CENTER FOR CLINICAL GUIDELINES | CANCER

Nimorazole

-Treatment with the hypoxic radiosensitizer Nimorazole in squamous cell carcinoma of the head and neck (HNSCC)

Version 3.0

APPROVAL
Content approval
22nd of January 2025 (DAHANCA)
Administrative approval
10th of March 2025 (Center for Clinical Practice Guidelines | Cancer)

REVISION
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KEYWORDS
Head and Neck Cancer, Radiotherapy Hypoxia, Hypoxic modification, Quality Assurance

Revisions to previous version (changelog)

Revisions to version 2.0

Guideline chapter	Description of revisions or additions
Recommendations	Recommendation 4 is changed; Nimorazole can be omitted if the diagnostic biopsy is characterized by a Less hypoxic gene expression as measured with the 15-gene hypoxia profile (A preliminary data). Where: chapter 3, scientific evidence, recommendation 4. The scientific evidence supporting a recommendation of nimorazole concurrent with curatively intended primary radio/chemoradiotherapy is substantiated with an up-dated meta-analysis. Where: chapter 3, scientific evidence, recommendation 1 and 2. Pharmacokinetics, compliance and side-effects have been updated with data from recent studies. No substantial or practice-changing events/effects have been observed. – -Furthermore appendix has been expanded with contraindications to nimorazole, and precautions in case of CNS symptoms or parallel treatment with disulfiram. Where: chapter 3, scientific evidence, recommendation 3 and appendix

Content

Background

This clinical practice guideline is developed in collaboration between the Danish Multidisciplinary Cancer Groups (DMCG.dk) and the Danish Clinical Registries (RKKP). The development is part of an intensified guideline effort launched in relation to the National Cancer Plan IV. The aim is to support high quality cancer care across the Danish healthcare system. The guideline content is approved by the disease specific Multidisciplinary Cancer Group, whereas the format is approved by the Center for Clinical Practice Guidelines | Cancer. Further information about clinical practice guidelines concerning cancer treatment in Denmark can be found here: www.dmcg.dk/kliniske-retningslinjer

The target users of this guideline are health care professionals working in the Danish healthcare system. The guideline consists of systematically prepared statements that can be used as a decision-making support tool by healthcare professionals and patients, when deciding on appropriate and correct care in a specific clinical situation.

Clinical practice guidelines concerning Danish cancer care is characterized as professional advice. The guidelines are not legally binding and professional judgment in the specific clinical context will always determine what the appropriate and correct medical care is. Adherence to the guideline recommendations is no guarantee for a successful outcome and sometimes care corresponding to a lower level of evidence will be preferred due to the individual patient's situation.

The clinical practice guideline contains central recommendations (chapter 1) and a description of the scientific evidence (chapters 3+4). Recommendations marked A are the strongest, whereas recommendations marked D are the weakest. For further information on strength of evidence see the"Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations", https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Information on the target population (chapter 2) and the method of development (chapter 5) is also included in the guideline. Please see the table of contents for page reference.

Information on the national integrated cancer pathways – descriptions of the patient journey through the healthcare system – can be accessed at the Danish Health Authority website:
https://www.sst.dk/en/disease-and-treatment/cancer/cancer-pathways

Development of this clinical practice guideline has been funded by The Danish Health Authority (National Cancer Plan IV) and the Danish Clinical Registries (RKKP).

1. Anbefalinger – Dansk (Quick guide)

1. **Den hypoxiske strålesensitizer Nimorazol bør anvendes konkomitant med kurativt intenderet ekstern primær strålebehandling/kemostrålebehandling af planocellulært carcinom i larynx (ekskl. stadium I glottisk tumor) pharynx, cavum oris og sinonasal regionen (A)**

2. **Nimorazol skal gives 90 minutter (+/- 30 min) før hver strålebehandlingsfraktion. Dosis er ca. 1,2g/m2 kropsoverflade. I forbindelse med en evt. anden daglig fraktion gives en reduceret dosis på 1 g uafhængigt af kropsoverflade (A)**

3. **Kvalme som er den væsentligste bivirkning til nimorazol bør behandles maksimalt antiemetisk forud for evt. seponering (D)**

4. **Nimorazol kan undlades, hvis der foreligger en Less hypoxic 15-gen hypoxi profil fra den diagnostiske biopsi (A præliminære data)**

Recommendations English (Quick guide)

1. **The hypoxic radiosensitizer nimorazole is recommended concurrent with curatively intended primary radiotherapy/chemo-radiotherapy of squamous cell carcinomas in the larynx (except stage I glottic tumors) pharynx, oral cavity and the sinonasal region (A)**

2. **Nimorazole should be administered orally 90 minutes (+/- 30 minutes) prior to each scheduled irradiation fraction. Scheduled dose should be approximately 1200 mg (1.2g)/m2 body surface. In case of two daily scheduled fractions, the dose administered prior to the second fraction should be reduced to 1000 mg (1 g) independent of body surface (A)**

3. **Nausea, which is the most frequent side effect to nimorazole, should be comprehensively treated with antiemetic drugs prior to possible discontinuation of nimorazole (D)**

4. **Nimorazole can be omitted, if the diagnostic biopsy is characterized by a less hypoxic gene expression as measured with the 15-gene hypoxia profile (A preliminary data)**

2. Introduction

Objective

The overall objective of this guideline is to support high quality cancer care across the Danish healthcare system.
The specific objective is to counteract/modify hypoxia-induced radioresistance by optimization and individualization of radiotherapy among patients with squamous cell carcinoma of the head and neck.

Target population

This guideline applies patients with macroscopic squamous cell carcinoma in the larynx (except stage I glottic tumors) pharynx, oral cavity and the sinonasal region. To patients with such tumors DAHANCA recommend addition of concurrent nimorazole to planned curatively intended (chemo-)radiotherapy.
If the tumor presents a less hypoxic gene expression as measured with the 15 gene hypoxia profile on the diagnostic biopsy nimorazole can be omitted.

Target User

This guideline has been developed with the aim of supporting clinical decision-making and quality improvement. Thus the target users are healthcare professionals working in Danish cancer care. The primary target group of this guideline is physicians and nurses involved in the treatment of patients with head and neck squamous cell carcinoma.

3. Scientific basis

1. **The hypoxic radiosensitizer nimorazole is recommended concurrent with curatively intended primary radiotherapy/chemo-radiotherapy of squamous cell carcinomas in the larynx (except stage I glottic tumors) pharynx, oral cavity and the sinonasal region (A)**

2. **Nimorazole should be administered orally 90 minutes (+/- 30 minutes) prior to each scheduled irradiation fraction. Scheduled dose should be approximately 1200 mg (1.2g)/m2 body surface. In case of two daily scheduled fractions, the dose administered prior to the second fraction should be reduced to 1000 mg (1 g) independent of body surface (A)**

Literature review and evidence description

The background for DAHANCA's recommendation 1 was initially the DAHANCA 5 double-blinded randomized prospective phase III study (1, 2) which since its completion have instituted such treatment as standard practice in Denmark. The study included 414 eligible patients and showed a significantly improved loco-regional control rate (49 versus 33%, p=0.002) (HR 0.69, CI: 0.53, 0.90) when conventional primary radiotherapy was supplemented with concurrent nimorazole compared with placebo (no nimorazole). Disease specific survival was also significantly improved (HR 0.76, CI: 0.58, 0.99), whereas only an insignificant trend towards improved overall survival was found (1)[1b].
Subsequent meta-analyses have substantiated the relevance of hypoxic modification in general, as well as the more specific use of hypoxic radiosensitizers in addition to radiotherapy with regard to locoregional control, disease specific survival and overall survival (3-5) [1a].

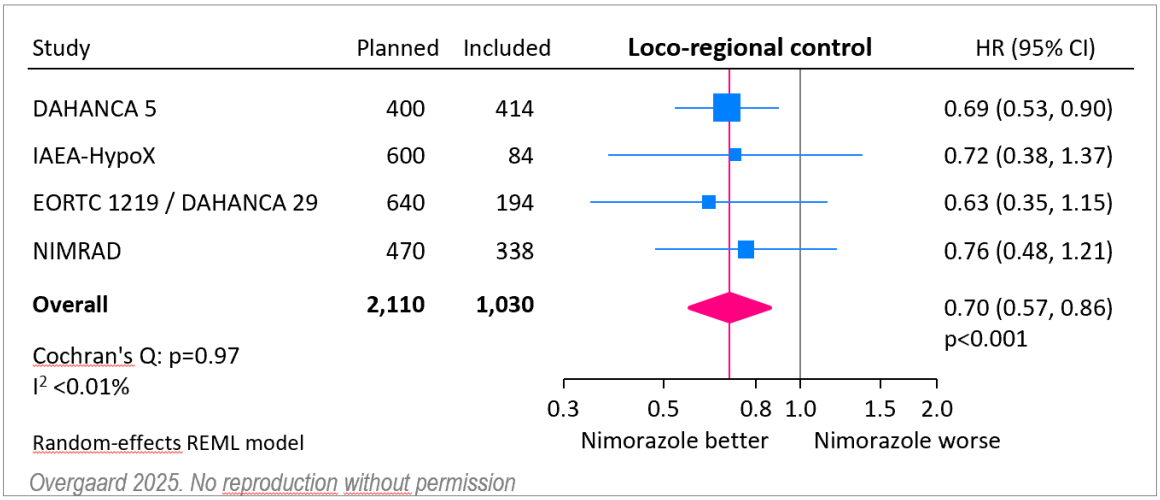
See Appendix for dose and administration.

Among the hypoxic radiosensitizers nimorazole is attractive due to its lack of late neurological side-effects. As DAHANCA 5 was the only randomized study evaluating specifically nimorazole, three additional trials have more recently been conducted in order to confirm and clarify (specifically for nimorazole), whether the initial observed effect was sustained in the more contemporary "accelerated chemo-radiotherapy" setting. Unfortunately all 3 trials were incomplete in their recruitment, but analysed together they add important supportive information.

The IAEA-HypoX study (**NCT01507467**) (6) included patients with HNSCC treated with accelerated radiotherapy and randomized to +/- concurrent nimorazole. Due to logistic problems the study was terminated prematurely, but analysis of the 84 enrolled patients showed a non-significant tendency towards beneficial locoregional control in the patients treated with concurrent nimorazole (HR: 0,72, CI: 0,38-1,37).

NIMRAD **(NCT01950689)** (7) included 338 HNSCC patients not fit for concurrent chemotherapy to be randomized to radiotherapy +/- nimorazole. Also in this study a non-significant tendency towards beneficial locoregional control in the patients treated with concurrent nimorazole was observed (HR: 0,76, CI: 0,48-1,21). EORTC 1219 **(NCT01880359)** (8) investigated nimorazole given to patients treated with accelerated fractionation and concurrent cisplatinum. Also this study was prematurely closed, primarily due to low recruitment and economic issues. A total of 194 patients were included and the study showed a 3 years locoregional control in favour of the patients having nimorazole (HR: 0,63, CI: 0,35-1,15).

Conclusively a range of studies with radiotherapy treated HNSCC +/- nimorazole all show a clear and comparable tendency in favour of supplemental hypoxic modification with nimorazole (HR ~ 0,7). As the majority of these above-mentioned studies did not attain enough power to individually show significant difference, a meta-analysis focusing distinctly on the relevance of hypoxic modification with nimorazole in the radiotherapeutic treatment of HNSCC has been performed based on the 4 randomized trials. The meta-analysis showed beneficial effect of adding nimorazole in terms of locoreginal control (HR: 0,70 (0,57-0,86), see figure, disease specific survival (HR: 0,79 (0,64-0,97) but not overall survival (HR:0,95 (0,79-1,12). The meta-analysis did also demonstrate that the four trials were very homogeneous in their outcome.



Since nimorazole was introduced as part of the standard radiotherapy regimen in most cases of HNSCC, the treatment has been modified and optimized with accelerated fractionation and concurrent chemotherapy. Along with the implementation of IMRT this optimization has improved the response (9-11). The effects of these different radiobiological modifications are largely independent and multivariate analysis of the DAHANCA trials showed an individual effect of nimorazole independent of accelerated fractionation and chemo-radiotherapy with a hazard ratio for loco-regional tumor control of 0.64 (0.52-0.80) (12).

These observations are supported by real life phase 4 data from the DAHANCA database (13), which based on more than 15.000 patients treated with primary radiotherapy for squamous cell carcinoma of the larynx and pharynx found nimorazole to be of significant benefit for locoregional control, disesease specific and overall survival independent of fractionation schedule, HPV status, and cisplatin treatment.

Rationale

Based on the above, the hypoxic radiosensitizer nimorazole is recommended concurrent with curatively intended primary radiotherapy/chemo-radiotherapy of squamous cell carcinomas in the larynx (except stage I glottic tumors) pharynx, oral cavity and the sinonasal region.

3. Nausea, which is the most frequent side effect to nimorazole, should be comprehensively treated with antiemetic drugs prior to possible discontinuation of nimorazole (D)

Literature review and evidence description

This recommendation is founded on good clinical practice and consensus among the working group/DAHANCA since there has been no scientific studies exploring the use of antiemetic drugs preceding discontinuation of nimorazole.

Pharmacokinetics, compliance, side effects and tolerance have been thoroughly examined in a PhD-study (14). The conclusion from this study is, that nimorazole basically can be administered concurrent to chemo- and radiotherapy but at the prize of potential (mainly) acute reversible side effects. These potential side effects results in relatively low compliance to nimorazole and it was found, that only around 60 % of patients completed the full extent of the prescribed nimorazole during the radiotherapy course. The main side effect and reason for discontinuation was nausea (87%) and it was found that all side effects ceased quickly after discontinuation (15, 16)[2b]. The two most recent conducted randomized trials (7, 8) where nimorazole was given blindly, did not observe any significant differences in compliance to the drug/placebo or radiotherapy. In the NIMRAD study there was significantly more Grade 1-3 nausea, but no significant difference in the degree of vomiting.

Patient values and preferences

The main side effect to nimorazole is nausea. This side effect can be problematic considering the contemporaneous strenuous (chemo-) radiotherapy treatment, where the nutritional status is often compromised. However, a PRO study of patients compliance and tolerance associated with the NIMRAD trial (7) did not report significant difference between patients treated with nimorazole versus placebo.

Rationale

With intent of the best possible outcome of the treatment for every individual patient, optimal supportive treatment is recommended if nausea occurs during treatment. If optimal supportive care is not sufficient, nimorazole should be discontinued. The rationale for this recommendation is that the individual patient should receive the best possible treatment effect, but only at the cost of endurable side effects. Radiotherapy or chemoradiotherapy is considered the cornerstone of the treatment. Recent studies where the effective drug has been blinded, have not revealed significant differences in compliance and severe side effects.

Comments and considerations

Further information on administration, dose, contraindications, side effects and interactions, see Appendix.

4. Nimorazole can be omitted, if the diagnostic biopsy is characterized by a less hypoxic gene expression as measured with the 15-gene hypoxia profile (A preliminary data)

Literature review and evidence description

As tumor hypoxia represents a clinically relevant problem, which is potentially modifiable and reducible, research has focused on methods to identify tumors characterized by hypoxia. Gene expression profiles are one of these methods.

A 15-gene hypoxia profile has been developed (17), and clinically and technically validated (17, 18). The gene profile has shown both prognostic ability to identify tumors characterized by (radioresistant) hypoxia, and more specific also being predictive for nimorazole as a hypoxic radiosensitizer (17, 19). As concurrent nimorazole is regularly causing side effects, it has also been a focus, whether it is possible to identify tumors characterized by less hypoxia. Such tumors would expectedly have less/no effect from concurrent nimorazole and therefore this side effect could be reduced by omitting the drug in the treatment of less hypoxic tumors.
The DAHANCA 30 study (NCT02661152) is a non-inferiority trial approaching this aspect. Recruitment was fulfilled in Dec 2024, and the study closed for randomization. Immediately after a preliminary analysis was made on patients with tumors characterized by a less hypoxic 15 gene expression profile, >1 year follow up and randomized to radiotherapy/radio-chemotherapy +/- nimorazole. There were 556 vs 564 patients in each treatment arm. Median follow up was 32(2-86) vs 34 (1-87) months and number of locoregional failures where 79 vs 87 respectively. The 3-year locoregional failure was 14,6% (11,5-17,7) vs 16,8% (13,6-19,9), (HR: 0,91, CI: 0,67-1,24).

The (preliminary) conclusion from the randomized DAHANCA 30 study is level [1b] evidence: that there is no indication that the two groups segregate from each other and thus it is considered reasonable to omit nimorazole in the less hypoxic tumors until the more detailed/final data are available within the next 3 years.

Rationale, comments and considerations

In order to optimize and individualize the treatment of patients with HNSCC the above-mentioned study has been performed. The preliminary data suggest, that guided by a pre-therapeutic test (15-gene profile), potential side-effects to nimorazole can be avoided for a considerable group of patients, without compromising the effect of the radiotherapy.
Until final data are available the DAHANCA group/board has decided, that the present data are strong enough for recommendation 4.

4. References

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5. Method

This guideline has been prepared on behalf of DAHANCA in a work group consisting of senior registrar Kasper Toustrup, prof. Jens Overgaard and prof. Jesper Grau Eriksen, whom collectively have been involved in most of the clinical and basic research founding the use of nimorazole in Denmark.
The decisions on the use of nimorazole and on the implementation of the hypoxia profile as a permanent part of the work-up have been taken by DAHANCA.

Literature search and review

No formalized literature review has been made, but results from relevant meta-analyses and a recent PhD thesis on nimorazole are the basis for the recommendations in the guideline. Co-authors for this guideline are the lead authors of the most substantial scientific literature on the subject.

Formulation of the recommendations

The recommendations of the guideline have been phrased by the work group for review in an action-oriented language which reflects the underlying evidence.

Stakeholder involvement

Only the group of authors and DAHANCA have been involved in the preparation of this guideline.

Hearing

The guideline has been reviewed by DAHANCA preceding approval on a DAHANCA board meeting on the 22th of January 2025.

Approval

Content approval:

The guideline has been reviewed by DAHANCA preceding approval on a DAHANCA board meeting on the 22th of January 2025.

Administrative approval:

The guideline is administratively approved by Center for Clinical Practice Guidelines | Cancer on the 10th of March 2025.

Recommendations that entail significant additional costs

None of recommendations in this guideline are expected to increase expenses.

Need for further research

DAHANCA 30 (NCT02661152) is a non-inferiority study aiming to determine, whether nimorazole can be omitted from the treatment without deteriorating outcome among patients with a hypoxic profile indicating well-oxygenated HNSCC. The preliminary results indicate that the gene-profile can predict tumors without indication for nimorazole, but the final results from the study is awaited.
Potentially, additional analysis of data, from the NIMRAD and EORTC 1219 trial, can add further information in terms of the usefulness of predictive testing with the 15-gene hypoxia profile .

EORTC 1219 (NCT01880359) is under final evaluation and presented in abstract format. The final report from this study is expected soon.

Authors and conflicts of interest

- Kasper Toustrup, senior registrar, ph.d., Department of Oncology, Aarhus University Hospital.
  Conflict of interest: Inventor of patent for the hypoxic gene profile. (owned by Aarhus University)

- Jens Overgaard, professor and consultant, DMSc, Department of Experimental Clinical Oncology, Aarhus University Hospital.
  Conflict of interest: Inventor of patent for the hypoxic gene profile (owned by Aarhus University)

- Jesper Grau Eriksen, professor og consultant, ph.d. Department of Oncology, Aarhus University Hospital.
  Conflict of interest: None.

For detailed cooperative relationships, please refer to the declaration via the Danish Medicines Agency's website: List of proprietary pharmacists, doctors, nurses, dentists, proprietary pharmacists and prescribing pharmacists who have a relationship with a company

Plan for revision

The guideline is expected to be updated in 2027.

Version of guideline template

The guideline has been developed in the 3.0 version of the template.

6. Monitoring

Standards and indicators

The administration information of nimorazole is registered in the DAHANCA database. Monitoring is continuously ongoing based on quality assurance indicators defined by DAHANCA. Results from this quality assurance is published yearly in cooperation with The Danish Clinical Quality Program– National Clinical Registries (RKKP)

Plan for audit and feedback

A continuous dialogue between the different centers at DAHANCA meetings aims to ensure feedback along with a national quality evaluation report of the clinical parameters in the DAHANCA database published yearly in cooperation with RKKP.

7. Appendices

Appendix – Administration, dose, side effects and interactions

Administration and dose

Nimorazole is administered 90 minutes (+/- 30 minutes) prior to the first of each daily radiotherapy treatment in a dose of approximately 1.2g (1200mg) per m^2 body surface. In case of accelerated radiotherapy regimen, the second daily dose of only 1g (1000 mg) is administered independent of body surface. y.

Height		m
Weight		kg
Body surface (m^2)		m^2

Body surface (m^2)	<1.6 m^2	1.6-1.9 m^2	>1.9 m^2
Dose nimorazole at 1st treatment	1.5 g (3 tabl)	2.0 g (4 tabl)	2.5 g (5 tabl)
Dose nimorazole at 2nd treatment	1 g (2 tabl)	1 g (2 tabl)	1 g (2 tabl)

The total dose during the radiotherapy course should be approximately 36 g(3600 mg)/m^2 and should not exceed 40 g/m^2 or in absolute 75 g. This dose is expected to result in maximum radiotherapy enhancement ratio and represents the maximal tolerable dose.

Contraindications

-Hypersensitivity to nimorazole
-Liver dysfunction
-Pregnancy
-Breastfeeding

Side effects

Potential side effects is registered in the patient journal and in the DAHANCA database under the label: "Kontrol under behandling(/follow-up during treatment)".

Most common side effects and treatment options (indent):

a. Gastrointestinal symptoms, especially **nausea** and **vomiting**.
    i. Antiemetic drugs can be used, just as the tablets can be ingested(/administered) in connection with a small meal.
    ii. If the patient is still suffering from nausea despite maximal antiemetic treatment a pause in treatment or dose reduction of nimorazole should be initiated. NB: seek for other causes of nausea (Irradiation, morphine treatment, chemotherapy, constipation, dehydration, electrolyte derangement, hypogeusia (taste disorders), mucositis, feeding tube, anxiety, pain, etc.)
b. **Flushing**: A subjective sensation of warmth and discomfort, normally without any objective findings (change in blood pressure, etc.). This symptom can occur shortly after administration of nimorazole and will most often spontaneously disappear within minutes or (rarely) hours. The symptoms are

transient in nature, hence the patients should, if possible, continue nimorazole treatment despite flushing.

c. **Skin rash**: some (appr. 8%(1)) patients experience skin rash and nimorazole should be discontinued if a causality with nimorazole is suspected.
d. If **paraesthesia** of **peripheral neuropathies** occur during treatment discontinuation or pause is recommended. It should be considered, that cisplatin too can cause these symptoms.
e. **CNS** symptoms are considered rare, if such appear after prolonged dosing it may be a sign of accumulation. Temporary or permanent cessation of nimorazole treatment is recommended as other potential causes for the symptoms are ruled out.
f. If **liver function** (hepatic quantities in blood samples) decreases during treatment with nimorazole, discontinuation should be considered, since the drug is primarily eliminated through hepatic metabolism.
g. A **disulfiram (Antabus)-like ,** as seldom described with metronidazole and alcohol intake, has not been reported in relation to nimorazole, and alcohol consumption *per se* should not exclude the use of concomitant nimorazole throughout the radiotherapy treatment.
   -Acute state of confusion can be a consequence of simultaneous administration of metronidazole and disulfiram (Antabuse), hence this combination of drugs should be avoided.
   Correspondingly, - temporary **discontinuation of disulfiram should be considered** during radiation treatment with concomitant nimorazole.

Interactions

To our knowledge, there has been no studies specifically investigating interactions with nimorazole. **However, since chemically similar drugs (i.e. metronidazole) might have somewhat similar interactions as nimorazole the following represent indicative/empirical guidelines regarding interactions with nimorazole:**

-Metronidazole is known to increase the anticoagulative effect of coumarines (Warfarin).
-Combining the use of phenytoin and/ phenobarbital can accelerate the degradation of metronidazole and thereby reduce the plasma concentration of metronidazole.
-Contrarily, combining the use of cimetidine and metronidazole can reduce the degradation of metronidazole and thereby result in an increase of the plasma concentration of metronidazole.
-Certain drugs have potential interactions with nimorazole: especially other nitroimidazoles (metronidazole, misonidazole, pimonidazole etc.) and aminoglycosides (streptomycin, gentamycin, etc.).

8. About this clinical guideline

This clinical practice guideline is developed in collaboration between the Danish Multidisciplinary Cancer Groups (DMCG.dk) and the Danish Healthcare Quality Institute (SundK). The development is part of an intensified guideline effort launched in relation to the National Cancer Plan IV. The aim is to support high-quality cancer care across the Danish healthcare system. The guideline content is approved by the disease-specific Multidisciplinary Cancer Group, whereas the format is approved by the Center for Clinical Practice Guidelines | Cancer. Further information about clinical practice guidelines concerning cancer treatment in Denmark can be found here: www.dmcg.dk/kliniske-retningslinjer

The guideline targets clinically active healthcare professionals in the Danish healthcare system and contains systematically developed statements that can be used as decision support by professionals and patients when deciding on appropriate and correct healthcare services in specific clinical situations.

Clinical practice guidelines concerning Danish cancer care is characterized as professional advice. The guidelines are not legally binding and professional judgment in the specific clinical context will always determine what the appropriate and correct medical care is. Adherence to the guideline recommendations is no guarantee for a successful outcome. Sometimes care corresponding to a lower level of evidence will be preferred due to the individual patient's situation.

The guideline includes, in addition to the central recommendations (chapter 1 – quick guide), a description of the basis for the recommendations – including the underlying evidence (chapter 3), references (chapter 4), and applied methods (chapter 5).
Recommendations marked A are based on the strongest evidence, while recommendations marked D are based on the weakest evidence. For further information on strength of evidence see the "Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations**",**
https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
This guideline also includes information on the target population (chapter 2) and the method of development (chapter 5) is also included in the guideline. See the table of contents for page references.

The guideline template has been prepared based on international quality requirements for the development of clinical guidelines as described by AGREE II, GRADE, and RIGHT.
For information on the Danish Health Authority's cancer packages – descriptions of the entire standard patient pathway specifying requirements for timelines and content – refer to the relevant disease area at:
https://www.sst.dk/en/english

The Danish Health Authority (National Cancer Plan IV) and the Danish Healthcare Quality Institute (SundK) funded the development of this clinical practice guideline.