Materials and Methods: The treatment plans for ten patients treated with a conventional approach to prostate LDR brachytherapy (145 Gy to entire prostate) were compared with plans for the same patients created with a biologically based inverse optimization planning process. To demonstrate functionality of the model, the biological optimizer applied a non-uniform distribution of tumor cell density through the prostate based on known and expected locations of tumor. Using an iterative local search approach, the algorithm determined the optimal needle and seed placement to achieve the target TCP value whilst constraining urethral doses. A range of optimization objectives were considered based on maximizing the TCP and minimizing dose to the urethra and the volume of tissue posterior to the prostate. For each clinical plan, 3 focal plans were generated based on 3 different planning approaches. The robustness of the plans was tested in the presence of random displacement of seeds.
Results: Depending on the planning approach, the volume of the urethra receiving 125% of the conventional dose prescription (145 Gy) was reduced on average from 64% (SD 17%) for the clinical plans to below 13% for the focal plans whilst maintaining high values of TCP through use of a biological optimization approach. The average number of planned seeds was reduced from 85 to less than 74 in all 3 focal planning approaches. The robustness of the plans was not inferior to the conventional plans when considering clinically realistic seed displacements. Clinically, this planning approach will use a combination of in-vivo multi-parametric MRI imaging (mp-MRI) data and biopsy data to populate the radiobiological model with patient specific tumor characteristics. Early work demonstrates that T2w, DCE, DWI and BOLD imaging are capable of providing a voxel map incorporating tumor location, tumor cell density, cell proliferation and hypoxia information. Future work is focused on modeling uncertainties in mp-MRI data and incorporating a statistical model to generate clinically robust focal brachytherapy plans using LDR or high dose rate brachytherapy.
Conclusions: We have demonstrated, using a combination of clinical and synthesized data, that a biologically based inverse planning approach to LDR treatments has the potential to maintain high rates of tumor control whilst minimizing dose to healthy tissue. The software is designed to use mp-MRI and biopsy data to inform the biological model.

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Rectal dose constraints for total and focal salvage Iodine-125 prostate brachytherapy

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Purpose/Objective: Organ-confined prostate cancer recurrences after primary radiotherapy can be curatively treated with salvage Iodine-125 brachytherapy (I-125 BT). Options include a complete re-implantation or focal salvage directed only at the recurrent tumor area. This study assesses the differences in rectal dosimetry between these two approaches and provides dose constraints to reduce late severe gastro-intestinal (GI) toxicity (>90 days after implantation).

Materials and Methods: Intraoperative dosimetry for 20 focal salvage (FS) and 28 total salvage (TS) BT patients was evaluated. Patients were treated from December 2001 until October 2012. The dosimetry recommendations for primary BT according to the American brachytherapy society (ABS) and the European Society for Radiotherapy and Oncology (ESTRO) were used. GI toxicity was evaluated using the CTCAE version 4. Differences between dosimetry variables were analyzed with a Mann-Whitney U test. Receiver operating characteristic (ROC)-analysis was used for dosimetry cutoff values to prevent late severe (≥ grade 2) GI toxicity.
Results: FS I-125 BT leads to a significant dose reduction in all analyzed parameters for the rectum compared to TS I-125 BT. Median reductions in D0.1cc, D1cc, D2cc and V100 were 38Gy (p=0.002), 46Gy (p<0.0001), 46Gy (p<0.0001) and 0.41cc (p=0.0001) for FS patients compared to TS patients (table 1). No late severe (≥ grade 2) GI toxicity was observed in the FS group. TS patients with severe GI toxicity (41%, n=11) showed significantly higher doses to the rectum than TS patients without GI toxicity (59%, n=16). The median difference in the D0.1cc, D1cc, D2cc and V100 were 29 Gy (p=0.0009), 17 Gy (p=0.001), 28 Gy (p=0.0007) and 0.45cc (p=0.001) between TS patients with and without late severe GI toxicity (figure 1). With ROC-analysis, restrictions for the D0.1cc, D1cc, D2cc and V100 are <160Gy (AUC 0.881, 95%CI: 0.755-1.000), <119Gy (AUC 0.869, 95%CI: 0.735-1.000), <102Gy (AUC 0.892, 95%CI: 0.772-1.000) and < 0.38cc (AUC 0.875, 95%CI: 0.747-1.000), respectively.
Conclusions: FS I-125 BT reduces the dose to the rectum significantly compared to TS. Centers performing TS I-125 BT have to be aware of the risk of cumulative rectal dose and subsequent severe GI toxicity. Based on these findings, the rectal D0.1cc, D1cc, D2cc and V100 should remain below 160Gy, 119Gy, 102Gy and 0.38cc.

Table 1: dosimetry differences between the focal and total salvage treatment plans

Organ	Variable	TS group (n=28)	FS group (n=20)	Median reduction	Recommendations*	p-value for difference
Rectum	D0.1cc, Gy	166 (90 - 289)	128 (90 - 181)	38 Gy	< 200 Gy	**0.002**
	D1cc, Gy	130 (59 - 185)	84 (61 - 111)	46 Gy	NA	**<0.0001**
	D2cc, Gy	111 (46 - 145)	65 (38 - 88)	46 Gy	≤ 100% (=145 Gy)	**<0.0001**
	V100, cc	0.43 (0 - 2.02)	0.02 (0 - 0.39)	0.41cc	<1 cc	**0.0001**
	V150, cc	0.01 (0 - 0.59)	0 (0 - 0.04)	0.01cc	NA	**0.037**

Abbreviations: FS=focal salvage; TS-=total salvage; Gy=Gray. Medians and their corresponding ranges are depicted.
***The recommendations are from the American Brachytherapy Society (ABS) and European Society for Radiotherapy and Oncology (ESTRO).**

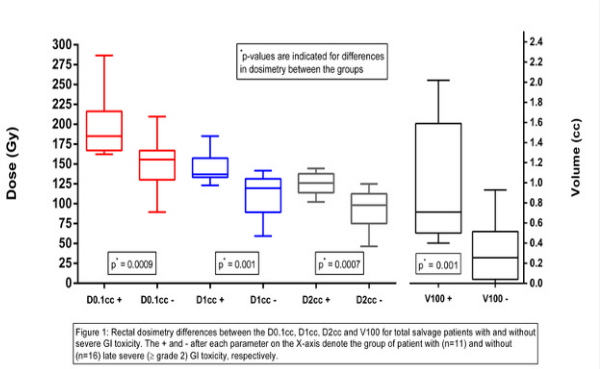

Figure 1: Rectal dosimetry differences between the D0.1cc, D1cc, D2cc and V100 for total salvage patients with and without severe GI toxicity. The + and - after each parameter on the X-axis denote the group of patient with (n=11) and without (n=16) late severe (≥ grade 2) GI toxicity, respectively.