Comparison of conventional and three-dimensional conformal CT planning techniques for preoperative chemoradiotherapy for locally advanced rectal cancer

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Objectives: We assessed the impact of three-dimensional (3D) conformal planning vs conventional planning of preoperative chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC) on small bowel and bladder sparing and in optimising coverage of tumour target volume.

Methods: Conformal and conventional plans were created for 50 consecutive patients. The conformal plan delineated a gross tumour volume (GTV), a clinical target volume (CTV) 1 to cover potential subclinical disease spread, a CTV2 to outline the mesorectum and lymph node areas at risk, and a planning target volume (PTV) to cover set-up error and organ movement. The conventional plan was created using digitally reconstructed radiographs (DRRs). Patients were treated with a dose of 45 Gy in 25 fractions with concurrent chemotherapy over 5 weeks. Dose–volume histograms (DVHs) were created and compared for GTV, PTV, small bowel and bladder. The GTV was covered by the conventional plan in all patients.

Results: Significant differences were shown for median PTV coverage with conformal planning compared with conventional planning: 99.2% vs 94.2% (range 95.9–100% vs 75.5–100%); $p < 0.05$. The median volume of irradiated small bowel was significantly lower for CT plans at all DVH levels. Median bladder doses did not differ significantly.

Conclusion: 3D conformal CT planning is superior to conventional planning in terms of coverage of the tumour volume. It significantly reduces the volume of small bowel irradiated with no decrease in the rate of R0 resection compared with published data, and at the present time should be considered as the standard of care for rectal cancer planning.

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Chemoradiotherapy (CRT) followed by total mesorectal excision is the standard of care when MRI staging demonstrates threatened surgical margins in locally advanced rectal cancer (LARC) [1, 2]. Radiotherapy planning for rectal cancer uses conventional orthogonal simulation with standardised radiation fields based on patterns of loco-regional relapse in relation to pelvic bony anatomy [3]. Three-field conventional orthogonal planning is considered an acceptable technique for planning preoperative CRT and major trials evaluating long-course chemoradiation for rectal cancer have permitted the use of conventional planning within their protocols [4, 5]. In recent years, the treatment of rectal cancer has improved through advances in the planning and delivery of radiotherapy as well as improved preoperative imaging with MRI, the development of surgical techniques using total mesorectal excision (TME) and more accurate histopathological reporting [6]. Radiotherapy planning must ensure all clinically and radiologically identifiable disease is encompassed while still minimising the dose to the surrounding organs at risk, particularly the small bowel and bladder. Potential areas of microscopic spread

and the appropriate pelvic lymph nodes should also be treated.

Preoperative MRI has improved the knowledge of pelvic anatomy and identification of pelvic lymph nodes at risk according to tumour location. This knowledge together with our current understanding of where rectal cancer recurs following TME and radiotherapy [7, 8] suggests that standard treatment planning by the use of traditional bony landmarks is now likely to be inadequate. Furthermore, clinical data indicate that the larger the volume of small bowel irradiated the higher the risk of acute and late toxicity [9–12]. Intensity-modulated radiotherapy (IMRT) has more recently been recommended as an advanced radiotherapy planning technique to optimise a reduction in the volume of small bowel irradiated [13–15]. However, at present there is limited Phase I and II trial data for IMRT in the treatment of locally advanced rectal cancer [16, 17], and currently in the UK many centres still use conventional planning techniques for preoperative CRT. Therefore, before advancing to and developing IMRT, we need to evaluate conformal three-dimensional (3D) CT planning. There is little published data directly comparing CT planning with conventional planning techniques [18]. This study aims to directly compare the techniques of conformal CT planning with conventional planning of preoperative CRT in the treatment of locally

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advanced rectal cancer, in terms of small bowel and bladder sparing, and in optimising coverage of the tumour target volume.

Methods and materials

Study design

All patients underwent similar pre-radiotherapy staging and received radiotherapy according to a standard protocol of 45 Gy in 25 daily fractions (1.8 Gy per day) prescribed to the International Commission on Radiation Units (ICRU) intersection point over 5 weeks with concurrent capecitabine 850 mg m⁻² twice daily on each day of radiotherapy. All fields were treated daily, five times a week. Pre-treatment investigations included biopsy, examination under anaesthetic (EUA), chest radiographs, liver imaging (ultrasound or CT scan), full blood count, urea, creatinine and electrolytes, liver function tests and carcinoma embryonic antigen. Pre-treatment tumour stage was determined by clinical examination, EUA and pelvic MRI scanning.

50 consecutive patients undergoing CRT for locally advanced rectal cancer were dual planned using both conventional orthogonal techniques and conformal 3D planning. Patients were planned prone using the CT planning system. All patients were scanned from the superior aspect of L5 to 2 cm below an anal margin marker to ensure coverage of the whole pelvis, recto sigmoid and rectum. All patients were instructed to have a comfortably full bladder prior to the CT scan and during radiotherapy.

For the CT plan a gross tumour volume (GTV) was defined using all available information from clinical examination and pelvic MRI. The GTV was then enlarged by 1 cm in all directions, except where constrained by bone, to create an expanded clinical target volume (CTV expanded) aimed to cover microscopic disease spread. A further CTV (CTV mesorectum) was then created to include the mesorectum and mesorectal nodes below the peritoneal reflection and also to include loco-regional lymph nodes at risk of involvement (internal iliac, medial rectal, obturator and presacral lymph nodes). The ischiorectal fossa was formally included (to encompass pudendal and inferior rectal nodes) only in low rectal tumours. The CTV mesorectum was expanded for at least 1 cm superiorly and inferiorly above the initially expanded CTV. A minimum superior border was defined as the S2/S3 vertebral space for lower rectal tumours and as the S1/S2 vertebral space for mid and upper rectal tumours. The combined CTV was expanded by 1 cm to a planning target volume (PTV) to allow for internal organ motion and set-up error. The margin of 1 cm to PTV is supported by published data [19]. The whole bladder and individual loops of small bowel within the pelvis were outlined on each slice of the planning CT scan to generate dose-volume histograms for the pelvic radiation field. A three- or four-field conformal plan was then produced. Patients received radiotherapy according to the CT plan.

All 50 patients were then retrospectively planned conventionally with the planner blind to the CT plan. All patient pre-treatment investigations, case notes, MRIs and colonoscopy reports were available at the time of conventional planning. Digitally reconstructed

radiographs (DRRs) in anterior-posterior and lateral views were generated and standard field borders applied according to those detailed in the Medical Research Council (MRC) CR07 protocol [4]. The whole bladder and small bowel were contoured as for the CT plans and dose-volume histograms were generated.

Patient demographics

50 consecutive patients were included in this study, who had all been CT planned for locally advanced rectal cancer between May 2007 and October 2007. The median age of the patients was 63 years; range 36–83 years. Patients were staged using the Union for International Cancer Control (UICC)/Tumour, Node, Metastasis (TNM) 2002 staging system. The patient and pre-treatment tumour characteristics are provided in Table 1. 4 patients (10%) had cT2 disease, 30 (71%) had stage cT3 and 8 (19%) had stage cT4. The four patients with stage cT2 disease had a threatened circumferential margin (CRM); two patients by virtue of an involved lymph node and two by a low tumour position below the levators. 24 patients (48%) had cancer in the low rectum, defined in this study as 0–5 cm from the anal verge; 18 patients (36%) had cancer in the mid rectum (6–10 cm from anal verge) and 8 patients (16%) had cancer in the upper rectum (10–15 cm from anal verge).

End points

The primary end points of the study were coverage of the CT-defined GTV and PTV by the conventional planning technique. The secondary end points were a comparison of PTV coverage between the two treatment planning techniques using the median coverage of the PTV receiving 42.8 Gy (V42.8 PTV). Dose to the organs at risk was compared for both small bowel and bladder using the median volume of small bowel receiving 20 Gy (v20) and 40 Gy (v40), and the median volume of bladder receiving 20 Gy (v20), 30 Gy (v30) and 40 Gy (v40).

Statistical analysis

Statistical comparisons were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL). A paired sample *t*-test was used to test for differences in the median coverage of the PTV (V42.8 PTV) and to test for differences in the median dose to the bladder and small bowel between the two planning techniques.

Results

The GTV as defined by CT planning was adequately covered by the conventional field borders in all patients. However, the planning target volume (PTV) as defined by CT planning was missed by conventional field borders in 29 patients (58%). This was shown to be statistically different with coverage of the PTV increasing from 94.2% with conventional planning to 99.2% with CT

Table 1. Patient and pre-treatment tumour characteristics

Males	32
Females	18
Mean age (years)	63
Range (years)	36–83
Tumour site	
Low rectum (0–5 cm from anal verge)	24
Mid rectum (6–10 cm from anal verge)	18
High rectum (10–15 cm from anal verge)	8
Tumour stage (UICC/TNM 2002)	
cT2	4
cT3	30
cT4	8
Node negative	12
N1/2	38
Mean conventional field border position	
Anterior (cm)	2.5 (range 2–5 cm)
Inferior (cm)	4.5 (range 3–5 cm)

UICC/TNM, Union for International Cancer Control/Tumour, Node, Metastasis.

planning ($p < 0.05$) (Table 2). The two most commonly threatened borders on conventional planning were the anterior and inferior field borders. In 24 patients the applied fields did not cover predicted tumour movement anteriorly (Figure 1). In 12 patients the conventionally applied inferior border missed the CT-defined PTV (Figure 2). In three patients, conventionally applied field borders missed the CT defined PTV in more than one orientation.

The CT-expanded volume extended a mean of 2.5 cm anterior to the sacral promontory. Although standard field arrangements would cover this in the majority of patients, the range for the conventionally applied anterior border was 2–5 cm. The anterior tumour movement is the most independent of bony anatomy and is also the most variable field edge between individual practitioners. The mean position of the inferior field border required below the inferior extent of the tumour was 4.5 cm, range 3–5 cm. The variability in defining the inferior field edge comes from the difficulty of accurately predicting the inferior extent of the tumour clinically without the ability for 3D imaging at the time of planning.

In 13 patients (26%) 1 or more conventional field borders applied were more generous than required from the CT-defined volume to cover the PTV (Figure 3). The use of CT planning resulted in a significantly lower median dose to the small bowel compared with the conventional plans, the median V20 was 25.8% *vs* 40.0%,

Table 2. Median and mean coverage of the planning target volume (PTV) receiving 42.8 Gy (V42.8 PTV) for three-dimensional conformal CT plans *vs* conventional plans

V42.8 PTV	Conformal	Conventional	<i>p</i> -value
Median %	99.2	94.2	< 0.05
Mean %	99.0	92.1	
Range %	95.9–100	75.5–100

Figure 1. A digitally reconstructed radiograph (DRR) showing conventionally applied field borders missing the CT-defined planning target volume (PTV) anteriorly. Anterior border shown by white arrow.

respectively ($p < 0.05$). With the median small bowel there was a V40 of 17.4% *vs* 26.8% ($p < 0.05$) (Table 3). There were no significant differences between the two planning techniques in the median dose to the bladder for V20, V30 and V40, as shown in Table 4.

The use of conformal CT planning for locally advanced rectal cancer does not appear to have impacted negatively on the R0 resection rates following preoperative CRT. Histopathology data are currently available on 38 patients of whom 29 (76%) have had a complete (R0) resection as defined as greater than 1 mm clear circumferential resection according to Quirke's [6] criteria. Three patients (8%) have had evidence of microscopic residual disease (R1), two patients have refused surgery with a radiological complete response (5%) and four patients had progressive disease (11%). This is similar to the published data [8, 20, 21].

Discussion

Locally advanced rectal cancer has a high risk of local recurrence and poor survival (50–60% at 5 years). The current practice of TME facilitates radical clearance not only of the primary tumour but also all mesorectal tissues enveloped in the visceral pelvic fascia. This technique has been clearly demonstrated to improve local recurrence rate and 5 year survival [22–24]. However, recent studies of more than 1000 patients even with optimal surgical technique have reported CRM involvement rates of between 6.7% and 7.5% after anterior resection and between 16.7% and 17.6% for low rectal cancers requiring abdominoperineal excision (APER) [8, 23]. The evidence base for radiotherapy in operable rectal cancer is discussed at length by Craven and Sebag-Montefiore [25]. In particular, three recent Phase III trials have led preoperative chemoradiation to

Figure 2. (a) Digitally reconstructed radiograph (DRR) of a three-dimensional conformal CT plan covering the planning target volume (PTV) (black arrow) and using multileaf collimation; gross tumour volume (white arrow). (b) DRR showing conventionally applied field borders missing the CT defined PTV inferiorly (black arrow).

be recommended as a standard of care for locally advanced rectal cancers [2, 5, 26]. Prior to the widespread use of TME surgery and improved histopathological reporting of the CRM, three-field conventional orthogonal planning was based on patterns of loco-regional relapse documented in historical series [3]. The bony

pelvic anatomy was used as conventional reference points for standardised fields. Conventional planning is still regarded as an acceptable technique and recent major trials evaluating pre-operative CRT have permitted the use of conventional planning within their trial protocol [4, 5]. However, with recent data for patterns of relapse following TME surgery [7], as well as the availability of modern pathological reporting techniques, conventional planning is now inadequate and individualised treatment volumes with 3D planning should be recommended [27].

In this study using our standard CT planning protocol we found that the CT-defined GTV was adequately covered by our conventional field borders in all cases. However, our CT-defined PTV was missed by conventional field borders in 29 patients (58%) in one or more sites, most frequently anteriorly ($n=24$) and inferiorly ($n=12$) (Figure 1 and 2). This suggests that target volume definition can be improved by the use of CT planning

Figure 3. A digitally reconstructed radiograph (DRR) showing conventionally applied field borders more generous superiorly than required from the CT-defined volume to cover the planning target volume (PTV) (black arrow). White arrow shows small bowel in treatment field owing to generous superior border.

Table 3. Median and mean V20, V30 and V40 for small bowel for three-dimensional conformal CT plans vs conventional plans

	Conformal	Conventional	p-value
V20			<0.05
Median %	25.8	40.0	
Mean %	28.0	42.6	
Range %	0–81.1	13.8–93.3	
V30			<0.05
Median %	20.8	32.4	
Mean %	22.6	34.3	
Range %	0–64.4	2.6–72.8	
V40			<0.05
Median %	17.4	26.8	
Mean %	18.0	27.5	
Range %	0–57.1	0.7–62.9	

Table 4. Median and mean V20, V30 and V40 for bladder for three-dimensional conformal CT plans vs conventional plans

	Conformal	Conventional	p-value
V20			
Median %	51.3	48.4	1.00
Mean %	53.9	53.9	
Range %	14–100	2.6–100	
V30			
Median %	41.7	40.5	0.354
Mean %	42.1	45.5	
Range %	7.4–80.7	0–98.6	
V40			
Median %	33.2	33.7	0.202
Mean %	34.3	38.9	
Range %	9.3–72.6	0–94.7	

and potentially avoid a geographical miss. This was also shown in a small study by Chao et al [28], who compared nine patient treatment fields using CT planning *vs* conventional orthogonal X-ray simulation. Under-coverage of the anterior border of the lateral field of up to 2.5 cm was noted in 7 of the 9 patients analysed. Our study is supported by the statistical analysis of median PTV coverage (v42.8 PTV), which was significantly better with conformal CT planning.

Conversely, 13 patients (26%) were found to have larger conventionally planned field borders than required to cover the CT-defined PTV, supporting the CT planning technique as a method of minimising the dose to organs at risk. In this study we did not demonstrate a significant difference in the median radiation dose to the bladder between the two planning techniques. This is likely to be because of individual patient variation in bladder filling, which remains an important technique for minimising the volume of small bowel within the radiation field. However, this study did show statistically lower median radiation doses to the small bowel using the conformal CT planning technique. Although this study lacks formal radiation toxicity data, numerous studies have shown a significant correlation between the volume of the small bowel irradiated and the increased incidence of acute and late toxicity [13–16]. Baglan et al [12] showed a highly significant association between the development of acute Grade 3+ small bowel toxicity and the volume of small bowel irradiated at each dose level from 5 Gy to 40 Gy in patients receiving preoperative CRT, with the volume of small bowel receiving at least 15 Gy (v15) strongly associated with the degree of toxicity. Gunnlaugsson et al [13] similarly demonstrated a strong correlation between the occurrence of Grade 2+ diarrhoea and the irradiated small bowel volume, most notably at doses above 15 Gy. These findings have led to recommendations to consider IMRT as a planning technique to minimise small bowel toxicity [13–15]. However, before progressing with IMRT treatment plans it is necessary to establish the exact CT anatomical target for the GTV and for the surrounding pelvic lymph nodes. We have proposed that the use of CT planning, as described, should be adopted as the standard planning technique for the forthcoming ARISTOTLE trial within the UK.

Despite the use of reduced overall field sizes, there has been no apparent reduction in the rates of pathological

complete response and complete resection compared with published series and in comparison with our prospectively maintained database. The reduction in overall field size and the apparent reduction in small bowel treated and likely reduced toxicity is important for the future development of CRT, especially for the introduction of new chemotherapy agents such as oxaliplatin and irinotecan. Phase II trials of these agents show improvements in the rates of R0 resection and complete pathological response; however, with significantly increased rates of unacceptable Grade 3 and 4 toxicity, especially bowel toxicity [29–31]. Systemic relapse, with the development of metastases, is more common than isolated local relapse with the improvements in surgical technique.

Conclusion

This study has demonstrated that conformal CT planning is superior to conventional simulation in the planning of locally advanced rectal cancer, in terms of better coverage of the PTV and a reduction in the median volume of surrounding organs at risk, especially the volume of small bowel irradiated. The R0 resection rate following CT planned preoperative CRT is maintained despite smaller treated volumes with this technique. CT planning also appears optimal over conventional simulation for accurate target volume definition, minimising the risk of a possible geographical planning miss. CT planning should be considered the standard for care for rectal cancer planning. Further developments in radiotherapy planning with the use of IMRT to optimise a reduction in the irradiated small bowel volume would seem appropriate.

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