Potential for Isotoxic Re-Irradiation SABR in Locally Recurrent Rectal Cancer

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Abstract

The non-surgical management of locally recurrent rectal cancer (LRRC) is an area of unmet need with no defined standard treatment and extremely poor outcomes. Patients typically receive radiotherapy during initial multimodality treatment and historically re-irradiation has been limited to conservative doses with subsequent short-term symptom control. Recently stereotactic ablative body radiotherapy (SABR) has shown promise in re-irradiation of LRRC in England but is limited to relatively modest dose prescription of 30Gy in 5. We propose SABR can be achieved in LRRC to higher doses using isotoxic dose prescription with fixed 15% per annum tissue recovery for acceptable organs at risk (OAR) constraints. Patients with LRRC at local centre treated with SABR re-irradiation were audited; patients identified, dose and time since previous radiotherapy determined, re-irradiation OAR constraints calculated, and retrospective re-planning carried out. In patients currently receiving SABR (17 patients, 21 targets) dose escalation above 30Gy in 5 was achievable, with biological effective dose (BED) of 80Gy (alpha/beta=10) deliverable to 80% or more of PTV in 8 out of the 21 targets. Isotoxic SABR re-irradiation should be considered a potential treatment option for LRRC to maximise patient outcomes whilst limiting excess toxicity. Whilst likely conservative, clinical outcome data is needed to determine suitability of OAR constraints using 15% per annum tissue recovery and the impact on local control rates, patient quality of life and overall survival of isotoxic SABR.

Keywords: Isotoxic SABR re-irradiation recurrent rectal cancer

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Introduction

Locally recurrent rectal cancer (LRRC) is a life-altering diagnosis. A population based cohort study from Sweden reported the average survival with a local recurrence is 10 months and >80% of patients suffer from symptoms [1], in comparison to the 18 month OS of patients with metastatic colorectal cancer from the national data from the same country [2]. The symptoms suffered by patients with LRRC include faecal incontinence, pain, discharge, recurrent abscesses, and fistulas. The associated social stigma can be very isolating and as a result quality of life (QoL) measures in this population are very poor [1,3].

Patients with LRRC have usually undergone radiotherapy as part of their initial multimodality treatment. The only potentially curative treatment is radical exenterative surgery, which carries significant morbidity, achieves a 5 year survival of 30% and a cure rate or 10 year survival which is unquantified [4]. Palliative options include chemotherapy, as suggested by the European Society of Medical Oncology (ESMO) guidance, however they acknowledge there is unlikely to be benefit [5]. Alternatively, conventionally fractionated re-irradiation, ideally delivered with IMRT, to doses of 30-40 Gray (Gy) offers good palliation of symptoms, with effects lasting <1 year [6]. A final option is standard palliative re-irradiation consisting of a simple conformal beam arrangement to 20Gy in 5 fractions. More recently, stereotactic body radiotherapy (SABR) has also been used, typically in patients who are not technically suitable for, not fit for, or opt not to proceed with surgery. SABR treatments are characterised by a high biological effective dose (BED) with steep dose gradient to surrounding normal tissue [7,8].

Following the Commissioning through Evaluation (CtE) program in England, SABR re-irradiation is available for all pelvic recurrences within a previous radiation field, a proportion of which are LRRC. Patients must meet eligibility criteria including have a gross tumour volume (GTV) size of <6cm and must have ≤3 lesions. The dose used in CtE was 30Gy in 5 fractions, which is equivalent in 2Gy/# to around 40Gy in LRRC cancer (alpha/beta: 10Gy). This low dose SABR is not an ablative dose and rarely results in complete response in LRRC [9]. A recent series of LRRC patients treated using 30Gy/5#, resulted in a 42.6% local recurrence rate, and 58.3% of deaths in the series were caused by consequences of uncontrolled pelvic disease [10]. Overall survival was good, likely due to patient selection; however, in view of the significant morbidity of uncontrolled pelvic disease, we need to further optimize SABR delivery in LRRC to improve QoL and potentially survival.

We propose an isotoxic SABR technique. In isotoxic dose prescription, the dose is escalated until the maximum pre-defined OAR constraints are met. Isotoxic radiotherapy was recently used in the FLAME study [11]. This phase III trial in prostate cancer compared standard radiotherapy to isotoxic

radiotherapy in the delivery of curative radiotherapy for prostate cancer. They demonstrated an improved number of patients free of disease at 5 year follow up from 85% to 92% while maintaining identical toxicity. LRRC is ideal for isotoxic radiotherapy because of the variety of anatomical pelvic sites (lymph node, bone, soft tissue), recurrence sizes, locations of both the previously treated primary tumour and the OARs in a previously irradiated and resected pelvis. These inter patient variations mean the appropriate dose in any one patient is likely to be very different from the next. Adopting a standard dose prescription for gross tumour coverage may result in overdosing some patients and underdosing others while an isotoxic dose will adapt to create an individualized approach.

Using a retrospective planning study we aim to test the hypothesis that with isotoxic SABR it is feasible to meaningfully increase dose prescription above current standard of care (SoC) prescription in patients currently meeting CtE criteria.

Methods and Materials

Patient selection and contouring

We identified all LRRC patients who had received SABR reirradiation within the CtE Program via our electronic radiotherapy system at our local institution between 2015 and 2020. GTV size, time since previous radiotherapy and previous dose prescription was recorded. All the original GTV and OAR were used. Contours were created with information from sigmoidoscopy (if appropriate), MRI, PET/CT (if performed) and planning CT scan acquired with IV contrast. Any OAR not contoured as part of previous radiotherapy were retrospectively contoured by a single consultant clinical oncologist specializing in lower GI to reduce inter observer variability. A uniform 5mm GTV to PTV margin was used in all cases.

OAR constraint calculation and retrospective re-planning

For OAR constraints, we propose using the previous dose in each patient plus a 15% recovery per annum to calculate an individualized OAR dose. While 15% per annum is an average, this is based on the average time to recurrence in different series ranging between 17 and 48 months [12,13] which results in what would be considered a typical recovery used since low dose NHS SABR was introduced of between 30-50%. Individual dose constraints for all patients were calculated retrospectively based on national consensus OAR constraints for volumes of 10cc or less [15] and

fixed 15% annual tissue recovery post previous radiotherapy using the following formula. OAR were assumed to receive full previous prescription doses.

$$EQD2_1 = D_1(d_1 + \frac{\alpha}{\beta})/(2 + \frac{\alpha}{\beta})$$

$$EQD2_2 = D_2(d_2 + \frac{\alpha}{\beta})/(2 + \frac{\alpha}{\beta})$$

$$TRF = 0.15 \times years\ post\ radiotherapy$$

$$Re - IrradiaitonConstraint = EQD2_1 - (EQD2_2 \times (1 - TRF))$$

Where D_1 is relevant national UK SABR constraints (d_1 per fraction constraint), D_2 is previous radiotherapy dose (d_2 per fraction previous dose), and TRF is the tissue recovery factor.

Considered OAR and alpha beta ratios used for constraint calculation are shown in table one, along with 5 fraction UK national dose constraints and example calculated dose constraints at 30 months post radiotherapy for 2 common dose regimes used in the UK (45Gy in 25 fractions and 50.4Gy in 28 fractions).

Cases were then retrospectively re-planned in Eclipse treatment planning system v15.6 (Varian, Palo Alto CA) to an isotoxic dose prescription in 5 fractions with mandatory re-calculated OAR constraints and mandatory coverage criteria of at least 60% PTV receiving prescription dose. Max dose 0.1cc was set at 110-130%. Isotoxic dose prescription was capped at 50Gy in 5 fractions, equivalent to 100Gy BED (alpha/beta: 10Gy).j

Dosimetric analysis

A predetermined meaningful increase in dose prescription of isotoxic SABR above SoC was set at re-irradiation dose prescription achieving an ablative threshold of 80Gy BED (alpha/beta: 10Gy) to at least 80% of PTV.

Results

Nineteen patients with local recurrences were identified who received current SoC SABR re-irradiation. Two patients were subsequently excluded from analysis; one due to less than 6 months since previous radiotherapy and the other due to limiting OAR not being considered a re-irradiation structure by the treating clinician as a consequence of anatomical changes in large bowel post-

surgical resection. Of the remaining 17 patients, four had two sites of local recurrence (21 targets total). Table two summaries patient demographics, GTV size, time since previous radiotherapy, and previous radiotherapy dose prescription. Compartment of largest GTV was recorded as per that described by Georgiou *et al* [16].

Replanning was carried out to prospective constraints for 7 target volumes where OARs were not actively spared in initial clinical plan. For all other clinical plans, plans were isotoxically renormalised to prospective constraints. Figure one shows 2 examples of SoC and prospective isotoxic plan dose distribution. Treatment plan dose metrics for the patient cohort are summarised in table 3. Median EQD2 deliverable to 80% or more of PTV increased from 43Gy to 61Gy under an isotoxic prescription, representing an increase from a median BED of 52Gy to 73Gy. 38% of targets (8/21) achieved our *a priori* feasibility definition of a meaningful increase in dose prescription of isotoxic SABR above SoC, set at re-irradiation dose prescription achieving an ablative threshold of 80Gy BED (alpha/beta: 10Gy) to at least 80% of PTV.

Discussion

Our planning study aimed to investigate the feasibility of an isotoxic SABR technique for the complex setting of LRRC re-irradiation [17]. Clinically significant dose escalation has been shown to be achievable in a significant number of the patient cohort currently receiving 30Gy in 5.

This planning study has been performed following the RATING guidance [18]. However, limitations of this work remain. It was a relatively small sample size and is single institution data reflecting the relative rarity of the disease and stringent eligibility criteria for treatment within CtE. Whilst the majority of voluming was performed prospectively, occasional OARs, particularly the lumbosacral plexus, were not contoured originally and was performed retrospective and unblinded. Additionally, quantification of previous radiotherapy dose simply assumed OAR received previous radiotherapy prescription dose. Whilst a more sophisticated approach would be to visualise previous radiotherapy plan and quantify the precise dose at relevant dose/volume levels [19], the authors note that relevant OAR structures are mobile and the precise dose delivered hard to quantify. Further, the precise tissue alpha-beta ratio, previous contouring method and acceptable tissue recovery/maximum cumulative doses would limit the benefit of such accuracy in LRRC reirradiation. This may change in the future as treatment planning systems increasingly incorporate dose deformation and radiobiological models for dose summation as routine. These results are relevant only for the cumulative dose constraint calculated in this study. However, 15% per annum was

selected as using median time to relapse from previous radiotherapy this equates to the majority of patients having a 30% - 50% recovery, which would be considered a typical recovery used since low dose NHS SABR was introduced. In supplementary table 1 we have provided a table demonstrating the differences in a constraints between our 15% per year cumulative OAR constraint, and an alternative cumulative OAR constraint assuming 30% recovering in patients whose previous reirradiation was 6 – 24 months ago and 50% recovery in patients whose previous radiation was >24 months ago. Constraints are less specific to an individual patient's recovery time but broadly speaking comparable and either maybe appropriate clinically with little data supporting a "correct" tissue recovery model. A limitation outside this study, but of relevance, is that the current evidence base for OAR constraints in SABR is weak. Uncertainties in what data does exist from non-standardized treatment techniques compound this problem [20]. Subsequently, constraints vary substantially internationally. In this study we have used UK consensus constraints as best possible current practice. A prospective trial with integrated radiotherapy quality assurance, quality of life and patient reported outcomes would be a valuable source of data to address these limitations.

We have used 5mm GTV to PTV margin as most of these patients are post op and have had previous radiotherapy, therefore mobility of soft tissue should be limited. However, we acknowledge there may be instances where a CTV is recommended due to concern about microscopic spread of a diffuse deposit. PTV margins are also centre specific depending on treatment unit, IGRT strategy and the expertise of staff involved. Within this study, pragmatism was used in applying the current upper value of UK standard SABR margin with reference to updated BIR guidance that "margin may also be informed by the nature of the treatment aim, the proximity and qualities of normal tissues and structures, clinical experience, and clinical trial evidence" [21]. Delivery on an MRL may offer more confidence regarding the position of the small bowel although currently there is no proven benefit or head-to-head comparison with high quality IGRT strategies on a standard linac. With limited population access to MRL, it is desirable to optimise conventional linac based treatments to achieve safe and effective delivery. We would note that as technology advances, considerations for best use of this technology in reirradiation are important to maintain progress in the field, particularly alongside advances in radiobiological approaches to reirradiation that has been the focus of the work presented here [22,23].

The NHS England commissioning statement acknowledge the uncertainty in prescription dose stating "*It is recognised that, in the re-irradiation setting, treatment technique and dose must be individualised. The dose and fractionation are dependent on the site of the disease and clinical scenario. However, it is expected that five fractions of SABR are used for pelvic tumours*". While the

UK have used 30Gy in 5 fractions, internationally there are a wide range of doses delivered from 15 Gy in 3 fractions to 60 Gy in 3 fractions [14]. While this is a planning study, the doses to target and OARs are comparable to those being used internationally and as such it is appropriate to use these doses routinely. However, the authors agree with the statement in the SABR reirradiation Delphi Consensus, "*long term disease outcomes and toxicity data should be prospectively recorded for patients treated with SABR re-irradiation in the pelvis*". As such, the UK SABR Consortium in collaboration with the Royal College of Radiologists Clinical Oncology Quality Improvement and Audit Committee, who have significant experience of successful practise changing audits [24–28] plan to perform a UK prospective audit of SABR reirradiation to gain valuable insights in multiple aspects of this complexed technique. In future work, we will investigate the impact of uncertainties and margins for this patient group by considering the optimal IGRT, patient immobilisation and planning techniques required for applicability of the results of this study

Conclusions

Clinicaly siginficant dose escalation above the current UK standard of 30Gy in 5# is achievable in a meaningful proportion of cases with a SABR technique when employing a 15% annual tissue recovery factor. SABR reirradiation is now routinely commissioned by NHS England and will be rolling out across the UK. We would encourage centres to consider isotoxic SABR reirradiation in LRRC, where improved local control has such a significant impact on QoL and potentially improves survival.

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OAR	alpha/ beta ratio	5 fraction constraints (no previous RT)			Example constraints with 30months post RT and 15% per annum tissue recovery					
					45Gy in 25 previous RT			50.4Gy in 25 previous RT		
		0.5cc	5cc	10cc	0.5cc	5cc	10cc	0.5cc	5cc	10cc
Small bowel	2	35.0		25.0	27.6		14.1	26.6		12.4
Large bowel/Rectum	5	32.0			19.5		<ALARP	17.7		<ALARP
Bladder	2	38.0			31.3		<ALARP	30.3		<ALARP
Femoral Head	3			30.0			19.5			18.0
Lumbosacral plexus	3	32.0	30.0		22.2	19.5		20.9	18.0	

Table One: Relevant OAR, alpha/beta ratios, national OAR constraints at 10cc or less and example calculated re-irradiation constraints at 30 months post radiotherapy (RT). All constraints are shown in Gy. ALARP: as low as reasonably practical.

	Patients n = 17
Median age (range)	61 (36 - 82)
Sex	
Male	14
Female	3
ECOG PS	
0	13
1	3
Unknown	1
Site of largest GTV	
Lymph node	13
Bone	2
Soft tissue	2
No of sites of targets	
1	13
2	4
Compartment of largest GTV	
Lateral	12
Central	1
AA PR	1
Posterior	3
Previous surgery	
APR	10
Anterior Resection	2
Hartmans	1
APR + resection of posterior vagina, uterus and pelvic side wall	1
Anterior resection + partial cystectomy	1
Anterior resection + cystoprostatectomy	1
Anterior resection followed by completion APR	1
Median GTV size (cc)	8.7 (0.5-121.7)

Median time since previous radiotherapy (years)	4.0 (1.3-7.0)
Previous radiotherapy dose prescription (Gy)	45 in 25# = 10, 50.4 in 28# = 4, 50-54 in 25# = 3.

Table Two: Patient demographics, site and size of GTV, previous surgery, median time since previous radiotherapy and previous radiotherapy prescription.

ECOG PS - Eastern Cooperative Oncology Group performance status; APR – Abdominoperineal resection; AAPR- Anterior above peritoneal reflection .

Target	Current D80%	Prospective Isotoxic D80%	Current D80% BED	Prospective Isotoxic D80% BED
1	29.9	30.4	47.8	48.8
2	33.9	50.0	56.9	100.0
3	33.9	50	56.9	100.0
4	31.9	42.6	52.3	78.9
5	33.2	32.1	55.2	52.7
6	27.1	26.2	41.8	39.9
7	31.5	49.3	51.3	97.9
8	32.6	43.5	53.9	81.3
9	29.4	36.1	46.7	62.2
10	30.5	25.8	49.1	39.1
11	31	40.5	50.2	73.3
12	31.9	31.9	52.3	52.3
13	30	50.0	48.0	100.0
14	32.7	46.6	54.1	90.0
15	29.8	30.9	47.6	50.0
16	29.1	40.9	46.0	74.4
17	31.8	39.4	52.0	70.4
18	33.5	50.0	55.9	100.0
19	32.1	50.0	52.7	100.0
20	31.5	35.2	51.3	60.0
21	31.8	35.6	52.0	60.9
Median	31.8 (27.1-33.9)	40.5 (25.8-50)	52.0 (41.8-56.9)	73.3 (39.1-100)

Table Three: Clinical and isotoxic PTV 80% coverage, expressed both as absolute and biologically effective dose (BED) in Gy.

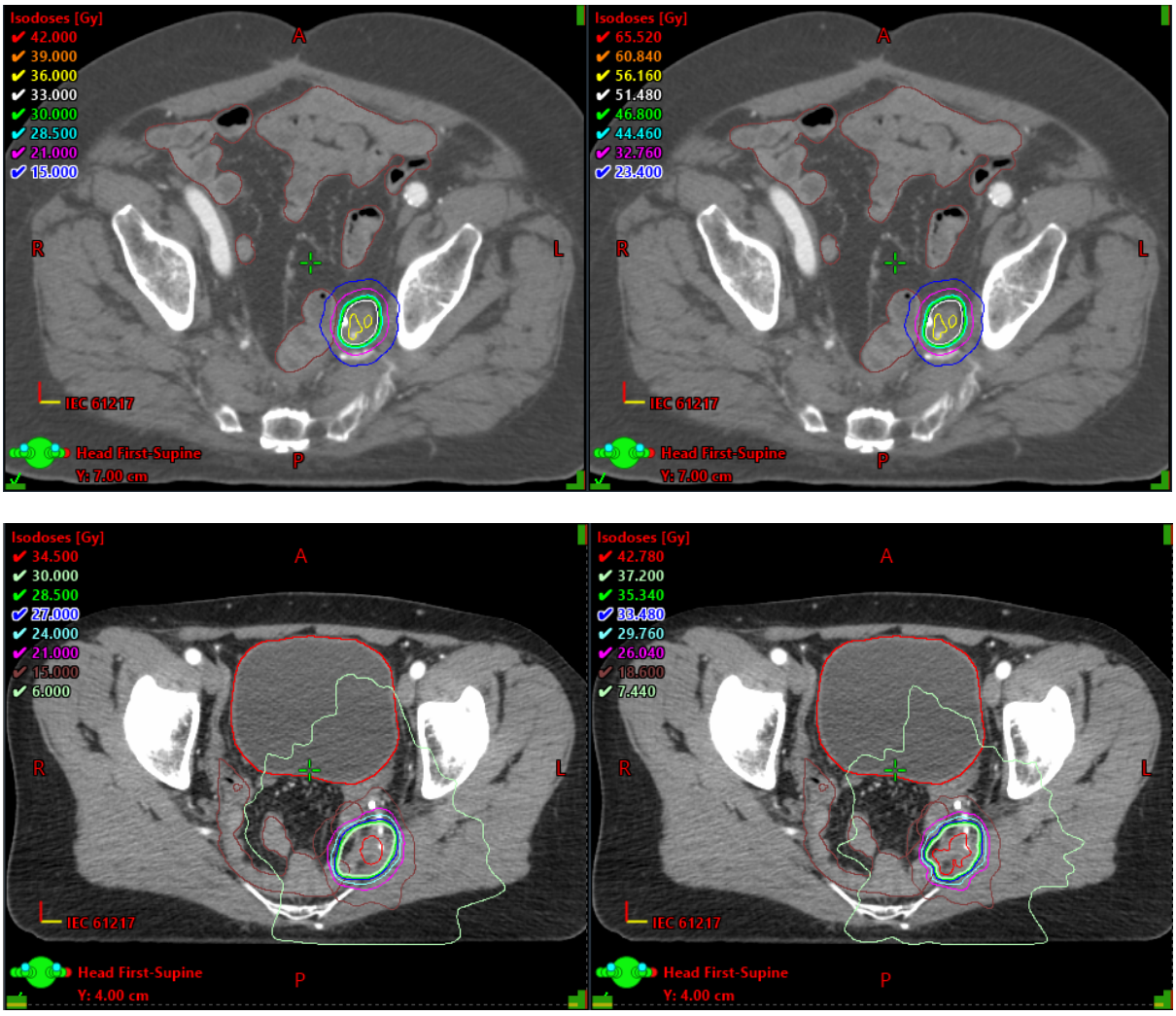

Figure One: delivered standard of care CtE SABR dose colour wash (left) and prospective deliverable isotoxic dose colour wash (right) for 2 selected case.