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Orignal Article

Importance of training in external beam treatment planning for locally advanced cervix cancer: Report from the EMBRACE II dummy run

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ABSTRACT

Background and purpose: The EMBRACE II study combines state-of-the-art Image-Guided Adaptive Brachytherapy in cervix cancer with an advanced protocol for external beam radiotherapy (EBRT) which specifies target volume selection, contouring and treatment planning. In EMBRACE II, well-defined EBRT is an integral part of the overall treatment strategy with the primary aim of improving nodal control and reducing morbidity. The EMBRACE II EBRT planning concept is based on improved conformality through relaxed coverage criteria for all target volumes. For boosting of lymph nodes, a simultaneous integrated boost and coverage probability planning is applied. Before entering EMBRACE II, institutes had to go through accreditation.

Material and methods: As part of accreditation, a treatment planning dummy-run included educational blocks and submission of an examination case provided by the study coordinators. Seventy-one centers submitted 123 EBRT dose distributions. Replanning was required if hard constraints were violated or planning concepts were not fully accomplished. Dosimetric parameters of original and revised plans were compared.

Results: Only 11 plans violated hard constraints. Twenty-seven centers passed after first submission. 27 needed one and 13 centers needed more revisions. The most common reasons for revisions were low conformality, relatively high OAR doses or insufficient lymph node coverage reduction. Individual feedback on planning concepts improved plan quality considerably, resulting in a median body V43Gy reduction of 158 cm^3 from first plan submission to approved plan.

Conclusion: A dummy-run as applied in EMBRACE II, consisting of training and examination cases enabled us to test institutes' treatment planning capabilities, and improve plan quality.

With the introduction of Image-Guided Adaptive Brachytherapy (IGABT), RetroEMBRACE and EMBRACE studies [1] have demonstrated improved local and pelvic control, improved survival [2], as well as low incidence of major morbidity in patients with locally advanced cervical cancer [3–6]. With the aim of further improving clinical outcome (both disease and morbidity endpoints), the EMBRACE study group initiated the EMBRACE II study [7,8] which includes a number of interventions based on clinical evidence from retroEMBRACE and EMBRACE [1]. In EMBRACE, external beam radiotherapy (EBRT) was delivered according to the practise of the participating centers, resulting in large variety of prescribed doses and treatment planning techniques [9]. EMBRACE II defines a joint approach to EBRT, which includes IMRT/VMAT as well as IGRT with margin reduction. The role of EBRT is to treat microscopic and macroscopic lymph node disease and provide a homogenous dose within the primary tumor target on which the steep dose gradient of brachytherapy takes off, to achieve the high dose needed to obtain high level of local control (Fig. 1). Simultaneously, the dose outside the EBRT target(s) should evidently be as low as possible.

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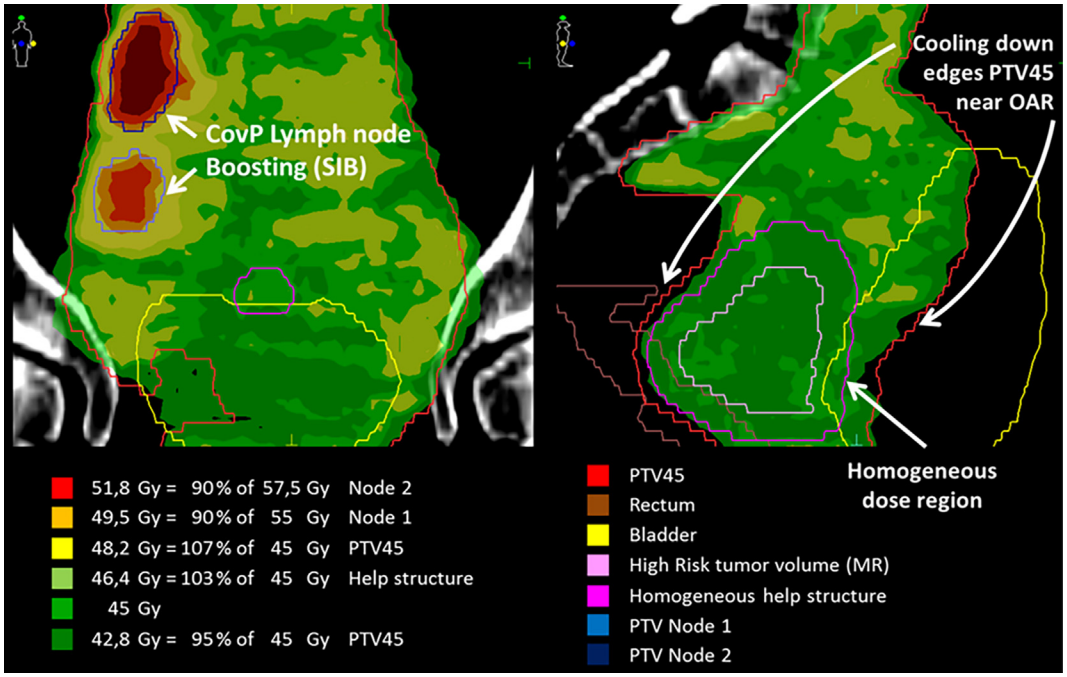

Fig. 1. EMBRACE II EBRT planning concepts. Arrows show coverage probability of nodal SIB (left panel) and in the right panel accepted underdosage at the PTV edges is shown, as well as the extra homogeneous dose region. The ITV45 is 5 mm smaller than PTV45 and should receive >95% of the prescribed dose.

Several studies [10–13] – including EMBRACE [14] – indicate that dummy runs should be standard for clinical trials: "*a comprehensive quality assurance program for radiotherapy trials should consist of a preliminary questionnaire-based credentialing for all the candidate centers and of an upfront dummy-run (or "dry run" according to RTOG/National Cancer Institute terminology), which is required to identify sources and magnitude of uncertainties and to assess the adherence to protocol guidelines*" [14]. EMBRACE II accreditation includes evaluation of centers' current practice through a "compliance questionnaire" on EBRT and brachytherapy. Furthermore, participation in dummy-runs on both EBRT and BT contouring as well as EBRT treatment planning and reporting is required. The purpose of these procedures is to ensure that centers have the infrastructure, expertise, and experience to comply with protocol requirements. This paper reports on the EBRT treatment planning dummy run.

Materials and methods

The EMBRACE II study was initiated in 2016, and by August 2018, 10 institutions had accrued 235 patients. It includes patients with histologically proven cancer of the uterine cervix, FIGO stage IB-IVB considered suitable for curative treatment with definitive radiochemotherapy and MRI guided brachytherapy.

EBRT target definition [7,8] was based on MRI and CT and included: initial GTV, initial High-Risk and Low-Risk CTV-T (Tumor) and internal target volume (ITV-T). The elective nodal target (CTV-E) was according to risk of nodal spread. ITV45 included ITV-T and CTV-E. The ITV45 to PTV45 margin was 5 mm isotropic. Patients were treated with IMRT, VMAT or tomotherapy, combined with daily on-board image guidance based on CBCT or 2D imaging with bony anatomy. A fixed dose prescription of 45 Gy in 25 fractions was applied to the targets related to the primary tumor and elective lymph nodes, respectively. The boost dose for pathological lymph nodes was recommended to be 55 Gy or 57.5 Gy in 25 fractions, depending on their location (inside and outside the true pelvis, respectively [8]), assuming that brachytherapy will contribute extra dose to the pelvic nodes [15]. The eventual choice for lymph node boost dose was left to the preference of individual institutes. The EBRT planning approach included the following principles (Fig. 1):

a. Relaxed coverage criteria for elective and primary tumor planning target volume (PTV45).
   - The requirement for PTV45 coverage was that 95% of the volume must be covered with at least 95% of 45 Gy. This means that 5% of the PTV could have received a lower dose. To prevent that this under-dosage was located within ITV45, 100% of the ITV45 was required to receive at least 95% of 45 Gy. This relaxed coverage criterion made it possible to further spare organs at risk [16].

b. Simultaneous integrated boost (SIB) and coverage probability (CovP) planning for boosted lymph nodes [17].
   - With this strategy, it was aimed to generate heterogeneous dose distributions across each PTV-N, such that CTV-N received at least 100% of the prescription dose, while the PTV-N edges could be cooled down to 90%. The center of CTV-N could have been be escalated to a max dose <107% of the lymph node prescription dose. In terms of coverage criteria, this meant that 98% of each CTV-N must have been covered by 100%, and 98% of the PTV-N must have been covered by 90% of the prescribed dose. The coverage criteria should have been applied for each node separately.

c. Special attention was needed to avoid hotspots in the region where the high brachytherapy dose would have been located.
   - To ensure homogeneous EBRT dose in the region where accumulated EBRT and BT dose was critical, a helper contour with a margin of 10 mm was generated around CTV-T HR. The dose within this contour should have been less than 103% of 45 Gy.

d. Requirements for high conformality and reduction of OAR dose.

- Bowel, bladder, rectum, sigmoid, femoral heads, spinal cord, vagina and kidneys were considered as organs at risk. Those organs differed in size and location from patient-to-patient and from day-to-day. In some patients OARs may overlap with PTV-Ns. The constraints to these organs were soft and more a statement of intent that the dose in these organs should be kept as low as possible. Centers were asked to be ambitious and optimize until the OAR dose was as low as possible without compromising target dose constraints, aiming for 70–80% compliance of all their patients. Additionally, by focusing on conformality of the dose plans and by relaxing on the coverage criteria for PTV45, further reduction of normal tissue dose could be obtained. Conformality was defined as the body volume receiving more than 43 Gy (V43Gy) divided by the PTV45 volume.

Hard and soft dose and volume constraints were according to EMBRACE II [8]. During the initial phase of EMBRACE II the EBRT constraints were updated. E.g. participating centers were working towards a slightly different soft constraint for conformality (1.15 instead of 1.1) because this constraint was less strict when the study started.

The EBRT treatment planning dummy-run consisted of different blocks:

Block 1: Three training cases with different levels of complexity based on clinical and CT-scan data were provided. For those cases, participants could develop their preferred planning policy, template or class solution and compare their results with a reviewed 'masterplan' that was available for guidance.

Block 2: At yearly international meetings, discussion and presentations about the planning approach were held in the form of a mini dummy-run and quizzes.

Block 3: Planning tricks and tips were provided on the accreditation website [18].

Block 4: Once the participants were satisfied with their training cases, they were asked to upload their results of a final dummy-run case for which no masterplan or guidance was given. Results included screenshots as well as a reporting sheet with a number of DVH parameters.

Dosimetric parameters of all original and revised plans were pairwise compared to a carefully optimized expert plan ("reference plan") which fulfilled all requirements and which had been discussed among EMBRACE study group centers.

For the final dummy-run case, this reference plan defined the expectations for participants' plans: thresholds were defined for each DVH parameter in order to categorize the given DVH parameter as "Major deviation", "Minor deviation", "good" or "excellent" (Supplementary material). "Major deviation" included hard constraints violations of more than 0.2 Gy. Negligible violations <0.2 Gy were categorized "Minor" if the rest of the parameters looked fine. The submitted plans were evaluated according to the following categories: 1: Coverage and dose in ITV45 and PTV45, 2: Coverage and dose in the two boosted lymph nodes (CTV-N and PTV-N), 3: Dose to organs at risk, 4: Dose homogeneity in helper contour, and 5: Conformality (Body V43Gy and V50Gy). Each category was scored according to the following scale: "Passed", "Passed, but could be improved", "Minor deviation" and "Major deviation" based on the performance of DVH parameters within each category. Individualized written feedback was provided for each category. Re-submission of revised plans was requested if there was a category with "Major deviation" or if there were several categories scored with "Minor deviation". For plans that were considered to be suboptimal, suggestions for revision were given, depending on the nature of deviations. Centers that boosted the lymph nodes to another dose than suggested by EMBRACE II, were free to re-submit. After evaluation of the first ~15 institutions, it was increasingly realized that the institutions were capable of achieving plans of quality similar to the reference plan, regardless of their technique and planning system, and the criteria for revision and feedback became a little stricter.

Results

By December 2018, 71 institutes had completed submission of which, at this time point, 67 EBRT plans were approved. IMRT, VMAT and tomotherapy were used in 7%, 88% and 5% of the centers, and 6, 10 and 15 MV in 71%, 24% and 5% of centers, respectively. It was possible to produce acceptable plans with all techniques, energies, and treatment planning systems. Eleven submitted plans (15%) violated hard constraints.

After first submission, 27 plans were directly approved, 27 plans after one feedback round. 13 plans had to undergo a second or third revision before approval regarding the new planning concepts. Two centers resigned before revision and two did not yet send in their revised plan. The overall number of reasons for improvement can be found in Fig. 2. The most common deviations were a high conformality index and insufficient reduction of dose to OARs. Six participants made an institutional decision to irradiate nodes to a different dose level than the reference plan, which is still according to the protocol. 52% of the passed centers participated in the annual meetings. They needed significantly fewer revisions (60% of the plans needing revision were sent in by non-participants, $p = 0.04$) and showed a better plan quality (Supplementary material).

Table 1 shows the achieved dose and volume parameters in targets and organs at risk for all passed and rejected plans as well as for the difference between first submissions and passed plans for institutions with at least one revision.

The majority (70%) of passed institutes cooled down edges and reduced coverage (V95) to 95–97.5% (Fig. 3). In original plans with V95 >97.5% and high organ doses, we guided the institutions to exploit the option of lowering doses at the PTV45 edges to lower the dose to OARs and body V43Gy. As a result, for revised plans, PTV coverage reduced with median 2%, resulting in a median body V43Gy reduction of 158 cm^3 (Fig. 3 and Table 1) and a general reduction of OAR doses. Fig. 4 shows the importance of cooling down PTV edges: in the dataset of all submitted plans, PTV V95% and conformality were correlated ($r = 0.65$, $p << 0.001$).

Lymph node coverage (Fig. 3), also improved for passed plans for both nodes. Although V50Gy for bowel was not specified as a hard constraint, the effect of cooling down lymph node edges resulted in median reduction of V50Gy of 1.8 and 13 cm^3 for bowel and body, respectively (Figs. 3 and 4).

Soft constraints for rectum were met for all submitted plans and for vagina (PIBS-2 cm point [19]) in all but 2 rejected plans. Encouragement to reduce dose even more in the recommendation letters resulted in reduction of rectum V40Gy of 5 percentage points. The variation (SD) between all plans reduced considerably for both OARs.

For bladder, a seven percentage point reduction was shown for the V40Gy after revision. Eight final plans were still above the soft constraint of 80% (max 88.7%) for V30Gy. Because the deviations were small and within normal variation and the V40Gy constraint was met in all cases, those plans were approved.

Although the variability between plans reduced after feedback, even for approved plans with all hard constraints met, plan quality still varied. The variation of all passed plans shows what is achievable with respect to plan variation between planners. For the target this can be reduced to 1–2%, but for the OARs 5–15% is more realistic. For example, the difference between the best and worst

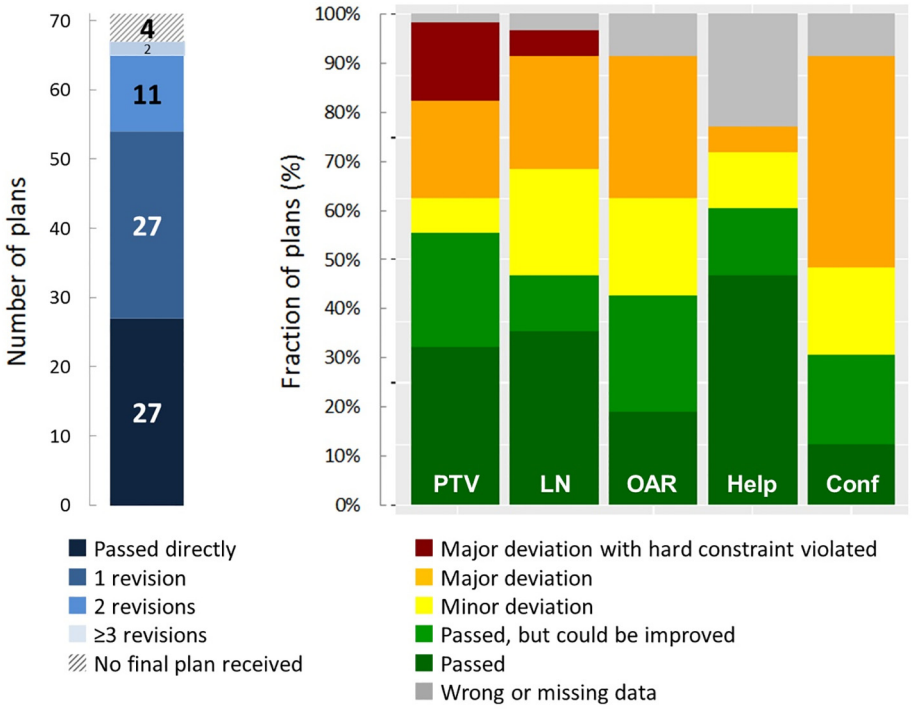

Fig. 2. Left panel: overview of the number of centers that passed directly or after one or more revisions. Right panel: compliance on different plan components of the plans needing revision. Note that an institute could have had more than one revision and different scores for each of the categories.

Table 1
Plan parameters and their median, SD values for all the passed plans, all rejected plans and the paired analysis between first and last plans submitted by centers that had at least one plan rejected. Before feedback, the variance was ~twice as high*. Minimum dose for ITV45 was defined as D99.9%.

Parameter	constraint	Passed	SD	(%)	Rejected	SD	(%)	Paired analysis Difference after revision (rejected – passed)
Nr of plans		68			55			38
PTV45 (%) V95	95	**96.8**	1.4	1%	**98.8**	2.2	2%	**2**
ITV45 (Gy) mindose	42.75	**43.4**	0.5	1%	**43.6**	1.1	2%	**0.3**
PTV-N1 CovP	90	**92**	2	3%	**97**	5	5%	**3**
PTV-N2 CovP	90	**92**	3	3%	**96**	4	4%	**2**
Conformality*	1.10	**1.04**	0.05	4%	**1.13**	0.15	13%	**0.06**
Bowel (cm^3) V30Gy	500	**431**	59	14%	**476**	100	21%	**64**
Bowel (cm^3) V40Gy	250	**164**	20	12%	**194**	51	27%	**34**
Sigmoid (%) V30Gy		**89**	8	9%	**92**	8	9%	0
Sigmoid (%) V40Gy		**69**	6	8%	**73**	8	11%	**2**
Bladder (%) V30Gy	80	**72**	9	12%	**75**	12	16%	**5**
Bladder (%) V40Gy	60	**42**	5	11%	**48**	11	22%	**7**
Rectum (%) V30Gy	95	**72**	5	7%	**75**	7	10%	0
Rectum (%) V40Gy	75	**51**	7	13%	**58**	11	18%	**5**
PIBS-2 cm (Gy)	5	**2.7**	0.5	19%	**2.8**	1.1	38%	0
Body (cm^3) V43Gy		**1731**	74	4%	**1883**	247	13%	**158**
Body (cm^3) V50Gy		**39**	11	29%	**52**	27	52%	**13**

For the paired analysis (t-test), bold values indicate statistically significant differences ($p < 0.05$).

approved plan was 310 cm^3 for body V43Gy. In Fig. 5, approved dose distributions of different centers are visualized.

The bowel V15Gy was not significantly different between tomotherapy, IMRT and VMAT plans. It was in the same range for 6MV and 10 MV plans, and somewhat lower for 15MV plans. However, the number of plans was too small for identifying statistically significant differences.

Discussion

Training, monitoring and early intervention in case of discrepancies is valuable to achieve a high consistency in plan quality among centers in multicenter trials – not only in measurable parameters but also in concept. This helps avoidance of protocol deviations that can lead to decrease of tumor control [20] or suboptimal planning that can lead to increased complication risk [21].

This analysis shows that even with a strict EBRT protocol there were significant variations in planning approach and plan quality between institutions accrediting for EMBRACE II. Through training and individual feedback, plan quality and consistency improved. We mainly experienced that improved organ sparing could be achieved; while clinically relevant violations of hard constraints were rarely seen. Individual feedback significantly reduced the body V43Gy by a median of 158 cm^3, which is likely to be of clinical relevance with regard to normal tissue complications [4,10,22–27]. This is especially important in large multicenter studies that aim to reduce EBRT related morbidity through reduction of irradiated volumes.

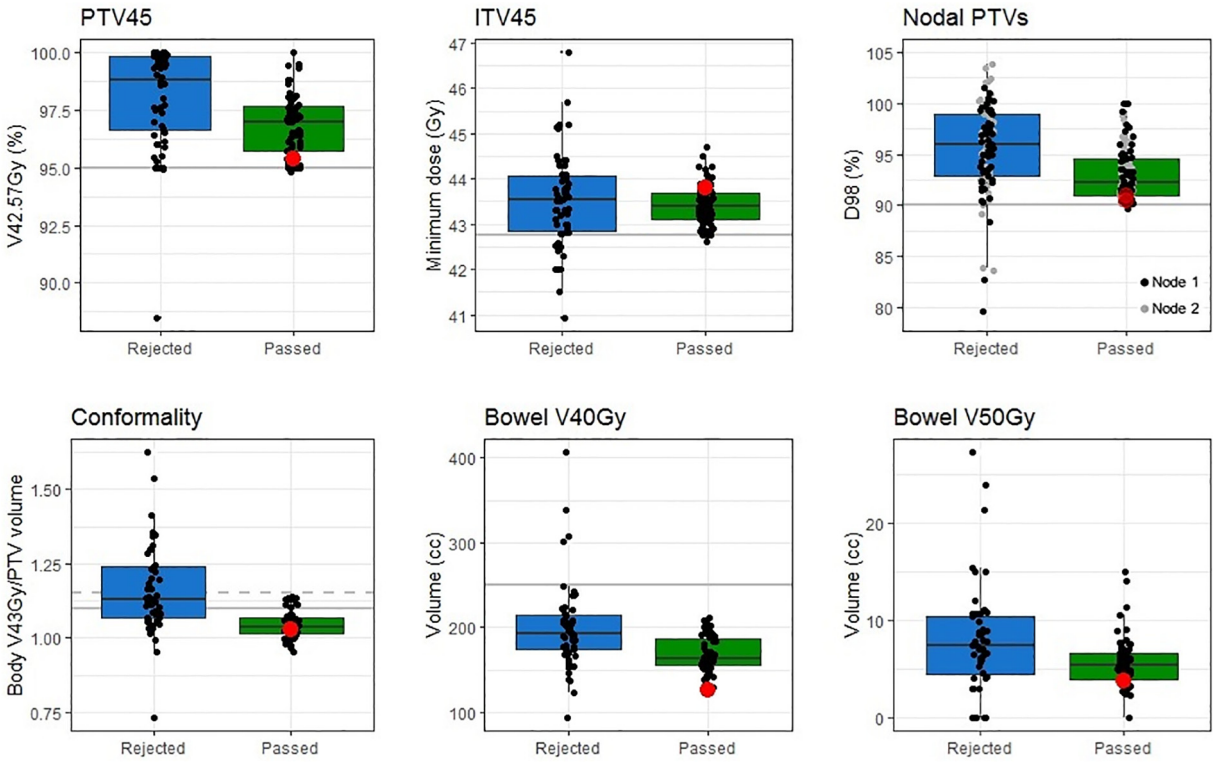

Fig. 3. Average and 25%/75% percentile values for *all* rejected (blue) and passed (green) plans for different dose–volume parameters. Solid lines: constraints*. Red dots: reference plan. Minimum dose for ITV45 was defined as D99.9%.* *Note* that for conformality, the soft constraint was less strict when the study started, indicated with a dashed line in the figures.

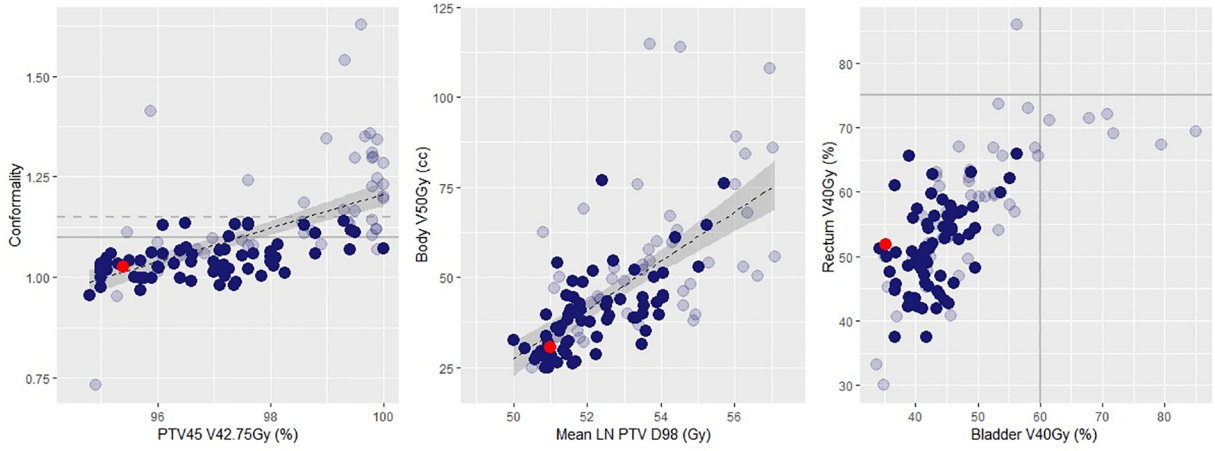

Fig. 4. Correlations between EBRT dose parameters for rejected (transparent circles) and passed (filled circles) plans. Soft dose constrains are indicated by a solid line*. Black dotted lines are fitted trend lines for all plans. Red dots: reference plan. **Note* that for conformality, the soft constraint was less strict when the study started, indicated with a grey dashed line in the left figure.

Photon beam energy, delivery technique and treatment planning system appeared to be of minor importance, as was also found by [28]: the highest possible degree of normal tissue sparing in a specific patient depends profoundly on individual anatomy. The compliance of a dose plan to fixed constraints alone is not a good indicator of plan quality, because for patients with favorable anatomy, fulfilled constraints – as in this dummy run example – do not indicate whether organ doses are as low as possible. In case of unfavorable anatomy (which was not the case for our dummy run patient), dose constraints may be exceeded even if the plan is optimal in the sense that organ doses cannot be further lowered while respecting certain target coverage.

All plans in this study required tweaking, even if templates/-class solutions were built in advance based on the training cases or institutional cases; it was not possible to obtain the 'optimal treatment plan' in one step by using pre-set constraints and objectives. This reflects very well the problems that treatment planners face every day: it is not a-priori known how far parameters can be improved. In a clinical planning environment there are no resources for individual feedback based on multiple planning

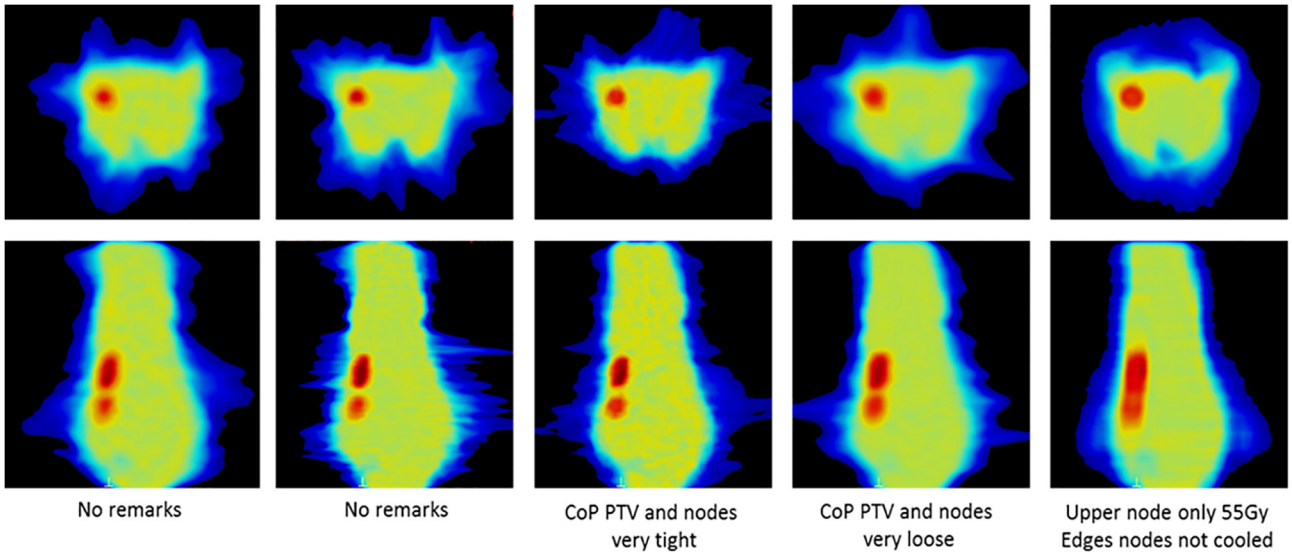

Fig. 5. Representative approved dose distributions of 5 centers. Although all plans were based on the same prescription protocol and all constraints were met, differences within the limits exist, depending on individual optimization characteristics and planning preferences.

systems and treatment techniques. This advocates any form of (pareto optimal) automated treatment planning where in the training phase of the systems much attention is given to discuss plan quality for each training case individually [29]. Especially systems that use knowledge based automated planning [30–32] should gather their optimal DVH shapes from reviewed and re-optimized plans instead of plans selected from routine clinical practice.

Previous studies on coverage probability planning [17,33] as well as this study, show that relaxed coverage criteria can lead to significant reduction of normal tissue irradiation. The new approach can be challenging as institutions are not used to the 90% or 95% coverage criteria for PTVs. Some treatment planning systems cannot steer the optimization to cover exactly 95% of the PTV to 95% of the prescribed dose, as some systems intrinsically assume that a high coverage is aimed for and optimize accordingly. Furthermore, many US centers have requirements to have the 100% isodose cover the target and therefore tend to have a higher mean dose to the target [34]. Despite these challenges, it was in general possible to train the institutions to work in the direction towards relaxed coverage criteria.

Many dummy runs combine delineation and treatment planning [35–38]. The large contouring variations that are present, also for cervical cancer delineation [39] make it hard to distillate differences that are pure treatment planning issues. Sharing plan data and philosophy is found to improve protocol understanding [40]. We therefore decided to separate contouring and planning dummy runs and focus on individual training and feedback. Feedback was not only about target coverage, which is generally well obeyed, but also very specific regarding soft constraints and OAR doses. Contouring variations will be discussed in a future paper.

The institutional practice in EMBRACE II may not follow the quality as found in approved dummy run plans, especially because individual feedback will be absent, as the examination was based on a single patient, and as the examination was per institution and not per treatment planner. In order to monitor post-dummy-run plan quality, the last EMBRACE II accreditation step is that 5 prospective clinical patients will be reviewed by the study group. Furthermore, throughout the EMBRACE II study, continuous monitoring of enrolled patients will be carried out. If a given center shows deviations, specific communication will be initiated to identify the source and to discuss a strategy that prevents similar deviations in future patients.

In conclusion, introducing new and complex planning concepts for a multi-institutional study requires well described concepts and balanced constraints and objectives. An accreditation and dummy-run procedure as applied to EMBRACE II enables testing institutes' capabilities and to train them on treatment planning. Individual feedback significantly improves plans and enables identification of planning problems.

Conflict of interest

The EMBRACE studies are supported by Varian Medical Systems and Elekta. The financial support by the Austrian Federal Ministry for Digital, Business and Enterprise and the National Foundation for Research, Technology and Development is gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.01.012.

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