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- Jack Fowler University of Wisconsin Award
- ESTRO-Accuray Award
- ESTRO-Varian Award
- ESTRO-Elekta Brachytherapy Award
- GEC-ESTRO Best Junior Presentation Elekta Award

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2 TABLE OF CONTENTS | CONGRESS REPORT
Looking back at ESTRO 36, I think we can say it was a success!

With its different tracks, the congress not only gave attention to the different professional disciplines of our Society, but also stimulated the interdisciplinary interaction among them. As always, we tried to bring a good blend of scientific topics, ranging from cutting-edge novelties, showing where our discipline is moving, to state-of-the-art radiotherapy, enabling professionals to pick up benchmarks for their daily clinical practice. Sessions covering the most frequent tumour types, which represent the largest part of our daily practice, alternated with sessions on less frequent sites or indications, such as small-cell lung cancer, extranodal lymphoma or paediatrics.

ESTRO 36 received almost 2,000 abstracts out of which 265 were selected for oral presentations, 524 for posters and 839 for e-posters. In addition, there were 234 invited speakers. It was remarkable to see that so many of the 5860 congress participants were presenting their work, a heart warming reflection of the interest and dynamism of radiation oncology professionals.

Novel technologies that are progressively diffusing into the clinic, such as particle therapy or the MR Linac, were obviously well represented. The same goes for adaptive radiotherapy, big data, predictive models, immunotherapy and oligo-metastatic disease, which remain hot topics and receive a lot of interest from the participants.

Personalised radiotherapy and patient reported outcomes were also very much at the heart of discussions, demonstrating our never-ending quest for the benefit and value of radiotherapy in the best interest of our patients.

With the lively end debate on the role of automation versus that of dedicated health care professionals, the conference finished in style.

The ESTRO Vision is always on our mind in the preparation of the programme of the annual congress. As already mentioned, our congress aims to give perspectives on up-to-date radiation therapy and on how its implementation improves the outcome of our patients. Being aware of the fact that we can always do better and that there are still too many patients that do not receive the radiotherapy they deserve, the Presidential Symposium addressed the gaps in radiotherapy, that may hamper optimal access. It is only by recognising these gaps, that we can further improve.

Looking at access from a global perspective, a symposium on the Global Task Force on Radiotherapy for Cancer Control (GTFRCC) addressed the challenge of closing the global inequity gap in access to radiotherapy. The GTFRCC, launched in 2013 under the auspices of the Union for International Cancer Control (UICC), has now been handed over to ESTRO. With the aim of bringing the GTFRCC calls to action to reality, the Global Impact of Radiation in Oncology (GIRO) project was launched at ESTRO 36. Together we can make a change!

Each year, we hear that radiation oncology professionals look forward to attending the ESTRO annual congress, not only as it is the premier platform for science in our discipline, but also because it is the place to meet and interact with peers. It gives them the opportunity to learn about the latest clinical evidence, to look at their own practice in the context of our evolving discipline, to see technical novelties that are soon to come into daily clinical practice. But on top of all that, it is always a feast to meet with colleagues from all over – and even outside - Europe, to share experiences and expand our scientific, professional and social networks. We will remember the social events, the Super Run in the famous lush Prater park of Vienna and the lively last evening party!

The next congress, ESTRO 37, will be in Barcelona, 20-24 April 2018. Another occasion for all of us, radiation oncology professionals, to get together once again!

Looking forward to meeting you there!

Yolande Lievens
ESTRO 36 Chair
## INTRODUCTION

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INTRODUCTION

Among the clinically oriented abstracts, the clear trend towards personalised radiation oncology is continuing. Personalised treatment requires the identification of candidate biomarkers that may in future be used to identify subpopulations of patients for specific treatment modifications. Such markers are usually defined preclinically, evaluated within clinical datasets for correlation to marker expression in biomaterials or imaging, then validated in another dataset, before finally a personalisation trial can start. Examples are the work of Tao et al on a post-hoc evaluation of the GORTEC trial and Jang et al on the definition of a gene signature for breast cancer. Other important aspects of clinical treatment optimisation, especially in the positive light of increasing rates of long-term survivorship, is the improvement of quality of life. Examples include maximising organ preservation, as investigated in rectal cancer by Vendrely et al, or by evaluation of different treatment schedules including combined short-term pre-operative radiotherapy and chemotherapy in rectal cancer by Marijnen et al. Last but not least, the EMBRACE study is a very good example of a large, well-conducted clinical trial utilised for different post-hoc analyses (e.g. Jensen et al.) in order to specify treatment related toxicities as a basis for a continued treatment optimisation.

Mechthild Krause
Chair, Scientific advisory group (SAG) for Clinical Radiotherapy
Impact of HPV on effect of chemotherapy in SCCHN: results of the GORTEC 2007-01 randomised trial

Xu Shan Sun1*, Yungan Tao2**, Anne Auperin2, Christian Sire1, Laurent Martin1, Cedric Khoury3, Philippe Maingon4, Etienne Bardet4, Michel Lapeyre4, Yoann Pointreau5, Nathalie Ollivier5, Alexandre Cornely5, Odile Casiraghi6, Jean Bourhis7 on behalf of GORTEC

1CHRU, Besançon and Hôpital du Nord Franche Comté, Montbéliard, France; 2Gustave Roussy, Villejuif, France; 3CH de Bretagne Sud, Lorient, France; 4Centre Le Conquérant, Le Havre, France; 5Centre Saint Louis, Toulon, France; 6Centre GF Leclerc, Dijon, France; 7Centre Gauducheau, Nantes, France; 8Centre Perrin, Clermont, France; 9Centre Jean Bernard - Victor Hugo Clinic, Le Mans, France; 10CHUV, Lausanne, Switzerland;

*Dr. Tao is the presenting author, **Dr. Sun, Dr. Tao and Dr. Auperin contributed equally.

CONTEXT OF THE STUDY
Both chemotherapy (CT) and cetuximab associated with radiotherapy (RT) were established as standard of care (SOC) in non-operated locally advanced head and neck squamous-cell carcinoma (LA-SCCHN). A growing proportion of cancer of the oropharynx is associated with human papillomavirus (HPV). The GORTEC 2007-01 randomised phase III trial has evaluated the potential benefit associated with the addition of chemotherapy to the SOC cetuximab and radiotherapy (cetux-RT) in patients with no or limited nodal spread. The results showed that addition of chemotherapy to cetux-RT backbone markedly improved both survival and tumour control (Bourhis et al ASCO 2016). The impact of HPV (measured by p16 expression) on treatment effect of these patients was not available at the time of first presentation.

OVERVIEW OF THE ABSTRACT
The aim of this study is to evaluate if presence or not of HPV in oropharyngeal carcinoma (OPC) could influence the outcome of this phase III trial. Patients were randomised to receive either cetux-RT (arm A) or chemotherapy plus cetux-RT (arm B). Cetuximab was given weekly during RT. Chemotherapy was 3 cycles of carboplatin + 5FU. HPV status was determined in these patients using p16 expression as a surrogate (immunohistochemistry). Smoking status was also collected. Primary endpoint was progression free survival (PFS).

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
265 (65%) of 406 randomised patients presented oropharyngeal cancers. The median follow-up was 4.4 years. Overall, p16 was assessed in 236 OPC (89%) patients (115 pts in arm A and 121 in arm B).

- The positive p16 was found in 21% of each arm. 15/49 (31%) p16+ patients were non-smokers, while 5/187 (3%) p16- patients were non-smokers.
- A significant improvement in PFS was found in p16+ compared to p16- OPC.
- A significantly improved PFS was observed when chemotherapy was used in addition to cetuximab and radiotherapy in p16- OPC as well as in p16+, and the interaction between p16 and treatment modality was not significant (p=0.13).

WHAT IMPACT COULD YOUR RESEARCH HAVE?
For loco-regional control, a similar additional effect of chemotherapy was found in both p16- and p16+ OPC with cetuximab and radiotherapy. No significant benefit of chemotherapy was found when added to cetuximab and radiotherapy for p16+ or p16- in terms of overall survival.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
The large majority of patients with oropharyngeal cancers randomised in this trial were p16- and smokers. The addition of concomitant chemotherapy to cetux-RT markedly improved survival and tumour control in patients with OPC regardless of HPV status. This is the first evidence of a clinical benefit for treatment intensification using the SOC cetuximab-RT as a backbone in LA-HNSCC. This new chemotherapy and cetuximab-RT combination appeared superior to the SOC cetuximab-RT regardless of the HPV status and hence potentially offers a “new standard option” of particular interest if high dose cisplatin cannot be used, and if the patients are eligible for carboplatin-5FU-based chemotherapy.
Figures A&B: Kaplan-Meier curves of progression-free survival comparing cetux-RT arm and CT-cetux RT arm in p16+ OPC (A) and p16- OPC (B)
2. BREAST

A radiosensitivity gene signature and PD-L1 predict clinical outcome of breast cancer in TCGA dataset

Bum-Sup Jang¹ and In Ah Kim²

¹Department of Radiation Oncology, Seoul National University Graduate School of Medicine, Seoul, South Korea; ²Department of Radiation Oncology, Seoul National University, School of Medicine, Seoul, South Korea

CONTEXT OF THE STUDY
Radiotherapy (RT) plays an important role in the management of breast cancer and one of the important issues is whether radiosensitivity of tumour predicts clinical outcome. Recently, the 31-gene signature representing radiosensitivity of tumour has been reported based on microarray data from NCI-60 cancer cells. Programmed death-ligand 1 (PD-L1) expression has been observed in several human malignancies and is suggested to be a marker of poor prognosis, however, the relationship between the underlying radiosensitivity and PD-L1 expression remains unclear.

OVERVIEW OF THE ABSTRACT
We validated the 31-gene signature related to radiosensitivity and investigated the PD-L1 status of invasive breast cancer in The Cancer Genome Atlas (TCGA) dataset. In total 1,065 patients were selected and divided into two clusters using a consensus clustering algorithm based on the expression profile in regard to the 31-gene signature: radiosensitive (RS) or radioresistant (RR). We also divided total patients into the PD-L1-high and the PD-L1-low group according to CD274 mRNA expression level, considering that PD-L1 is a synonym for CD274. Subsequently, we evaluated the correlations with radiosensitivity and PD-L1, and analysed the clinical outcomes to propose a potential group that would be most likely to benefit from combination therapy.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
The RS group had a better RFS (recurrence-free survival) rate than the RR group when patients were treated with RT, and this difference was not observed for patients who did not receive RT. This finding supports the fact that the 31-gene signature is a predictive marker for breast cancer patients who were treated with RT. Among patients treated with RT, the RS group had significantly better RFS rate than the RR group especially in the PD-L1-high group. Patients in the PD-L1-high group were two times more frequently observed in the RS group, and this tendency remained significant in multivariate analysis.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
Radiosensitivity (the RS versus the RR group) and PD-L1 are predictive for clinical outcome of adjuvant RT for patients with breast cancer. To our knowledge, this is the first study to investigate relationship between radiosensitivity gene signature and PD-L1 for patients with breast cancer in TCGA dataset. These results could contribute to the selection of patients who could benefit from radiation therapy combined with immune check-point blockade, particularly anti-PD-1 or PD-L1 blockade.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
In the era of precision medicine, exploration of radiosensitivity at the genome level has attracted much attention. Although there have been some alleged genomic indicators representing radiosensitivity for various malignancies, their prognostic or predictive value should be validated in the independent dataset. In this study, we showed that the 31-gene signature and PD-L1 predict clinical outcomes in TCGA breast cancer dataset and took a step towards personalised immunotherapy combined with radiation therapy.
Figure 1. Heatmap illustrating the relationship between radiosensitivity and PD-L1 status. Columns represent samples, and rows indicate annotations of PD-L1 status and radiosensitivity, and lists of genes composing the 31-gene signature.

Legend: light pink, PD-L1-low group; dark pink, PD-L1-high group; light blue, radioresistant (RR) group; dark blue, radiosensitive (RS) group.

Figure 2. Kaplan-Meier method was used to plot curves of recurrence-free survival (RFS) in patients treated with radiotherapy (RT) according to radiosensitivity and stratified to the PD-L1-low group (a) and the PD-L1-high group (b). Abbreviations: PD-L1, programmed death-ligand 1; RT, radiation therapy; RR, radioresistant; RS, radiosensitive; HR, hazard ratio. P-value was estimated by Cox proportional-hazard regression test. 95% CIs for hazard ratios (HRs) and 10-year survival rates are presented.
Organ preservation for rectal cancer: the GRECCAR 2 randomised phase III trial


Bordeaux University Hospital (France) and the GRECCAR

3. RECTAL

CONTEXT OF THE STUDY
For T3–4 rectal cancers and T2 of the low rectum, the current standard of care consists of neoadjuvant chemoradiation followed by radical surgery with total mesorectal excision (TME), resulting in good oncologic outcomes but high morbidity and poor functional results. Since radiochemotherapy achieves 16 % histological complete response, rectal preservation, using a local excision (LE) or an observational strategy has been recently debated for good responders.

OVERVIEW OF THE ABSTRACT
We conducted a prospective multicenter national randomised trial comparing LE and TME in patients who were good responders after chemoradiotherapy for T2/T3N0-1 lower rectal cancer. In the LE group, patients with a good pathologic response (ypT0-1) had a follow-up, whilst those with a poor pathologic response (ypT2-3 or R1) had a completion TME. The primary objective of the study was to test the overall superiority of LE compared to TME with regards to a composite endpoint of efficacy and safety (death, recurrence, major surgical morbidity, and severe side-effects at 2 years); secondary objectives were assessment of the tumour response, local recurrence and disease-free survival at 3 years.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
Our study reported that after chemoradiotherapy, 75% of patients had a good clinical response (≤ 2 cm), which was associated with 61% of good pathologic tumour response (ypT0-1) that correlated with a low risk of positive lymph nodes (100% ypN0).

The oncologic safety of the strategy was suggested because 3-year local recurrence and disease-free survival did not statistically differ between local excision and rectal excision arms (5.4% vs. 5.6% and 78.3% vs. 76.1% respectively).

The intention to treat analysis, the strategy of local excision was not superior to the conventional surgery, due to a high rate of completion surgery, which increased morbidity and side-effects at 2 years. The study also showed a low rate of positive lymph nodes (8%) in such small irradiated tumours, indicating that completion surgery should be limited to < 10% (ypT2/N1 and ypT3).

WHAT IMPACT COULD YOUR RESEARCH HAVE?
We reported the first phase 3 multicentre national randomised trial comparing local excision and rectal excision in clinical good responders after chemoradiotherapy for T2/T3N0-1 low rectal cancer with the objective to evaluate both oncologic and non-oncologic issues. We demonstrated that patients with rectal cancer stage T2 and even T3, but maximum size 4 cm, are good candidates for organ preservation. Better patient selection avoiding unnecessary completion TME could improve the strategy.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
Organ preservation is a new concept for good responders after radiochemotherapy for rectal cancers. Several retrospective or prospective non-comparative studies have been reported over the last decade and a major interest has grown for such a strategy. However, major questions have also been raised regarding oncologic safety, patient selection, tumour response evaluation and morbidity of salvage surgery. We believe that our study brings important relevant information about oncologic safety even if LE was not superior to TME when the composite endpoint was considered. Improvement of patient selection and response evaluation could offer a promising new standard of care for patients treated by chemoradiotherapy for rectal cancer.
Lower rectal carcinoma T2T3N0
≤ 8 cm from the anal verge and size ≤ 4 cm

Chemoradiotherapy
50 Gy in 5 weeks
Concomitant Capecitabine and Oxaliplatine

Good response
(x = < 2 cm)
Randomization

Poor response
(x = > 2 cm)

Arm A
Local excision

Arm B
TME

TME
Follow-up every 4 months

Arm A Local excision (LE) n=74

Arm B Total Mesorectal Excision (TME) n=72

Patients included n=148
Poor responder patients
Not randomized n=3

Patients randomized n=145

Patients analyzed n=145

Figure 1: Design of the study

Figure 2: Flowchart

Figure 3: Disease free survival after Local Excision (LE) vs. Total Mesorectal Excision (TME)
4. RECTAL

Neoadjuvant chemoradiotherapy or 5x5 Gy followed by chemotherapy in rectal cancer: the RAPIDO trial

Corrie Marijnen, on behalf of the cooperative trial group of the RAPIDO trial

Leiden University Medical Center, Netherlands

CONTEXT OF THE STUDY
Current standard for the most locally advanced rectal cancers is preoperative chemoradiotherapy (CRT), and, variably per institution, postoperative adjuvant chemotherapy. Short-course preoperative radiation with delayed surgery induces tumour down-staging in both randomised and observational studies. In the RAPIDO trial, the value of short-term preoperative radiotherapy with 5x5 Gy followed by neoadjuvant chemotherapy was investigated in a randomised fashion.

OVERVIEW OF THE ABSTRACT
Patients with rectal cancer with high-risk features for systemic or local failure on magnetic resonance imaging were eligible. Randomisation took place between a standard arm A: long course chemoradiotherapy (25 x 2 Gy with daily capcitabine 825mg/m2 bid) followed by TME surgery and optional postoperative chemotherapy and an experimental arm B: short course radiation (5 x 5 Gy) followed by six cycles of full-dose CAPOX or nine cycles of FOLFOX and TME surgery.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
A total of 920 patients were included, with 33% cT4 and 68% cN2 disease. MRI-based extramural vascular invasion was diagnosed in 30% of the patients, whereas the mesorectal fascia was considered at risk in 61%, indicating these patients were truly locally advanced.
In the experimental arm 100% of patients completed radiotherapy and 72% of patients completed all scheduled cycles of neoadjuvant chemotherapy. Another 9% completed the last course(s) without oxaliplatin. In the standard arm, 96% received all scheduled radiotherapy fractions and 94% received 5 weeks of preoperative capcitabine combined with radiotherapy.
In total, 19% of patients had a ypT0N0, and 89% had a negative circumferential resection margin.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
Final oncological results are awaited. However, high compliance rate in the experimental arm indicates that short course radiotherapy followed by neoadjuvant chemotherapy is well tolerated. In addition, this study already gives important information on the relevance of good quality preoperative imaging to allow for appropriate patient selection.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
The debate about the role of adjuvant chemotherapy in rectal cancer is still ongoing and its value remains unclear. A possible explanation for this is the limited compliance after surgical treatment for rectal cancer. With the introduction of neoadjuvant chemotherapy, compliance is considerably better and may ultimately result in an increase in DFS. The combination of short course radiotherapy and chemotherapy is an attractive way to limit the duration of neoadjuvant therapy. In addition to this, the role of neoadjuvant (chemo)radiotherapy in intermediate risk tumours, is increasingly investigated to allow for organ preservation after good responses. The best strategy to achieve a high pCR rate is still unclear. Strategies like the experimental arm in Rapido trial will help to define optimal neoadjuvant therapy.
Deadlines:
Abstract submission: 23 October 2017
Early registration: 17 January 2018

Innovation for Value and Access

WWW.ESTRO.ORG
5. GYNAECOLOGY

Reporting on local control and morbidity within the multi-institutional EMBRACE study (2008-2015)

Nina Boje Kibsgaard Jensen, Max Schmid, Lars Ulrik Fokdal, Stephanie Smet, Dina Najjari-Jamal, Christian Kirisits, Jacob Chr. Lindegaard, Kathrin Kirchheiner, Kari Tanderup, Richard Pötter on behalf of the EMBRACE study and research group.

EMBRACE institutions.

CONTEXT OF THE STUDY
Standard of care in patients with locally advanced cervical cancer (LACC) is definitive radiochemotherapy (RCHT) comprising external beam radiotherapy (EBRT) and brachytherapy. With MRI based image guided adaptive brachytherapy (IGABT), an adaptive and advanced imaging and treatment technique has been introduced. In parallel with improved local tumour control, the use of IGABT has resulted in reduced morbidity in LACC patients compared to historical outcomes.

The aim of the EMBRACE study, launched by GEC-ESTRO, was to introduce and benchmark MRI based IGABT in a multi-institutional setting within the framework of a prospective observational study, and to correlate image based dose-volume parameters for the clinical target volume and organs at risk (OAR) with outcome.

From July 2008 to December 2015, a total of 1419 patients from 24 institutions within Europe, Asia and North America were enrolled in the EMBRACE study (An international study on MRI-guided brachytherapy in locally advanced cervical cancer, www.embracestudy.dk).

OVERVIEW OF THE ABSTRACTS
The following report is a summary of the EMBRACE abstracts presented at ESTRO 36. The purpose was to describe patterns of local failure (LF) and morbidity after RCHT and IGABT in LACC patients, analysing both physician assessed morbidity (CTCAE v. 3.0) and patient reported outcomes, PROs (EORTC QlQ C30 and CX24). The following morbidity endpoints are highlighted in this report - bladder and bowel symptoms, unspecific symptoms (fatigue, insomnia), hot flashes and limb edema. Traditionally, morbidity research has been focused on severe treatment related toxicity, but it is becoming more evident, that the symptom burden of mild to moderate morbidity is a considerable problem for cancer survivors, impacting quality of life (QoL).

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
Local failures occurred in a limited number of patients after RCHT and IGABT (LFs=80 in 1230 patients). Approximately 50% of patients had synchronous nodal and/or distant disease. Most local failures were within the high-risk and intermediate-risk clinical target volume (CTVHR and CTVIR). Severe to life-threatening morbidity was limited (table 1). However, mild and moderate (G1-G2) toxicity were prevalent to some degree for all endpoints (table 1). This corresponded to a considerable burden of symptoms reported by the patients (table 2).

Prevalence rates of any bladder and bowel symptoms (G≥1) increased gradually from baseline (figure 1). The prevalence of urinary frequency G≥1 fluctuated over time. The prevalence of diarrhea was already significant at three months and remained elevated. Urinary and faecal incontinence G≥1 increased gradually up to 5 years. Limb edema also showed a slowly progressive pattern. Fatigue and insomnia were present before radiation to a substantial degree, and remained elevated during the overall observation period. Hot flashes typically occurred shortly after treatment and persisted over time.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
The demonstration of excellent local control and limited severe morbidity in LACC patients treated with RCHT and IGABT is strong evidence for the 3D image guided adaptive approach. In addition, the comprehensive morbidity scoring in the EMBRACE study with both physician and patient reported symptoms has helped in understanding the burden of treatment-related toxicity. The results from the EMBRACE study indicate that the burden of mild to moderate late side effects has a significant effect on QoL. This overview and insight into the incidences of LFs and treatment-related morbidity, is important for the new interest in “cancer survivorship”, which is relevant for other solid tumours.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
Image Guided Adaptive Brachytherapy (IGABT), with repetitive MRI is increasingly recognised as the new gold standard, replacing 2D BT throughout the world. The Gyn GEC ESTRO Recommendations I-IV have been provided the conceptual framework for these developments during the last decade and are now embedded into the new ICRU/GEC ESTRO report 89 published in 2016.

The EMBRACE II study with interventions derived from the evidence collected within the EMBRACE study was started in 2016. This prospective interventional study will implement and validate a multi-parametric IGABT prescription protocol for response adaptive targets and OARs.
Table 1. Actuarial estimates of individual physician assessed symptoms according to Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v.3.0) and overall bladder- and bowel morbidity in 1168-1176 patients at 5 years.

<table>
<thead>
<tr>
<th>Actual estimates, CTCAE v.3.0</th>
<th>Urinary frequency</th>
<th>Urinary incontinence</th>
<th>Ureteral stenosis</th>
<th>Diarrhea</th>
<th>Anal incontinence</th>
<th>Bowel stenosis</th>
<th>Fatigue</th>
<th>Insomnia</th>
<th>Hot flashes</th>
<th>Limb edema</th>
<th>Overall bladder morbidity*</th>
<th>Overall bowel morbidity**</th>
</tr>
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<tbody>
<tr>
<td>Grade 21</td>
<td>66.4%</td>
<td>51.9%</td>
<td>6.7%</td>
<td>53.4%</td>
<td>20.5%</td>
<td>6.7%</td>
<td>72.5%</td>
<td>54.0%</td>
<td>61.3%</td>
<td>38.7%</td>
<td>77.3%</td>
<td>72.0%</td>
</tr>
<tr>
<td>Grade 22</td>
<td>10.4%</td>
<td>10.3%</td>
<td>5.0%</td>
<td>12.5%</td>
<td>3.5%</td>
<td>3.0%</td>
<td>33.5%</td>
<td>20.6%</td>
<td>21.9%</td>
<td>6.6%</td>
<td>31.1%</td>
<td>20.7%</td>
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<td>Grade 23</td>
<td>1.9%</td>
<td>2.1%</td>
<td>3.4%</td>
<td>1.8%</td>
<td>0.5%</td>
<td>2.6%</td>
<td>6.7%</td>
<td>4.7%</td>
<td>2.2%</td>
<td>0.5%</td>
<td>4.7%</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

*Symptoms included: frequency, incontinence, bladder spasm, bladder stenosis, bleeding, cystitis and fistulas. **Symptoms included: diarrhea, fistulas, incontinence, stenosis, fistulas and ‘other’ bowel symptoms reported in a free text field. One grade 5 bowel event occurred.

Table 2. Patient reported outcomes of “a little” and “quite a bit”/“very much” symptoms grouped together according to EORTC QLC-C30 version 3.0 questionnaire and the disease-specific module EORTC QLC-CX24. Crude incidences reflecting the maximum grading over the follow-up period are shown.

<table>
<thead>
<tr>
<th>EORTC QLC-CX24</th>
<th>Frequent urination</th>
<th>Leaking of urine</th>
<th>Difficulty emptying the bladder</th>
<th>Burning sensation during urination</th>
<th>Diarrhea</th>
<th>Constipation</th>
<th>Abdominal cramps</th>
<th>Difficulty controlling bowel</th>
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<tr>
<td>&quot;A little&quot;</td>
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EORTC = European Organisation for Research and Treatment of Cancer.

Figure 1. Overall bladder- (except ureter stenosis) and bowel morbidity in prevalence rates for all CTCAE gradings in a 5 year follow-up period. CTCAE = Common Terminology Criteria for Adverse Events version 3.0; BL = baseline; M = months; Patients = # of patients in follow-up.
INTRODUCTION

1. Experimental verification of dose enhancement effects in a lung phantom from inline magnetic fields

2. Lateral response heterogeneity of Bragg peak ion chambers for narrow-beam photon and proton dosimetry

3. Late toxicity in HYPRO randomised trial analysed by automated planning and intrinsic NTCP-modelling

4. Validation of a fully automatic real-time liver motion monitoring method on a conventional linac
INTRODUCTION

The ESTRO 36 physics programme, compared to previous years, saw an even stronger reflection of the growing number of particle therapy centres and the increasing initiatives of treatment machines with onboard MRI. This clearly led to a revival of traditionally strong physics themes such as dosimetry, dose measurements and dose calculations: Three out of 10 submitted abstracts were associated with these themes and many highly rated abstracts within these themes were connected to the advent of these emerging developments.

Furthermore, we received physics abstracts from 54 different countries clearly underlining the international character of our meeting. It is also noticeable that 180 abstracts (22%) were submitted from countries outside the European continent. This also indicates that the ESTRO convention is becoming more and more attractive in the global arena.

Both observations were also mirrored by the following five selected physics abstracts that reflect important milestones in radiation oncology physics.

The first abstract from Oborn and colleagues reports on the first experimental evidence of lung dose enhancement effects of 12% caused by strong inline magnetic fields. This phenomenon arises from a relative reduction in the amount of lateral secondary electron scatter in the low density lung medium, which could potentially complement the precise treatment of small tumours embedded in lung tissue.

The second abstract from Kuess and colleagues presents some very interesting and practical work on the lateral response of large area Bragg peak ion chambers. A pronounced heterogeneity of the spatial responses was observed in both the thick and thin window chambers, highlighting the need for chamber-dependent response maps for absolute and relative dosimetry with proton pencil beams or small photon beams.

The third abstract from Sharfo and co-workers presents an interesting study on auto-planning. The investigators retrospectively re-planned a study cohort of 430 prostate patients and linked the dosimetric improvements to the NTCP models obtained from the same study. A significant reduction of GI toxicity probabilities was demonstrated, possibly related to improvements in the treatment planning system (TPS) and/or automation of planning. This study indicates that clinically relevant benefits can be obtained from critically assessing plan quality.

Finally, the fourth abstract (and also highest rated physics abstract) from Bertholet and colleagues presents a framework for fully automatic monitoring of thoracic and abdominal tumours on a conventional linac. The framework combines auto-segmentation of arbitrarily shaped implanted fiducial markers in CBCT projections and intra-treatment kV images with simultaneous streaming of an external optical motion signal. A real-time 3D tumour motion monitoring method was established and experiments using known Calypso-recorded liver tumour motion showed good agreement in 10 liver patients.

Gert J. Meijer
Chair, Scientific advisory group (SAG) for Radiation Physics
Experimental verification of dose enhancement effects in a lung phantom from inline magnetic fields

Brad Oborn1,2, Maegan Gargett1,5, Trent Causer1,6, Nicholas Hardcastle1, Peter Metcalfe1,5, Paul Keall1,5

1 Illawarra Cancer Care Centre, Wollongong Hospital, NSW 2500 Australia; 2 Centre for Medical Radiation Physics, University of Wollongong, NSW 2500 Australia; 3 Royal North Shore Cancer Care Centre, St Leonards, NSW 2065 Australia; 4 Peter MacCallum Cancer Institute, Melbourne, VIC 3000 Australia; 5 Ingham Institute for Applied Medical Research, Liverpool, NSW 2170, Australia; 6 Sydney Medical School, University of Sydney, NSW 2006 Australia

CONTEXT OF THE STUDY
A paradigm shift is occurring in radiotherapy with the clinical implementation of real-time adaptive MRI guided radiotherapy; treatment of patients with x-rays whilst inside the bore of an MRI scanner. This has generated new challenges in patient dose planning and dosimetry. X-rays deliver dose to a patient by colliding with electrons in the tumour. These electrons, being charged particles, are now subject to the magnetic Lorentz force. As a result there can be a significant change in the planned tumour dose. Much work has focused on recovering the negative effects caused by magnetic fields that are perpendicular to the x-ray beam, typical of current MRI-xray systems. In this work we report on a positive result for inline magnetic fields in lung based radiotherapy.

OVERVIEW OF THE ABSTRACT
The purpose of this work is to present the first experimental evidence of how strong inline magnetic fields (i.e. parallel to the radiation beam) helps to localise the dose delivered by the x-ray beam in a lung phantom. In essence, this localising effect sets up a relative enhancement to the irradiated volume, as compared to the scattered dose outside the beam. The x-ray beam effectively becomes more efficient; with higher dose in the beam area for the same out-of-field dose.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
1. A confirmation of the lung dose enhancement effect as predicted in previous Monte Carlo based work was observed.
2. Simulations describe a clear trend with enhancement amount that is connected to magnetic field strength and x-ray field size. Smaller tumours will benefit more than larger ones, particularly in higher magnetic fields of 1 T or greater.
3. An important conclusion related to small field dosimetry in lung tissue is that there is reduced setup error sensitivity in the inline orientation as compared with the perpendicular magnetic fields.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
Small lung tumours will be ideal candidates for real-time MRI guided radiotherapy. The real-time MR based image guidance is well suited to determine the location and movement pattern of a small lung tumour during radiotherapy. This work presents a compelling argument for the use of inline magnetic field based MRI-linac technology. The impact on research may cause a shift in the direction of progressing inline MRI-linac prototypes to clinical systems much sooner than expected. With robust MLC tracking, a more conformal tumour dose with fewer side effects would be naturally expected. Further to this, the breadth of lung tumour cases treatable with x-rays may well expand according to the new standard on offer.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
Real-time MRI-guided radiotherapy is growing as confidence increases in the ability to see and treat dynamic tumours with adaptive planning methods. Inline prototype MRI-linac systems are under development. These systems offer a less complicated dosimetry correction process, as compared with perpendicular orientation systems. The bigger trend that we expect in oncology research is that of an acceleration and broadening of the work performed in bringing these inline prototype MRI-linac systems to the clinical age. More targeted research will be performed in expanding on the current prototype inline MRI-linac systems found in Sydney (Australia) and Alberta (Canada).
Fig. 1. Experimental setup of the lung phantom inside the pole gap of the permanent magnet system. For the reference measurements ($B = 0$ T) the steel cones were removed and repositioned around the phantom to relocate the scattering conditions of the measurements at 1.2 T.

Fig. 2. Schematic diagram of the magnetic field map around the device and x-ray beam direction. The x-ray beam is parallel to the magnetic field across the pole gap.

Fig. 3. Diagram of the experimental phantom setup. A small lung density equivalent phantom was positioned inside a 1.2 T inline magnetic field. EBT3 films was used to map out the dose changes that occurred due to the inclusion of the magnetic field. Both 6MV and 10MV beams were investigated.

Fig. 4. A summary of the magnetic field effects on a 6MV x-ray beam for a small field size. EBT3 films were taken at 0 T and 1.2 T inline magnetic field. Within the beam cross section, a 12% dose enhancement effect was recorded (14% for 10MV beam). The magnetic field causes a reduction in the amount of lateral scatter of the secondary electrons liberated in the lung material by the x-ray beam.
Lateral response heterogeneity of Bragg peak ion chambers for narrow-beam photon and proton dosimetry

Peter Kuess1,2, Till Böhlen3, Wolfgang Lechner1,2, Alessio Elia3, Dietmar Georg1,2, Hugo Palmans3,4

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CONTEXT OF THE STUDY
Large area ionisation chambers (LAICs) were investigated with respect to their spatial response behaviour (homogeneous or non-homogeneous over the sensitive area). These detectors are used for scanned particle beams since they integrate pencil beam dose at a given depth laterally. Also some usage for small field photon dosimetry has been proposed. LAICs are available as thick chambers that can also be submerged in water as well as thin chambers which can only be utilised in air. The thickness in this case refers to the entrance window of the chamber, i.e. the protecting cover in front of the sensitive detector.

OVERVIEW OF THE ABSTRACT
Large area ionisation chambers (LAICs) can be used to measure output factors of narrow beams. Using such detectors requires detailed information on the uniformity of the signal response along the sensitive area of a LAIC. A non-homogeneous ionisation chamber response can result in non-negligible dose differences that have to be accounted for in the dosimetric protocols.

In this study the response maps were generated by using a collimated X-ray beam (Figure). The effects of the measured non-homogenous response of eight different chambers were investigated for proton pencil beams as well as for narrow photon beams.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
The response of thick LAICs generally decreased with increasing radius, resulting in a correction of the response of up to 5%. The response correction for thin LAIC was more pronounced and more diverse (up to 10%).

Considering a proton pencil beam the systematic offset for absolute dosimetry varies between 2.4% and 4.1% for thick LAICs and between -9.5% and 9.4% for thin LAICs.

For relative dosimetry (e.g. integral depth-dose profiles) the beam size increase with increasing depth was investigated as the influencing factor. Systematic response variation by 0.36% and 1% at the most were found for the investigated LAICs.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
This study highlights the need for chamber-depended response maps when using LAICs for absolute and dosimetry with proton pencil beams or small photon beams. By using these correction maps the overall uncertainty of dosimetric measurements using such LAICs could be reduced. For relative proton dosimetry the correction factors are in an order of magnitude (<0.5%) that imply that measuring without applying these factors is feasible.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
Upcoming ion beam therapy centres are mostly using scanning systems and thus dosimetry with narrow beams is becoming more and more important. Large area chambers have been suggested for dosimetric procedures for some time. The investigation of the response homogeneity as well as the limitations caused by non-homogeneous response has so far not been thoroughly addressed in the literature.
Figure: Typical response maps of two large area ionisation chambers (top: thick entrance; bottom: thin entrance window)
Late toxicity in HYPRO randomised trial analysed by automated planning and intrinsic NTCP-modelling

A.W.M. Sharfo1, M.L.P. Dirkx1, R.G. Bijman1, W. Schillemans1, S. Breedveld1, S. Aluwini1, F. Pos2, L. Incrocci1, B.J.M. Heijmen1.

1Erasmus MC Cancer Institute, Radiation Oncology, Rotterdam, The Netherlands; 2Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Radiation Oncology, Amsterdam, The Netherlands.

CONTEXT OF THE STUDY
In radiotherapy, the goal of treatment planning is to establish patient-specific treatment machine parameters to adequately irradiate the tumour, while keeping doses to surrounding healthy organs as low as possible in order to prevent radiation-associated complications. Between 2007 and 2010, a multicentre randomised trial (HYPRO) for intermediate- and high-risk localised prostate cancer was conducted in the Netherlands to investigate advantages of hypofractionated external beam radiotherapy (EBRT) (19 days with 3.4 Gy) compared with conventional fractionated EBRT (39 days with 2.0 Gy). Patients in this study were treated with conventional, manual treatment planning. Recently, we developed a new tool for automated treatment plan generation. For several tumour sites, superiority of automated planning over manual planning has been observed in terms of quality of delivered dose distributions.

OVERVIEW OF THE ABSTRACT
In this study we investigated to what extent the patients in the HYPRO trial could have benefitted from automated instead of manual planning. Normal Tissue Complication Probability (NTCP) models derived from toxicity observed in the HYPRO trial were used to quantify differences in plan quality between manual and automated planning.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
Large dose reductions in the patients’ rectum and bladder doses were observed in the automatically generated plans, while equally high doses were delivered to the tumour (Figure 1). Significant reductions in rectal NTCPs were observed in automatically generated plans, with relative reductions of 10.5% for late GI grade ≥ 2 toxicity, 16.8% in stool incontinence, and 18.7% in rectal bleeding (p<0.001), see Figure 2.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
For the first time, clinical advantages of automated planning have been demonstrated for a huge number of patients using (intrinsically derived) NTCPs. Apart from the highly significant reductions in treatment complications, automated planning also vastly reduces the treatment planning workload and the need for highly trained planners. Moreover, automated planning can contribute to more uniform treatment.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
Automation of treatment planning is currently getting high attention in radiotherapy research. Apart from the gain in plan quality and the logistic/economic advantages, automated planning can also play an essential role in the promising field of adaptive radiotherapy, and it can be used for bias-free treatment technique comparisons, e.g. to select patients for highly expensive treatments that are expected to really benefit from it (e.g. proton therapy). It is believed that automated planning can play a crucial role in a worldwide increase in quality of radiotherapy care, including lower and middle income countries.

REFERENCES
Figure 1. Average DVHs of prostate patients in the standard fractionation arm, and the hypofractionation arm.

Figure 2. Reductions in NTCPs for GI toxicity symptoms with automated planning.
Validation of a fully automatic real-time liver motion monitoring method on a conventional linac

Jenny Bertholet¹, Rune Hansen¹, Esben S. Worm¹, Jakob Toftegaard¹, Hanlin Wan¹, Parag J. Parikh², Morten Høyer¹ and Per R. Poulsen¹

¹Department of Oncology, Aarhus University Hospital, DK; ²Department of Radiation Oncology, Washington University School of Medicine, St-Louis, USA

CONTEXT OF THE STUDY
Radiotherapy treatments are planned on static images of the patient and later delivered in several fractions with the underlying hypothesis that the patient's anatomy is reproduced at each fraction. However, the anatomy may change from day to day and during the treatment itself. Particularly in the thorax and abdomen, respiratory motion of the tumour compromises treatment delivery. Patients often have implanted radio-opaque fiducial markers acting as surrogate for the tumour position. Kilovoltage Intrafraction Monitoring (KIM) is a method that allows real-time motion monitoring based on continuous x-ray imaging with the standard kV x-ray imager of a conventional linac. This work overcomes some of the limitations of KIM.

OVERVIEW OF THE ABSTRACT
Real-time treatment adaptation such as gating or tracking may improve radiotherapy of mobile tumours, but it requires reliable target motion monitoring. The purpose of our study was to develop and validate a framework for fully automatic monitoring of thoracic and abdominal tumours on a conventional linac. The framework combines auto-segmentation of implanted fiducial markers in x-ray images acquired before and during treatment with simultaneous streaming of an external optical motion signal of the patient’s abdomen (Fig A). The method was validated through experiments and simulations using known external and internal motion for 10 liver patients.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
The main finding of our study is that accurate marker-based real-time tumour motion monitoring can be performed fully automatically during thoracic and abdominal radiotherapy treatments by combining reliable marker segmentation in x-ray images and an external optical signal. The validation showed that a localisation accuracy of 1.7 mm can be achieved for liver SBRT (Fig B).

The method can be used on a conventional linac with few modifications of the current workflow.

Unlike KIM, the method is compatible with non-coplanar fields where no images can be taken. Furthermore, fewer intra-treatment images are needed and they are not affected by noise from the treatment beam since they are acquired during short beam pauses.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
Our research could improve radiotherapy of moving tumours on a conventional linac. Motion during treatment can deteriorate the dose distribution delivered to the tumour. Without motion mitigation, large margins are needed to ensure tumour coverage. Our method could be used to adapt treatment delivery in real-time to restore the planned dose by gating or tracking. This would allow reduced treatment margins and thereby reduced irradiation to the healthy tissues. The dose could be escalated and/or the side effects reduced.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
Modern technology has given us the possibility to deliver highly conformal dose distributions even with conventional linacs. Other methods allow real-time tumour motion monitoring (Calypso) or even tracking of moving tumours (CyberKnife, Vero), but they require highly specialised and expensive equipment. The ESTRO vision for 2020 is that every patient will have access to state of the art radiation therapy. This calls for versatile methods that can be used on conventional equipment like the KIM method, which has been used clinically for prostate radiotherapy since September 2014 in Sydney. Our method can overcome some of the KIM limitations without added specialised hardware.
A. Workflow of the fully automatic monitoring method.
(ECM = external correlation model, CBCT = Cone-beam CT)

B. 3D internal position for the experiment. The ground truth is shown in black along the right-left (RL), superior-inferior (SI) and antero-posterior (AP) axis. The superior-inferior tumor motion range is ~2 cm. The shaded areas indicate when the treatment beam was off. The red line shows the estimated position. The mean 3D localization error for the simulations was 1.7 mm.
## INTRODUCTION

1. Single dose compared to fractionated high-dose rate brachytherapy for localised prostate cancer  
2. Comparison of clinical outcomes of APBI using interstitial brachytherapy as per ESTRO & ASTRO guidelines  
3. Reporting on local control and morbidity within the multi-institutional EMBRACE study (2008-2015)  
4. Brachytherapy for conservative treatment of penile carcinoma: prognostic factors and outcome
ESTRO 36 had a lot to offer those colleagues interested and experienced in brachytherapy. Several highlight abstracts presented new results on its potential within radiotherapy. The GEC-ESTRO pre-meeting workshop on "Innovations in brachytherapy" was a forum to present and discuss the latest techniques, procedures and technology. Experts, presenters and participants were invited to discuss which should be considered state of the art, which are perhaps high-tech aspirations for the future, and which are probably not for routine clinical practice.

There were teaching lectures on target definition protocols for breast brachytherapy and commissioning of dose calculation for treatment planning. For both topics, there have been recent major developments and there is a need to integrate long established experience with new recommendations and procedures.

The symposia on Saturday dealt with expanding brachytherapy indications and economics of brachytherapy including the new Brachy-HERO initiative. It is important to gain insight on how a brachytherapy programme in a centre can be applied to several disease sites with health economics benefits.

Paediatric brachytherapy was the topic for the Sunday symposium. With the emergence of new technology with photon and particle therapy, it is easy to forget the long lasting and successful experience with paediatric brachytherapy. With the decline in patient numbers, our young colleagues have little opportunity to learn these procedures and even for experts, it is a challenge to keep up to date with techniques and dose constraints. We hope that the overview in this symposium will rekindle interest and trigger future developments.

The final symposium should clarify the mystery of registration and fusion techniques in brachytherapy. There are few other topics which cause so much confusion, misunderstanding, and even wrong conclusions.

The proffered paper sessions included several top abstracts grouped into two prostate sessions, one breast session and one gynaecology session. Some work on prostate is described in the report of Hoskin et al, and on breast by Telkhade et al. We were encouraged by the number of submissions on eye, skin and keloid treatments, for oral or poster presentations. The skin and keloid abstracts were of such quality that a dedicated proffered paper session with five oral presentations could be organised. The highlight was the combined clinical/GEC session on gynaecology. Several abstracts from the EBRACE trials and top mono-center trials were gathered together, addressing clinical issues related to external beam radiotherapy and brachytherapy. Gynaecology is perhaps a model for how to combine the most advanced techniques for each treatment modality for maximum benefit.

Two physics proffered paper sessions on treatment verification and dosimetry once again showed the close integration of brachytherapy physics to clinical application. The majority of abstracts presented the close interdisciplinary collaboration between physicists and clinicians. The abstract by Beld et al about a feasibility study for a MRI-compatible afterloader received the highest score and was proposed for the ESTRO-Elekta Brachytherapy Award (see report under "Awards").

The abstract chosen for the highlights of proffered papers session was by Escande et al reporting on a huge clinical experience of brachytherapy for conservative treatment of penile carcinoma. It underlined the general trend that brachytherapy is not confined to the main clinical sites like prostate, gynaecology and breast. Advances in technology, treatment/target concepts and innovative application techniques have been developed over the past few years. Most of them have been for disease sites with high patient numbers but there is a revival for brachytherapy applications which have gone out of favour, as well as totally new indications. Combining long established clinical experience with the lessons learned from the recent developments in gynaecology, prostate and breast could be the basis for expanding brachytherapy indications to the benefit of patients.

A wish for the future is for better geographical distribution of presented abstracts. Our GEC-ESTRO working groups, the ESTRO school with brachytherapy-related courses, and the GEC-ESTRO workshops, are all wonderful opportunities to network. We would especially encourage the young generation in European countries to become even more active in the coming meetings.

I would like to thank all authors, reviewers and members of the Scientific Advisory Group for their immense work in creating the brachytherapy track of ESTRO 36.

Christian Kirisits
Chair, Scientific advisory group (SAG) for Brachytherapy
1. CONTEXT OF THE STUDY
High dose rate (HDR) brachytherapy is now well established in the treatment of prostate cancer when used as a boost for dose escalation in combination with external beam therapy. It has also been shown effective when used alone delivered in two to four fractions. The ultimate development of this approach is to deliver HDR monotherapy as a single dose overcoming the logistic issues of repeated fractionation and providing a comparable experience to LDR brachytherapy whilst retaining the potential radiobiological advantage of a high dose per fraction.

OVERVIEW OF THE ABSTRACT
We have explored the use of single doses of HDR brachytherapy in two prospective cohorts of patients with localised intermediate or high risk prostate cancer delivering 19Gy and 20Gy. These have been compared with previous cohorts receiving 26Gy in 2 fractions, 31.5Gy in 3 fractions and 34-36Gy in 4 fractions. Acute toxicity has been previously reported with an increase in urinary toxicity in the 20Gy cohort. End points in this analysis were late genitourinary and gastrointestinal toxicity and tumour control using biochemical (PSA) relapse free survival. Median follow up was 54mo (19Gy), 48mo (20Gy), 62mo (26Gy), 107mo (31.5Gy), 129mo (34Gy) and 121(36Gy).

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
RTOG severe urinary toxicity was seen in 0-4% of all cohorts at 4, 5 and 7 years; IPSS scores ≥ 20 were seen on 4-5% of single dose patients at 4 years compared to 3-5% in the other cohorts.

Severe GI toxicity ranged from 0 to 5% at 4 years and 0 to 2% at 5 years across the cohorts.

PSA relapse free survival was between 91 and 96% across all cohorts at 4 and 5 years.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
These results support further evaluation of single dose HDR brachytherapy for localised intermediate and high risk prostate cancer using a single dose of 19Gy. Comparison with LDR brachytherapy and stereotactic or VMAT hypofractionated external beam therapy is warranted.

Single dose compared to fractionated high-dose rate brachytherapy for localised prostate cancer

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IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
The use of hypofractionated radiotherapy for localised prostate cancer has gained momentum recently with several large trials of external beam therapy showing equivalence with conventional schedules and the development of stereotactic techniques delivering 4 to 6 fraction schedules. The ultimate adaptation of hypofractionation is a large single dose which this data shows can be safely delivered with HDR brachytherapy with remarkably high biochemical control rates in a cohort of intermediate and high risk patients.
2.

Comparison of clinical outcomes of APBI using interstitial brachytherapy as per ESTRO & ASTRO guidelines

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Tata Memorial Hospital, Mumbai, India

CONTEXT OF THE STUDY
Accelerated partial breast irradiation (APBI) is a well-established treatment for women with early breast cancer treated with radiation therapy. The equivalence of APBI with whole breast irradiation (WBRT) has been proven in the GEC-ESTRO randomised trial. Advantages of APBI over WBRT are shorter treatment time, high dose conformity, reduced volume of normal breast irradiation thus conferring better cosmesis and lesser radiotherapy induced late effects. GEC-ESTRO, ASTRO, ABS and other professional societies recommend the use of guidelines in selecting patients for APBI. Lack of consistency in recommendations with respect to clinical or pathological criteria still poses a dilemma for patient selection. The aim of the study was to evaluate the long term clinical outcomes based on the risk stratification given by ESTRO and ASTRO consensus guidelines.

OVERVIEW OF THE ABSTRACT
Two hundred and forty two women with early breast cancer underwent APBI using interstitial brachytherapy during July 2000 to March 2013. Radiation was delivered using HDR 192Ir source to a dose of 34Gy in 10 fractions with bid regimen. As per analyses with ASTRO consensus, our cohort consisted of 32(13.2%), 143 (59.1%) and 67(27.7%) patients belonging to suitable, cautionary and unsuitable group, respectively. According to ESTRO guidelines, 148(61.2%), 54(22.3%) and 40 (16.5%) patients were categorised as low, intermediate and high risk group, respectively. The long term clinical outcomes in terms of local control (LC), disease free survival (DFS) and overall survival (OS) of these risk stratification groups were studied.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
1. The patients in this study have excellent local control of 94.3% at 7 years irrespective of their risk group.
2. There was no statistically significant difference in the local control rates for both ASTRO and ESTRO consensus groups at the median follow up of 90 months. Patient selection as per both ESTRO and ASTRO consensus guidelines did not have any impact on local control rates for patients treated with APBI.
3. The DFS (p=0.008), CSS (p=0.004) and OS (p=0.007) rates were significantly correlated with GEC-ESTRO consensus guidelines for patient selection while none of our outcomes correlated with ASTRO consensus guidelines (Table1).

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<td>96%</td>
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<tr>
<td>OS</td>
<td>Low</td>
<td>98%</td>
<td>Intermediate</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>98%</td>
<td>High</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>98%</td>
<td>Suitable</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cautionary</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>unsuitable</td>
<td>96%</td>
</tr>
</tbody>
</table>

Table1: Long term (at 5 and 7 years) local control (LC), disease free survival (DFS), cause-specific survival (CSS) and overall survival (OS) according to risk stratification groups as per ESTRO and ASTRO consensus guidelines.
WHAT IMPACT COULD YOUR RESEARCH HAVE?
The local control rates with APBI are excellent. However, we
demonstrate the poor prognostic power of current ASTRO
and ESTRO consensus guidelines for risk stratification in
differentiating patients at increased risk of IBTR with APBI.
ASTRO guidelines also failed to predict DFS, CSS and OS
amongst three risk groups. Based on our long term results it
appears that there is a need to revise the current consensus
guidelines of both ESTRO and ASTRO.

IS THIS RESEARCH INDICATIVE OF A BIGGER TRENDS IN ONCOLOGY?
We observed excellent long term clinical outcomes for all
patients treated with APBI regardless of risk group stratification;
hence denying APBI especially to cautionary/intermediate
risk group patients will not be advisable. We urge to refine
clinicopathological criteria by evaluating the most important
variables predicting IBTR in larger databases across the world
and incorporate them to stratify patients so that APBI can be
safely delivered to eligible patients.
Graphs for local control with ESTRO and ASTRO risk stratification

Graphs for disease free survival with ESTRO and ASTRO risk stratification

Graphs for overall survival with ESTRO and ASTRO risk stratification
3.

Reporting on local control and morbidity within the multi-institutional EMBRACE study (2008-2015)

Nina Boje Kibsgaard Jensen, Max Schmid, Lars Ulrik Fokdal, Stephanie Smet, Dina Najjari-Jamal, Christian Kirisits, Jacob Chr. Lindegaard, Kathrin Kirchheiner, Kari Tanderup, Richard Pötter on behalf of the EMBRACE study and research group

EMBRACE institutions

CONTEXT OF THE STUDY
Standard of care in patients with locally advanced cervical cancer (LACC) is definitive radiochemotherapy (RCHT) comprising external beam radiotherapy (EBRT) and brachytherapy. With MRI based image guided adaptive brachytherapy (IGABT), an adaptive and advanced imaging and treatment technique has been introduced. In parallel with improved local tumour control, the use of IGABT has resulted in reduced morbidity in LACC patients compared to historical outcomes.

The aim of the EMBRACE study, launched by GEC-ESTRO, was to introduce and benchmark MRI based IGABT in a multi-institutional setting within the framework of a prospective observational study, and to correlate image based dose-volume parameters for the clinical target volume and organs at risk (OAR) with outcome.

From July 2008 to December 2015, a total of 1419 patients from 24 institutions within Europe, Asia and North America were enrolled in the EMBRACE study (An international study on MRI-guided brachytherapy in locally advanced cervical cancer, www.embracestudy.dk).

OVERVIEW OF THE ABSTRACT
The following report is a summary of the EMBRACE abstracts presented at ESTRO 36. The purpose was to describe patterns of local failure (LF) and morbidity after RCHT and IGABT in LACC patients, analysing both physician assessed morbidity (CTCAE v. 3.0) and patient reported outcomes, PROs (EORTC QlQ C30 and CX24). The following morbidity endpoints are highlighted in this report - bladder and bowel symptoms, unspecific symptoms (fatigue, insomnia), hot flashes and limb edema. Traditionally, morbidity research has been focused on severe treatment related toxicity, but it is becoming more evident, that the symptom burden of mild to moderate morbidity is a considerable problem for cancer survivors, impacting quality of life (QoL).

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
Local failures occurred in a limited number of patients after RCHT and IGABT (LFs=80 in 1230 patients). Approximately 50% of patients had synchronous nodal and/or distant disease. Most local failures were within the high-risk and intermediate-risk clinical target volume (CTVHR and CTVIR).

Severe to life-threatening morbidity was limited (table 1). However, mild and moderate (G1-G2) toxicity were prevalent to some degree for all endpoints (table 1). This corresponded to a considerable burden of symptoms reported by the patients (table 2).

Prevalence rates of any bladder and bowel symptoms (G≥1) increased gradually from baseline (figure 1). The prevalence of urinary frequency G≥1 fluctuated over time. The prevalence of diarrhea was already significant at three months and remained elevated. Urinary and faecal incontinence G≥1 increased gradually up to 5 years. Limb edema also showed a slowly progressive pattern. Fatigue and insomnia were present before radiation to a substantial degree, and remained elevated during the overall observation period. Hot flashes typically occurred shortly after treatment and persisted over time.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
The demonstration of excellent local control and limited severe morbidity in LACC patients treated with RCHT and IGABT is strong evidence for the 3D image guided adaptive approach. In addition, the comprehensive morbidity scoring in the EMBRACE study with both physician and patient reported symptoms has helped in understanding the burden of treatment-related toxicity. The results from the EMBRACE study indicate that the burden of mild to moderate late side effects has a significant effect on QoL. This overview and insight into the incidences of LFs and treatment-related morbidity, is important for the new interest in “cancer survivorship”, which is relevant for other solid tumours.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
Image Guided Adaptive Brachytherapy (IGABT), with repetitive MRI is increasingly recognised as the new gold standard, replacing 2D BT throughout the world. The Gyn GEC ESTRO Recommendations I-IV have been provided the conceptual framework for these developments during the last decade and are now embedded into the new ICRU/GEC ESTRO report 89 published in 2016.

The EMBRACE II study with interventions derived from the evidence collected within the EMBRACE study was started in 2016. This prospective interventional study will implement and validate a multi-parametric IGABT prescription protocol for response adaptive targets and OARs.
Table 1. Actuarial estimates of individual physician-observed symptoms according to Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v.3.0) and overall bladder- and bowel morbidity in 1168-1176 patients at 5 years.

<table>
<thead>
<tr>
<th>Actuarial estimates, CTCAE v.3.0</th>
<th>Urinary frequency</th>
<th>Urinary incontinence</th>
<th>Urethral stenosis</th>
<th>Diarrhea</th>
<th>Anal incontinence</th>
<th>Bowel stenosis + fistulas</th>
<th>Fatigue</th>
<th>Insomnia</th>
<th>Hot flashes</th>
<th>Limb edema</th>
<th>Overall bladder morbidity</th>
<th>Overall bowel morbidity**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1A</td>
<td>66.4%</td>
<td>61.0%</td>
<td>6.7%</td>
<td>63.4%</td>
<td>20.5%</td>
<td>6.7%</td>
<td>72.8%</td>
<td>54.0%</td>
<td>61.3%</td>
<td>39.7%</td>
<td>77.3%</td>
<td>72.0%</td>
</tr>
<tr>
<td>Grade 2A</td>
<td>16.4%</td>
<td>15.0%</td>
<td>6.8%</td>
<td>5.8%</td>
<td>3.6%</td>
<td>3.9%</td>
<td>33.8%</td>
<td>20.6%</td>
<td>21.9%</td>
<td>6.6%</td>
<td>31.1%</td>
<td>26.7%</td>
</tr>
<tr>
<td>Grade 3A</td>
<td>1.9%</td>
<td>2.1%</td>
<td>3.4%</td>
<td>1.6%</td>
<td>0.5%</td>
<td>2.6%</td>
<td>6.7%</td>
<td>4.7%</td>
<td>2.2%</td>
<td>0.0%</td>
<td>4.7%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Pts. with grade 3-4/ total # of pts</td>
<td>14/1174</td>
<td>19/1176</td>
<td>19/1176</td>
<td>17/1176</td>
<td>4/1176</td>
<td>17/1176</td>
<td>46/1170</td>
<td>35/1168</td>
<td>18/175</td>
<td>41/171</td>
<td>39/1176</td>
<td>42/1176</td>
</tr>
</tbody>
</table>

*Symptoms included: frequency, incontinence, bladder spasm, bladder stenosis, bleeding, cystitis and fistulas. **Symptoms included: diarrhea, fistula, incontinence, stenosis, fistulas and “other” bowel symptoms reported in a free text field. One grade 5 bowel event occurred.

Table 2. Patient reported outcomes of “a little” and “quite a bit”/“very much” symptoms grouped together according to EORTC QLQ-C30 version 3.0 questionnaire and the disease-specific module QLQ-CX24. Crude incidences reflecting the maximum grading over the follow-up period are shown.

<table>
<thead>
<tr>
<th>EORTC C30+CX24</th>
<th>Frequent urination</th>
<th>Leaking of urine</th>
<th>Difficulty emptying the bladder</th>
<th>Burning sensation during urination</th>
<th>Diarrhea</th>
<th>Constipation</th>
<th>Abdominal cramps</th>
<th>Difficulty controlling bowel</th>
</tr>
</thead>
<tbody>
<tr>
<td>“A little”</td>
<td>32.6%</td>
<td>32.4%</td>
<td>23.3%</td>
<td>27.2%</td>
<td>38.9%</td>
<td>26.7%</td>
<td>38.6%</td>
<td>34.2%</td>
</tr>
<tr>
<td>“Quite a bit”</td>
<td>39.0%</td>
<td>17.4%</td>
<td>12.8%</td>
<td>13.4%</td>
<td>25.0%</td>
<td>13.9%</td>
<td>24.3%</td>
<td>17.3%</td>
</tr>
<tr>
<td>“Very much”</td>
<td>45.4%</td>
<td>37.3%</td>
<td>41.1%</td>
<td>44.3%</td>
<td>44.3%</td>
<td>24.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EORTC = European Organisation for Research and Treatment of Cancer.

Figure 1. Overall bladder- (except urethral stenosis) and bowel morbidity in prevalence rates for all CTCAE gradings in a 5 year follow-up period. CTCAE = Common Terminology Criteria for Adverse Events version 3.0. BL = baseline, M = months. Patients = # of patients in follow-up.
Brachytherapy for conservative treatment of penile carcinoma: prognostic factors and outcome


Gustave Roussy, France

CONTEXT OF THE STUDY
Penile carcinoma is a rare disease, for which surgical amputation is often proposed as the primary treatment. However, the functional sequelae of surgery have prompted an interest in organ sparing strategies.

OVERVIEW OF THE ABSTRACT
Here we report the largest experience of brachytherapy as an organ sparing strategy for penile glans carcinoma. Brachytherapy is a form of radiotherapy where a sealed radiation source is inserted directly into the volume to be treated. We report our institutional experience of 201 selected patients treated by brachytherapy for early stage penile glans carcinoma without infiltration of the corpus cavernosum. Needles or plastic tubes were implanted under general anaesthesia and brachytherapy was delivered through low dose rate or pulsed dose rate irradiation, see Figure 1.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
Patients treated with brachytherapy achieved high local control rates (82% at 5 years). Most patients with local relapse were salvaged by surgery, and remained in complete remission at last follow-up (77.4%).

Most acute toxicities were mild to moderate. The most significant long-term toxicities were urethral stenosis requiring dilatation, and painful ulceration, both of which rarely required surgical intervention. The risk of complications (urethral stenosis or painful ulceration) correlated with the dose, treated volume, and dose rate.

At five years, 85% of patients who were alive had preserved their penis, showing that brachytherapy is an effective organ sparing strategy. Presence of inguinal lymph node involvement, larger tumour size, and increase in white cell count were found to correlate with poorer outcome.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
This large retrospective study shows the possibility to use brachytherapy as the primary conservative treatment of penile cancer in selected patients without invasion of corpus cavernosum, provided that patients are adequately informed of the risk of tumour relapse and are willing to commit to close clinical surveillance. High local control rates can be achieved and most local relapses are effectively salvaged by surgery. Prognostic and predictive factors were well identified.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
There is an increasing trend in oncology to develop organ sparing strategies which preserve patient quality of life without jeopardising survival. In experienced hands, brachytherapy remains the best modality for delivering high doses of radiotherapy, and should have a major role in the treatment of penile carcinoma, as part of a multimodal approach.
Figure 2. Example of an implantation for treatment of a penile carcinoma. Three needles were implanted in the target volume. Treatment dose was 60 Gy.
## INTRODUCTION

<table>
<thead>
<tr>
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<th>37</th>
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<tbody>
<tr>
<td>1.</td>
<td>Investigating reporting-and-learning systems of Irish radiation therapy: Can standards be improved?</td>
</tr>
<tr>
<td>2.</td>
<td>4D-MRI based evaluation of moving lung tumour target volumes</td>
</tr>
</tbody>
</table>
INTRODUCTION

In the radiation therapist (RTT) section of this congress report we want to bring three RTT abstracts to your attention. The submitted abstracts are blind reviewed by a group of 6-7 RTTs, and these three abstracts were awarded the highest scores. Each one represents a specific point of interest in radiation therapy. The three abstracts are presented to you as an overview and were randomly ordered in this report.

The first abstract "Investigating reporting-and-learning systems of Irish radiation therapy: Can standards be improved?” by Dowling et al reports on a study that identified aspects of Irish event reporting-and-learning systems wherein improvements are necessary. In the field of radiation therapy it is of importance that safety reporting systems are improved and operate at the same high level as proposed by literature. With this study the radiation therapy centres in Ireland gained insight in their compliance. Furthermore, this method can also be applied worldwide.

In the past years the benefits of the MRI have been put forward. Since patients are positioned for a prolonged period they may experience procedure-related problems. The second abstract by Düsberg et al describes treatment delivery under real-time MR-guidance. To gain insight into patient tolerance and experiences, patient-reported outcome questionnaires were distributed and collected. It appeared that the treatment was well tolerated. Only one of the 57 patients found the fraction duration time of 75 minutes unacceptably long. Anxiety remains an item that needs specific attention, two patients withdrew because of severe claustrophobia.

The third abstract focuses on motion in lung cancer irradiation. With 4D-MRI based evaluation of moving lung tumour target volumes the authors developed a workflow for 4D-magnetic resonance imaging (4D-MRI) based target volume evaluation and determination. 4D-MRI based target volume delineation appeared to be feasible and improved the detection of the tumour motion.

Hopefully these studies will contribute to the improvement of the safety and quality of radiation treatment.

On behalf of the SAG members,

Mirjam Mast
Chair, Scientific advisory group (SAG) for Radiation Technology
Investigating reporting-and-learning systems of Irish radiation therapy: Can standards be improved?

Kevin Dowling, Sarah Barrett, Laura Mullaney, Claire Poole

Applied Radiation Therapy Trinity, Discipline of Radiation Therapy, School of Medicine, Trinity College Dublin, Ireland

CONTEXT OF THE STUDY
Due to the extremely detrimental effects that incorrect treatment delivery can have on a patient’s life, error prevention is imperative in the field of radiation therapy. Reporting-and-learning systems are implemented within radiation therapy practice as a means to reactively learn from events (incidents/errors and near-misses), and thereby minimise future risk and promote patient safety. Based on literary evidence, a process map has been developed to illustrate the general stages involved in these systems [see Figure 1].

OVERVIEW OF THE ABSTRACT
The aim of this study was to identify and evaluate the reporting-and-learning systems implemented in Irish radiation therapy departments. In doing so, recommendations on methods of optimising such systems were made. By enhancing protocols followed in the aftermath of incidents and near-misses, the level of reactive learning can be increased, thereby minimising the potential for future error. The implementation of the study’s recommendations will therefore allow for an improvement in the standard of safety in the field of radiation therapy. The recommendations made are evidence-based and applicable worldwide, and as such, can enhance service quality across the globe.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
1. Considerable variation exists between the various classification/taxonomy systems used to define and analyse events. As such, the ease with which interdepartmental learning can occur is stunted.
2. Use of external reporting-and-learning systems is low. Therefore, a widespread improvement in patient safety cannot easily result from a single event that occurs, nor can the invaluable event databases of such systems be utilised to minimise future risk.
3. The dissemination of lessons-learned beyond an individual centre to wider audiences is inadequate. As a result, the positive impact event-reporting can potentially achieve is diminished, compared to if a more collaborative approach was taken.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
This study identified aspects of Irish reporting-and-learning systems wherein improvements can be made. With the implementation of the resultant recommendations, a nationwide increase in the standard of incident and near-miss management can occur. Due to their evidence-based nature, the recommendations may similarly be applied to the systems of other countries, thereby enhancing the safety-culture of radiation therapy on a global level. As the study’s methodology was designed with the aim of being applicable to international practice, it may also be used as a guide to evaluating standards in other countries. This would facilitate treatment centres to identify areas specific to them that require improvement, again allowing for wide-scale optimisation of service quality.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
The World Health Organisation has postulated that the recent rapid rate of advancements in radiation therapy practices will lead to increased potential for error. This, along with the continuing increase in worldwide cancer incidence, implies that error prevention has never been more important. EU legislation states that reporting-and-learning systems must be used, and particularly emphasises the importance of the dissemination of lessons-learned. There has, in recent years, been an increase in attention given to the risk management aspect of radiation therapy practice. This study identifies that further implementation of the ever-growing evidence-base into practice is required. In doing so, the potential risk involved in the delivery of radiation therapy can be minimised, while its overall efficacy is heightened.
2.

4D-MRI based evaluation of moving lung tumour target volumes

M. Düsberg1,2, S. Neppl1, S. Gerum1, F. Roeder1, R. Reiner1, N. H. Nicolay1,4, H.-P. Schlemmer1, J. Debus1,4, C. Thieke1, J. Dinkel6, K. Zinke1, C. Belka1, F. Kamph1

1LMU Munich, Department of Radiation Oncology, Munich, Germany; 2University of Applied Sciences Giessen, Institut für Medizinische Physik und Strahlenschutz IMPS, Gießen, Germany; 3German Cancer Research Center DKFZ, CCU Molecular Radiation Oncology, Heidelberg, Germany; 4University Hospital Heidelberg, Department of Radiation Oncology, Heidelberg, Germany; 5German Cancer Research Center DKFZ, Radiology, Heidelberg, Germany; 6LMU Munich, Institute for Clinical Radiology, Munich, Germany; 7 Comprehensive Pneumology Center (CPC) Member of the German Center for Lung Research (DZL) Munich, Germany

CONTEXT OF THE STUDY

Tumour movement induced by respiratory motion is a substantial concern during the treatment of lung tumours with External Beam Radiation Therapy.

To account for this respiratory motion in the radiation therapy planning process, the International Commission on Radiation Units and Measurements (ICRU) defines the "Internal Target Volume" (ITV), which encompasses the tumour volume in every moment, shape and position. The state-of-the-art technology for ITV determination is four dimensional computed tomography (4D-CT) which is limited in capturing daily and cycle-to-cycle variations of the breathing because of its averaging acquisition scheme and the radiation dose.

The use of four dimensional magnetic resonance imaging (4D-MRI) could be a solution to overcome these limitations. 4D-MRI allows repetitive scanning covering the complete breathing motion because no ionising radiation is involved.

OVERVIEW OF THE ABSTRACT

We used 4D-MRI technology to monitor target volumes of moving lung tumours. The diaphragm positions in the 4D-MRI and in the planning CT were used to identify corresponding positions in the respiratory cycle for the subsequent multimodal image registration.

A combination of rigid and non-rigid registration facilitated automated detection of the "Gross Target Volumes" (GTVs) on the 4D-MRI. This was used to verify the 4D-CT-based ITV-4D-CT over several breathing cycles. A 4D-MRI-based ITV4D-MRI was created covering all determined GTV positions.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?

1. The image registration techniques on the 4D-MRI yielded reliable results for verifying the motion of the GTV.
2. The proposed technique is able to detect situations in which the GTV exceeds the ITV_{4D-CT}. As an example a 4D-MRI slice at a moment of strong expiration is shown in Fig. 1. The area of the GTV that lies outside the ITV_{4D-CT} is marked in red.
3. The developed workflow is capable of defining 4D-MRI based ITV structures using multiple breathing cycles. Such ITVs contain more information about the tumour motion than 4D-CT based ITV. Fig. 2 shows a comparison of the different ITVs which were generated using the two imaging modalities.

WHAT IMPACT COULD YOUR RESEARCH HAVE?

The proposed technique can be included in the target volume definition. The results show that an integration of 4D-MRI into the treatment planning process has the potential to improve the tumour coverage. Patients may benefit from a more precise ITV definition.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?

In the last years the integration of MR imaging into the radiotherapy process is a topic of high interest. Considering the emerging MR-Linac systems, the proposed procedure could be integrated in the clinical routine. In this way, the impact of variations in the daily breathing on the position of the target volumes could be evaluated directly before irradiating the patient.
Fig 1: 4D-MRI slice at a moment of strong expiration. \( \text{ITV}_{4D-CT} \) is the ITV definition based on the 4D-CT. \( \text{GTV}_{\text{deformed}} \) is the non-rigid deformed GTV structure. In this case, the algorithm detected that \( \text{GTV}_{\text{deformed}} \) partly exceeds the \( \text{ITV}_{4D-CT} \). The missed voxels are highlighted in red.

Fig 2: Planning-CT with ITV structures based on 4D-CT and 4D-MRI, respectively. In this example the \( \text{ITV}_{4D-MRI} \) additionally includes voxels in the cranial tumor region.
Patient tolerance of stereotactic MR-guided adaptive radiation therapy: an assessment using PRO’s

Roosje Bakker, Marloes Jeulink, Shyama Tetar, Suresh Senan, Ben Slotman, Frank Lagerwaard, Anna Bruynzeel

VU University Medical Center, Amsterdam, The Netherlands

CONTEXT OF THE STUDY
MR-guided radiation therapy is a novel treatment paradigm. Although only six centres worldwide currently offer MR-guided daily plan adaptation, it is anticipated that this technique will become more widely available in the coming years. One key feature is delivery of radiation while patients are positioned for a prolonged period within the MRI bore, and therefore may experience procedure-related problems such as anxiety, noise and other MR-related undesired signals. In this study we evaluated patient experiences undergoing MR-guided stereotactic radiotherapy in the first 6 months of implementation at the VU University medical center.

OVERVIEW OF THE ABSTRACT
Since mid-2016, MR-guided radiation therapy has been implemented clinically at VUMC, using the MRIdian system (0.35 Tesla). Our workflow for each fraction includes all features of MR-guided radiotherapy, i.e. MR-guided setup, daily re-optimisation of treatment plans and gated delivery in breath-hold under MR guidance (for thoracic and abdominal tumours). Consequently, duration of all steps for a single fraction on average range from 45 minutes to 60 minutes. We designed patient-reported outcome questionnaires (PRO-Q) to gain insight into patient tolerance and experiences; results from the first 90 patients are reported.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
Three patients chose not to undergo MR-guided treatment because of claustrophobia during the simulation MRI; no patient interrupted treatment as a result of this complaint. However, as some extent of anxiety was reported by approximately 20% of patients, this remains a point of attention. Other potential MR-related undesired signals such as dizziness, local heat sensations or metallic taste sensations were very rare, with the exception of sensations of feeling cold (due to the cooling system) and excessive noise despite the use of headphones. With regard to total treatment duration, only 4 of patients (4.4%) reported this as being unacceptably long. Paresthesia, mainly due to prolonged positioning with the arms up, was also reported commonly, however usually as non-severe.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
This constitutes the first experience from the patients’ perspective in MR-guided radiotherapy. Patients were prospectively asked to report their experiences after the last fraction of treatment using a standardised, in-house developed questionnaire. The finding of anxiety, even in patients that do not experience extreme claustrophobia, indicates the importance of audio feedback to patients during the procedure. Prolonged treatment with arms up can be troublesome, which has resulted in a change in policy, treating some patients with a single arm along the body and taking this into account during planning.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
Being the first in its nature, these patient reported outcome measures may serve as a reference for future MR-guided radiotherapy reports, e.g. using 1.5 Tesla machines. This will become increasingly relevant, in regard of the rapid dissemination of this technique.
Figure: PRO-Q responses on SMART delivery by 90 patients
### INTRODUCTION

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<tbody>
<tr>
<td>1.</td>
<td>Dermatan sulfate mitigates radiation-induced oral mucositis (mouse) – biological mechanisms</td>
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<td>2.</td>
<td>Cytokine-dependent regulation of prostate cancer stem cell maintenance in response to irradiation</td>
<td>47</td>
</tr>
<tr>
<td>3.</td>
<td>Circulating exosomal miRNA related to chemoradiotherapy outcome in locally advanced rectal cancer</td>
<td>48</td>
</tr>
</tbody>
</table>
INTRODUCTION

This year for ESTRO 36 in Vienna, which is ranked by Mercer as the city with the highest for quality of living for the 8th year in a row, we again received a high number of abstracts. The concept of the radiobiology part of this ESTRO meeting was however a bit different from usual. In March 2016, a workshop in the series ESTRO presented by the Clinical Committee/Radiobiology Committee was organised by Brad Wouters and Daniel Zips to identify the top opportunities for precision radiation medicine and to set goals. Five tumour sites were chosen for discussion, based on potential opportunities for improving on current local control rates; namely breast, head and neck, prostate, colorectal and lung cancer. The 30 participants from the ESTRO clinical committee and radiobiology committee membership spent a day discussing how we could achieve improved local control within the next 5–10 years. The radiobiology programme of ESTRO 36 followed up on that concept with a pre-congress course on the clinical application of biomarkers of both normal tissue and tumour responses, as such biomarkers may become important in selecting patients for personalised medicine.

Next, we spent two days discussing the five sites in terms of normal tissue effects. First, leading experts on the state of art regarding heart, lung, gut and brain normal tissue effects presented overviews on their current standing. Next, novel approaches to pharmacological modulation, dose delivery, sparing and responses, stem cells and regeneration were presented. Since particle therapy is particularly aimed at sparing normal tissue, a special session was focussed on their biological effects, RBE, and novel tumour and normal tissue models. To link the normal tissue aspects to the subsequent two days of tumour biology, a session was organised where preclinical models combining both (orthotopic) tumour and relevant normal tissue were considered, very relevant for assessment of the efficacy of novel drugs as radiosensitising agents and potential translation to the clinic. In the final two days of the meeting, the programme focussed on the above-mentioned tumour sites in further attempt to review current standing and upcoming and novel approaches to enhance tumour response. The radiobiological opportunities for head and neck, prostate, thoracic, colorectal and poorly controlled tumour sites were considered. The whole programme was melded together with a teaching lecture on topics on novel developments in radiobiology, such as gene editing, the use of 3D organoids, targeting histones and extracellular vesicles in radiation oncology, all emerging fields of which a lot is expected in the future. The last closing symposium addressed in general novel approaches on tumour vaccination and molecular therapies for paediatric tumours, so it was certainly be worthwhile staying until the end.

In addition to all these preselected presentations, even more exciting were the large number of abstracts that we received from scientists from 25 different countries from all over the world showing that ESTRO 36 is more than a European meeting. Emerging fields/techniques in radiobiology, such as normal and tumour stem cell research, proteomics and transcriptomics and (circulating) microRNA studies have been well represented. From these I would like to highlight three selected preferred presentations which interest me personally. First, a home game from Silvia Gruber who presented on “Dermatan sulfate mitigates radiation-induced oral mucositis (mouse) – biological mechanisms”, indicating that strengthened epithelial anchorage and the modulation of inflammatory processes underlie dermatan sulfate’s protective effects. Next, Claudia Peitzsch from Dresden’s presentation on “Cytokine-dependent regulation of prostate cancer stem cell maintenance in response to irradiation” is very interesting, where she showed that the combination of irradiation with CXCR4-CXCL12 signaling modulation increases therapeutic potential, and expression levels might be used for prediction of response in prostate cancer patients. Sebastian Meltzer, from Oslo’s presentation on “Circulating exosomal miRNA related to chemoradiotherapy outcome in locally advanced rectal cancer” showed nicely where the field is moving to, as his data showed the potential use of plasma exosomal miRNAs to predict both CRT response and survival in patients with advanced rectal cancer. With this programme, we have tried to highlight new developments in the hope that more people will implement them and keep our radiobiology research at the cutting edge of science. We hope to indicate where radiobiology is heading in the near future and hope to motivate ESTRO members to potentially translate these biological findings to the clinic.

Rob Coppes
Chair, Scientific advisory group (SAG) for radiobiology
Dermatan sulfate mitigates radiation-induced oral mucositis (mouse) – biological mechanisms

S. Gruber1,2, E. Bozsaky1,2, K. Frings1, M. Arnold1, V. Gernedl1, S. Hetzendorfer1, J. Mayer1, S. Morava1, S. Pfaffinger1, P. Kuess2, W. Dörr1

1 ATRAB - Applied and Translational Radiobiology; 2 Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Department of Radiotherapy, Medical University of Vienna, Vienna, Austria

CONTEXT OF THE STUDY
Oral mucositis represents the most frequent, often dose-limiting early side effect of radio(chemo)therapy of advanced head-and-neck tumours. Despite a plethora of preclinical and clinical research, no biology-based treatment strategy has been implemented into clinical routine to date. Currently, symptomatic treatment mainly focuses on oral hygiene, antibiotic therapy and pain management.

OVERVIEW OF THE ABSTRACT
With the onset of radiotherapy, a variety of biological processes are induced in (oral) mucosal tissues, including a reduction in cell proliferation and consequent hypoplasia/ulceration, local hypoxia and inflammation. Dermatan sulfate (DS) targets many of these processes. Therefore, the mucoprotective potential of this drug was assessed and the underlying biological mechanisms were investigated in the established mouse tongue model. Fractionated irradiation was performed with 5x3 Gy/week over one or two weeks, followed by graded top-up doses to generate complete dose-effect curves for ulcer induction. DS was administered over varying time intervals. Immunohistochemical studies were performed for mechanistic studies.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
DS significantly increased the isoeffective doses for ulcer induction in almost all protocols. DS furthermore prolonged the latency to epithelial ulceration and reduced the time to ulcer healing.

The radiation-induced increase in the expression of adherens junction proteins (e-cadherin and β-catenin) and tight junction proteins (claudin, occludin) occurred significantly earlier and in a more pronounced manner with additional DS treatment. A representative histophotograph of DS-modulated occludin expression is shown in figure 1.

The expression of the inflammatory markers IL-1β and NF-κB increased substantially during irradiation alone. DS treatment significantly inhibited the increase of IL-1β. In contrast, no systematic effect on the expression of NF-κB was observed.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
The evaluation of radiation-induced modulation of signalling pathways involved in the clinical manifestation of oral mucositis, e.g. by specific drugs, is of major (radio)biological relevance. It may permit the identification of early biomarkers of the severity of the response, e.g. in mucosal smears. Moreover, new, biologically targeted prophylactic strategies, such as DS, may be developed. However, potential tumour-protective effects of DS need to be excluded before implementation into clinical practice. If selectivity is proven, then DS would represent a novel approach for the alleviation of radiation-induced oral mucositis, to be tested in clinical studies.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
The vast majority of radiobiological investigations focus on intensification of tumour effects. In contrast, studies into selective, biology-based strategies for normal tissue protection or mitigation are just beginning to gain increasing attention. However, despite highly conformal radiotherapy techniques, in curative treatment settings, substantial volumes of normal tissues must inevitably be exposed to marked radiation doses, thus posing a certain risk for adverse events, which significantly impact on the patients' quality of life. Normal tissue protective or mitigating strategies thus will broaden the therapeutic window and can contribute to improve the therapeutic outcome.

Fig.1: Epithelial occludin expression, day 14, after two weeks of fractionated irradiation, without/with additional DS administration starting at day -3 before the onset of irradiation
2.

Cytokine-dependent regulation of prostate cancer stem cell maintenance in response to irradiation


National Center for Tumour Diseases Dresden (NCT), supported by the German Cancer Research Center (DKFZ, Heidelberg), c/o OncoRay–National Center for Radiation Research in Oncology, Medical Faculty Carl Gustav Carus, Technische Universität Dresden, Germany

CONTEXT OF THE STUDY
Intratumoural heterogeneity describes the different phenotypical features and functional properties of malignant cells within a particular tumour and is one of the main factors impacting on tumour growth, metastasis and therapy resistance. The source of this cellular heterogeneity is the flexible adaptation of cancer cells to changing microenvironmental conditions (e.g. lack of oxygen, nutrients, and immune cell attack) or anti-cancer therapies. On the cellular level, this process is driven by the Darwinian evolution concept (‘survival of the fittest’) in combination with the hierarchical organisation of tumour cells with cancer stem cells (CSC) at the apex of this tumour hierarchy. According to the CSC model of tumour development, CSCs are thought to be at the apex of the cellular differentiation tree possessing the highest self-renewal capacity and largest differentiation potential. This means that one single CSC has the potential to initiate tumour relapse and cancer cure can only be achieved through the eradication of all potential CSCs. Novel findings indicate that this strict linear differentiation from undifferentiated CSCs via transient progenitor cells to fully differentiated malignant cells is modified in several tumour entities (e.g. prostate or breast cancer). In parallel to the linear differentiation, it was shown that non-CSCs are able to transdifferentiate into cells with stem cell-like properties. Moreover, different CSC clones with different phenotypes and properties (e.g. quiescent, highly proliferative or migratory) can exist within one tumour. This cellular plasticity of CSCs is challenging for the development of specific therapeutic targeting strategies.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
1. The aldehyde dehydrogenase (ALDH)-positive CSC population in PC is highly radioresistant with enhanced DNA repair capacity and reduced production of reactive oxygen species (ROS) and is maintained directly via the Wnt/β-catenin signaling pathway
2. Ionising radiation induces and selects CSCs in a dose- and time-dependent manner and this cellular plasticity is regulated via modulation of the histone methylation code
3. Stem cell-like and radioresistant properties of prostate cancer cells are regulated via a CXCR4-dependent mechanism implicating a predictive and/or therapeutic potential

WHAT IMPACT COULD YOUR RESEARCH HAVE?
CSC-targeting therapies in combination with conventional radio/chemotherapy or surgery can increase efficacy of cancer treatment. Unfortunately, clinical studies indicating that these CSC-targeting strategies exhibit high toxicity rates due to the targeting of e.g. self-renewal signalling (e.g. Wnt, notch, hedgehog), important for the maintenance of normal stem cells. Further pre-clinical research is necessary to identify CSC-specific regulatory mechanisms and markers to circumvent this toxicity issue. In addition, pre-clinical studies at the single cell level are necessary to unravel the molecular and cellular mechanisms involved in the IR-induced cellular plasticity and to identify therapeutic targets to prevent the IR-induced trans-differentiation of non-CSCs into CSCs.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
Deeper understanding of the molecular and cellular mechanisms involved in cancer cell resistance, in metastasis formation or in tumour heterogeneity is necessary to identify specific therapeutic targets and/or predictive biomarkers for patient stratification and adaptation of treatment schedules according to the specific tumour characteristics of each individual patient to improve cancer cure rates.

OVERVIEW OF THE ABSTRACT
Within the present study we hypothesised that CSCs are the major cell population within prostate cancer (PC) responsible for therapy resistance and that the evaluation of CSC-specific markers in pre-treatment biopsies of PC patients is of predictive value. Surprisingly, we found that ionising radiation (IR) could induce CSCs and that this observed IR-induced cellular plasticity was regulated via an epigenetic mechanism based on changes within histone methylation marks. In addition, we found a cytokine-dependent regulatory mechanism based on the chemokine receptor CXCR4 signaling pathway involved in this CSC regulation.
3.

Circulating exosomal miRNA related to chemoradiotherapy outcome in locally advanced rectal cancer

Sebastian Meltzer1,2, Lars-Gustav Lyckander1, Anne Hansen Ree1,3, Kathrine Røe Redalen1

1Department of Oncology, Akershus University Hospital, Lørenskog; 2Department of Pathology, Akershus University Hospital, Lørenskog; 3Institute of Clinical Medicine, University of Oslo, Oslo

CONTEXT OF THE STUDY
In cancer management, several treatment modalities can be used based on the clinical presentation and biological characteristics of the tumour. In this project, we looked at patients with rectal cancer who were referred for radiation and chemotherapy before surgery. Some of the patients had cancers that had already spread to the liver at the time of diagnosis.

Exosomes are small vesicles secreted by cells. Traditionally viewed upon as waste, they are now acknowledged as cellular postmen that send biological cargo between cells as a means of communication. Exosomes are known to be very stable, keeping their characteristics and contents unchanged when stored or treated for scientific purposes. This makes them particularly interesting in a research setting, making scientific methods and results more reliable. In exosomes, you can find proteins, DNA and signal gene material that can be traced back to the cell of origin. One type of signal genes called microRNAs have been found to be involved in the development and aggressiveness of several cancer types.

OVERVIEW OF THE ABSTRACT
Exploring markers of tumour aggressiveness and treatment resistance, and at the same time hoping to gain insight into biological mechanisms underpinning these traits, we looked at microRNAs in circulating exosomes. In a biomarker setting, microRNAs are interesting because they are simultaneously both markers of disease and possible targets for treatment. We have used a broad microRNA panel to analyse exosomal microRNA content, and selected three microRNAs based on their strong link to systemic spread of the disease, and radiotherapy resistance.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
In our panel of exosomal microRNA we found two microRNAs that were associated with radiotherapy resistance. Lower expression of miR-20b-3p and miR-301a-3p reflected a poor treatment outcome, as measured by the tumour regression grade (TRG, see figure), after preoperative chemoradiotherapy. High levels of a third microRNA, miR-141-3p, were strongly associated with spread of the cancer to the liver at the time of diagnosis. Further, medium-high levels of this microRNA were associated with rapid development of liver metastasis shortly after chemoradiotherapy and surgical removal of the primary tumour. The association between miR-141-3p and liver metastasis has been validated in an independent patient cohort.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
In rectal cancer management, the precision of the diagnosis is crucial for optimal treatment results. A reliable marker of systemic spread of the disease could increase precision and influence the choice of treatment, as well as give insight to the aggressive traits of the tumour biology. Here we have shown an association between factors readily available in patient blood samples at the time of diagnosis, and tumour aggressiveness and treatment outcome. In addition to being markers of tumour traits, our discoveries could represent potential targets for treatment of these patients.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
Currently around 15,000 markers of the biology of different diseases exist, of which less than 0.1% are in use in clinical practice. Besides lack of sensitivity and specificity, stability and reproducibility of the markers remain a major challenge. A massive hunt for disease biomarkers is underway, with exosomes and their content among the latest. Exosomal microRNA, in addition to providing insight into the biological mechanisms in cancer development and progression, are possible treatment targets. For several microRNAs, targeting agents have already been developed and are under evaluation, presenting promising results in a spectrum of diseases including cancer. MicroRNA thus represents a promising new area of research not only in cancer treatment.
microRNA expression and tumour regression grade (TRG)

miR-20b-5p

miR-301a-3p

miR-141-3p, liver metastasis at diagnosis, or rapid progression after treatment

**LIFETIME ACHIEVEMENT AWARDS**

- Annette Bøjen (DK)
- Alan Effraim Nahum (UK)
- Jens Overgaard (DK)
- Hans Peter Rodemann (DE)
- Paul Van Houtte (BE)

**ESTRO AWARD LECTURES**

**Emmanuel van der Schueren award**
"Substantial and “for free” improvement of radiotherapy practice in high and low income countries”
Ben Heijmen (NL)

**Iridium award**
"Brachytherapy physics developments: look back in anger, grateful, and with hope”
Jack Venselaar (NL)

**Honorary physicist award**
"Cognitive perspective in the radiation oncology physics domain”
Vincenzo Valentini (IT)

**Honorary member’s award**
"Optimising the treatment of HPV-related oropharyngeal cancer: the difficult journey back”
Brian O’Sullivan (CA)

- "Potential of radiation therapy to convert the tumour into an in situ vaccine”
  Silvia Formenti (USA)

- "Quality improvement in radiotherapy: history, significance and impact of dosimetry audits”
  Joanna Izewska (AT)

**Regaud award**
"More than one century after the serendipitous discovery of X-rays, there is still a bright future for radiation oncology…”
Jean Bourhis (CH)

**Klaas Breur award**
"The 5 R(elevant) principles of radiotherapy in multimodal cancer treatment”
Claus Rödel (DE)

**Donal Hollywood award**
"In vitro prediction of DNA repair defects reveals association with poor clinical outcome in HNSCC”
Paul Essers (NL)

**ESTRO - ELSEVIER AWARD LECTURE**

**Jens Overgaard legacy award**
“Individual patient data meta-analysis in head and neck cancer: an international and multidisciplinary collaboration”
Jean Pierre Pignon (FR), Jean Bourhis (CH), Pierre Blanchard (FR)

**ACADEMIC AWARD LECTURE**

**Jack Fowler University of Wisconsin Award**
"Dosimetric quantification of the incidental irradiation of the “true” (deep) ano-inguinal lymphatic drainage of anal cancer patients not described in conventional contouring guidelines”
Hendrik Dapper (DE)

**COMPANY AWARD LECTURES**

**ESTRO-Accuray Award**
“Limited interfractional variability of respiration-induced tumour motion in esophageal cancer RT”
Peng Jin (NL)

**ESTRO-Varian Award**
“Trajectory Optimisation in Radiotherapy Using Sectioning (TORUS)”
Christopher B Locke (USA)

**ESTRO-Elekta Brachytherapy Award**
“Testing an MR-compatible afterloader for MR-based source tracking in MRI guided HDR brachytherapy”,
Ellis Beld (NL)

**GEC-ESTRO Best Junioir Presentation Elekta Award**
“Improved class solutions for prostate brachytherapy planning via evolutionary machine learning”
Stefanus C. Maree (NL)

**BEST POSTER AWARDS**

**Radiation Oncologist**
"Tumor Regression Grading in the CAO/ARO/AIO-04 phase 3 trial in locally advanced rectal carcinoma”
Emmanouil Fokas (DE)

**Physicist**
“A pencil beam algorithm for protons including magnetic fields effects”
Fatima Padilla (AT)
Radiation Therapist (RTT)
“Comparison of 3 Image-guided Adaptive Strategies for Bladder Radiotherapy”
Vickie Kong (CA)

ESTRO – ELSEVIER BEST POSTER AWARDS

The three ESTRO-Elsevier open access journals: ctRO (clinical), phiRO (physics) and tipsRO... also awarded the best poster in their category as follows:

ctRO
Radiation Oncologist
“Factors associated with complete response after brachytherapy for rectal cancer; the HERBERT study”
Eva Rijkmans (NL)

phiRO
Physicist
“LRPM for fast automated high quality treatment planning – towards a novel workflow for clinicians”
Rens van Haveren (NL)

tipsRO
Radiation Therapist (RTT)
“Feasibility of stereotactic ablative radiotherapy for locally-advanced non-small cell lung cancer”
Katrina Woodford (AU)

Details on the best poster awardees will be presented in the July-August issue of the newsletter.
On the following pages you can find summaries of reports by authors of abstracts which were selected for some of the award sessions at ESTRO 36.

**Donal Hollywood Award**

“*In vitro* prediction of DNA repair defects reveals association with poor clinical outcome in HNSCC”
Paul Essers (NL)  

**Jack Fowler University of Wisconsin Award**

“Dosimetric quantification of the incidental irradiation of the “true” (deep) ano-inguinal lymphatic drainage of anal cancer patients not described in conventional contouring guidelines”
Hendrik Dapper (DE)  

**ESTRO-Accuray Award**

“Limited interfractional variability of respiration-induced tumour motion in esophageal cancer RT”
Peng Jin (NL)  

**ESTRO-Varian Award**

“Trajectory Optimisation in Radiotherapy Using Sectioning (TORUS)”
Christopher B Locke (USA)  

**ESTRO-Elekta Brachytherapy Award**

“Testing an MR-compatible afterloader for MR-based source tracking in MRI guided HDR brachytherapy”
Ellis Beld (NL)  

**GEC-ESTRO Best Junior Presentation Elekta Award**

“Improved class solutions for prostate brachytherapy planning via evolutionary machine learning”
Stefanus C. Maree (NL)
In vitro prediction of DNA repair defects reveals association with poor clinical outcome in HNSCC

P. Essers, C. Verhagen, M. Van der Heijden, Michiel Van den Brekel, H. Bartelink, M. Verheij, C. Vens

Netherlands Cancer Institute, The Netherlands

CONTEXT OF THE STUDY
During their development, tumours often develop defects in the machinery that repairs damage to their DNA. On the one hand, this can lead to an accumulation of unrepaired mutations, resulting in progression of the tumour. On the other hand, this makes tumour cells particularly sensitive to DNA damaging agents, such as chemotherapy and radiotherapy, as well as novel drugs that further impair DNA repair.

OVERVIEW OF THE ABSTRACT
It is currently not possible to determine whether DNA repair defects (DNA-RD) are present in a tumour from a biopsy alone. We aimed to develop a method to identify cells with DNA-RD based on their gene expression.

In a panel of cell lines we determined both sensitivity to the DNA damaging agents mitomycin C and olaparib, as a measure for DNA-RD, and gene expression profiles. We then used machine learning techniques to make a predictive model that uses gene expression as input to predict the presence of DNA-RD.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
We found regulation of genes characteristic for activation of the DNA damage response (DDR) in the cell lines with DNA-RD. This is presumably due to the presence of unrepaired DNA damage, which would keep the DDR constantly activated. It was possible to predict DNA-RD based on expression of these genes in other cell lines and breast cancer xenografts.

We used the predictive model to find DNA-RD in a cohort of head and neck squamous cell carcinoma (HNSCC) patients. Although these patients were treated with chemo- and radiotherapy, the patients with the highest probability of having DNA repair defects had worse prognosis. This suggests that the danger of mutation accumulation in repair defective tumours outweighs their sensitivity for the DNA damaging agents used in current treatment.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
To accurately assess the therapeutic potential of novel drugs, selection of the patients most likely to benefit is essential.

Predicting DNA-RD in tumour biopsies from gene expression would enable easy pre-selection of patients for trials with DNA repair inhibitors such as olaparib. Our finding that tumours with olaparib-sensitive like gene expression show poor prognosis with the current treatment suggests that their prognosis could be greatly improved by treatment with DNA repair inhibitors.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
The paradigm of personalised medicine is that each patient should receive treatment based on the characteristics of his or her tumour. Using RNA sequencing, highly detailed information on the status of biological processes in the tumour can be captured. Combined with advances in machine learning technology, this has made it possible to predict complex phenotypes based on interactions between high numbers of genes. Efforts such as the current study are important to allow precise phenotyping of tumours to determine the best course for treatment.
Dosimetric quantification of the incidental irradiation of the “true” (deep) ano-inguinal lymphatic drainage of anal cancer patients not described in conventional contouring guidelines

Hendrik Dapper, Gregor Habl, Michael Mayinger, Markus Oechsner, Stephanie E. Combs & Daniel Habermehl

Department of Radiation Oncology, Klinikum rechts der Isar, Public Law Institution, Munich, Germany

OVERVIEW OF THE ABSTRACT
The ano-inguinal lymphatic drainage (AILD) to the inguinal lymph nodes is located in the subcutaneous adipose tissue on the medial thigh. Currently contouring guidelines suggest delineation of the primary tumour region, the mesorectum, inguinal and iliac lymph nodes but do not advise the inclusion of the “true” AILD. Particularly for high risk patients it could be important to include the AILD in the target volume to prevent disease recurrence. We performed a retrospective analysis of the incidental dose to the AILD in treatment plans of anal cancer patients that were treated according to current guidelines (Fig. 1). We found that the incidental dose to the AIDL, especially the caudal parts, did not equate to that required for an elective treatment dose. This may result in worse loco-regional control.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
1. Mean V30, V40, V45, V50 and Mean dose to AILD was 71%, 55%, 45%, 31% and 5.5%, respectively.
2. At least 71% of the volume of the expected AILD received at least a dose of 30Gy which would be required for elective treatment incidentally.
3. The caudal parts of the created volumes in particular which are a considerable distance from the PTV, received an insufficient dose.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
This research could help to specify recommendations for treatment of anal cancer patients. Including the AILD in contouring guidelines could help to prevent relapse in high risk patients and might even improve overall survival. This approach could be included in prospective studies to quantify inguinal relapse rates and toxicity.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
The lymphatic drainage is not always just located next to the big vessels but also in small vessels in the subcutaneous adipose tissue. Because they are invisible on CT-scan with individual variation such micro-anatomical structures are often disregarded in the definition of target volumes. Despite this, lymph node vessels often receive a required elective treatment dose because of CTV-PTV-expansion. In anal cancer patients especially, the AILD is of great interest because lymph node metastasis occurs in even low stage cancer. The increased use of IMRT, VMAT and TOMO-therapy leads to changes in dose distribution with for example a steep dose drop at the edge compared with less conformal 3D-techniques. This could have an influence on locoregional control in other tumour entities e.g. the axilla in breast cancer.
Figure 1. Definition of the ano-inguinal lymphatic drainage at the level of the cranial end of the tuberosum minor (0.5 cm below the caudal end of the anus).
Limited interfractional variability of respiration-induced tumour motion in esophageal cancer RT

Peng Jin, Maarten C.C.M. Hulshof, Niek van Wieringen, Arjan Bel, Tanja Alderliesten

Academic Medical Center, The Netherlands

OVERVIEW OF THE ABSTRACT
The primary tumour of oesophageal cancer moves freely relative to the bony anatomy during radiation therapy due to respiration. The motion amplitude and variability of the amplitude are key uncertainties in radiation dose delivery. The purpose of our research was to investigate the interfractional variability, i.e., from day to day, of the respiration-induced motion of the oesophageal tumour. Because of the limited soft-tissue contrast in CT and cone-beam CT (CBCT) scans, we implanted fiducial gold markers around the primary tumor for improved visualisation. With the help of 4D-CBCT scans, which were acquired prior to the daily treatment, we could quantify the respiration-induced marker motion relative to the bony anatomy on the treatment days (Figure 1).

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
• As shown in Figure 2, the interfractional mean amplitude and variability of amplitudes were found to be significantly larger in the cranial-caudal direction compared to that in the left-right and anterior-posterior directions. They were also found to be significantly larger for the distal oesophagus and proximal stomach than the proximal and middle oesophagus (p<0.05).
• The standard deviation of the marker motion amplitudes and marker positions at the inhalation and exhalation breathing phases were ≤2.1mm in all the three directions. These findings suggest a small interfractional variability of amplitudes and stable motion trajectory shape.
• The interfractional variability of amplitudes and trajectory shape were found to be correlated with the interfractional mean amplitude (Fig. 3). This implies that the amplitude of the respiration-induced motion plays a role in the interfractional variability. Some other factors such as abdominal filling might also affect the interfractional variability.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
This research, based on the use of fiducial gold markers and 4D-CBCT imaging, presents novel findings that can guide the improvement of oesophageal cancer treatment. It showed that the interfractional variability of the respiration-induced tumour motion in terms of amplitude and trajectory shape was quite limited. It suggests that a single planning 4D-CT could be sufficient for predicting the respiration-induced motion over the treatment course. In addition, it suggests that the margin that is required to take into account the respiration-induced tumour motion needs to be anisotropic (i.e. larger in the cranial-caudal direction than in the left-right and anterior-posterior directions) and its size should be dependent on the tumor location in the oesophagus.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
This research falls within the field of image guided adaptive radiation therapy and is part of our oesophageal cancer research line in which we investigate the geometrical uncertainties and new techniques (e.g., marker implantation, novel imaging modalities) to decrease the uncertainties in oesophageal cancer radiation therapy as much as possible. By quantifying the interfractional tumour position variation and intrafractional tumour motion with its day-to-day variability, we are aiming to derive a fact-based margin recipe to compensate for the geometrical uncertainties to ensure sufficient target coverage and spare the organs at risk as much as possible in the meantime.
Figure 1 Example of 4D-CBCT at end of inhalation (top row) and end of exhalation (bottom row) breathing phases (green) overlaid on the 3D planning-CT (purple) with both scans registered on vertebrae. The arrow indicates the position of a marker.

Figure 2 Illustration of the average trajectory (black lines) and the 95% confidence interval of the mean marker positions (grey area) of the markers throughout the breathing cycle in the four regions of the esophagus. The trajectories are projected on the coronal (left) and sagittal (right) views of the schematic esophagus drawing. Note: the trajectories and the 1.0 mm scale are not scaled to the esophagus drawing.

Figure 3 Interfractional mean amplitude versus interfractional variability measured by the standard deviation (SD) of (left panel) the amplitudes of respiration-induced motion, (middle panel) the marker positions at the end of inhalation, and (right panel) the marker positions at the end of exhalation, in the left-right, cranial-caudal, and anterior-posterior directions.
OVERVIEW OF THE ABSTRACT
IMRT/VMAT relies upon inverse optimisation techniques and cost function minimisation as a primary means to create treatment plans. We often blindly accept that our mathematical search has found a global cost minimum and that our algorithms are robust in finding an optimal modulated plan. Thousands of patients are treated every day assuming our plans are of the highest possible quality. Our research finds that this is often not the case. By developing a sophisticated forward planning technique (TORUS) to help determine optimal trajectories and arcs, traditional inverse optimisation approaches can be intelligently primed and guided to more reliably find a better cost minimum and a more optimal plan for our patients.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
1. The common Progressive Resolution Optimization (PRO) approach to VMAT often results in MLC aperture forming contention issues due to the initial coarse sampling of control points. For complex targets and avoidance of normal anatomy, this results in MLC confusion and excessive exposure of healthy tissue. The TORUS approach to radiation trajectory optimisation generates trajectories which specifically avoid such MLC contention, resulting in plans which improve sparing to organs at risk for tumour geometries that are complex from the beam’s eye view.

2. When applied to chest-wall (see figure) and scalp cases with static couch and collimator, the TORUS arcs have shorter delivery times, improved organ at risk sparing, dose conformity, and homogeneity compared to traditional 7 field IMRT and 2 arc VMAT plans.

3. Dosimetric improvements can be achieved for many treatment sites without having to introduce dynamic couch or collimator. Smart choices of gantry starting and stopping angles, and static collimator and jaw coordinates are enough to achieve improvement.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
TORUS is a new approach to trajectory optimisation in radiotherapy that uses a novel graph optimisation technique. The unexplored potential with this approach could spark renewed interest in research of graph approaches in radiotherapy treatment planning.

The quality of plans possible when using TORUS can improve substantially, bringing an expected reduction in morbidity and toxicity in radiotherapy.

The TORUS algorithm’s heuristic approach to generating trajectories closely approximates decisions that expert planners make in the early stages of forward planning complex plans. Therefore, if this approach were to be integrated into a commercial planning system we expect an improvement in plan quality from less experienced planners who then have the ability to create expert plans easily, raising the standard of treatment for some treatment sites.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
Dynamic gantry treatments have become very common in practice over the last eight years in radiotherapy due to the introduction of VMAT. This trend toward increasing the dynamic capabilities of treatments to improve quality of treatment is also evident in the increasing popularity of robotic arm radiosurgery.

The next logical step forward for C-arm delivered plans is to enable dynamic motion of the collimator head and/or the patient couch. However, one difficulty in such dynamic trajectory optimisations is that total search space is vastly too large for current inverse optimisation techniques alone. Trajectory optimisation research today predominantly focuses on reducing the optimisation space to that of conventional VMAT by heuristically determining gantry, couch, collimator motion which makes up the trajectory geometry. TORUS is a new heuristic approach to this optimisation problem.
Currently, no accurate verification of the actual delivered dose in high-dose-rate (HDR) brachytherapy exists. However, verification is highly important for accurate and safe dose delivery, especially if a high dose is given in a single fraction. In this study, we focus on developing a method for verification of HDR brachytherapy based on MRI guidance of the source during dose delivery.

OVERVIEW OF THE ABSTRACT
This study proposes a method for real-time MRI-guided HDR source tracking for HDR brachytherapy verification. To introduce MRI-guided HDR source tracking, an important requirement is that MR imaging should be possible with the afterloader positioned aside the patient and the MRI scanner, while controlling the delivery of the HDR source to the predefined dwell positions. A prototype MR-compatible afterloader was tested, while operating simultaneously with MR imaging. The goal was to test the concurrent functioning of both the afterloader and MR imaging, together with a method for real-time HDR source position verification.

WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?
First, the research demonstrated that the recently developed MR-compatible afterloader and the MRI scanner fully functioned, while operating simultaneously; the afterloader was able to drive the HDR source to the predefined dwell positions while MR images were acquired.

Second, the source positions could be determined from the MR images by the localisation method. The short dynamic scan time (~0.15 s per image) and the fast reconstruction and post processing (<0.15 s) guarantee the ability of real-time source localisation.

Last, these results demonstrate that our developed method, real-time source localisation in combination with application of the MR-compatible afterloader, can be applied for real-time treatment verification of HDR brachytherapy.

WHAT IMPACT COULD YOUR RESEARCH HAVE?
Our research stimulates the development of an MR-compatible afterloader. Once it can be introduced into clinical practice, it would enable us to verify the actual dose delivered to the tumour. It would increase the safety of the treatment, because possible human errors, for example incorrect catheter reconstruction or incorrect catheter connection, can be detected to stop the treatment directly. Also, when using a dummy source, we can apply the described method for catheter reconstruction, eliminating the sometimes difficult and inaccurate manual reconstruction procedure, thereby increasing the accuracy. Moreover, the accuracy also increases when combining it with adaptive treatment planning.

IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?
In the field of HDR brachytherapy, considerable research has been conducted on both image guidance and on verification of the treatment. Advanced image guidance is important and developments have led to an increased application of MRI. Furthermore, a trend exists in research into methods for verification of HDR brachytherapy, for example electromagnetic (EM) tracking and in-vivo dosimetry. So, yes, MRI guidance and real-time treatment verification are indicative of a bigger trend in the HDR brachytherapy field. However, real-time MRI guided HDR brachytherapy source tracking is a unique combination.

More generally, the use of MRI for radiotherapy purposes has gained an increased interest in the past years. In our department, the main research focus is on MRI guided radiotherapy with the development of an MR-compatible afterloader and an MR-linac.
Figure 1. Experimental set-up with the prototype MR compatible afterloader placed next to the MRI scanner, a phantom placed inside the MR bore and the afterloader connected to a tube positioned in the phantom.

Figure 2. Sagittal slices (a and d) and coronal slices (b and e) presenting the MR artifacts induced by the HDR source for the case where the afterloader sent the source (I) to 10 dwell positions with a 10 mm step size (a-c) and (II) to 20 dwell positions with a 5 mm step size (d-f). The determined HDR source dwell positions for the depicted positions (position 5 in a-b and position 9 in d-e) are overlaid in red and the other determined dwell positions are overlaid in yellow. Figures c and f show the distances of the HDR source positions determined with respect to the first position, calculated from the 3D coordinates (with average determined step sizes of 9.9±0.2 mm and 5.0±0.2 mm respectively).
When treating prostate cancer patients using brachytherapy, the treatment must be planned in limited time, as the patient is waiting with the catheters implanted. Multiple optimisation algorithms are available to simplify and speed up the treatment planning process. In these algorithms, the user has to set parameters to give a weight to the many different treatment planning objectives. These parameters are patient specific, which make setting them a difficult and delicate task. To this end, an initial parameter set is used for all patients, called a class solution, which is then adapted per patient. The better the class solution, the less manual fine-tuning is required. We used evolutionary machine learning to automatically find the best class solution for a dataset of previously accepted treatment plans.

To demonstrate our method, we find class solutions for the well-known IPSA optimisation algorithm, based on a dataset of 20 previously treated patients, of which the treatment plans were created by manual graphical optimisation. Using our method, we first automatically find for each individual patient separately the IPSA parameter set (IPSA-I) such that the resulting plan replicates the associated treatment plan as well as possible. Then, a first class solution (CS-M) is created by calculating the mean of the IPSA-I parameters. We further use our method to directly find a class solution (CS-S) by aiming it at minimising the sum of plan differences for multiple patients simultaneously. We compare our findings with the current clinical class solution (CS-C).

First, we demonstrated that it is possible, by applying evolutionary machine learning to IPSA parameters, to replicate with IPSA treatment plans that were created manually with a plan difference of 3%, representing a 0-3% difference in the measured DVH indices on average, as shown in the figure. Second, for 13 of 20 patients, the class solution found using evolutionary machine learning outperforms the other two class solutions. Finally, and most important, we observe a big gap between the individually optimised treatment plans IPSA-I, and all of the class solutions.

The large performance gap between patient-specific optimization IPSA-I and the class solutions shows that there is still much room for improvement by moving towards a patient-tailored approach for automated brachytherapy treatment planning. Our work achieves a first step in that direction.

The use of data and statistics in oncological research has been one of the founding pillars for decades, but only recently, as more and more data becomes available and data sharing is encouraged, the application of techniques from fields such as machine learning become feasible, providing new insights and unlocking new possibilities. Our work in brachytherapy contributes to these new developments that are more and more accepted and applied in oncology and in the clinic in general.
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