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Abstract

Background: The present paper reports on analysis of 184 patients who were diagnosed with endometrial cancer. The main objective of this study was to address parameter $V_{rec(30Gy)}$ which determines a volume of the rectum irradiated with a dose of 30 Gy during radiotherapy.

Material and methods: All patients were irradiated with an IMRT technique on linear accelerators. The planning target volume (PTV) contour was determined by a radiation oncologist. The clinical target volume (CTV) was drawn on CT images obtained in a prone position. For statistical analysis, appropriate tests (e.g. the Shapiro-Wilk, Wilcoxon) were used.

Results and discussion: The performed analysis showed that the recommended condition for $V_{rec(30Gy)}$ is met only in 3% of patients and the observed median value exceeds 90%. The obtained results were compared with the studies in which the $V_{rec(30Gy)}$ values were related to various radiotherapy techniques.

Conclusions: The analysis showed that the condition for $V_{rec(30Gy)}$ is satisfied in the case of only 3% of patients. Due to the difficulty with meeting the condition, it should be reconsidered based on real results.

Key words: radiotherapy; medical physics; radiation oncology; endometrial neoplasms; rectum

Introduction

Modern radiotherapy techniques allow a homogeneous dose distribution to be delivered to the tumor region while minimizing the dose to the surrounding healthy tissues. The approach to protect healthy tissues depends on the structure of the organs at risk (functional subunit organization) and on the ability to repair radiation damage and restore normal function after receiving a given dose of radiation [1]. Information about dose limits for a given organ at risk — dose (Gy) or dose-volume parameters and the associated risk (%) was provided by RTOG 0418 Quantec Reports. When preparing a treatment plan, this data help to define acceptable dose limits and estimate the risk of radiation-induced complications. Endometrial cancer is the sixth most common cancer in women and it constitutes 4.4% of all cases. In 2018, about 382,069 women were diagnosed with endometrial cancer [2]. The survival is relatively high — the 5-year relative survival is about 81% [3]. With greater numbers of long-term survivors, there is a growing need to reduce the toxicity of treatment to the organs at risk and develop better ways to measure and treat late-onset side effects [4]. In the case of postoperative endometrial cancer, one of the organs at risk is the rectum. The most commonly reported side effects occurring for the rectum after radiation therapy are defecation urgency, rectal bleeding and bloating [5, 6]. To avoid such adverse effects, the RTOG Reports recommend that the dose of 30 Gy should not exceed 60% of the rectum volume ($V_{rec(30Gy)} < 60\%$). The RTOG restriction is difficult to be satisfied because of the concave-shaped target and the closeness of the rectum. The rectum is contained inside the concavity and very often has a common part with the irradiated area. During the evaluation of a treatment plan, usually two solutions are considered: acceptance of the dose distribution with an increased probability of rectal complications or sparing of the rectum with RTOG guidelines with a decreased dose in the tumor area.

Materials and methods

The retrospective study involved all 184 patients (2013–2018) treated for postoperative endometrial cancer in the West Pomeranian Oncology Center in Szczecin, Poland. The patients underwent intensity-modulated radiation therapy (IMRT) that included a therapeutic dose of 45 Gy in 25 fractions. Each planning target volume (PTV) contour was determined and constructed by a radiation oncologist following the institutional protocol. The clinical target volume (CTV) was drawn on CT images obtained in a prone position with a full bladder (at least 0.5 hour after drinking 0.7 dm^3 of water) and the empty rectum. Those CT images were fused with images performed after emptying the bladder. The CTV contour consisted of the ITV covering the parametrial and vaginal cuff (drawn on CT with a full and empty bladder) and the nodal CTV (drawn on CT with a full bladder) covering the internal, external, common iliac, obturator and presacral lymph nodes on both sides. Than the margin to generate PTV was added: 5 mm for the ITV and 8 mm for the nodal CTV. Treatment was planned in the Prowess Panther (Radiology Oncology Systems, Inc., San Diego, CA, USA), version 5.10, using 9–10 6 MeV photon beams and it was assumed that over 98% of the PTV should receive at least 95% of assigned dose, and no more than 2% of the PTV should exceed 107% of the assigned dose. The acceptable rectal dose was as that recommended by the Radiation Therapy Oncology Group (RTOG) 0418 — rectum volume < 60% to receive a dose 30 Gy. All patients were irradiated with a step-and-shoot IMRT technique on Siemens linear accelerators (Siemens Healthcare, Erlangen, Germany).

Figure 1 shows the clinical volumes used in the statistical analysis. For the numerical purposes, the Python language together with SciPy, Statistics and Matplotlib modules were used [7, 8]. The dimensionless parameter describing the ratio of the rectum volume in a target and the total rectum volume $V_{rec(tar)}/V_{rec(tot)}$ was introduced and used in the analysis. The normality of the data distribution and correlations between particular parameters were examined using the Shapiro-Wilk test and the Spearman correlation analysis, respectively. The analyzed data were compared with the results obtained in several papers [9–18] in which different types of radiation therapy used in the patient treatment were described. The statistical significance of differences between calculated values was verified by the one-sample Wilcoxon non-parametric hypothesis test. The examined $V_{rec(30Gy)}$ data were compared with respective $V_{rec(30Gy)}$ values from the mentioned papers. The objective of this prospective study was to evaluate the parameter $V_{rec(30Gy)}$ and its correlation with the naturally fixed parameters such as: rectum volume in a target ($V_{rec(tar)}$), total rectum volume ($V_{rec(tot)}$), planned target volume (V_{PTV}) and ratio of the rectum volume in target and total rectum volume ($V_{rec(tar)}/V_{rec(tot)}$). An important part of the proposed study was also the comparison of the obtained data with those from other clinical trials. Finally, the last purpose of the presented research was to create an additional statistical tool to evaluate and predict the dose distribution in the rectum by relating the obtained results to the population of patients irradiated due to postoperative endometrial cancer.

Results and discussion

The Shapiro-Wilk test showed that most of the data considered are not normally distributed (Tab. 1). For this reason the correlation analysis was performed using the Spearman method.
Table 2 gives the exact values of the Spearman coefficient and the p-value for particular data. It is noticeable that the strongest linear correlation occurs between $V_{rec(30Gy)}$ and $V_{rec(tar)}/V_{rec(tot)}$, V_{PTV} and $V_{rec(tar)}/V_{rec(tot)}$ as well as in case $V_{rec(tar)}$ and $V_{rec(tot)}$ (however, a relatively strong correlation between $V_{rec(tot)}$ and $V_{rec(tar)}$ seems to be obvious). The correlation analysis shows that there is no linear relationship between $V_{rec(tot)}$ and other parameters, or it is very weak. It is worth noting that the introduced parameter $V_{rec(tar)}/V_{rec(tot)}$ has a linear relationship mostly with $V_{rec(tar)}$ (a linear correlation of $V_{rec(tot)}$ and $V_{rec(tar)}/V_{rec(tot)}$ should be considered as irrelevant).

Parameter of interest — $V_{rec(30Gy)}$

One of the objectives of this study was to examine how $V_{rec(30Gy)}$ changes due to the naturally fixed parameters. Figures 2–5 show relations between the parameter of interest and other parameters. It is noticeable that most of the patients are generally distributed in the closeness of the highest $V_{rec(30Gy)}$ value. From a medical point of view, this is not a desirable result - in paper [9] it is strongly recommended that the limit: „Rectum < 60% to receive ≥ 30 Gy" be kept — nevertheless, this is the case.

$V_{rec(30Gy)}$ comparison

Because of the non-normal distribution of data the median was used as a measure of the central tendency. The obtained median $V_{rec(30Gy)}$ value is 93.6%. It means that the previously mentioned condition „Rectum < 60% to receive ≥ 30 Gy" is definitely not satisfied.
In this subsection, we tried to show how difficult it is to satisfy the condition presented in paper [9], in spite of the fact that in the RTOG 0418 study patients underwent postoperative IMRT with prescribed dose of 50.4 Gy in 28 fractions. The analyzed data were compared with the results obtained in several papers [9–18] in which different types of radiation therapy used in the patient treatment were described.
The examined data for $V_{rec(30Gy)}$ were compared with respective $V_{rec(30Gy)}$ values from the mentioned papers. In Table 3, the results of the Wilcoxon test are presented.
First, the significance of the difference between the condition from paper [9] and the analyzed $V_{rec(30Gy)}$ data was examined. It is not surprising that the mathematical difference between the condition $V_{rec(30Gy)} < 60\%$ and the obtained median $V_{rec(30Gy)} = 93.6\%$ value is also statistically significant (Tab. 3). A comparable value, $V_{rec(30Gy)} = 65.1\%$, is presented in paper [10], in which twenty-eight patients receiving postoperative IMRT for gynecological malignancies

were examined. From the statistical point of view, a difference between the $V_{rec(30Gy)}$ value presented in [10] and the obtained median is indisputably significant.

Paper [11], in which 10 histologically confirmed cervical cancer patients were enrolled, shows that the use of helical tomotherapy (HT) significantly decreases the average percentage of the rectum dose-volume (compared to the conventional radiotherapy) (see Tab. 3). A very similar conclusion was made in papers [12, 14] — $V_{rec(30Gy)} \sim 87-90\%$ in the case of using IMRT techniques for gynecologic treatment. Nevertheless, the presented values definitely differ from the condition $V_{rec(30Gy)} < 60\%$ from paper [9]. Although statistical comparison between $V_{rec(30Gy)}$ presented in [11] (in the case of the conventional and IMRT techniques) and the analyzed data showed significant differences (Tab. 3), both can be considered to be at similar level. To conclude, in paper [11] (as well in [12–14]) the same „problem" of relatively large values of the parameter $V_{rec(30Gy)}$ also occurred.

The ability of IMRT to reduce the volume of small bowel irradiated in women with gynecologic malignancies receiving whole pelvic radiotherapy has been investigated by in a paper by Roeske et al. [15]. The analysis was carried out on a group of ten women with cervical or endometrial cancer. The effect of radiotherapy on the bladder and rectum was taken into account. As a result, the average rectum dose-volume for 30 Gy decreased by 3.5%. Even greater volume reductions were observed for 40 and 45 Gy, 19.6% and 28%, respectively. The parameter $V_{rec(30Gy)}$ for the conventional and IMRT techniques is presented in Tab. 3. The statistical analysis showed significant differences between these values and the considered data. Nevertheless, the reported values are greater than the criterion $V_{rec(30Gy)} < 60\%$.

In paper [16] an attempt was made to compare two techniques of radiotherapy in terms of dosimetric benefits for early stage endometrial cancer patients. The study concerned the conformal radiotherapy (CRT) and the field-in-field technique (FIF). Ten patients were included in the study for whom two treatment plans were created. In the case of the FIF technique, a reduction in radiation doses was observed for most parameters, e.g. PTV. The biggest difference was observed especially for doses > 45 Gy — the irradiated volumes of OAR (organs at risk) were significantly reduced with the FIF technique. For $V_{rec(30Gy)}$ however, only the bowel irradiated volume was significantly reduced. The rectum volume irradiated by 30 Gy changed from 97.4 (FIF) to 97.7 (CRT). When compared to the analyzed data, a significant difference for the rectum volume was observed for both FIF and CRT results (see Tab. 3).

A comparison of volumetric modulated arc therapy employing a dual-layer stacked multi-leaf collimator and helical tomotherapy for cervix uteri cancer has been presented in paper [17]. A retrospective treatment planning study was performed on a cohort of 20 patients. Ten cases were selected with positive lymph nodes and 10 without positive nodes. The retrospective treatment planning study suggested the essential equivalence between Halcyon based [18] and helical tomotherapy based plans. In fact, even with the new Halcyon radiotherapy platform, the achieved $V_{rec(30Gy)}$ value exceeds 80% and 90% for node positive and node negative patients, respectively. The statistical comparison is presented in Table 3.

Figures 6 and 7 show histograms related to $V_{rec(tar)}/V_{rec(tot)}$ and $V_{rec(30Gy)}$, respectively. Additional (red and blue) lines (Fig. 7) indicate the first decile and median values for the considered parameter. The quantile analysis showed exactly the small number of patients for whom the $V_{rec(30Gy)}$ value satisfied the condition presented in [9], i.e. $V_{rec(30Gy)} < 60\%$ (see Tab. 4). In fact, the condition $V_{rec(30Gy)} = 60\%$ is the third percentile of the analyzed data.

Conclusions

The main objective of this study was to address the $V_{rec(30Gy)}$ which determines a volume of the particular organ at risk (i.e. the rectum) irradiated with a dose of 30 Gy during radiotherapy. The statistical analysis mainly included the correlation analysis between $V_{rec(30Gy)}$ and other collected parameters. The strongest correlation was observed in the case of the introduced parameter $V_{rec(tar)}/V_{rec(tot)}$.

The second part of the study concerned the problem of compliance with the condition from paper [9] - $V_{rec(30Gy)} < 60\%$. The presented analysis showed that the condition was satisfied in the case of only 3% of patients. The observed median $V_{rec(30Gy)}$ value was 93.6% and it is comparable, in mathematical sense, with the values achieved in many papers, e.g. [11–17]. Definitely, the problem with meeting the condition $V_{rec(30Gy)} < 60\%$ is not related to the radiotherapy technique. The use of relatively new techniques of radiotherapy did not solve this „problem" either. In our opinion, the condition $V_{rec(30Gy)} < 60\%$ from paper [9] should be reconsidered based on real results obtained in different radiotherapy centers.

Because of the issues mentioned above, it is difficult to propose a universal statistical tool to evaluate and predict a dose in the rectum area. Despite the significant linear correlation between $V_{rec(30Gy)}$ and $V_{rec(tar)}/V_{rec(tot)}$, it is not possible to predict the rectal dose distribution based on the introduced ratio parameter $V_{rec(tar)}/V_{rec(tot)}$.To develop a statistical tool for predicting the dose distribution in the rectum, more information should be taken into account (e.g. patient anatomy, age, etc.) — this will be the objective of our further research.

Conflicts of interest

None declared.

References

1. Malicki J, Slosarek K. Planowanie leczenia i dozymetria w radioterapii. Via Medica, Gdańsk 2016.

2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394–424, doi: 10.3322/caac.21492, indexed in Pubmed: 30207593.

3. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivor-ship statistics. CA Cancer J Clin. 2019; 69(5): 363–385, doi: https://doi.org/10.3322/caac.21565, indexed in Pubmed: 31184787.

4. Andreyev HJN. Gastrointestinal problems after pelvic radiotherapy: the past, the present and the future. Clin Oncol (R Coll Radiol). 2007; 19(10): 790–799, doi: 10.1016/j.clon.2007.08.011, indexed in Pubmed: 17904338.

5. Mitra D, Nout R, Catalano PJ, et al. Rectal bleeding after radiation therapy for endometrial cancer. Radiother Oncol. 2015; 115(2): 240–245, doi: 10.1016/j.radonc.2015.03.030, indexed in Pubmed: 26003340.

6. Kuku S, Fragkos C, McCormack M, et al. Radiation-induced bowel injury: the impact of radiotherapy on survivorship after treatment for gynaecological cancers. Br J Cancer. 2013; 109(6): 1504–1512, doi: 10.1038/bjc.2013.491, indexed in Pubmed: 24002603.

7. McKinney W. Python for Data Analysis: Data Wrangling with Pandas, NumPy, and IPython. 2 ed . O'Reilly Media, Farnham 2017.

8. Bruce P, Bruce A. Practical Statistics for Data Scientists. 50 Essential Concepts. 1st editon. O'Reilly Media, Farnham 2017: 1491952962.

9. Jhingran A, Winter K, Portelance L, et al. A phase II study of intensity modulated radiation therapy to the pelvis for postoperative patients with endometrial carcinoma: radiation therapy oncology group trial 0418. Int J Radiat Oncol Biol Phys. 2012; 84(1): e23–e28, doi: 10.1016/j.ijrobp.2012.02.044, indexed in Pubmed: 22543211.

10. Wu CC, Wuu YR, Yanagihara T, et al. Rectal balloon use limits vaginal displacement, rectal dose, and rectal toxicity in patients receiving IMRT for postoperative gynecological malignancies. Med Dosim. 2018; 43(1): 23–29, doi: 10.1016/j.meddos.2017.07.011, indexed in Pubmed: 28870525.

11. Hsieh CH, Wei MC, Lee HY, et al. Whole pelvic helical tomotherapy for locally advanced cervical cancer: technical implementation of IMRT with helical tomothearapy. Radiat Oncol. 2009; 4(1), doi: 10.1186/1748-717x-4-62, indexed in Pubmed: 20003321.

12. Georg P, Georg D, Hillbrand M, et al. Factors influencing bowel sparing in intensity modulated whole pelvic radiotherapy for gynaecological malignancies. Radiother Oncol. 2006; 80(1): 19–26, doi: 10.1016/j.radonc.2006.04.014, indexed in Pubmed: 16766068.

13. Menkarios C, Azria D, Laliberté B, et al. Optimal organ-sparing intensity-modulated radiation therapy (IMRT) regimen for the treatment of locally advanced anal canal carcinoma: a comparison of conventional and IMRT plans. Radiat Oncol. 2007; 2(1), doi: 10.1186/1748-717x-2-41, indexed in Pubmed: 18005443.

14. Mell L, Tiryaki H, Ahn KH, et al. Dosimetric Comparison of Bone Marrow-Sparing Intensity-Modulated Radiotherapy Versus Conventional Techniques for Treatment of Cervical Cancer. Int J Radiat Oncol Biol Phys. 2008; 71(5): 1504–1510, doi: 10.1016/j.ijrobp.2008.04.046, indexed in Pubmed: 18640499.

15. Roeske J, Lujan A, Rotmensch J, et al. Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. Int J Radiat Oncol Biol Phys. 2000; 48(5): 1613–1621, doi: 10.1016/s0360-3016(00)00771-9, indexed in Pubmed: 11121668.

16. Yavas G, Yavas C, Acar H, et al. Dosimetric comparison of 3-dimensional conformal and field-in-field radiotherapy techniques for the adjuvant treatment of early stage endometrial cancer. Phys Med. 2013; 29(6): 577–582, doi: 10.1016/j.ejmp.2012.11.002, indexed in Pubmed: 23219336.

17. Panda S, Swamidas J, Chopra S, et al. Treatment planning comparison of volumetric modulated arc therapy employing a dual-layer stacked multi-leaf collimator and helical tomotherapy for cervix uteri. Radiat Oncol. 2020; 15(1), doi: 10.1186/s13014-020-1473-z, indexed in Pubmed: 32000832.

18. Lim TY, Dragojević I, Hoffman D, et al. Characterization of the Halcyon multileaf collimator system. J Appl Clin Med Phys. 2019; 20(4): 106–114, doi: 10.1002/acm2.12568, indexed in Pubmed: 30889312.

Table 1. The Shapiro-Wilk test results for the data considered

Parameter	**p-value**
$V_{rec(30Gy)}$ (%)	< 0.01*
$V_{rec(tar)}$ [cc]	< 0.01*
$V_{rec(tot)}$ [cc]	< 0.01*
V_{PTV} [cc]	0.52
$V_{rec(tar)/Vrec(tot)}$	< 0.01*

Significance level = 0.05. Particular symbols denote: $V_{rec(30Gy)}$ — rectum volume (in %) with 30 Gy dose, Vrec(tar) — rectum volume in a target, Vrec(tot) — total rectum volume, V_{PTV} — planned target volume, $V_{rec(tar)}/V_{rec(tot)}$ — ratio of the rectum volume in a target and total rectum volume.*significant results

Table 2. Results of the Spearman correlation analysis

		$V_{rec(30Gy)}$	**$V_{rec(tar)}$**	**$V_{rec(tot)}$**	**V_{PTV}**	**$V_{rec(tar)/Vrec(tot)}$**
$V_{rec(30Gy)}$	Spearman coeff.	–	–0.21	–0.19	0.21	0.48
	p-value	–	< 0.01*	0.01*	< 0.01*	< 0.01*
$V_{rec(tar)}$	Spearman coeff.	0.21	–	0.65	0.37	0.71
	p-value	< 0.01*	–	< 0.01*	< 0.01*	< 0.01*

$V_{rec(tot)}$	Spearman coeff.	-0.19	0.65	–	0.06	–0.01
	p-value	0.01*	< 0.01*	–		
V_{PTV}	Spearman coeff.	0.21	0.37	0.06	–	0.48
	p-value				–	
$V_{rec(tar)/Vrec(tot)}$	Spearman coeff.	0.48	0.71	–0.01	0.48	–
	p-value	< 0.01*	< 0.01*	0.91	< 0.01*	–

*significant results (significance level = 0.05).

Table 3. One-sample Wilcoxon test results

$\mathbf{V_{rec(30Gy)}}$ **[%]**	**p-value**	**Source**	**Comments**	**Dose [Gy]/fractions**
60.0	< 0.01*	[9]	IMRT	50.4/28
65.1	< 0.01*	[10]	IMRT	–
82.2	< 0.01*	[11]	HT	50.4/28
98.4	< 0.01*	[11]	CT	
97.9	< 0.01*	[15]	CT	47.8/–
94.5	< 0.05*	[15]	IMRT	47.4/–
97.7	< 0.01*	[16]	CRT	45.0/25
97.4	< 0.01*	[16]	FIF	
81.9	< 0.01*	[17]	Halcyon (node positive patients)	45.0–55.0/25
89.7	0.5	[17]	HT (node positive patients)	
92.4	0.07	[17]	Halcyon (node negative patients)	
97.4	< 0.01*	[17]	HT (node negative patients)	

IMRT — intensity-modulated radiation therapy; HT — helical tomotherapy; CT — conventional therapy; CRT — conformal radiotherapy; FIF — field-in-field technique; *significant results (significance level = 0.05)

Table 4. Results of the quantile analysis — decile values

Deciles	$\mathbf{V_{rec(30Gy)}}$
1	70.2

2	79.0
3	84.1
4	89.8
5	93.6
6	96.4
7	99.0
8	100.0
9	100.0

Figure 1. Clinical volumes: rectum volume in a target ($V_{rec(tar)}$) outlined in blue hatched area; total rectum volume ($V_{rec(tot)}$) outlined in green; planned target volume (V_{PTV}) outlined in red

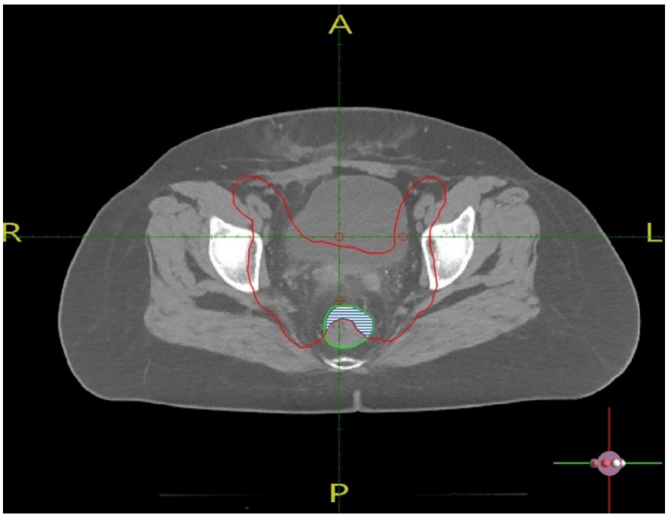

Figure 2. Patient distribution: $V_{rec(30Gy)} – V_{rec(tar)}$

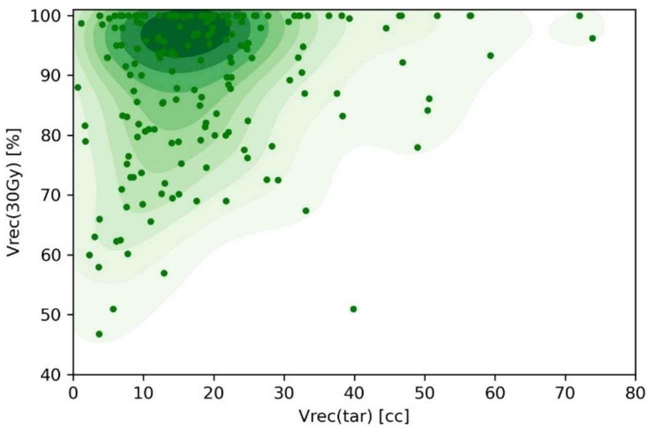

Figure 3. Patient distribution: $V_{rec(30Gy)} – V_{rec(tot)}$

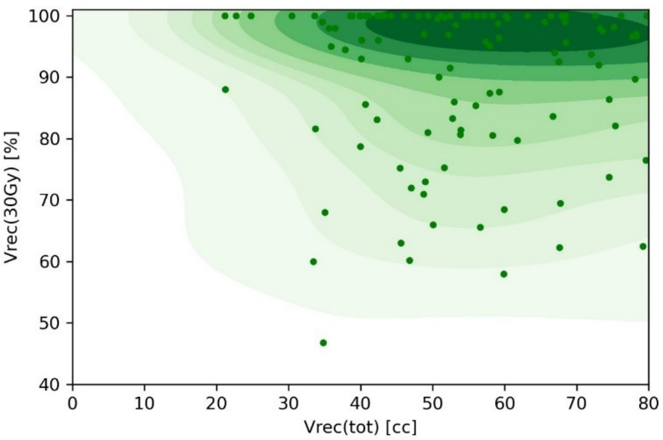

Figure 4. Patient distribution: $V_{rec(30Gy)} - V_{rec(tar)}/V_{rec(tot)}$

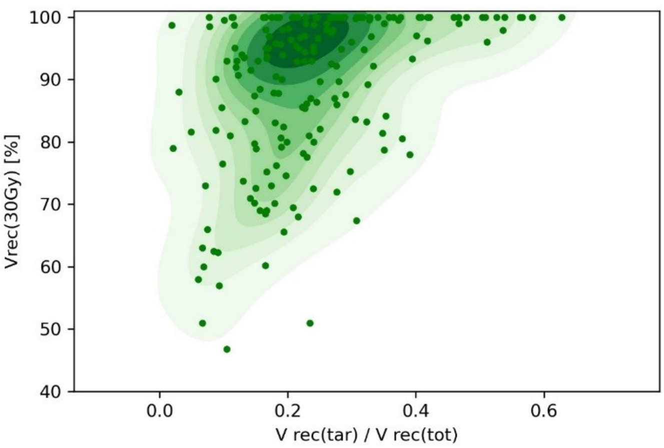

Figure 5. Patient distribution: $V_{rec(30Gy)} - V_{PTV}$

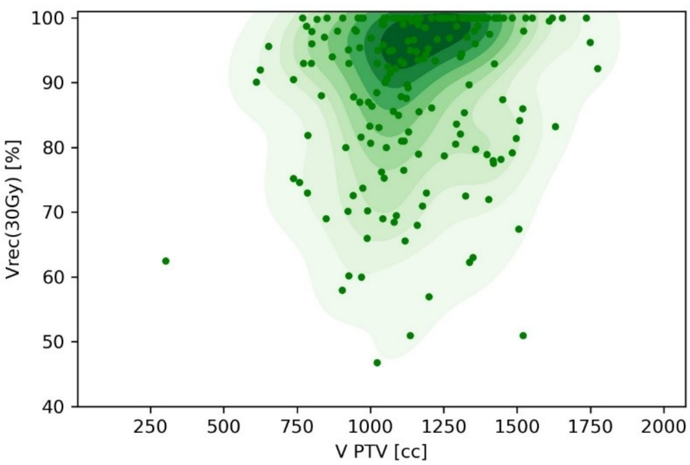

Figure 6. Histogram and patient density distribution function: $V_{rec(tar)}/V_{rec(tot)}$

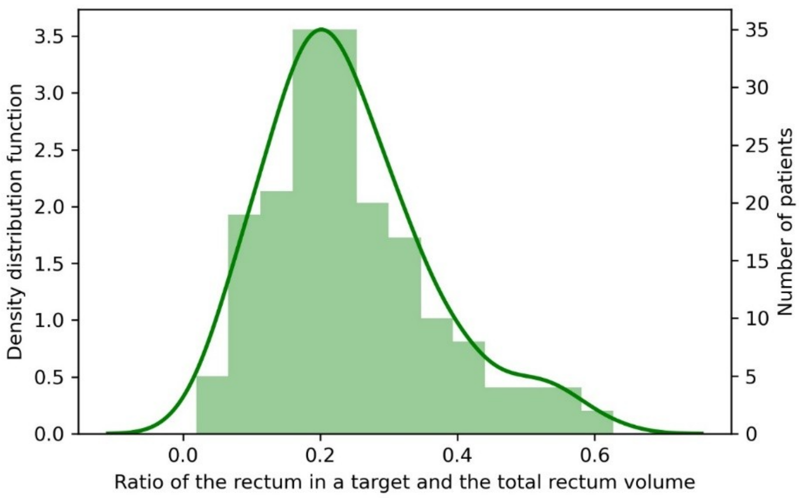

Figure 7. Histogram and patient density distribution function: $V_{rec(30Gy)}$