Full-term evaluation of the Danish National Research Center for Radiotherapy

April 2023

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Scientific Evaluation - Danish National Research Centre for Radiotherapy (DCCC RT)

Background

In 2016 the Danish Cancer Society awarded 203M Danish Krone (DKK) from the Knæk Cancer collection for the establishment of 12 national thematic research centres in strategic areas of cancer care, as part of the Danish Comprehensive Cancer Center (DCCC). In 2018, 25M DKK was awarded over five years to the Danish National Research Centre for Radiotherapy (DCCC RT) initiative. The funding of DCCC-RT was based in the following requirements: i] a national research centre of excellence within their area of expertise and a part of the DCCC based on a national collaboration; ii] initiate and strengthen collaboration between all relevant research and clinical environments in Denmark; iii] ensure dissemination of new knowledge nationwide; iv] ensure that new knowledge from research reaches all relevant clinical environments in Denmark to the patient's benefit; v] managerial and financial support from the hospitals and the regions hosting the centre.

Scientific Evaluation

This report describes the externally assessed scientific evaluation of DCCC-RT at the end of the five-year grant that was held at the office of the Danish Cancer Society on Monday 20th March 2023.

The international external panel ("the Panel") comprised:

- David Sebag-Montefiore (Chair) - Audrey and Stanley Burton Professor of Clinical Oncology and Health Research, University of Leeds and Leeds Teaching Hospitals NHS Trust, United Kingdom
- Mechthild Krause - Professor for translational Radiation Oncology, Department of Radiotherapy and Radiation Oncology, Technische Universität Dresden, Germany
- Marianne Grønlie Guren - Professor, Consultant oncologist, Department of Oncology, Oslo University Hospital, Norway

Prior to the evaluation, the panel were provided with the following documents: the funding application call; the DCCC-RT grant application; the mid-term self -evaluation and evaluation reports and the end of grant self-evaluation report. On the day of the evaluation, the panel received presentations from members of the DCCC-RT team in the morning session and interviews with team members on the research achievements in the afternoon (Appendix A). The remit of the panel was to provide a scientific evaluation concerning research quality, originality and relevance, organization and management of the centre, international outreach, publishing and funding.

Conduct of the evaluation

The Panel wish to commend the DCCC-RT team on the excellent organisation of the evaluation including the excellent high-quality reports, presentations and slide content that was shared on the day of the evaluation and the multidisciplinary contributions across several topics to the afternoon interviews.

Overarching aims of DCCC-RT

The Panel wish to congratulate the DCCC-RT team on the successful delivery of all the overarching aims of the grant. Through DCCC-RT a vibrant and comprehensive national network of collaboration with a strong focus on translational and clinical research of high clinical relevance has been established and is operating at an internationally leading level. The research activities includes all relevant national tumour groups and involvement of all radiotherapy centers. The enthusiasm, motivation and impressive interdisciplinary collaborative team ethos of the DCCC-RT team was evident throughout the evaluation. The panel commended the group on the involvement of all stakeholders including the Ministry of Health, Danish Regions and hospitals, Danish Cancer Society, and Danish Universities in the development and delivery of DCCC-RT.

Research quality, originality and focus

The Panel considered that the overall scientific plan that combined translational research focus areas with national infrastructure and the interventional protocols was ambitious and of high quality and well-constructed building on clinical and research strengths in Denmark. This has enabled the DCCC-RT group to deliver on its overall goals to improve the treatment of cancer with radiotherapy at all centres through comprehensive collaboration, utilising and providing equity of access to state-of-the-art infrastructure and equipment.

The research plans and outputs have built strong clinical collaborative platforms for radiotherapy research with high quality protocol-driven photon, MRI-linac and proton beam facility excellence. The single national proton beam facility and the co-operative collaborative network provides a very valuable high-quality platform for an inclusive proton beam clinical and associated pre-clinical research that Denmark can both lead and participate in with other centres in Europe and beyond.

The top 5 research outputs provide evidence of high-quality research across a broad spectrum aligned with the overall plans of the grant. The Panel noted high quality co-funded PhD projects closely aligned and well distributed across the translational work packages including the presented examples of imaging biomarkers, adaptive radiotherapy, experimental radiation oncology and the national dosimetry laboratory. The National Dose Plan Bank unique research infrastructure is considered a major highlight and the Panel commended the DCCC-RT team on the successful award of 15M DKK for the DESIRE infrastructure grant from the Novo Nordisk Foundation.

Organization and management of the centre

The Panel consider the management and governance of the centre to be highly effective, organised and democratic with the appropriate scale and expertise within the Centre Management team and Steering Committee. The operational elements have appropriate representation across the participating centres and were appropriately responsive and pragmatic to finding solutions to challenges including those faced during the COVID pandemic.

A particularly successful example is the investment in the training of future leaders, including the use of 7M DKK in future leaders through the funding of twenty-three PhD stipends and a total of 86 PhD projects co-funded or related to DCCC-RT. The Panel commend the DCCC-RT on the integration of early career researchers in their annual meetings through flash talks, webinars and networking opportunities

National and international outreach, publishing and funding

National Collaboration

The panel consider the establishment of a vibrant, inclusive and effective collaborative radiotherapy research network to be an outstanding highlight for DCCC-RT. This is exemplified by the clinical trial portfolio where 27 studies are national or include over three centres, comprising 60% of the interventional protocols. It is particularly impressive that 10,505 patients were included in curative intent protocols out of an estimated total of 45,200 curative intent patients. It is noteworthy that trial inclusion and even trial leaderships were realised in all centres, including those who have been less or not active in clinical trials before, representing a major success of the structures established by DCCC-RT

Other noteworthy achievements are the national collaboration between the three MRI-Linac Centres and the national provision of proton beam radiotherapy for the country located at Aarhus. It is an outstanding achievement that there are a total of nine national and international proton beam therapy trials including five randomised studies representing one third of all ongoing proton beam trials in Europe.

International Collaboration

Whilst there are examples of long-standing international collaborations with the Nordic countries and also through EU collaborative grants, the Panel considered that this was a relative weakness during the current grant period. It recognises that the pandemic resulting in limited international travel during the majority of the grant was a significant factor.

Given the relatively small size of the Danish population, the ambition for high rates of clinical trial participation, and significant associated investments in MR-Linac and Proton beam technology, the Panel consider that there are unrealised opportunities to build and create new international collaborations following conclusion of the DCCC-RT grant. With respect to clinical trials these international collaborations are most effective at a very early stage of clinical trial development enabling alignment of standards of care and co-funding opportunities.

Scientific outputs and impact

The DCCC-RT team presented strong evidence to support Denmark's continued high international standing in radiation oncology. Whilst Denmark's world leading publication impact was placed at the top of the European league table at the start of the grant, the Panel were impressed by the presented output metrics for DCCC-RT including 588 scientific papers, 45 clinical interventional trials (including 10,770 participants), and 21 networks and national initiatives. The continued increase in the number of ESTRO abstracts and 50-70% rate of best scored abstracts, and the very favourable comparative benchmarking of clinical trial activity with Norway were considered noteworthy.

Noteworthy examples of areas of research impact include the MR-linac collaboration between the three Danish departments including technical developments, quality assurance, documentation of clinical treatments, and prospective clinical protocols; Proton beam therapy collaboration between the DMCGs; the DcmCollab national infrastructure (DcmCollab) enabling big data research at scale (13.000 cases) and Artificial Intelligence for radiotherapy (automation and improving medical image analysis and dose planning).

Funding

The panel commend the DCCC-RT team on the grant leverage achieved including 32M DKK direct / specific co-funding, 5M DKK in-kind funding to support DCCC-RT activities at participating centres and 100M DKK obtained by investigators and sponsors behind individual projects and trials.

Noteworthy examples include 30M DKK for national clinical trials; 20M DKK EU funding including Marie Sklodowska-Curie European Training Networks (RAPTOR and HYPERBOOST) and Innovative Medicines Initiative funding of the PROTECT study; and 15M DKK Novo Nordisk funding for the DESIRE data science initiative.

Whilst recognising that not all of the awards are directly attributable to the DCCC-RT investment, the Panel consider the "multiplier-effect" achieved from the 25M DKK investment to be impressive and a clear indicator of the success of the DCCC-RT initiative.

Patient involvement and public engagement

The Panel noted the leading role of the patient involvement representative Susanne Hvass Aalders in the Steering Committee and the patient representatives in the DMCG's, user panels and patient boards. The social media coverage through Twitter and Linkedin and the "Stage" initiative at ESTRO 2022 were considered noteworthy highlights. Moving forward, the Panel considered that further efforts to place patients at the heart of research and their role in inspiring and engaging the public were opportunities that the group could explore further. This would include learning from other countries, such as the UK, that have developed world-leading expertise in public and patient involvement and the Panel noted that through links with Dr Ane Appelt, this is already being explored.

Conclusion and future direction

The Panel consider that the DCCC-RT has been an outstanding success and has built a truly national collaborative network integrating clinical and translational research that is performing at an internationally leading level evidenced by the metrics of publication outputs, grant leverage, achievements, collaborations and impact. The investment in the radiotherapy research leaders of the future is particularly noteworthy. We commend the Steering Group and Management team who have provided exemplary, effective and democratic leadership of DCCC-RT.

The panel identified future investment in national infrastructure for clinical trial delivery, accelerating translational research including combination studies with novel agents and imaging and molecular biomarkers, funding to support a high-quality public and patient network and building on and creating new international collaborations as important future priorities for the DCCC-RT.

We understand that the future plans of the DCCC-RT group are in development and that these may be influenced by the feedback of the evaluation panels. We would be very pleased to discuss and comment on these plans at a later date.

The Panel consider that the investment of 25M DKK over the last five years represents very good value for money and strongly encourages future investment in DCCC-RT. The Panel strongly support the plans to continue the DCCC-RT collaboration and consider that future direct and in-kind investment is essential to effectively build on the success of DCCC-RT.

Appendix A

Program for the evaluation visit 20 March 2023
The Danish National Research Center for Radiotherapy

08.30 - 08.45: **Welcome, background and aims of the evaluation and presentation of the evaluation panelists**
Pernille Slebsager, The Danish Cancer Society

08.45 - 09.30: **Presentation of the DCCC RT and overview of activities during the grant period**
Cai Grau, Director, DCCC RT

09.30 - 09.45: **Funding and output**
Cai Grau, Director, DCCC RT

09.45 - 10.15: **National focus areas and infrastructures with examples**
Stine Korreman, Deputy Director, DCCC RT

10.15 - 10.30: Break

10.30 - 11.15: **Clinical trials with examples**
Jesper Eriksen, Deputy Director, DCCC RT

11.15 - 11.30: **Health care involvement and national collaboration**
Cai Grau, Director, DCCC RT

11.30 - 11.45: **Public and patient involvement**
Jesper Eriksen, Deputy Director, DCCC RT

11.45 - 12.30: Lunch break

12.30 - 14.30: **Interviews on research achievements** (External panelists) **Interviews on implementation and anchoring** (DCS and DCCC panelists)

14.30 - 14.45: Break

14.45 - 15.30: **Panel internal work – summary of the interviews**

15.30 - 15.55: **Feedback, preliminary observations, and further process**
Joint discussion with the center leadership

15.55 - 16.00 **End of meeting**
Pernille Slebsager, The Danish Cancer Society

Program for the parallel interviews

	Interviews on research achievements by the external panel		**Interviews on implementation and anchoring by the Danish Cancer Society and Danish Comprehensive Cancer Center panel**
12.30 - 13.00:	Challenges and opportunities for clinical radiotherapy research in a national collaborative setting *Karen-Lise Spindler (tbc)* *Jeppe Friborg (tbc)* *Cai Grau*	12.30 - 13.00:	Patient and public involvement *Jesper Eriksen*
13.00 - 13.30:	Role of DCCC RT in quality assurance, automation and use of artificial intelligence *Stine Korreman* *Christian Rønn Hansen*	13.00 - 13.30:	Management of DCCC RT *Cai Grau,* *Jesper Grau Eriksen*
13.30 - 14.00:	Conducted research SWOT *Jesper Eriksen* *Stine Korreman*	13.30 - 14.00:	Anchoring of DCCC RT and continuation of the activities in the future *Cai Grau*
14.00 - 14.30:	Management of DCCC RT *Cai Grau* *Stine Korreman* *Jesper Grau Eriksen*	14.00 - 14.30:	Impact of DCCC RT at the local departments *DCCC RT Steering group*

Evaluation report on implementation and anchoring - Danish National Research Center for Radiotherapy (DCCC-RT)

Background

For a description of the evaluation process please consult 'Frame for the evaluation visit DCCC-RT' with the program for the evaluation visit on March 20, 2023.

This report supplements the report on the scientific evaluation conducted by a panel of external evaluators concerning research quality, originality and relevance, organization and management of the center, international outreach, publishing, and funding.

The evaluation report by consultants from the Danish Cancer Society (DCS), and representative from the Danish Comprehensive Cancer Center (DCCC) has a focus on national collaboration, dissemination of knowledge, influences on policy and clinical practice, anchoring of the research center, patient involvement and public awareness. The report is based on the DCCC-RT grant application for funding from the DCS, the midterm and full-term self-evaluation completed by the DCCC-RT before the evaluation visit, and the evaluation visit on March 20, 2023.

Collaboration across Denmark and dissemination of knowledge

According to the full-term self-evaluation, major goals of DCCC-RT have been to support the creation of national infrastructures, databases, and clinical protocols, with the objective of securing the same high treatment standards and participation in clinical trials regardless of which hospital the patients are affiliated with.

The Danish radiotherapy community has had a tradition for national collaboration since the establishment of the Center for Interventional Research in Radiation Oncology (CIRRO) in 2009. DCCC-RT has continued the national collaboration and created a national platform for radiotherapy research where all Danish radiotherapy centers, research institutions and Danish Multidisciplinary Cancer Groups (DMCGs) have been involved in the grant application and have contributed to a framework for the implementation of evidence-based radiotherapy in Denmark.

The DCCC-RT steering committee is national and consists of representatives from each of the participating departments, DTU, and a patient representative. Chairing of the committee has changed once a year. The steering committee has been responsible for distributing grant resources to research projects based on e.g., national, or multicenter involvement, and geographic considerations.

According to the DCCC-RT, national collaboration has been strengthened though: 45 prospective clinical trials launched in a national setting for various cancer diseases; 86 PhD projects affiliated with DCCC-RT during the funding period; annual national meetings open for everyone in DCCC-RT; monthly webinars; workshops; and new networks and partnerships for increasing quality and development of radiotherapy.

DCCC-RT has actively worked toward opening all trials for national enrollment, which has resulted in 27/45 protocols (25 interventional) involving more than three centers. The national infrastructure for quality assurance using the dose plan bank and the associated software for centralized quality assurance has enabled improved workflow for multi-institutional studies and thus removed some of the barriers in such a setup. This has made it possible also for smaller units to participate in studies. However, the proportion of patients in clinical trials differ between cancer sites with a mean on 47 pct. included. DCCC-RT aims to increase the proportion of patients in clinical trials, and access to trials at all centers in Denmark. A present DCCC-RT study focus on whether patients are informed about ongoing trials, are eligible patients, and whether there are protocols offered at all sites.

DCCC-RT has been an active partner in the DCCC. DCCC-RT state that they have appreciated the political focus set by the DCCC on enabling and promoting national collaboration. There has been a fruitful collaboration with the DCCC and a joint dissemination of knowledge to the professional community, the patients, and the public. This is seen by the more than 20 DCCC affiliate projects and networks based on or originating from the DCCC-RT work packages (WP) and interventional protocols (IP) and at the Danish Cancer Research Days.

Concluding comments from the Evaluation Committee

DCCC-RT has successfully organized a formalized national collaboration regarding grant application, steering group members, number of national multicenter trials, and networks. Furthermore, DCCC-RT register and investigate data regarding patients' participation in clinical trials which helps optimizing processes to ensure national inclusion of patients. DCCC-RT has succeeded in disseminating knowledge in various ways and at different occasions.

Influences on policy and clinical practice

According to the application, an ambition of DCCC-RT was to build a unique national platform for radiotherapy research, operating at the highest international competitive level. The treatment concepts and hypotheses generated was expected to consequently be tested in national clinical trials and/or population-based investigations, which would lead to improved knowledge of how a specific radiotherapeutic intervention would influence outcome in the population.

Many of the DCCC-RT national focus areas, the national infrastructures as well as the planned clinical protocols focus on developing national interdisciplinary protocols and development of national consensus and guidelines for optimal treatment planning for all relevant treatment modalities. They also focus on contributing to the development of new dosimetric protocols, and generating and share knowledge needed for correct implementation, including development and use of methods for calibrations, intercomparisons and reference measurements.

In the full-term self-evaluation DCCC-RT describes a strong connection between research and the clinic, and thus DCCC-RT contributes to a swifter implementation of research results in relevant clinical settings. Data from the finalized studies and randomized trials have continuously been implemented in clinical guidelines, as members of the DCCC-RT typically also are key clinical leaders within radiotherapy, and/or members of the DMCGs responsible for the national DMCG-RKKP guidelines (RKKP: The Danish Clinical Quality Program – National Clinical Registries). An example is the implementation of partial breast irradiation for patients with low-risk breast cancer.

Much of the clinical evidence supporting the development of clinical guidelines is generated from phase IV studies where the clinical quality databases hosted by the DMCGs in collaboration with RKKP are pivotal. DCCC-RT recognizes the value of phase IV data as a supplement to prospective studies, and thus one of the work packages (WP6) had phase IV studies as their major endpoint. This work package has initiated several retrospective national phase IV studies in head and neck cancer, based on data from the clinical quality databases and has been instrumental in establishing the national prospective registration studies of non-melanoma skin cancer treated with primary radiotherapy.

Implementation of research results requires proper quality assurance of the data produced - including the radiotherapy given. DCCC-RT has supported and further developed the national dose-plan bank DcmCollab and the infrastructures for quality assurance (WP12 and WP13) of the treatment plans. This work will be further extended in the coming years with the DESIRE grant (Data Science Research Infrastructure in Radiotherapy) from the Novo Nordisk Foundation.

According to the full-term self-evaluation, the DCCC-RT center activities (research results, workshops, education, and quality assurance projects) have significantly influenced guidelines and policy documents, prompting high and equal quality of care at Danish radiotherapy departments. At the evaluation visit the DCCC-RT mentioned that radiotherapy data are not yet permanently transferred into registers. And that this could be easily done, for example within the framework of RKKP.

Concluding comments from the Evaluation Committee

DCCC-RT has indeed succeeded in building a national platform for interdisciplinary radiotherapy research. The comprehensive and close collaboration between all radiology centers has been a strong base for developing policies and clinical practice, resulting in regular implementation of research results into clinical practice.

Anchoring of the research center – managerial and financial support

The DCCC-RT has been well-anchored with substantial managerial and financial support from both hosting institutions, DCCC and other sources. The institutions behind the main applicant, Aarhus University, Aarhus University Hospitals (AUH) and Central Denmark Region, have, as promised, supported the center by housing the administration and covering administrative costs.

The DCCC-RT has, on a national level, received managerial support from the staff at DCCC both in terms of how to handle barriers in relation to the national collaboration and for public awareness activities, including events and social media.

At the evaluation visit the grant from the DCS (25 mil DKK) was described as a kick starter for new ways of collaborating across departments in Denmark.

Total direct/specific co-funding
According to the full-term self-evaluation and the evaluation visit, the total direct specific co-funding of the research center amounts to 32 mil DKK. Aarhus University, Aarhus University Hospital and Central Denmark Region, have supported the center by housing the administration office, free support for accounting and other administrative functions, and refrained any overhead at a total value of 1 mill DKK. Aarhus University Hospital has supported the activities as part of a strategic grant in the period 2018-22 with 15 mil DKK. The contribution of staff salary for the center leadership amounts to 1 mil DKK, and the Novo Nordisk Foundation has granted 15 mil DKK to expand research infrastructure around the DcmCollab.

Other co-funding
The in-kind co-funding to support the DCCC-RT activities at the participating centers is estimated at 5 mil DKK. Significant funding has been obtained by the investigators and sponsors behind the individual projects and trials (estimated 100 mil DKK since 2018). Sources of funding include hospitals, universities, industry, DCCC, EU and foundations e.g., the DCS and Novo Nordisk Foundation.

Researchers within DCCC-RT have actively used the platform to seek funding from both national and international sources. Directly for the co-financed PhD projects, where 18 specific PhD grants awarded (6 mil DKK) from DCCC-RT was matched with 27 mil DKK from other sources such as Danish Universities and companies. Indirectly in the many project grants obtained for DCCC-RT related projects from national foundations, including the DCS, Novo Nordisk Foundation, and The Lundbeck Foundation.

At the evaluation visit different challenges regarding anchoring were outlined:
- The DCCC-RT experiences difficulties getting funding for national research infrastructure.
- The DCCC-RT finds it increasingly hard to buy out clinicians, despite finances for it.
- Shorter follow-programs makes it difficult for clinical researchers to follow patients in clinical trials. Consequences are that clinical trials must fund the cost of follow-up consultations.
- DCCC-RT experience legal challenges hindering research, both in terms of lack of consensus/alignment across universities and regions and regarding contract negotiations and data protection and exchange.

Initiatives to secure further funding
In 2021, the DCCC-RT steering committee decided that the center would make every effort to continue after the end of the DCS funding period, albeit so far with no funding but using the current structural setup. This includes the WP/IP structure, annual meetings, webinars, website, and social media. The direct costs for supporting these activities are expected to be modest

(0,6 mil DKK/year), for part-time administrative support, website, and annual meetings. The collaborative national setting will be used to apply for joint research funding. The strategic decision to pursue continuation was well received at the annual meeting in 2022, where the attendees used a whole day to brainstorm on future developments and focus areas.

The DCCC-RT started in 2021 to seek funding for the next period of DcmCollab, and in 2022 received a positive evaluation from the Novo Nordisk Foundation for the 5-year project DESIRE. The grant (15 mil DKK over 5 years) will start in 2023.

Concluding comments from the Evaluation Committee

The center holds a strong position, and Danish radiotherapy and DCCC-RT have the potential to be even stronger in the future. This will though require a continued strategic and concerted effort and financial support, especially for infrastructures, coordination, and dissemination.

At the evaluation visit the DCCC-RT management expressed a strong wish for more permanent funding of research infrastructure. Regional funding was mentioned as a way of securing the center infrastructure supporting coordination and dissemination of knowledge, and the center holds an additional large clinical operational potential for the regions. We hope that the DCCC-RT succeeds in getting permanent research funding as a national collaboration. And that the center and thereby also the national collaboration will continue.

Patient involvement and public awareness

At the evaluation visit collaboration with the patients was described as essential. Patient involvement in clinical decision making, outcome reporting and clinical trials has been a focus for DCCC-RT since the beginning. Since DCCC-RT was established, there has been a patient representative in the steering committee. The overall impression is that patient involvement in the different steps of research brings quality to science. During the grant period patients have been involved in the preparation of the grant application, and patient information sheets for clinical trials.

Patient involvement though also holds some challenges, as described in the full-term self-evaluation. The greatest challenge is lack of sufficient experience and infrastructure to support the activities in the clinical research setting. Also finding the right patients with the right qualifications is a challenge and there is a need for a proper introduction to the task as patient representative but also continuous professional support. In the full-term self-evaluation, the DCCC-RT suggests a coordinated and centrally organized setup involving hospitals, universities, and DCS to solve such challenges.

Patient and public-oriented activities hosted by DCCC-RT include webinars e.g. 'What is radiotherapy?' and 'Significant research from ESTRO2022' explained to patients and the public. At the Stage at ESTRO2022, DCCC-RT hosted a daily program for patients and professionals, and at the Danish Cancer Research Days 2022 patient involvement was a topic. Moreover, DCCC-RT members have held several presentations and seminars for patient organizations e.g., at the annual National Head and Neck Cancer Days. The DCCC-RT communicates actively via the center

webpage and social media (Twitter and LinkedIn). The website is patient friendly with information on diseases and research. The most searched words on the webpage are 'side effects' and 'types of radiotherapy' indicating that the public audience is reached.

Concluding comments from the Evaluation Committee

DCCC-RT involves patients both in research and other center activities. In the full-term self-evaluation and at the evaluation visit it was though enhanced that patient involvement currently is not at an optimal level and that patients are not involved in all stages of research. We acknowledge the centers early experience regarding patient involvement, and their great potential to continue and improve this area.