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Research article

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Harmonization of breast cancer radiotherapy treatment planning in the Netherlands

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ARTICLE INFO

Keywords: Breast cancer Radiotherapy Treatment planning Consensus Guideline National

ABSTRACT

Purpose: The aim was to reach consensus in The Netherlands on which parameters should be used to evaluate breast cancer radiotherapy (RT) plans.

Materials and methods: A Benchmark Case with delineated planning target volumes (PTVs) and Organs At Risk (OARs) was sent to all Dutch radiotherapy centres in combination with a questionnaire, with the request to generate RT plans prescribing 15 times 2.67 Gy for four different treatment indications according to the institutional irradiation technique. The plans and accompanying questionnaire answers were analysed using descriptive statistics. These results, together with a harmonisation proposal, were sent to all centres. The proposal was discussed at a meeting of the Dutch Society of Radiation Oncology breast cancer platform. Distinct parameters were accepted if consensus on them was reached.

Results: 19 out of 20 Dutch departments participated in this study. PTV coverage varied considerably, with D98% between 63% and 99% for the breast and between 37% and 97% for the internal mammary nodes (IMN). Also substantial OAR dose differences were observed, with e.g. mean heart doses ranging between 1.85 Gy and 5.42 Gy in case the IMN were included in the PTV. For evaluation of the PTVs D98%, D2% and Dmean were chosen to report on, with target values of \geq 95% (90% for the PTV_IMN), \leq 107%, and 99–101%, respectively. For OARs, consensus was reached on the parameters to be evaluated, without target values: Dmean of the heart, Dmean and V5% of the lungs, and in case of periclavicular radiotherapy V30Gy of the thyroid gland. For patients younger than 40 years a contralateral mean breast dose of \leq 1 Gy was agreed upon.

Conclusion: A new Dutch consensus guideline for evaluation of breast cancer RT plans has been established.

Introduction

Postoperative breast cancer radiotherapy (RT) reduces the risk of local recurrence with a factor of 3–4 [1]. In The Netherlands the standard schedule for breast radiotherapy has been 15 fractions of 2.67 Gy since 2013, based on 10-year follow-up results of the START B trial [2]. When designing an RT plan, a continuous trade off between optimal dose to the target versus optimal sparing of organs at risk (OAR) needs to be made. As the relationship between dose-volume parameters, local control and side-effects is not very clear, and because the acceptance of a

local recurrence risk and side effects differ per physician and per patient, a wide practice variation exists in the trade-offs made. To be able to adequately compare the quality of RT plans, there is a need for consensus about dose-volume parameters to be evaluated for both target volumes and organs at risk. There is however a reasonable consensus about delineation of target volumes and OARs for breast cancer patients [3–5].

In treatment plan comparison studies, often the volume receiving 95% (V95%) or 107% (V107%) of the prescribed dose is used as a criterion to evaluate the RT plan [6], while the dose received by 98%

https://doi.org/10.1016/j.tipsro.2021.06.004

Received 22 June 2021; Received in revised form 29 June 2021; Accepted 30 June 2021

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(D98%) and 2% (D2%) of the volume [7] or the dose to 99% and to maximally 2 cc [8] can also be used. Some studies use the homogeneity index (HI) and conformity index (CI) as the main target volume parameters to compare plans [8,9] or a combination of HI, V95% and V107% [10].

In addition, the exact target volume for which dose evaluation criteria are reported varies; some studies report the dose to the breast and lymph nodes combined, others separately report the dose to the breast and dose to the lymph nodes [10], while some report the dose to the breast and to each individual lymph node level.

Furthermore, clinical factors like age or co-morbidity, are often implicitly taken into account during clinical plan evaluation. This variety of contributing factors may introduce interobserver variation in plan evaluations. Such factors should be taken into account in plan comparison studies as they might help in the development of even more patient specific tailored treatments.

Therefore, the aim of the current work was to develop a national consensus guideline on which dose volume and clinical parameters should be used in the evaluation of breast cancer radiotherapy plans irrespective of the irradiation technique used, using 15 fractions of 2.67 Gy, as this was the national consensus fractionation at that time.

Materials and methods

Outline of the study

First, a questionnaire was developed to gain insight into local protocols and local trade-offs that are applied for RT plan-optimization and evaluation. Second, target volumes were delineated for a CT-scan of a randomly selected left-sided breast cancer patient who had undergone a lumpectomy. Both the questionnaire and the delineated CT scan were subsequently sent out to all 20 Dutch RT centres with the request to make four different RT plans for four different target volumes, according to their local protocols and using their own RT technique, without altering the delineation. After analysis of the RT plans and questionnaires, a concept-protocol was developed for RT plan evaluation. Finally, a consensus meeting was organized with the Dutch Society of Radiation Oncology Breast cancer platform which led to a finalized consensus protocol.

Questionnaire

The questionnaire included a table in which those volumes considered for RT plan optimization and evaluation, and DVH criteria used for these volumes could be filled in. In addition, four questions were asked related to possible compromises in target coverage that might be made

Table 1

Results of the benchmark cases performed by 19 centres, presented according to the parameters as agreed upon during the consensus meeting together with the conformity index.

		Median (min–max):out of tolerance ^a	Median (min–max):out of tolerance	Median (min–max):out of tolerance	Median (min-max):out of tolerance
Volume	Criterion	Case A	Case B	Case C	Case D
PTV_Breast ^b	D98% (%) > 95%	96 (63–98): 3	95 (66–98): 2	95 (87–100): 6	95 (90–98): 3
	_ Dmean (%) 100%± 1%	100 (98–101): 1	107 (106–109)	100 (99–102): 4	101 (100–103): 5
	D2% (%) ≤ 107%	104 (102–105): 0	125 (122–128)	104 (102–106): 0	105 (103–110): 1
	Conformity	0.76 (0.72–0.81)	0.72 (0.66–0.80)	NA	NA
Lungs	Dmean (cGy)	205 (150–226)	287 (256–385)	505 (363–770)	680 (565–910)
	V5Gy (%)	8 (5–9)	13 (10–23)	20 (17–27)	26 (24–40)
Heart	Dmean (cGy)	150 (81–192)	178 (107–275)	179 (115–352)	310 (185–542)
Contralateral breast	Dmean (cGy)	35 (13–77)	48 (15–165)	64 (23–113)	169 (37–501)
Thyroid	V30Gy (%)	0 (0–0)	0 (0–0)	1 (0–15)	1 (0-6)
PTV_Boost	D98% (%) ≥ 95%	NA	95 (94–98): 1	NA	NA
	Dmean (%)	NA	100 (98–101): 1	NA	NA
	D2% (%)	NA	103 (101–106): 0	NA	NA
	Conformity	NA	0.79 (0.70–0.88)	NA	NA
PTV_N1n2pect ^c	D98% (%) ≥ 95%	NA	NA	94 (89–99): 8	95 (89–98): 7
	Dmean (%)	NA	NA	100 (98–102)	100 (99–102)
	D2% (%)	NA	NA	103 (101–106)	103 (101–106)
PTV_N3n4 ^d	D98% (%) ≥ 95%	NA	NA	94 (79–98): 12	95 (79–97) : 7
	Dmean (%)	NA	NA	100 (98–103)	100 (98–102)
	D2% (%)	NA	NA	105 (102–108)	104 (102–107)
PTV_IMN ^e	D98% (%) ≥ 90%	NA	NA	NA	89 (37–97): 8
	Dmean (%)	NA	NA	NA	99 (96–102)
	D2% (%)	NA	NA	NA	105 (103–107)

^a : Number of plans that did not meet the evaluation criterion as agreed upon during the consensus meeting.

^b : All target volumes are expansions of their respective CTV by 5 mm and are clipped 5 mm below the skin.

^c PTV_N1n2pect: PTV of the lymph node levels 1 and 2 and the interpectoral lymph nodes.

^d PTV_N3n4: PTV of the lymph node levels 3 and 4.

^e PTV_IMN: PTV of the internal mammary lymph nodes.



Fig. 1. The results for Case A are given for the 3 institutes that had either a relatively poor or good treatment plan. The values given in this figure are the relative values as compared to the average values found over all institutes. For example, institute C had a 1.41 times higher mean heart dose than the mean heart dose averaged over all 19 institutes. RVR: Remaining Volume at Risk.

in clinical practice (Supplementary Questionnaire A1).

Benchmark cases

Target volume delineation of the breast, regional lymph nodes and tumour bed was performed based on the ESTRO guidelines [3]. The heart, lungs, thyroid, humeral head and contralateral breast were delineated as OAR. The participating RT centers were requested to submit the following four photon treatment plans, without altering the delineations: Case A: irradiation of the breast only with a fractionation of 15*2.67 Gy. Case B: irradiation of the breast including an integrated boost of 20*2.18/2.67 Gy. Case C: irradiation of the breast and the regional axillary and periclavicular lymph nodes (level 1 to 4 and the interpectoral lymph nodes) with a fractionation of 15*2.67 Gy. Case D was equivalent to case C, but also including the left sided internal mammary lymph nodes (IMN). Clinical details of patient and tumour characteristics were also provided (Supplementary Table A1). For all cases, the skin was not considered to be at risk for invasion and thus not part of the CTV.

Treatment plan results were centrally collected and processed using Raystation v.8b (Raysearch, Stockholm). Several DVH, average dose and conformity data were thereafter imported in Microsoft Excel 2013 to generate descriptive statistics (e.g. median, range) over all plans per submitted case. Among others, D98%, D2%, Dmean and the van 't Riet conformity index [11] were evaluated for the PTVs.

Consensus meeting

The DVH analyses, in combination with data from literature and the results of the questionnaire, were used to formulate a consensus proposal. The results and the proposal were sent to all RT centres in the Netherlands with the request to analyse the proposal and collect feedback from the colleagues in their own department.

The proposal was thereafter discussed at a consensus meeting of the

Dutch Society of Radiation Oncology breast cancer platform, in which representatives from all RT centres in the Netherlands participated. The platform consists of both radiation oncologists as well as medical physicists of all radiotherapy centres in the Netherlands specialized in breast cancer radiotherapy. During this meeting the proposal and suggestions for adaptations were discussed per evaluation item and per target volume and OAR. Distinct evaluation parameters were accepted if consensus on them was reached, i.e. if no one objected. The revised proposal was thus formulated and formally approved by the platform.

Results

Results of the questionnaire

19 out of 20 Dutch departments participated in the questionnaire and the benchmark study. One institute did not participate due to time limitations. A wide variation between local protocols was seen: institutes cropped Clinical target volumes (CTVs) and planning target volumes (PTVs) with various margins beneath the skin, and PTV_Breast was sometimes also cropped to exclude the lungs, again with various margins.

Institutes used a variety of PTVs combinations for evaluation, varying from one PTV for all target volumes, to evaluation of each lymph node level and PTV_Breast separately. The PTV evaluation parameters used clinically also varied considerably, as nine different dose/volume criteria for PTV coverage were reported.

Of the OARs, the heart and lungs were used most often. The mean dose was regularly used as an evaluation criterion for these OARs, while the corresponding constraint varied strongly between centres (Supplementary Table A2). For the lungs, sometimes one or more other DVH criteria were used, which also differed per institute. Relatively few institutes included the thyroid, spinal cord, humeral head or brachial plexus as OAR [12].

All institutes replied that sometimes compromises were made in



Fig. 2. Axial CT slice showing the dose distribution for Case A for respectively institutions C, G and N.

target coverage. Half of the institutes take clinical factors into consideration when delineating the CTV. The main clinical factor considered during CTV delineation is tumour location, but also cardiac and pulmonary risk factors are considered. Smoking history and gene-mutations were rarely reported as a reason to compromise PTV coverage. Clinical factors were generally not considered in the expansion of the CTV to PTV. When compromises in target coverage were made, this was usually done without predefined criteria (See Supplementary Table A1 for more details).

Results of the benchmark cases

The overall results of the planning study are given in Table 1. The results for the individual institutes are given graphically in the appendix (Supplementary Figs. A1 to A4).

The D98% for the PTV of the locoregional lymph node volumes was in general somewhat lower than for PTV_Breast, and was the lowest for PTV_IMN. For case B, a large variation in boost dose conformity values was found (range: 0.70 to 0.88). The median dose did not differ much from the mean dose, with an average difference of 0.5%, 0.2%, 0.4% and 0.2% for the dose to PTV_Breast for cases A to D, respectively.

In Figs. 1 and 2, the results for case A are given for three institutes which had either a relatively poor or good treatment plan to illustrate the variety in treatment plan quality. Institute C had higher OAR doses with almost equal target coverage as the institutes N and G, indicating that institute C could improve its treatment plan. Both institutes N and G had a relatively low heart and lung dose, but the PTV coverage (D98%) of institute G was much lower than the average D98% over all centres. This was caused by blocking the heart with a margin of 5 mm in the tangential fields. In addition, in institute G the dose to the target volume was evaluated using a PTV which excludes the 5 mm closest to the heart seen from the beams-eye-view of the tangential fields. As such, they do not report the lower DVH value of the original PTV.

The institutions were actually requested to repeat the benchmark 4 months after consensus was reached. For completeness, results of the second benchmark are given in Table 2. Not much difference was observed between the first and second benchmark.

Results of the consensus meeting

At the consensus meeting, the results of the planning study and the proposal for DVH criteria for plan evaluation were discussed. DVH criteria for which consensus was reached are summarized in Tables 3 and 4; the parameters for which no consensus was reached are given in Table A3 in the Appendix.

Consensus for target volumes

It was agreed that both CTV and PTV should be clipped 5 mm below the skin for reporting purposes. It also became clear that the breast CTV is sometimes deliberately delineated smaller than prescribed by the guidelines, in order to facilitate sparing of the OARs while still reaching the required target coverage. While this might lead to an acceptable plan, this hampers proper reporting of the actually planned dose to the breast if it would have been defined according to the guideline. It was therefore agreed to adhere to the delineation guidelines and, in case of underdosage, to report the reason why this was accepted.

For all cases, consensus was obtained to use D98%, Dmean and D2% as parameters to evaluate the near minimum, mean and near maximum dose, as D98% and D2% are also recommended by ICRU 91 [13]. There was some discussion regarding whether it would be better to evaluate Dmedian, as recommended by ICRU 91, instead of Dmean. As the general consensus was that these two values would not differ much and that Dmean is reported in most treatment planning systems, contrary to Dmedian, it was decided to choose Dmean as parameter.

It was agreed that D98% should be \geq 95% and D2% should be \leq 107%, largely matching with the ICRU recommendation. There was also consensus to strive for a Dmean within plus or minus 1% from the prescription dose for the breast in plans without a boost.

In the draft, the suggestion was made to optionally evaluate the dose values for the CTV, to make plan comparisons with proton plans easier, as proton plans usually report dose to CTV and not to PTV. However, as photon plans would need to be based on a probability based planning for a proper comparison with proton plans, this motion was not supported.

In case of breast with boost plans, it was agreed upon that Dmean should be evaluated for the boost PTV (PTV_Boost). However, striving to

Table 2

Results of the repeat Benchmark Case performed by 17 centres F and P did not repeat the Benchmark Case). Some institutes improved their treatment plan. As a consequence, the number of out-of-tolerance values reduced slightly.

		Median (min–max): out of tolerance ^a	Median (min–max): out of tolerance	Median (min–max): out of tolerance	Median (min–max): out of tolerance
Volume	Criterion	Case A-Repeat	Case B-Repeat	Case C-Repeat	Case D-Repeat
PTV_Breast ^b	D98% (%) Dmean (%) D2% (%) Conformity	96 (63–98): 1 101 (98–102): 2 104 (102–106): 0 0.76 (0.72–0.82)	96 (66–98): 1 108 (106–110) 126 (123–128) 0.71 (0.67–0.80)	96 (87–98): 3 100 (99–103): 4 104 (102–106): 0 NA	95 (90–97): 2 101 (99–103): 2 104 (103–107): 0 NA
Lungs	Dmean (cGy)	194 (142–235)	275 (232-391)	493 (406–563)	628 (531-910)
	v5Gy (%)	8 (6–10)	12 (9–23)	21 (17-23)	25 (20–40)
Heart	Dmean (cGy)	137 (80–189)	169 (104–233)	179 (125–267)	290 (186–542)
Contralateral breast	Dmean (cGy)	38 (13–68)	45 (15–164)	64 (13–210)	143 (32–501)
Thyroid	V30Gy (%)	0 (0–0)	0 (0–0)	1 (0–15)	1 (0–3)
PTV_Boost	D98% (%)	NA	95 (95–99): 0	NA	NA
	Dmean (%)	NA	100 (98–103): 3	NA	NA
	D2% (%)	NA	104 (102–105): 0	NA	NA
	Conformity	NA	0.76 (0.64–0.88)	NA	NA
PTV_N1n2pect ^c	D98% (%)	NA	NA	96 (89–99): 4	96 (92–98): 2
	Dmean (%)	NA	NA	100 (99–101)	100 (98–103)
	D2% (%)	NA	NA	104 (102–105)	104 (102–105)
PTV_N3n4 ^d	D98% (%)	NA	NA	95 (91–98): 9	96 (93–97): 4
	Dmean (%)	NA	NA	100 (99–102)	101 (99–102)
	D2% (%)	NA	NA	104 (102–107)	105 (101–107)
PTV_IMN ^e	D98% (%)	NA	NA	NA	92 (0.77–0.95): 4
	Dmean (%)	NA	NA	NA	100 (98–102)
	D2% (%)	NA	NA	NA	105 (102–107)

^a : Number of plans that did not meet the evaluation criterion.

^b : All target volumes are expansions of their respective CTV by 5 mm and are clipped 5 mm below the skin.

^c PTV_N1n2pect: PTV of the lymph node levels 1 and 2 and the interpretoral lymph nodes. ^dPTV_N3n4: PTV of the lymph node levels 3 and 4.

^e PTV_IMN: PTV of the internal mammary lymph nodes.

Table 3

National consensus on dosimetric parameters and target volume names to be used in the evaluation of a breast cancer RT-plan.

	D98%	Dmean	D2%
PTV_Breast	$\geq 95\%$	99–101% ^a	$\leq 107\%$
PTV_Boost	$\geq 95\%$	100% ^b	$\leq 107\%$
PTV_N1n2pect ^c	$\geq 95\%$	No target value given	No target value given
PTV_N3n4 ^c	$\geq 95\%^{ m d}$	No target value given	No target value given
PTV_IMN ^e	$\geq 90\%^{ m c}$	No target value given	No target value given

^a: With the exception of plans including a boost volume.

^b : 100% is given as target value but may differ per patient. No consensus was reached what range of values would be acceptable.

^c: These node levels can be jointly evaluated.

 d : In case this PTV includes lung, a concession to this target value is allowed. e : D98% should be $\geq\!95\%$ for CTV_IMN, also taking into account set-up uncertainty.

Table 4

National consensus dosimetric parameters and OAR volume names.

	Parameter	Remark
Lungs	Dmean and V5Gy	No threshold value specified
Heart	Dmean	No threshold value specified
Contralateral breast	$\begin{array}{l} \text{Dmean} \leq 1\\ \text{Gy} \end{array}$	Only for patients $<$ 40 years. Delineation if needed.
Thyroid	V30Gy	Only if lymph node levels 3 and 4 are included in the target volume. No threshold value specified.

contain this value within 1% of the prescription dose was deemed neither needed nor desired.

A proposal was offered to report Dmean and D2% for PTV_Breast excluding the PTV_Boost (PTV_Breast-PTV_Boost). This proposal was not adopted as such values would vary considerably between patients.

For scientific reasons, it would provide most information when for regional radiotherapy the dose would be evaluated for all lymph node levels separately. However, to limit work in clinical practice, where often levels 1 and 2 and interpretoral nodes, and likewise levels 3 and four, are combined, it was agreed upon to report dose to these two combined volumes and to the IMN separately.

For the coverage of PTV_IMN, a D98% of >90% was deemed sufficient as long as the D98% to CTV_IMN would remain >95%. This consensus was based on the fact that the dorsal part of PTV_IMN often includes lung, resulting in reduced build-up and thus underdosage. If one would still try to reach a dose of 95% in this part of PTV_IMN, this would lead to a relatively high increase in lung and heart dose. Because the dose to CTV_IMN would probably only change slightly if the optimal dose level for PTV_IMN would be set at 90%, further increasing the coverage and therefore the lung and heart dose was considered unacceptable.

Consensus for organs at risk

For the OARs several proposals were discussed. For the lungs and the heart, it was agreed upon to evaluate the mean dose, as this is the most used parameter in literature [14–18], as well as in the Dutch institutes. The suggestion to include V5Gy for the lungs was approved, as it was considered that this dose level could correlate with the possible effects of switching from tangential techniques to VMAT techniques, which may

cause a larger volume of the lungs to be irradiated to lower dose levels. As there was consensus that the lung and heart dose can differ considerably between patients due to their varying anatomy, no threshold values for heart and lung doses were yet specified. Presently, contralateral breast cancer induction is mainly reported for patients < 40 years with a mean contralateral breast dose > 1 Gy [19]. Thus, consensus was reached that delineation of the contralateral breast should be performed in those individual patients < 40 years in which this dose level might be reached. For the thyroid, it was concluded that V30Gy should be evaluated when lymph node levels 3 and 4 are part of the target volume [20].

Consensus on clinical factors

Besides the dosimetric parameters presented in Tables 3 and 4, it was agreed upon that apart from tumour related parameters, also (risk factors for) cardiac morbidity, smoking history and age should be considered in the decision whether or not to irradiate, or to do concessions to target coverage. Furthermore, when concessions are made to target coverage in order to spare organs at risk, both the stage of the disease as well as the location of the tumour should be considered. The new national guideline was approved in November 2019 and is presented in Tables 3 and 4.

Discussion

A breast cancer radiotherapy benchmark study with four clinical cases was conducted in 19 out of 20 Dutch RT centres. We did not only find considerable variation in target dose coverage and dose to OARs, but also a wide variation in dose volume histogram parameters used to evaluate the treatment plans. Based on the results of the benchmark study and a consensus meeting, a new guideline for evaluation of breast cancer RT planning was established.

A next step could be to further harmonise the criteria for plan optimisation for patients where compromises need to be made. The further development and validation of NTCP and TCP models might make this process easier in the future.

There are only a few published (national) guidelines involving breast radiotherapy treatment plan evaluation criteria. Duma et al. recently published a recommendation on heart sparing techniques of the breast cancer expert panel of the German society of radiation oncology (DEGRO) [21]. They restated their recommendation for dose constraints for the heart and highly encouraged reporting of a wide number of parameters: mean dose to heart and left ventricle (LV) and Left Anterior Descending Artery (LAD) as well as V5GyLV, V23GyLV, V30GyLAD and V40GyLAD. Although we agree that reporting all these parameters may lead to a better knowledge on toxicity, we proposed a limited number of essential parameters to encourage its use by all institutes in The Netherlands as much as possible. DEGRO also gave upper limits for these criteria. In our consensus meeting we discussed that this would not be optimal, as we formulated that the dose should be as low as possible for each individual patient and due to the widely varying anatomy, these values are highly patient dependent. Further studies are required to investigate whether strict upper limits may still be defined for the OARs for different target volumes to be irradiated.

In a consensus statement of the Royal College of Radiologists (UK) dating from 2016, besides treatment indications for breast radiotherapy, also some DVH constraints were given [22]. For example, for patients receiving IMN treatment: heart V17Gy < 10%, ipsilateral lung V17Gy < 35% and mean contralateral breast dose < 3.5 Gy. They included a target mean heart dose as this would help departments to implement breath-hold techniques. This argument is not valid for the Dutch guideline, as all Dutch institutes already have implemented breath-hold for left-sided breast radiotherapy.

Nielsen et al. [23] also reported dose constraints for breast cancer patients, given 25 fractions of 2 Gy. They used specific DVHs points to report on the heart and lung dose, while we prefer to use the mean heart and lung dose as these are commonly reported on in the literature and correlate with toxicity [14,15]. Furthermore, they included constraints for the spinal cord and maximum dose of 54 Gy outside the PTV or in the plexus brachialis. We did not include this standardly in our evaluation, as our prescription dose in the benchmark cases was much lower.

This Dutch consensus guideline is based on the current scientific knowledge and available technology in the Netherlands. As such, this consensus should be periodically updated.

In conclusion, utilizing the results of a benchmark and a questionnaire, a new guideline for treatment plan evaluation for breast cancer patients was generated. This guideline is one of the most detailed national consensus statements up until now concerning breast radiotherapy plan evaluation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors highly appreciate all the discussions that have taken place and have contributed to the generation of the consensus guideline. We acknowledge all the work the radiation oncologists, clinical physicists and especially RTTs have done to provide us with the planned benchmark cases. The critical English review by An-Sofie Verrijsen is also highly appreciated. The project was sponsored by Stichting Kwaliteitsgelden Medisch Specialisten.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tipsro.2021.06.004.

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