Strål
säkerhets
myndigheten
Swedish Radiation Safety Authority

Research

2011:25

Report from SSM's scientific council on ionizing radiation within oncology, 2010

Report number: 2011:25 **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 first report presented.

Objectives

The scientific council is obliged to produce an annual report on radiotherapy issues. The report will summarize recent scientific knowledge.

Results

In this report, three main areas have been highlighted: quality assurance (QA), quality control (QC) and late side-effects including the risk of radiation-induced secondary malignancies. These areas reflect the ongoing activities in leading international radiotherapy organisations. Specific attention is given to new technologies such as image-guided radiotherapy and intensity-modulated radiotherapy and how these influence QA, QC and late side-effects. Late side-effects of radiotherapy are also discussed in the context of paediatric oncology and radiotherapy in combination with chemotherapy. The council states that there is a lack of consensus, both nationally and internationally, on how to optimally perform QA of radiotherapy with advanced technologies.

The council therefore recommends that SSM increase its commitment to QA and QC in radiotherapy. The council has also identified a limited knowledge base for late side-effects of both old and new forms of treatment. Within radiotherapy, the advice given to SSM is to support and emphasize the importance of registration of quality parameters and long-term outcomes in order to increase the knowledge base for late effects. SSM should also support development of a system in which new and unexpected adverse effects of radiotherapy can be reported and systematically compiled.

Project information

Contact persons at SSM: Peter Björk and Catarina Danestig Sjögren
Reference: SSM 2009/3757

Strål
säkerhets
myndigheten
Swedish Radiation Safety Authority

Author: SSM's scientific council on ionizing radiation within oncology

2011:25

Report from SSM's scientific council on ionizing radiation within oncology, 2010

Date: September 2011
Report number: 2011:25 **ISSN:** 2000-0456
Available at www.stralsakerhetsmyndigheten.se

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.

Table of contents

Abbreviations

AAPM	American Association of Physicists in Medicine
ACR	American College of Radiology
ALARA	As Low As Reasonably Achievable
ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
ASTRO	American Society for Radiation Oncology
BEIR	Biological Effects of Ionizing Radiation
BFCO	the Board of the Faculty of Clinical Oncology (of the Royal College of Radiologists)
CBCT	Cone-beam CT
CR	Complete Remission
CRT	Chemo-RadioTherapy
CTDI	Computed tomography dose index
CT	Computed Tomography
CTV	Clinical Target Volume
DAP	Dose Area Product
DFS	Disease Free Survival
DG	Dentate Gyrus
DLP	Dose Length Product
EFS	Event-Free Survival
EIR	European Institute of radiotherapy
ESTRO	European Society for Therapeutic Radiology and Oncology
EuroNet-PHL	EuroNet-Paediatric Hodgkin's Lymphoma group
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FMEA	Failure Mode and Effect Analysis
GHSG	German Hodgkin Study Group
GI	Gastro Intestinal
GTV	Gross Tumour Volume
Gy	Gray
HL	Hodgkin's Lymphoma
HDR	High Dose Rate
HDRBT	High-Dose Rate Brachytherapy
HR	Hazard Ratio
IAEA	International Atomic Energy Agency
ICRU	International Commission on Radiation Units & Measurements
ICRP	International Commission on Radiological Protection
IGRT	Image-guided radiotherapy
IMRT	Intensity-modulated radiotherapy
IMXT	Intensity Modulated Photon Therapy (the X stands for x-rays)
IPEM	Institute of Physics and Engineering in Medicine
IPS	International Prognostic Score
kV	kilo Volt
LESG	Late Effects Study Group
MRI	Magnetic Resonance Imaging
MV	Mega Volt
mSv	milli Sievert
NAL	No Action Level
NCI	National Cancer Institute

OED	Organ Equivalent Dose
OS	Overall Survival
PFS	Progression-Free Survival
PSA	Prostate-specific antigen
PTV	Planning Target Volume
QA	Quality assurance
QC	Quality control
QoL	Quality of Life
QUANTEC	QUantitative Analyses of Normal Tissue Effects in the Clinic
RATHL	Response Adapted Therapy Hodgkin Lymphoma
RCA	Root Cause Analysis
SPC	Statistical Process Control
SSM	Strålsäkerhetsmyndigheten (The Swedish Radiation Safety Authority)
SBU	Statens beredning för medicinsk utvärdering. Kunskapscentrum för hälso- och sjukvården (Swedish Council on Technology Assessment in Health Care)
SGZ	SubGranular Zone
SPCG	Scandinavian Prostatic Cancer Group
SST	Secondary Solid Tumours
SVZ	SubVentricular Zone
TG	Task Groups
TG Hodgkin	Treatment Group Hodgkin's Lymphoma
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
VMAT	Volumetric Modulated Arc Therapy
WG	Working Groups
3DCRT	Three-dimensional conformal radiotherapy

Introduction

Aim

The Swedish Radiation Safety Authority scientific council is obliged to produce a yearly report concerning questions of radiation therapy. The objective with this report is to map the current level of knowledge and to advise SSM regarding different aspects of radiation therapy of relevance for the safety of this treatment.

Radiation therapy

The Swedish Council on Technology Assessment in Health Care (SBU) has twice, in 1996 and 2003, evaluated the role of radiotherapy for treatment of tumours and described the current use in Sweden [1, 2]. These evidence-based analyses revealed that radiotherapy has an important role in the cure and palliation of many cancer patients. It contributes to cure in about 40% of the patient and ranks second to surgery. The scientific evidence-base for the favourable effects is mostly at a very high level due to many large randomised studies. Radiotherapy is, despite high investment costs, also a highly cost-effective treatment [3].

The SBU reports anticipated that the importance of radiotherapy in cancer treatments would increase in the future thanks to a rapid technical development in the entire radiation therapy process [4].

The future role of radiation in the treatment of cancer was also explored in an investigation about radiotherapy research by the Swedish Cancer Society [5]. It was emphasized that radiotherapy plays an increasingly important role in curative and palliative tumour treatment and presents a considerable challenge to research. The report stated "the new tumour and molecular biology will lead to improved and more effective treatments, which will probably have a favourable effect mainly on disseminated, usually microscopic disease. The value of local treatment methods will increase as systemic treatment of microscopic disease becomes more effective. Some of the development in progress in the field of radiation therapy is aimed at increasing its accuracy and (accordingly) making it gentler on normal tissue. Taken together, these developments indicate that the value of radiation therapy will not only be undiminished but will likely increase, also for reasons of high cost-effectiveness". There is nothing in the development during the past 7 – 8 years that have changed these predictions.

This report will not deal with the favourable effects on tumour outcomes from radiotherapy but focus on important aspects of the safety of the cancer patients treated with radiotherapy. The focus will be on the most recent development where uncertainties about potential pitfalls still exist. A comprehensive description of the risks with external radiation therapy will thus not be made.

Summary of the Report

The report of 2010 displays a survey of the areas of priority according to importance and research intensity in leading international organisations of radiation therapy. Quality assurance (QA), quality control (QC) and late side-effects including the risk of secondary malignancies are the main areas. Image-guided radiotherapy (IGRT) and intensity-modulated radiotherapy (IMRT) as new and more and more commonly used methods are discussed. New technologies within external radiation therapy mean new challenges, both concerning QA and

QC and in the evaluation of particularly late side-effects. The present knowledge about such late effects is based upon the techniques that were used in the past. The follow-up of patient groups treated with the techniques used today and in the future is very limited and thus all predictions due to the changed dose distributions must be modelled. Although radiation therapy has been used worldwide for more than hundred years, the knowledge about dose-response relationships is still rather limited. This is particularly true for the so called "dose-bath" created by many of the new techniques.

There is still great uncertainty about the increase of secondary malignancies from intensity modulation, for a given dose to the tumour, compared to that of more conventional conformal radiotherapy with beams shaped with multileaf collimators.

Combinations with old and newly developed cytotoxic agents are also increasingly used due to favourable effects seen in randomised clinical trials. The influence of these combination therapies on the risks of late toxicity is also reviewed, again finding that the knowledge of late effects is limited. The lack of consensus about how to report late effects contributes to the limited knowledge.

The relevance of appropriate radiotherapy utilization is particularly important in paediatric oncology due to often excellent cure rates and long expected survival times. The development of the use of radiation in the treatment of childhood Hodgkin's lymphoma (HL) illustrates the need to tailor treatment not to give too much but at the same time not to give too little. A comparison with the same development in adult HL is made. An overview of the biological basis for the radiotherapy effects on the developing brain is also made.

Summary of recommendations

The scientific council recommends the Swedish Radiation Safety Authority to increase its cooperation with the hospitals concerning the QA and QC programmes in connection with radiotherapy. There is a need to create an authority similar to the Swedish Drug Authority (Läkemedelsverket) where new and unexpected adverse effects from radiation therapy can be reported and systematically compiled. This reporting should be separated from consequences due to malpractice. The Swedish Radiation Safety Authority should also emphasize and support the relevance of quality registration of treatments and long-term outcomes in order to increase the knowledge base about old and new treatments.

Endpoints used in the evaluation of side effects are not well defined and different scales are used. Hence evaluation of late effects becomes difficult. The radiotherapy community needs to decide on a common validated toxicity scale where acute and late morbidity should be reported in a standardised way to facilitate the comparison between different treatments. Reporting to the national quality registries must be improved. The information about given radiotherapy is very limited, and must be more detailed. Development of systems that can collect information of radiation doses, including dose-volume histograms, and link it to the clinical information in the quality registers must be given high priority.

Regarding x-ray based IGRT from a radiation protection point of view the scientific council recommends that before clinical implementation, all IGRT procedures should be assessed with respect to their justification and possible optimisation opportunities.

Today's rapid development in radio-physics, radiotherapy and radiobiology will give access to treatment modalities that we 10 years ago could only dream of. Of importance is that these developments are accompanied by programmes for effective education and – not the least - continuous medical education.

The members of the Scientific Council on ionising radiation within oncology producing this report were as follows:

PhD Pia Baumann, oncologist (*secretary*)
Onkologkliniken, Karolinska Universitetssjukhuset, Stockholm

Professor Klas Blomgren, paediatric oncologist
Barncancercentrum, Drottning Silvias barn- och ungdomssjukhus, Göteborg

Associate professor Crister Ceberg, medical physicist
Avdelningen för Medicinsk Strålningsfysik, Lunds Universitet, Lund

Associate professor Giovanna Gagliardi, medical physicist
Avdelningen för sjukhusfysik, Karolinska Universitetssjukhuset, Stockholm

Professor Bengt Glimelius, oncologist *(chairman)*
Onkologiklinikerna, Akademiska sjukhuset, Uppsala och Karolinska Universitetssjukhuset, Stockholm

Associate professor Elisabeth Kjellén, oncologist
Skånes onkologiska klinik, Skånes Universitetssjukhus Lund

Professor Per Nilsson, medical physicist
Cancercentrum Norrlands Universitetssjukhus Umeå och Skånes Onkologiska klinik, Skånes Universitetssjukhus Lund

Professor Sten Nilsson, oncologist
Onkologkliniken, Karolinska Universitetssjukhuset, Stockholm

References

1. SBU - The Swedish Council on Technology Assessment in Health Care, *Radiotherapy for cancer. Vol 1 and 2,* Acta Oncol, 1996. 35 (Suppl 6): p. 31-33.
2. Ringborg, U., 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. 42(5-6): p. 357-65.
3. Norlund, A., *Costs of radiotherapy.* Acta Oncol, 2003. 42(5-6): p. 411-5.
4. Svensson H and Möller T, *Developments in radiotherapy.* Acta Oncol, 2003. 42: p. 430-442.
5. Mattsson, S., et al., *Swedish Cancer Society radiation therapy research investigation.* Acta Oncol, 2002. 41(7-8): p. 596-603.

1. Review of current activities in selected international societies

One of the starting points for the work of the group was a thorough review of current work within a number of international societies in order to get a view of recently published reports and on-going work in the area of radiation therapy and the safety of the irradiated patient. The above selected focus areas are to some extent based on the findings from this analysis. The societies chosen were

- American Association of Physicists in Medicine (AAPM), http://www.aapm.org
- American Society for Radiation Oncology (ASTRO), http://www.astro.org
- European Society for Therapeutic Radiology and Oncology (ESTRO), http://www.estro.org
- The International Commission on Radiation Units & Measurements (ICRU), http://www.icru.org
- International Atomic Energy Agency (IAEA), http://www.iaea.org
- International Commission on Radiological Protection (ICRP), http://www.icrp.org

These organizations are involved in numerous activities many of which have implications new radiation technologies. Present activities in the above mentioned organisations mainly focus on IMRT and IGRT, which are the main topics also in this report. Brachytherapy is thus e.g. not dealt with.

1.1. AAPM

has a large number of active working groups (WG) and task groups (TG) in the therapy physics area. The present sub-committees are currently working in the following fields: Biological effects, brachytherapy, calibration laboratory accreditation, quality assurance & outcome improvement, radiation dosimetry & treatment planning, radiation safety, treatment delivery and therapy emerging technology assessment. Of special interest in our context is the work of the following task groups:

- TG100 Method for Evaluating QA Needs in Radiation Therapy
- TG101 Stereotactic Body Radiotherapy
- TG119 Writing group on IMRT QA [1]
- TG120 Writing group on IMRT Metrology
- TG132 Use of Image Registration and Data Fusion Algorithms and Techniques in Radiotherapy Treatment Planning
- TG147 QA for Non-Radiographic Radiotherapy Localisation and Positioning Systems
- TG148 QA for Helical Tomotherapy [2]
- TG155 Small Fields and Non-Equilibrium Condition Photon Beam Dosimetry
- TG157 Commissioning of beam models in Monte Carlo-based clinical treatment planning
- TG158 Measurements and calculations of doses outside the treatment volume from external Beam Radiation Therapy
- TG166 Use and quality assurance of biologically-related models for treatment planning
- TG174 Utilization of 18F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) in Radiation Therapy

- TG179 Quality Assurance for image-guided radiation therapy utilizing CT-based technologies
- TG180 Modelling and Accounting for the Imaging Guidance Radiation Doses to Radiotherapy Patients in Treatment Planning

1.2. ASTRO

has together with the American College of Radiology (ACR) made practice guidelines for IMRT and recently also IGRT available [3, 4]. These guidelines are meant as educational tools for practitioners and not as rules or requirements of practice. In addition a workgroup within ASTRO Radiation Physics Committee has developed a set of recommendations for documenting IMRT treatments [5].

1.3. ESTRO

has published a number of handbooks and booklets on various topics. The most recent booklet [6] was published in 2008 and deals with guidelines for the verification of IMRT. To provide guidelines on topics of practical relevance for radiation oncology, the European Institute of radiotherapy (EIR) has been established by ESTRO. The report from the first task group by EIR-ESTRO is on 3D CT-based in-room image guidance (3DCT-IGRT) systems [7]. It gives an overview and current status of 3DCT-IGRT systems addressing the rationale, objectives, principles, applications, and process pathways for treatment delivery and QA. Solutions for kV CT and kV CBCT (cone-beam CT) as well as MV CT and MV CBCT are covered.

1.4. ICRU

has published two reports in the past years in the field of radiation therapy, both on prescribing, recording, and reporting radiation therapy. Report no 78 [8] on proton-beam therapy also covers radiation biology, proton-beam delivery and properties, dosimetry, geometric and dose-volume terms, treatment planning, uncertainties in dose delivery, motion management and QA. Report no 83 [9] on IMXT provides information necessary to standardise techniques and procedures and to harmonise the prescribing, recording and reporting of IMRT where possible with those of other modalities. Applicable concepts and recommendations in previous ICRU reports are adopted and extended where required. The report also describes the physical, technical, treatment planning and clinical aspects of IMRT. Clinical examples are provided in both reports to illustrate the application of the recommendations.

1.5. IAEA

Has published several highly relevant radiotherapy documents that can be freely downloaded from http://www.iaea.org/Publications/index.html.
In the Division of Human Health part (http://www-naweb.iaea.org/nahu/default.asp) specific chapters are dedicated to Applied Radiation Biology and Radiotherapy, and to Dosimetry and Medical Radiation Physics.
A report on the “Transition from 2D radiotherapy to 3D conformal and Intensity Modulated Radiotherapy” is given in the publication IAEA-TECDOC-1588 (2008). A dedicated report about imaging is also provided (http://www-naweb.iaea.org/nahu/dmrp/imaging.shtm).

1.6. ICRP

has recently published a report [10] on prevention of accidental exposures from new external beam radiation therapy technologies. The recommendations and safety issues in this report are based on lessons from accidental exposures with conventional and as well as with new technologies.

Worth mentioning in the context of IMRT are two reports from the Institute of Physics and Engineering in Medicine, **IPEM**. Report 96 gives guidance on commissioning and clinical implementation of IMRT based on established methods [11]. A report on "small field MV photon dosimetry" will also soon be published by IPEM.

1.7. References

1. Ezzell, G.A., et al., *IMRT commissioning: multiple institution planning and dosimetry comparisons, a report from AAPM Task Group 119.* Med Phys, 2009. **36**(11): p. 5359-73.
2. Langen, K.M., et al., *QA for helical tomotherapy: report of the AAPM Task Group 148.* Med Phys, 2010. **37**(9): p. 4817-53.
3. Hartford, A.C., et al., *American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) Practice Guidelines for Intensity-Modulated Radiation Therapy (IMRT).* Int J Radiat Oncol Biol Phys, 2009. **73**(1): p. 9-14.
4. Potters, L., et al., *American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for image-guided radiation therapy (IGRT).* Int J Radiat Oncol Biol Phys, 2010. **76**(2): p. 319-25.
5. Holmes, T., et al., *American Society of Radiation Oncology recommendations for documenting intensity-modulated radiation therapy treatments.* Int J Radiat Oncol Biol Phys, 2009. **74**(5): p. 1311-8.
6. Georg, M.a., *Guidelines for the Verification of IMRT.* ESTRO 2008. **Booklet 9**.
7. Korreman, S., et al., *The European Society of Therapeutic Radiology and Oncology-European Institute of Radiotherapy (ESTRO-EIR) report on 3D CT-based in-room image guidance systems: a practical and technical review and guide.* Radiother Oncol, 2010. **94**(2): p. 129-44.
8. *ICRU Report 78, Prescribing, Recording, and Reporting Proton-Beam Therapy.* Journal of the ICRU, December 2007. **Vol 7**(Issue 2).
9. *ICRU Report 83: Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT.* Journal of the ICRU, April 2010. **Vol 10**(Issue 1).
10. *ICRP Publication 112: Preventing Accidental Exposures from New External Beam Radiation Therapy Technologies.* Ann. ICRP 2009. **Vol 39** (Issue 4).
11. *IPEM report 96: Guidance for the Clinical Implementation of Intensity Modulated Radiation Therapy.* ISBN 9781903613344, 2008.

2. Intensity modulated radiotherapy IMRT from a radiation protection point of view

2.1. Introduction

There is a growing body of evidence for reduced toxicity of radiotherapy with intensity-modulation techniques as compared to conventional conformal radiotherapy [1-3]. It can therefore be expected that the use of IMRT in its various forms (conventional fixed-beam IMRT, volumetric intensity-modulated radiotherapy, helical tomotherapy, etc) will become more frequent in the very near future.

There are many reasons, however, for being cautious when implementing IMRT in the clinic. IMRT-techniques require a new level of detail of the treatment prescriptions, specifying dose-volume constraints and objectives, which in turn necessitate a more elaborate definition of targets and segmentation of organs at risk and other normal tissue structures, and the associated dose levels.

Furthermore, the radiobiological consequences of the highly modulated delivery and sometimes extended treatment fractions are still not fully elucidated. There has also been a concern regarding the so called dose-bath – *i.e.* large volumes of normal tissues receiving relatively low dose levels – and its potentially harmful effects in the long perspective such as radiation induced secondary cancer. The dose-bath is a general consequence of the increased high-dose conformity of the IMRT-techniques. The high demand for conformity also requires frequent use of image guidance (IGRT), which adds to the dose-bath. The effects of combinations of IMRT and chemotherapy are little known in this respect.

From a radiation safety point of view, a well-designed QA programme is of vital importance. However, there is a lack of consensus regarding dosimetric methods for IMRT treatment verification. It is also not clear what needs to be done in order to fulfil present regulatory requirements.

The aim of this report is to highlight some of these issues. We have chosen to focus on the following items:

- The evolution of radiation therapy complexity (with prostate cancer and Hodgkin's lymphoma as illustrative examples)
- Late effects including secondary malignancies
- Quality management of advanced external radiation therapy technologies
- Image-guided radiotherapy from a radioprotection point-of-view

2.1.1. References

1. Veldeman, L., et al., *Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies.* Lancet Oncol, 2008. **9**(4): p. 367-75.
2. Staffurth, J., *A review of the clinical evidence for intensity-modulated radiotherapy.* Clin Oncol (R Coll Radiol), 2010. **22**(8): p. 643-57.
3. Nutting C, H.K., Rogers S, Sydenham M, A'Hern R and Hall E, *Results of a Phase III Multi-centre Randomised Controlled Trial of Intensity Modulated (IMRT) vs Conventional Radiotherapy (RT) in Head and Neck Cancer.* Clin Oncol, 2010. **Vol 22**: p. Page 899.

2.2. The evolution of radiation therapy – increased complexity and changed indications

The implementation of IMRT in the clinic puts new requirements on every step in the chain of events, all the way from the prescription to the delivery of the radiation treatment. In this section, we will discuss some of the most important issues regarding the prescription of IMRT, including target volume definitions and the articulation of the treatment objectives. As an example, we have chosen to use prostate cancer. This is a diagnosis for which the use of IMRT is expected to increase, and all of the new, advanced techniques such as VMAT, RapidArc, and helical tomotherapy are in use. Although many of the issues discussed below are specific to prostate cancer, we believe that the considerations are similar for other sites as well, and that the principle arguments are fairly general.

2.2.1. Radiotherapy in prostate cancer

Prostate cancer is distinguished, from a radiotherapy point of view, from many other malignancies in that this is one of the few cancers in which radiotherapy is one of the major curative treatment modalities and, thus, radiotherapy is the primary treatment for many patients. The second evidence-based treatment modality for this disease is radical prostatectomy. Paradoxically, there are no comparative, randomised, studies on the concept radiotherapy versus surgery as primary treatment in prostate cancer. The first study on this theme is the UK ProtecT trial, which randomises patients with low-risk cancer to radiotherapy or prostatectomy or active monitoring [1]. The first results from this study are not expected to exist until 2015 and overall survival data will be obtained many years later. In patients with intermediate- and high-risk prostate cancer the main options, radiotherapy and surgery, remain but no prospective randomised studies have so far been announced. One can only speculate on the cause of the reluctance from the profession as well as from health authorities in initiating randomised studies on this theme. One reason may – from a speciality point-of-view – be strategic, i.e. the surgical and radiotherapeutic professions do not want to risk losing such a comparison. There could certainly also exist additional rational as well as irrational reasons – e.g. strong belief that one treatment is actually superior to the other - for this lack of interest in initiating comparative studies on the topic.

2.2.1.1. Radiotherapy as primary treatment

Radiotherapy is, from a scientific point of view, currently the one of the two treatment modalities that has the highest level of evidence. The recently published SPCG-7 trial indicates that the addition of curative radiotherapy to endocrine treatment prolongs survival by nearly 10 % in patients with locally advanced, non-metastatic prostate cancer [2]. This is the first time that a curative treatment modality has been shown to prolong overall survival in prostate cancer. The closest that has been shown in this way with respect to surgery is the SPCG-4 trial, which randomised patients with localised prostate cancer to radical prostatectomy or watchful waiting [3]. This study did not reveal a survival benefit, except in a subgroup of patients under the age of 65. In this subgroup a survival benefit was seen in the order of 5 % [3].

2.2.1.2. Adjuvant and early salvage radiotherapy

The value of adjuvant radiotherapy after non-radical prostatectomy has been investigated in three large randomised studies [4-6]. Two of these have shown an overall survival benefit in the order of 10 %, while the third [6] is not yet mature for OS evaluation. All studies showed, in comparison to no postoperative radiotherapy, statistically significant differences in disease-free survival, metastasis-free survival, local progression and cancer-specific mortality at advantage for radiotherapy. Still, the question whether the post-operative treatment is best served in a strictly adjuvant setting or if this treatment could also well be given as so-called early salvage radiotherapy has to be answered. Randomised studies on this concept are under way but are not expected to give definite answer with respect to OS within the next 5 - 10 years.

2.2.1.3. Neoadjuvant, concomittant and adjuvant endocrine therapy

The value of combination treatment - radiotherapy and endocrine therapy - has been studied in multiple randomised trials [7, 8]. These have clearly shown the benefit of this concept with respect to local control, distant metastasis-free survival, disease-free survival, cancer-specific mortality and overall survival. However, there are some important factors to take into consideration. All major trials have exclusively included patients with high-risk disease, i.e. patients with locally advanced and/or poorly differentiated cancer, all with radiological verified and/or high risk for lymph node metastatic disease. In the majority of the studies, the radiotherapy was given with doses that, with today's knowledge, are not sufficient to achieve sterilisation of the tumour. Another important component of the radiotherapeutic approach has been to provide radiation to the whole pelvis to 50 Gy and then give final radiation boost to the prostatic gland [7]. The combination treatment with endocrine therapy and radiotherapy will within the next few years most certainly be challenged by the concept curative treatment with high-dose radiotherapy as mono therapy (dose-escalated 3DCRT or 3DCRT plus HDRBT) to the primary tumour, thus omitting the hormonal part. The major argument against the combination concept (radiotherapy combined with endocrine treatment) has been – and still is - that the radiotherapy used actually needed the hormonal therapy part to compensate for the non-adequate radiation doses that could be delivered with the techniques that were at hand when the trials were designed. Some observational studies suggest that the hormonal neoadjuvant and adjuvant treatment can be excluded from the curative treatment provided that adequate radiation therapy is given.

2.2.1.4. Lymph node irradiation - to be or not to be?

As mentioned above, the older radiotherapy protocols included whole-pelvis irradiation and a radiation boost to the prostate [7]. However, with the introduction of 3DCRT during the 1990s and that only patients with low risk for metastatic disease or patients with N0 disease – i.e. negative diagnostic lymph node dissection – were accepted for curative treatment, whole-pelvic radiotherapy was abandoned at most centres. We still do not know exactly how this change in inclusion criteria has influenced the therapeutic outcome. It may be that - although not proven - the "old" technology of radiation to the whole pelvis - especially in combination with endocrine therapy - had a value in the sterilisation of micro-metastatic disease. The pendulum has struck back again to the increased interest around the inclusion of regional lymph node metastases in radiation volume for curative radiotherapy – especially in patients with high risk (> 15 per cent) of having lymph node metastatic disease [9-12]. One of the reasons is that we have gained more knowledge about the obvious shortcomings of diagnostic lymph-node dissection [13]. Only about 30 per cent of the lymph node stations are actually examined in routine lymph node dissection. Another reason for the increasing interest in

irradiation of regional lymph node is that we with current radiotherapy techniques, such as IMRT, are now able to administer radiotherapy to the nodes in a more conformal manner than before, thus being able to minimise the radiation to surrounding normal tissue.

2.2.1.5. Importance of sufficiently high radiation dose to the prostate

An important lesson learned over the years is that the radiation doses that were previously administered routinely in the curative treatment have been far from adequate. Well into the 1980s and early 1990s doses of 66-70 Gy were routinely used, delivered with 1.8 - 2.0 Gy fractions, sometimes even with a pause for 14 days after 40 Gy. Several randomised trials have demonstrated the need for higher doses to achieve sterilisation of the primary tumour. One important analysis of these studies are reported in a recent meta-analysis of Viani et al. [14] One of the major conclusions is that a dose-response relationship is also seen in so-called low-risk tumours. This information is contrary to the earlier prevailing view, that the total doses around 70-74 Gy would be sufficient to cure low-risk disease. By utilizing today's technology with 3DCRT dose escalation or combination therapy 3DCRT plus HDRBT [15], doses above 80 Gy are administered to the prostate gland. The highest radiation doses (> 116 Gy) that can be administered locally to the prostate gland are achieved with the latter technique, 3DCRT plus HDRBT [15-18]. The importance of adequate dose for the sterilisation of the primary tumour is supported by biopsy data. Several studies show the link between residual cancer and the risk of local progression, metastatic disease and increased cancer-specific mortality [19-23]. This has also recently been shown in a biopsy study from the above SPCG-7 trial in which residual cancer was verified in 22 per cent of patients after more than three years and that this presence was associated with the above negative factors including increased cancer-specific mortality [23]. Equally alarming was that the residual cancer showed low differentiation grade (Gleason sum 8) in all positive biopsies [23].

2.2.1.6. Hypo-fractionation

In recent years much knowledge has been gained in the field of radiation biology with respect to prostate cancer. Ample data exist to show that this tumour precipitates from several others by a low level of so-called α/β value [16, 24]. This has led to considerable interest around the theme hypofractionation. Numerous studies have been designed on this concept.Arcangeli et al. have recently published data from the first randomised trial [25]. This is not yet mature for evaluation of treatment effect – other than freedom from PSA recurrence - but the data show that the toxicity of the hypofractionation as used in this study is acceptable [25]. Several additional studies are on their way and the future will tell whether hypofractionation should be used routinely in the curative treatment of prostate cancer. Of importance is, however, to note that the concept is based on the fact that prostate cancer is often a quite slowly proliferating tumour. The warning flag that we must keep in mind is that prostate cancer, not infrequently, shows a varied picture with the presence of islands of both well, moderately well and poorly differentiated cancer. The poorly differentiated cancer is often more highly proliferative, and it may very well be that these tumour components are not suitable for hypofractionation [26, 27]. Of importance, therefore, is that all hypofractionation protocols include assessment of tumour biological parameters such as – in particular - proliferative properties.

2.2.1.7. IMRT and Proton therapy

Although IMRT is currently being used on a routine basis at many centres in curative treatment of prostate cancer, there are still no randomised studies comparing this technique with conventional 3DCRT. On the other hand, there are a number of non-randomised studies which have evaluated the role of IMRT in radiation dose escalation in prostate cancer [28-35]. A systematic review on the clinical effectiveness and economic evaluation of IMRT was recently reported from the British Health Technology Assessment Programmeme (National Institute for Health Research, NIHR) [36]. The main conclusion from this is that IMRT can, like the 3DCRT, be used for dose escalation and that doses up to 81 Gy may improve biochemical relapse-free survival in patients with localised prostate cancer. Data also suggest that toxicity can be reduced by increasing conformality of treatment, particularly with respect to gastrointestinal toxicity, which can be more easily achieved with IMRT than 3DCRT. However, the size of this reduction and its cost-effectiveness is still unclear [36]. The additional cost of IMRT compared with 3DCRT was in this systematic review estimated to be £ 1100, arising from additional medical, radiographer and physics staff time [36]. Prospective randomised trials comparing outcome, side-effects and cost-effectiveness of 3DCRT versus IMRT are warranted.

The vast majority of patients currently treated with proton therapy are those with prostate cancer. Although this technology has been used for over two decades, there are still no randomised studies comparing proton monotherapy with conventional radiotherapy utilizing photons. One trial, PROG/ACR 95-09, was designed to test the hypothesis that increasing radiation dose improves clinical outcome in patients with early-stage prostate cancer [37]. Proton therapy was in this study used as radiation boost to the prostate after given photon therapy. The results show, in accordance with those obtained from other dose-escalation studies using 3DCRT, that long-term cancer control is superior with high-dose (79.2 Gy equivalents) versus conventional-dose (70.2 Gy equivalents) for men with localised prostate cancer. The high-dose combined treatment could be delivered without an increase in $\geq$ grade 3 late urinary/rectal morbidity [37]. A number of review articles deal with the topic proton therapy versus conventional photon therapy in prostate cancer [38-41]. The conclusion from these is that outcomes of these two modalities seem to be comparable [41]. Noteworthy is, however, that the potential for treatment errors is considerably larger in proton therapy than in photon therapy [42]. For this reason, it is of great importance that treatment with protons is given at institutions with extensive experience with this modality.
The role for protons in the treatment of locally advanced prostate cancer with high risk for seminal vesicle invasion and/or extra capsular extension, and thereby high risk for gastrointestinal and genitourinary toxicity, is still unclear and should be challenged in prospective trials.

2.2.1.8. Future aspects – from a medical and radiation safety point of view

There are very good reasons to expect that the role of radiation therapy will increase in coming years, and that the need for studies in the area will also increase. Primarily awaited are randomised trials between curative radiation therapy and radical prostatectomy. Healthcare authorities have an important task to mandate such trials. This would in the end benefit the patients. Strong growth is expected in the areas of dose escalation, both with external beam radiation therapy as monotherapy and combination treatment with external therapy and brachytherapy. In all dose escalation protocols, the need for minimising the margins of surrounding normal tissue is imperative. The need for improved positioning is becoming increasingly important. The trend towards hypofractionation has certainly come to

stay - a fact which again highlights the need for adequate visualisation of the prostatic gland and the positioning of it with techniques such as IGRT. The need for IMRT will increase for treatment of regional lymph node stations in patients with high risk prostate cancer. The reason for this is that the patient population that is still mostly referred for radiotherapy is that with high risk disease, i.e. those with high likelihood of lymph node metastatic disease and in whom we do not have the availability of reliable diagnostic methods, neither radiological nor nuclear medicine or - as mentioned above - surgical methods for histopathological assessment of lymph node metastatic disease and tumour staging.

The trend towards even higher doses of radiation to the prostate gland and the balance between efficacy and toxicity makes greater demands on the technical development and adequate use of this and - above all an understanding of its limitations. The treatment with increasing radiation volumes to include regional lymph nodes requires us to pay attention to the risk of excessive radiation doses to normal tissues with its risk of long-term sequelae, particularly in the form of induction of secondary malignancies [43, 44]. The latter aspect is not insignificant, with the fact that the average age of today's prostate cancer patients is falling and that the vast majority have an expected survival of well over 10-15 years, i.e. the period within which secondary malignancies can be expected to develop. The value of adjuvant - or early salvage - radiotherapy of non-radically operated prostate cancer exhibits level 1 evidence. Almost every second patient undergoing curative prostatectomy will ultimately relapse in his cancer. In fact, this group is now the largest group prevalent in the United States. These patients are all by definition young - chronologically and/or biologically - and with today's evidence-based medicine will be offered adjuvant - or early salvage - radiotherapy. From a socio-economic and medical point of view, it is important that these patients are offered effective and safe radiation treatment.

In conclusion; the evolution from conventional 3D radiotherapy to IMRT implies more elaborate treatment prescriptions. Primarily, all relevant target volumes have to be defined, including margins. The GTV normally includes the entire tumour volume. The margins applied for the PTV may differ depending on fractionation and fixation method, as well as whether on- or off-line IGRT is used. In IMRT, also organs at risk and other normal tissue structures have to be segmented. When this has been done, adequate dose-volume constraints and objectives have to be specified in detail. Inverse treatment planning also requires that weighting factors are applied to the different objectives. There is no general theory, however, on how these weighting factors should be chosen and the treatment planning process may, therefore, have to be iterated a few times before arriving at a clinically acceptable treatment plan. In the case of prostate cancer, there can be large differences between dose distributions obtained with conventional 3D treatment plans, IMRT, and rotational techniques. Using a few fixed beam angles, critical structures can be spared to a great extent, while other tissues may receive larger but tolerable dose levels to small volumes. With rotational techniques, however, high dose maxima may be avoided but, instead, large volumes are exposed to a small dose.

2.2.1.9. References

1. Lane, J.A., et al., *Latest results from the UK trials evaluating prostate cancer screening and treatment: the CAP and ProtecT studies.* Eur J Cancer. **46**(17): p. 3095-101.

2. Widmark, A., et al., *Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial.* Lancet, 2009. **373**(9660): p. 301-8.
3. Bill-Axelson, A., et al., *Radical prostatectomy versus watchful waiting in localised prostate cancer: the Scandinavian prostate cancer group-4 randomised trial.* J Natl Cancer Inst, 2008. **100**(16): p. 1144-54.
4. Thompson, I.M., et al., *Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomised clinical trial.* J Urol, 2009. **181**(3): p. 956-62.
5. Bolla, M., et al., *Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911).* Lancet, 2005. **366**(9485): p. 572-8.
6. Wiegel, T., et al., *Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95.* J Clin Oncol, 2009. **27**(18): p. 2924-30.
7. Gottschalk, A.R. and M. Roach, 3rd, *The use of hormonal therapy with radiotherapy for prostate cancer: analysis of prospective randomised trials.* Br J Cancer, 2004. **90**(5): p. 950-4.
8. Shelley, M.D., et al., *A systematic review and meta-analysis of randomised trials of neo-adjuvant hormone therapy for localised and locally advanced prostate carcinoma.* Cancer Treat Rev, 2009. **35**(1): p. 9-17.
9. Nguyen, P.L. and A.V. D'Amico, *Targeting pelvic lymph nodes in men with intermediate- and high-risk prostate cancer despite two negative randomised trials.* J Clin Oncol, 2008. **26**(12): p. 2055-6; author reply 2056-7.
10. Roach, M., 3rd, *Targeting pelvic lymph nodes in men with intermediate- and high-risk prostate cancer, and confusion about the results of the randomised trials.* J Clin Oncol, 2008. **26**(22): p. 3816-7; author reply 3817-8.
11. Wang, D. and C. Lawton, *Pelvic lymph node irradiation for prostate cancer: who, why, and when?* Semin Radiat Oncol, 2008. **18**(1): p. 35-40.
12. Kim, B.S., et al., *Effect of pelvic lymph node irradiation in salvage therapy for patients with prostate cancer with a biochemical relapse following radical prostatectomy.* Clin Prostate Cancer, 2004. **3**(2): p. 93-7.
13. Ordon, M. and R.K. Nam, *Lymph node assessment and lymphadenectomy in prostate cancer.* J Surg Oncol, 2009. **99**(4): p. 215-24.
14. Viani, G.A., E.J. Stefano, and S.L. Afonso, *Higher-than-conventional radiation doses in localised prostate cancer treatment: a meta-analysis of randomised, controlled trials.* Int J Radiat Oncol Biol Phys, 2009. **74**(5): p. 1405-18.
15. Pieters, B.R., et al., *Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: a systematic review.* Radiother Oncol, 2009. **93**(2): p. 168-73.
16. Fowler, J.F., *The radiobiology of prostate cancer including new aspects of fractionated radiotherapy.* Acta Oncol, 2005. **44**(3): p. 265-76.
17. Hermesse, J., et al., *Dosimetric comparison of high-dose-rate brachytherapy and intensity-modulated radiation therapy as a boost to the prostate.* Int J Radiat Oncol Biol Phys. **76**(1): p. 269-76.
18. Hoskin, P.J., et al., *High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial.* Radiother Oncol, 2007. **84**(2): p. 114-20.

19. Crook, J.M., et al., *Twenty-four-month postradiation prostate biopsies are strongly predictive of 7-year disease-free survival: results from a Canadian randomised trial.* Cancer, 2009. **115**(3): p. 673-9.
20. Vance, W., et al., *The predictive value of 2-year posttreatment biopsy after prostate cancer radiotherapy for eventual biochemical outcome.* Int J Radiat Oncol Biol Phys, 2007. **67**(3): p. 828-33.
21. Zelefsky, M.J., et al., *Influence of local tumour control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer.* J Urol, 2008. **179**(4): p. 1368-73; discussion 1373.
22. Coquard, R., *Re: Influence of local tumour control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer: M. J. Zelefsky, V. E. Reuter, Z. Fuks, P. Scardino and A. Shippy. J Urol 2008; 179: 1368-1373.* J Urol, 2008. **180**(5): p. 2258; author reply 2258.
23. Solberg, A., et al., *Residual Prostate Cancer in Patients Treated with Endocrine Therapy with or Without Radical Radiotherapy: A Side Study of the SPCG-7 Randomised Trial.* Int J Radiat Oncol Biol Phys. 2010 Jun 30.
24. Williams, S.G., et al., *Use of individual fraction size data from 3756 patients to directly determine the alpha/beta ratio of prostate cancer.* Int J Radiat Oncol Biol Phys, 2007. **68**(1): p. 24-33.
25. Arcangeli, G., et al., *A prospective phase III randomised trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer.* Int J Radiat Oncol Biol Phys. 2010 Sep 1;78(1):11-8.
26. Lennernas, B., S. Nilsson, and S.H. Levitt, *Hypofractionation for radiotherapy of prostate cancer using a low alpha/beta ratio - possible reasons for concerns? An example of five-dimensional radiotherapy.* Acta Oncol, 2011. In press.
27. Miles, E.F. and W.R. Lee, *Hypofractionation for prostate cancer: a critical review.* Semin Radiat Oncol, 2008. **18**(1): p. 41-7.
28. Kupelian, P.A., et al., *Preliminary observations on biochemical relapse-free survival rates after short-course intensity-modulated radiotherapy (70 Gy at 2.5 Gy/fraction) for localised prostate cancer.* Int J Radiat Oncol Biol Phys, 2002. **53**(4): p. 904-12.
29. Sanguineti, G., et al., *Does treatment of the pelvic nodes with IMRT increase late rectal toxicity over conformal prostate-only radiotherapy to 76 Gy?* Strahlenther Onkol, 2006. **182**(9): p. 543-9.
30. Shu, H.K., et al., *Toxicity following high-dose three-dimensional conformal and intensity-modulated radiation therapy for clinically localised prostate cancer.* Urology, 2001. **57**(1): p. 102-7.
31. Vora, S.A., et al., *Analysis of biochemical control and prognostic factors in patients treated with either low-dose three-dimensional conformal radiation therapy or high-dose intensity-modulated radiotherapy for localised prostate cancer.* Int J Radiat Oncol Biol Phys, 2007. **68**(4): p. 1053-8.
32. Yoshimura, K., et al., *Health-related quality-of-life after external beam radiation therapy for localised prostate cancer: intensity-modulated radiation therapy versus conformal radiation therapy.* Prostate Cancer Prostatic Dis, 2007. **10**(3): p. 288-92.
33. Zelefsky, M.J., et al., *Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localised prostate cancer.* Int J Radiat Oncol Biol Phys, 2008. **70**(4): p. 1124-9.
34. Ashman, J.B., et al., *Whole pelvic radiotherapy for prostate cancer using 3D conformal and intensity-modulated radiotherapy.* Int J Radiat Oncol Biol Phys, 2005. **63**(3): p. 765-71.

35. Lips, I., et al., *Health-related quality of life in patients with locally advanced prostate cancer after 76 Gy intensity-modulated radiotherapy vs. 70 Gy conformal radiotherapy in a prospective and longitudinal study.* Int J Radiat Oncol Biol Phys, 2007. **69**(3): p. 656-61.
36. Hummel, S., et al., *Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation.* Health Technol Assess. 2010 Oct;14(47):1-108, iii-iv
37. Zietman, A.L., et al., *Randomised trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09.* J Clin Oncol, 2010. **28**(7): p. 1106-11.
38. Brada, M., M. Pijls-Johannesma, and D. De Ruysscher, *Proton therapy in clinical practice: current clinical evidence.* J Clin Oncol, 2007. **25**(8): p. 965-70.
39. Olsen, D.R., et al., *Proton therapy - a systematic review of clinical effectiveness.* Radiother Oncol, 2007. **83**(2): p. 123-32.
40. Schulz-Ertner, D. and H. Tsujii, *Particle radiation therapy using proton and heavier ion beams.* J Clin Oncol, 2007. **25**(8): p. 953-64.
41. Brada, M., M. Pijls-Johannesma, and D. De Ruysscher, *Current clinical evidence for proton therapy.* Cancer J, 2009. **15**(4): p. 319-24.
42. Goitein, M., *Magical protons?* Int J Radiat Oncol Biol Phys, 2008. **70**(3): p. 654-6.
43. Dasu, A., et al., *Secondary malignancies from prostate cancer radiation treatment: a risk analysis of the influence of target margins and fractionation patterns.* Int J Radiat Oncol Biol Phys, 2011. **79**(3): p. 738-46.
44. Schneider, U., et al., *The impact of dose escalation on secondary cancer risk after radiotherapy of prostate cancer.* Int J Radiat Oncol Biol Phys, 2007. **68**(3): p. 892-7.

2.2.2. Radiotherapy in Hodgkin's lymphoma

2.2.2.1. Quality control – exemplified by the development of European protocols for treatment of Hodgkin's lymphoma in children

Satisfactory disease control rates (>90%) can be achieved in paediatric Hodgkin's lymphoma with established therapeutic modalities, as documented for the GPOH-HD study group since the DAL-HD-82 study [1]. The remaining challenges for further treatment optimization are:

- Reduction of acute and long-term toxicity of the chemotherapy and radiotherapy employed.
- Reduction of the amount of treatment in those children who are currently over-treated

The currently used treatment protocol, the EuroNet-Paediatric Hodgkin's Lymphoma group (EuroNet-PHL-C1), builds on the experience from six successive DAL / GPOH study generations that step by step optimised the treatment of paediatric Hodgkin's lymphoma starting in 1978 and established the de facto treatment standard in the participating countries. Already the first study generation DAL-HD 78 set the general therapeutic paradigm: Chemotherapy starting with 2 courses of intense and effective OPPA (vincristine, procarbazine, prednisone and doxorubicin), followed by COPP (cyclophosphamide, vincristine, procarbazine and prednisone) consolidation in intermediate and advanced stages, plus radiotherapy. In 1978 radiotherapy consisted of 36 – 40 Gy to the involved field and 18 – 20 Gy in the adjacent fields [2]. Later study generations modified treatment within this

framework mainly with the objective to reduce acute and long-term toxicity while preserving good treatment results.

Stages of Hodgkin's lymphoma *(The Cotswolds revision of the Ann Arbor staging system)*

- **I** - Involvement of a single independent lymph node region or lymph node structure
- **II** - Involvement of 2 or more lymph node regions on the same side of the diaphragm
- **III** - Involvement of lymph node regions or lymph node structures on both sides of the diaphragm
- **IV** - Involvement of extra-nodal sites beyond E-sites (involvement of a single extra-nodal site contiguous or proximal to known nodal site). Liver or bone marrow involvement always implies stage IV.

Annotations to stage definitions:

- No B symptoms
- B symptoms: at least one of the following:
  - a. Inexplicable weight loss of more than 10% within the last 6 months
  - b. Unexplained persisting or recurrent temperature above 38 °C
- c. Drenching night sweats

- E. Involvement of a single extra-nodal site contiguous or proximal to known nodal site.

Treatment groups

Children:

- TG-1: patients of stages I A/B and II A
- TG-2: patients of stages I_EA/B, II_EA, II B or III A
- TG-3: patients of stages II_EB, III_EA/B, III B or IV A/B

Adults: (classical HL, supra diaphragmatic presentation)

- Early disease: patients of stages IA and IIA
  - Favourable: No risk factor
  - Unfavourable (intermediate): One or more risk factors:
    - bulky disease
    - >2 involved locations
    - ESR ≥50 mm

- Advanced disease: patients of stages (I-)*IIB, IIIA-IVB)
  - Sub-grouped according to number of risk factors (IPS):
    - Male
    - >45 years
    - Stage IV
    - Haemoglobin <105 g/L
    - S-albumin <40 g/L
    - LPK>$15x10^9$
    - B-lymphocytes <8% or <$0.6x10^9$/L.

*Stage IB can be considered as early disease (with risk factor) or as advanced disease.

In the second study generation DAL-HD 82 [1], patients for the first time were divided into three **treatment groups** (TG-1, TG-2, TG-3) based on stage (see below). The number of consolidation COPP cycles was scaled according to treatment group (0, 2 or 4). Irradiation volume was reduced from extended to involved field. The indication for splenectomy was limited and the number of splenectomies dropped to about 40%. Radiation doses were reduced to 35, 30 or 25 Gy in TG-1, TG-2 and TG-3, respectively. In case of insufficient response to chemotherapy the radiation dose was increased by 5 to 10 Gy. Five-year event-

free survival (EFS) rates of 99%, 96% and 90% in TG-1, TG-2 and TG-3, respectively [3] were observed. Due to these excellent results, DAL-HD 82 for a long time was regarded as the gold standard.

Third generation: After the gonadotoxic effect of procarbazine became apparent this drug was completely eliminated from OPPA–COPP chemotherapy in the DAL-HD 85 study generation. Chemotherapy was OPA-COMP (vincristine, prednisone, doxorubicin – cyclophosphamide, vincristine, methotrexate, prednisone), so that in the first two cycles only three agents were administered and procarbazine was replaced by methotrexate in the consolidation. Involved field radiotherapy was dosed according to TG, resulting in 35, 30 or 25 Gy for TG1, TG2 and TG3, respectively [3]. By eliminating procarbazine, fertility in boys indeed was preserved [4, 5], but treatment efficacy was compromised. For patients with early stages (TG-1) the 10-year EFS rate dropped to 85%, however, practically all patients could be salvaged by relapse therapy and an overall survival rate of 98% after 10 years was seen [6]. For patients in intermediate (TG-2) and advanced stages (TG-3) the 3-year EFS rates dropped to unacceptable 59% and 62%, respectively [7].

In the fourth study generation, DAL-HD 87, procarbazine was reintroduced into the COPP cycles while it was still not administered in the OPA. In addition, the radiation dose was further reduced to 30, 25 and 20 Gy for TG-1, TG-2 and TG-3, respectively [8]. The indications for splenectomy were further restricted so that only in 29% of the patients the spleen was removed. The 7-year EFS and overall survival (OS) rates for all patients (85% and 97%, respectively) were better than in the DAL-HD 85, but still clearly worse than those of the DAL-HD 82 study generation and were felt to be unsatisfactory.

In the fifth generation, the DAL-HD 90 study, the initial therapy was re-intensified. All girls got OPPA again. Boys got OEPA, i.e. OPPA with procarbazine replaced by 500 mg/m^2 etoposide given over 4 days, in the hope that this would preserve fertility [9]. Splenectomy was abandoned and the radiotherapy dose was further reduced to 25, 25 and 20 Gy for TG-1-3, respectively. With this strategy, a 5-year EFS rate of 91% was achieved with OPPA and 89% with OEPA. Overall survival after 5 years was 98% in both groups. The results are comparable with the very good results of the DAL-HD 82 study, although therapy intensity was clearly reduced. By introducing etoposide the infertility rate of boys was significantly reduced in TG-1, while about half of the male patients in TG-2 and TG-3 still showed abnormal FSH values after the COPP cycles [10]. In the study generation DAL-HD 90 a real-time central review process for all patients was established. Staging, therapy group assignment and response assessment for all patients was performed centrally, assessing the clinical data and reviewing all cross-sectional imaging. In about 20% of the patients the stage was revised by central appraisal. A total of 11.7% of patients were assigned to a higher therapy group while 1.6% was down-staged to a lower therapy group [11].

Sixth generation: A major concern apart from infertility in boys is the development of secondary malignancies. The rate of secondary haematological malignancies, which occur mostly 1 – 10 years after therapy, is very low. The estimated risk after 15 years is about 1% for the patients in the DAL-HD 78 to DAL-HD 90 studies [12]. After the introduction of etoposide no leukaemias have been reported so far [13]. On the other hand, the number of non-haematological secondary tumours still increases after a latency period of 20 years and more. The cumulative risk of secondary solid tumours for the DAL / GPOH-HD study patients was 5.7% after 20 years (± 1.5%). This is almost identical to the 20-year risk for solid tumours reported by the American Late Effects Study Group (LESG). In their study the rate

of secondary tumours increased steeply between 20 and 30 years after therapy. After 30 years the rate of secondary malignant tumours approached 25% [14]. Secondary solid tumours (SST) are the main cause for this late increase. The most important risk factor for the development of SST is radiation therapy [15] and 22 of the 25 SST occurred in or at the border of the radiation field. Therefore, in the GPOH-HD 95 study generation the dose of radiotherapy was reduced to 20 Gy in all treatment groups. In addition, radiotherapy was omitted in patients with complete remission (CR) at the end of chemotherapy. EFS after 5 years was 88% for all patients and overall survival was 97% [16]. In TG-1 there was no significant difference in EFS between patients with (94%) and without (97%) radiotherapy. Therefore, omission of radiotherapy in CR patients was adopted as standard treatment. However, in TG-2 and TG-3 omission of radiotherapy for CR patients led to a significant decrease in EFS (without radiation 79%, with radiation 91%). Therefore, radiotherapy for TG-2 and TG-3 remained standard.

In the GPOH-HD 2002 Pilot study, all boys received an intensified OE*PA therapy (20% more Etoposide) and COPDAC (cyclophosphamide, vincristine, prednisone and dacarbazine) instead of the COPP cycles. In the previous studies DAL-HD 90 and GPOH-HD 95, boys showed a tendency towards worse EFS than girls. In the GPOH-HD 95 study boys had significantly worse 5-year DFS rates than girls (0.86 vs. 0.93%; p=0.006). This may or may not be related to girls receiving OPPA and boys receiving the less gonadotoxic OEPA. Male gender has been reported as unfavourable prognostic factor in the adult setting and is in the international prognostic score [17]. Based on the interpretation that OEPA was less effective than OPPA, OEPA was intensified in the GPOH-HD 2002 Pilot study extending etoposide administration from 4 to 5 days. Procarbazine was replaced by dacarbazine, which is less likely to cause infertility in males and premature menopause in females. The previous studies DAL-HD 82 and DAL-HD 87 showed that procarbazine could not safely be dropped without being replaced by an appropriate substitute. A median observation time of 15 months had passed until the start of the EuroNet-PHL-C1, which was too short to assess treatment efficacy. As of May 2005, EFS curves of both girls (N=129) and boys (N=159) in TG-2+TG-3 were in the order of 90% at 18 months as expected. No etoposide induced secondary leukaemias were observed.

The CT/MRI imaging techniques used cannot reliably distinguish between active and fibrotic/necrotic residual masses. Therefore sensitivity (rate of test-positive results in true positives) is reasonably high, but the specificity (rate of test-negative results in true negatives) is rather low (in the order of 30%) and a high negative predictive value can only be achieved, if most patients are already cured after chemotherapy. This was the case in TG-1, in which excellent results in CR patients without radiotherapy were seen. In TG-2 and TG-3 probably one third of all patients still require radiotherapy for cure. In this setting, patients with radiotherapy did better than patients in CR without radiotherapy. Meanwhile, fluorodeoxyglucose positron emission tomography (FDG-PET) has become available and is routinely used in most centres. FDG-PET can better distinguish between vital and fibrotic/necrotic residual masses and thus may resolve the specificity problem of CT/MRI [18-21]. In the EuroNet-PHL-C1 study FDG-PET is formally integrated into staging and response assessment. In order to safeguard against possible uptake artefacts and to avoid a major shift in staging results, the integration of FDG-PET results into staging and response assessment is based on two principles:

1. All functional FDG-PET information formally used in staging and response assessment must be paired with findings on conventional imaging.

2. At diagnosis FDG-PET results are only used to decide on involvement in regions that are suspicious but inconclusive by conventional imaging.

In the pilot study GPOH-HD 2002 200 children were staged with FDG-PET between November 2002 and March 2005. In regions in which both CT/MRI and PET were evaluable and conclusive, FDG-PET results were concordant in 4481/4857 (92.3%), discordantly positive in 240/4857 (4.9%) and discordantly negative in 136/4857 (3.0%) cases. In 241 regions CT/MRI was unclear and FDG-PET decided on the involvement following the principles outlined above. Concordance rates were below 90% in the following regions: high-cervical, cervical, lung hilum, and supra-diaphragmatic recesses. It is known that false negative [22] and false positive FDG-PET can be seen after chemotherapy. However it is important to minimise delay between chemotherapy cycles. The timing of FDG-PET is therefore crucial. The EORTC recommendations [23] state that at least 2 weeks should elapse after chemotherapy prior to FDG-PET. Therefore in the EuroNet-PHL-C1 study the early response assessment FDG-PET is scheduled on day 14 after the last chemotherapy application. All imaging data, including CT and FDG-PET images, are sent to the study centre for evaluation and decision on radiotherapy. Pilot data strengthen the expectation that in TG-1 radiotherapy can safely be omitted in PET-negative cases. In TG-2 and TG-3 it may be anticipated that about 1/3 of the patients will be PET-negative after 2 OEPA.

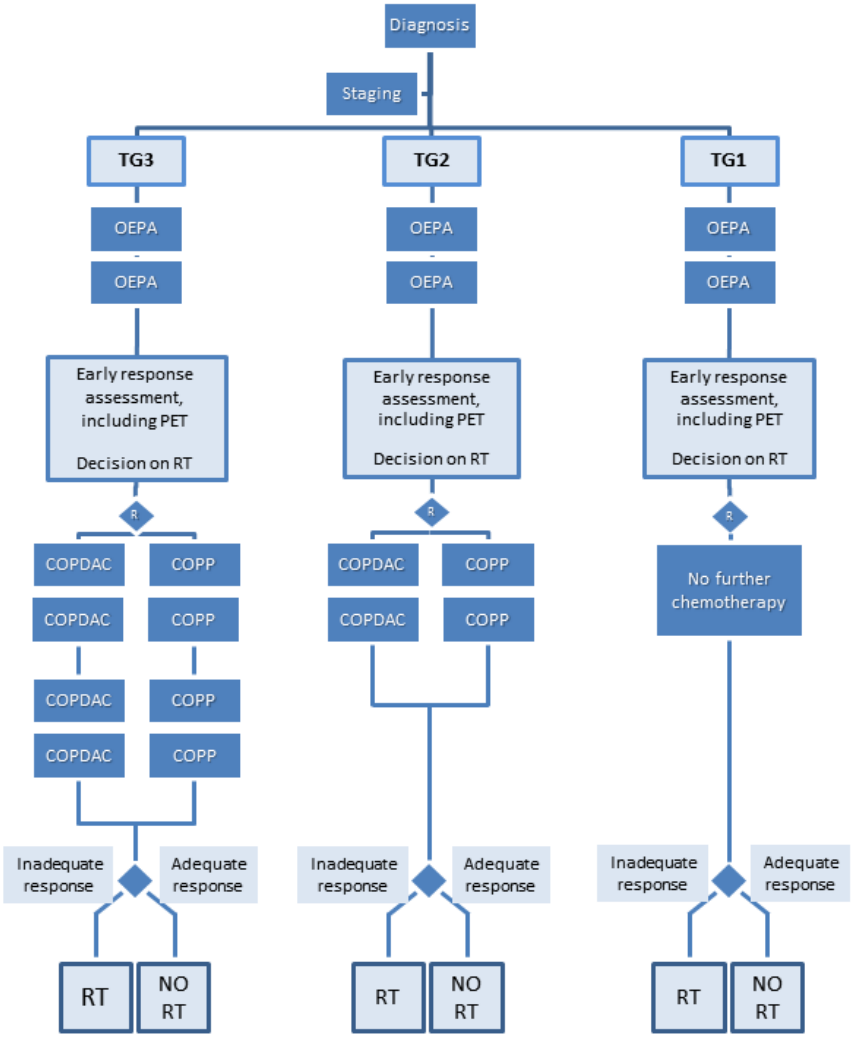

Figure 1: Flowchart for the EuroNet-PHL-C1 protocol. TG: treatment group (for definition of treatment groups, see the text box "Treatment groups" above), OEPA: cyclophosphamide, vincristine, etoposide and prednisone, COPDAC: cyclophosphamide, vincristine, prednisone and dacarbazine, COPP: cyclophosphamide, vincristine, procarbazine and prednisone, RT: radiotherapy.

Given the widespread use of FDG-PET and the potential of early FDG-PET-based response assessment, radiotherapy can be modified in the current EuroNet-PHL-C1 study. In all three treatment groups the indication for radiotherapy is based on early response assessment with CT/MRI and FDGPET after 2 OEPA. Patients with adequate response after two OEPA will not be irradiated. Radiation fields and technique: According to the GPOH experience, opposed field radiotherapy is performed to all initially involved lymph nodes with a safety margin of 1-2 cm. CT based 3D dose calculation is now recommended for all children. Radiation dose: During the past studies, the radiation dose has been reduced gradually. In case of incomplete response after 2 cycles of chemotherapy all primarily involved lymph nodes now receive a dose of 19.8 Gy. All patients with poor response get an additional boost of 10 Gy. Boost radiotherapy is based on response after two cycles of chemotherapy. Poor response is defined as follows: 1) residual volume larger than 25% of initial volume (i.e. <75% response) and residual volume >5 cm^3 *or* 2) residual volume >100 cm^3. Patients with an adequate response after 2 OEPA will not be irradiated. This holds for all treatment groups. The objective is to show that 5-year EFS rates in these positively selected patients without radiotherapy are consistent with a target rate of 90%.

In summary, the development of European protocols for the treatment of Hodgkin's lymphoma in children constitutes a good example of how treatments have been adjusted in paediatric haematology and oncology, gradually shifting the focus from cure at any price towards minimizing the sometimes debilitating late effects and secondary malignancies observed.

2.2.2.2. Hodgkin's lymphoma treatment in adults – a comparison

A challenge in paediatric oncology treatment studies is the relatively low number of patients, necessitating multi-centre designs and/or longer duration to obtain reliable results. Because of the generally higher number of patients in adult oncology, studies can come to conclusions more rapidly. As mentioned above, the paediatric protocols have moved from radiation of extended fields to involved fields and primarily involved nodes only. Since also the prescribed dose has successively been diminished the overall radiation burden has been reduced. In adult protocols, the development during the past almost 30 years has progressed in a similar way from radiation of extended fields, via locally extended fields to involved fields and to involved nodes together with a reduction in doses. Despite this similarity in development, there has during the past about 30 years been a common opinion in Sweden, the other Nordic countries and in at least parts of remaining Europe that the recommendations in paediatric Hodgkin's lymphoma have resulted in more radiotherapy being used in children than in adults. A direct comparison is difficult, and not the intention of this description, but the decreases in radiation burden have occurred some 3 – 5 years earlier in adult compared to paediatric Hodgkin's lymphoma oncology.

Most changes in Sweden and in the other Nordic countries have been done based on own experience together with results from sometimes also large randomised studies. The latter has been particularly the case during the past 10 – 15 years, and then based upon a series of trials, especially those run by the German Hodgkin Study Group (GHSG).

Discussions about the intensity of staging and treatment had been extensive in Sweden during the 1970s and early 1980s.

In Sweden, the first national Hodgkin's lymphoma care programme was approved and in use since 1984. The recommendations were tailored to patient and tumour characteristics and extent of disease, having the focus of cure with as little late effects as possible. Compared to the intensity of staging and extent of treatment, that was used at internationally renowned centres [24], splenectomy was used much less frequent and treatment intensity was reduced in most stages. The reduction in treatment affected both radiation therapy (chiefly volume, to some extent dose) and chemotherapy (chiefly number of cycles) in early, intermediate and advanced stages. At the same time, the quality of the radiation delivery was standardised towards improved dose homogeneity to the nodal volumes intended to be irradiated. This resulted in lower radiation doses to certain volumes, like the neck, but more radiation to e.g. the lungs to adequately cover mediastinal and hilar nodes with the 40 – 44 Gy considered necessary to bulky disease sites [25]. Later evaluations of the dose-response relationships in Hodgkin's lymphoma have not been able to detect any improved local control above 32.5 Gy [26, 27]. The classical analysis by Kaplan was based upon poorly performed radiation therapy where the true dose to relevant volumes was lower than the prescribed dose in the centre of the target.

Based upon the information collected prospectively and retrospectively from 5/6 Swedish health care regions in a quality registry, treatment results were well in line with those at major international sites, in spite of reduced staging intensity and treatment [28-30]. An exception was treatment of patients older than 60 years of age that had a much worse prognosis than those less than 60 years [31]. A modified care programme for the elderly was activated in 1989. Treatment after failure on primary treatment was also found to be suboptimal and a modification was activated in 1988. Later evaluations have found improved results of the modifications [32, 33].

Based upon our own experience and results from international studies, a new care programme was approved in 1994. Staging splenectomy was no longer recommended and the treatment recommendations were further tailored to prognostic factors. In 1997, discussions about joint protocols were initiated within the Nordic Lymphoma Group. These also led in 1999 to separate protocols in early-intermediate and advanced Hodgkin's lymphoma. In both protocols, the use of radiotherapy diminished and both radiation doses and volumes were further reduced.

With slight modifications, meaning even further reduced radiotherapy doses and irradiated volumes, these guidelines are still valid (see Figure 2). Adult patients with Hodgkin's lymphoma in early stages receive two cycles of chemotherapy followed by involved node irradiation to 20 Gy. In patients with intermediate stage disease, treatment is 4 cycles followed by involved node radiation to 30 Gy. In advanced stages, chemotherapy is the only treatment and based upon the number of risk factors according to IPS. In case of poor response, the chemotherapy is intensified and radiotherapy is only exceptionally given.

The recommendations used in 2010 in early and intermediate stages (TG1+2) do not differ substantially between paediatric and adult Hodgkin's lymphoma patients. The interpretation of what is PET-negative or PET-positive after a limited number of chemotherapy cycles differs slightly. In an individual case, it is impossible to state that one or the other evaluation is right or wrong, but the evaluation for paediatric patients done centrally in Germany are that children more often receive radiotherapy than if the evaluation had been done only in Sweden (Lund is the reference centre in RATHL)(Gunilla Enblad, Daniel Molin, personal communication). In the advanced stages, radiotherapy is still frequently given to children not responding rapidly to chemotherapy, whereas this is as said rarely given to adults.

During the past decades, informal discussions between the Hodgkin's Lymphoma groups have now and then taken place. This was formalised in November 2010 when a meeting took place in Stockholm. It then became clear that major differences exist in how patients not responding well to chemotherapy in advanced stages are treated. Radiation therapy for adults (≥18 years) is presently discussed at national video-conferences according to approved definitions of target volumes. This will (hopefully) also be the case with paediatric patients. For all cases, proton therapy plans will be made to gain experience prior to the start of the proton beam therapy centre, the Scandion Clinic in Uppsala in 2014.

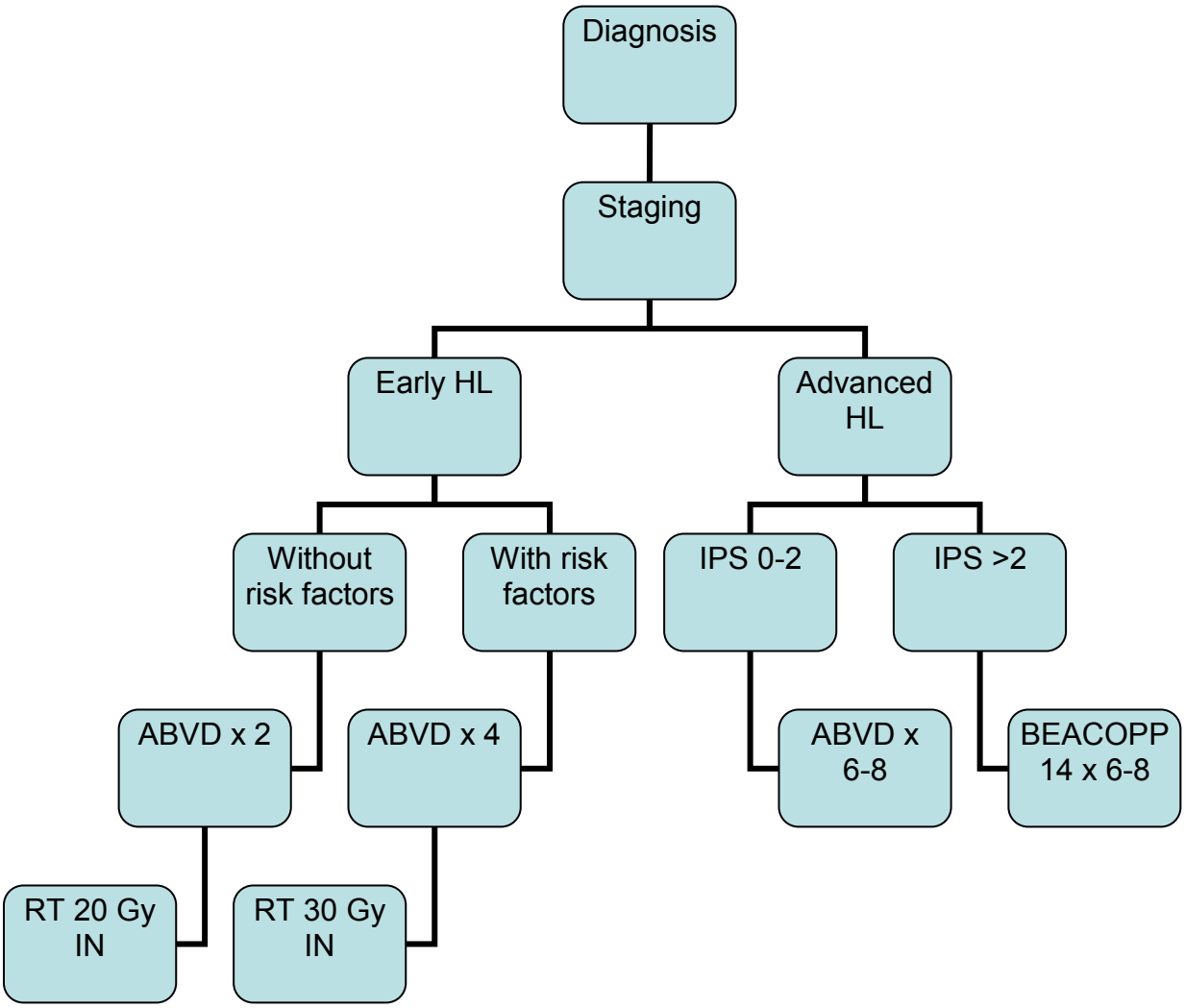

Figure 2. Present (061020-120630) national Swedish guidelines for treatment of patients 18 - ≤70 years with Hodgkins lymphoma; ABVD: doxorubicin, bleomycin, vinblastin, dacarbacin; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbacine, prednisolon; RT: radiotherapy; IN: involved node. Most patients with Advanced HL (IPS 0-7) participate in the RATHL study, where all start with ABVDx2. Further treatments depend upon PET response. Note that RT is not part of primary treatment in advanced HL in adults

In conclusion; radiotherapy remains an important treatment modality for some patients with Hodgkin's lymphoma, but because of the potential side effects, mainly secondary malignancies, heart disease and lung disease, development of new protocols have moved towards lower doses and smaller radiation fields. This is important, particularly in children, where the life expectancy is long. QC has been performed in Europe in the treatment of children with Hodgkin's lymphoma and treatment protocols have been modified accordingly. However, compared with protocols for adults' protocol changes happen at a slower rate and there is a widespread notion that more radiotherapy is used in the treatment of children than in adults. This remains a challenge in the development of future paediatric protocols.

2.2.2.3. References

1. Schellong, G., et al., *[Combined treatment strategy in over 200 children with Hodgkin's disease: graduated chemotherapy, involved field irradiation with low dosage and selective splenectomy. A report of the cooperative therapy study DAL-HD-82]*. Klin Padiatr, 1986. **198**(3): p. 137-46.
2. Schellong, G., et al., *Prediction of splenic involvement in children with Hodgkin's disease. Significance of clinical and intraoperative findings. A retrospective statistical analysis of 154 patients in the German therapy study DAL-HD-78.* Cancer, 1986. **57**(10): p. 2049-56.
3. Schellong, G., et al., *An approach to reduce treatment and invasive staging in childhood Hodgkin's disease: the sequence of the German DAL multicenter studies.* Bull Cancer, 1988. **75**(1): p. 41-51.
4. Brämswig, J.H., et al., *The effects of different cumulative doses of chemotherapy on testicular function. Results in 75 patients treated for Hodgkin's disease during childhood or adolescence.* Cancer, 1990. **65**(6): p. 1298-302.
5. Hassel, J.U., et al., *[Testicular function after OPA/COMP chemotherapy without procarbazine in boys with Hodgkin's disease. Results in 25 patients of the DAL-HD-85 study]*. Klin Padiatr, 1991. **203**(4): p. 268-72.
6. Schellong, G., et al., *Hodgkin's disease in children: combined modality treatment for stages IA, IB, and IIA. Results in 356 patients of the German/Austrian Pediatric Study Group.* Ann Oncol, 1994. **5 Suppl 2**: p. 113-5.
7. Schellong, G., et al., *[Significance of procarbazine in the chemotherapy of Hodgkin's disease--a report of the Cooperative Therapy Study DAL-HD-85]*. Klin Padiatr, 1988. **200**(3): p. 205-13.
8. Schellong, G., et al., *[Reducing radiation dosage to 20-30 Gy in combined chemo-/radiotherapy of Hodgkin's disease in childhood. A report of the cooperative DAL-HD-87 therapy study]*. Klin Padiatr, 1994. **206**(4): p. 253-62.
9. Schellong, G., et al., *High cure rates and reduced long-term toxicity in pediatric Hodgkin's disease: the German-Austrian multicenter trial DAL-HD-90. The German-Austrian Pediatric Hodgkin's Disease Study Group.* J Clin Oncol, 1999. **17**(12): p. 3736-44.
10. Gerres, L., et al., *The effects of etoposide on testicular function in boys treated for Hodgkin's disease.* Cancer, 1998. **83**(10): p. 2217-22.
11. Dieckmann, K., et al., *Up-front centralized data review and individualized treatment proposals in a multicenter pediatric Hodgkin's disease trial with 71 participating*

hospitals: the experience of the German-Austrian pediatric multicenter trial DAL-HD-90. Radiother Oncol, 2002. **62**(2): p. 191-200.
12. Schellong, G., et al., *Low risk of secondary leukemias after chemotherapy without mechlorethamine in childhood Hodgkin's disease. German-Austrian Pediatric Hodgkin's Disease Group.* J Clin Oncol, 1997. **15**(6): p. 2247-53.
13. Schellong, G., *Pediatric Hodgkin's disease: treatment in the late 1990s.* Ann Oncol, 1998. **9 Suppl 5**: p. S115-9.
14. Bhatia, S., et al., *High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group.* J Clin Oncol, 2003. **21**(23): p. 4386-94.
15. Meadows, A.T., et al., *Second malignant neoplasms following childhood Hodgkin's disease: treatment and splenectomy as risk factors.* Med Pediatr Oncol, 1989. **17**(6): p. 477-84.
16. Dörffel, W., et al., *Preliminary results of the multicenter trial GPOH-HD 95 for the treatment of Hodgkin's disease in children and adolescents: analysis and outlook.* Klin Padiatr, 2003. **215**(3): p. 139-45.
17. Hasenclever, D. and V. Diehl, *A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease.* N Engl J Med, 1998. **339**(21): p. 1506-14.
18. Dittmann, H., et al., *Comparison of 18FDG-PET with CT scans in the evaluation of patients with residual and recurrent Hodgkin's lymphoma.* Oncol Rep, 2001. **8**(6): p. 1393-9.
19. Spaepen, K., et al., *Can positron emission tomography with [(18)F]-fluorodeoxyglucose after first-line treatment distinguish Hodgkin's disease patients who need additional therapy from others in whom additional therapy would mean avoidable toxicity?* Br J Haematol, 2001. **115**(2): p. 272-8.
20. de Wit, M., et al., *18FDG-PET following treatment as valid predictor for disease-free survival in Hodgkin's lymphoma.* Ann Oncol, 2001. **12**(1): p. 29-37.
21. Langen, K.M., et al., *QA for helical tomotherapy: report of the AAPM Task Group 148.* Med Phys, 2010. **37**(9): p. 4817-53.
22. Cremerius, U., et al., *FDG PET for detection and therapy control of metastatic germ cell tumor.* J Nucl Med, 1998. **39**(5): p. 815-22.
23. Young, H., et al., *Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group.* Eur J Cancer, 1999. **35**(13): p. 1773-82.
24. Kaplan, H.S., *Hodgkin's disease: unfolding concepts concerning its nature, management and prognosis.* Cancer, 1980. **45**(10): p. 2439-74.
25. Kaplan, Cancer Research, 1966. **26**: p. 1221-4.
26. Vijayakumar, S. and L.C. Myrianthopoulos, *An updated dose-response analysis in Hodgkin's disease.* Radiother Oncol, 1992. **24**(1): p. 1-13.
27. Brincker, H. and F. D'Amore, *A retrospective analysis of treatment outcome in 106 cases of localized gastric non-Hodgkin lymphomas. Danish Lymphoma Study Group, LYFO.* Leuk Lymphoma, 1995. **18**(3-4): p. 281-8.
28. Glimelius, B., et al., *Treatment of Hodgkin's disease: the Swedish National Care Programmeme experience.* Leuk Lymphoma, 1996. **21**(1-2): p. 71-8.
29. Amini, R.M., et al., *Treatment outcome in patients younger than 60 years with advanced stages (IIB-IV) of Hodgkin's disease: the Swedish National Health Care Programmeme experience.* Eur J Haematol, 2000. **65**(6): p. 379-89.

30. Glimelius, I., et al., *Bulky disease is the most important prognostic factor in Hodgkin lymphoma stage IIB.* Eur J Haematol, 2003. **71**(5): p. 327-33.
31. Enblad, G., B. Glimelius, and C. Sundstrom, *Treatment outcome in Hodgkin's disease in patients above the age of 60: a population-based study.* Ann Oncol, 1991. **2**(4): p. 297-302.
32. Enblad, G., et al., *Methyl-GAG, ifosfamide, methotrexate and etoposide (MIME) as salvage therapy for Hodgkin's disease: a prospective study.* Eur J Haematol, 1998. **60**(3): p. 166-71.
33. Amini, R.M., et al., *A population-based study of the outcome for patients with first relapse of Hodgkin's lymphoma.* Eur J Haematol, 2002. **68**(4): p. 225-32.

3. Late effects including secondary malignancies

3.1. Secondary malignancies and IMRT

3.1.1. Introduction and background

Secondary cancer following radiotherapy is a radiation protection issue for the cancer patient. This is becoming more important due to the increase in both the number of irradiated patients and in survival after radiotherapy. A widely discussed aspect connected to the introduction of new dose-delivery technologies is their impact on late complications. The risk of secondary malignancy is one of these complications. It is also one of the most feared, as it encapsulates the dichotomy between need for therapy and the resulting side-effects.

Several clinical studies indicate an increased risk of secondary malignancies as a result of treatment by ionising radiation. A broad overview of the biological effects of ionising radiations, including carcinogenesis, can be found in the UNSCEAR 2000 [1] and 2006 [2] reports, in the BEIR VII [3] report and in ICRP Publication 103 [4] which replaced ICRP Publication 60 [5]. In particular, a number of epidemiological studies reveal an increase in the incidence of secondary cancers after radiotherapy [2]. Among the groups showing an increased incidence of second malignancies after radiotherapy are patients treated for Hodgkin's lymphoma [6,7], breast cancer [8, 9], paediatric cancer and prostate cancer [10-12].

Specific criteria are required to make sure that these events are induced by radiotherapy and are not simply metastases, an extension of the first tumour (i.e. which was not controlled locally) or, of course, a tumour which has no connection at all with radiation exposure. Risk factors, usually derived for the general population, may not be applicable; patients who have already developed a cancer may have a different underlying risk because of age, life expectancy, genetic and environmental factors [13]. As an example, recent studies show that the risk of having lung cancer, as a secondary malignancy following radiation therapy for breast cancer, is due to the combination of radiation therapy and smoking. Other risk factors like age, hormonal status [14,15] and chemotherapy [6,14,16] have also been shown to significantly affect this risk. The individual genetic profile play also an important role [17,18].

One of the greatest difficulties concerning studies on secondary malignancy following radiotherapy is the "fragility" of the datasets (dose-volume information and clinical information) to be analysed. This is due to the nature of the event, requiring large patient populations, and long follow-up. At the moment the available dose-volume information refers to the pre-3D era and therefore include several sources of uncertainty [19]. As a consequence

the analysis of the dose-volume/outcome data, including modelling solutions, have not yet provided a stable reference frame [20]. For newer delivery techniques (e.g. IMRT or protons and other heavy charged particle beams) no outcome data are yet available simply due to the fact that the follow-up times have been insufficient. In order to assess the risk of radiation-induced malignancies for any particular radiotherapy technique one would need a good understanding, for each specific organ or tissue type, of the connection between total dose and its distribution, fraction size, volume, dose rate and the probability of a second cancer. Today our understanding is partial; however various models have been proposed and/or analyses made by e.g. Lindsay et al [21], more recently Schneider *et al* [22], Sachs and Brenner [23], and Daşu et al [24].

Schneider et al [22] introduced the concept of organ equivalent dose (OED), defined as the single uniform dose to the organ which gives the same second cancer risk as the (non-uniform) dose distribution in the treatment plan. The model is based on the product of a linear term (mutagenesis) and a negative exponential term (cell killing). As an example it has been used to investigate the impact of dose escalation on second cancer risk following prostate cancer radiotherapy [25].

Sachs and Brenner [23] developed a model for the yield of pre-malignant stem cells, accounting for cell proliferation and repopulation effects together with dose fractionation. They showed how this could account for the clinical findings of an increased risk of radiation-induced cancer at high total doses, in contrast to the then prevailing model of the risk going through a maximum at around 5-10 Gy total dose [21]. The key aspect in the modelling is the competition between mutagenesis and cell killing.

The Daşu et al [24] analysis included both fractionation and, more particularly, non-uniform dose distributions.

3.1.2. IMRT vs non-IM radiotherapy

What can we say about (photon) IMRT versus 3D conformal photon RT regarding second cancer risk?

Firstly, it has been suggested that IM ought to induce significantly more second cancers than non-IM treatments [26]. Their starting point was the observation that the greater number of Monitor Units required to deliver a given dose to the tumour/target volume using IM, results in an increased dose to parts of the patient's body outside the treatment fields i.e. those parts which are only irradiated due to leakage through the treatment head (jaws, multileaf collimators etc.). Initially the assumption was that this out-of-field dose, though extremely low compared to the in-field doses (a few per cent at most, but generally far lower than this), is responsible for a significant fraction of the second cancers (in the radiotherapy-treated population). However it has recently been shown that the relative contribution to the probability of a second cancer is much greater from *in-field* compared to *out-of-field* doses [25]. The Schneider study, together with others comparing out-of-field doses from different dose delivery modalities and beam energies [27] will help to better understand the implications of the use of IM beams in terms of second cancer risk.

Secondly it has been generally accepted that the integral dose, defined as the total energy delivered by all the radiation fields (mathematically the integral of dose with respect to mass = energy), together with the dose distribution in the normal tissue, influence the carcinogenic

risk. According to "conventional wisdom" IMRT would lead to a *greater integral dose* per unit tumour dose (compared to 3D-CRT) to normal tissue, and therefore to a possible increase of secondary cancer by a factor of 1.2-8 [26, 28, 29]. In this case the integral dose refers primarily to the in-field situation. The integral dose argument deserves reflection. For any reasonably *centrally* located tumour irradiated by an arbitrary number of *co-planar* beams (both these conditions are important) the integral dose will be approximately constant (per unit tumour dose) irrespective of the number of beams and whether they are modulated in intensity or not.

A larger number of beams, which is typically the case with IMRT, will irradiate a larger volume of tissue to a lower dose; this is sometimes referred as the 'dose bath' situation (as opposed to a few-beam 'shower'). The ultimate 'dose bath' occurs with rotational IMRT such as Tomotherapy, RapidArc, SmartArc or VMAT.

The argument at this point becomes complex, as it requires knowledge of the relationship between dose level and second cancer induction probability (per unit volume of tissue irradiated). Various formalisms have been suggested [21, 24], assuming that the probability of secondary cancer goes through a maximum at doses of around 5 Gy and then decreases fairly rapidly due to the dominating effect of cell killing above a certain dose (i.e. dead cells cannot become malignant later on). This model does lead to a lower cancer induction probability for fewer fields at higher doses compared to the (low) 'dose bath'. Recently instead a plateau like function for carcinoma induction based on large cell repopulation rates has been proposed [30]. If IMRT does not result in any greater integral dose it follows that its use ought not to result in any higher risk of secondary malignancy [31]. Interesting results in this direction are also provided by the recent paper by Huang et al [32].

3.1.3. Proton therapy

In the panorama of new radiation-delivery technologies, protons have been indicated as favourable for the treatment of young patients. The primary reason is the significantly lower integral dose delivered by proton beams (always per unit dose to the tumour) compared to any kind of photon beam [33, 34]. Thus the use of protons as opposed to photons (for the same or similar dose to the tumour) should significantly reduce the risk of secondary malignancy, provided that the additional dose from the accompanying neutrons is kept below a certain limit [35].

3.1.4. Conclusions

Summarising, there are still several question marks about the increase of second cancer risk from intensity modulation, for a given dose to the tumour, compared to that of more conventional conformal radiotherapy with (flat) beams shaped by multileaf collimators. Fortunately answers may become available in the near future thanks to new data.

3.1.5. References

1. Radiation), U.U.N.S.C.o.t.E.o.A., *Report to the General Assembly: Sources and Effects of Ionising Radiation, with Scientific Annexes. Annex I: Epidemiological evaluation of radiation induced cancer*. 2000.
2. Radiation), U.U.N.S.C.o.t.E.o.A., *Report to the General Assembly: Effects of Ionising Radiation, with Scientific Annexes. Annex A: Epidemiological studies of radiation and cancer*. 2006.
3. Report, B.V., *Health Risks from Exposure to Low Levels of Ionising Radiation*. National Academies Press 2006.
4. 103, I.P., *Recommendations of the International Commission on Radiological Protection*. Annals of the ICRP 37 (2-4), 2007.
5. 60, I.P., *Recommendations of the International Commission on Radiological Protection*. Annals of the ICRP 21 (1-3), 1990.
6. Ng, A.K., et al., *Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors*. Blood, 2002. **100**(6): p. 1989-96.
7. Travis, L.B., et al., *Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma*. J Natl Cancer Inst, 2005. **97**(19): p. 1428-37.
8. Kirova, Y.M., et al., *Risk of second malignancies after adjuvant radiotherapy for breast cancer: a large-scale, single-institution review*. Int J Radiat Oncol Biol Phys, 2007. **68**(2): p. 359-63.
9. Berrington de Gonzalez, A., et al., *Second solid cancers after radiotherapy for breast cancer in SEER cancer registries*. Br J Cancer, 2010. **102**(1): p. 220-6.
10. Brenner, D.J., et al., *Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery*. Cancer, 2000. **88**(2): p. 398-406.
11. Brenner, D.J., et al., *Prostate radiotherapy is associated with second cancers in many organs, not just the colorectum*. Gastroenterology, 2005. **129**(2): p. 773-4; author reply 774-5.
12. Froehner, M. and M.P. Wirth, *Response to "The rate of secondary malignancies after radical prostatectomy versus external beam radiation therapy for localised prostate cancer: a population-based study on 17,845 patients." (Int J Radiat Oncol Biol Phys 2010;76:342-348)*. Int J Radiat Oncol Biol Phys, 2010. **78**(4): p. 1279; author reply 1280.
13. Tubiana, M., *Can we reduce the incidence of second primary malignancies occurring after radiotherapy? A critical review*. Radiother Oncol, 2009. **91**(1): p. 4-15; discussion 1-3.
14. Rubino, C., et al., *Radiation dose, chemotherapy, hormonal treatment and risk of second cancer after breast cancer treatment*. Br J Cancer, 2003. **89**(5): p. 840-6.
15. van Leeuwen, F.E., et al., *Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease*. J Natl Cancer Inst, 2003. **95**(13): p. 971-80.
16. Travis, L.B., et al., *Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease*. J Natl Cancer Inst, 2002. **94**(3): p. 182-92.
17. Heymann, S., et al., *Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome*. Radiat Oncol, 2010. **5**: p. 104.
18. Bernstein, J.L., et al., *Radiation exposure, the ATM Gene, and contralateral breast cancer in the women's environmental cancer and radiation epidemiology study*. J Natl Cancer Inst, 2010. **102**(7): p. 475-83.

19. Xu, X.G., B. Bednarz, and H. Paganetti, *A review of dosimetry studies on external-beam radiation treatment with respect to second cancer induction.* Phys Med Biol, 2008. **53**(13): p. R193-241.
20. Kry, S.F., et al., *Uncertainty of calculated risk estimates for secondary malignancies after radiotherapy.* Int J Radiat Oncol Biol Phys, 2007. **68**(4): p. 1265-71.
21. Lindsay, K.A., et al., *Radiation carcinogenesis modelling for risk of treatment-related second tumours following radiotherapy.* Br J Radiol, 2001. **74**(882): p. 529-36.
22. Schneider, U., et al., *Estimation of radiation-induced cancer from three-dimensional dose distributions: Concept of organ equivalent dose.* Int J Radiat Oncol Biol Phys, 2005. **61**(5): p. 1510-5.
23. Sachs, R.K. and D.J. Brenner, *Solid tumour risks after high doses of ionising radiation.* Proc Natl Acad Sci U S A, 2005. **102**(37): p. 13040-5.
24. Dasu, A., et al., *The use of risk estimation models for the induction of secondary cancers following radiotherapy.* Acta Oncol, 2005. **44**(4): p. 339-47.
25. Schneider, U., et al., *The impact of dose escalation on secondary cancer risk after radiotherapy of prostate cancer.* Int J Radiat Oncol Biol Phys, 2007. **68**(3): p. 892-7.
26. Hall, E.J. and C.S. Wuu, *Radiation-induced second cancers: the impact of 3D-CRT and IMRT.* Int J Radiat Oncol Biol Phys, 2003. **56**(1): p. 83-8.
27. Kry, S.F., et al., *Monte Carlo study shows no significant difference in second cancer risk between 6- and 18-MV intensity-modulated radiation therapy.* Radiother Oncol, 2009. **91**(1): p. 132-7.
28. Kry, S.F., et al., *The calculated risk of fatal secondary malignancies from intensity-modulated radiation therapy.* Int J Radiat Oncol Biol Phys, 2005. **62**(4): p. 1195-203.
29. Verellen, D. and F. Vanhavere, *Risk assessment of radiation-induced malignancies based on whole-body equivalent dose estimates for IMRT treatment in the head and neck region.* Radiother Oncol, 1999. **53**(3): p. 199-203.
30. Schneider, U., *Mechanistic model of radiation-induced cancer after fractionated radiotherapy using the linear-quadratic formula.* Med Phys, 2009. **36**(4): p. 1138-43.
31. Ruben, J.D., et al., *The effect of intensity-modulated radiotherapy on radiation-induced second malignancies.* Int J Radiat Oncol Biol Phys, 2008. **70**(5): p. 1530-6.
32. Huang, J., et al., *Analysis of second malignancies after modern radiotherapy versus prostatectomy for localised prostate cancer.* Radiother Oncol, 2011. **98**(1): p. 81-6.
33. Lee, M., et al., *A comparison of proton and megavoltage X-ray treatment planning for prostate cancer.* Radiother Oncol, 1994. **33**(3): p. 239-53.
34. Widesott, L., et al., *Intensity-modulated proton therapy versus helical tomotherapy in nasopharynx cancer: planning comparison and NTCP evaluation.* Int J Radiat Oncol Biol Phys, 2008. **72**(2): p. 589-96.
35. Jarlskog, C.Z. and H. Paganetti, *Sensitivity of different dose scoring methods on organ-specific neutron dose calculations in proton therapy.* Phys Med Biol, 2008. **53**(17): p. 4523-32.

3.2. Late effects of radiotherapy in combination with chemotherapy

The combined effect of radiotherapy and chemotherapy on tumour and normal tissues is extremely complex. Numerous drugs have been, and are used, with the goal of a therapeutic gain compared to single modality treatment [1]. It can be expected that the many new targeted drugs also will be explored in combination with radiotherapy. The purpose of combining radiotherapy and chemotherapy is basically two-fold. Firstly, to add the systemic effect of chemotherapy (reduction of distant metastases) to the local tumour control achieved with radiotherapy. Secondly, to enhance the local radiotherapy effect and achieve a higher tumour control rate. Today's many different drugs as well as the variation in radiotherapy doses, timing and fractionation open for multiple potential modes of action which are not easily described. Drug administration before (neoadjuvant) or after (adjuvant) a course of radiotherapy is commonly used but also chemotherapy during radiotherapy (concurrent treatment) is frequently used in many solid malignancies.

Multiple trials in many different tumour types have compared radiotherapy with combinations of radiotherapy and chemotherapy. The results of the trials differ between tumour types, although a general finding is that local control is improved whereas it has been much more difficult to show an overall survival benefit. The gain in local tumour control has rarely been large, although by many clinicians considered sufficient for providing combined therapy in clinical routine. The gains in survival, if seen, have been minimal or limited, and have usually required meta-analyses of the individual trials to reveal statistical significance. Combination therapy always leads to enhanced acute side effects in normal tissues e.g. in skin, mucosal membranes and bone marrow. This increased acute toxicity has not prevented the use of combined modality treatment in patients considered fit for this. Late effects, of high importance in surviving patients, are however scarcely reported and if so, hard to evaluate. Knowledge of late morbidity is fundamental in order to get a complete picture of pros and cons with combined modality treatments. The purpose of this report is to give a brief summary of the present literature-based knowledge about late effects after chemoradiotherapy in relation to radiotherapy alone.

A systematic approach to literature was aimed at, but it is beyond the scope of this report to present a full comprehensive overview. PubMed and Cochrane were used as main sources. A supplement of "The QUantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)"[2] was used as a basis and reference report. In this report Marks et al.[3] summarises the problem as follows: *"*Use of sequential/concurrent chemotherapy/radio-therapy is increasing for many tumours. Concurrent chemotherapy is typically believed to exacerbate the severity of normal tissue reactions, but data quantifying this is often lacking. Even when such data are available, the chemotherapy doses, schedules and agents—which may influence outcomes—are in evolution". It should be noted that due to lack of precise data, the QUANTEC report is very superficial concerning whether late toxicity is increased or not after combined modality therapy compared to radiotherapy alone.

3.2.1. Cervical cancer

In the Cochrane report from 2010 [4] the collaboration evaluated concurrent chemoradiotherapy in cervical cancer. The authors conclude that concurrent therapy resulted in an increased chance of survival than treatment with radiotherapy alone. There was however implications of a decreasing relative effect on survival with increasing tumour stage. The estimated absolute survival benefit at 5 years was 10% in stages 1-2a, 7% in stage 2b and 3% in stage 3-4a. However, when applying the overall HR (0.81) to each of the stages an

improvement in OS at 5 years was seen for all. This confirms the benefit of chemoradiotherapy in women with cervical cancer, despite stage, although the absolute magnitude of the benefit varies. The acute side effects of the combined treatments were manageable. Serious haematological toxicity increased approximately two- to ten-fold in individual trials and there was a significant increase in serious GI toxicity (grade 3-4) when platinum-based chemoradiotherapy was used (OR=1.98, $p<0.00001$).

Data on late toxicity was scarce and no conclusions could be drawn. In total, 24 studies included almost 5 000 patients that were randomised to radiotherapy alone or combined chemoradiation and were still not able to give any conclusive answer about late toxicity. In seven trials data on late rectal toxicity were available and in five trials late bladder toxicity were reported. Late intestinal and late vaginal toxicity were only reported in four trials. Furthermore, even within these trials the data was incomplete with substantial lack of information. In general, late toxicity was defined as toxicity three or more months after treatment but "late" toxicity is ordinarily considered to occur years after treatment. The available data suggests that a variable number of women across all trials (1 to 55%) experience late toxicities, mostly grade 3 – 4 but grade 5 with eight deaths were also reported. Due to the lack of prospective recording in many of these trials data may not be representative. Only one trial reported quality of life data.

In conclusion; the benefit of concurrent treatment in cervical cancer is evident in terms of survival and disease control. Early toxicity is increased but knowledge of whether late treatment-related side-effects are increased is missing.

3.2.2. Breast cancer

Several early breast cancer trials showed that concurrent radiotherapy and chemotherapy with CMF is feasible but that late side effects were increased. More recently introduced drugs in breast cancer treatment have shown radiosensitising properties, e.g. docetaxel and doxorubicin. For these drugs an increased risk of pneumonitis, congestive heart failure, coronary artery disease and other late radiation sequelae are seen [5] and the present recommendations are to terminate chemotherapy before radiotherapy is initiated [6, 7]. The Arcosein study [8] explored a combination of mitoxantrone, fluorouracil and cyclophosphamide in a phase III trial of patients with early breast cancer. The patients were randomised between concurrent or sequential radiotherapy and chemotherapy. There was no difference in DFS at 5 years but an increase in late radiation side effects was noted in the concurrent arm.

The knowledge of whether late toxicity is increased using the monoclonal antibody trastuzumab with radiation is limited due to too short follow-up [9]. Increased late brachial plexus damage following combined treatment was reported by Olsen et al [10], describing a definite or probable radiation plexopathy in 42% of patients treated with chemotherapy (tamoxifen, cyclophosphamide or CMF) and radiotherapy versus 26% in patients treated with radiotherapy alone.

In conclusion; chemotherapy, including targeted drugs and radiotherapy are established treatments for many groups of patients with early breast cancer since they contribute to better disease control and improved survival. Late toxicity is increased when drugs and radiation are given together, and the recommendations are to avoid concurrent administration.

3.2.3. Head and neck cancer

Trials in head and neck cancer have shown that the frequency of swallowing dysfunction after radiotherapy with concurrent chemotherapy is increased from 10% to 56%, compared to radiotherapy alone [11]. In another trial [12] in patients with oropharyngeal carcinoma, where radiotherapy was compared to concurrent chemoradiotherapy, a statistically significant improvement in loco-regional control but with a significant increase in acute toxicity (severe mucositis) was seen. At 2 years 51% of patients in the chemoradiation arm were dependent on a feeding tube compared to 25% (p=0.02) in the radiotherapy alone arm. G-CSF was in this trial reported to reduce acute mucositis but at the cost of a decreased local control rate.
In the meta-analysis of head-and-neck trials evaluating the effects of chemotherapy in combination with radiotherapy [13], the authors conclude that a significant effect on survival can be seen (4.5% at 5 years for all trials (HR 0.88) and 6.5% for concomitant chemotherapy (HR 0.81). However, there is no analysis of late toxicity data.

The addition of concurrent chemotherapy to high-dose radiotherapy at least doubles the risk of laryngeal oedema and dysfunction, as stated in the QUANTEC report [14].

In conclusion; the use of concomitant chemoradiotherapy, including cetuximab (a monoclonal antibody inhibitor of the epidermal growth factor receptor) in head and neck cancer is extensive since randomised trials, and meta-analyses have shown clinical gains. The knowledge of late toxicity is though very limited but some trials imply increased risks after concomitant treatment.

3.2.4. Rectal cancer

In rectal cancer, but also in most other gastrointestinal tumour sites, concomitant 5-fluorouracil (5-FU) has been given together with radiation for decades. Its use was based upon a few small randomised trials performed decades ago, revealing improved local control and survival [15]. Slightly above ten years ago, three large co-operative groups challenged this generally held view and initiated controlled clinical phase III trials with radiotherapy only as the control treatment. The studies in rectal cancer were adequately powered to evaluate local control, and acute toxicity, but not late toxicity. The three trials [16-18] all noticed improved local control rates in the combined groups (8 – 10% vs 15 – 17% in [16, 17], including intermediately advanced tumours and 18% vs 33% in [19], including the most locally advanced tumours). Survival did not differ between treatment groups in the first two trials, but tended to do so in the trial including the most advanced tumours (overall survival at 5 years 65% vs 53%, p=0.09; cancer-specific survival 72% vs 55%, p=0.02). Acute toxicity (grade 3-4) is increased from 3 – 5% with radiotherapy alone (46 – 50 Gy in 5-6 weeks) to 10-15% with chemoradiotherapy with 5-FU. When radiotherapy was combined with other drugs, like oxaliplatin, further improvements was claimed, still though not proven, and 30-40% of the patients reported acute grade 3-4 toxicity, chiefly gastrointestinal. Late toxicity was however only briefly reported in the original publications, claiming no differences. Long-term quality-

of-life was recently reported from French patients in one of the trials [16], describing decreased role and social functioning, poorer global QoL and more diarrhoea in the CRT group [20]. Braendengen et al [21], noted increased incidence with poor anal functioning (89% vs 70%, p=0.046) and a tendency to increased bowel obstruction (28% vs 15%, p=0.2) in the CRT group. Social functioning was also poorer in the CRT group, 71 vs 78 (p=0.14), but otherwise no differences were seen in QoL aspects (Braendengen et al, unpublished).

In conclusion; similar to the situations in cervical cancer and head-and-neck cancer, improved outcomes are seen with concomitant chemoradiotherapy, and this treatment is routine at most sites worldwide. In Sweden, radiotherapy alone is used for intermediate cancers (the "bad" group, about 50% of all rectal cancers) and chemoradiotherapy with 5-FU only for the advanced cancer ("ugly" group, about 10-15%). The knowledge of late toxicity from radiation alone is extensive, and it is thus presently used more selective than in the past. Whether combinations with chemotherapy increase late toxicity even further is poorly known, but the most recent trials imply that this may be the case.

3.2.5. Discussion

An important statement is that QoL, acute and late treatment side effects as well as treatment costs are important issues to explore when introducing new treatments including drug-radiation combinations in clinical practise. While the antitumour effect and acute toxicity are the focus of most reports exploring different chemoradiotherapy protocols, late treatment effects are rarely reported and it is not possible to conclude whether late toxicity is increased or not from chemoradiotherapy relative to radiotherapy alone.

Bentzen et al [22] concluded that "First, morbidity, especially late, is frequently inadequately recorded and reported. The lack of standardized scoring systems and the often poor quality control of morbidity scores limit the value of much of the published literature. Second, even when morbidity is reported, the statistical power of the trial is not sufficient to resolve a clinically important change in this endpoint. Thus, in most trials, the possible change in therapeutic gain cannot be reliably judged. This is clearly a field in which more research is urgently needed". After having completed this report, we can in early 2011 completely agree with the statements from 2003.

Besides sparse reporting of side effects, a major problem in evaluating late effects is the lack of a common toxicity scoring system. Trotti et al [23] suggested a common scoring system for side effects whether single modality treatment or combined treatments are used. A combination of existing drug- and radiotherapy-related toxicity scores will probably not be relevant for scoring side-effects of combination therapies. The QUANTEC report [24] recognizes the major problems of incomplete reporting of results and the use of incompatible or ambiguous endpoints. The report aims to provide methods of defining suitable endpoints in order to facilitate meta-analysis.

The knowledge we use today is based on normal tissue tolerance for single modality treatment with radiotherapy. Generally there is an acceptance for severe late damage in 5% of the patients undergoing curative treatments, e.g. a 5% risk of osteoradionecrosis, severe swallowing dysfunction and fibrosis in head and neck cancer patients. Introducing

chemoradiation protocols, along with new radiotherapy techniques creates uncertainties in defining constraints for normal tissue tolerance.
Importantly, late effects can develop and progress for many years after treatment. Symptoms of nerve damage following radiotherapy for breast cancer can occur 15 years after the treatment [25]. Studies of heart complications after radiation therapy for breast cancer have revealed a latency period of 10 years between treatment and cardiovascular disorders [26]. Thus, regarding cardiovascular side effects a follow-up time of 15-20 years is necessary for proper evaluation.

One problem in the reporting and evaluating of radiotherapy side-effects is the lack of follow-up data. If follow-up is maintained it is often undertaken in local hospitals, with a focus on diagnosis of a relapse rather than recording side-effects. There is in Sweden, and likely also world-wide no capacity at the referral clinics for regular follow-up and important information is lost for the treating specialists.

The use of chemotherapy or targeted drugs in Sweden (both concurrent or sequentially) in combination with radiotherapy will change the frequency and panorama of both early and late radiation side effects. The mandatory tumour-group specific Quality Registers may enhance the knowledge in present treatment regimens in Sweden. From these registers it will be possible to identify subgroups of patients for further studies on specific drugs, treatments and side-effects.

3.2.6. Recommendation

Reporting of severe and unexpected side effects
A central board should be established in Sweden for the registration of severe and unexpected side effects (acute and late) from radiation therapy. The proposed board should on an annual basis analyse and summarise reported side effects. Through this action it would be possible to early detect a specific side effect or a high frequency of severe side effects associated with a particular drug or radiation technique. Early actions could hence be taken.

Reporting of endpoints
Endpoints used in the evaluation of side effects are not well defined and different scales are used. Hence evaluation of late effects becomes difficult. This is clearly stressed in the QUANTEC report.

The radiotherapy community needs to decide on a common validated toxicity scale where acute and late morbidity should be reported in a standardised way to facilitate the comparison between different treatments. All new radiotherapy protocols should include this scoring system.

Reporting to the national quality registries must be improved. Presently, complete registration is only done in a few diagnoses. Even in these, only early outcomes, together with overall survival gathered from another registry, are reported. The information about given radiotherapy is very limited, and must be more detailed. Development of systems that can collect information of radiation doses, including dose-volume histograms, and link it to the clinical information in the quality registers must be given high priority. Not to forget, radiotherapy is an important treatment modality for a substantial group of cancer patients but its potential late side-effects must be considered carefully especially as it may be aggravated by adding medical treatments.

3.2.7. Conclusions

- Acute radiation toxicity is enhanced by chemoradiation.
- Local control and possibly also survival is increased in several tumour locations.
- Reports are limited regarding late radiation side effects, but some reports indicate that increased late radiation toxicity can be expected.
- There is a lack of common criteria and scales for the registration of late side effects.
- There is a lack of resources in Sweden for the follow-up of treated patients.
- Research is highly needed is this area.

3.2.8. References

1. SBU, *Statens beredning för medicinsk utvärdering, rapport 155. Cytostatikabehandling vid cancer.* 2001.
2. QUANTEC, *QUantitative Analyses of Normal Tissue Effects in the Clinic.* Int J Radiat Oncol, Biol, Phys 2010. **76**(3): p. suppl.
3. Marks, L.B., et al., *Use of normal tissue complication probability models in the clinic.* Int J Radiat Oncol Biol Phys, 2010. **76**(3 Suppl): p. S10-9.
4. Green, J., et al., *Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix (Review).* Cochrane Database Syst Rev, 2010(1): p. CD002225.
5. Gagliardi, G., et al., *Radiation dose-volume effects in the heart.* Int J Radiat Oncol Biol Phys, 2010. **76**(3 Suppl): p. S77-85.
6. Goldhirsch, A., et al., *Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005.* Ann Oncol, 2005. **16**(10): p. 1569-83..
7. Recht, A., et al., *Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology.* J Clin Oncol, 2001. **19**(5): p. 1539-69.
8. Toledano, A.H., et al., *Does concurrent radiochemotherapy affect cosmetic results in the adjuvant setting after breast-conserving surgery? Results of the ARCOSEIN multicentre, Phase III study: patients' and doctors' views.* Int J Radiat Oncol Biol Phys, 2007. **68**(1): p. 66-72.
9. Halyard, M.Y., et al., *Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG Phase III Trial N9831.* J Clin Oncol, 2009. **27**(16): p. 2638-44.
10. Olsen, N.K., et al., *Radiation-induced brachial plexus neuropathy in breast cancer patients.* Acta Oncol, 1990. **29**(7): p. 885-90.
11. Langendijk, J.A., et al., *A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer.* Radiother Oncol, 2009. **90**(2): p. 189-95.
12. Staar, S., et al., *Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy--results of a multicentric randomised*

German trial in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys, 2001. **50**(5): p. 1161-71.
13. Pignon, J.P., et al., *Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients.* Radiother Oncol, 2009. **92**(1): p. 4-14.
14. Rancati, T., et al., *Radiation dose-volume effects in the larynx and pharynx.* International Journal of Radiation Oncology Biology Physics, 2010. **76**(3 Suppl): p. S64-9.
15. *NCI advocates use of adjuvant therapy for rectal cancer.* Am Fam Physician, 1991. **43**(4): p. 1440-2, 1444.
16. Bosset, J.F., et al., *Chemotherapy with preoperative radiotherapy in rectal cancer.* N Engl J Med, 2006. **355**(11): p. 1114-23.
17. Gerard, J.P., et al., *Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203.* J Clin Oncol, 2006. **24**(28): p. 4620-5.
18. Braendengen M, et al., *A randomised phase III study (LARCS) comparing preoperative radiotherapy alone versus chemoradiotherapy in non-resectable rectal cancer.* J Clin Oncol, 2008. **26**: p. 3687-3694.
19. Braendengen, M., et al., *Randomised phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer.* J Clin Oncol, 2008. **26**(22): p. 3687-94.
20. Tiv, M., et al., *Long-term quality of life in patients with rectal cancer treated with preoperative (chemo)-radiotherapy within a randomised trial.* Cancer Radiother, 2010. **14**(6-7): p. 530-4.
21. Braendengen M, et al., *Late patient-reported toxicity after preoperative radiotherapy or chemoradiotherapy in nonresectable rectal cancer: Results from a randomised phase III study.* Int J Radiat Oncol Biol Phys, 2011. **in press**.
22. Bentzen, S.M., *From clincal trials to clinical practice: A user's guide to evidence-based oncology.* Eur J Cancer Suppl, 2003. **1**: p. 77-91.
23. Trotti, A., et al., *CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment.* Semin Radiat Oncol, 2003. **13**(3): p. 176-81.
24. Jackson, A., et al., *The lessons of QUANTEC: recommendations for reporting and gathering data on dose-volume dependencies of treatment outcome.* International Journal of Radiation Oncology Biology Physics, 2010. **76**(3 Suppl): p. S155-60.
25. Johansson, S., H. Svensson, and J. Denekamp, *Dose response and latency for radiation-induced fibrosis, edema, and neuropathy in breast cancer patients.* International Journal of Radiation Oncology Biology Physics, 2002. **52**(5): p. 1207-19.
26. Harris, E.E., *Cardiac mortality and morbidity after breast cancer treatment.* Cancer Control, 2008. **15**(2): p. 120-9.

3.3. Paediatric oncology – late effects after radiotherapy

3.3.1. Background

The number of patients surviving their cancer diagnosis has increased. Today, 6 in 10 adult patients who were diagnosed with cancer 10 years ago are still alive, and 8 in 10 children become long-term survivors [1]. This positive development has shifted the focus in cancer therapy from survival at any cost to survival at a reasonable cost, particularly in children,

where the expected life span is particularly long. The intensified therapy often results in adverse side effects appearing long after the end of treatment, so called late effects. These late effects can be caused by different treatment modalities, but it is well documented that radiotherapy underlies severe cognitive, endocrine, reproductive, cardiac, pulmonary and other late effects. In addition, ionising radiation increases the risk of secondary malignancies. Radiotherapy to the developing brain, for example, causes progressively debilitating cognitive deficits. The younger the patients at the time of treatment, the more severe are the late effects. If the patients are younger than 3-4 years, radiotherapy to the brain is generally not even considered because of the devastating consequences. The biological basis for this, however, remains largely unknown, but recent discoveries in neural stem cell biology and brain plasticity have provided clues towards a deeper understanding of the effects of ionising radiation on the developing brain. Continuous efforts are made to reduce or even eliminate radiotherapy, when possible, not only for central nervous system disease. An example of such efforts is the case of the European protocol for treatment of Hodgkin's lymphoma in children.

3.3.2. Novel aspects on CNS late effects in paediatric oncology

Brain tumours constitute approximately one third of all childhood neoplasms and survival rates after primary or metastatic tumours located within or close to the central nervous system (CNS) have increased over the last decades [2]. Despite improved techniques in neurosurgery and advances in chemotherapy, radiation therapy remains an essential treatment modality for malignant brain tumours, as well as for CNS involvement of leukaemia and lymphoma. Whole body radiation therapy, including the head, is also used in some conditioning protocols prior to hematopoietic stem cell transplantation (also called bone marrow transplantation). However, radiation therapy is also one of the major causes of long-term complications seen in survivors of paediatric brain tumours. Intellectual and memory impairments as well as perturbed growth and puberty are some of the so-called late effects seen after radiation therapy [3-7]. These impairments have been shown to be more severe in children younger than 3 years of age at the time of radiation therapy [8-10].

Ionising radiation can produce free radicals and DNA damage, causing mainly proliferating cells to undergo apoptosis or mitotic catastrophe. Cells may also enter into a quiescent state and die at a later time point. The brain is relatively radio-resistant, because of postmitotic neurons and limited proliferation of other cell types. Neural stem and progenitor cells have a prominent proliferative capacity and are therefore highly vulnerable to irradiation. The two main neurogenic areas, the subventricular zone (SVZ) of the lateral walls of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus, are highly susceptible to irradiation-induced injury. This has been demonstrated in rodents [11-14] and appears to be true also for humans [15]. A single dose of 6 Gy to young rat [16] or mouse brains [17], produced a long-lasting, apparently permanent, decrease in hippocampal neurogenesis [12]. A single dose of 8 Gy to the young rat brain virtually abolished growth of the DG and the SVZ, with no morphological recovery, as judged by the size of the neurogenic regions [11]. There was a difference between the DG and the SVZ, though, such that BrdU incorporation and neurogenesis in the rat SVZ recovered with time, to approximately 50% of control values, but neurogenesis in the DG remained reduced to 5% of control levels [16]. A single irradiation dose of 8 Gy applied to the rodent brain corresponds approximately to 18 Gy delivered in 2 Gy fractions to patients, according to the linear quadratic formula and an alpha/beta ratio of 3 for late effects in the normal brain tissue [18]. Patients with acute lymphoblastic leukaemia (ALL) who have an increased risk of CNS relapse (such as T-cell ALL, overt CNS involvement, high-risk cytogenetic features, or poor response to remission

induction treatment), and patients with acute myeloid leukaemia (AML) who present with overt CNS disease at diagnosis, are treated with 12-18 Gy cranial irradiation. The dose used for treatment of paediatric brain tumours like medulloblastoma is higher, up to 55 Gy to the tumour bed, combined with 35 Gy craniospinal radiation.

The relatively greater susceptibility of the young DG to irradiation, which abolishes neurogenesis and further growth of the DG, may help explain the cognitive deficits observed in paediatric patients treated with cranial radiotherapy. Non-CNS cancer survivors had similar education, employment, and income as the general population in adjusted models, whereas survivors of CNS tumours more often than the general population had only basic education, less often attained education beyond secondary school, and were less often employed [19]. The cognitive deficits may not be obvious until months or years after radiotherapy and usually become more pronounced over the years to follow, such that the difference between the patients and their peers becomes greater with time. The reason for this is that cognitive capacity of normal, non-treated children increases with age; however, the capabilities of the children treated with cranial radiation therapy increased either more slowly, not at all, or even decreased [20] resulting in a decline in IQ relative to the peer group. Most likely, cognitive deficits are a result of failure to learn at a rate that is appropriate for the age of the child, rather than a loss of previously acquired knowledge [21]. They remember what they learned earlier but have difficulties learning new things. Learning disabilities in children treated with cranial radiotherapy are, at least partly, due to poor attention and deficient working memory. The hippocampus is known to be important in memory function and the lifelong birth of new granule neurons in the DG of rodents and humans is considered to be important for maintaining memory function and being able to adapt to a changing environment [22-24]. This leaves us with a possible target for novel rehabilitation strategies of patients treated with cranial radiation therapy.

It is known that voluntary running increases cell proliferation and neurogenesis in the hippocampus of rodents [25, 26], with concomitant improvements in cognitive function, spatial memory and learning [27, 28]. Cranial irradiation (6 Gy) of 9-day-old male mice decreased the number of undifferentiated (GFAP+ / SOX2+) stem cells and reduced hippocampal neurogenesis 3 months later. Four weeks of voluntary running, introduced 2 months after irradiation, not only restored stem cell and neurogenesis levels, but also ameliorated the hyperactive behaviour caused by irradiation [17]. Interestingly, irradiation not only reduced neurogenesis, it also perturbed the structural integration of newborn, DCX-positive neurons as late as 3 months after irradiation, as judged by disoriented dendritic processes, and this disorientation was normalised by physical exercise [17]. In another, recent study young adult (8 weeks old) female mice were irradiated (5 Gy) and given free access to a running wheel from one month after irradiation, demonstrating that voluntary running ameliorated the progressive memory decline observed after irradiation and partly restored neurogenesis [29]. It is also possible that replacing the lost neural stem and progenitor cells with new ones, may have beneficial effects. Most transplantation paradigms aim at replacing differentiated cells, for example neurons, after an injury. In this case, however, the purpose would be to replace lost undifferentiated cells with other undifferentiated cells. The positive effects observed in such experiments [30] are presumably the result both of stem cells differentiating into neurons and glial cells, but perhaps the greatest effects are mediated by growth factors and tropic factors secreted by the undifferentiated neural stem cells. These studies inspire hope that physical exercise can be used in the rehabilitation of young and adult cancer survivors. It is interesting to note that it was possible to wait until adulthood to introduce physical exercise, even when the mice were irradiated during early childhood [17].

Based on current knowledge, it is not known when the optimal time point would be to introduce exercise in rehabilitation programmes, but it is encouraging that physical fitness is correlated with increased hippocampal volume and superior relational memory task performance in preadolescent children [31] and that also in elderly humans fitness correlated with increased hippocampal volume and better spatial memory performance [32]. Healthy but sedentary elderly humans who participated in an aerobic training programme displayed significant increases in brain volume, in both grey and white matter regions, unlike the control group, participating in toning and stretching only [33]. It was also shown that one year of aerobic training improved the aging brain's resting functional efficiency in higher-level cognitive networks [34]. Hence, further studies are needed to address when and to what extent exercise should be introduced in the rehabilitation of young and adult cancer survivors.

In conclusion; radiotherapy to the developing brain is known to cause progressively debilitating cognitive deficits. The biological basis for this, however, remains largely unknown, but recent discoveries in neural stem cell biology and brain plasticity have provided clues towards a deeper understanding of the effects of ionising radiation on the developing brain and a summary of these findings is included.

3.3.3. References

1. Cancerfonden, ed. *Cancer i siffror*. ed. E. Johansson. 2009, Socialstyrelsen. 60.
2. Gustafsson, G., M. Heyman, and Å. Vernby, *Childhood cancer incidence and survival in Sweden 1984-2005*. 2007, Karolinska Institute. p. 1-92.
3. Lannering, B., et al., *Long-term sequelae after pediatric brain tumors: their effect on disability and quality of life.* Med Pediatr Oncol, 1990. **18**(4): p. 304-10.
4. Lannering, B., I. Marky, and C. Nordborg, *Brain tumors in childhood and adolescence in west Sweden 1970-1984. Epidemiology and survival.* Cancer, 1990. **66**(3): p. 604-9.
5. Lannering, B., et al., *Reduced growth hormone secretion with maintained periodicity following cranial irradiation in children with acute lymphoblastic leukaemia.* Clin Endocrinol (Oxf), 1995. **42**(2): p. 153-9.
6. Spiegler, B.J., et al., *Change in neurocognitive functioning after treatment with cranial radiation in childhood.* J Clin Oncol, 2004. **22**(4): p. 706-13.
7. Hoffman, K.E. and T.I. Yock, *Radiation therapy for pediatric central nervous system tumors.* J Child Neurol, 2009. **24**(11): p. 1387-96.
8. Chin, H.W. and Y. Maruyama, *Age at treatment and long-term performance results in medulloblastoma.* Cancer, 1984. **53**(9): p. 1952.
9. Duffner, P.K., et al., *The long-term effects of cranial irradiation on the central nervous system.* Cancer, 1985. **56**(7 Suppl): p. 1841.
10. Packer, R.J., et al., *Long-term sequelae of cancer treatment on the central nervous system in childhood.* Med Pediatr Oncol, 1987. **15**(5): p. 241-53.
11. Fukuda, A., et al., *Age-dependent sensitivity of the developing brain to irradiation is correlated with the number and vulnerability of progenitor cells.* J Neurochem, 2005. **92**(3): p. 569-84.
12. Fukuda, H., et al., *Irradiation-induced progenitor cell death in the developing brain is resistant to erythropoietin treatment and caspase inhibition.* Cell Death Differ, 2004. **11**(11): p. 1166-78.

13. Raber, J., et al., *Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis.* Radiat Res, 2004. **162**(1): p. 39-47.
14. Tada, E., et al., *X-irradiation causes a prolonged reduction in cell proliferation in the dentate gyrus of adult rats.* Neuroscience, 2000. **99**(1): p. 33-41.
15. Monje, M.L., et al., *Impaired human hippocampal neurogenesis after treatment for central nervous system malignancies.* Ann Neurol, 2007. **62**(5): p. 515-20.
16. Hellström, N.A., et al., *Differential recovery of neural stem cells in the subventricular zone and dentate gyrus after ionizing radiation.* Stem Cells, 2009. **27**(3): p. 634-41.
17. Naylor, A.S., et al., *Voluntary running rescues adult hippocampal neurogenesis after irradiation of the young mouse brain.* Proc Natl Acad Sci U S A, 2008. **105**(38): p. 14632-7.
18. Fowler, J.F., *The linear-quadratic formula and progress in fractionated radiotherapy.* Br J Radiol, 1989. **62**(740): p. 679-94.
19. Boman, K.K., F. Lindblad, and A. Hjern, *Long-term outcomes of childhood cancer survivors in Sweden: a population-based study of education, employment, and income.* Cancer, 2010. **116**(5): p. 1385-91.
20. Packer, R.J., et al., *A prospective study of cognitive function in children receiving whole-brain radiotherapy and chemotherapy: 2-year results.* J Neurosurg, 1989. **70**(5): p. 707-13.
21. Mulhern, R.K., et al., *Late neurocognitive sequelae in survivors of brain tumours in childhood.* Lancet Oncol, 2004. **5**(7): p. 399-408.
22. Markakis, E.A. and F.H. Gage, *Adult-generated neurons in the dentate gyrus send axonal projections to field CA3 and are surrounded by synaptic vesicles.* J Comp Neurol, 1999. **406**: p. 449-60.
23. Madsen, T.M., et al., *Arrested neuronal proliferation and impaired hippocampal function following fractionated brain irradiation in the adult rat.* Neuroscience, 2003. **119**(3): p. 635-42.
24. Zhu, C., et al., *Isoflurane anesthesia induced persistent, progressive memory impairment, caused a loss of neural stem cells, and reduced neurogenesis in young, but not adult, rodents.* J Cereb Blood Flow Metab, 2010. **30**(5): p. 1017-30.
25. van Praag, H., G. Kempermann, and F.H. Gage, *Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus.* Nat Neurosci, 1999. **2**(3): p. 266-70.
26. Naylor, A.S., et al., *Extended voluntary running inhibits exercise-induced adult hippocampal progenitor proliferation in the spontaneously hypertensive rat.* J Neurophysiol, 2005. **93**(5): p. 2406-14.
27. van Praag, H., et al., *Running enhances neurogenesis, learning, and long-term potentiation in mice.* Proc Natl Acad Sci U S A, 1999. **96**(23): p. 13427-31.
28. Anderson, B.J., et al., *Exercise influences spatial learning in the radial arm maze.* Physiol Behav, 2000. **70**(5): p. 425-9.
29. Wong-Goodrich, S.J., et al., *Voluntary Running After Whole-Brain Irradiation Prevents Progressive Memory Decline and Increases Adult Hippocampal Neurogenesis and Growth Factor Expression.* Cancer Res, 2010.
30. Acharya, M.M., et al., *Rescue of radiation-induced cognitive impairment through cranial transplantation of human embryonic stem cells.* Proc Natl Acad Sci U S A, 2009. **106**(45): p. 19150-5.
31. Chaddock, L., et al., *A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children.* Brain Res, 2010. **1358**: p. 172-83.

32. Erickson, K.I., et al., *Aerobic fitness is associated with hippocampal volume in elderly humans.* Hippocampus, 2009. **19**(10): p. 1030-9.
33. Colcombe, S.J., et al., *Aerobic exercise training increases brain volume in aging humans.* J Gerontol A Biol Sci Med Sci, 2006. **61**(11): p. 1166-70.
34. Voss, M.W., et al., *Plasticity of brain networks in a randomized intervention trial of exercise training in older adults.* Front Aging Neurosci, 2010. **2**.

4. Quality management of advanced radiation therapy technologies

4.1. Quality assurance dosimetry

The complexity of many steps in the radiotherapy process has escalated during the past years. The increased complexity has given us tools to better treat patients in a more effective manner and also to potentially increase the therapeutic ratio. New computer driven radiotherapy equipment with advanced commercially available imaging and delivery techniques (IMRT, IGRT, IMAT, VMAT) are implemented in the clinics at a high pace. The use of imaging modalities such as PET and MR, co-registered with the treatment planning CT, has also been introduced as important aids in the segmentation process of target volumes and organs at risk. In order to reduce adverse consequences to the treatment a decrease in CTV-PTV margins is discussed and also implemented in some instances. As a consequence, increased use of image guidance, preferably soft tissue image guidance, for increasing the precision and accuracy in the radiation delivery is stipulated in more and more study protocols and health care programmes. In addition 4D CT based treatment planning, taking target movements into consideration in the delivery process, is also making its way into the clinic, via gating [1] and tracking techniques [2-4]. The ultimate step is to follow tumour shrinkage and adapt the delivery with the use of daily soft tissue imaging techniques with instant re-planning based on "target-of-the-day" [5].

It should be stressed though that the positive reports of a reduced toxicity with IMRT compared to 3DCRT [6, 7] is to some extent hampered by other reports where tumour control has been worse compared to 3D-CRT due to a reduction in margins [8]. Hence, in order to really increase the therapeutic ratio great caution should be taken when introducing these new techniques, especially regarding margins and CTV delineation [9, 10].

The introduction of a large number of new complex steps in the radiotherapy chain has put focus on how to deal with the increased burden of quality assurance and quality controls needed in order to keep the entire process, from segmentation to radiation delivery, safe and within acceptable tolerance limits.

The traditional approach of QA is prescriptive based on guidelines with a list of tests and tolerance values for measured parameters. There are numerous published recommendations and guidelines from different societies on quality control of radiotherapy equipment and related procedures, i.e. CT-scanners and virtual simulation [11, 12], beam data commissioning [13], treatment planning systems [14-16], medical accelerators [17-19], image verification systems [1, 20-22], IMRT commissioning and implementation [23-25], IT networking [26].

The amount of device specific QA items is hence today massive and thereby very time consuming and staff intensive. There have been a number of reports in the literature focusing on this problem suggesting new directions and tools for QA of the modern radiotherapy process. Specification of operating limits for equipment and procedures is still an essential part of a quality programme but a more process-oriented type of QA, using industry engineering quality management tools, has been proposed [27]. Examples of tools widely used in industry are e.g. Statistical Process Control (SPC), Failure Mode and Effect Analysis (FMEA), Root Cause Analysis (RCA), amongst others. SPC has been proposed as a suitable method for radiotherapy QA by e.g. Pawlicki et al [28, 29]. The AAPM Task Group 100 on "Methods for evaluating QA needs in radiation therapy" has also taken a new QA approach based on risk assessment. TG 100 suggests FMEA for IMRT and HDR brachytherapy. Their objective is to determine the specific areas that have been omitted in previous reports and which need better coverage to develop a suitable general QA programme. They will identify a structured systematic QA programme approach that balances patient safety and quality versus resources commonly available. The final report of the task group is yet not published.

An excellent collection of papers on QA of modern radiotherapy techniques was published as a supplement in Int. J. Radiation Oncology Biol. Phys., Vol. 71, 2008, presenting work from an interdisciplinary symposium entitled ''Quality Assurance of Radiation Therapy: The Challenges of Advanced Technologies,'' held in Dallas, TX, 2007. This meeting was sponsored jointly by the American Society for Therapeutic Radiology and Oncology (ASTRO), the American Association of Physicists in Medicine (AAPM), and the National Cancer Institute (NCI). The goal of the meeting was "to address the widespread concern that, in patients receiving radiation therapy with advanced technologies, current QA practices and protocols do not provide adequate or cost-effective safeguards against treatment delivery errors that have the potential to degrade the expected therapeutic ratio or, in extreme cases, to cause acute injury" [30].

The conclusions of the symposium were summarised by Williamson et al 2008. The main consensus findings were:

- The current device-centred QA approach is not optimal for advanced radiation therapy technologies
- New approaches to QA are needed to manage risk/mitigate errors and minimise the risk for catastrophic events
- A more multidisciplinary process-oriented, risk-based QA approach is needed, balancing resources and quality.

ESTRO has also realized the need for addressing the issue of quality management with advanced radiotherapy techniques and has recently initiated the formation of a task group working with the subject.

4.1.1. Recommendation

The number of IMRT treatments in Sweden is still quite low but they are assumed to increase rapidly in the near future at university hospitals as well as at non-university hospitals. It is generally agreed that the QA burden associated with IMRT is a hampering factor in increasing the number of IMRT treatments. IMRT routine QA is today usually patient specific, e.g. the treatment plan is transferred to a homogeneous phantom containing a 2D ion-chamber or diode detector array. The composite 2D measured dose distribution is then

compared with the Treatment Planning System calculated and usually evaluated in term of distance-to-agreement and dose-difference criteria with the so called gamma-method. The drawbacks with these detectors are their relatively poor resolution and that the measurements are very time consuming and simply not possible to do in every patient if we would like to give IMRT to all patients we think would benefit from it. In addition the gamma test criteria is usually set at some arbitrary test value, e.g. 3%/3mm with a pass rate of 90%, irrespective of the complexity (e.g. modulation) of the IMRT-treatment and irrespective of the anatomical site and/or diagnosis treated.

More sophisticated 3D and even 4D QA-devices are now commercially available for IMRT and VMAT pretreatment verification [31-33] which can reconstruct measured dose onto a patient CT data set and hence facilitate comparisons in terms of e.g. DVHs. Independent dose calculation tools are also becoming more advanced [34]. How measurements and calculations should be combined in an optimal way still need further investigation.

In conclusion; there is a lack of consensus, both nationally and internationally, on how to optimally perform QA of radiotherapy with advanced technologies. As mentioned previously, a number of international societies are working on this matter. The Swedish Society of Radiation Physics recently also decided to start a workgroup with the aim to compile a report with national guidelines on routine QA of IMRT. We recommend SSM to specifically keep abreast of the progress in this area and to follow the work of the upcoming task group of the Swedish Society of Radiation Physics.

4.1.2. References

1. Korreman, S., et al., *The European Society of Therapeutic Radiology and Oncology-European Institute of Radiotherapy (ESTRO-EIR) report on 3D CT-based in-room image guidance systems: a practical and technical review and guide.* Radiother Oncol, 2010. **94**(2): p. 129-44.
2. Falk, M., et al., *Real-time dynamic MLC tracking for inversely optimized arc radiotherapy.* Radiother Oncol, 2010. **94**(2): p. 218-23.
3. Poulsen, P.R., et al., *Implementation of a new method for dynamic multileaf collimator tracking of prostate motion in arc radiotherapy using a single kV imager.* Int J Radiat Oncol Biol Phys, 2010. **76**(3): p. 914-23.
4. Cho, B., et al., *First demonstration of combined kV/MV image-guided real-time dynamic multileaf-collimator target tracking.* Int J Radiat Oncol Biol Phys, 2009. **74**(3): p. 859-67.
5. Yan, D., *Adaptive radiotherapy: merging principle into clinical practice.* Semin Radiat Oncol, 2010. **20**(2): p. 79-83.
6. Pow, E.H., et al., *Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial.* Int J Radiat Oncol Biol Phys, 2006. **66**(4): p. 981-91.
7. Nutting C, H.K., Rogers S, Sydenham M, A'Hern R and Hall E, *Results of a Phase III Multi-centre Randomised Controlled Trial of Intensity Modulated (IMRT) vs Conventional Radiotherapy (RT) in Head and Neck Cancer.* Clin Oncol, 2010. **Vol 22**: p. Page 899.

8. Engels, B., et al., *Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distended rectum on the planning computed tomogram despite image guidance by implanted markers.* Int J Radiat Oncol Biol Phys, 2009. **74**(2): p. 388-91.
9. Chen, A.M., et al., *Marginal Misses after Postoperative Intensity-Modulated Radiotherapy for Head and Neck Cancer.* Int J Radiat Oncol Biol Phys, 2010.
10. Cannon, D.M. and N.Y. Lee, *Recurrence in region of spared parotid gland after definitive intensity-modulated radiotherapy for head and neck cancer.* Int J Radiat Oncol Biol Phys, 2008. **70**(3): p. 660-5.
11. Mutic, S., et al., *Quality assurance for computed-tomography simulators and the computed-tomography-simulation process: report of the AAPM Radiation Therapy Committee Task Group No. 66.* Med Phys, 2003. **30**(10): p. 2762-92.
12. AAPM, *Comprehensive Methodology for the Evaluation of Radiation Dose in X-Ray Computed Tomography: Report of AAPM Task Group 111.The Future of CT Dosimetry.* February 2010.
13. Das, I.J., et al., *Accelerator beam data commissioning equipment and procedures: report of the TG-106 of the Therapy Physics Committee of the AAPM.* Med Phys, 2008. **35**(9): p. 4186-215.
14. ESTRO, *Quality Assurance of Treatment Planning Systems - Practical Examples for Non-IMRT Photon Beams.* ESTRO Booklet 7, 2004.
15. Chetty, I.J., et al., *Report of the AAPM Task Group No. 105: Issues associated with clinical implementation of Monte Carlo-based photon and electron external beam treatment planning.* Med Phys, 2007. **34**(12): p. 4818-53.
16. IAEA, *Commissioning of Radiotherapy Treatment Planning Systems: Testing for Typical External Beam Treatment Techniques.* TECDOC 2008. **Series No.1583**.
17. Klein, E.E., et al., *Task Group 142 report: quality assurance of medical accelerators.* Med Phys, 2009. **36**(9): p. 4197-212.
18. Langen, K.M., et al., *QA for helical tomotherapy: report of the AAPM Task Group 148.* Med Phys, 2010. **37**(9): p. 4817-53.
19. Kirby M, R.S., Hall C. , *Acceptance Testing and Commissioning of Linear Accelerators. Institute of Physics and Engineering in Medicine.* IPEM report 94, 2007.
20. Murphy, M.J., et al., *The management of imaging dose during image-guided radiotherapy: report of the AAPM Task Group 75.* Med Phys, 2007. **34**(10): p. 4041-63.
21. AAPM, *The Role of In-Room kV X-Ray Imaging for Patient Setup and Target Localization: Report of AAPM Task Group 104* AAPM report 104, Dec. 2009.
22. Pfeiffer, D., et al., *AAPM Task Group 128: quality assurance tests for prostate brachytherapy ultrasound systems.* Med Phys, 2008. **35**(12): p. 5471-89.
23. James H, B.A., Budgell G, Clark C, Convery D, Mott J, Dearnaley D, Perry R, Scrase C., *IPEM report 96. Guidance for the Clinical Implementation of Intensity Modulated Radiation Therapy.* Institute of Physics and Engineering in Medicine, 2008.
24. Georg, M.a., *Guidelines for the Verification of IMRT.* ESTRO 2008. **Booklet 9**.
25. McDermott, L.N., et al., *3D in vivo dose verification of entire hypo-fractionated IMRT treatments using an EPID and cone-beam CT.* Radiother Oncol, 2008. **86**(1): p. 35-42.
26. Kirby M, C.D., Lawrence G, Poynter A, Studdart P., *IPEM report 93: Guidance for Commissioning and QA of a Networked Radiotherapy Department.* Institute of Physics and Engineering in Medicine, 2006.
27. Pawlicki, T. and A.J. Mundt, *Quality in radiation oncology.* Med Phys, 2007. **34**(5): p. 1529-34.

28. Pawlicki, T., M. Whitaker, and A.L. Boyer, *Statistical process control for radiotherapy quality assurance.* Med Phys, 2005. **32**(9): p. 2777-86.
29. Pawlicki, T., et al., *Process control analysis of IMRT QA: implications for clinical trials.* Phys Med Biol, 2008. **53**(18): p. 5193-205.
30. Williamson, J.F. and B.R. Thomadsen, *Foreword. Symposium " Quality Assurance of Radiation Therapy: The Challenges of Advanced Technologies".* Int J Radiat Oncol Biol Phys, 2008. **71**(1 Suppl): p. S1.
31. Bedford, J.L., et al., *Evaluation of the Delta4 phantom for IMRT and VMAT verification.* Phys Med Biol, 2009. **54**(9): p. N167-76.
32. Yan, G., et al., *Calibration of a novel four-dimensional diode array.* Med Phys, 2010. **37**(1): p. 108-15.
33. J Crass, M.M.-P., and C Coffey, *Commissioning, Validation, and Implementation of the COMPASS System into a Clinical Intensity Modulated Radiotherapy Quality Assurance Program.* Med. Phys., 2010. **37(6):3229**
34. Georg, D., et al., *Patient-specific IMRT verification using independent fluence-based dose calculation software: experimental benchmarking and initial clinical experience.* Phys Med Biol, 2007. **52**(16): p. 4981-92.

4.2. Image-guided radiotherapy IGRT from a radiation protection point-of-view

The principal purpose of image-guided radiotherapy (IGRT) is to measure and correct for unwanted geometric displacements of the patient and the treatment beams, as compared to the treatment plan. At the same time, the information obtained through imaging may also be used to revise the original treatment plan, and IGRT then can become an iterative, adaptive process.

IGRT can be conceived as a classical radiation protection dilemma. Clearly, it is expected that improved imaging, in general, will be beneficial for the patient. This assertion is based on the fact that good imaging allows for safe geometric corrections, giving a potential for reducing the margins. This, in turn, could lead to better conformity to target structures, and better avoidance of risk organs, which is commonly assumed to result in better radiotherapy, with a higher probability of complication-free survival. A great break-through in this respect will be the introduction of adaptive radiotherapy. In addition, improved imaging will also increase the chances for detecting treatment errors in an early stage, thus avoiding potential mistreatments. On the other hand, the unwanted additional dose from intensified imaging may be detrimental to the patient. The imaging dose is generally not included in the treatment planning process, and does not contribute constructively in a conformal treatment. On the contrary, it will result in a non-specific radiation exposure to large regions of the patient, in most cases including also the risk organs intended to be spared from radiation. Thus, the imaging dose may increase both the short-term complication probability and the long-term risk for secondary cancers.

In conclusion, there is a real and urgent need for evaluating radiotherapy guidance using x-ray imaging with respect to its justification and possible optimization opportunities. Data on dose-levels are plentiful and scattered throughout the literature. However, there are very few reports approaching the problem from a radiation protection point of view. Two excellent exceptions are the TG-75 report of AAPM [1] and the BFCO(08)5 joint report of RCR/IPEM/SCR (2008) [2]. The AAPM TG-75 report also provides a very good compilation of dose-levels for the different imaging techniques.

In this report, we have reviewed the available data on imaging doses from different modalities, and from these data estimated the total effective dose from several different imaging strategies. We have then used these results in an attempt to illustrate the trade-off between gains in accuracy on one hand, and increased imaging dose to the patient on the other. The results can be used in the discussion of justification of intense image-guidance in radiotherapy.

4.2.1. Imaging technologies used in radiotherapy

In the preparation and planning process, imaging is used for several purposes. Computed tomography (CT) is used to create a patient model for treatment planning in 3D or 4D (time resolved), and at the same time to provide an electron density matrix for the dose calculations. Fluoroscopy is used to monitor internal movements of the patient, but also as an aid when positioning brachytherapy sources. Conventional simulation, however, has nowadays largely been replaced by digitally reconstructed radiographs obtained from the treatment planning CT. This is a rare example where accuracy has actually been improved while decreasing the image dose to the patient. For certain palliative treatments, a simple beam configuration with one or two beams can often be defined without the aid of a treatment planning CT, in which case the associated dose could be spared.

When the patient arrives to the treatment, various types of imaging are used to ensure that the position on the treatment couch is as close as possible to the treatment planning position. Planar images of the treatment fields and/or isocentric orthogonal projections are obtained, either with the MV linac beam, or with a machine-integrated kV x-ray device. Double-exposed combinations of the treatment-field and a full-aperture beam are sometimes used to facilitate anatomical matching, primarily with bone structures. CT imaging is increasingly used, either with a separate unit, or with integrated fan- or cone-beam devices, which to some extent makes it possible to do anatomical matching using soft tissue structures. Repeated imaging is common after patient positioning corrections are made, and it is expected that CT imaging in the future will be used also for adaptive radiotherapy with repetitive adjustments of the target volumes.

The largest imaging doses are obtained in cases of live imaging, such as for instance for the positioning of brachytherapy sources during fluoroscopy, or for real-time monitoring of breathing motion. With the fixed orthogonal kV-panels on the CyberKnife unit, using 30-50 images, patient doses of up to 20-200 mGy can be reached in one fraction. Similar techniques are in principal available also with the BrainLab ExacTrac, Varian's OBI, and Elekta's XVI equipment. One exception to this is when the MV treatment beam is viewed in cine-mode by using the EPID unit, in which case there is no extra dose to the patient.

The prime source of data on dose levels from the different imaging modalities has been the report of the AAPM Task Group 75 on the management of imaging dose during image-guided radiotherapy [1]. Additional data on MV-imaging with Siemens equipment can be found in the reports by Pouliot et al [3]. The AAPM Task Group 75 states that the associated uncertainty factor is on the order of 2.

4.2.2. Imaging strategies and protocols

Depending on the goals of a particular treatment, different imaging strategies may be employed. Such strategies can be either "on-line", where imaging and necessary corrections are made prior to each treatment session (i.e. reducing the overall uncertainty to a minimum),

or “off-line”, where imaging is used only sparsely, according to a suitable protocol aimed at minimising the systematic deviations as compared to the treatment plan (i.e. an improved trueness). The summation of the total imaging dose is not entirely straight-forward, however, as data on dose contributions from different modalities are in general presented in different ways. The actual absorbed dose to the patient is rarely reported explicitly for a specific examination. Data is more often given in terms of different dose indices (such as CTDI, DAP, DLP, etc), air kerma, or, for accelerator based imaging, sometimes even only as the number of given monitor units. Furthermore, the dose distribution may be very different between different imaging modalities (e.g. planar vs. tomographic imaging). In principle, it is of course possible to calculate the dose distribution due to imaging [4, 5], and then to sum all contributions, but a more practical approach, which was adopted by [1], may be to measure the detrimental effects of imaging in terms of the effective dose. The AAPM TG75 report describes how to convert dose indices (such as CTDI or DAP) to effective dose, and also lists conversion factors for a number of different kV and MV examinations [1]. The contribution to the effective dose from different imaging procedure can then be tabulated, and added together for a particular imaging strategy. The summed value for the entire treatment course can also be used to estimate the associated risk for secondary malignancies by using the ICRP risk factor ($5 \cdot 10^{-5}$ mSv^{-1}).

4.2.3. The trade-off in IGRT

Common for all imaging strategies is that there is, in general, a trade-off between gain in accuracy on the one hand and work-load on the other. More important for this work, however, is that there may also be a trade-off between gain in accuracy and imaging dose to the patient. In order to illustrate this, we have in this report considered three different hypothetical imaging strategies, all applied to a treatment of 30 fractions in the pelvic region. For all strategies, we have assumed that the treatment plan is based on a regular CT. For the rest of the treatment, the strategies differ with respect to the imaging protocol used for set-up corrections. In the first example, which is representative for current common practice, we assume an off-line no-action level (NAL) protocol, where orthogonal planar images are acquired for the first three fractions, and then once every second week. In the second example, on-line corrections are made at each fraction based on orthogonal planar images. The third example, which is an example of extremely intensive IGRT, is similar to the second case, replacing the orthogonal images with cone-beam CT.

By using the data from the AAPM Task Group 75 report, the total effective dose was calculated for these three different imaging strategies, and the results are shown in Table 1, together with the associated ICRP risk for secondary malignancies.

	Strategy 1	Strategy 2	Strategy 3
Planning CT	9 mSv	9 mSv	9 mSv
NAL (3 first + 1/2 w)	6x1.5 mSv	-	-
On-line orthogonals	-	30x1.5 mSv	-
On-line CBCT	-	-	30x6 mSv
Total effective dose Risk	18 mSv 0.1%	54 mSv 0.3%	189 mSv 0.9%

Table 1. The total effective dose due to the three different imaging strategies, together with the associated ICRP risk for secondary malignancies

From the above, it is clear that the potential benefits of IGRT come with a cost. As it is expected that the increased effective dose for the on-line strategies pays off in terms of better accuracy, one may envision a trade-off between required margins and total effective dose. In an attempt to find approximate numerical values for this trade-off, one may use commonly applied margins for off-line and on-line IGRT. Let us therefore assume that a 10 mm margin would be appropriate when using the NAL off-line imaging strategy, while it could shrink to about 5-7 mm for the on-line strategies (the higher value for orthogonal images and the lower for cone-beam CT). Then, the anticipated trade-off can be visualized in a graph such as the one presented in Figure 1.

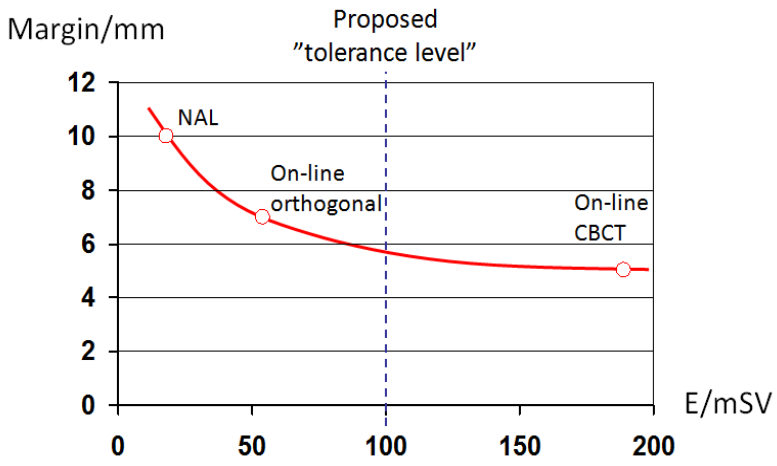

Figure 1. Trade-off between required margins and total effective dose for a treatment with 30 fractions in the pelvic region

4.2.4. Discussion

The primary goal of IGRT should be to mitigate the effects of uncertainty in the tumour position, which, in combination with inadequate margins, is otherwise associated with a risk for geographical misses, particularly in the case of mobile targets [6]. In addition, IGRT also brings a potential for reducing the margins, maintaining adequate target coverage, which hopefully will lead to less toxicity to surrounding healthy tissues [6, 7].

Added together, however, the total dose from all imaging procedures during a course of radiotherapy can amount to a significant contribution to the target, far greater (10-100 times) than common diagnostic reference levels. “Aggressive” imaging protocols may yield an extra 10-50 mGy per fraction, i.e. up to several per cent of the target dose. For adjacent risk organs, the therapeutic dose may already be close to the tolerance level, and the sum of all imaging dose contributions could therefore potentially be very important.

Although the actual numbers are associated with great uncertainties, Figure 1 may serve well to illustrate the diminishing return from increasing IGRT efforts. Going from off-line to on-line imaging may allow for a significant reduction of the margins, but going from planar imaging to cone-beam CT imaging may not give substantial further reduction. In particular, there is a lower limit to margin reduction due to residual uncertainties, which cannot be eliminated by ever so much imaging. Since more imaging always leads to a higher effective dose, it is therefore reasonable to assert that there is a point beyond which further IGRT may be deemed ineffective. It has been proposed that this point should be set as a maximum tolerable total effective dose from imaging, and that a reasonable value for this threshold

could be 100 mSv (see Figure 1), corresponding to an ICRP risk for secondary malignancies of 0.5 % [2, 8]. In our example case, this would mean that imaging strategy 2 gives the best result with respect to its potential for margin reduction, without exceeding the effective dose tolerance level. It should be emphasised that this is only a hypothetical example, and that no general conclusions can be drawn from this, except that it seems possible to construct this type of trade-off scenarios in order to help decide on what is the most adequate imaging strategy for a particular situation.

In Table 1, the usually quoted risk figure of 5% per Sv has been used but it should be noted, that this number is age dependent and can be up to 15% per Sv for children [9]. It is also not clear if these figures apply in the radiotherapy setting, where the concomitant exposure to a high therapeutic dose and a low imaging dose to a large volume may generate bystander responses hitherto only scarcely understood [10].

Technically, the calculated image dose distribution could be added to the treatment plan [4], which in turn may be modified (*e.g.* with smaller field sizes) to account for information acquired as a consequence of using more frequent imaging. However, although the physical doses from imaging and therapy are additive, the corresponding biological effects are probably not. Theoretically, some of the radiobiological effect of the imaging dose may be lost due to repair of sub lethal damage during the delay between imaging and treatment [11]. Furthermore, the small imaging dose given at some time before the treatment may even have an influence on the effect of the treatment itself. It has been demonstrated in cell experiments, that a small pre-treatment imaging dose may increase the radioresistance of the tumour cells [12]. Together, these results suggest that a procedure to account for the imaging dose simply by reducing the treatment dose with an equal amount could lead to reduced tumour control probability.

One obvious way to allow for more frequent imaging without exceeding the effective dose tolerance level is of course to find ways to reduce the imaging doses. There are many opportunities to do this. One way may be to use implanted geometrical markers, given that the associated discomfort and any possible risk of complications are considered acceptable. In specific cases, IGRT based on planar kV imaging together with implanted markers may do the job just as well as cone-beam CT, in which case less dose will be required [13]. Many times, the imaging protocols used in radiotherapy are copied from diagnostic radiology. By adapting the protocols specifically for IGRT, imaging doses could be reduced substantially. In general, the requirement on overall image quality is not as high for IGRT as for diagnostic radiology. For instance, field sizes or scan lengths should be limited to cover only the anatomical landmarks, or implanted markers needed for correct patient/target localisation. The largest imaging doses are obtained during live imaging, such as in real-time monitoring of breathing motion, but also in this case dose reducing measures can be taken. For instance, the number of frames per second could be reduced from 15-30 fps down to 3-4 fps without any considerable loss of accuracy. If adequate information can be obtained by imaging using the treatment fields, such procedures should be preferred. Finally, non-radiological localisation methods may also be considered when applicable, such as video, ultrasound, or electromagnetic markers. For advanced soft-tissue IGRT, MRI may be the modality of choice in the future.

The first step towards lower imaging doses in radiotherapy, however, is to increase the awareness among the practitioners. While image doses are under strict control in other image-guided procedures, such as image-guided surgery and interventional radiography, they are in radiotherapy widely disregarded. This is in contrast to other concomitant dose contributions

from scattered radiation and leakage, which has given rise to a concerned discussion about the risk for induction of secondary malignancies after intensity-modulated radiotherapy in its different forms. For radiation leakage there are even recommendations on dose limits. It is our belief that an analysis of the trade-off between the potential gains in accuracy *vs.* the increased imaging dose from intensified imaging, similar to what has been presented in this report, may help increase the awareness about concomitant dose contributions also from IGRT.

4.2.5. Conclusions

- IGRT is an essential tool to ensure target conformity and to avoid target misses
- IGRT may be used as a basis for margin reductions, but this should be done only with great care
- IGRT gives an extra, non-specific dose contribution, which may push OARs above tight tolerance limits or imply an increased risk for radiation induced secondary malignancies
- IGRT dose subtraction may affect the treatment efficacy, and should be done with care

4.2.6. Recommendation

In this section, we have discussed x-ray based IGRT from a radiation protection point of view. While increased image guidance may help improve radiotherapy in terms of better target coverage and possibly smaller irradiated volumes, it also comes with an additional, unwanted and possibly detrimental imaging dose, which cannot easily be accounted for. Thus, there is a cost-benefit trade-off involved, and effectively a diminishing return from intensified IGRT. Given the principle of ALARA, it is therefore recommended that before clinical implementation, all IGRT procedures should be assessed with respect to their justification and possible optimisation opportunities.

4.2.7. References

1. Murphy, M.J., et al., *The management of imaging dose during image-guided radiotherapy: report of the AAPM Task Group 75.* Med Phys, 2007. **34**(10): p. 4041-63.
2. The Royal College of Radiologists, S.a.C.o.R., Institute of Physics and Engineering in Medicine:. *On target - ensuring geometric accuracy in radiotherapy.* ISBN 978-1-905034-33-8. RCR Ref No. BFCO(08)5. The Royal College of Radiologists, London, 2008.
3. Pouliot, J., et al., *Low-dose megavoltage cone-beam CT for radiation therapy.* Int J Radiat Oncol Biol Phys, 2005. **61**(2): p. 552-60.
4. Alaei, P., G. Ding, and H. Guan, *Inclusion of the dose from kilovoltage cone beam CT in the radiation therapy treatment plans.* Med Phys, 2010. **37**(1): p. 244-8.

5. Ding, G.X. and C.W. Coffey, *Radiation dose from kilovoltage cone beam computed tomography in an image-guided radiotherapy procedure.* Int J Radiat Oncol Biol Phys, 2009. **73**(2): p. 610-7.
6. Potters, L., et al., *American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for image-guided radiation therapy (IGRT).* Int J Radiat Oncol Biol Phys, 2010. **76**(2): p. 319-25.
7. Pawlowski, J.M., et al., *Reduction of dose delivered to organs at risk in prostate cancer patients via image-guided radiation therapy.* Int J Radiat Oncol Biol Phys, 2010. **76**(3): p. 924-34.
8. Waddington, S.P. and A.L. McKenzie, *Assessment of effective dose from concomitant exposures required in verification of the target volume in radiotherapy.* Br J Radiol, 2004. **77**(919): p. 557-61.
9. Hall, E.J., *Intensity-modulated radiation therapy, protons, and the risk of second cancers.* Int J Radiat Oncol Biol Phys, 2006. **65**(1): p. 1-7.
10. Prise, K.M. and J.M. O'Sullivan, *Radiation-induced bystander signalling in cancer therapy.* Nat Rev Cancer, 2009. **9**(5): p. 351-60.
11. Flynn, R.T., *Loss of radiobiological effect of imaging dose in image guided radiotherapy due to prolonged imaging-to-treatment times.* Med Phys, 2010. **37**(6): p. 2761-9.
12. Yang W, W.L., Read P et al, *Increased tumour radioresistance by imaging doses from volumetric image guided radiation therapy.* Med Phys 36:2808, 2009, 2009.
13. Barney, B.M., et al., *Image-Guided Radiotherapy (IGRT) for Prostate Cancer Comparing kV Imaging of Fiducial Markers With Cone Beam Computed Tomography (CBCT).* Int J Radiat Oncol Biol Phys, 2010 Sep 22.

2011:25

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 270 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.

Strålsäkerhetsmyndigheten
Swedish Radiation Safety Authority

SE-171 16 Stockholm
Solna strandväg 96

Tel: +46 8 799 40 00
Fax: +46 8 799 40 10

E-mail: registrator@ssm.se
Web: stralsakerhetsmyndigheten.se