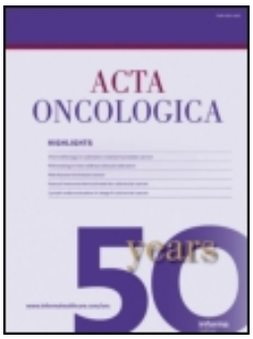

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Samantha Warren, Mike Partridge, Emmanouil Fokas, Cynthia L. Eccles & Thomas B. Brunner

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LETTERS TO THE EDITOR

Comparing dose-volume histogram and radiobiological endpoints for ranking intensity-modulated arc therapy and 3D-radiotherapy treatment plans for locally-advanced pancreatic cancer

SAMANTHA WARREN[1,2], MIKE PARTRIDGE[1,2], EMMANOUIL FOKAS[1,2,*], CYNTHIA L. ECCLES[1,2] & THOMAS B. BRUNNER[1,2,#]

[1]*The Gray Institute of Radiation Oncology and Biology, Department of Oncology, University of Oxford, Old Road Campus Research Building, Oxford, UK and* [2]*Oxford Cancer Centre, Churchill Hospital, Oxford University Hospitals, Headington, Oxford, UK*

To the Editor,

Pancreatic adenocarcinoma patients have a poor prognosis, with the five-year overall survival rate $<5\%$ [1]. Treatment options for these patients may include pre-operative or definitive chemo-radiotherapy (CRT). Patterns of failure suggest that inclusion of elective lymph nodes in the treatment volume may improve local control [2]. These extended volumes, in conjunction with large margins to account for breathing motion, generate substantial planning treatment volumes (PTV) which may increase the risk of gastro-intestinal (GI) toxicity. Several publications have investigated the use of intensity-modulated radiotherapy (IMRT) [3–7] and intensity-modulated arc therapy (IMAT) [8–11] for treatment of pancreatic cancer, where the improved dose conformation may reduce dose to surrounding normal tissue, and allow dose escalation for improved local control.

Despite studies showing a correlation between dosimetric parameters and GI toxicity for three-dimensional (3D)-RT and IMRT [12] there is some debate over dose constraints for stomach, duodenum and small bowel. Differences in organ delineation and prescribed dose may limit the comparison of dose-volume histogram (DVH) parameters, and a standard dose-volume analysis is often limited to only a few points in the DVH data, which may not always correspond directly to a clinical outcome. However, radiobiological modelling evaluates treatment plans by analysing the entire DVH and reducing this multifactorial comparison into a single clinically relevant parameter. As the parameters used for modelling normal tissue complication probability (NTCP) are derived from observed rates of toxicity in clinical trials, these parameters should be cited as a range of values (e.g. covering a 95% confidence interval). Each parameter set is specific for a selected endpoint and is also dependent on the patient cohort and the treatment technique used. Careful comparison of the predicted complications with observed clinical toxicity is required to validate each set of NTCP parameters which may be found in the literature [13]. Nonetheless, radiobiological modelling may be useful for assessing different planning techniques and dose prescriptions, and has been applied to compare predicted toxicity to stomach and duodenum for a dose escalation study using tomotherapy plans for pancreatic cancer [5].

The current study compares the use of NTCP models and dose-volume metrics to analyse RapidArc (IMAT) and three-dimensional conformal treatment (3D-RT) plans for locally-advanced pancreatic cancer (LAPC). Using commercially available biological evaluation software module (Eclipse, Varian, Palo Alto,

Current addresses: *Department of Radiation Therapy and Oncology, Johann Wolfgang Goethe University, Frankfurt, Germany and #Department of Radiotherapy and Radiation Oncology, University of Freiburg, Freiburg, Germany.
Correspondence: S. Warren, The Gray Institute of Radiation Oncology and Biology, Department of Oncology, University of Oxford, Old Road Campus Research Building, Roosevelt Drive, Oxford, OX3 7DQ, UK. Tel: +44 1865 857045. Fax: +44 1865 857127. E-mail: Samantha.warren@oncology.ox.ac.uk

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CA, USA), we sought to understand the effect of using a range of different NTCP model parameters on the predicted toxicity for each patient, and on the relative ranking of these two planning techniques when considering dose sparing to gastro-intestinal organs.

Material and methods

Eleven consecutive patients (detailed in Supplementary Table I, available online at http//informahealthcare.com/doi/abs/10.3109/0284186X.2013.813072) with stage IIB pancreatic cancer were identified retrospectively from those recruited to an ethically approved clinical trial ARC-II (EudraCT 2008-006302-42) for inoperable LAPC patients. Contouring and treatment plans were prepared using Eclipse version 10 (Varian). Full details of the contouring and treatment protocol have been previously reported [14], specifically, PTV2 includes appropriate margins to allow for tumour movement, and PTV1 includes PTV2, any enlarged regional lymph nodes and elective nodal regions of important vascular areas such as the aorta and inferior vena cava, portal vein and celiac trunk. The maximum PTV1 volume was limited to 800 cm^3, in order to limit toxicity. Patient positioning was verified using daily cone beam imaging and to check that target motion remained within the PTV margins, but detailed analysis of the effects of inter-fraction motion is beyond the scope of the current study. The dose prescription for the two phase 3D-RT plans used for patient treatment was PTV1: 50.4 Gy/28 fractions, followed by an additional 9 Gy/5 fractions to PTV2 (PTV2 total dose: 59.4 Gy/33 fractions). Retrospectively, a RapidArc (IMAT) plan was created for each patient to deliver an integrated boost in 33 fractions with 52 Gy to PTV1, and 59.4 Gy to PTV2 [15]. Plans were normalised so that the median dose to PTV2 was 100% of the prescribed dose. The primary organs at risk (OAR) were kidneys, liver, spinal cord, with (strict) dose constraints as listed in the second column of Table I. Other OAR dose objectives (goals) were: stomach wall $D_{2\%} < 60$ Gy (maximum dose to 2% of the stomach volume should be less than 60 Gy) and $D_{15\%} < 45$ Gy, duodenum $D_{2\%} < 60$ Gy and $D_{33\%} < 45$ Gy, and small bowel $D_{2\%} < 54$ Gy and $D_{15\%} < 45$ Gy. Small bowel was contoured using two methods: as individual loops, and as a small bowel (SB) region, similar to the method of Eppinga [8]. A combined stomach wall and duodenum structure "StoDuo" was created, for comparison with previously published data [12,16], as well as OAR volumes *excluding* the PTV, e.g. "stomach_out".

The ability to meet the planning dose-volume constraints was analysed, as well as the PTV conformality index $CI_{95\%}$ (where $CI_{95\%}$ is the ratio of the volume of the 95% isodose to the volume of the PTV). Dose to GI organs was analysed in 5 Gy dose bins, as well as the following parameters: stomach $D_{2\%}$ (maximum dose to 2% of the stomach volume), stomach V_{50} (the absolute volume receiving 50 Gy or more) and StoDuo V_{50}. Stomach V_{50} is the best predictor of *acute* GI bleeding risk, with $V_{50} > 16$ cm^3 the threshold for grade 2 toxicity and StoDuo $V_{50} > 33$ cm^3 the best predictor for upper gastrointestinal bleeding [12]. Dose to duodenum was evaluated as V_{35}, V_{40} and V_{55}, as acute toxicity seems to correlate with the volume of duodenum receiving high dose [17]. For small bowel, the V_{45} dose metric for the small bowel region was also used to compare plans, as this is thought to be significant for acute toxicity [18]. In the analysis below, values are quoted as the mean ± 1 standard deviation and the 3D and IMAT planning techniques were compared using a paired two-tailed Student's

Table I. Comparison of DVH metrics for 3D-RT vs IMAT plans for cord, liver and kidney. For each dose constraint, the number of patients whose plans achieved the dose constraints is noted in brackets for each technique. PD = prescribed dose, NS = not significant.

Dosimetric constraints		3D-RT plans mean (Gy) ± 1 SD	IMAT plans mean (Gy) ± 1 SD	p-value
PTV1	$D_{99\%} > 95\%$ PD	$CI_{95\%} = 1.64 \pm 0.18$	$CI_{95\%} = 1.23 \pm 0.08$	< 0.0001
PTV2	$D_{max} \leq 107\%$ PD	$CI_{95\%} = 1.83 \pm 0.25$	$CI_{95\%} = 1.08 \pm 0.03$	< 0.0001
R kidney	$D_{50\%} < 20$ Gy	12.1 ± 5.4 (11/11)	14.1 ± 2.2 (11/11)	NS
L kidney	$D_{30\%} < 20$ Gy	19.5 ± 4.3 (6/11)	15.6 ± 2.0 (11/11)	0.04
Liver	$D_{50\%} < 20$ Gy	6.7 ± 5.1 (11/11)	7.2 ± 5.2 (11/11)	NS
Cord	$D_{0.1cc} < 40$ Gy	35.4 ± 2.9 (11/11)	38.3 ± 0.7 (11/11)	0.008
Stomach wall	$D_{2\%} < 60$ Gy	59.5 ± 2.2 (4/11)	57.7 ± 3.8 (9/11)	NS
	$D_{15\%} < 45$ Gy	44.3 ± 11.3 (4/11)	40.6 ± 11.6 (6/11)	0.007
Duodenum	$D_{2\%} < 60$ Gy	61.1 ± 1.0 (1/11)	59.7 ± 0.2 (11/11)	0.001
	$D_{33\%} < 45$ Gy	58.8 ± 1.6 (0/11)	56.7 ± 2.5 (0/11)	0.0006
Small bowel	$D_{2\%} < 54$ Gy	60.4 ± 0.7 (0/11)	58.6 ± 1.3 (0/11)	0.001
	$D_{15\%} < 45$ Gy	44.1 ± 9.9 (5/11)	41.0 ± 7.5 (8/11)	0.017

t-test, with $p < 0.05$ considered as statistically significant.

The Eclipse biological evaluation (BE) module version 8.8 (Varian) was used to calculate NTCP and to compare the conformal and IMAT plans. Tests were performed to check the validity of NTCP calculations in the Eclipse module, using the phantom and structures indicated in the AAPM TG 166 report [19], and using independent software (BIOPLAN) [20] or a spreadsheet (agreement within 1.5%). The physical dose values were converted to equivalent 2 Gy fractions using the linear quadratic equation with $\alpha/\beta = 3$ Gy before calculation of NTCP. The Lyman-Kutcher-Burman (LKB) model of NTCP was used to model GI toxicity with a range of parameters according to values found in the literature (Supplementary Table II, available online at http//informahealthcare.com/doi/abs/10.3109/0284186X.2013.813072).

Results

The PTV conformation index $CI_{95\%}$ calculated for 3D-RT versus IMAT is shown in Table I. The IMAT plans show a tighter conformation of the high dose region to the target volumes, though with a larger low dose bath. For cord and liver, the differences between 3D-RT and IMAT plans were not statistically significant. For the kidney, IMAT plans produced better *bilateral* kidney sparing and met kidney dose constraints for all 11 patients, whereas 3D-RT met the constraints for only six patients.

For the 11 patients studied, there was, on average, no significant difference between the two techniques for stomach $D_{2\%}$, yet there was a reduction in the average stomach V_{50} for IMAT plans (IMAT mean 18.7 ± 12.3 cm^3 vs. 3D-RT mean 28.1 ± 20.4 cm^3, $p = 0.009$). The improved dose conformation of IMAT plans was particularly important for the stomach_out volume where a $V_{50} < 16$ cm^3 was achieved for all 11 patients. There is a statistically significant reduction in dose to the hottest 2% of the duodenum volume when using IMAT (Table I). Duodenum V_{35} shows no significant differences between the two techniques, but there is a reduction in duodenum V_{50} of at least 10% for all patients when using IMAT and this effect is even greater for the duodenum_out volume (average reduction in V_{50} of 37.0%). The extent of this improvement is highly patient-specific, due to variations in duodenal volume, the overlap between duodenum and PTV and the optimised dose distribution (see Supplementary Figure 1, available online at http//informahealthcare.com/doi/abs/10.3109/0284186X.2013.813072). The average StoDuo V_{50} was improved for all patients (reduced from 33.7 ± 8.1 cm^3 for 3D-RT plans to 26.4 ± 5.8 cm^3 for IMAT plans, $p < 0.001$). For small bowel, there is a modest improvement in dose sparing at higher doses (3D-RT mean $V_{45} = 348.8 \pm 147.3$ cm^3 vs. IMAT mean $V_{45} = 285.1 \pm 124.1$ cm^3, $p < 0.001$), which is offset by an increase in low dose for IMAT plans.

NTCP comparison

NTCP values calculated for spinal cord, liver and kidney were below 1% for all but one of the patient plans, in line with the strict adherence to the dose constraints for these critical organs. For one patient, the 3D-RT plan produced a predicted risk of liver injury of 1.8%, which was reduced to 0.3% using IMAT; although on average the differences between IMAT and 3D-RT plans for spinal cord, liver and kidneys were not statistically significant.

For the stomach, the absolute NTCP for each patient lies within the range of 10–30% (Figure 1a) depending on the choice of parameters used for modelling. Whilst the *absolute* value of NTCP may vary, the *relative* ranking of IMAT versus 3D-RT plans is *always* in favour of IMAT (Figure 1c) with a reduction of around 5% in predicted toxicity seen for IMAT in each case. NTCP calculations for duodenum showed a relatively low *absolute* risk of complications (Figure 2), with little difference between techniques: IMAT mean NTCP $7.2 \pm 0.3\%$ versus 3D-RT mean NTCP $7.7 \pm 0.3\%$ ($p < 0.001$). When applying the model parameters for StoDuo a much larger *absolute* risk for duodenal toxicity is predicted for all patients but with a clear advantage of IMAT plans: IMAT mean NTCP $43.9 \pm 5.7\%$ versus 3D-RT mean NTCP $52.1 \pm 5.0\%$ ($p < 0.001$). An analysis of the StoDuo volume predicted a reduction in NTCP of 7.2% with IMAT planning (IMAT mean NTCP $28.7 \pm 2.8\%$ vs. 3D-RT mean NTCP $35.3 \pm 3.6\%$, $p < 0.001$). Although there is a large variation in predicted risk of complications for the small bowel loops there is always a reduction in the predicted risk with IMAT rather than 3D-RT, (IMAT mean NTCP $4.8 \pm 3.8\%$ vs. 3D-RT mean NTCP $7.5 \pm 5.2\%$, $p < 0.001$).

Discussion

As expected, IMAT plans resulted in better dose conformation to the target volume (PTV $CI_{95\%}$), as has been observed for IMRT versus 3D-RT plans [7,21], and also improved dose sparing for bilateral kidney [8–10]. However, the major limiting factor in treatment of LAPC patients with concurrent chemo-radiotherapy is the occurrence of acute gastro-intestinal toxicity and occasionally severe gas-

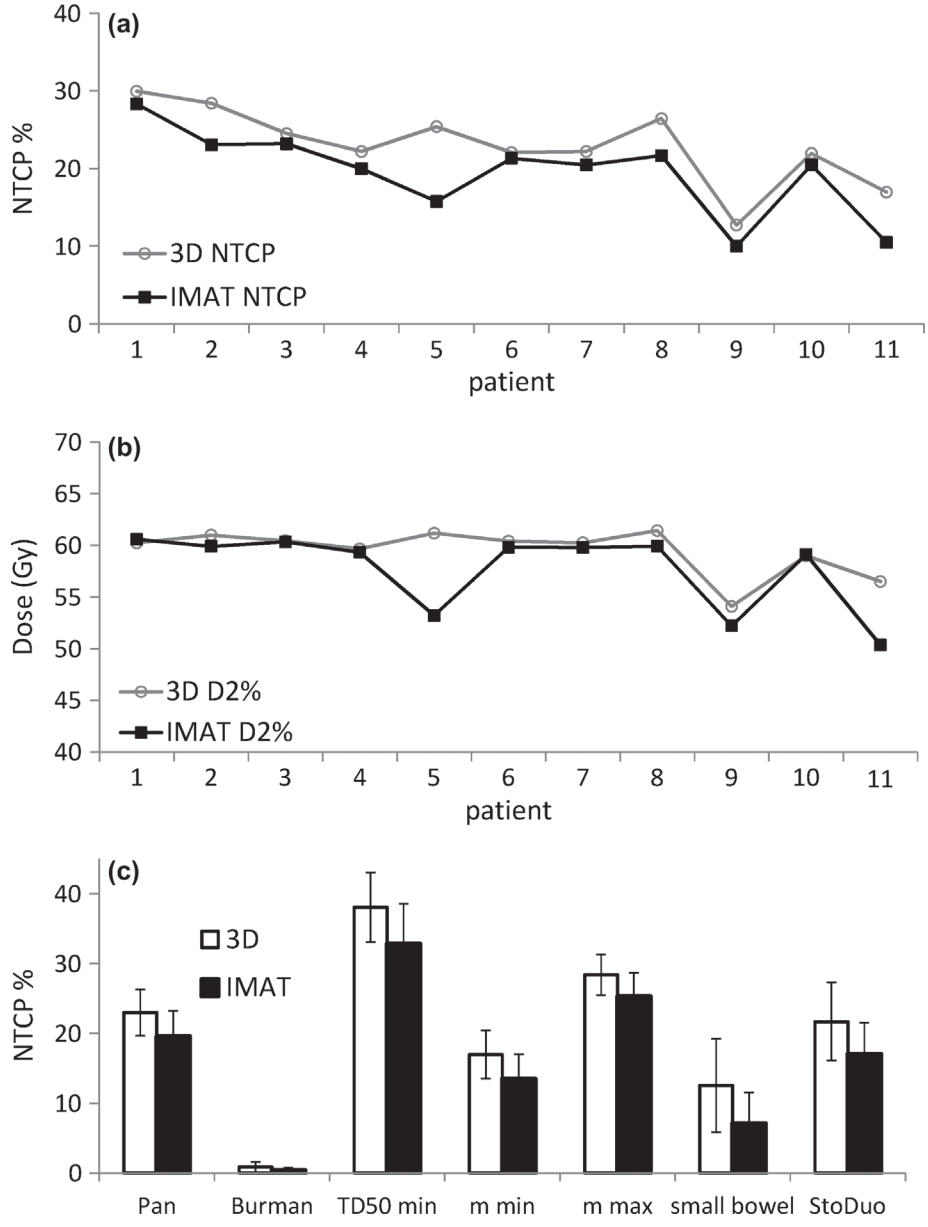

Figure 1. (a) NTCP for stomach each patient using Pan parameters [16]; (b) stomach $D_{2\%}$ for each patient; and (c) average stomach NTCP for different models. TD_{50}, m and n values are listed in Supplementary Table II: Pan [16] and Burman [24], or using range of values from Pan of $TD_{50} = 53$ Gy (TD_{50} min), $m = 0.23$ (m min), $m = 0.39$ (m max) or small bowel or combined stomach-duodenum (StoDuo) parameters.

tro-intestinal bleeding. A comparison of IMAT versus 3D-RT dose distributions within the upper GI organs is complicated by the large inter-patient variability, and it is often difficult to select a single dose-volume parameter for plan ranking. Radiobiological analysis is shown here to be a more robust method for comparing rival plans, and shows that IMAT planning reduced the risk of toxicity for stomach, duodenum and small bowel for all patients.

For stomach (Figure 1b), observed differences in the maximum dose for IMAT and 3D-RT are small, and may not be clinically significant. However, the predicted NTCP for these patients shows a reduction of around 5% with IMAT, regardless of the choice of NTCP model value. Toxicity is still limited by the overlap of the PTV and future work may also need to focus on safely reducing the PTV volume, by defining which elective lymph nodes are most at risk [14,22]. In addition, planning margins could be reduced by the use of 4D-CT, breath-hold or abdominal compression techniques combined with daily image guidance to reduce uncertainties arising from patient movement [5]. This would then require a more detailed investigation of the effects of move-

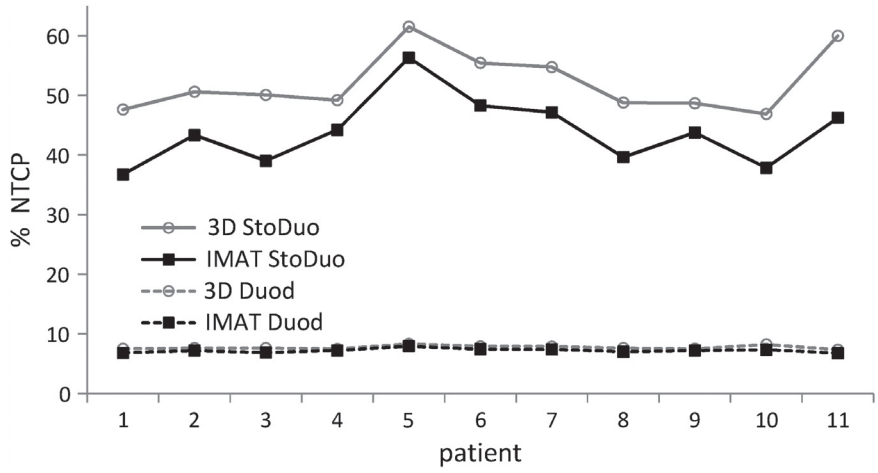

Figure 2. NTCP for duodenum as calculated using the parameters for combined stomach and duodenum (StoDuo) and duodenum only (Duod) [16].

ment on the dose distribution and observed toxicity, and is outside the scope of the current study.

The NTCP values for duodenum indicate very little difference between IMAT and 3D-RT, with a risk of around 7% for all patients. The StoDuo NTCP parameters applied to the duodenal volume give a higher *absolute* risk for all plans, but increases the predicted advantage of using IMAT rather than 3D-RT planning. For the combined StoDuo volume, the estimated incidence of gastric bleed would be reduced to 0% for all patients if treated with IMAT according to toxicity data from Nakamura [12].

From our study, IMAT is also predicted to reduce acute small bowel toxicity, whilst maintaining local tumour control. According to a recent comparison of IMRT and 3D-RT for pancreatic and ampullary cancers, IMRT significantly reduced both *acute* GI toxicity in the bowel, and late effects, and there was no increase in toxicity observed with increased low doses from IMRT [21].

Projects such as QUANTEC [23] which derive dose-volume parameters for specific organs from clinical outcomes, together with clear guidelines for delineation are required to verify the NTCP model predictions. It is also important to stress that organ motion may need to be taken into account when correlating toxicity with the dose distribution observed using the planning CT. Future work investigating the use of IGRT with elastic registration and dose mapping may be required to accurately calculate dose delivered to normal tissues, in order to confirm the superiority of IMAT planning over the entire course of radiotherapy treatment.

The use of radiobiological modelling for NTCP evaluation can greatly simplify the task of comparing different planning techniques, and is more robust than dose-volume parameters for analysis of dose sparing of the gastro-intestinal tract irrespective of the uncertainties in NTCP model parameters. For the 11 LAPC patients studied here, NTCP modelling supports the introduction of IMAT in the treatment of locally advanced pancreatic cancer by chemo-radiotherapy. Careful monitoring of patients would validate the predicted reduction in gastro-intestinal toxicity in clinical practice.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Figure 1.
Supplementary Tables I and II.