Dual Energy CT – a tool for delineation of tumor and organs at risk in radiotherapy

(DART)

Dansk:
Dual Energy CT – et redskab til indtegning af tumor og risikoorganer i stråleterapi

NCT number: Pending

Document date: 30.05.2025

Project organization

Primary investigator and sponsor

Department of Oncology, Department of Medical Physics,
Aalborg University Hospital
Hobrovej 18-22
9000 Aalborg, Denmark

Co-investigators at Copenhagen University Hospital Herlev and Gentofte:

Department of Oncology, Division of Radiation Therapy
Borgmester Ib Juuls Vej 7, 2nd floor
2730 Herlev, Denmark

Co-investigators at Odense University Hospital

Department of Oncology
Kløvervænget 4
5000 Odense C, Denmark

Project team

The project team consists of the primary investigator, co-investigators, and individuals appointed by an investigator (primary or co-investigator) from all participating centers.

All individuals appointed as project team members work in the radiotherapy section of their respective departments and are involved in the patients' radiotherapy, either during planning or delivery.

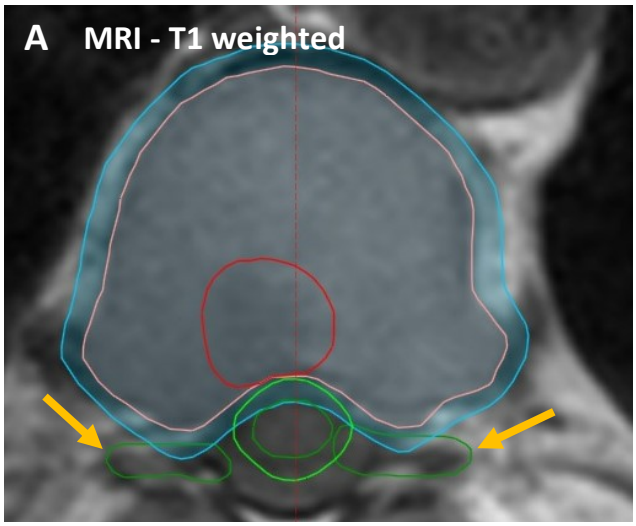
Table of content

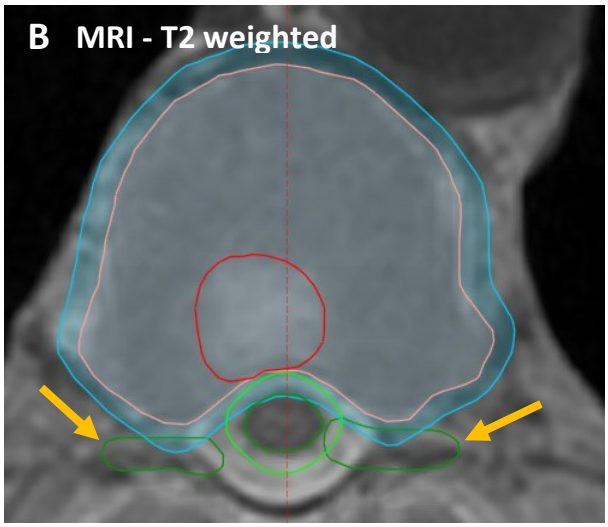
1. Background and rationale

1.a. Standard imaging in RT

A single-energy CT scan (SECT) has traditionally been used for the delineation of tumors and organs-at-risk (OAR) in radiotherapy (RT) for cancer patients. SECT provides detailed information about the patient's anatomy, offering particularly high visual contrast between structures with considerable difference in tissue densities, such as bones and airways [1]. However, it is more challenging to differentiate between soft tissues with similar densities, such as muscle, fat, and cancerous tissue, which is why magnetic resonance imaging (MRI) scans are often used to distinguish malignant areas from normal tissue in cancer diagnosis and treatment [2].

Examples of situations and tissues in modern RT where a SECT scan does not provide sufficient capability to adequately highlight structures include metastases in the brain [3], the bone marrow, the nerve roots associated with the spine, the spinal cord itself, cauda equina, or the sacral plexus. Consequently, MRI is the preferred imaging modality for this purpose today [4]. Multiple MRI sequences can be acquired to achieve the desired image contrast, such as T1- and T2-weighted imaging with and without contrast media, diffusion-weighted imaging (DWI), and inversion recovery (IR) for fat suppression. However, even with MRI, the delineation of structures like spinal nerve roots remains challenging due to insufficient image quality *(Figure 1)*.





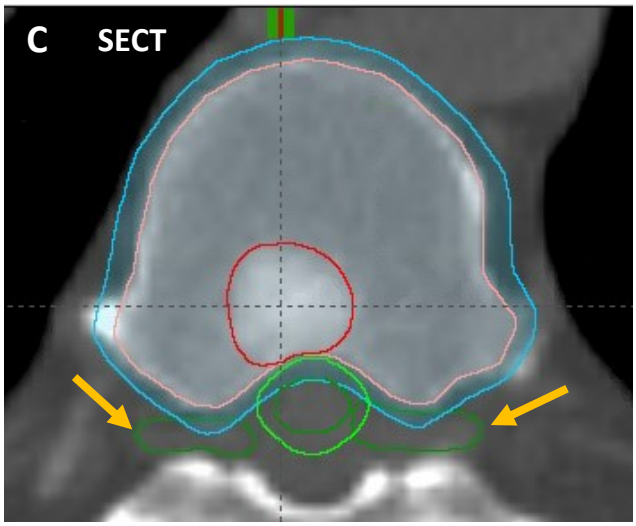


Figure 1.
Transvers images of a bone metastasis in a vertebral column.
Patient from Aalborg University Hospital.

A) T1-weighted MRI-scan.
B) T2-weighted MRI-scan.
C) SECT-scan.

Red contour: GTV (Gross Tumor Volume, macroskopic visible).
Pink contour: CTV (Clinical Target Volume, the whole vertebral).
Blue contour: PTV (Planning Target Volume, 2mm margin around CTV).
Dark Green contours by Orange Arrows: Spinal Nerve Roots.
Dark Green contour: Spinal Cord.
Light Green contour: 2mm uncertainty margin around the Spinal Cord.

1.b. DECT imaging in RT

In contrast to SECT, where a single X-ray energy spectrum is used (typically 120 kVp in RT), dual-energy CT (DECT) utilizes data from two separate X-ray energy spectra. These typically consist of a combination of low- and high-energy photons, such as 80 kVp and 140 kVp [5]. This facilitates analysis of energy-dependent changes in the tissue attenuation, providing a more detailed characterization of tissue. Consequently, it allows DECT to generate an alternative type of image reconstruction known as virtual monoenergetic images (VMI). VMI series resemble conventional SECT images but can be virtually reconstructed to represent images at a specific photon energy. The key advantage of reconstructed VMI series is their ability to enhance small contrast differences [6][7], providing DECT images with a level of contrast that was previously achievable only with MRI sequences *(Figure 2A and 2B)*.

In addition to the VMI series, DECT can also provide material-specific reconstructions. In material-specific reconstructions, materials/tissues are differentiated based on their atomic composition [8]. This allows for reconstructions that e.g. highlight iodine contrast (iodine mapping) *(Figure 2C)*.

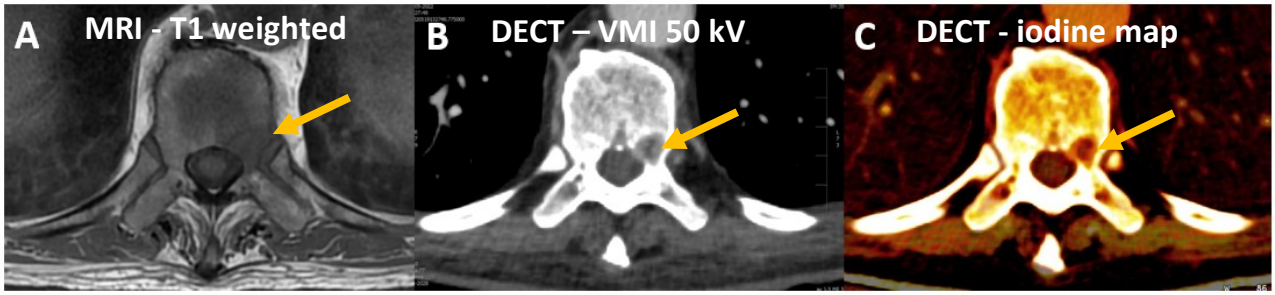


Figure 2. Axial images of a bone metastesis (orange arrow) with discrete epidural growth in a vertebral column. A) T1 weighted MRI, B) contrast enhanced DECT (VMI 50 kV) and C) iodine map reconstruction from DECT. *Courtesy of Erik Brandt (MD), Copenhagen University Hospital Herlev and Gentofte.*

In addition, DECT offers several other advantages when used in combination with RT, positioning it as a potentially more practical and efficient solution compared to MRI in certain scenarios:

1. **Seamless Image Registration**: In RT, CT is essential for dose calculation. DECT enables both imaging and dose calculation within a single scan, eliminating the need for additional image registration and avoiding alignment uncertainties that may arise when combining MRI with CT.

2. **Rapid Scanning**: DECT scans can be completed in under a minute, significantly faster than the 30 minutes typically required for a set of MRI sequences. This speed reduces the likelihood of patient discomfort or fatigue during the procedure.

3. **Reduced Motion Sensitivity**: DECT's quick scan time minimizes the impact of patient movement and internal organ motion (e.g., breathing or bowel activity) on image quality, providing more consistent and reliable results compared to MRI.

4. **Flexible Reconstruction**: DECT allows for retrospective reconstruction of all desired image types from a single DECT scan. In contrast, MRI requires separate scan sequences for each reconstruction, which can be time-consuming and inconvenient.

5. **Geometric and Chemical Stability**: DECT produces geometrically accurate and chemically stable images, ensuring reliable anatomical delineations. By comparison, MRI images can suffer from geometric distortions and chemical shifts, which may introduce uncertainties when delineating anatomical structures critical for RT [9].

6. **Compatibility with Metal Implants**: Unlike MRI, DECT can safely be used for patients with metal implants such as pacemakers or certain prosthetics, expanding its applicability to a broader patient population.

7. **Cost and Accessibility**: DECT-capable CT scanners are more affordable to install and maintain than MRI systems. Furthermore, DECT scanners are widely available in RT departments worldwide, making them an accessible option for most centers.

DECT scanners from various manufacturers have been on the market for approximately 30 years, but significant progress in the development of this technology has only occurred in the past decade. In recent years, DECT technology has also become more widespread in Danish hospitals, primarily in research settings. Globally, research is currently being conducted on the application of this technology mainly for diagnostic purposes. However, the investigation into the impact of DECT on tumor delineation has primarily focused on signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR), rather than on delineation variability [10]. The impact of DECT on the delineation of OARs has not been investigated so far.

In conclusion, research on the use of DECT in RT for cancer patients, with the aim of facilitating the delineation of both tumors and OARs, remains very limited, making further studies in this area highly valuable.

1.c. Aim and Purpose

The primary aim of this protocol ***D****ual Energy CT –* ***a*** *tool for delineation of tumor and organs at risk in* ***r****adio****t****herapy (****DART****)* is to evaluate whether DECT is at least as effective as MRI in delineating both tumors and OARs in patients referred for RT. This primary aim will be explored in patient groups where the performance of DECT for RT has been described in the literature (but mostly based on SNR and/or CNR), such as brain metastases [3] and head and neck cancer [11]. Additionally, ***DART*** will explore diagnoses not yet studied in the literature, such as bone metastases.

If DECT could be demonstrated to achieve delineations for RT in both tumors and OARs that are equally accurate as those based on MRI, it could offer significant advantages by being faster and more cost-effective, making DECT a valuable alternative to MRI in clinical practice.

As a secondary aim, the study will evaluate whether ***DART*** offers benefits when added to standard RT imaging for tumor and OAR delineation:

- For lung cancer patients (where MRI scans are typically not valuable due to tumor motion caused by breathing), ***DART*** will assess whether DECT performed in breath-hold provides added value compared to the SECT scan conducted during free breathing, as used in current clinical practice.
- For head and neck cancer patients, ***DART*** will evaluate whether DECT offers added value compared to the PET/CT scan currently used in clinical practice.

2. Method

2.a. Patient cohorts

Patients to be enrolled in ***DART*** will be divided into four cohorts:

Cohort A: ***DART Brain***

Initially 20 patients with 1-5 brain metastases referred for either whole brain *(**DART Brain (whole)**)* or stereotactic RT *(**DART Brain (SRS)**)*.

Cohort B: ***DART Bone***

Initially 20 patients with bone metastases in one or more regions of the vertebral column (C1-C7, Th1-12, L1-L5, Os Sacrum) referred for either palliative ***(DART Bone (pall))*** or stereotactic RT ***(DART Bone (SBRT))***.

- Vertebral column was chosen due to the proximity of spinal cord, spinal nerve roots, cauda equina and sacral plexus to the tumors.
- Only patients without medullary involvement.

Cohort C: ***DART H&N***

Initially 20 patients with head and neck cancer referred for RT.

- Patients must have undergone a PET/CT scan during the diagnostic evaluation for cancer.

Cohort D: ***DART Lung***

20 patients with lung cancer referred for palliative RT with a maximum of 10 fractions.

For patient cohorts A, B and C, the initial target of 20 patients may be increased if power calculations after the inclusion of the first 20 patients per cohort indicate the need for a larger sample size, as described in Section 3.d.

For patient cohort D, the initial target of 20 patients will not be changed.

2.b. Scanning modalities

In *Figure 3-6* in this section, the term 'standard' will refer to the current RT department scanning practice, while 'project' will refer to the scanning setup performed on patients enrolled in *DART*.

The duration of a SECT scan is approximately 10 seconds for all patients, while a DECT scan takes approximately two times 10 seconds for all patients.

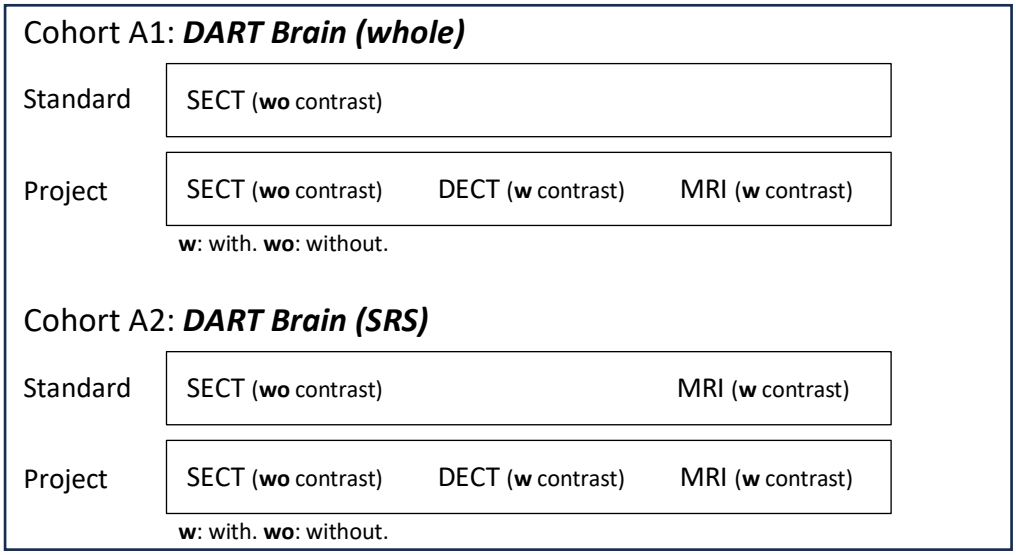


Figure 3. 'Standard' and 'project' scanning setup for patients enrolled in ***DART Brain (whole):*** Patients with brain metastases referred for whole brain RT and ***DART Brain (SRS):*** Patients with brain metastases referred for stereotactic RT.

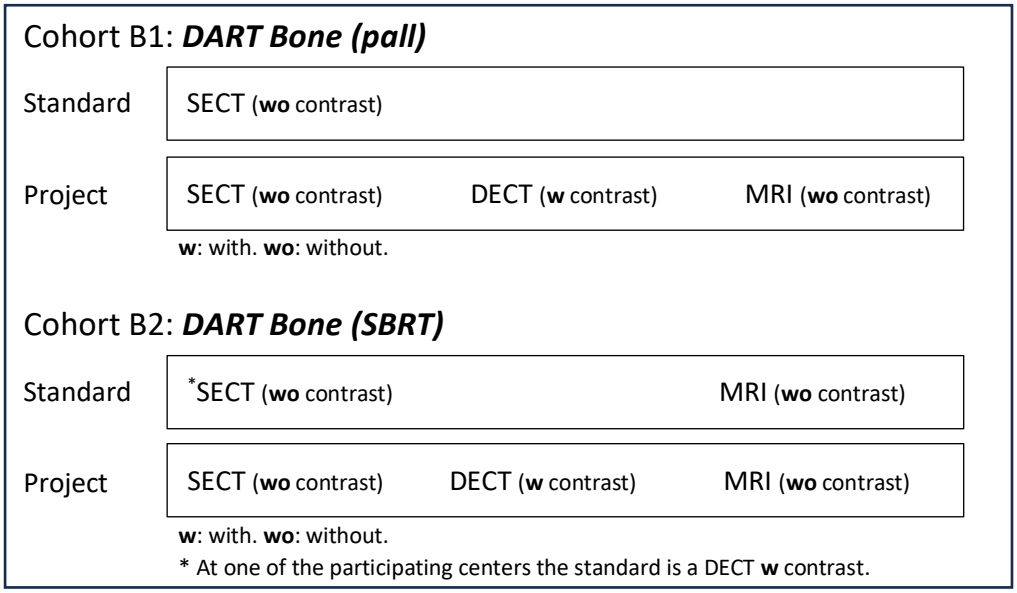


Figure 4. 'Standard' and 'project' scanning setup for patients enrolled in ***DART Bone (pall):*** Patients with bone metastases referred for palliative RT and ***DART Bone (SBRT):*** Patients with bone metastases referred for stereotactic RT.

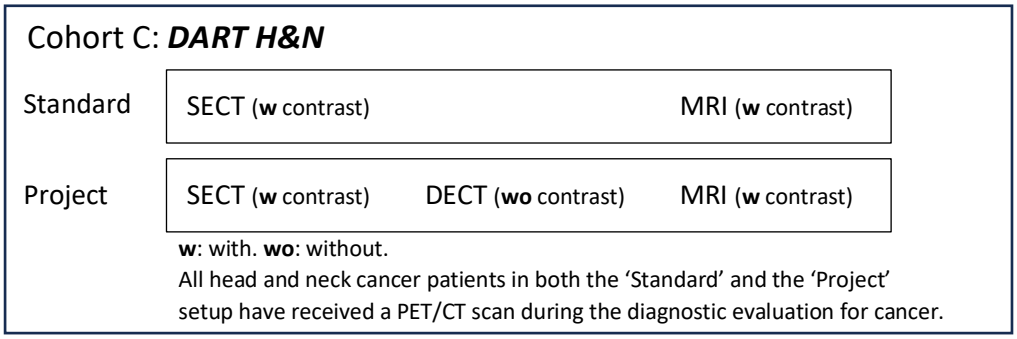


Figure 5. 'Standard' and 'project' scanning setup for patients enrolled in ***DART H&N:*** Patients with head and neck cancer referred for RT.

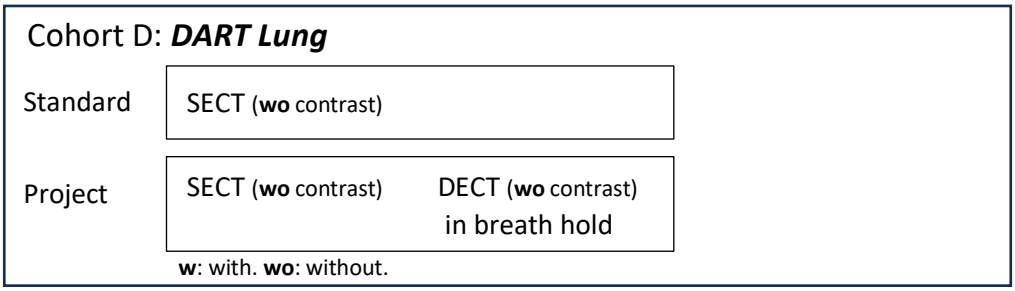


Figure 6. 'Standard' and 'project' scanning setup for patients enrolled in ***DART Lung:*** Patients with lung cancer referred for palliative RT with a maximum of 10 fractions.

For all patients following the project scanning setup, the DECT scan will be performed in the same scan sequence as the SECT, without the patient leaving the CT scanner in between, (cohorts A1, A2, B1, B2, C, D).

For all patients following the project scanning setup, the time between the CT and MRI scans will adhere to institutional practice, (cohorts A1, A2, B1, B2, C).

For all patients enrolled in ***DART H&N*** (cohort C), the contrast administered for the CT scan will be optimized for the SECT images. However, since contrast for these cancer patients is optimized for the late venous phase, there will still be sufficient contrast remaining after the SECT scan (taking approximately 10 seconds) to ensure comparable quality during the DECT scan.

All SECT and DECT scans will be performed on the local CT scanner available at each participating center, specifically dedicated to RT scanning and equipped with the DECT feature. MRI scans will be performed on the local MRI scanner available for RT scanning at each participating center. Scan and reconstruction parameters for SECT and MRI scans will follow the local clinical standards as currently practiced at each center. Optimized scan and reconstruction parameters for DECT for each patient cohort included in ***DART*** will be determined involving oncologists and radiologists before the commencement of DECT delineations.

2.c. Delineation analysis

For patients enrolled in cohorts A, B and C, the accuracy of manual delineations of tumors and OARs on DECT scans will be compared to those manually performed on a combination of SECT and MRI scans for each patient. For patients enrolled in ***DART H&N*** (cohort C) the comparison will also be done to the PET/CT scan conducted during the diagnostic evaluation for cancer. Four to six experienced oncologists and radiologists will perform the delineations. To minimize memory bias between delineations on different scan modalities, a time delay of approximately 1 month will be introduced between the delineations for the same patient. Furthermore, to avoid bias, the order of DECT and SECT/MRI will be randomized and balanced.

All delineations will be performed with access to all relevant clinical information and contouring guidelines, in accordance with clinical standards. Furthermore, all contouring clinicians will have access to the same clinical information and will be instructed to use the same contouring guidelines.

A reduction in inter-observer variability in delineations will serve as an indicator of improved contour accuracy for both tumors and OARs. Inter-observer variability for tumor and OAR delineations on DECT and SECT/MRI scans, respectively (and, for patients enrolled in ***DART H&N*** (cohort C), also PET/CT scans), will be assessed as geometric differences between individual manual delineations and consensus structures for each tumor and OAR. Consensus structures will be generated on both DECT and SECT/MRI scans using the STAPLE function with a 50% agreement threshold [12]. Variations relative to the consensus structures will be evaluated using various metrics, including volume and surface differences.

For all patient cohorts (A, B, C, D), a qualitative evaluation of image quality for tumors and OARs will be performed using the Likert scale (or a comparable method) and compared between image modalities.

The delineation studies and qualitative evaluation for each patient will commence only after the patient has completed their RT treatment.

2.d. Delineation decisions for RT treatment in patients enrolled in *DART*

For all patient cohorts included in ***DART***, *Figure 3-6* demonstrates that the standard scanning practice is incorporated into all project scanning setups.

For all patients enrolled in ***DART*** (cohorts A, B C, D), no RT treatment decisions will be based on delineations performed on DECT. All delineation decisions for patients enrolled in ***DART*** will be made based

on standard scanning practices, together with relevant clinical information and contouring guidelines, as per clinical standards.

3. Statistics

Sections 3.a-3.e pertain solely to the statistical analysis of the non-inferiority part of this ***DART*** protocol involving only patients enrolled in cohorts A, B, and C. For patients enrolled in ***DART H&N*** (cohort C), also PET/CT scans

For patients enrolled in cohort D, where assessments are limited to qualitative evaluations of the added value of DECT compared to SECT, the following applies: A total of 20 patients will be included in this cohort, and at least four doctors will evaluate the added value using a Likert scale or a comparable method.

3.a. Trial design

- The aim is to demonstrate that DECT is non-inferior to SECT/MRI for each of the cohorts A, B and C (described in section 2.a). That is, to show that DECT is not clinically significantly worse than SECT/MRI. For patients enrolled in ***DART H&N*** (cohort C) information from the PET/CT scan will be combined with the information from SECT/MRI for evaluation.
- Within each cohort, non-inferiority will be evaluated for each tumor and OAR individually to determine whether DECT meets the non-inferiority criteria in comparison to SECT/MRI.
- If DECT meets the non-inferiority criteria across all relevant structures within a given cohort, it will be considered a viable alternative to SECT/MRI for that cohort.

- For cohorts A and B, at least six doctors will delineate tumors and OARs for 20 patients from each cohort, using both DECT and SECT/MRI. For cohort C, at least four doctors will be included.
    - An even number of doctors will be included to ensure unambiguous output from the STAPLE function, which operates at a 50% agreement threshold, as described below. Within each cohort, the same doctors will perform delineations on all 20 patients.
    - These 20 patients represent the initial sample for each cohort and are used exclusively for power calculations (see section 3.d). While these 20 patients are not specifically selected to represent the final study population, they will be included in the final analyses. This is considered appropriate, as no hypothesis testing is performed on this sample prior to the power estimation.
- Low inter-observer variability in delineations will serve as an indicator of high contour accuracy for both tumors and OARs. Inter-observer variability for tumor and OAR delineations on DECT and SECT/MRI scans will be assessed as geometric differences between individual manual delineations and consensus structures. Consensus structures will be generated separately for each tumor and OAR. Consensus structures will be generated on both DECT and SECT/MRI scans using the STAPLE function with a 50% agreement threshold [12].
    - Variations from the consensus structures will be evaluated using Mean Surface Distance (MSD), which will also serve as the primary metric for assessing non-inferiority.
    - The Volume Dice Coefficient, Surface Dice Coefficient at 1 mm and 3 mm, and Hausdorff Distance 98% will be used as secondary evaluation metrics only, and will not be used to assess non-inferiority.

- For both MSD and the secondary evaluation metrics, a linear mixed-effects model (LMM) with random intercepts only, will be used to test the effect of imaging modality (SECT/MRI vs DECT, as a fixed effect) on both tumor and OAR delineations, with patient and doctor included as random effects.
    - Specifically, the LMM estimates the additional inter-observer variability associated with DECT compared to SECT/MRI, along with a corresponding confidence interval (CI).
    - The use of random intercepts only implies the assumption that the effect of imaging modality is consistent across all doctors and patients.
    - To apply the LMM, a linear relationship is assumed between imaging modality (SECT/MRI vs DECT) and MSD.
- Non-inferiority is defined as an acceptable additional variability of up to 1-2 mm beyond the inter-observer variability observed on SECT/MRI, evaluated separately for each tumor site and OAR.
    - The 1-2 mm margin was selected because the typical slice thickness of CT and MRI images ranges from 1 to 2 mm, and because oncologists agreed in discussion that this threshold is clinically acceptable.
    - Before analyzing data from a given cohort, a specific non-inferiority margin of 1-2 mm for the tumor and each OAR included in the cohort will be selected and maintained. The non-inferiority margin does not need to be identical for the tumor and each involved OAR.
    - The Statistical Analysis Plan (SAP), as described in section 3.a-3.e of this ***DART*** protocol, will be uploaded to the online platform Open Science Framework (OSF). The non-inferiority margins will be updated in the uploaded SAP prior to data analysis.
- DECT will be considered non-inferior to SECT/MRI if the one-sided 95% CI, calculated using LMM, for the added inter-observer variability (measured by MSD) between DECT and SECT/MRI does not include the predefined non-inferiority margin of 1-2 mm.

3.b. Null Hypothesis (H_0)

For each tumor and OAR individually, the one-sided 95% CI, calculated using LMM, for the added inter-observer variability (measured by MSD) between DECT and SECT/MRI includes the predefined non-inferiority margin of 1-2 mm.

3.c. Alternative Hypothesis (H_1)

For each tumor and OAR individually, the one-sided 95% CI, calculated using LMM, for the added inter-observer variability (measured by MSD) between DECT and SECT/MRI does not include the predefined non-inferiority margin of 1-2mm.

3.d. Power calculations

1. Power calculations will be conducted after the inclusion of the first 20 patients in each cohort.
2. The calculations will be performed solely to adjust the sample size for the remainder of the study.
3. Power will be evaluated within each patient cohort and separately for the tumor and each OAR. The structure (tumor or OAR) requiring the largest sample size will determine the final power calculation within each patient cohort.
4. The target power level is set at 80%.
5. The non-inferiority margin is set at 1-2 mm.
6. The following parameters will be estimated from the first 20 patients for the purpose of blinded sample size adjustment. No effect size will be estimated during this step. Specifically:

   a. Blinded preliminary standard deviation (SD) of inter-observer variability for SECT/MRI and DECT, measured by MSD.
   b. Blinded preliminary estimate of added inter-observer variability (measured by MSD) and its one-sided 95% CI, calculated using LMM (SECT/MRI vs DECT, as a fixed effect).
   c. 1000 simulations incorporating random-effect variation between doctors and patients.
7. The simulations assume normally distributed residuals and random effects. Within each structure (tumor or OAR), residuals are assumed to be with homogeneous variance and independent. Furthermore, random-effects and residual variances are assumed to be equal for SECT/MRI and DECT, as no random slope for modality is included in the LMM.
8. No adjustments for multiple testing will be applied, as each tumor and OAR is considered clinically independent for the purpose of non-inferiority assessment.
9. The calculated sample sizes, based on the inclusion of the first 20 patients in each cohort, will for each cohort be submitted to the Scientific Ethics Committee of the North Denmark Region as a protocol amendment. The amendment will for each cohort in turn specify the updated sample size requirements based on the power calculations.

3.e. Final analysis

1. The final analysis will be conducted after the full sample size has been included for each cohort.
2. The null hypothesis (H_0), as described in section 3.b, will be tested separately for each cohort and for each tumor and OAR.
   a. If the null hypothesis can be rejected, the alternative hypothesis (H_1), as described in section 3.c, will be accepted, and non-inferiority will be concluded.
   b. If the null hypothesis cannot be rejected, non-inferiority cannot be claimed.

4. Patients

4.a. Inclusion criteria

- Age ≥18 years
- ECOG performance status (PS) 0-2
- Assessed to be able to complete the protocol scanning regime
- Referred for RT
- For head and neck cancer patients, a PET/CT scan must have been performed during the diagnostic evaluation for cancer
- Signed informed consent

4.b. Exclusion criteria

- Pregnancy
- Previous RT in the same anatomical area now referred for RT
- Previous surgery in the same anatomical area now referred for RT
- Participation in conflicting protocols
- If relevant for the protocol scanning regime: Allergic to contrast agent
- If relevant for the protocol scanning regime: Contraindication to iodine-based contrast agent for CT (as determined by the physician)

- If relevant for the protocol scanning regime: Contraindication to Gadolinium-based contrast agent for MRI (as determined by the physician)
- If relevant for the protocol scanning regime: Contraindication for MRI (pacemaker, metal, non-MRI, compatible implants etc.)
- Incapable of understanding the patient information

5. Risks and side effects

5.a. Contrast agent and extra DECT scan

DART is a non-interventional observational study with no immediate treatment impact on the enrolled patients. The only potential risks are associated with the administration of contrast agents for CT and MRI (applicable only to some of the enrolled patients who will receive additional contrast agents) and the additional radiation dose from the extra DECT scan. Both risks are described in details below.

Contrast agent:
Only patients enrolled in cohorts A1, A2, B1, and B2 will receive additional contrast compared to the standard scanning technique.

To administer the contrast agent (iodine for CT and gadolinium for MRI), a vein catheter must be inserted in the elbow area. The needle prick may cause minor pain and, in some cases, bruising. In very rare instances, an infection could occur. The contrast agents themselves generally have few adverse effects. Rarely, allergic reactions such as asthma-like symptoms or skin rashes may occur. Specifically for iodine contrast agents used in CT scans, patients may experience transient side effects, including a warm sensation in the head, a metallic taste in the mouth, or an urge to urinate.

Extra DECT scan:
The standard pre-RT planning SECT will be supplemented with a DECT, which has a radiation dose considered equivalent to that of the SECT. Consequently, the total radiation dose for the patient includes the conservative addition of one extra DECT scan.

Based on the dose-length products (DLP) from DECT examinations performed on an anthropomorphic phantom (CT Whole Body Phantom – PBU-60) within the intended anatomical sites of investigation, we estimate a conservative value of 778 mGy·cm. Applying a conservative conversion factor averaged across body sites and genders of 0.007 mSv/(mGy·cm) [13], this corresponds to an effective dose of 5.4 mSv for the additional DECT scan a project patient will undergo. The total dose burden from this additional CT scan is well below the deterministic dose threshold.

Using the values provided in NVK Appendix 2 (2011), this corresponds to less than two years of background radiation (3 mSv/year) [14]. The increased risk of inducing incurable cancer from this exposure is calculated as 5%/Sv × 0.0054 Sv = 0.027%. It is important to note that patients referred for RT typically receive a prescribed radiation dose of at least 30 Gy, which can often exceed double this amount. The surrounding OARs may receive mean doses of approximately 40% of the prescribed dose. These therapeutic doses are several orders of magnitude higher than the planned imaging doses. Consequently, the risk of inducing secondary cancer from therapeutic radiation is significantly greater than the risk associated with the additional imaging doses discussed above.

5.b. Extra MRI scan

For patients who do not undergo an MRI examination as part of the standard scan procedure (patients enrolled in ***DART Brain (whole)*** (cohort A1) and ***DART Bone (pall)*** (cohort B1)):

The MRI examination does not involve exposure to ionizing radiation, and there are no additional risks associated with the added MRI examination. Patients will undergo a standard screening prior to the MRI examination to minimize the risk of harm due to energy absorption and to ensure compatibility with approved implanted devices, in accordance with the MRI safety list (https://www.mrisafety.com/). The risks associated with the additional contrast agent used in the MRI examination are described above. Patients will be provided with earplugs for noise reduction and a manual alarm that can be activated at any time during the scans. The additional MRI examination will be synchronized with the MRI procedures for patients enrolled in ***DART Brain (SRS)*** and ***DART Bone (SBRT)***, respectively, and will last approximately 15–20 minutes. Patients will need to spend additional time in the clinic to undergo the MRI examination. All scans will be scheduled as conveniently as possible to accommodate the patient's clinical schedule.

6. Biological patient material

No biological material will be collected or used in ***DART***.

7. Data from patient records

7.a. Patient records with consent

All patients must provide written informed consent prior to inclusion in ***DART***, in accordance with ethical standards. By signing the informed consent form, the patient agrees to allow researchers and other relevant parties, such as sponsors, to directly access and collect protocol-relevant information from their patient files (both electronic and paper), as necessary to conduct and complete the study.

In addition to the various SECT, DECT, MRI, and PET/CT reconstruction data, the following information will be obtained from the patient files for use in the study: name and CPR number (for traceability), age, sex, PS, TNM stage, histology (and for head and neck cancer patients, also p16 status), metal implants and RT dose planning parameters (such as contours, dose distribution, dose-volume parameters, etc.). These data are necessary to fulfill the objectives of the study. Information from the patient files will only be retrieved after the patients have signed the informed consent form.

8. Data protection

DART will be reported to the Data Protection Agency (Datatilsynet) through the North Denmark Region framework notification system. All patient data related to ***DART*** will be protected and treated confidentially in accordance with the EU General Data Protection Regulation (Databeskyttelsesforordningen) and the Danish Data Protection Act (Databeskyttelsesloven).

Data will be registered in a protocol-specific REDCap database. All relevant imaging data (SECT, DECT, MRI, PET/CT) and RT dose planning parameters (such as contours, dose distribution, dose-volume parameters, etc.) for patients enrolled in ***DART***, retrospectively extracted for analysis, will be shared between

participating centers through the national dose plan bank (DCMCollab). These data will be stored in a pseudo-anonymized form on a protected network drive in the North Denmark Region, assemble only to the primary investigator. The patient traceability key will be stored separately on another protected drive, also assemble only to the primary investigator, in accordance with the rules and practices governed by the approval from the Data Protection Agency.

9. Personal data sharing outside Denmark

No personal data from patients enrolled in ***DART*** will be shared with partners outside Denmark. However, if a patient enrolled in ***DART*** also participates in another project with a legally valid agreement permitting international data sharing, their data may be shared outside Denmark as part of that specific project.

10. Economy

DART is an investigator-initiated study receiving financial support from the 'Region Nordjylland Research Fund' (84.250 DKK), the 'Danish Comprehensive Cancer Center' (200.000 DKK), and a grant from the 'Siemens Healthineers Company' (100.000 EUR) to cover the initiation of the study at all participating centers and the salary for a PhD student.

All funding is managed by Aalborg University Hospital on behalf of the sponsor-investigator. The funds are transferred to a hospital-dedicated project account and are subject to revision in accordance with hospital regulations.

None of the individuals responsible for or involved in conducting ***DART*** have any financial relationships or conflicts of interest with Siemens Healthineers.

All additional scans and delineations of tumors and OARs related to ***DART*** will be provided by the participating centers.

11. Remuneration

No remuneration will be provided to the patients participating in ***DART***.

12. Recruitment

Potential candidates from cohort A, B and D, as described in Section 2.a, who meet the inclusion criteria, will be identified at the time of referral for RT through screening conducted by members of the project team.

At the outpatient visit in the oncology day unit, candidates from cohort A, B and D will receive oral information about the study in connection with their referral for radiotherapy. They will also be provided with written information material and informed of their right to bring an assessor. This ensures that patients will have at least 24 hours to consider participation before the scheduled scan in the radiotherapy department, where they will have the opportunity to ask additional questions to a representative from the project team.

Specific to the recruitment of patients in cohort C, please see below.

The candidates from all patient cohorts, will be provided with comprehensive and adequate information about the objectives, study design, and the potential risks and benefits of participating in ***DART***. They will be informed that they can withdraw their signed informed consent at any time without any consequences for their treatment. Additionally, the candidates will be clearly informed that all data collected in ***DART*** will remain anonymized and will not identify any participant, in compliance with the Data Protection Act and the General Data Protection Regulation (GDPR) (EU) 2016/679.

Written informed consent must be obtained from all candidates from all patient cohorts prior to their enrollment in ***DART***. The informed consent form must also be signed, at the same time, by the member of the project team who provided the written and verbal information.

Specific to the recruitment of patients in *DART H&N* (cohort C) **only:**
Patients scheduled for head and neck cancer RT will be informed about ***DART H&N*** when they attend their planning CT scan in the RT department. This approach is anticipated to significantly increase the number of patients enrolled in this cohort, as it eliminates the need for complex coordination and recruitment across different oncology specialist teams. Consequently, this reduces the risk of premature enrollment termination due to slow recruitment rates.

For this specific patient cohort, we consider this procedure ethically acceptable because the only difference between the standard and project scan procedures for patients enrolled in ***DART H&N*** is the addition of a DECT scan. The DECT scan is performed without the use of additional contrast agent, takes only an extra 20 seconds, and is conducted as a direct continuation in the same positioning as the SECT scan. Patients enrolled in ***DART H&N*** will still receive the same written and verbal information by a member of the project team in an undisturbed room or area, as described above, along with the opportunity to ask additional questions. However, the 24-hour reflection period will be reduced, and if patients have not brought an assessor, they will not have the opportunity to bring one.

13. Publication of results

For each patient cohort described in Section 2.a, a publication may be submitted once the minimum required number of patients in that cohort (as determined by the power calculations) has been enrolled, and the data have been analyzed and verified by all actively participating investigators.

All actively participating investigators will be offered co-authorship in accordance with the Vancouver guidelines. ***DART*** is planned to be registered and published on https://www.clinicaltrials.gov/. All results, whether positive, negative, or inconclusive, are intended to be published in peer-reviewed journals.

14. Ethics

All DECT scans (with or without contrast) are carried out on and within the framework of CE-marked equipment.

Approval by the Regional Committee on Health Research Ethics (Videnskabsetisk komité) and the Danish Data Protection Agency (Videnscenter for dataanmeldelser) will be obtained prior to initiation of ***DART***. ***DART*** will be performed in accordance with the Declaration of Helsinki (B) and under Danish law. ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) will be followed.

All risks, including the additional radiation dose from the DECT scan, are considered acceptable compared to the potential benefits from the outcome of ***DART*** for future cancer patients treated with RT as already described in Section 1.a.

15. Compensation

The patients participating in ***DART*** are covered by the national patient compensation scheme (Patienterstatningen).

16. References

[1] L. W. Goldman, “Principles of CT and CT technology.,” *J. Nucl. Med. Technol.*, vol. 35, no. 3, pp. 115–130, Sep. 2007, doi: 10.2967/jnmt.107.042978.

[2] “What is an MRI scan and what can it do?,” *Drug Ther. Bull.*, vol. 49, no. 12, pp. 141–144, Dec. 2011, doi: 10.1136/dtb.2011.02.0073.

[3] J. Kraft *et al.*, “Assessment of dual-energy computed tomography derived virtual monochromatic imaging for target volume delineation of brain metastases,” *Radiother. Oncol.*, vol. 187, p. 109840, 2023, doi: 10.1016/j.radonc.2023.109840.

[4] M. A. Schmidt and G. S. Payne, “Europe PMC Funders Group Radiotherapy Planning using MRI,” *Phys. Med. Biol.*, vol. 60, no. 22, pp. R323–R361, 2015, doi: 10.1088/0031-9155/60/22/R323.Radiotherapy.

[5] T. R. C. Johnson, “Dual-energy CT: general principles.,” *AJR. Am. J. Roentgenol.*, vol. 199, no. 5 Suppl, pp. S3-8, Nov. 2012, doi: 10.2214/AJR.12.9116.

[6] C. H. McCollough, S. Leng, L. Yu, and J. G. Fletcher, “Dual- and Multi-Energy CT: Principles, Technical Approaches, and Clinical Applications.,” *Radiology*, vol. 276, no. 3, pp. 637–653, Sep. 2015, doi: 10.1148/radiol.2015142631.

[7] M. H. Albrecht *et al.*, “Review of Clinical Applications for Virtual Monoenergetic Dual-Energy CT.,” *Radiology*, vol. 293, no. 2, pp. 260–271, Nov. 2019, doi: 10.1148/radiol.2019182297.

[8] G. J. Pelgrim *et al.*, “Accuracy of iodine quantification using dual energy CT in latest generation dual source and dual layer CT,” *Eur. Radiol.*, vol. 27, no. 9, pp. 3904–3912, 2017, doi: 10.1007/s00330-017-4752-9.

[9] S. Y. Huang, R. T. Seethamraju, P. Patel, and P. F. Hahn, “Body MR Imaging : Artifacts ,” pp. 1439–1460, 2015, [Online]. Available: 10.1148/rg.2015140289

[10] M. F. Kruis, “Improving radiation physics, tumor visualisation, and treatment quantification in radiotherapy with spectral or dual-energy CT,” *J. Appl. Clin. Med. Phys.*, vol. 23, no. 1, pp. 1–17, 2022, doi: 10.1002/acm2.13468.

[11] F. K. Lohöfer *et al.*, “Improved detection rates and treatment planning of head and neck cancer using dual-layer spectral CT,” *Eur. Radiol.*, vol. 28, no. 12, pp. 4925–4931, 2018, doi: 10.1007/s00330-018-5511-2.

[12] A. Akhondi-Asl and S. K. Warfield, “A Tutorial Introduction to STAPLE,” no. May, pp. 1–27, 2012.

[13] T. M. Buzug, *Computed tomography*, 1st ed. Lübeck, Germany: Springer, 2008.

[14] NVK, “Retningslinjer om anvendelse af ioniserende stråling i sundhedsvidenskabelige forsøg,” 2011.