Strål
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Swedish Radiation Safety Authority

Author: Scientific council on ionizing radiation within oncology

Research

2016:22

Clinical radiotherapy research activities in Sweden

Trends and terms during two decades

Report number: 2016:22 **ISSN:** 2000-0456
Available at www.stralsakerhetsmyndigheten.se

SSM perspective

Background

In 2009, the Swedish Radiation Safety Authority (Strålsäkerhetsmyndigheten, SSM) appointed a scientific council on ionizing radiation within oncology. The council consists of scientific experts in the fields of oncology, radiobiology and medical physics. Their task is to annually review and evaluate scientific developments in radiotherapy and to give SSM advice in issues where a scientific examination of different views is necessary. The council began its work in the autumn of 2009 and this is the fourth report presented.

Objective

The council summarizes the recent scientific knowledge in the field of radiotherapy in an annual report.

Results

In order to investigate the conditions for Swedish contemporary clinical radiotherapy a combined approach was undertaken by the scientific council. A literature analysis in combination with an overview of grants from the major funding sources of cancer research and a questionnaire regarding on going trials was performed. The council was focused only on external radiotherapy.

In this report the council has identified the following needs for clinical radiotherapy research:

- To turn the negative trend in publication rates, as compared with similar countries
- To increase the funding from national research foundations
- To develop a central infrastructure to support national multicentre trials

The objective of this characterisation and quantification of Swedish radiotherapy research was to identify possible unmet needs in clinical radiotherapy research and compare Swedish radiotherapy research to the scientific development in other European countries.

Project information

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Reference: SSM 2012-4950

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This report concerns a study which has been conducted for the Swedish Radiation Safety Authority, SSM. The conclusions and viewpoints presented in the report are those of the author/authors and do not necessarily coincide with those of the SSM.

SSM 2016:22

1. Introduction

Radiotherapy is one of the most important tools in cancer care used for curative treatment as well as local control and palliative treatment. Radiotherapy is today an integrated part of modern cancer treatment used in combination with medical and surgical treatment approaches. Approximately half of all cancer patients are prescribed radiotherapy during their course of disease. In Sweden approximately 22 000 treatments were prescribed 2003 when the last SBU (the Swedish council on technology assessment in health care) survey was performed (1) and the number of treatments were then anticipated to increase during the forthcoming decade. There are no indications that this trend is changing.

Radiotherapy has developed significantly during its first centennium of existence (2). This development is based on technical development as well as development in research fields such as radiation physics and radiobiology. During the last decades major improvements in imaging and accelerator technology have resulted in new radiotherapy treatment modalities such as stereotactic radiotherapy (SRT), image-guided radiotherapy (IGRT) and intensity modulated radiotherapy (IMRT), which are steps towards personalised radiotherapy. This rapid development has been possible due to major research efforts. During the last decades Swedish radiotherapy research have made major contributions including basic research resulting in modern treatment planning and delivery techniques such as IMRT as well as protocols for SRT. This development has gone hand-in-hand with a strong developmental focus in Swedish companies providing technology for radiotherapy.

The randomised clinical trial as a base for evaluation of new treatment modalities is undisputed. In medical oncology, large randomised trials are the base for the regulatory authorities´ improvement of new cancer drugs and major resources are allocated to clinical trials by the pharmaceutical industry as well as the academic community and its sponsors. In radiotherapy no similar formal regulatory authorities exist and new technology may be introduced without prior randomised trials. The rapid development of radiotherapy increases the need for randomised controlled trials for a safe introduction of new technology and new protocols. Randomised trials not only provide necessary data for evaluation of the effect and side effects of new methods but also contribute to patient safety indirectly by building a developmental-friendly clinical environment where quality assurance is in focus.

In order to investigate the conditions for Swedish contemporary clinical radiotherapy research a combined approach was undertaken. A literature analysis in combination with an

overview of grants from the major funding sources of cancer research and a questionnaire regarding on going trials was performed. The literature analysis of published radiotherapy research was compared to Denmark, the Netherlands and the United Kingdom. The results from the initial search for published Swedish radiotherapy research was further analysed in order to identify randomised prospective trials, fulfilling strict criteria. The proportions of funding for clinical radiotherapy research from all the major national funding organisations (Swedish Cancer Society (Cancerfonden), the Swedish Research Council (Vetenskapsrådet), the Swedish Childhood Cancer Foundation (Barncancerfonden) and Sweden's Innovation Agency (Vinnova)) were investigated. Finally a questionnaire regarding on-going trials was distributed to all radiotherapy departments in Sweden.

The objective of this characterisation and quantification of Swedish radiotherapy research was to identify possible unmet needs in clinical radiotherapy research and compare Swedish research to the scientific development in other European countries. We believe that clinical radiotherapy research is a prerequisite for the building of future Swedish radiotherapy as an important part of Swedish cancer care. In this report, we have focused on external beam radiotherapy.

2. Literature analysis

Analysis of the scientific literature

In an attempt to quantitatively assess the scientific research within the field of clinical radiotherapy in Sweden, a basic literature analysis was performed through the library of the faculty of medicine at Lund University. The primary indicator was the raw publication count per year during the period from 1994-2013. The search criteria were chosen to identify publications associated with prospective, Swedish randomised clinical trials (RCT), with a scientific question related to radiotherapy. Publications were identified as Swedish if at least one of the authors was affiliated to an organisation in Sweden. All searches were performed in Web of Science, PubMed, and Embase, and duplicates were removed. The complete search strategies can be found in Appendix 1a.

Comparisons

In order to put these results in a wider perspective, two additional searches were made. Firstly, three other European countries were selected for an international comparison; Denmark, the Netherlands and UK. These countries were chosen, as they are otherwise similar with respect to demographic and socio-economic factors, although with different population size. The results are shown in Figure 1. It is notable that the increase in number of publications per year during this time period is lower in Sweden (slope 2.1 as estimated by

linear regression) and Denmark (1,7) compared with the increase in the Netherlands (7.3) and the UK 8.6).

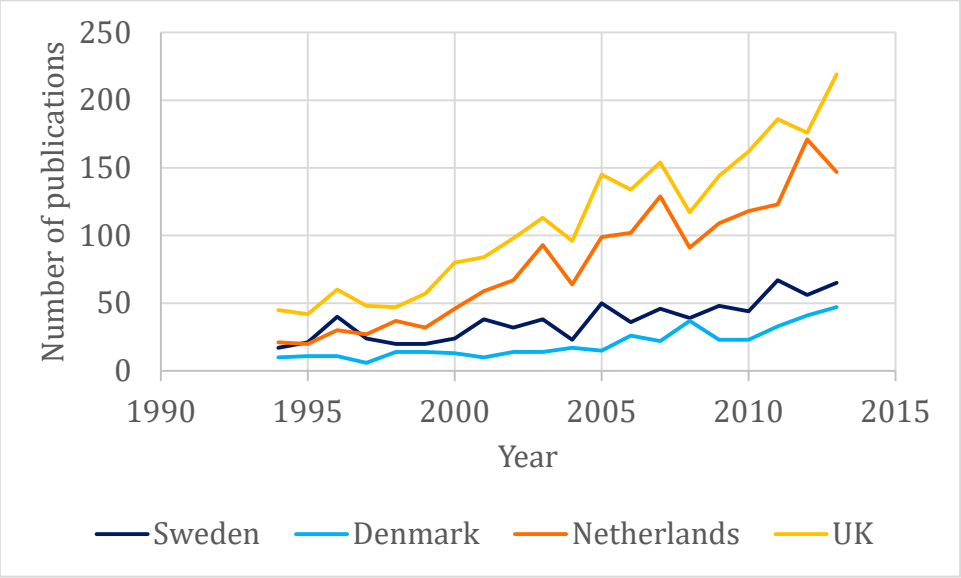

Figure 1. The raw publication count per year from the basic search on publications associated with prospective RCTs and a scientific question related to radiotherapy for Sweden, Denmark, the Netherlands and UK. The slopes of the increase of publications are 2.1 (SWE), 1.6 (DK), 7.3 (NL) and 8.6 (UK) as estimated by linear regression.

A similar search was carried out for RCT in the field of chemotherapy in Sweden. In this case, the radiotherapy-related search terms were replaced by chemotherapy-related terms. All other search criteria were kept the same, see Appendix 1b. The results are shown in Figure 2. The number of publications within radiotherapy during all the years studied is much lower compared to the number of publications within chemotherapy. One reason for this could be the different funding for those types of studies. Chemotherapy studies are often funded by the pharmaceutical companies while radiotherapy studies almost never are funded by the industry.

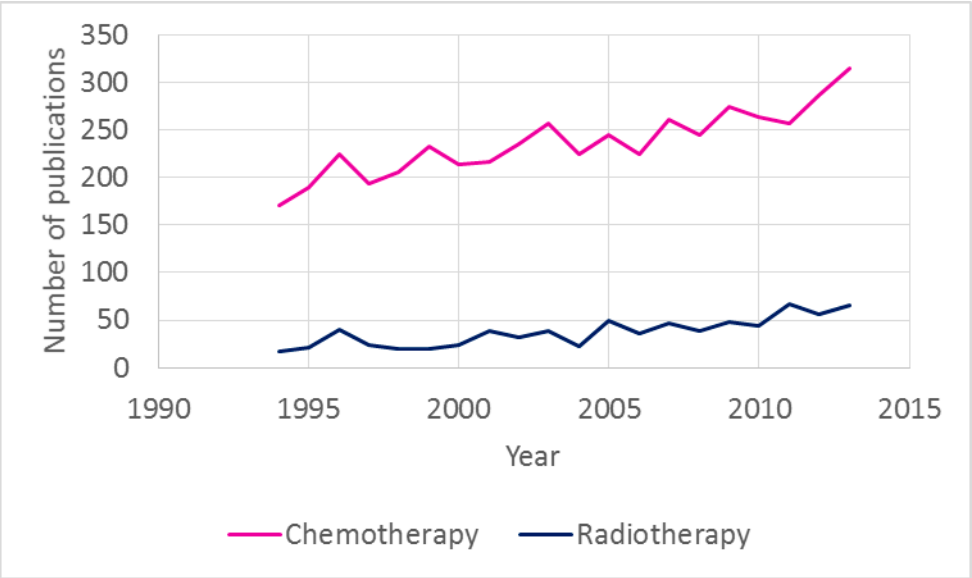

Figure 2. The raw publication count per year from the basic search on publications associated with prospective RCTs and a scientific question related to radiotherapy or chemotherapy.

Refined analysis of Swedish clinical radiotherapy research

Finally, as the search result could be expected to include some degree of false compliances, the publications obtained through the search for Swedish RCT in radiotherapy were subjected to a more thorough review. In this review, the true compliance with the original search criteria was critically examined. From the literature search, Swedish randomised controlled studies and meta-analyses on external RT aimed at comparing different modes of radiotherapy (e.g. fractionation, timing, dose, volume, technique) or the role of radiotherapy, were manually selected. RCT with the same or similar RT treatment in all study arms (e.g. RT +/- chemotherapy) were excluded. The publications found in the refined review are listed in Table 1.

In total 43 Swedish publications of true RCTs were found during the period from 1994-2013, with no trend for either increase or decrease in number of publications during the period. It is clear that high impact radiotherapy scientific research is being practiced in Sweden. Whether 43 scientific publications of RCTs during 20 years is a high or low number can be discussed.

It may be concluded that the same RCT often results in several publications and we identified 26 unique RCTs. The majority concern breast, rectal and prostate cancer. Most of the RCTs contain major contributions from Swedish centres. The meta-analyses illustrate

that even smaller studies may be important to perform since they may give important contributions to the knowledge base in an international context.

It is notable that many of those studies have had impact on radiotherapy treatments worldwide. This implies that Swedish expertise and knowledge within clinical radiotherapy research is high.

3. Review of funding for Swedish radiotherapy research

The funding from the major research foundations providing grants for cancer research was studied over the time period 2006 to 2014. Open sources provided by the organizations and accessible from internet were used. The foundations studied were The Swedish Cancer Society (Cancerfonden), the Swedish Research Council (Vetenskapsrådet), the Swedish Childhood Cancer Foundation (Barncancerfonden) and Sweden's Innovation Agency (Vinnova). Only prospective studies on humans with clinical endpoint related to external radiotherapy were selected.

The research foundations investigated approved grants for clinical radiotherapy projects between 2006 and 2014 to a total amount of 70 250 kSEK, on average 7 800 kSEK/year (figure 3). The funding on average per project was 2600 kSEK. Notably, Vinnova represent 15% of the value with only one project granted. The relative contribution from the different research foundations is shown in figure 4.

Between 2006 and 2010 Cancerfonden was the single largest donor without any competition with 93% of the grants approved (figure 5). After 2010, Cancerfonden has only contributed to 13% (figure 6). The last two years no project has been granted at all by Cancerfonden. Obviously, in cancer research Cancerfonden is a large donor entity contributing with 300-400 MSEK/year. The funding for external RT was only a few percent (0.9±0.9%) of the total sum handed out (figure 7). The other foundations have increased their grants keeping the average funding about the same but still on a low level over the total period studied. It should be noted that the grant by Vinnova is directed towards innovation and implementation rather than science.

A limitation of the present data is that we have no information on the number applications submitted and/or rejected. Few or no approved grants may, of course, be the consequence of a limited number of applications. Alternatively, applications may have been submitted but

been regarded as of low quality and not approved. Detailed knowledge on application statistics has not been obtained from the research foundations.

Another limitation is that we have not been able to quantify the support from the local funds for each region. We are aware that these research funds are very important for the local researchers and the grants may be substantial. However, support from the national research foundations are of great importance especially for multicentre trials.

In summary the funding from the research foundations for prospective studies on humans with clinical endpoint related to external radiotherapy is very limited. If the declining contribution from Cancerfonden continues it raises concern for the future.

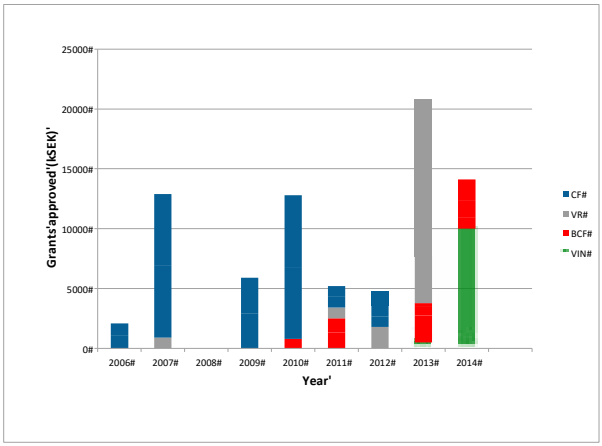

Figure 3. *The grants (2006-2014) from the major cancer research foundations to prospective studies on humans with clinical endpoint related to external radiotherapy (CF=Cancerfonden, VR=Vetenskapsrådet, BCF=Barncancerfonden, VIN=Vinnova)*

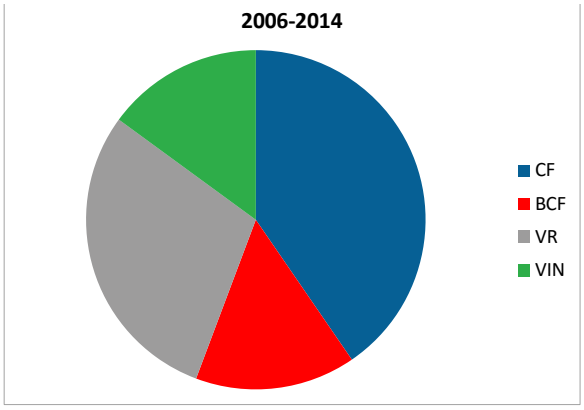

Figure 4. *The relative contribution from the major cancer research foundations 2006-2014. CF=40%, BCF=15%, VR=30%, VIN=15%.*

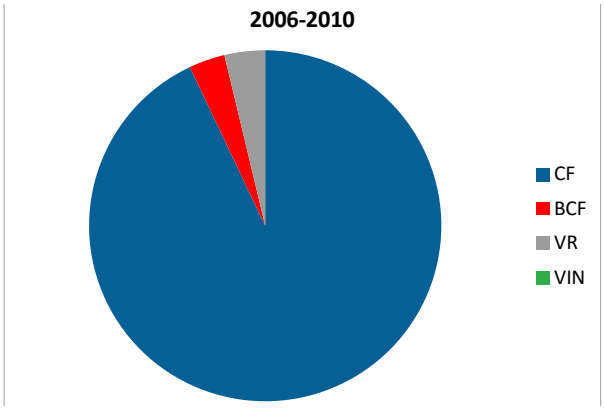

Figure 5 *The relative contribution from the major cancer research foundations 2006-2010*

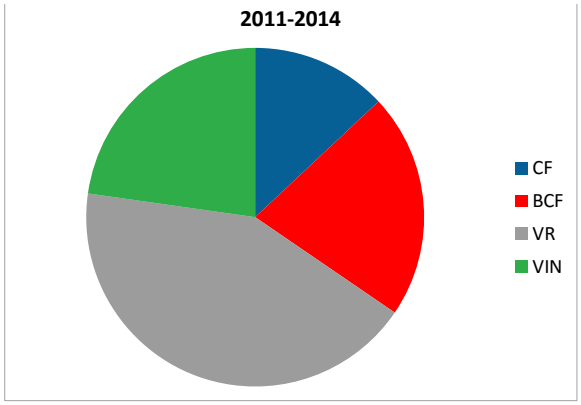

Figure 6. *The relative contribution from the major cancer research foundations 2011-2014.*

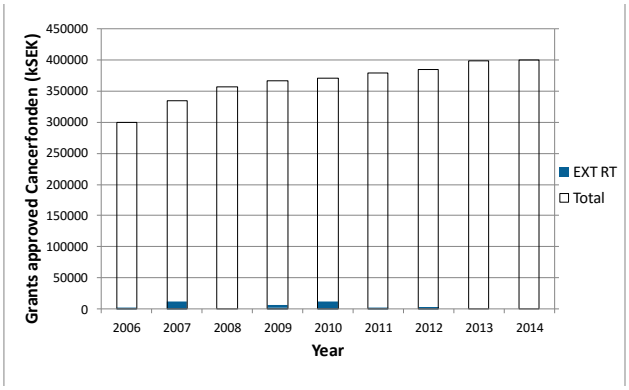

Figure 7. *The grants (2006-2014) from Cancerfonden. Blue bar=To prospective studies on humans with clinical endpoint related to external radiotherapy, Unfilled bar=Total grants approved for research from Cancerfonden.*

4. Ongoing radiotherapy research in Sweden, results from a questionnaire

From the previous results, it seems obvious that the, apparently modest, funding of clinical radiotherapy research does not reflect the actual activities in the area. For that reason a questionnaire was distributed to all the 15 radiotherapy centres in Sweden. The aim was to collect information on number of studies, number of patients per study, design, end-points and funding. The questionnaire (in Swedish) is found in Appendix 2.

Results

Eight radiotherapy centres answered the questionnaire, six (out of seven) university hospitals and two county centres.

Eighteen multicentre studies were reported. Twelve studies are RCTs where endpoints concern tumour effect and/or side effects. Of these RCTs, four were head and neck cancer trials, three lung cancer trials and one each concerning prostate cancer, breast cancer, oesophageal cancer, gastric cancer and rectal cancer. Of the remaining six multicentre studies, five were prospective studies, either phase I or II or register studies of e.g. late side effects. One was a retrospective study.

Two of the university hospitals reported several ongoing local studies, e.g. implementation of new techniques for imaging, finding predictive factors for response to RT and evaluation of palliative treatment. Only a few local studies were reported from the other hospitals that answered the questionnaire.

Most of the studies in the reporting centres were locally funded, either from local research foundations or comprised in the clinical budget (table 2). It is perhaps noteworthy that many of the larger multicentre trials had their major funding from local or regional sources.

5. Discussion

In this study we identified an active community performing clinical radiotherapy research with a small and decreasing funding. The research activity in Sweden appears to loose momentum compared with countries as the Netherlands and UK.

Radiotherapy has undertaken a major leap forward during the last decades. The stepwise introduction of modern imaging tools support the optimisation of the treatment for each individual patient. Presently, that is mainly for anatomy based personalisation but in the future also for using functional imaging for gathering information on individual tumour properties and response (3). The development of new tools for optimising dose distributions are accompanied by improved delivery techniques such as intensity modulated radiotherapy (IMRT), volumetric arc therapy (VMAT) and advanced proton techniques. This development of new technology and procedures is internationally an active area of research. The implementation of new radiotherapy protocols increases the demand for patient oriented translational clinical radiotherapy research and ultimately increases the need for randomised controlled trials (RCTs) in radiotherapy.

Several important medical technology companies have been founded in Sweden, perhaps as a consequence of a strong tradition of research leading to preservation of a high level of expertise within the area of radiotherapy. The results of Swedish cancer treatment are still among the best in Europe (4). This fact supports that the focus on one of the main treatments of cancer i.e. radiotherapy actually benefit the Swedish cancer patients. This development has been recognised by the responsible authorities and large investments have been made in sophisticated new equipment, e.g. the national proton facility “The Skandion Clinic”. It has been proposed that The Skandion Clinic will be the platform on which the scientific evidence for proton therapy applications should be obtained. However, this investment in infrastructure has not been accompanied with the corresponding funding required to perform the clinical studies needed to create the evidence. Neither, to the best of our knowledge, has there been any Swedish consortium created to apply for funding for this purpose.

The basic literature analysis showed that the increase in number of research publications per year during the period from 1994-2013 is lower in Sweden and Denmark compared to the increase in Netherlands and UK. The reason for this negative trend for Sweden is unclear. It might originate from difficulties in receiving funding, lack of possibilities for research studies at the university hospitals for example because of high pressure of clinical work in combination with lack of staff, or from lack of natural platforms for stimulating national research collaborations. Both Sweden and Denmark are relatively small countries and introducing studies in collaboration between the two countries might be beneficial and break the negative trend shown in comparison with the Netherlands.

A survey of on-going clinical radiotherapy research revealed several prospective, randomised multicentre trials with hard clinical endpoints. Although some of them are initiated outside Sweden, patients are included from many of the Swedish centres. These trials will give answers to pertinent radiotherapy related problems. Because of the low frequency of replies on our submitted questionnaire we do not have a full survey of local studies with alternative endpoints. However, we still have the response from the major players, i.e. the university clinics. We know that development and implementation of new techniques in the radiotherapy process are in progress, such as imaging, gating, tracking, and probably also local studies with related endpoints. In the present survey of ongoing trials we have focused on studies with end-points related to the outcome of RT. As a contrast to clinical studies in medical oncology, there is usually no commercial interest or major external support for clinical radiotherapy research. In combination with the poor support from the major research funds it is therefore surprising to find that clinical research with high impact is actually performed in a majority of the university hospitals and in several county hospitals. Remarkable, is the extremely small fraction of the funding from Cancerfonden that is directed towards external radiotherapy. Since we lack information on the proportion and quality of applications within each area of research it is not possible to draw conclusions on the cause of the poor outcome.

The absolute number of unique Swedish RCTs found in publications during 1994-2013 is small but most of them were reported to have taken more than a decade from the first patient accrual until reporting the study results. Because of the fact that results and publications appear years after study initiation, the revenue for funding bodies may thus appear low with the currently prevailing methods of weighing scientific production (i.e. number of publications, journal impact factor etc.). Nevertheless, many of the studies have had a major impact on patient care, safety and prognosis. In several cases this impact is manifested in care programs, guidelines, and regional recommendations. It may be concluded that the impact of

e.g. the breast, prostate and colorectal cancer studies represent scientific breakthroughs that have improved the outcome for large numbers of patients.

This report raises concerns regarding the development of radiotherapy research in comparison to other European countries. The literature review performed shows a slower development, measured as number of publications, than in countries with comparable standards of living and economical resources. This decrease in scientific production is connected to a small and decreasing proportion of funding of clinical radiotherapy research. The reason for the lack of funding from the larger institutions cannot be established based on the present review. There may be several explanations such as a low priority for such projects or failure to submit an application at all. However, it may be noted that even quite large randomised clinical studies, that are granted economical support, only receives a fraction of the actual cost.

In contrast to the impression given by studying the funding, the research activity in comparison with funding seems to be high in many institutions. As stated previously, it is also obvious that the clinical impact of performed randomised controlled trials (RCTs) has been high. The results from several of the listed RCTs have been implemented in Swedish care programmes as well as international guidlines. As an exemple the introduction of pre-operative radiotherapy for rectal cancer which has improved outcome for this patient group. This may lead to the conclusion that the level of competence in the radiotherapy community is high. It also shows that local funding probably is a major source for ongoing clinical research that is closely patient related. This is indeed a contradiction. The clinical studies of this character are of national (and often international) interest. However, many of the high profile research and development efforts such as multicentre trails, national proton projects, and national efforts to introduce new techniques (e.g. MR in radiotherapy), are probably greatly hampered by lack of central funding and support. In many cases, national collaboration has been very successful.

The development of a national infrastructure for support of clinical radiotherapy research may be an important step in the process of developing better treatments and techniques and efficiently taking advantage of the major investments in equipment in the treatment of cancer patients. Such efforts may stimulate the recruitment of skilled researchers and staff to produce safer and more efficient methods of radiotherapy. In the end this will benefit the patient directly by faster access to new treatment protocols.

To summarise, we have identified the following needs for clinical radiotherapy research in Sweden

- To turn the negative trend in publication rates, as compared with similar countries

- To increase the funding from national research foundations
- To develop a central infrastructure to support national multicentre trials

6. Recommendations

Based on our structured review of the contemporary clinical radiotherapy research activity in Sweden and the present funding for this research we have a few suggestions to further improve Swedish clinical radiotherapy including personalized radiotherapy, increased optimisation of the risk-benefit balance for each patient and patient safety in the near future:

- Evidence-based medicine based on clinical trials is of paramount interest for patient safety. In order to maintain safety a national infrastructure for clinical trials to support the conduction of clinical radiotherapy trials would greatly facilitate patient oriented radiotherapy research. The structure and function of this infrastructure should be carefully discussed but administrative as well as financial support must be implemented in this national network for clinical radiotherapy research.

- A dialog with the major funding organizations is needed in order to understand the underlying background to low level of funded application and in order to improve the research funding to clinical studies in radiotherapy.

- A national resource for financing clinical research in general should be organised. Clinical studies are expensive to conduct and in radiotherapy the external fundings for performing RCTs are limited.

The organisation of a national infrastructure for clinical radiotherapy research would not only facilitate academic research but also have major impacts on patient safety, industrial development and finally patient outcome.

The objective of this characterisation and quantification of Swedish radiotherapy research was to identify possible unmet needs in clinical radiotherapy research and compare Swedish radiotherapy research to the scientific development in other European countries. We believe that clinical radiotherapy research is a prerequisite for the building of future Swedish radiotherapy as an important part of Swedish cancer care.

7. Tables

Table 1

First author	(n)	Year	Type[1]	End point(s)[2]	Title
Arriagada R	2140	1994	M	OS	Effect of thoracic radiotherapy on mortality in limited small-cell lung-cancer - a metaanalysis of 13 randomized trials among 2,140 patients
Borgström S	195	1994	RCT	OS	Mastectomy only versus radical-mastectomy and postoperative radiotherapy in node-negative, resectable breast-cancer - a randomized trial.
Liljegren G	381	1994	RCT	LRC	Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial. Uppsala-Orebro Breast Cancer Study Group.
Näslund I	168	1994	RCT	OS	Hyperfractionated radiotherapy of bladder-cancer - a 10-year follow-up of a randomized clinical-trial.
Ringdén O	167	1994	RCT	CSS	A randomized trial comparing busulfan with total body irradiation as conditioning in allogeneic marrow transplant recipients with leukemia: a report from the Nordic Bone Marrow Transplantation Group
Cedermark B	850	1995	RCT	LRC, OS	The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Colorectal Cancer Study Group.
SCRCSG	557	1996	RCT	LRC, OS	Randomized study on preoperative radiotherapy in rectal carcinoma.
Swedish Rectal Cancer Trial	1168	1996	RCT	LRC OS	Local recurrence rate in a randomised multicentre trial of preoperative radiotherapy compared with operation alone in resectable rectal carcinoma.
Liljegren G	381	1997	RCT	Morb	Arm morbidity after sector resection and axillary dissection with or without postoperative radiotherapy in breast cancer stage I. Results from a randomised trial. Uppsala-Orebro
Påhlman L	1168	1997	RCT	OS	Improved survival with preoperative radiotherapy in resectable rectal cancer.
Gyenes G	960	1998	RCT	Cardiac toxicity	Long-term cardiac morbidity and mortality in a randomized trial of pre- and postoperative radiation therapy versus surgery alone in primary breast cancer.
Martling A	557	2001	RCT	LRC, OS, mortality	The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: Long-term follow-up of a population-based study.
Socie G	488	2001	M	OS	Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: Long-term follow-up of 4 randomized studies.
Malmström P	1187	2003	RCT	LRC	Breast conservation surgery, with and without radiotherapy, in women with lymph node-negative breast cancer: a randomised clinical trial in a population with access to public mammography screening.

Sorbe B	98	2003	RCT	PFS	Consolidation treatment of advanced ovarian carcinoma with radiotherapy after induction chemotherapy.
Sorbe B	172	2003	RCT	PFS	Consolidation treatment of advanced (FIGO stage III) ovarian carcinoma in complete surgical remission after induction chemotherapy: A randomized, controlled, clinical trial comparing whole abdominal radiotherapy, chemotherapy, and no further treatment.
Tyrell C J	106	2004	RCT	Gynecomasty	Prophylactic breast irradiation with a single dose of electron beam radiotherapy (10 Gy) significantly reduces the incidence of bicalutamide-induced gynecomastia.
Birgisson H	1147	2005	RCT	Morb	Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial.
Folkesson J	908	2005	RCT	OS, LRC	Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate.
Van Den Bent MJ	311	2005	RCT	PFS, OS	Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: The EORTC 22845 randomised trial.
Emdin S	1046	2006	RCT	LRC	SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening.
Kaasa S	376	2006	RCT	Pain rel	Prospective randomised multicenter trial on single fraction radiotherapy (8 Gy x 1) versus multiple fractions (3 Gy x 10) in the treatment of painful bone metastases.
Pollack J	252	2006	RCT	Morb	Late adverse effects of short-course preoperative radiotherapy in rectal cancer.
Killander F	724	2007	RCT	LRC	Radiotherapy and tamoxifen after mastectomy in postmenopausal women - 20 year follow-up of the South Sweden Breast Cancer group randomised trial SSBCG II : I
Birgisson H	454	2008	RCT	Morb	Late gastrointestinal disorders after rectal cancer surgery with and without preoperative radiation therapy.
Holmberg l	1067	2008	RCT	LRC	Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast.
Fokstuen T	274	2009	RCT	Morb and mort	Postoperative morbidity and mortality in relation to leukocyte counts and time to surgery after short-course preoperative radiotherapy for rectal cancer.
Fransson P	54	2009	RCT	QoL	Health-related quality of life 10 years after external beam radiotherapy or watchful waiting in patients with localized prostate cancer.
Fransson P	872	2009	RCT	QoL	Quality of life in patients with locally advanced prostate cancer given endocrine treatment with or without radiotherapy: 4-year follow-up of SPCG-7/SFUO-3, an open-label, randomised, phase III trial.
Killander F	367	2009	RCT	LRC, OS	Efficient reduction of loco-regional recurrences but no effect on mortality twenty years after postmastectomy radiation in premenopausal women with stage II breast cancer - a randomized trial from the South Sweden Breast Cancer Group.
Nyman J	152	2009	RCT	TTP, OS	How to improve loco-regional control in stages IIIa-b NSCLC? Results of a three-armed randomized trial from the Swedish Lung Cancer Study Group.

Widmark A	875	2009	RCT	CSS	Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial.
Lundstedt D	422	2010	RCT	Morb	Symptoms 10-17 years after breast cancer radiotherapy data from the randomised SWEBCG91-RT trial
Pettersson D	303	2010	RCT	Side effects	Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer.
Solberg A	120	2011	RCT	PSA relapse	Residual prostate cancer in patients treated with endocrine therapy with or without radical radiotherapy: A side study of the SPCG-7 randomized trial.
van Gijn W	1861	2011	RCT	OS	Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial.
Yarnold J	915	2011	RCT	Morb	First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015).
Zackrisson B	750	2011	RCT	LRC, OS	Two-year results from a Swedish study on conventional versus accelerated radiotherapy in head and neck squamous cell carcinoma The ARTSCAN study.
Malmström A	342	2012	RCT	OS	Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial.
Mauguen A	2000	2012	M	OS	Hyperfractionated or accelerated radiotherapy in lung cancer: An individual patient data meta-analysis.
Sorbe B	527	2012	RCT	LRC, OS	External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma--a prospective randomized study.
Sorbe B	527	2012	RCT	QoL	External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma: a prospective, randomized study--quality-of-life analysis.

Table 1: *Swedish randomised controlled clinical trials and meta-analysis 1994-2013. [1]Study type(RCT, randomised controlled trial; M, meta-analysis) [2]Endpoints (OS, overall survival; PFS, progression free survival, LRC; loco-regional control; Morb, morbidity; CSS, cancer specific survival; QoL, Quality of life)*

Table 2

Title of study	Description	Primary Endpoint[1]	Multicentre	n	Type of study[2]
ARTSCAN 2	Preoperative accelerated vs. postoperative conventional radiotherapy in patients with resectable cancer of the oral cavity	LRC (DFS, OS, Toxicity)	Yes	260	RCT (Ph III)
ARTSCAN 3	A randomized multicenter phase III study of cisplatin plus radiotherapy compared to cetuximab plus radiotherapy in locally advanced head and neck cancer	OS	Yes	650	RCT (Ph III)
HYPO-PC-RT	HYPO-fractionated Radiotherapy of Intermediate risk Localised Prostate cancer	LC (PSA progress)	Yes	2000	RCT (Ph III)
HILUS	A phase II study of SBRT in patients with centrally located tumours	LC, Toxicity	Yes	60?	Prospective (Ph II)
RAPIDO	Randomized Multicentre Phase III Study of Short Course Radiation Therapy Followed by Prolonged Pre-operative Chemotherapy and Surgery in Primary High Risk Rectal Cancer Compared to Standard Chemoradiotherapy and Surgery and Optional Adjuvant Chemotherapy	DFS	Yes	885	RCT (Ph III)
CRITICS	ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach	OS	Yes	788	RCT (Ph III)
SENOMAC	Sentinel node biposy in breast cancer	OS	Yes	3700	RCT (Ph III)
NEORES II	Neoadjuvant treatment for oesophageal cancer	CR	Yes		RCT (Ph III)
ACCROBAT II	Treatment of H&N cancer	OS	Yes		RCT (Ph III)
PLANET	Dose intesified radiochemotherapy for locally advanced lung cancer (closed)	PFS	Yes		RCT (Ph III)
RISK	Late effects after childhood radiotherapy	Toxicity	Yes		Observational
SPACE	SBRT for stage I lung cancer (closed)	LRC, Toxicity	Yes		RCT (Ph III)
OLIGO	SBRT for oligometastasizing lung cancer	LRC	Yes		Prospective
	Cohort study for ca mammae	LRC	Yes	600	Observational
ARTFORCE	Lung cancer	PFS	Yes	106	RCT (Ph III)
ARTFORCE II	H & N cancer	LRC, Toxicity	Yes	268	RCT (Ph III)
	Late effects vs dose in breast cancer	Toxicity	Yes	1500	Retrospective

	Ca mam postop brachytherapy	Feasability	Yes	50	Prospective (Ph II)
PALAESTRA,	Palliative short-course hypofractionated radiotherapy followed by chemotherapy in adenocarcinoma of the esophagus or eophagogastric junction trial - a phase II clinical trial protocol	Toxicity	No	23	Prosepective (Ph I)
	Imaging tissue microstructure in brain tumors- improved diagnostics using advanced diffusion MR in glioma	Treatment effect, cognitive functions	No	40	Observational
	Value of MRI and 18F-FET-PET prior to and after radiation therapy of brain metastases to evaluate short and long term treatment effects and predict overall survival	Evaluation of short and long term treatment effects and predict overall survival	No	100	
	Characterization of brain metastases using state of the art magnetic resonance imaging techniques	Characterisation of brain metastases using advanced MRI technology	No	80	
	Head & neck side-effects after H & N treatement	Dose-volume response	No	150	Retrospective
	PSA and salvage radiotherapy	PSA response at 6 months	No	300	Observational
	Motion management for breast cancer and MB Hodgkin	Change in irradiated cardiac volume	No		Observational
	Tonsillar cancer.	Late toxicity	No	50	Observational
	PET and MRi for response prediction in brain tumours	Response prediction	No	30	Observational
No Harm	Reduction of rectal side effects after radiotherapy for prosttate cancer	Toxicity	No	30	Prospective (Ph2)
	PET and MRi for response prediction in H & N cancer	Response prediction	No	25	Observational
PARAPLY	Local boost for prostate cancer	Relapses, toxicity	No	80	Prospective (Ph2)
	Gating for breast cancer	Toxicity	No		Observational

Table 2: *Ongoing radiotherapy studies 2014 as reported in questionnaire. [1] Primary endpoints (LRC, loco regional control; OS, overall survival; PFS, progression free survival; DFS, disease free survival) [2]Type of study (RCT, prospective randomised clinical tria; Ph, phase).*

8. Acknowledgements

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9. References

1. Ringborg U, Bergqvist D, Brorsson B, Cavallin-ståhl E, Ceberg J, Einhorn N, et al. The Swedish Council on Technology Assessment in Health Care (SBU) Systematic Overview of Radiotherapy for Cancer including a Prospective Survey of Radiotherapy Practice in Sweden 2001--Summary and Conclusions. Acta Oncol. 2003 Jan;42(5-6):357–65.

2. Möller TR, Einhorn N, Lindholm C, Ringborg U, Svensson H. Radiotherapy and Cancer Care in Sweden. Acta Oncol. 2003 Jan;42(5-6):366–75.

3. Zackrisson B, editor. Research 2014:51. Stockholm: SSM; 2014 Feb.

4. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. Lancet Oncol. 2014 Jan;15(1):23–34.

10. Appendices

Appendix 1a. Search strategies for radiotherapy clinical trials

Web of Science

No.	***Search***	***Counts***
#1	TOPIC: (”radiation therapy” OR ”radiotherapy” OR ”radiotherapies” OR ”radiation therapies”) *Time span=1994-2013*	146 861
#2	TOPIC: (“randomized controlled trials” OR “randomized control trial” OR “randomized” OR “randomised controlled trial” OR “randomized clinical trial” OR “randomised control trial” OR “randomized trial” OR ”randomised”) *Time span=1994-2013*	490 388
#3	#1 AND #2	19 538

#4	#3 refined by COUNTRIES/TERRITORIES: (SWEDEN) AND DOCUMENT TYPES: (ARTICLE OR PROCEEDINGS PAPER OR REVIEW)	514
#5	#3 refined by COUNTRIES/TERRITORIES: (DENMARK) AND DOCUMENT TYPES: (ARTICLE OR PROCEEDINGS PAPER OR REVIEW)	251
#6	#3 refined by COUNTRIES/TERRITORIES: (NETHERLANDS) AND DOCUMENT TYPES: (ARTICLE OR PROCEEDINGS PAPER OR REVIEW)	1 100
#7	#3 refined by COUNTRIES/TERRITORIES: (ENGLAND) AND DOCUMENT TYPES: (ARTICLE OR PROCEEDINGS PAPER OR REVIEW)	1 714

PubMed

No.	***Search***	***Counts***
#1	"Radiotherapy"[Mesh] OR "radiation therapy" or radiotherapies or "radiation therapies"	290 273
#2	#1 AND (((sweden[Title/Abstract]) OR sweden[Affiliation]) OR sweden[MeSH Terms]) AND ("Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR ((randomized OR randomised) AND controlled)) *Filter: Publication date from 1994/01/01 to 2013/12/31, abstract*	228
#3	#1 AND (((denmark[Title/Abstract]) OR denmark [Affiliation]) OR denmark [MeSH Terms]) AND ("Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR ((randomized OR randomised) AND controlled)) *Filter: Publication date from 1994/01/01 to 2013/12/31, abstract*	143
#4	#1 (((netherlands[Title/Abstract]) OR netherlands[Affiliation]) OR netherlands [MeSH Terms]) AND ("Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR ((randomized OR randomised) AND controlled)) *Filter: Publication date from 1994/01/01 to 2013/12/31, abstract*	448
#5	#1 AND ((“great Britain”[Title/Abstract]) OR “united kingdom”[Title/Abstract] OR “united kingdom”[Affiliation] OR “great britain”[Affiliation] OR "uk"[affiliation] OR “great Britain”[MeSH Terms]) AND ("Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR ((randomized OR randomised) AND controlled)) *Filter: Publication date from 1994/01/01 to 2013/12/31, abstract*	874

Embase

No.	***Search***	***Counts***
#1	'radiotherapy'/exp OR 'radiotherapy' OR 'radiation therapy'/exp OR 'radiation therapy' OR radiotherapies OR 'radiation therapies'	540 540
#2	#1 AND (sweden:ad,ab,ti OR 'sweden'/exp) AND ('randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR (randomized OR randomised AND controlled)) *limit to [1994-2013]/py*	404

	limit: has abstract	
#3	#1 AND (denmark:ad,ab,ti OR 'denmark'/exp) AND ('randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR (randomized OR randomised AND controlled)) *limit to [1994-2013]/py* *limit: has abstract*	239
#4	#1 AND (netherlands:ad,ab,ti OR 'netherlands'/exp) AND ('randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR (randomized OR randomised AND controlled)) *limit to [1994-2013]/py* *limit: has abstract*	801
#5	#1 AND ('united kingdom'/exp OR 'united kingdom':ad OR 'great britain':ad OR 'uk':ad) AND ('randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR (randomized OR randomised AND controlled)) *limit to [1994-2013]/py* *limit: has abstract*	1 736

Appendix 1b. Search strategies for chemotherapy clinical trials

Web of Science

No.	*Search*	*Counts*
#1	TOPIC: (”*chemotherap*” OR ”antineoplastic agents”) AND TOPIC: (“randomized controlled trials” OR “randomized control trial” OR “randomized” OR “randomised controlled trial” OR “randomized clinical trial” OR “randomised control trial” OR “randomized trial” OR “randomised”) *Time span=All years*	40 134
#2	#1 refined by DOCUMENT TYPES: (ARTICLE OR PROCEEDINGS PAPER OR REVIEW)	36 909
#3	#2 refined by COUNTRIES/TERRITORIES: (SWEDEN) AND DOCUMENT TYPES: (ARTICLE OR PROCEEDINGS PAPER OR REVIEW) *Time span=1994-2913*	771

PubMed

No.	*Search*	*Counts*
#1	(("Maintenance Chemotherapy"[Mesh] OR chemotherapy OR chemotherapies)) OR "Antineoplastic Agents"[Mesh]	2 689 179
#2	#1 AND ((sweden[Title/Abstract]) OR sweden[Affiliation]) AND (("Randomized Controlled Trials as Topic"[Mesh]) OR ((randomized OR randomised) AND controlled)) AND (Journal Article[ptyp] OR Review[ptyp] OR systematic[sb]) AND hasabstract[text] AND ("1994/01/01"[PDat]:"2013/12/31"[PDat])	3 679

Embase

No.	*Search*	*Counts*
#1	'chemotherapy'/exp OR chemotherapy OR chemotherapies OR 'antineoplastic agent'/exp	1 811 810
#2	#1 AND sweden:ad,ab,ti AND ('randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'randomized controlled' OR 'randomised controlled') AND ([article]/lim OR [conference paper]/lim OR [review]/lim) AND [1994-2013]/py	1 125

Appendix 2. Questionnaire (Swedish)

Enkät till verksamhetschefer i onkologi och medicinsk fysik angående pågående kliniska studier inom radioterapi.

Strålsäkerhetsmyndigheten (SSM) har ett Vetenskapligt råd för frågor om joniserande strålning inom onkologi. Med målet att utreda hur kompetensförsörjning och utveckling inom området tillgodoses gör rådet en undersökning av forskningsaktiviteten inom klinisk strålbehandlingsverksamhet liksom förutsättningarna för sådan aktivitet.

Färre kliniska studier inom radioterapi publiceras från Sverige jämfört med liknande länder i Europa. För att försöka finna orsaker till detta och kanske kunna förbättra förutsättningarna så önskar man kartlägga pågående studier i landet. Vi ber er därför att delta i detta projekt genom att fylla i nedanstående enkät.

De finansiella förutsättningarna för klinisk forskning inom radioterapi kommer också att undersökas via olika bidragsgivare.

1. Hur många studier med radioterapeutiska endpoints pågår vid ditt center?

2. Pågående studier:

    a. titel
    b. hypotes/endpoint
    c. antal patienter som skall inkluderas
    d. typ av studie prospektiv retrospektiv
    e. deltagande center lokal multicenter

3. Finansiering, hur?
    a. Enbart extern industrifinansiering
    b. Akademisk studie med huvudsakligen ALF
    c. Akademisk studie med bidrag från nationell/internationell organisation (t.ex. Cancerfonden, Barncancerfonden, Vetenskapsrådet, Stiftelsen för strategisk forskning)
    d. Lokal eller klinikanknuten fond
    e. ”Intern” finansiering t.ex. inom klinikbudget
    f. Annat, ange

4. Extern finansiering, hur mycket?
    a. 100 %
    b. 75 %
    c. 50 %
    d. 25 %
    e. Specifik summa

5. Hur många studier har inte kunnat startas under det senaste året p.g.a att man sökt men fått finansiering?

2016:22

The Swedish Radiation Safety Authority has a comprehensive responsibility to ensure that society is safe from the effects of radiation. The Authority works to achieve radiation safety in a number of areas: nuclear power, medical care as well as commercial products and services. The Authority also works to achieve protection from natural radiation and to increase the level of radiation safety internationally.

The Swedish Radiation Safety Authority works proactively and preventively to protect people and the environment from the harmful effects of radiation, now and in the future. The Authority issues regulations and supervises compliance, while also supporting research, providing training and information, and issuing advice. Often, activities involving radiation require licences issued by the Authority. The Swedish Radiation Safety Authority maintains emergency preparedness around the clock with the aim of limiting the aftermath of radiation accidents and the unintentional spreading of radioactive substances. The Authority participates in international co-operation in order to promote radiation safety and finances projects aiming to raise the level of radiation safety in certain Eastern European countries.

The Authority reports to the Ministry of the Environment and has around 300 employees with competencies in the fields of engineering, natural and behavioural sciences, law, economics and communications. We have received quality, environmental and working environment certification.

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