Supplementary Information:

DIR Methodology (see also Supplementary Figures 1 and 2):

The choice of DIR algorithm was limited to those available in the RayStation 9B Treatment Planning System. However, these algorithms are representative of the range of approaches available commercially, encompassing grey-scale driven (correlation and mutual information), biomechanical and contour-driven methods. The Anaconda algorithm is capable of combining greyscale and contour registration and, herein, we have additionally combined biomechanical registration with Anaconda.

Whilst many other DIR software platforms and algorithms exist, these do not fundamentally differ from the algorithms used here. Our focus was to explore the potential for combinations of existing DIR methods to overcome challenges in the case of extreme pelvic anatomical changes, so we have not attempted an algorithmic comparison. However, we would expect our findings to apply to any combination of similar grey-scale and biomechanical DIR algorithms in other contexts and systems, given an appropriate workflow as outlined below.

DIR results (see also Supplementary Table 2 and Figure 3 and 4):

Jacobian analysis:

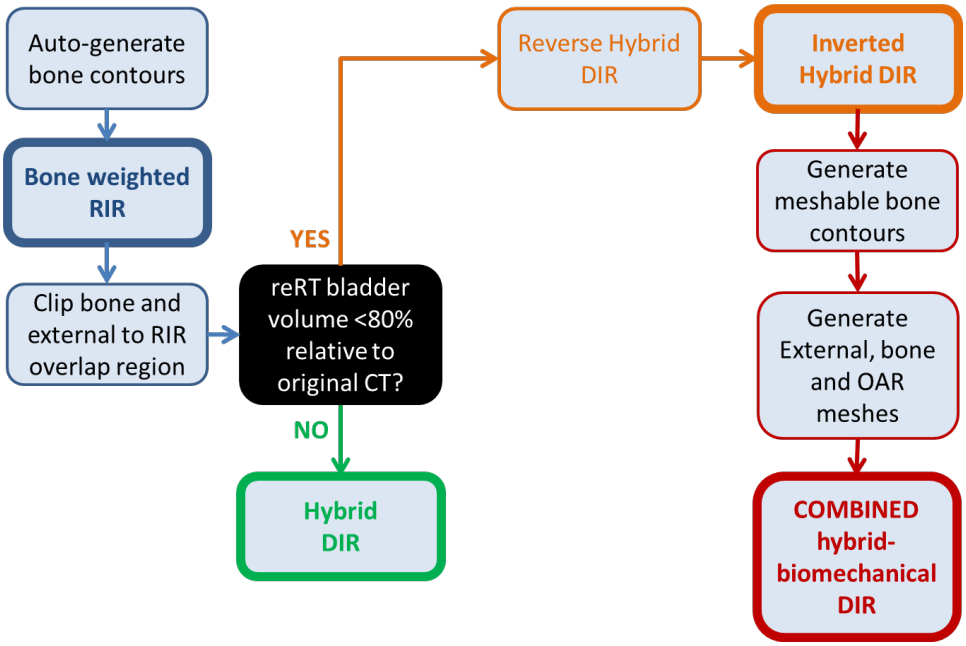
Clinical significance for reRT was assessed by overlaying the negative element mask onto the reRT CT image and combined dose distribution. In two cases the folding was <1 grid voxel (2.5 mm) and clinically insignificant. In one case, folding ~20 mm was observed, along the bladder-rectal interface. This case fell >3 s.d. from the mean for bladder DSC (0.81 vs. 0.95[0.04]) and precision (0.68 vs. 0.9[0.06]), and ~2 s.d. from the mean for correlation coefficient (0.67 vs 0.83[0.07]). This folding was considered clinically insignificant due to the location of the reRT PTV, ~10cm superior of the folded region.

Correlation coefficient:

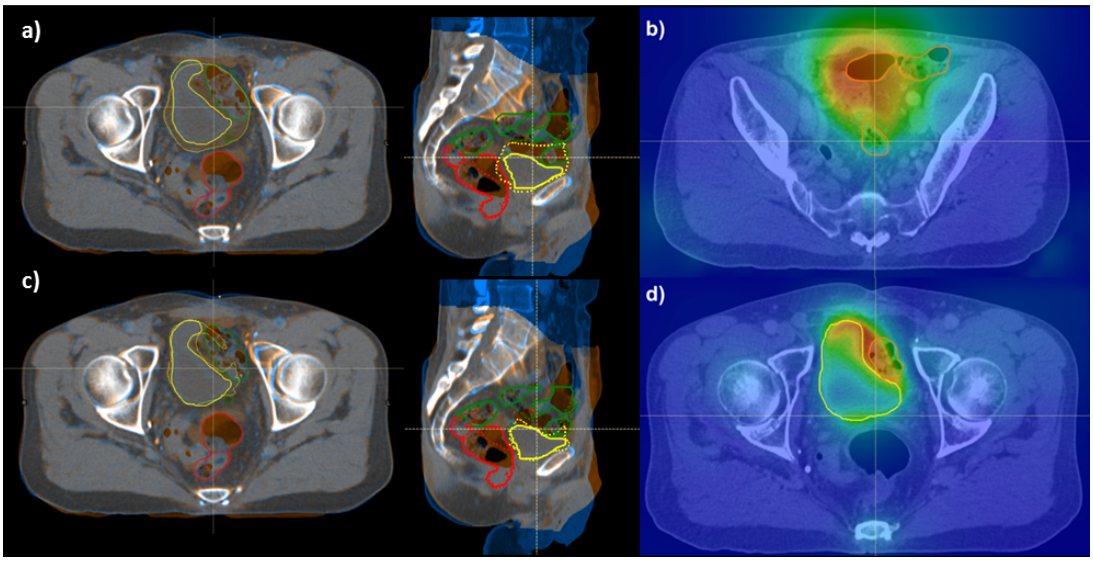
Correlation coefficient was found to be indicative of overall DIR quality, falling below 0.8 in only 4/21 cases. Each of these cases exhibited patient specific issues which limited DIR

accuracy, either surgical resection, prone-to-supine treatment position change or extreme (600%) bladder-volume change. Mean correlation coefficient was not significantly different between the forward DIR and inverse BM-DIR sub-cohorts (two tailed t-test, p=0.43).

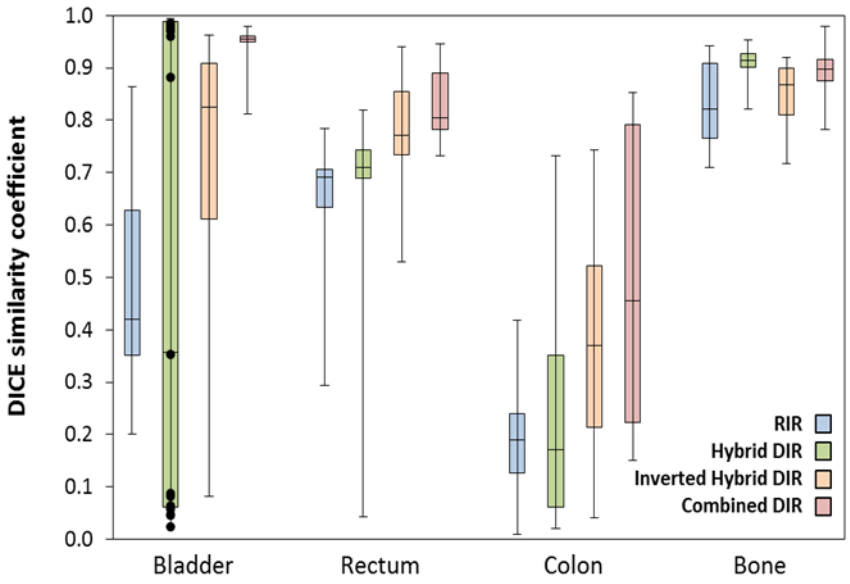
Supplementary Figure 1: Novel registration methodology for variable bladder-filling changes. Following initial RIR, hybrid DIR (ANACONDA) is performed in either the forwards or reverse direction, ensuring the larger bladder is the reference. Reversed DIR is computationally inverted and a second biomechanical (MORFEUS) registration performed to correct residual errors.

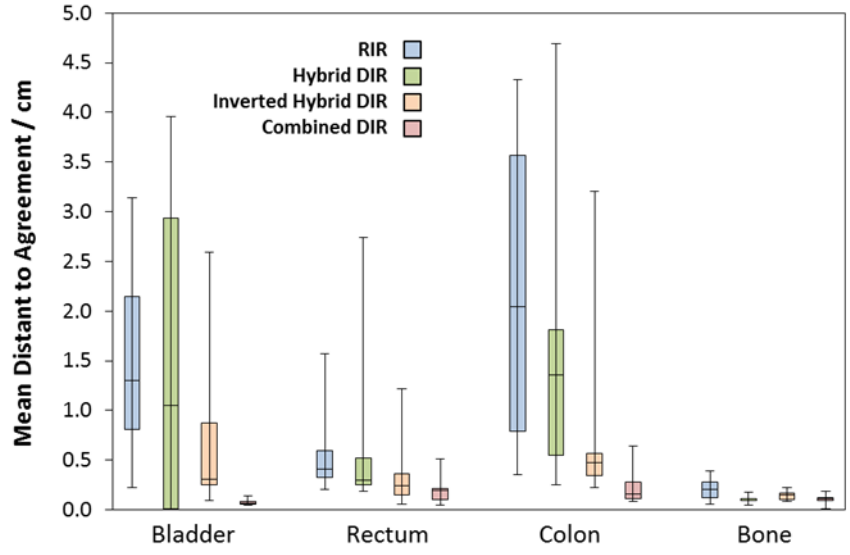


Supplementary Figure 2. The combined DIR pathway within STRIDeR DIR, showing: a) Inverted hybrid DIR, showing incomplete compression of the bladder with significant bone deformation. b) Inverted DVF magnitudes from the hybrid DIR. c) Subsequent biomechanical correction (BM-DIR) improves both bladder compression and bony registration, yielding a clinically usable DIR result for extreme bladder compression. d) DVF from BM-DIR correction step, showing corrections primarily around the bladder and colon.

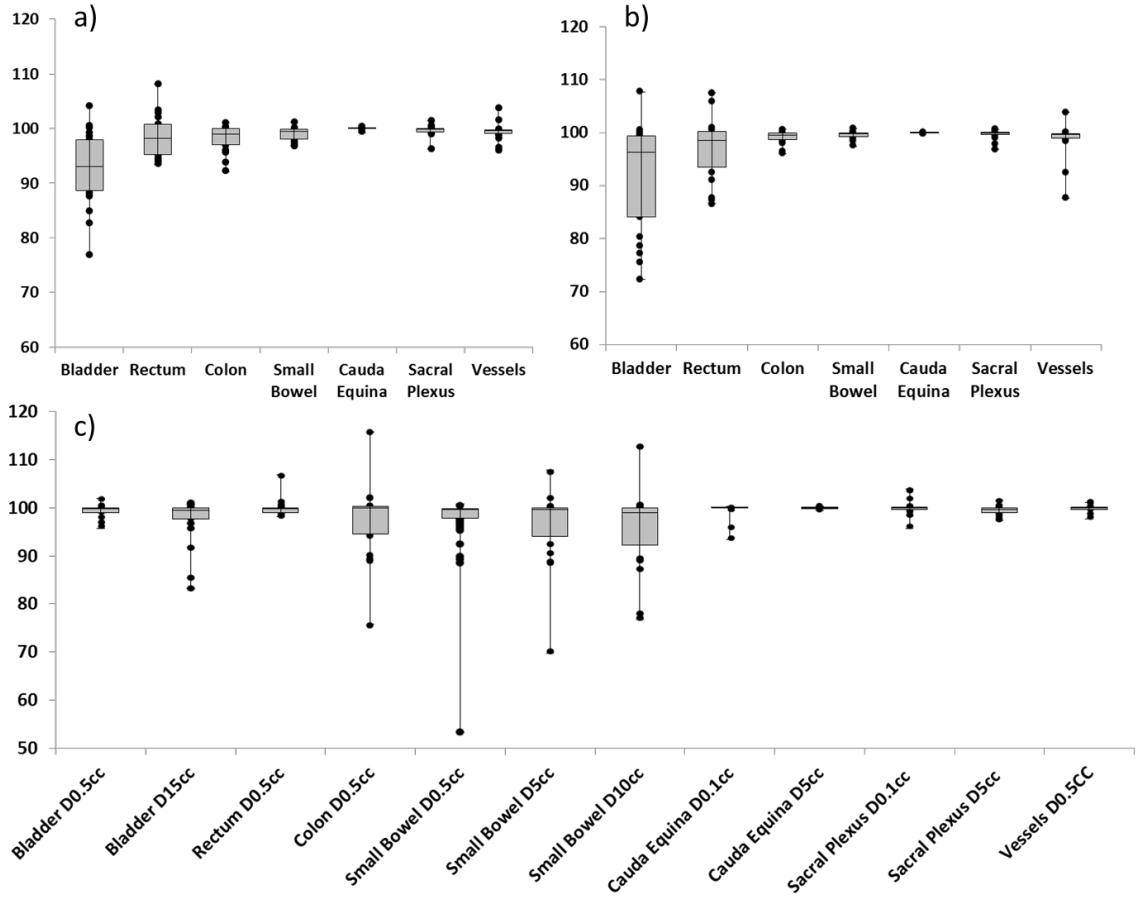


Supplementary Figure 3. a) Dice Similarity Coefficient (DSC) and b) Mean distance to agreement (MDA) for organs at risk (OARs) involved in pelvic reRT, under various registration schemes. Results only displayed for those cases which underwent all four methods of registration (n=15). Combined hybrid and biomechanical DIR outperforms other approaches for all OARs. Median, inter-quartile range and extrema are shown. Note that extreme bladder deformation causes the hybrid-only method to perform worse than RIR in some cases, leading to a strongly bimodal distribution (individual data points shown).





Supplementary Figure 4. Impact of STRIDeR DIR on dose statistics derived from per-voxel EQD2 dose summation for various OARs. Box and whisker plots show median, inter-quartile range and extrema. Dosimetric changes are shown relative to equivalent per-voxel EQD2 dose summation using RIR. a) Population median mean dose, b) Population median $D_{50\%}$, c) Population median dose to OAR-specific threshold volume.



Supplementary Table 1. Pelvic SABR constraints for 5-fraction treatment[1] (used as cumulative maxima for determining remaining doses for re-irradiation). Where original doses were too high to allow a meaningful reRT dose to be delivered, it was left to the clinician's discretion to assume a degree of repair (thus permitting a higher cumulative total dose) and/ or under-cover the target. Also shown are constraints in EQD2 to allow comparison with calculated cumulative doses in Tables 2-3 (α/β=3Gy for all structures except nerves, where α/β=2Gy).

	Maximum dose to 0.5cm^3		**Threshold volume**	**Threshold constraint**	
	5-fraction	**EQD2**		**5-fraction**	**EQD2**
Small bowel	30Gy (optimal) 35Gy (mandatory)	54Gy (optimal) 70 (mandatory)	5cm^3 (optimal) 10cm^3 (mandatory)	25Gy 25Gy	40Gy 40Gy
Colon	32Gy	60.16Gy	-		
Rectum	32Gy	60.16Gy	-		
Vessels	53Gy	144.16Gy	-		
Sacral plexus*	32Gy	67.2Gy	5cm^3	30Gy	54Gy
Cauda equina*	32Gy	67.2Gy	5cm^3	30Gy	54Gy
Bladder	38Gy	80.56Gy	15cm^3	18.3Gy	24.38Gy
Femoral heads	-	-	10cm^3	30Gy	54Gy

* Maximum dose reported to 0.1cm^3 for neural structures

Supplementary Table 2. Mean and standard deviation of metrics for analysis of OAR overlap, following the proposed bladder-volume-guided STRIDeR DIR procedure. Cases may have undergone hybrid-only DIR, or combined DIR, dependent on bladder-volume and are analysed separately. For combined DIR, some OARs were excluded from the biomechanical step and others included, on a per-patient basis.

		Hybrid Only n=5		Combined (OAR excluded) n=0		Combined (OAR included) n=16	
Organ	**Metric**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Bladder	**DSC**	0.97	0.01	-	-	0.95	0.04
	HD	0.41	0.17	-	-	0.42	0.11
	MDA	0.03	0.01	-	-	0.07	0.02
	Precision	0.94	0.01	-	-	0.90	0.06
	Sensitivity	0.97	0.01	-	-	0.96	0.04
	Specificity	0.98	0.00	-	-	0.96	0.03
		n=4*		**n=11***		**n=3**	
Rectum	**DSC**	0.84	0.19	0.80	0.06	0.92	0.02
	HD	0.71	0.47	1.36	0.90	0.74	0.28
	MDA	0.18	0.22	0.24	0.12	0.09	0.02
	Precision	0.76	0.25	0.67	0.09	0.85	0.04
	Sensitivity	0.88	0.14	0.79	0.09	0.93	0.02
	Specificity	0.76	0.31	0.83	0.09	0.93	0.03
		n=4*		**n=4*†**		**n=5**	
Colon	**DSC**	0.56	0.24	0.29	0.11	0.74	0.10
	HD	3.67	0.89	1.53	0.83	1.01	0.38
	MDA	0.74	0.51	0.36	0.18	0.14	0.06
	Precision	0.43	0.22	0.17	0.08	0.63	0.08
	Sensitivity	0.81	0.12	0.22	0.12	0.71	0.10
	Specificity	0.16	1.73	0.73	0.16	0.93	0.03
		n=5		**n=5**		**n=16**	
Bone	**DSC**	0.90	0.07	-	-	0.86	0.05
	HD	2.18	0.78	-	-	1.69	0.65
	MDA	0.10	0.05	-	-	0.12	0.03
	Precision	0.83	0.10	-	-	0.76	0.07
	Sensitivity	0.95	0.02	-	-	0.85	0.05
	Specificity	0.87	0.14	-	-	0.90	0.05
Correlation Coefficient		**0.86**	0.06			**0.83**	0.07

*** 3 patients had undergone total or partial colorectal resection at primary treatment. Rectum and/or colon were excluded from analysis for these patients.**

† 5 patients had reRT to bone metastases or nodal volumes far from colon. Colon was therefore not included in DIR at either stage of the combined pathway and metrics were excluded from analysis.

[1] NHS England. Commissioning through Evaluation. Standards for the provision of stereotactic ablative radiotherapy. 2016.