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Pelvic re-irradiation using stereotactic ablative radiotherapy (SABR): a systematic review and discussion

Supplementary Material

Table 1. Quality Assessment for included studies (also included as Excel file for increased clarity)

Question	Was hypothesis stated?			Was the study prospective?			Were cases collected from more than one centre?			Were patients recruited consecutively?			Were patient characteristics described?			Were eligibility criteria (inclusion and exclusion) clearly stated?			Was the intervention clearly described?			Were relevant outcome measures established a priori?			Were the relevant outcomes measured using appropriate methods?			Was follow-up long enough for important events to occur? (all FU>6m score 2, all 3-6m score 1)			Were losses to follow-up reported?			Were adverse events reported?			Were conclusions supported by results?			Final score
Answer	Yes	Partial	No	Yes	Unclear/no information	No	Yes	Unclear	No	Yes	Unclear/NA	No	Yes (incl previous RTI doses)	Partial	No	Yes	Partial if presented as case report(s)	No	Yes (including constraints and margins)	Partial	No	Yes	Partial if presented as case report(s)	No	Yes	Partial	No	Yes max 2	Unclear	No	Yes or none	Unclear or N/A if single case report	No	Yes (incl low grade tox)	Partial	No	Yes	Partial	No	max 22
Score	2	1	0	1	0	0	1	0	0	1	0	0	2	1	0	2	1	0	2	1	0	2	1	0	2	1	0			0	1	0	0	2	1	0	2	1	0	
Abusaris et al	2					0			0			0	2				1		2			2			2					0	1			2			2			16
Dagoglu et al	2					0			0			0	2				1			1		2			2			2				0		2			2			16
Defoe et al	2					0			0			0	2				1			1		2			2			2			1				1		2			16
Deodato et al	2			1					0			0	2				1			1		2			2					0	1			2			2			16
Dewas et al	2					0			0			0	2				1			1		2			2					0		0		2			2			14
Guckenberger et al	2				0			0				0		1			1			1		2			2			2				0		2			2			15
Kim et al	2					0			0			0		1		2				1		2			2			2			1			2			2			17
Kunos et al 2008	2					0			0			0	2				1			1			1		2					0	1			1			2			13
Mucacevic et al	2				0			0				0		1			1			1			1		2					0		0			1			2			11
Vavassori et al	2					0			0			0	2				1			1		2			2			2				0		2			2			16
Jereczek-Fossa et al	2				0		1			1				1			1		2			2			2			1			1			2			2			18
Fuller et al 2008	2			1			1				0		2			2			2			2			2			1				0		2			2			19
Zerini et al	2					0		0			0		2			2			2			2			2			2				0		2			2			18
Arcangeli et al	2					0			0			0	2				1		2				1		2			2				0		2			2			16
Kunos et al 2009	2					0			0	1			2				1			1			1		2			1			1	0		2			2			16
Yazici et al	2					0			0			0	2				1			1			1		2			1			1				1		2			14
Park et al	2					0	1					0		1		2				1		2			2					0			0	2			2			15

Table 2. Summary of pelvic SABR re-irradiation studies: general features

Study	Period included and nature of study	Number of patients	Median follow-up (months)	Primary tumour site (n)	Site of re-irradiation (n)	GTV volume (cm^3, median and (range))	GTV-CTV margin (mm)	CTV-PTV margin (mm)	Technique	IGRT	Re-irradiation dose and fractionation Median (range) where applicable
Kunos et al 2008[1]	2007 Retrospective	3 (4 lesions)	3 (2-4)	vulvar (3) (one patient previously irradiated for anal cancer)	local (3) nodal (1)	24.9 (6.6-34.7)	NR	NR	Cyberknife, median isodose 75% (70-80), vacuum bag immobilisation	Fiducial tracking	24Gy in 3 fractions
Kunos et al 2009[2]	2007-2008 Retrospective	5	9 (4-19)	endometrial (1) cervical (1) ovarian (3)	proximal vagina	20.8 (18.5-217.5)	NR	NR	Cyberknife, median isodose 70% (70-80), 2 pin pelvic immobilisation	Fiducial tracking	19.5Gy (15-24) in 3 fractions (one patient received EBRT then SABR as boost)
Vavassori et al 2010[3]	2007-2008 Retrospective	6	11.3 (9.6-18.6)	prostate	local: intra-prostatic recurrence	37.6 (14.2-47.2)	CTV: whole prostate	NR	Cyberknife	Fiducial tracking	30Gy in 5 fractions
Defoe et al 2011[4]	2003-2008 Retrospective	14	16.5 (6-69)	rectum	pre-sacral region: soft tissue (8) bone (1) soft tissue and bone (2)	52.5 (19-110)	0	5	Cyberknife, 80% isodose, customised immobilisation device	Fiducial tracking	36Gy in 3 fractions (n=11) 12-18Gy in 1 fractions (n=3)
Dewas et al 2011[5]	2007 onwards Retrospective	16	10.6 (1.9-20.5)	rectum (4) anal canal (6) cervix (4) endometrial (1) bladder (1)	lateral pelvis	median size: 34.5mm (15-50)	0	3	Cyberknife, 80% isodose, vacuum bag immobilisation	Vertebral body tracking	36Gy in 6 fractions (15), 45Gy in 3 fractions (1)
Abusaris et al 2012[6]	2005-2009 Retrospective	21 pelvic re-irradiation (plus 6 abdomen re-irradiation)	15 (2-52)	rectum (13) cervix (6) ovarian (2) sarcoma (2) other (4)	pelvic (21) intra-abdominal (6; excluded from summary statistics)	PTV: 154 (6.7-1114.5)	0	2-3	Cyberknife, median isodose: 80% (65-86%), vacuum bag immobilisation	Fiducials	32Gy (16-60) in 4 fractions (2-6)

Table 2 continued. Summary of pelvic SABR re-irradiation studies: general features

Study	**Period included and nature of study**	**Number of patients**	**Median follow-up (months)**	**Primary tumour site (n)**	**Site of re-irradiation (n)**	**GTV volume (cm^3, median and (range))**	**GTV-CTV margin (mm)**	**CTV-PTV margin (mm)**	**Technique**	**IGRT**	**Re-irradiation dose and fractionation Median (range) where applicable**
Arcangeli et al 2015[7]	2013	1	6	prostate	local recurrence: prostate bed (1)	Dimensions: 6 x 7mm	0	5mm	Tomotherapy	MV CT	30Gy in 5 fractions
Dagoglu et al 2015[8]	2006-2012 Retrospective	18 (22 lesions)	38 (6-86)	rectum (15) colon (3)	pelvic side wall (12) presarcal (5) central pelvis (2) presarcal and pelvic side wall (1) pubic area (1)	90.1 (36.8-1029.4)	NR	NR	Cyberknife, median isodose 78% (69-86%), vacuum bag immobilisation	Fiducial tracking	25Gy (24-40) in 5 fractions (3-6)
Fuller et al 2015[9]	2009-2014 Prospective	29	24 (3-60)	prostate	Local: prostate	Prostate volume on ultrasound: 21.7 (10.7-47.1)	CTV: Whole prostate volume +/- extra-prostatic extension	0	Cyberknife	Fiducial tracking	34Gy in 5 fractions

Table 2 continued. Summary of pelvic SABR re-irradiation studies: general features

Study	Period included and nature of study	Number of patients	Median follow-up (months)	Primary tumour site (n)	Site of re-irradiation (n)	GTV volume (cm^3, median and (range))	GTV-CTV margin (mm)	CTV-PTV margin (mm)	Technique	IGRT	Re-irradiation dose and fractionation Median (range) where applicable
Zerini et al 2015[10]	2008-2013 Retrospective	31 (one additional patient in series received 30Gy in 10 fractions- excluded form this count; may include 2 patients from Jereczek-Fossa et al, below, these 2 patients only counted once for summary statistics)	21.3 (12-53)	prostate	local: prostatic recurrence or prostatic bed recurrence (31)	NR	CTV: whole prostate if remaining or nodule if prostate bed	3-7mm	Cyberknife, VMAT, Vero, dynamic conformal arc*	Fiducial tracking with Cyberknife, Vero: MV portal imaging, cone beam CT, real time fluoroscopy and ExacTrac infrared monitoring	25Gy (25-30) in 5 fractions (n=30), 15Gy in 3 fractions (n=1)

CTV: clinical target volume, GTV: gross tumour volume, IGRT: image guided radiotherapy, MV: megavoltage, NR: not reported, PTV: planning target volume, VMAT: volumetric modulated arc therapy, * the group distinguished patients as those treated with SABR and those who received image-guided intensity modulated therapy or image-guided 3 dimensional conformal radiotherapy- all doses were extremely hypofractionated (5-6Gy per fraction) and delivered with image guidance and so were considered as SABR for this review.

Table 3. Summary of pelvic SABR studies that include re-irradiated and never previously irradiated patients: general features (specific outcomes for re-irradiated patients presented where possible)

Study	**Period included and nature of study**	**Number of patients**	**Median follow-up (months (range))**	**Primary tumour site (n)**	**Site of re-irradiation (n)**	**GTV volume (cm^3, median and (range))**	**GTV-CTV margin (mm)**	**CTV-PTV margin (mm)**	**Technique**	**IGRT**	**Re-irradiation dose and fractionation Median (range) where applicable**
Kim et al 2008[11]	2002-2006 Retrospective	4 re-irradiated patients (23 total)	re-irradiated: 32.5m (19-54) all: 31 (7-65)	rectal (23)	all: pre-sacral nodal (7) pelvic wall nodal (16)	26 (12-122) In re-irradiated: 48 (14-103)	0	3	Cyberknife, prescription isodose range: 73-85%, cradle immobilisation	Fiducial tracking	re-irradiated: 37.5Gy (36-39) in 3 fractions (all: 39Gy (36-51) in 3 fractions in 18 patients, 16Gy in 1 fraction in 5 patients
Deodato et al 2009[12]	2005-2007 Prospective	5 patients re-irradiated in pelvis (11 total, 12 lesions)	all: 19m (2-37)	re-irradiated: cervical (3) endometrial (2)	re-irradiated: pelvic nodal (3) presacral nodal (1) local (cervix) (1)	24.4 (0.1-190.0) PTV: 42 (4-273)	0	≥10	Linear accelerator Prescribed to isocentre 4 non-coplanar beams, body frame	Portal images	re-irradiated: 30Gy (20-30) in 5 fractions (all: 30Gy (20-30) in 5 fractions)
Muacevic et al 2009[13]	2005-2007 Prospective	7 re-irradiated patients (total 38 patients, 51 lesions)	all: 12.7 (2-35)	variety (urogenital 24)	all: pelvic bone: sacrum: (30) acetabulum (9) iliac bone (7) pubic bone (5)	mean: 25 (1.9-104.3)	NR	NR	Cyberknife, median isodose 65% (40-70)	vertebral body tracking	mean dose: 19.4Gy (13.5-24) in 1 fraction
Guckenberger et al 2010[14]	1997-2007 Retrospective	7 re-irradiated patients (including 4 brachytherapy alone) (19 total)	all: 22 (minimum 11)	all: cervical (12) endometrial (7)	all: central (7) central to pelvic side wall (6) pelvic side wall (6) primary (local) disease (16) nodal (3)	45 (12-475) PTV: 92 (37-619)	2-3mm	5	Linear accelerator median isodose 65% (65-80), body frame or vacuum bag immobilisation	Planning CT scanner or cone beam CT	Patients previously irradiated with EBRT: 30Gy (28-30) in 3 fractions (3-4) Patients previously irradiated with brachytherapy alone: EBRT followed by SABR boost: EBRT: 50Gy med (46-52Gy) in 1.8 or 2Gy fractions SABR boost: 15Gy (10-20) in 3 fractions (2-5)

Table 3 continued. Summary of pelvic SABR studies that include re-irradiated and never previously irradiated patients: general features (specific outcomes for re-irradiated patients presented where possible)

Study	Period included and nature of study	Number of patients	Median follow-up (months (range))	Primary tumour site (n)	Site of re-irradiation (n)	GTV volume (cm^3, median and (range))	GTV-CTV margin (mm)	CTV-PTV margin (mm)	Technique	IGRT	Re-irradiation dose and fractionation Median (range) where applicable
Jereczek-Fossa et al 2012[15]	2007-2009 ? mixed retrospective and prospective	27 re-irradiated lesions in at least 23 patients (total 34 patients, 38 lesions) NOTE- includes the 6 patients from Vavassori et al (only counted once for summary statistics)	all: 16.9 (3-35.2)	prostate (27 lesions re-irradiated, at least 23 patients)	re-irradiated: intra-prostatic recurrence (15) anastomotic recurrence (4) pelvic lymph nodes (8)	NR	0	1 to 2	Cyberknife, mean isodose 80%, vacuum bag immobilisation	fiducials or vertebral body tracking	intra-prostatic/ anastomotic: 30Gy in 5 fractions nodal: 33Gy in 3 fractions
Yazici et al 2013[16]	2007-2010 Retrospective	11 re-irradiated patients (16 total)	All: 12 (3-36)	all: cervical (11) endometrial (4) ovarian (1)	all: central pelvis (9) para-iliac (4) pelvic side wall (2) low para-aortic (1)	mean: 111.1 (25.7-310)	NR	NR	Cyberknife mean isodsoe 76% (60-76%)	NR	Mean: 26.6Gy (15-40) in 3-5 fractions
Park et al 2015[17]	2002-2013 Retrospective	20 re-irradiated pelvic lymph nodes, at least 12 patients (total 85 patients, 100 lesions, 32 considered re-irradiated (multiple sites), though overlap with previous field in 68	All: 20.4 (2.1-128.2)	cervical	re-irradiated: pelvic nodes (20) all: para-aortic (52) pelvic (31) cervix/ parametrium (3- unclear if re-irradiated or not) other (14)	NR	usually 0	3	Cyberknife median isodose 80% (76-83) cradle immobilisation	Fiducial tracking	all: mode: 39Gy (27-51) in 3 fractions in 96 patients 4 patients: 30-45Gy in 5-10 fractions (all re-irradiated)

CTV: clinical target volume, GTV: gross tumour volume, IGRT: image guided radiotherapy, NR: not reported, PTV: planning target volume

Table 4. Doses from previous EBRT and SABR in studies of pelvic SABR re-irradiation

Study	**Initial EBRT dose (Gy) and fractionation**	**Initial EQD2 (Gy) (α/β=10Gy)**	**Initial EQD2 (Gy) (α/β=3Gy)**	**Interval since first irradiation (months) (median and (range))**	**Re-irradiation dose (Gy) and fractionation**	**Re-irradiation EQD2 (Gy) (α/β=10Gy)**	**Re-irradiation EQD2 (Gy) (α/β=3Gy)**	**Cumulative EQD2 (Gy) (α/β=10Gy)***	**Cumulative EQD2 (Gy) (α/β=3Gy)***	**High grade toxicity (CTCAE or RTOG)**
Kunos et al 2008[1]	54Gy in presumed 30 fractions (45 in presumed 25 fractions to 74.6 in 38 fractions)	53.1 (44.3-74.5)	51.8 (43.2-74.3)	6 (5-36)	24Gy in 3 fractions	36	52.8	89.1 (80.3-110.5)	104.6 (96.0-127.1)	None observed
Kunos et al 2009[2]	external beam: 45Gy in 25 fractions (n=3) brachytherapy: 25.5Gy (21-30) in 2 fractions (1-3) (n=2) intra-operative radiotherapy: 10Gy in 1 fractions (n=2)	44.3 (based on external beam radiotherapy only)	43.2 (based on external beam radiotherapy only)	16 (10-26)	19.5Gy (15-24) in 3 fractions	26.8 (18.8-36)	37.1 (24-52.8)	71.1 (63.1-80.3) (external beam components only)	80.3 (67.2-96) (external beam components only)	1 grade 3 event
Vavassori et al 2010[3]	80 (70-80Gy) Presumed 2Gy per fraction	80 (70-80)	80 (70-80)	NR	30Gy in 5 fractions	40	54	120 (110-120)	134 (124-134)	None observed
Defoe et al 2011[4]	50.4Gy (20-81) 1.8Gy per fraction presumed	49.6 (19.7-79.7)	48.4 (19.2-77.8)	NR	36Gy in 3 fractions (n=11) 12-18Gy in 1 fractions (n=3)	66 (22-66)	108 (36-108)	115.6 (41.7-145.7)	156.4 (55.2-185.8)	None observed

Table 4 continued. Doses from previous EBRT and SABR in studies of pelvic SABR re-irradiation

Study	**Initial EBRT dose (Gy) and fractionation (median (and range))**	**Initial EQD2 (Gy) (α/β=10Gy)**	**Initial EQD2 (Gy) (α/β=3Gy)**	**Interval since first irradiation (months) (median and (range))**	**Re-irradiation dose (Gy) and fractionation (median (and range))**	**Re-irradiation EQD2 (Gy) (α/β=10Gy)**	**Re-irradiation EQD2 (Gy) (α/β=3Gy)**	**Cumulative EQD2 (Gy) (α/β=10Gy)* (median (and range))**	**Cumulative EQD2 (Gy) (α/β=3Gy)* (median (and range))**	**High grade toxicity (CTCAE or RTOG)**
Dewas et al 2011[5]	45Gy (20-75) (3 patients had conventional radiotherapy for recurrence prior to SABR: median dose: 53.7 (36-66))	From paper: 72 (53-96) If external beam and SABR at recurrence: 106 (72-110)	From: paper: 45 (33-58) If external beam and SABR at recurrence: 65 (45-66)	Time to recurrence (not necessarily re-irradiation): 27 (4-148)	36Gy in 6 fractions (n=15), 45Gy in 3 fractions (n=1)	48 (48-93.8)	64.8 (64.8-162)	120 (101-189.8) In patients irradiated with external beam RT for recurrences: 154 (120-203.8)	109.8 (97.8-220) 129.8 (109.8-228)	None observed
Abusaris et al 2012[6]	EQD2, α/β=10Gy: 48Gy (31-87)	From paper: 48 (31-87)		NR	32Gy (16-60) in 4 fractions (2-6)	48 (24-150)	70.4 (32.4-276)	96 (55-237)	From paper: rectum: 104 (65-129) bladder: 113 (79-235) bowel: 98 (56-144)	None observed
Arcangeli et al 2015[7]	66Gy in 33 fractions	66	66	45 approx.	30Gy in 5 fractions	40	54	106	120	None observed
Dagoglu et al 2015[8]	50.4Gy (25-100.4) 1.8Gy per fraction presumed	49.6 (24.6-98.7)	48.4 (24-96.4)	22 (15-336)	25Gy (24-40) in 5 fractions (3-6)	31.3 (insufficient information to calculate range)	40.0 (insufficient information to calculate range)	80.9 (55.9-130)	88.4 (64-136.4)	2 grade 3 events 1 grade 4 event

Table 4 continued. Doses from previous EBRT and SABR in studies of pelvic SABR re-irradiation

Study	Initial EBRT dose (Gy) and fractionation (median (and range))	Initial EQD2 (Gy) (α/β=10Gy)	Initial EQD2 (Gy) (α/β=3Gy)	Interval since first irradiation (months) (median and (range))	Re-irradiation dose (Gy) and fractionation (median (and range))	Re-irradiation EQD2 (Gy) (α/β=10Gy)	Re-irradiation EQD2 (Gy) (α/β=3Gy)	Cumulative EQD2 (Gy) (α/β=10Gy)* (median (and range))	Cumulative EQD2 (Gy) (α/β=3Gy)* (median (and range))	High grade toxicity (CTCAE or RTOG)
Fuller et al 2015[9]	73.8Gy (64.8-81) 1.8Gy per fraction presumed (excludes 2 patients, 1 who had brachytherapy and one who had previous SABR)	72.3 (63.7-79.7)	70.8 (62.2-77.8)	88 (32-200)	34Gy in 5 fractions	47.6	66.6	119.9 (111.3-127.3)	137.4 (128.8-144.4)	7% grade 3+ 1 acute and late grade 3 urinary event 1 late grade 4 urinary event
Zerini et al 2015[10]	74Gy (50-80) Presumed 2Gy per fraction (excludes 3 patients who received LDR brachytherapy 145Gy)	74Gy (50-80)	74Gy (50-80)	115 (33-182) (from diagnosis of prostate cancer rather than first irradiation)	25Gy (25-30) in 5 fractions (n=30) 15Gy in 3 fractions (n=1)	31.3 (18.8-40)	40 (24-54)	105.3 (68.8-120)	114 (74-134)	None observed

CTCAE: Common Terminology Criteria for Adverse Events, EQD2: equivalent dose in 2Gy fractions, NR: not reported, LDR: low dose rate, RTOG: Radiation Therapy Oncology Group *Note: cumulative doses have largely been calculated by simple summing of median and range of values from initial radiotherapy and subsequent re-irradiation SABR prescription doses, and are not based on individual patient data, which is frequently not available. This approach assumes the re-irradiated lesion was located within the high dose region of the original dose distribution.

Table 5. Summary of pelvic SABR studies that include re-irradiated and never previously irradiated patients: doses (specific outcomes for re-irradiated patients presented where possible)

Study	**Initial EBRT dose (Gy) and fractionation (median (and range))**	**Initial EQD2 (Gy) (α/β=10Gy)**	**Initial EQD2 (Gy) (α/β=3Gy)**	**Interval since first irradiation (months) (median and (range))**	**Re-irradiation dose (Gy) and fractionation (median (and range))**	**Re-irradiation EQD2 (Gy) (α/β=10Gy)**	**Re-irradiation EQD2 (Gy) (α/β=3Gy)**	**Cumulative EQD2 (Gy) (α/β=10Gy)* (median (and range))**	**Cumulative EQD2 (Gy) (α/β=3Gy)* (median (and range))**	**High grade toxicity (CTCAE or RTOG)**
Kim et al 2008[11]	NR	-	-	NR	re-irradiated: 37.5Gy (36-39) in 3 fractions (all: 39Gy (36-51) in 3 fractions, n=18, 16Gy in 1 fraction, n=5)	Re-irradiated: 70.3 (66.0-74.8)	Re-irradiated: 116.3 (108-124.8)	-	-	None observed in re-irradiated (1 grade 4 event in never previously irradiated)
Deodato et al 2009[12]	50.4Gy (45-65) Presumed 1.8Gy per fraction	49.6 (44.3-63.9)	48.4 (43.2-62.4)	NR	re-irradiated: 30Gy (20-30) in 5 fractions (all: 30Gy (20-30) in 5 fractions)	Re-irradiated: 40 (23.3-40)	Re-irradiated: 54 (28-54)	89.6 (67.6-103.9)	102.4 (71.2-116.4)	None observed
Muacevic et al 2009[13]	NR	-	-	3-10 months	all: mean dose: 19.4Gy (13.5-24) in 1 fraction	47.5 (26.4-68)	86.9 (44.6-129.6)	-	-	None observed
Guckenberger et al 2010[14]	NR (includes brachytherapy alone or EBRT and BT in some)	-	-	interval since initial surgery or RT: 26 (3-84)	SABR alone: 30Gy (28-30) in 3 fractions (3-4) SABR boost immediately after EBRT: 15Gy (10-20) in 3 fractions (2-5) (EBRT: 50Gy (46-52) in 1.8-2Gy fractions)	50 (39.7-50) 18.8 (10-25)	78 (56-78) 24 (10-32)	-	-	In re-irradiated patients: 2 grade 4 events In not previously irradiated: 1 grade 4 event Also: 1 grade 3 event where uncertain if in re-irradiated patient or not

Table 5. Summary of pelvic SABR studies that include re-irradiated and never previously irradiated patients: doses (specific outcomes for re-irradiated patients presented where possible)

Study	Initial EBRT dose (Gy) and fractionation (median (and range))	Initial EQD2 (Gy) (α/β=10Gy)	Initial EQD2 (Gy) (α/β=3Gy)	Interval since first irradiation (months) (median and (range))	Re-irradiation dose (Gy) and fractionation (median (and range))	Re-irradiation EQD2 (Gy) (α/β=10Gy)	Re-irradiation EQD2 (Gy) (α/β=3Gy)	Cumulative EQD2 (Gy) (α/β=10Gy)* (median (and range))	Cumulative EQD2 (α/β=3Gy) (Gy)* (median (and range))	High grade toxicity (CTCAE or RTOG)
Jereczek-Fossa et al 2012[15]	NR	-	-	all: interval since diagnosis to SABR: 66 (24-180)	intra-prostatic/ anastomosis: 30Gy in 5 fractions nodal: 33Gy in 3 fractions	40 57.8	54 92.4	-	-	4 grade 3 events
Yazici et al 2013[16]	Post-operative radiotherapy: median 50.4Gy (45-60) Presumed 1.8Gy per fraction Primary radiotherapy including BT: 85-90Gy to point A	Post-operative radiotherapy: 49.6 (44.3-59.0)	Post-operative radiotherapy: 48.4Gy (43.2-57.6)	time to recurrence or progression after primary treatment: 20 (6-63)	all: mean: 26.6Gy (15-40) in 3-5 fractions	insufficient information to calculate	insufficient information to calculate	-	-	3 grade 4 events 1 grade 3 event 3 grade 2-3 events
Park et al 2015[17]	NR	-	-	NR	all: mode: 39Gy (27-51) in 3 fractions in 96 patients 4 patients: 30-45Gy in 5-10 fractions (all re-irradiated)	For 96 patients: 74.8Gy (42.8-114.8) insufficient information to calculate remaining 4 patients	For 96 patients: 124.8Gy (64.8-204) insufficient information to calculate remaining 4 patients	-	-	pelvic re-irradiation patients: 2 grade 3 events 2 grade 4 events all: 3 grade 3 events 2 grade 4 events

BT: brachytherapy, CTCAE: Common Terminology Criteria for Adverse Events, NR: not reported, RTOG: Radiation Therapy Oncology Group *Note: cumulative doses have been calculated by simple summing of median and range of values from initial radiotherapy and subsequent re-irradiation SABR prescription doses, and are not based on individual patient data which is frequently not available. This approach assumes the re-irradiated lesion was located within the high dose region of the original dose distribution.

Table 6. Summary of pelvic SABR re-irradiation studies: outcomes and detailed toxicity (CTCAE or RTOG)

Study	Acute toxicity (n, %)	Late toxicity (n, %)	Local control	Symptomatic response	Progression free/ disease free survival	Overall survival	Constraints	Comments
Kunos et al 2008[1]	No grade 3+	No grade 3+	50% at 3 months	NR	0% at 4 months	100% at 3 months	NR	
Kunos et al 2009[2]	Grade 3 fatigue (1, 20%) Grade 2 (one event (20%) of each of): urinary infection, GI obstruction, urinary obstruction, thrombosis, tenesmus, urinary urgency, diarrhoea, pain	No grade 3+	100% at 6 months	NR	median progression free survival: 9.0 months	80% at 1 year	NR	
Vavassori et al 2010[3]	No grade 3+ Grade 2: perineal pain (2, 33%)	No grade 3+	NR as short follow-up and androgen deprivation therapy used in 4 patients	NR	67% had biochemical progression at median of 8.4 months, 50% had clinical progression at median of 9.9 months	NR	rectum: Dmax<75% of prescription dose, urethra: Dmax <125% of prescription dose	4 patients received androgen deprivation before and concurrently with SABR
Defoe et al 2011[4]	No grade 3+	No grade 3+	90.9% at 1 year 68.2% at 2 years	57.1% reduction in pain	NR	90% at 1 year 78.8% at 2 years	NR	
Dewas et al 2011[5]	No grade 3+ Grade 2: nausea and vomiting (1, 6.3%)	No grade 3+ Grade 2: leg oedema (1, 6%) anorexia (1, 6%) gastrointestinal (1,6%)	51.4% at 1 year	50% reduction in pain	median disease free survival: 8.3 months 63% at 6 months	median 11.5 months 46% at 1 year	NR	trend towards improved local control in adenocarcinoma primaries

Table 6 continued. Summary of pelvic SABR re-irradiation studies: outcomes and detailed toxicity (CTCAE or RTOG)

Study	Acute toxicity (n, %)	Late toxicity (n, %)	Local control	Symptomatic response	Progression free/ disease free survival	Overall survival	Constraints	Comments
Abusaris et al 2012[6]	No grade 3+ Grade 2: nausea (3, 11%) pain (2, 7%) skin (2, 7%) diarrhoea (1, 4%) vomiting (1, 4%)	No grade 3+ Grade 2: limb dysfunction (2, 7%) nerve complaints (1, 4%) dysuria (1, 4%) pain (1, 4%) skin (1, 4%)	64% at 1 year 53% at 2 years	100% reduction in tumour size 95% reduction in pain 75% had reduction in bleeding	NR	median 14 months 52% at one year 37% at 2 years	rectum Dmax to 10cm^3 ≤110Gy (cumulative EQD2, α/β=3Gy), bladder Dmax to 10cm^3 ≤120Gy (cumulative EQD2, α/β=3Gy), bowel Dmax to 10cm^3 ≤110Gy (cumulative EQD2, α/β=3Gy) (constraints could be exceeded if tumour within these organs)	Local control better with doses >60Gy (EQD2, α/β=10Gy)
Arcangeli et al 2015[7]	No grade 3+ Grade 1 urinary only	None at 6 months (1 patient only)	100% at 6 months (1 patient only)	Asymptomatic but PSA falling	100% at 6 months (1 patient only)	100% at 6 months (1 patient only)	Urethra Dmax <125% of prescription dose Rectal Dmax <75% of prescription dose	Hydrogel spacer used to separate prostate bed from rectum
Dagoglu et al 2015[8]	Timing of events NR: Grade 4 small bowel perforation (1, 6%) Grade 3 neuropathy (1, 6%) Grade 2 neuropathy (1, 6%)	Grade 3 hydronephrosis secondary to ureteric stricture (1, 6%)	100% at 1 years 93.7% at 2 years 85.9% at 3 years	100% reduction in pain	NR	median 40 months 76.8% at 1 year 65.9% at 2 years 59.3% at 3 years	rectum: Dmax 25Gy in 5 fractions, colon: Dmax 25Gy in 5 fractions, small bowel: Dmax 20Gy in 5 fractions, bladder: Dmax 25Gy in 5 fractions, sacral plexus: Dmax 30Gy in 5 fractions	"ALARA principle" for normal tissues
Fuller et al 2015[9]	Grade 3 urinary (1, 3.4%) No rectal toxicity > grade 1	Grade 2 urinary (3, 10.3%) Grade 3 urinary (1, 3.4%) Grade 4 haemorrhagic cystitis (1, 3.4%,) No rectal toxicity > grade 1	100% at 2 years	NR	2 year biochemical disease free survival (Phoenix definition): 82% 2 year clinical disease free survival 100%		Urethra: Dmax 120% of prescription dose, Dose received by 50%: 105% Rectal wall: Dmax 100% of prescription dose Rectal mucosa: Dmax 75% of prescription dose Bladder wall: Dmax 100% of prescription	Patients excluded who had toxicity >grade1 from initial radiotherapy One of the cases of severe toxicity had received initial brachytherapy rather than external beam

							dose	

Table 6 continued. Summary of pelvic SABR re-irradiation studies: outcomes and detailed toxicity (CTCAE or RTOG)

Study	Acute toxicity (n, %)	Late toxicity (n, %)	Local control	Symptomatic response	Progression free/ disease free survival	Overall survival	Constraints	Comments
Zerini et al 2015[10]	No grade 3+ Grade 2 urinary (dysuria, 2, 6%) Grade 2 rectal (1, 3%)	No grade 3+ Grade 2 urinary (1, 3%)	87.5% after median follow-up (21.3 months, out of 32 patients including 1 who received 30Gy in 10 fractions)	NR	40.6% alive without evidence of disease after median follow up (21.3 months, out of 32 patients including 1 who received 30Gy in 10 fractions)	87.5% alive after median follow-up (21.3 months, out of 32 patients including 1 who received 30Gy in 10 fractions)	Rectum: Mean dose to 30%: <13.8Gy for prostate <8.4Gy for prostate bed Mean dose to 60%: <6.69Gy for prostate <4.08Gy for prostate bed Bladder: Mean dose to 30%: <10.58Gy for prostate <3.94Gy for prostate bed	About 1/3 of patients received concomitant androgen deprivation with SBRT

ALARA: as low as reasonably applicable, CTCAE: Common Terminology Criteria for Adverse Events, Dmax: maximum dose (point dose unless otherwise specified), EQD2: equivalent dose in 2Gy fractions, NR: not reported, PSA: prostate specific antigen, RTOG: Radiation Therapy Oncology Group

Table 7. Summary of pelvic SABR studies that include re-irradiated and never previously irradiated patients: outcomes and toxicity (CTCAE or RTOG, specific outcomes for re-irradiated patients presented where possible)

Study	Acute toxicity (n)	Late toxicity (n)	Local control	Symptomatic response	Progression free/ disease free survival	Overall survival	Constraints	Comments
Kim et al 2008[11]	No complications of any grade in re-irradiated (1 grade 4 event in non-re-irradiated: rectal perforation at 1 month)	No complications of any grade in re-irradiated	all: 74.3% at 4 years	NR	all: median 55 months all: 51.5% at 4 years	re-irradiated: median 26 months, 25% at 4 years (all: 24.9% at 4 years)	NR	lesions >8cm were excluded, up to 3 lesions permitted if <3mm between lesions, no significant difference in survival between re-irradiated and never previously irradiated
Deodato et al 2009[12]	re-irradiated: no grade 3+ re-irradiated: grade 2: nausea (1), proctitis (1)	re-irradiated: no grade 3+ re-irradiated: no grade 2	all: 81.8% at 2 years (local progression free survival)	NR	NR	re-irradiated: median: 28, 1 and 2 years: 60% (all: 63.6% ay 2 years)	NR	
Muacevic et al 2009[13]	all: no acute toxicity	NR	95% (time point NR)	all: 71% reduction in pain	NR	NR	NR	phantom study demonstrated vertebral body tracking suitable for lesions at a distance

Guckenberger et al 2010[14]	all: grade 3 urinary frequency (1) grade 2 toxicity (5)	re-irradiated: 2 grade 4 events: small bowel ileus (previous EBRT and brachytherapy) intestino-vaginal fistula (previous brachytherapy, received EBRT and SABR boost) non-re-irradiated: 1 grade 4 event: intestino-vaginal fistula	re-irradiated with previous EBRT: 100% at 3 years all: 81% at 3 years	NR	NR	all: median 25 59% at 2 years 34% at 3 years	NR	trend towards higher rectal/ small bowel doses in patients with high grade toxicity

Table 7 continued. Summary of pelvic SABR studies that include re-irradiated and never previously irradiated patients: outcomes and toxicity (CTCAE or RTOG, specific outcomes for re-irradiated patients presented where possible)

Study	**Acute toxicity (n)**	**Late toxicity (n)**	**Local control**	**Symptomatic response**	**Progression free/ disease free survival**	**Overall survival**	**Constraints**	**Comments**
Jereczek-Fossa et al 2012[15]	re-irradiated for local/ anastomotic recurrence: grade 3 incontinence (1) grade 2 urinary toxicity (2) nodal recurrence (50% of patients re-irradiated): grade 3 haematuria (1, unclear if in re-irradiated patient or not)	re-irradiated for local/ anastomotic recurrence: grade 3 incontinence (1) grade 2 urinary toxicity (1) nodal recurrence (50% of patients re-irradiated): grade 3 haematuria (1, unclear if in re-irradiated patient or not)	re-irradiated: 89% (time point not specified) all: 92% (time point not specified)	NR	all: median 10 months (range: 2-17)	NR	rectum: Dmax <100% of prescription dose bladder: Dmax <120% of prescription dose urethra: Dmax <120% of prescription dose small bowel: Dmax to 1cm^3 <21Gy	Androgen deprivation had no impact on time to progression, Suggestion that lymph node recurrences had improved progression free survival than other sites of recurrence
Yazici et al 2013[16]	all: timing NR: grade 2-3 proctitis (3) grade 3 thrombosis (1; grade 3 presumed from description)	all: grade 4 vaginal fistula (2) grade 4 bowel obstruction (1)	all: 94% at median follow up of 12 months	NR	All: 59% at 1 year	all: 1 year: 60.3% 2 year: 40.2%	NR	

Park et al 2015[17]	Pelvic re-irradiation patients: Grade 3 enterocolitis (1)	Pelvic re-irradiation patients: grade 4 recto-vaginal fistula (2) grade 3 urethral stricture (1)	re-irradiation at all sites (i.e. including para-aortic nodes): 60.2% at 2 years all: 82.5% at 2 years, 78.8% at 5 years	NR	all: median 14.3 months 42.4% at 2 years, 34.4% at 5 years	all: median 32.7 months 57.5% at 2 years 32.9% at 5 years	NR	Local control inferior with re-irradiated lesions (all sites of treatment) compared to non-re-irradiated patients (p<0.001) but doses lower in re-irradiated patients Trends to improved local control with higher doses and disease free interval >36 months) Overall survival inferior in re-irradiated patients (p=0.023; all sites of treatment)

CTCAE: Common Terminology Criteria for Adverse Events, Dmax: maximum point dose, NR: not reported, GU: genitourinary, GI: gastrointestinal, RTOG: Radiation Therapy Oncology Group

Figure 1a. Median (blue diamond) and range of SABR prescription doses for re-irradiated patients. Asterisks indicate the dose-fractionation schedules where high grade toxicity occurred. Numbers too low to warrant statistical analysis.

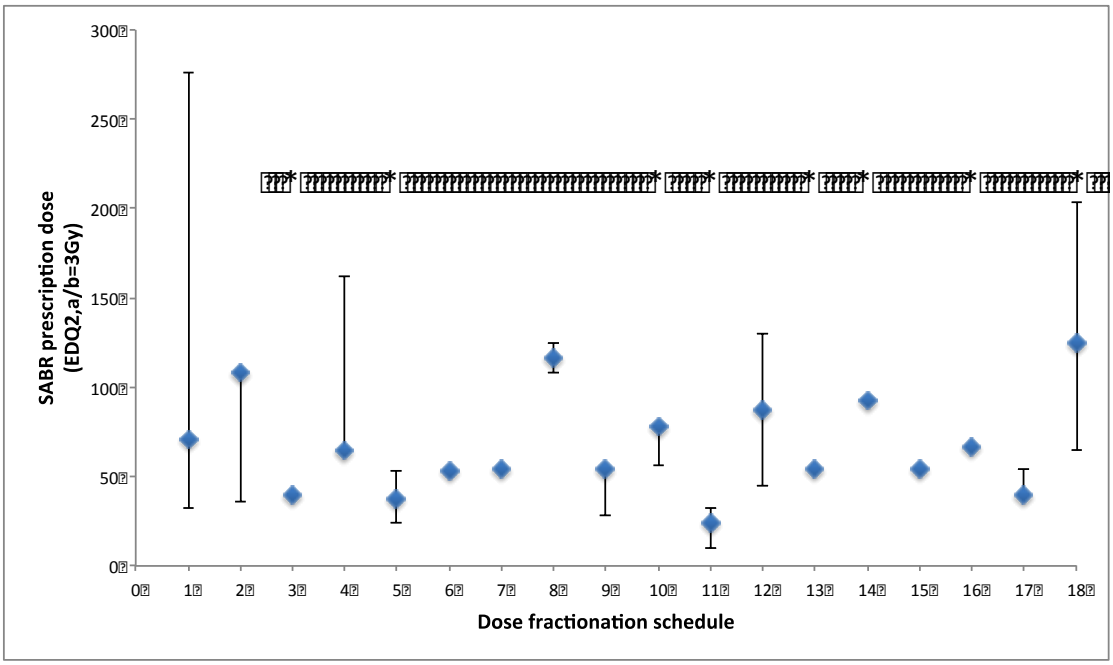
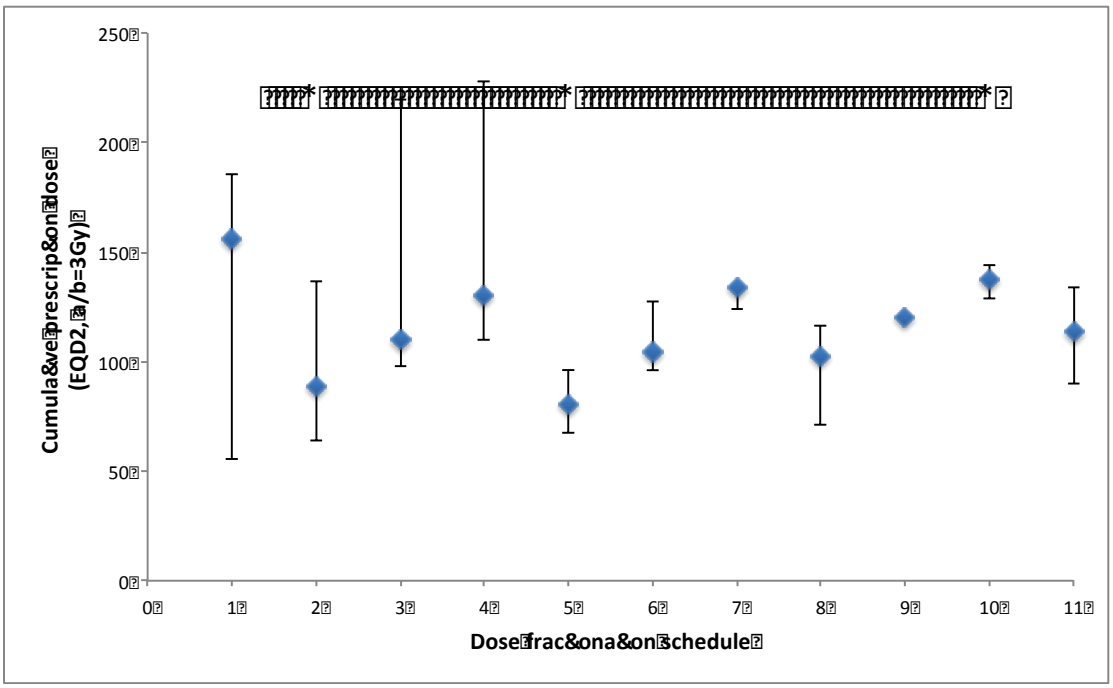


Figure 1b. Median (blue diamond) and range of available cumulative prescription doses for re-irradiated patients. Stars indicate the schedules where high grade toxicity occurred. Numbers too low to warrant statistical analysis



Detailed discussion regarding re-irradiation organ at risk constraints

Determining the most appropriate constraints for pelvic Stereotactic Ablative Radiotherapy (SABR) re-irradiation is one of the most challenging components of re-irradiation. Table 8 illustrates three strategies for determining organ at risk (OAR) constraints for pelvic SABR re-irradiation using a variety of first irradiation normal tissue doses. The first strategy uses the same cumulative constraints as described by Abusaris et al[6]. The second and third strategies use conventional first irradiation dose constraints as cumulative constraints, initially assuming no repair and then assuming 50% repair between irradiations. To utilise cumulative constraints, the original dose must be converted to the EQD2 or BED (e.g. using α/β=3Gy) and subtracted from the cumulative constraint in EQD2 or BED (example of calculation provided in Figure 1). In the situation of 50% repair, 50% of the original dose is subtracted from the cumulative constraint. The remaining dose is what is remaining for the OAR for SABR re-irradiation in EQD2 or BED (α/β=3Gy). This is converted to the equivalent dose in the required number of fractions for SABR delivery (5-fraction SABR in these examples). For comparison, the final column in Table 2 shows the constraints contained in the report of the American Association of Physicists in Medicine (AAPM) for pelvic SABR, intended for first irradiation[18]. Intuitively, it would seem reasonable that constraints for SABR re-irradiation do not exceed those for first SABR irradiation. The principal pelvic OARs are considered below.

As discussed in the main paper, for small bowel, the most conservative and thus safest approach to re-irradiation would be to use traditional first irradiation constraints as cumulative constraints without allowing any repair. While this would be the preferred strategy, the dose remaining for SABR re-irradiation of small bowel could be prohibitively small, particularly in cases where the small bowel is within or close to the PTV. This method for defining constraints may be unnecessarily conservative if a degree of normal tissue repair occurs following first irradiation. The constraints described by Abusaris et al, in contrast, are considerably more lenient[6]. Abusaris et al adopted these constraints based on

the fact that the re-irradiated volume was likely to be small, although how the actual cumulative values were determined was not discussed. Despite this leniency, no high-grade toxicity was reported. It can also be seen from the table that the AAPM SABR constraints for small bowel for *first* irradiation are more conservative than those used by Abusaris et al for *re*-irradiation[6,18]. When traditional constraints are used in a cumulative manner, but allowing 50% repair, the remaining dose, in the most part, remains more conservative than the constraints used by Abusairs et al.

Considering all of the above, the preferred option for small bowel re-irradiation would be to meet the traditional constraints, used in a cumulative manner, without including repair (first choice: 'best case scenario'). If this is not possible, then an alternative strategy must be adopted. As a pragmatic compromise, to allow more freedom in dose prescription, yet remain more conservative than the constraints described by Abusaris et al, the traditional constraints could be used in a cumulative manner, but including a degree of recovery, which could be influenced by the interval between first and second irradiation. If using this approach, however, it must be accepted that the assumption of 50% recovery, or otherwise, is empirical rather than evidence based. Alongside this cumulative constraint, the AAPM small bowel volume-based constraint for first SABR should also be respected (19.5Gy to <5cm^3), and the lower of the two maximum point doses (i.e. AAPM *vs* that calculated when allowing a degree of recovery) should be selected as the maximum dose constraint.

For the rectum and bladder, drawing comparisons between constraints is more difficult as these apply over different volumes and, for the bladder, the structure also differs (i.e. whole bladder vs. bladder wall). If the rectum and bladder are both relatively empty prior to re-irradiation (thus 10cm^3 of rectum or bladder (to which the Abusairs et al constraints apply) is likely to be a larger volume than 15% of rectum or bladder (to which the conventional constraints apply; table 8), then for most part, the constraints described by Abusaris et al appear the most lenient while the traditional constraints, used cumulatively but without repair, appear most restrictive. Again, if possible in practice, the traditional constraints,

used in a cumulative manner without any repair, would be respected but if not possible, as a pragmatic compromise, the traditional constraints could be used cumulatively, but including a degree of repair, alongside the AAPM first SABR irradiation constraints. The only exception would be for overlapping fields in previous high dose (e.g. >54Gy) rectal regions, where the constraints described by Abusaris et al appear more conservative than AAPM constraints. In this scenario, the cumulative traditional constraints allowing a degree of repair could be used in conjunction with the Abusaris et al cumulative constraints.

For the sacral plexus, Abusaris et al did not specify constraints. Considering the traditional constraints, which are specified to a 0.5% volume, equivalent to 0.35 to 0.6cm^3 of sacral plexus (based on a lumbosacral plexus volume of between 70 and 120cm^3[19]), these appear more conservative than the APPM constraints. Again, meeting the traditional constraints, used cumulatively without any repair, would be the preferred strategy, but if not possible, as a pragmatic compromise, the traditional constraints could be used cumulatively, allowing a degree of repair.

The correct approach to defining OAR constraints for SABR pelvic re-irradiation is unknown. Ideally traditional constraints would be used in a cumulative manner, without repair, and the remaining dose would not be exceeded by the re-irradiation SABR plan if feasible. As mentioned above, such constraints may be prohibitive to delivering meaningful SABR doses. The pragmatic, alternative approach outlined above, is summarised in Table 9, but in more detail than in Table 2 in the main document. Based on the above discussion and the values in Table 8, it seems likely that when patients have previously received conventionally fractionated pelvic doses of up to about 54Gy, then there should be dosimetric capacity to deliver SABR re-irradiation doses of 25-30Gy in 5 fractions while respecting at least the 'second choice' constraints, assuming 50% repair. Previous plans should always be reviewed, and ideally formally combined to evaluate the normal tissue doses. For previous irradiation doses of greater than about 54Gy and/or when brachytherapy has been given to the region

requiring re-irradiation, the re-irradiation dose prescriptions may need to be more restrictive.

There are huge uncertainties in the above and this discussion aims to illustrate options rather than provide definitive solutions. For some exploratory calculations we included 50% repair. As before, this figure is more empirical than evidence based. Length of time between irradiation may influence the degree of repair, although clinical evidence to determine such factors for normal pelvic tissues is severely lacking[20]. As mentioned in the main document, it should also be noted that additional patient related factors such as diabetes and vascular disease may also contribute to the risk of toxicity following re-irradiation, although there is insufficient evidence to know how these should be incorporated. The uncertainties involved merely highlight the importance of high quality prospective evaluation of future patients, including dosimetric analysis. Going forward, when there is more prospective data to guide constraints, these should be to absolute volumes rather than percentage volumes to reduce the impact of contouring variability[21,22].

Table 8. Remaining normal tissue doses for SABR re-irradiation based on variety of initial radiotherapy normal tissue doses and variety of cumulative constraints

Possible dose (Gy) received by normal tissue at first irradiation	No. fractions	Dose per fraction (Gy)	EQD2 (α/β=3Gy)	Remaining dose constraint for 5 fraction SABR based on Abusaris et al cumulative constraints[6§] (Gy)	Remaining dose constraint for 5 fraction SABR based on conventional first irradiation volume constraint used cumulatively, assuming no recovery)* (Gy)	Remaining dose constraint for 5 fraction SABR based on conventional first irradiation volume constraint used cumulatively, assuming 50% recovery* (Gy)	AAPM constraints (Gy) for 5 fraction pelvic SABR as **first** irradiation[18] included for comparison only
Small bowel							
30	15	2.00	30.00	**37.8 to 10cm³**	**18.4 max point**	**24.8 max point**	19.5 to < 5cm³/ 35 point**
34	15	2.27	35.81	**36.2 to 10cm³**	**15.4 max point**	**23.7 max point**	19.5 to < 5cm³/ 35 point**
34	28	1.21	28.66	**38.2 to 10cm³**	**19.1 max point**	**25.1 max point**	19.5 to < 5cm³/ 35 point**
42	25	1.68	39.31	**35.2 to 10cm³**	**13.4 max point**	**23.0 max point**	19.5 to < 5cm³/ 35 point**
45	25	1.80	43.20	**34.0 to 10cm³**	**11.0 max point**	**22.2 max point**	19.5 to < 5cm³/ 35 point**
50.4	28	1.80	48.38	**32.5 to 10cm³**	**7.1 max point**	**21.1 max point**	19.5 to < 5cm³/ 35 point**
50	25	2.00	50.00	**31.9 to 10cm³**	**5.6 max point**	**20.7 max point**	19.5 to < 5cm³/ 35 point**
54	28	1.93	53.23	**30.9 to 10cm³**	**2.0 max point**	**20.0 max point**	19.5 to < 5cm³/ 35 point**
70	39	1.79	67.13	**26.1 to 10cm³**	Nil remaining	**16.6 max point**	19.5 to < 5cm³/ 35 point**
78	39	2.00	78.00	**21.8 to 10cm³**	Nil remaining	**13.6 max point**	19.5 to < 5cm³/ 35 point**
80	39	2.05	80.82	**20.5 to 10cm³**	Nil remaining	**12.8 max point**	19.5 to < 5cm³/ 35 point**

Rectum							
30	15	2.00	30.00	**37.8 to 10cm^3**	**26.7 to <15%**	**31.8 to <15%**	25 to < 20cm^3/ 38 point
34	15	2.27	35.81	**36.2 to 10cm^3**	**24.5 to <15%**	**30.9 to <15%**	25 to < 20cm^3/ 38 point
34	28	1.21	28.66	**38.2 to 10cm^3**	**27.2 to <15%**	**32.0 to <15%**	25 to < 20cm^3/ 38 point
42	25	1.68	39.31	**35.2 to 10cm^3**	**23.1 to <15%**	**30.3 to <15%**	25 to < 20cm^3/ 38 point
45	25	1.80	43.2	**34.0 to 10cm^3**	**21.5 to <15%**	**29.7 to <15%**	25 to < 20cm^3/ 38 point
50.4	28	1.80	48.38	**32.5 to 10cm^3**	**19.2 to <15%**	**28.8 to <15%**	25 to < 20cm^3/ 38 point
50	25	2.00	50.00	**31.9 to 10cm^3**	**18.4 to <15%**	**28.5 to <15%**	25 to < 20cm^3/ 38 point
54	28	1.93	53.23	**30.9 to 10cm^3**	**16.8 to <15%**	**27.9 to <15%**	25 to < 20cm^3/ 38 point
70	39	1.79	67.13	**26.1 to 10cm^3**	**8.1 to <15%**	**25.4 to <15%**	25 to < 20cm^3/ 38 point
78	39	2.00	78.00	**21.8 to 10cm^3**	Nil remaining	**23.3 to <15%**	25 to < 20cm^3/ 38 point
80	39	2.05	80.82	**20.5 to 10cm^3**	Nil remaining	**22.7 to <15%**	25 to < 20cm^3/ 38 point
Bladder							
30	15	2.00	30.00	**40.5 to 10cm^3**	**29.2 to <15%**	**34.0 to <15%**	18.3 to <15cm^3/38 point†
34	15	2.27	35.81	**39.0 to 10cm^3**	**27.2 to <15%**	**33.1 to <15%**	18.3 to <15cm^3/38 point†
34	28	1.21	28.66	**40.9 to 10cm^3**	**29.7 to <15%**	**34.2 to <15%**	18.3 to <15cm^3/38 point†
42	25	1.68	39.31	**38.0 to 10cm^3**	**25.9 to <15%**	**32.6 to <15%**	18.3 to <15cm^3/38 point†
45	25	1.80	43.20	**37.0 to 10cm^3**	**24.4 to <15%**	**32.0 to <15%**	18.3 to <15cm^3/38 point†
50.4	28	1.80	48.38	**35.5 to 10cm^3**	**22.3 to <15%**	**31.1 to <15%**	18.3 to <15cm^3/38 point†
50	25	2.00	50.00	**35.0 to 10cm^3**	**21.6 to <15%**	**30.9 to <15%**	18.3 to <15cm^3/38 point†
54	28	1.93	53.23	**34.0 to 10cm^3**	**20.2 to <15%**	**30.4 to <15%**	18.3 to <15cm^3/38 point†
70	39	1.79	67.13	**29.6 to 10cm^3**	**13.0 to <15%**	**28.0 to <15%**	18.3 to <15cm^3/38 point†
78	39	2.00	78.00	**25.8 to 10cm^3**	**4.7 to <15%**	**26.0 to <15%**	18.3 to <15cm^3/38 point†
80	39	2.05	80.82	**24.7 to 10cm^3**	**1.3 to <15%**	**25.5 to <15%**	18.3 to <15cm^3/38 point†
Sacral plexus$^\Omega$							
30	15	2.00	30.00	Not reported	**20 to <0.5%**	**25.4 to <0.5%**	30 to <5cm^3/ 32 point
34	15	2.27	36.27	Not reported	**17.4 to <0.5%**	**24.4 to <0.5%**	30 to <5cm^3/ 32 point
34	28	1.21	27.32	Not reported	**21.0 to <0.5%**	**25.9 to <0.5%**	30 to <5cm^3/ 32 point
42	25	1.68	38.64	Not reported	**16.3 to <0.5%**	**24.0 to <0.5%**	30 to <5cm^3/ 32 point
45	25	1.80	42.75	Not reported	**14.2 to <0.5%**	**23.2 to <0.5%**	30 to <5cm^3/ 32 point
50.4	28	1.80	47.88	Not reported	**11.4 to <0.5%**	**22.3 to <0.5%**	30 to <5cm^3/ 32 point

50	25	2.00	50.00	Not reported	**10.0 to <0.5%**	**21.9 to <0.5%**	30 to <5cm^3/ 32 point
54	28	1.93	53.03	Not reported	**7.8 to <0.5%**	**21.4 to <0.5%**	30 to <5cm^3/ 32 point
70	39	1.79	66.41	Not reported	Nil remaining	**18.7 to <0.5%**	30 to <5cm^3/ 32 point
78	39	2.00	78.00	Not reported	Nil remaining	**16.1 to <0.5%**	30 to <5cm^3/ 32 point
80	39	2.05	81.03	Not reported	Nil remaining	**15.4 to <0.5%**	30 to <5cm^3/ 32 point

§ Abusaris et al cumulative constraints [6] small bowel: 110Gy (as EQD2, α/β=3), dose to no more than 10cm^3, rectum: 110Gy (as EQD2, α/β=3), dose to no more than 10cm^3, bladder: 120Gy (as EQD2, α/β=3), dose to no more than 10cm^3

*Conventional constraints: small bowel: e.g. max dose 55Gy[23], based on 28 fraction treatment; rectum: QUANTEC V75Gy<15%[24] based on 38 fraction treatment, bladder: QUANTEC, whole organ, V80<15%[25] based on 38 fraction treatment; sacral plexus: Tunio et al, volume described in paper, V60<0.5% (0.5cm^3 approx.)[19] based on 30 fraction treatment.

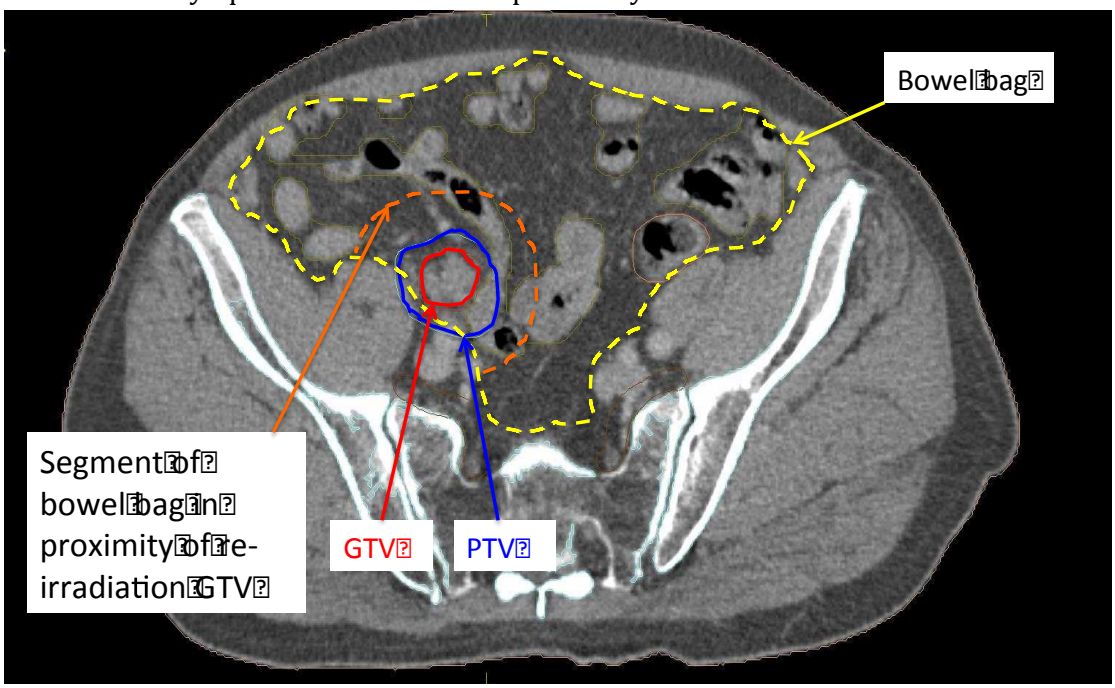
**AAPM constraints are those for ileum and jejunum, †SABR constraints apply to the bladder wall rather than the whole organ, Ω sacral plexus estimations calculated for α/β=2Gy.

Table 9. Suggested pragmatic conservative approach for organ at risk constraint definition for SABR re-irradiation (a simplified version is shown in the main document)

Organ	**Previous dose range**	**Organ at risk constraint determination**				
		First choice ('best case scenario')	**If first choice constraints not feasible**	**Second choice ('pragmatic compromise')**		
Small bowel	All	Subtract previous dose from traditional constraint, no repair permitted		Subtract previous dose from traditional constraint, allowing degree of repair	AND	Respect AAPM[18] constraints
Rectum	Up to 54Gy approx	Subtract previous dose from traditional constraint, no repair permitted		Subtract previous dose from traditional constraint, allowing degree of repair	AND	Respect AAPM[18] constraints
Rectum	Above 54Gy approx	Subtract previous dose from traditional constraint, no repair permitted		Subtract previous dose from traditional constraint, allowing degree of repair	AND	Respect Abusaris[6] et al cumulative constraints
Bladder	Up to 54Gy approx	Subtract previous dose from traditional constraint, no repair permitted		Subtract previous dose from traditional constraint, allowing degree of repair	AND	Respect AAPM[18] constraints
Bladder	Above 54Gy approx	Subtract previous dose from traditional constraint, no repair permitted		Subtract previous dose from traditional constraint, allowing degree of repair	AND	Respect AAPM[18] [18]constraints
Sacral plexus	All	Subtract previous dose from traditional constraint, no repair permitted		Subtract previous dose from traditional constraint, allowing degree of repair	AND	Respect AAPM[18] constraints

Figure 1.Example of SABR constraint calculation using cumulative constraints

1. Pelvic lymph node recurrence in previously irradiated area



2. Maximum point dose bowel bag closest to area of proposed re-irradiation determined from original plan (e.g. area within 1-2cm of recurrent lymph node)

   e.g. 42Gy in 25 fractions

3. Original dose converted to EQD2 and BED (α/β=3Gy)

   $EQD2_{3Gy} = D((d+\alpha/\beta)/2+\alpha/\beta) = 42((42/25+3)/(2+3)) = 39.312Gy$

   $BED_{3Gy} = D(1+d/(\alpha/\beta)) = 42(1+(42/25)/3) = 65.52Gy$

4. Subtract original point dose as $EQD2_{3Gy}$ from cumulative constraint to establish remaining dose (using Abusaris et al constraint as example[6])

   Constraint as $EQD2_{3Gy}$: $D_{10cm^3} \leq 110Gy$

   Constraint as BED_{3Gy}: $D_{10cm^3} \leq 183.333$

   Remaining dose as $EQD2_{3Gy}$= 110-39.31 $= D_{10cm^3} \leq 70.688$

   Remaining dose as BED_{3Gy}= 183.333-65.52 $= D_{10cm^3} \leq 117.8113$

5. Convert dose to equivalent dose for 5 fraction SABR

   $BED_{3Gy} = D(1+d/(\alpha/\beta))$

   $117.8133 = nd(1+d/(\alpha/\beta)) = nd + nd^2/(\alpha/\beta) = 5d + 5d^2/3$

$0 = 1.67d^2 + 5d - 117.8133$

To solve the quadratic equation: a=1.67, b=5 and c=-117.8133

$d = (-b + \sqrt{(b^2-4ac)})/2a = (-5 + \sqrt{(5^2-4*1.67*-117.8133)})/(2*1.67) = 7.035Gy$

6. Dose constraint for 5 fraction SABR (D) = 5*7.04 = 35.2Gy

7. Remaining dose (35.2Gy) applies to any hottest $10cm^3$ within the organ at risk

   The achievable prescription dose is unlikely to be higher than this if organ at risk within and close to PTV.

Note. It is intentional that it is the maximum *point* dose from the original plan is subtracted from the cumulative dose constraint even in the setting of a constraint to a maximum absolute volume (in this case $10cm^3$) as this is a more conservative approach than recording the dose to the absolute volume specified in the constraint.

This method assumes that a full 3-dimensional means of combining former and re-irradiation plans, with adaptation for anatomical changes and fractionation correction, as described in the main paper, is unavailable.

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