



## Guideline Letter

## The Danish Head and Neck Cancer Group (DAHANCA) 2020 radiotherapy guidelines



Kenneth Jensen<sup>a</sup>, Jeppe Friberg<sup>a,b</sup>, Christian Rønn Hansen<sup>a,c</sup>, Eva Samsøe<sup>a,d</sup>, Jørgen Johansen<sup>a,c</sup>, Maria Andersen<sup>e</sup>, Bob Smulders<sup>a,b</sup>, Elo Andersen<sup>d</sup>, Martin Skovmos Nielsen<sup>e</sup>, Jesper Grau Eriksen<sup>f,h</sup>, Jørgen Brede Baltzer Petersen<sup>f</sup>, Ulrik Vindelev Elstrøm<sup>f</sup>, Anne Ivalu Holm<sup>f</sup>, Mohammed Farhadi<sup>g</sup>, Morten Hjørtald Morthorst<sup>g</sup>, Peter Sandegaard Skyt<sup>a</sup>, Jens Overgaard<sup>h</sup>, Cai Grau<sup>a,f</sup>

<sup>a</sup>Danish Centre for Particle Therapy, Aarhus University Hospital, Denmark; <sup>b</sup>Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Denmark; <sup>c</sup>Department of Oncology, Odense University Hospital, Denmark; <sup>d</sup>Department of Oncology, Herlev University Hospital, Denmark; <sup>e</sup>Department of Oncology, Aalborg University Hospital, Denmark; <sup>f</sup>Department of Oncology, Aarhus University Hospital, Denmark; <sup>g</sup>Department of Oncology, Næstved Hospital, Denmark; <sup>h</sup>Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark

## ARTICLE INFO

## Article history:

Received 13 July 2020

Received in revised form 21 July 2020

Accepted 21 July 2020

Available online 8 August 2020

## Keywords:

Head and Neck Cancer  
Guidelines

© 2020 Published by Elsevier B.V. Radiotherapy and Oncology 151 (2020) 149–151

## Background

The Danish Head and Neck Cancer Group (DAHANCA) was founded in 1976. Over the years the group successfully conducted clinical trials and has developed national guidelines for all aspects of the treatment of head and neck cancer. The first national recommendations for radiotherapy was included as an appendix to the DAHANCA 2 and DAHANCA 5 protocols [1,2] in 1979 and 1986, respectively. A thorough description of doses and treatment fields were in 1991 included in the large DAHANCA 6&7 randomized trial [3] and later in the DAHANCA 9 protocol [4].

The first DAHANCA radiotherapy quality assurance (QA) project was performed in 1997, and a formal QA group was established in 2002, responsible for the national evolution and dissemination of the guidelines. The 2004 edition introduced the CTV for postoperative radiotherapy and included an updated recommendation of elective nodal irradiation [5]. Guidelines for the use of IMRT, including fractionation and normal tissue constraints was included and used for the DAHANCA 10 and 18 trials [6–8], as well as in the imaging and hyperfractionation studies [9–12]. The fourth edition (2013) included a thorough revision of all chapters to comply with the ICRU 83 guidelines and to define QA parameters. Furthermore, a detailed list of sensitive normal tissues and constraints was added. Most importantly, the guidelines introduced the (5 + 5)

mm concentric margin concept with an addition of 5 mm from GTV to CTV1 (high risk volume) and a further 5 mm to CTV2 (intermediate risk volume). A revision was approved in 2014 bringing the guidelines up to date with published evidence [13] and national guidelines for e.g. unknown primary tumor.

## Impact of the 2013 guidelines

The simple, but reproducible concentric (5 + 5) mm geometric expansion of the GTV has shown to increase consistency of CTV delineation [14]. The 2013 guidelines have made international impact inspiring Gregoire et al. [15] and Lee et al. [16] to produce international guidelines for the delineation of CTV for all subsites of the larynx and pharynx. Gregoire and Lee thoroughly evaluated the DAHANCA guidelines in large international, multi-organizational settings. As a result, their guidelines have become the product of consensus between more diverse traditions and the simple DAHANCA principle [17–20]. As expected, the resulting guidelines are more complex.

## The present 2020 version of the guidelines

In turn, DAHANCA has re-evaluated the Danish recommendations and a new version of the guidelines is presented here in the

supplementary material. The novelty of the new guidelines is inspired by the international guidelines, as well as a need for a more detailed description of CTV definition in the post-operative setting, as DAHANCA has embarked on a randomized trial of robotic surgery versus radiotherapy for early oropharyngeal cancer (DAHANCA 34).

The delineation guidelines for organs at risk have been updated to approach recently published guidelines [21,22]. The nomenclature has been updated to align with the Santanam et al. guidelines [23]. Since the opening of the Danish Centre for Particle Therapy an introductory chapter on proton therapy has been added to describe the principles for application of the guidelines to proton radiotherapy endeavouring maximal concordance between photon and proton radiotherapy, as DAHANCA has initiated the DAHANCA 35 randomized trial of photon versus proton radiotherapy with a model based enriched population of squamous cell pharynx and larynx cancer patients [24].

Nuclear medicine specialists, radiologists and clinical oncologists from all Danish Centres have agreed on common guidelines for the use of imaging for target volume delineation [25]. These guidelines have been incorporated into the radiotherapy guidelines.

The Danish Clinical Quality Program – National Clinical Registries (RKKP) constitutes the infrastructure of the Danish clinical quality registries and the Danish Multidisciplinary Cancer Groups (DMCG). All new national clinical guidelines must now be written in the same format and with a level of evidence behind any recommendation, graded according to AGREE-II [26]. As expected, the far majority of recommendations in the current guideline are level D.

## Future and on-going projects

A new recommendation [27] for the selection of elective nodal areas will be reviewed in conjunction with a planned analysis of the regional recurrence pattern in a Danish population treated according to the guidelines. DAHANCA 34 (surgery versus radiotherapy) is including patients and their target- and normal tissue delineation as well as dose plans with be scrutinized according to the quality assurance criteria specified in the guidelines, during the first 4 fractions. Patients in DAHANCA 30 (nimorazole gene-signature guided non-inferiority RCT) and DAHANCA 35 (protons versus photons) will be retrospectively quality assured according to the guidelines. We are awaiting an analysis of an organ at risk delineation workshop and a dose audit, both performed in 2019. Furthermore, we plan an evaluation of our margins [28].

## Conclusion

With the 2020 guidelines we aim for high quality standard treatment as well as reproducible treatment within clinical trials. We will continue to monitor our results closely. With the English translation of the guidelines we strive for international scrutiny and productive discussions.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2020.07.037>.

## References

- [1] Overgaard J, Sand Hansen H, Andersen AP, Hjelm-Hansen M, Jørgensen K, Sandberg E, et al. Misonidazole combined with split-course radiotherapy in the treatment of invasive carcinoma of larynx and pharynx: report from the DAHANCA 2 study. *Int J Radiat Oncol Biol Phys* 1989;16:1065–8. [https://doi.org/10.1016/0360-3016\(89\)90917-6](https://doi.org/10.1016/0360-3016(89)90917-6).
- [2] Overgaard J, Sand Hansen H, Overgaard M, Bastholt L, Berthelsen A, Specht L, et al. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85. *Radiother Oncol* 1998;46:135–46. [https://doi.org/10.1016/s0167-8140\(97\)00220-x](https://doi.org/10.1016/s0167-8140(97)00220-x).
- [3] Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. *Lancet* 2003;362:933–40. [https://doi.org/10.1016/s0140-6736\(03\)14361-9](https://doi.org/10.1016/s0140-6736(03)14361-9).
- [4] Evensen JF, Sand Hansen H, Overgaard M, Johansen J, Andersen LJ, Overgaard J. DAHANCA 9 – a randomized multicenter study to compare accelerated normofractionated radiotherapy with accelerated hyperfractionated radiotherapy in patients with primary squamous cell carcinoma of the head and neck (HNSCC). *Acta Oncol* 2019;58:1502–5.
- [5] Grégoire V, Levendag P, Ang KK, Bernier J, Braaksmas M, Budach V, et al. CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines. *Radiother Oncol* 2003;69:227–36. <https://doi.org/10.1016/j.radonc.2003.09.011>.
- [6] Overgaard J, Hoff CM, Hansen HS, Specht L, Overgaard M, Lassen P, et al. DAHANCA 10 – Effect of darbeopetin alfa and radiotherapy in the treatment of squamous cell carcinoma of the head and neck. A multicenter, open-label, randomized, phase 3 trial by the Danish head and neck cancer group. *Radiother Oncol* 2018;127:12–9. <https://doi.org/10.1016/j.radonc.2018.02.018>.
- [7] Hansen CR, Johansen J, Kristensen CA, Smulders B, Andersen LJ, Samsøe E, et al. Quality assurance of radiation therapy for head and neck cancer patients treated in DAHANCA 10 randomized trial. *Acta Oncol* 2015;54:1669–73. <https://doi.org/10.3109/0284186x.2015.1063780>.
- [8] Bentzen J, Toustrup K, Eriksen JG, Primdahl H, Andersen LJ, Overgaard J. Locally advanced head and neck cancer treated with accelerated radiotherapy, the hypoxic modifier nimorazole and weekly cisplatin. Results from the DAHANCA 18 phase II study. *Acta Oncol* 2015;54:1001–7. <https://doi.org/10.3109/0284186x.2014.992547>.
- [9] Johansen J, Buus S, Loft A, Keiding S, Overgaard M, Hansen HS, et al. Prospective study of 18FDG-PET in the detection and management of patients with lymph node metastases to the neck from an unknown primary tumor. Results from the DAHANCA-13 study. *Head Neck* 2008;30:471–8.
- [10] Mortensen LS, Johansen J, Kallehauge J, Primdahl H, Busk M, Lassen P, et al. FAZA PET/CT hypoxia imaging in patients with squamous cell carcinoma of the head and neck treated with radiotherapy: results from the DAHANCA 24 trial. *Radiother Oncol* 2012;105:14–20. <https://doi.org/10.1016/j.radonc.2012.09.015>.
- [11] Saksø M, Andersen E, Bentzen J, Andersen M, Johansen J, Primdahl H, et al. A prospective, multicenter DAHANCA study of hyperfractionated, accelerated radiotherapy for head and neck squamous cell carcinoma. *Acta Oncol* 2019;58:1495–501. <https://doi.org/10.1080/0284186x.2019.1658897>.
- [12] Saksø M, Jensen K, Andersen M, Hansen CR, Eriksen JG, Overgaard J. DAHANCA 28: A phase I/II feasibility study of hyperfractionated, accelerated radiotherapy with concomitant cisplatin and nimorazole (HART-CN) for patients with locally advanced, HPV/p16-negative squamous cell carcinoma of the oropharynx, hypopharynx, larynx and oral cavity. *Radiother Oncol* 2020;148:65–72. <https://doi.org/10.1016/j.radonc.2020.03.025>.
- [13] Grégoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA, et al. Delineation of the neck node levels for head and neck tumors: A 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol* 2014;110:172–81. <https://doi.org/10.1016/j.radonc.2013.10.010>.
- [14] Hansen CR, Johansen J, Samsøe E, Andersen E, Petersen JBB, Jensen K, et al. Consequences of introducing geometric GTV to CTV margin expansion in DAHANCA contouring guidelines for head and neck radiotherapy. *Radiother Oncol* 2018;126:43–7. <https://doi.org/10.1016/j.radonc.2017.09.019>.
- [15] Grégoire V, Evans M, Le QT, Bourhis J, Budach V, Chen A, et al. Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. *Radiother Oncol* 2018;126:3–24. <https://doi.org/10.1016/j.radonc.2017.10.016>.
- [16] Lee AW, Ng WT, Pan JJ, Poh SS, Ahn YC, AlHussain H, et al. International guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma. *Radiother Oncol* 2018;126:25–36. <https://doi.org/10.1016/j.radonc.2017.10.032>.
- [17] Grégoire V, Grau C, Lapeyre M, Maingon P. Target volume selection and delineation (T and N) for primary radiation treatment of oral cavity, oropharyngeal, hypopharyngeal and laryngeal squamous cell carcinoma. *Oral Oncol* 2018;87:131–7. <https://doi.org/10.1016/j.oraloncology.2018.10.034>.
- [18] Bondue C, Racadot S, Coutte A, Dupuis P, Biston MC, Grégoire V. Volumetric and dosimetric comparison of two delineation guidelines for the radiation treatment of laryngeal squamous cell carcinoma. *Clin Transl Radiat Oncol* 2019;19:1–11. <https://doi.org/10.1016/j.ctro.2019.06.003>.
- [19] Lee AW, Ng WT, Pan JJ, Chiang C-L, Poh SS, Choi HC, et al. International guideline on dose prioritization and acceptance criteria in radiation therapy planning for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2019;105:567–80. <https://doi.org/10.1016/j.ijrobp.2019.06.2540>.

- [20] Christiaens M, Collette S, Overgaard J, Gregoire V, Kazmierska J, Castadot P, et al. Quality assurance of radiotherapy in the ongoing EORTC 1219-DAHANCA-29 trial for HPV/p16 negative squamous cell carcinoma of the head and neck: results of the benchmark case procedure. *Radiother Oncol* 2017;123:424–30. <https://doi.org/10.1016/j.radonc.2017.04.019>.
- [21] Christianen MEMC, Langendijk JA, Westerlaan HE, van de Water TA, Bijl HP. Delineation of organs at risk involved in swallowing for radiotherapy treatment planning. *Radiother Oncol* 2011;101:394–402.
- [22] Brouwer CL, Steenbakkers RJHM, Bourhis J, Budach W, Grau C, Grégoire V, et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. *Radiother Oncol* 2015;117:83–90. <https://doi.org/10.1016/j.radonc.2015.07.041>.
- [23] Santanam L, Hurkmans C, Mutic S, van Vliet-Vroegindewij C, Brame S, Straube W, et al. Standardizing naming conventions in radiation oncology. *Int J Radiat Oncol Biol Phys* 2012;83:1344–9. <https://doi.org/10.1016/j.ijrobp.2011.09.054>.
- [24] Hansen CR, Friberg J, Jensen K, Samsøe E, Johnsen L, Zukauskaitė R, et al. NTPC model validation method for DAHANCA patient selection of protons versus photons in head and neck cancer radiotherapy. *Acta Oncol* 2019;58:1410–5. <https://doi.org/10.1080/0284186X.2019.1654129>.
- [25] Jensen K, Al-Farra G, Dejanovic D, Eriksen JG, Loft A, Hansen CR, et al. Imaging for Target delineation in head and neck cancer radiotherapy. *Semin Nucl Med.* <https://doi.org/10.1053/j.semnuclmed.2020.07.010> [in press].
- [26] Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *Can Med Assoc J* 2010;182:E839–42. <https://doi.org/10.1503/cmaj.090449>.
- [27] Biau J, Lapeyre M, Troussier I, Budach W, Giralt J, Grau C, et al. Selection of lymph node target volumes for definitive head and neck radiation therapy : a 2019 Update. *Radiother Oncol* 2019;134:1–9. <https://doi.org/10.1016/j.radonc.2019.01.018>.
- [28] Zukauskaitė R, Hansen CR, Grau C, Samsøe E, Johansen J, Petersen JBB, et al. Local recurrences after curative IMRT for HNSCC: effect of different GTV to high-dose CTV margins. *Radiother Oncol* 2018;126:48–55. <https://doi.org/10.1016/j.radonc.2017.11.024>.