 1.003–1.044) of toxicity. The area under the curve was 0.632 (0.516–0.747) with toxicity risk 33/66 (50%) above and 5/25 (20%) below the optimal discriminatory threshold (7.1 cm^3). Using a threshold of 30 cm^3, risk was 13/20 (65%) versus 25/71 (35%). The optimal multivariable logistic regression model incorporated patient sex, chemotherapy regimen and stomach $V_{35–45Gy}$. Receiving gemcitabine rather than capecitabine (odds ratio 3.965, 95% confidence interval 1.274–12.342) and weight loss during induction chemotherapy (1.216, 1.043–1.419) were significant predictors for the SCALOP cohort, whereas age predicted toxicity risk in ARCII only (1.344, 1.015–1.780). Duodenum dose–volume did not predict toxicity risk or severity in any cohort.
Conclusions: In chemoradiotherapy for LAPC the volume of stomach irradiated to a moderately high dose (35–45 Gy) predicts the incidence and severity of acute toxicity. Other predictive factors can include age, sex, recent weight loss and concomitant chemotherapy agents.

Key words: NTCP; pancreatic cancer; stomach; toxicity

Introduction

Patients with locally advanced pancreatic cancer (LAPC) 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 an increased dose could achieve better tumour control. However, the radiotherapy dose that can be delivered is limited by gastrointestinal 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 radiotherapy parameters and subsequent risk of toxicity [5,7–12].

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We analysed toxicity outcomes in patients with LAPC 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: (i) identify normal tissue dose–volume histogram (DVH) parameters associated with increased risk of toxicity; (ii) develop and validate predictive multivariable models for personalised estimation of risk that might be utilised in the clinic; (iii) investigate possible associations of toxicity and survival outcomes.

Materials 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 after radiotherapy, and 3 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, gastrointestinal bleeding/perforation, bowel obstruction, anorexia ± weight loss) were pooled to generate a single end point of 'upper gastrointestinal toxicity' (UGIT) [17]. The maximal grade of any of these symptoms suffered by each patient during 3 months (90 days) from the onset of radiotherapy was collated. The toxicity outcome was dichotomised according to a threshold of grade $\geq$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 in the other was due to unrelated medical comorbidity. One patient from SCALOP was excluded due to gastric outlet obstruction on planning computed tomography causing abnormal stomach dilatation (measured stomach volume was 2954 cm^3). The median stomach volume was 361 cm^3 (interquartile range 255–541 cm^3). Radiotherapy dose data were 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, 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 Eastern Cooperative Oncology Group (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 computed tomography with lymph nodes $>$ 1 cm diameter; the planning target volume was defined as the GTV plus a 20 mm margin in the craniocaudal direction and a 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 five fractions to the primary tumour planning target volume (also defined as GTV plus 20 mm in the craniocaudal direction and 15 mm in other directions). Phase 1 was delivered using intensity-modulated radiotherapy 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 (100–200 ml) for treatment planning imaging was specified in both studies. For ARCII, patients were fasted for 2 h before 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, whereas 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 contraindicated.

The stomach and duodenum were contoured retrospectively according the Radiation Therapy Oncology Group 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 computed tomography and dose data were anonymised and imported into the Computational Environment for Radiotherapy Research software package [22] and cumulative absolute dose–volume data were exported in 5 Gy bins (i.e. V_{5Gy}, V_{10Gy} etc.).

Statistics

Radiotherapy dose–volume data were not normally distributed, hence non-parametric tests were used for

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