UNIVERSITEIT GENT

Faculty of Medicine and Health Sciences

Department of Radiation Oncology and Experimental Cancer Research

Introducing Intensity Modulated Arc Therapy in the multimodality treatment of pelvic gynaecological tumours: Thinking out of the box.

Katrien Vandecasteele

2012

Promotor:
Prof. Dr. Gert De Meerleer
Co-Promotor:
Prof. Dr. Wilfried De Neve

Thesis submitted in fulfilment of the requirements
for the degree of Doctor in Medical Sciences

Promotor:
Prof. Dr. Gert De Meerleer (Universitair Ziekenhuis Gent)

Co-promotor:
Prof. Dr. Wilfried De Neve (Universitair Ziekenhuis Gent)

Chairman of the examination commission:
Prof. Dr. Carlos De Wagter (Universitair Ziekenhuis Gent)

Examination commission:
Prof. Dr. Tom Boterberg (Universitair Ziekenhuis Gent)
Prof. Dr. Geert Braems (Universitair Ziekenhuis Gent)
Prof. Dr. Véronique Cocquyt (Universitair Ziekenhuis Gent)
Prof. Dr. Eric De Jonge (Ziekenhuis Oost-Limburg)
Prof. Dr. Ingeborg Goethals (Universitair Ziekenhuis Gent)
Prof. Dr. Marc Mareel (Universitair Ziekenhuis Gent)
Prof. Dr. Erik Van Limbergen (Universitair Ziekenhuis Leuven)

Table of contents

Abbreviations

aPFS	abdominal progression free survival
^{18}FDG-PET	2-deoxy-2-[18] fluoro-D-glucose positron emission tomography
ACRIN	American College of Radiology Imaging Network
APPA	AnteroPosterior-PosteroAnterior
BED	Biological Equivalent Dose
BT	Brachytherapy
CA	Cancer Antigen
CBCT	Cone Beam CT
CC	Cervical Cancer
CRT	Chemoradiation
CSS	Cause Specific Survival
CTC	Common Toxicity Criteria
CTV	Clinical Target Volume
DC	Distant Control
DCE	Dynamic Contrast Enhanced
DFS	Disease Free Survival
EBRT	External Beam Radiation Therapy
EC	Endometrial Cancer
EH	Extrafascial Hysterectomy
EOC	Epithelial Ovarian Cancer
EPI	Electronic Portal Imaging
EPID	Electronic Portal Imaging Device
FIGO	International Federation of Gynaecology and Obstetrics
GI	Gastro-Intestinal
GTV	Gross Tumour Volume
GU	Genito-Urinary
GUH	Ghent University Hospital
HIF 1-α	Hypoxia-Inducable Factor 1-α
HUN	Hydro-uretronephrosis
IGABT	Image Guided Adaptive Brachytherapy
IM	Intensity Modulated
IMAT	Intensity Modulated Arc Therapy
IMRT	Intensity Modulated Radiation Therapy
KPS	Karnofsky Performance Score
LACC	Locally Advanced Cervical Cancer
LC	Local Control
LRC	Locoregional Control
LRR	Local Recurrence Rates
LVSI	lymphovascular space invasion
MBO	Malignant Bowel Obstruction
MLC	Multileaf Collimator
MRI	Magnetic Resonance Imaging
NID2	Normalized Iso-effective Dose
NPV	Negative Predictive Value

OAR(s)	Organ(s) At Risk
OAV	Optimization Aid Volumes
OS	Overall Survival
OTT	Overall Treatment Time
PALN	Para-aortic Lymph Nodes
PBO	Peripheral Blood Count
pCR	pathological Complete Remission
PFS	Progression Free Survival
PORTEC	PostOperative Radiation Therapy in Endometrial Carcinoma
PPV	Positive Predictive Value
PTV	Planning Target Volume
QA	Quality Assurance
QOL	Quality of Life
RC	Regional Control
RSI	Relative Signal Intensity
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SB	Small Bowel
SIB	Simultaneously Integrated Boost
SUV	Standardized Uptake Value
URR	Unadjusted Relative Risk
VMAT	Volumetric Modulated Arc Therapy
WAPRT	Whole Abdomino-Pelvic Radiotherapy
WHO	World Health Organization

Summary

In the 90s, Ghent University Hospital was one of the pioneers in successful implementation of IMRT in several tumour sites. Subsequently, the need for an efficient and fast technique to irradiate large concave targets lead to the introduction of rotational intensity modulated RT: intensity modulated arc therapy (IMAT). Introducing IMAT in the multimodality treatment of pelvic gynaecologic tumours was a logical consequence. In the first place, the use of box (or other conventional) techniques in cervical and endometrial cancer is synonymous to irradiation of large parts of Organs At Risk (OARs) lying within the concavity of the horseshoe-shaped target volume. Secondly, dose limits to kidneys and liver and adequate irradiation of the whole peritoneal cavity in case of ovarian cancer are incompatible using conventional techniques. Reducing toxicity by implementing IMAT in the radiotherapeutic treatment of gynaecological cancer was however not the only aim of this thesis. Triggered off by the high local recurrence rates in locally advanced cervical cancer (LACC) and the poor prospects of women with chemotherapy-resistant ovarian cancer we dared to think out of the box and to challenge some dogmas. Could we challenge the gold standard chemoradiation + brachytherapy by re-introducing surgery in the treatment of LACC and if so, how could we overcome the scepticism of the treating physicians towards surgical toxicity? Does the dogma that a whole abdominopelvic RT for advanced ovarian cancer is infeasible and too toxic still stand in this era of modern RT? After all: *"Convention is the enemy of progress" (Trevor Bayliss)*.

Early-stage cervical carcinoma and endometrial carcinoma patients are initially treated with a hysterectomy and lymph node dissection. If findings in the surgical specimen suggest a high-risk of pelvic (and/or systemic) recurrence, post-operative (chemo) radiation therapy (RT) is recommended. Two-field or box irradiation of the pelvis encompasses large parts of OARs. This is even more pronounced in the postoperative setting where small bowel tends to fall into the vacated space in the true pelvis. Not surprisingly, substantial severe acute and late complication rates are unavoidable using conventional techniques. The entrance of modern RT-techniques such as IMRT and IMAT allows better sparing of those OARs. Whether this reflects in lower toxicity rates (acute and late) in the postoperative treatment of endometrial and early stage cervical cancer, as described in **publication 1**.

Definitive chemoradiation (CRT) is standard of care in locally advanced cervical cancer (LACC) and consists of a combination of external beam radiotherapy (with concomitant administration of cisplatin) and brachytherapy. Unfortunately, despite the advent of image-guided dose-intensified brachytherapy, local control remains the major cause of treatment failure. Removing chemo- and radioresistant foci by performing a post-CRT hysterectomy seems therefore a valid treatment option and has been used successfully in the past. However, since 1 randomized trial failed to prove survival benefit and due to the fear of excessive toxicity, this treatment option has sunk into oblivion. We hypothesized that the chance of surgery-related toxicity using IMAT would be reduced in a twofold way. At first, the use of IMAT leads to less irradiation of surrounding tissues and should therefore result in less toxicity. Secondly, substituting the brachytherapeutic boost by a simultaneously integrated boost (SIB) using IMAT should allow reducing the dose distribution uncertainties inherent to two treatment modalities which are difficult to add up. A SIB, by delivering a higher dose to the tumour or affected lymph nodes without changing the amount of treatment fractions and thus delivering a higher dose per fraction, theoretically results in a double control benefit. Indeed, in cervical cancer the positive relationship between higher doses, shorter overall treatment time and tumour control is well established. In **publication 2**, we concluded that the implementation of a SIB in the treatment of LACC using IMAT was feasible without compromising the dose to the elective lymph node areas or the OARs. The observation that using IMAT with a SIB is associated with low toxicity rates, allows a safe

post-CRT hysterectomy and leads to promising local control and survival rates is discussed in **publication 3**. The decision about extrafascial hysterectomy is made multidisciplinary and depends on local response diagnosed clinically, by Magnetic Resonance Imaging (MRI) and ^{18}FDG PET-CT. Reports concerning the value of MRI and ^{18}FDG PET-CT in predicting radical resectability of locally advanced cervical cancer after neo-adjuvant CRT are sparse, our results are presented in **publication 4**.

The evolution in chemotherapeutic and targeted therapies for advanced stages ovarian cancer in the last decades has been impressive. Unfortunately, this did not translate into a corresponding evolution in survival benefit. Over 70% of women presenting with advanced stage ovarian carcinoma will relapse eventually, of whom 85% solely within the abdominal cavity. For patients with progressive disease after second- or third-line chemotherapy, therapeutic options are limited and often restricted to best supportive care. However, ovarian cancer is known to be radio-sensitive and RT has been used successfully for curative whole abdomino-pelvic treatment and localized palliative care in the past. Excessive treatment morbidity and mortality and the entrance of chemotherapeutic agents have finished the role of RT in the treatment of ovarian cancer. Introducing IMAT for whole-abdominal pelvic radiotherapy (WAPRT) has proven to be feasible and is an important palliative treatment for patients with peritoneal carcinomatosis. The use of WAPRT in the palliative treatment of chemotherapy-resistant patients is discussed in **publication 5** and updated in the discussion section.

IMAT allows a challenging combination of reducing dose at the surrounding tissues while intensifying the radiation dose to the tumour at the same time. Consequently both in the endometrial and early stage (FIGO I and IIA, non bulky) cervical cancer as well as in the primary treatment of LACC toxicity rates are low and tumour control high. IMAT allows a safe adjuvant hysterectomy in LACC. Finally, in ovarian cancer, WAPRT revived in the palliative setting with important symptom palliation and response rates.

Several hypotheses described in this thesis remain to be tested. The hardest challenge however, lies in convincing the radiotherapeutic and gynaecologic community to embrace the opportunities created by new radiation techniques and to rethink the existing dogmas.

Samenvatting

Het universitair ziekenhuis Gent was in de jaren ’90 één van de pioniers die succesvol intensiteitsgemoduleerde radiotherapie (IMRT) voor multipele tumorlokalisaties implementeerde. Een blijvende vraag naar een efficiënte en snelle radiotherapietechniek die de bestraling van grote concave doelvolumes mogelijk maakte, leidde tot de ontwikkeling van een intensiteitsgemoduleerde radiotherapietechniek die in boogvorm wordt uitgevoerd: intensiteitsgemoduleerde boogtherapie (IMAT). De intrede van IMAT in de algemene aanpak van pelviene gynaecologische tumoren was een logische stap. Het gebruik van conventionele radiotherapie zoals een 2-velden (voorachterwaartse of APPA) of 4-velden (box) techniek in de behandeling van baarmoeder- of baarmoederhalstumoren staat gelijk met behandeling van grote volumes risico-organen tot een hoge dosis, gezien het doelvolume een hoefijzervorm aanneemt dat grote volumes gezonde weefsels (=risico-organen) omvat. Daarenboven is voor gevorderde ovariumtumoren een homogene behandeling van de volledige peritoneale holte tot een adequate dosis met conventionele technieken niet mogelijk; bij deze dosis wordt de tolerantiedosis van nieren en lever immers overschreden. Afname van toxiciteit door middel van de integratie van IMAT in de behandeling van pelviene gynaecologische tumoren was echter niet het enige doel van dit onderzoek. Geïnspireerd door het grote risico op lokaal herval bij patienten met lokaal gevorderde baarmoederhalstumoren en door het gebrek aan behandelopties bij platinum-resistente ovariumtumoren stelden we enkele vastgeroeste dogma’s in vraag. Is het mogelijk om de gouden standaard (chemoradiotherapie + brachytherapy) in de behandeling van lokaal gevorderde baarmoederhalstumoren aan te vullen met heelkunde? Zo ja, hoe kunnen we het scepticisme van de behandelende artsen betreffende de postoperatieve morbiditeit doen afnemen? En houdt de stelling dat pan-abdominopelviene RT bij patienten met platinum-resistente ovariumcarcinoom te moeilijk en te toxisch is, eigenlijk wel nog steek na de intrede van moderne RT? Immers: *“convention is the enemy of progress”(Trevor Bayliss)*.

Baarmoedertumoren en lokaal beperkte baarmoederhalstumoren worden in eerste instantie heelkundig benaderd. Indien welbepaalde microscopische bevindingen een hoog risico op locoregionaal (en/of metastatisch) herval voorspellen, wordt adjuvante (chemo)radiotherapie voorgesteld. Twee-velden of box bestraling van het desbetreffend doelvolume omhelst echter ook de bestraling van grote hoeveelheden gezond weefsel. In deze postoperatieve setting, waar de dundarm de ruimte inneemt die de verwijderde baarmoeder nalaat, is dit effect nog groter. Met conventionele bestralingstechnieken is ernstige acute en late toxiciteit dan ook onvermijdbaar. De intrede van moderne RT-technieken zoals IMRT en IMAT laten toe om deze risico-organen beter te sparen. Dat weerspiegelt zich in een lage toxiciteit (zowel acuut als laattijdig) in de postoperatieve behandeling van baarmoeder- en baarmoederhalstumoren, zoals werd neergeschreven in **publicatie 1**.

De standaardbehandeling van lokaal gevorderde baarmoederhalstumoren bestaat uit een combinatie van externe radiotherapie (met concomittante toediening van chemotherapie) en brachytherapie. Ondanks de intrede van beeldvormingsgeleide, hoge dosis brachytherapie blijft lokaal recidief een belangrijke oorzaak van ziekteherval. Het uitvoeren van een hysterectomie na chemoradiotherapie, waarbij potentieel chemo- en radiotherapieresistente tumorhaarden worden verwijderd, lijkt dan ook een valabele behandelingsoptie die in het verleden reeds met succes werd toegepast. Eén gerandomiseerde studie, waarbij geen overlevingsvoordeel van hysterectomie na chemoradiotherapie kon worden aangetoond, en de angst voor onaanvaardbare toxiciteit zorgden er echter voor dat deze behandeloptie in onmin raakte.

De hoop op afname van het hoger beschreven risico op toxiciteit door middel van IMAT is tweeledig. Enerzijds wordt de dosis op de omliggende risico-organen beperkt, anderzijds

vermindert het gebruik van een simultaan geïntegreerde boost (SIB) de dosimetrische onzekerheid die aanwezig is bij de combinatie van een externe en brachytherapeutische behandeling. Het gebruik van een SIB, wat neerkomt op het toedienen van een hogere dosis op de tumor of aangetaste lymfeklieren zonder het aantal behandelingen te laten toenemen, houdt een dubbel voordeel in. Het is immers reeds lang gekend dat bij baarmoederhalstumoren zowel een hogere dosis als een kortere behandelingsduur beiden leiden tot een grotere kans op (lokale) controle van de tumor. In **publicatie 2** konden we besluiten dat een SIB door middel van IMAT veilig kan worden geïmplementeerd in de behandeling van lokaal gevorderde baarmoederhalstumoren zonder een toename van dosis te veroorzaken in de omliggende gezonde weefsels of electieve lymfeklierregio's. In **publicatie 3** wordt beschreven hoe deze techniek de patiënten ernstige toxiciteit bespaart en toelaat om op een veilige manier een hysterectomie uit te voeren na een chemoradiotherapeutische behandeling. De daaruit volgende lokale controle en overlevingscijfers zijn dan ook veelbelovend.

Het al dan niet uitvoeren van een extrafasciale hysterectomie wordt multidisciplinair beslist en hangt af van de lokale respons. Deze lokale respons wordt geëvalueerd door middel van gynaecologisch onderzoek, NMR en ^{18}FDG PET-CT. De evidentie voor het gebruik van NMR of ^{18}FDG PET-CT in het voorspellen van radicale reseceerbaarheid van lokaal gevorderde tumoren na neo-adjuvante chemoradiotherapie is echter zeldzaam. Ons onderzoek in deze setting werd neergeschreven in **publicatie 4**.

In schril contrast met het grote aantal nieuwe chemotherapeutische en doelgerichte "targeted" therapieën die de laatste decennia op de markt kwamen voor de behandeling van gevorderde ovariumcarcinomen staat de beperkte winst in overleving. Nog steeds zullen meer dan 70% van de patienten met gevorderd ovariumcarcinoom in de loop der tijd hervallen, in 85% van de gevallen beperkt dit herval zich tot de abdominale holte. Voor patiënten met progressieve ziekte na 2^{e} of derdelijnschemotherapie beperken de therapeutische opties zich vaak tot palliatieve zorgen. Ovariumcarcinoom is nochtans stralingsgevoelig en radiotherapie werd in het verleden reeds met succes toegepast in zowel de curatieve (pan-abdominopelviene bestraling) als de palliatieve setting. De vaak ernstige bijwerkingen en de komst van een arsenaal aan chemotherapeutische agentia heeft de rol van radiotherapie in deze setting echter in de vergeethoek geduwd. Pan-abdominopelviene radiotherapie (WAPRT) mits het gebruik van IMAT is in het verleden reeds veilig en uitvoerbaar gebleken. Het inzetten van WAPRT door middel van IMAT als wapen in de palliatieve behandeling van chemotherapeutisch uitbehandelde ovariumcarcinoom patienten wordt besproken in **publicatie 5**. De meest recente gegevens hieromtrent werden neergeschreven in de discussie.

Intensiteitsgemoduleerde boogtherapie laat toe om gelijktijdig zowel een dosisreductie (omliggende organen) als een -escalatie (tumor of aangetaste lymfeklieren) uit te voeren. Dit resulteert zowel in de postoperatieve behandeling van endometrium- en lokaal beperkte baarmoederhalstumoren als in de primaire behandeling van lokaal gevorderde baarmoederhalstumoren in een beperkte toxiciteit en zeer goede overleving. Dit laat ons toe om op een veilige wijze heelkunde te implementeren in de behandeling van lokaal gevorderde baarmoederhalstumoren. Tenslotte kon de panabdominopelviene behandeling bij gevorderde ovariumcarcinomen met succes vanonder het stof worden gehaald met een goede respons op de behandeling en belangrijke symptoompalliatie.
Er is nog heel wat werk voor de boeg, meerdere onderzoeksvragen en hypothesen verdienen verder onderzoek. De grootste uitdaging ligt echter in het overtuigen van de radiotherapeutische en gynaecologische gemeenschap dat dit tijdperk, met nieuwe moderne bestralingstechnieken, heel wat nieuwe (of oude) deuren opent.

Chapter 1: Introduction

1. Intensity-Modulated Arc Therapy in cervical and endometrial cancer: rationale.

External Beam Radiation Therapy (EBRT) (1) is a standard component in the multi-modality approach of cervical and endometrial carcinomas (2-5). Endometrial carcinoma and/or early-stage cervical carcinoma patients are initially treated with a hysterectomy and lymph node dissection. Post-operative radiation therapy (RT) is often recommended if findings in the surgical specimen suggest a high-risk of pelvic recurrence.

In case of endometrial cancer, the indication for postoperative RT is highly controversial. There is though agreement that the presence of 2 or more of the following findings suggest a high risk of recurrence: grade 3 differentiation, invasion of the outer half of the myometrium, lymphovascular space invasion (LVSI), pN+, age > 60 years, cervical stromal invasion (6). For patients with early cervical cancer the presence of LVSI and/or affected lymph nodes, >1/3 cervical stromal invasion or large tumours (>4cm) justifies postoperative RT, mostly combined with chemotherapy (7-9). In more advanced cervical cancers (≥ FIGO IIB or tumours ≥ 4cm) primary chemoradiation (CRT) is standard treatment.

Although the planning target volume (PTV) differs between primary (tumour and unaffected cervix, uterus, parametria and superior 1/3 to half of the vagina) and postoperative (operation bed, superior third of the vagina) setting, the PTV encompassing the nodes (common, external and internal iliac nodes, the obturator region and the presacral region in case of cervical involvement) is identical (10, 11). This PTV structure forms a “cup” located right against the inner side of the bone marrow harbouring pelvic bones (itself also being an organ at risk) and contains large parts of the organs at risk (OARs) such as small bowel (SB), sigmoid, rectum and bladder (Figure 1).

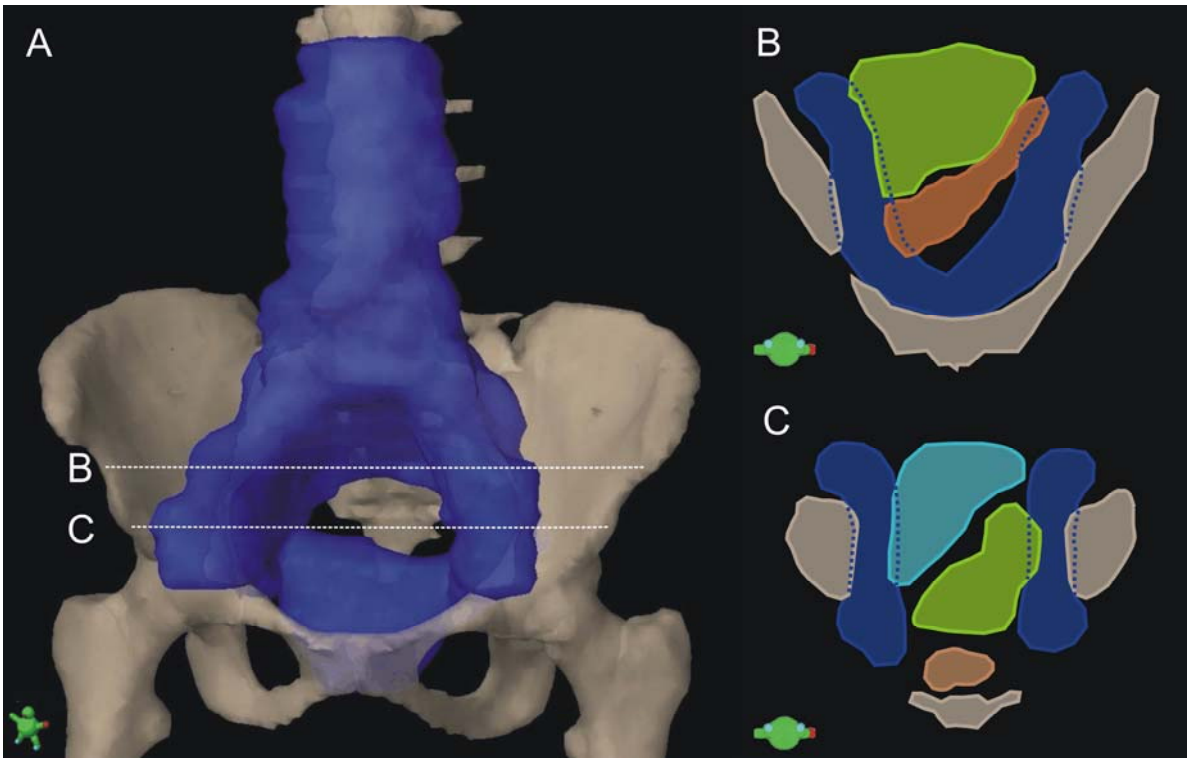

Figure 1.1: Relation of the target volume to its neighbouring organs.
A: The PTV (encompassing the common, external and internal iliac nodes, the para-aortic nodes, the presacral and obturator region) forms a cup between the pelvic cavity and the pelvic bones. B: transversal slicing at the level of the lower sacro-iliacal joints results in a horseshoe-shaped PTV lying against the pelvic bones and encompassing large parts of the intestine (small intestine: green; sigmoid: brown). C: transversal slicing at the level of the coccyx shows that the bladder (blue), small intestine (green) and the rectum (light brown) are sandwiched between the left and right side of the PTV.

With traditional conformal RT delivered in an "anteroposterior-posteroanterior (APPA)" or "four-field" (box) technique based on bony anatomic landmarks, it is impossible to treat this cup without irradiating its content (figure 1.2. A-C). Intensity Modulated RT (IMRT) with fixed gantry angles allows sparing of the OARs by moulding the prescribed dose to the shape of the target tissues resulting in reduced toxicities (13-16). With a large inner radius of the target volume, as in pelvic gynaecologic malignancies, a higher number of beam incidences is needed for homogeneous coverage of the target volumes and sparing of the OARs (17-19) (figure 1.2. D and E). Intensity Modulated Arc Therapy (IMAT) is a fast and easy way to deliver a large number of beam incidences (20) achieving beam intensity modulation by superimposing multiple arcs and/or by regulating the dose-rate and the MLC leaf movement dynamically and relatively to the speed of the rotating gantry. An example of the target coverage achieved with IMAT while sparing the OAR is illustrated in Figure 1.2 F. The use of positioning devices proved to be efficient in reducing irradiated SB volume. As compared to the supine position or the prone position alone, a prone treatment position combined with a belly board resulted in a decrease of irradiated SB volume for both 3D-conformal RT and IMRT treatment plans (21). The benefit of a prone position with belly board in combination with IMRT is though smaller to absent in low dose areas when using extended arc techniques (22). Moreover, there is no proven benefit towards other OAR such as bladder, rectum and bone marrow.

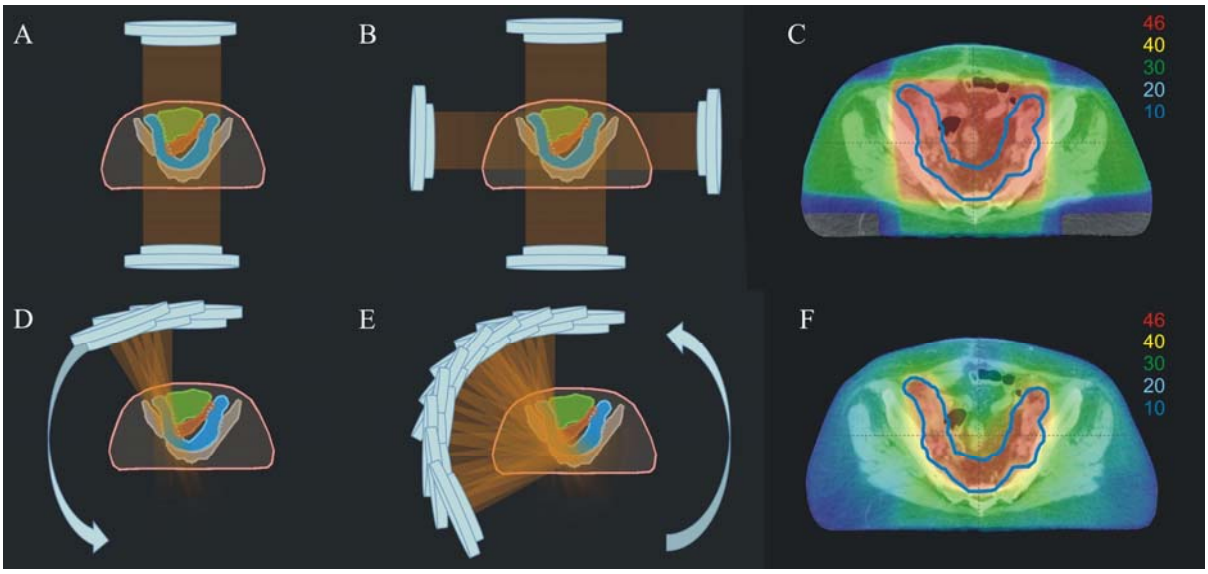

Figure 1.2 Treatment of a horseshoe-shaped PTV with conventional techniques and IMAT.
A conventional APPA (A) or box (B) treatment of a horseshoe-shaped PTV (blue structure) leads to inclusion of large parts of the OARs (SB: green; sigmoid: brown) in the treatment fields (orange bars). In the case of a box treatment this results in a rectangular high dose area (red area) encompassing all OARs lying within the PTV (C). Using IMAT (D and E) the high dose area (F, red area) is limited to the PTV resulting in gradually lower doses (from yellow to blue as the dose decreases) to the OARs.

In cervical cancer, the positive relationship between higher dose and tumour control is well established (23, 24). Ideally, this higher dose should be given without prolonging the overall treatment time (OTT) to avoid loss of tumour control by cancer cell proliferation (25-28). In addition to generating concave dose distributions and tight dose gradients for dose-escalation, IMRT (29-33) and IMAT (34) allow simultaneous treatment of multiple targets with different total doses. This simultaneous integrated boost (SIB) technique is also known as dose-painting (35-37)(Figure 1.3).

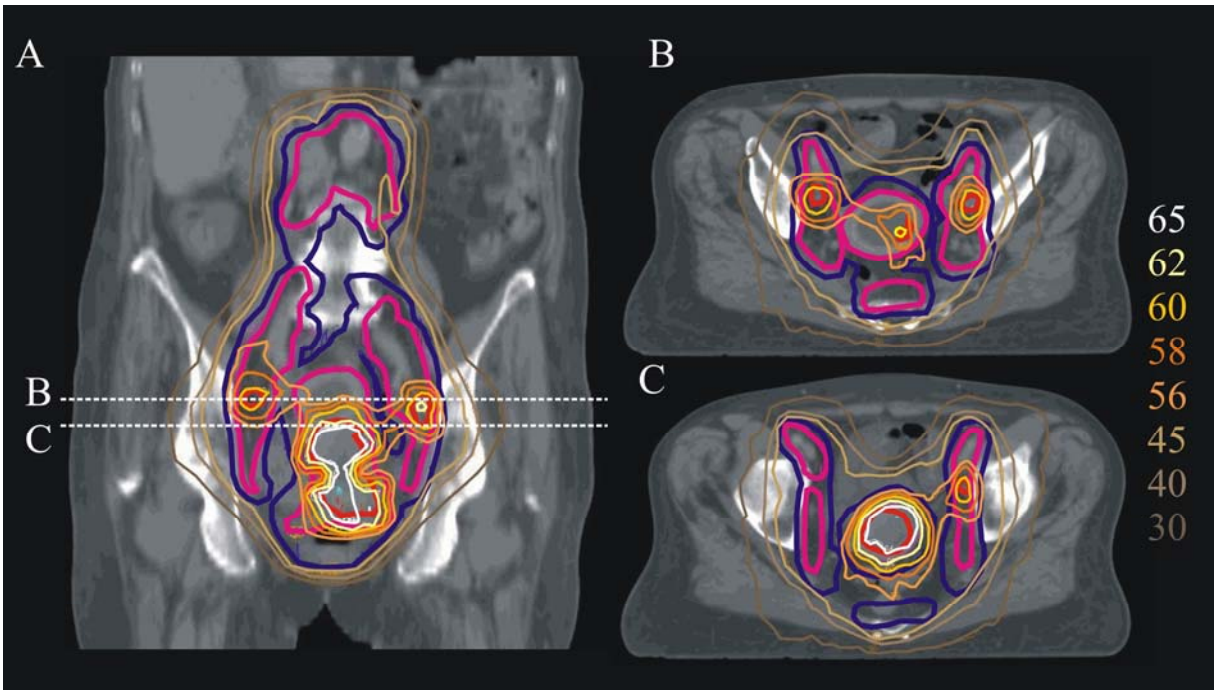

Figure 1.3: Dose-painting for lymph node positive locally advanced cervical cancer (LACC) using IMAT. A: coronal view of the isodoses for a patient with LACC with affected lymph nodes. The median prescribed dose to the primary tumour and affected lymph nodes (both contoured in red) is 62 and 60Gy respectively. This dose is delivered simultaneously and in the same amount of fractions as the minimal prescribed dose of 45Gy to the clinical target volume (CTV, pink) and PTV (blue) without influencing the dose on the OARs. B: transversal view at the level of the two affected lymph nodes. C: transversal view at the level of the cervical tumour and the affected lymph node in the right external iliac lymph node area.

2. Intensity-Modulated Arc Therapy in ovarian cancer: rationale.

Ovarian cancer tends to metastasize through the peritoneal cavity, mandating the inclusion of the whole peritoneal cavity in the treatment fields. Renal and hepatic tolerances are often set at a median dose of 18 and 33 Gy respectively (38). Consequently, with conventional APPA treatment, underdosage of peritoneal regions after blocking the kidneys and/or liver for radiation is unavoidable if a dose higher than their tolerance levels is prescribed (Figure 1.4 A-B). Moreover, the entire lumbar spine and pelvic bones are irradiated leading to substantial haematological toxicity. The potential of arc therapy to spare kidneys, liver and bone marrow in this setting stands out and was investigated before (17, 39) (Figure 1.4 C-D).

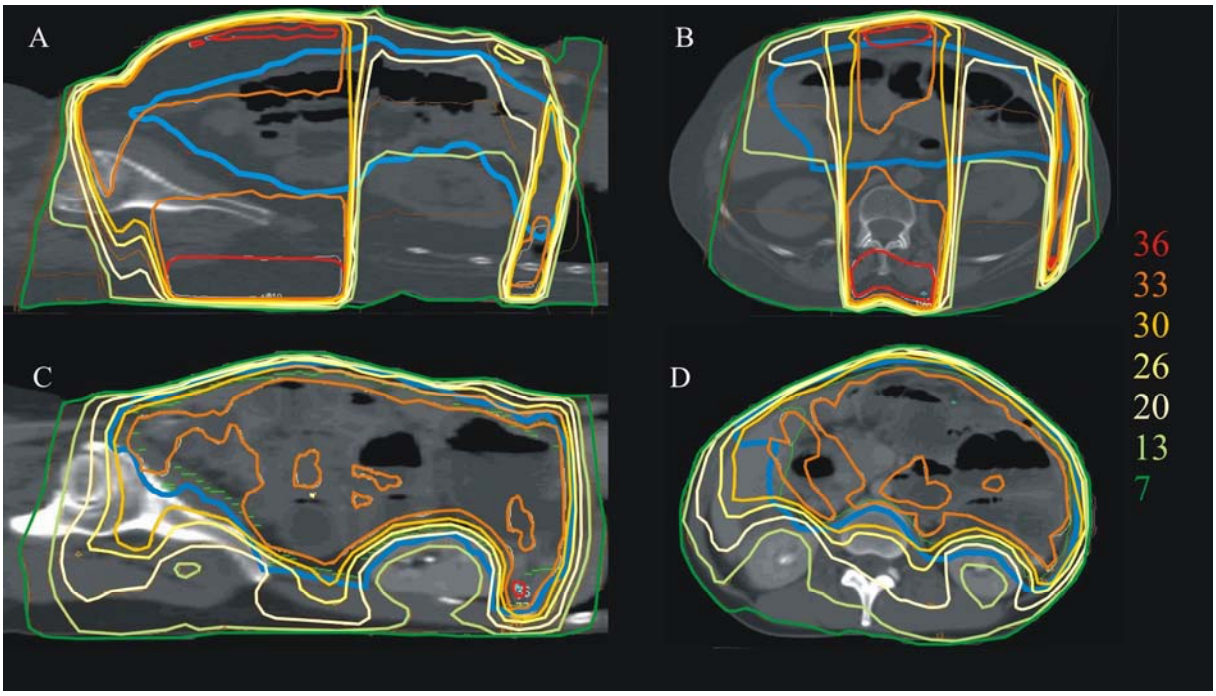

Figure 1.4: Whole abdominal pelvic RT (WAPRT) with conventional techniques and IMAT.
Conventional WAPRT (A and B) leads to underdosage (green to yellow isodose lines entering the blue PTV structure) of large parts of the peritoneal cavity (= PTV = blue) after blocking the kidneys as well as to important overdosage near the bone marrow harbouring pelvic bones (red lines). IMAT (C and D) enables sparing the OARs (bone marrow (D) and kidneys (C)), avoids large high dose areas as well as it results in adequate target (PTV, blue) coverage.

3. IMRT/IMAT at Ghent University Hospital (GUH) as it applies to this thesis.

Until the 90s, radiation oncologists employed beams with aperture shapes that encompassed the whole tumor and had an equal intensity across this aperture. In the mid-90s, a handful of research centers including GUH, explored a technique of narrower beams (beamlets) that irradiated only a part of the tumor each (40). By putting many beamlets upon and next to each other, all with their own tuned or modulated intensity, new beams with modulated intensity across there aperture were created. This approach, called IMRT, has the unique potential to create homogeneous concave dose distributions for target volumes wrapped around an OAR (41) (Figure 1.5; avoidance IMRT). Shortly after, GUH again was one of the leading centres to investigate the hypothesis that IMRT could decrease radiotherapy-induced toxicity in several tumour types (19, 42-44), confirmed by clinical studies a decade later (45). In 2002, after adaptation of IMRT planning tools for IMAT, GUH became one of the very few and first centres that could apply IMAT as a routine treatment (17, 34, 46). Details concerning technical aspects, treatment planning flow charts and general rationale of IMAT can be found in the theses of Werner De Gersem (43), Wim Duthoy (19) and Valérie Fonteyne (44).
Subsequently, by its ability to avoid toxicity in surrounding organs, IMRT/IMAT was used to study dose-intensification to obtain better cancer cure rates, without loosing the OARs–sparing effect. Where dose-intensification using biological image guided IMRT was obtained in whole tumour regions first (Figure 1.5: Regionally intensified IMRT), research rapidly evolved towards targeted dose-intensification on, by ^{18}FDG-PET or MR-spectroscopy, estimated radio-resistant regions (Figure 1.5: Dose-painting IMRT) within the tumour (35, 43, 44, 47, 48). Ongoing research focuses now on the paradoxical combination of further reduction of toxicity (by regularly adapting the treatment to changing anatomy; Figure 1.5:

Adaptive dose-painting) and dose-intensification (by simultaneously updating the dose-painting and hereby securing optimal targeting of radioresistant parts of the tumor).

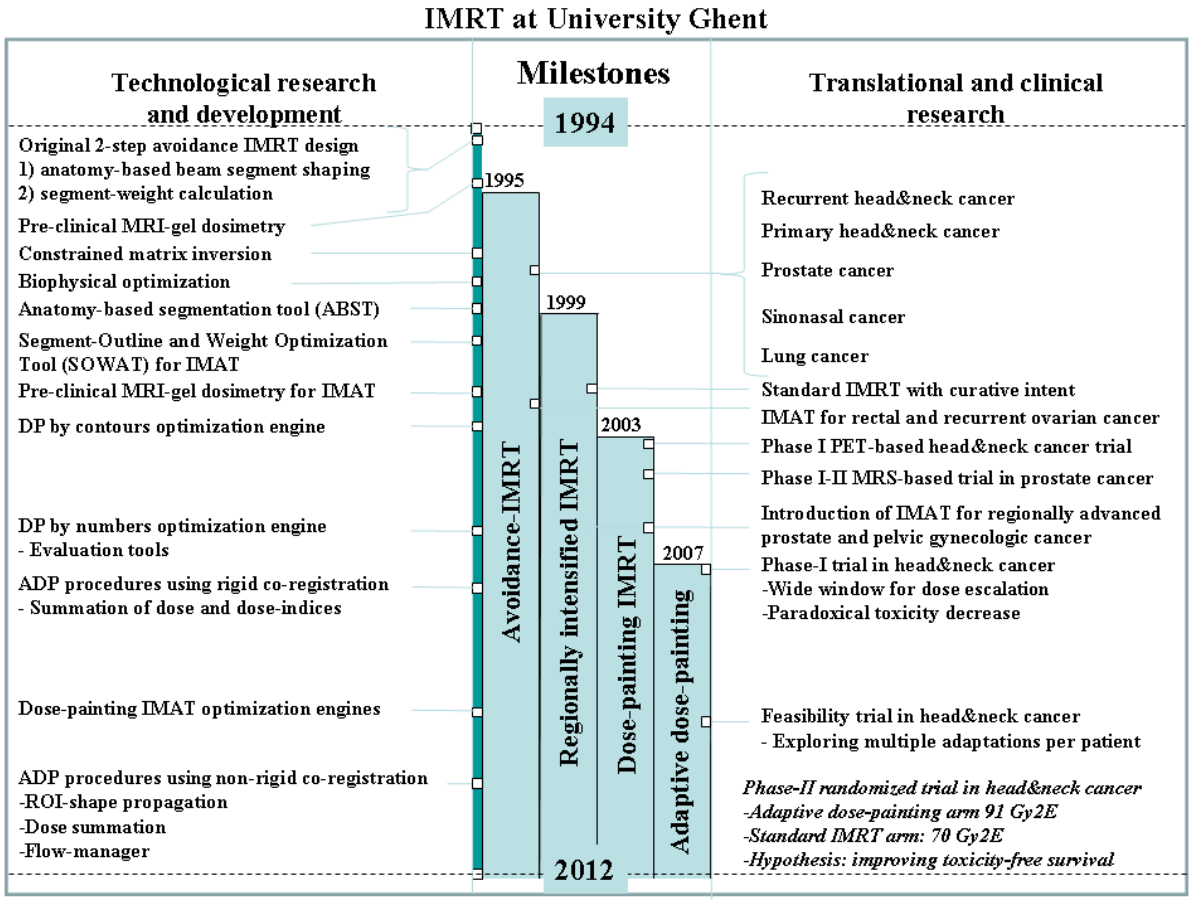

Fig.1.5 Evolution of IMRT/IMAT at GUH.
The technological research and development (left side) and the translational and clinical research (right side) resulted from close collaboration between engineers, radiation physicists, technologists, nurses and radiation oncologists. DP = dose-painting; ADP = adaptive dose-painting; ROI = region of interest. (Figure courtesy W. De Neve).

Chapter 2: Objectives and outlines

1. Endometrial/cervical cancer

Conventional two-field or box irradiation of the pelvis encompasses large parts of OARs: SB, rectum, sigmoid, bladder and bone marrow. Rates of severe (≥ grade 3) complications, even with modest doses of 45–50 Gy, as high as 7% (urinary), 8% (intestinal) and 13% (hematologic) are reported (4, 49). This is even more pronounced in the postoperative setting where small bowel tends to fall into the vacated space in the true pelvis.

1.1. Postoperative treatment of cervical and endometrial cancer.

Combining chemo- and radiotherapy improves overall survival (OS) in patients with cervical cancer needing an adjuvant therapy (7). A similar tendency has been shown in the adjuvant treatment of endometrial cancer (50) and currently the effect of adding chemotherapy to postoperative irradiation in the treatment of high-risk endometrial cancers is evaluated in the randomized phase III PORTEC-3 trial (clinical trials.gov: NCT00411138). In exchange for an improved OS, adding chemotherapy to RT for cervical cancer has doubled the risk of severe acute hematologic and gastro-intestinal toxicity and tripled platelet toxicity (49). Life-threatening GI-toxicity occurred in 8% of the patients (49). Up to 27% of patients were not able to finish their programmed treatment if chemotherapy was given before RT in endometrial cancer (50).

Intensity Modulated Radiotherapy has been available and in use for over 10 years and has shown considerable promise in reducing toxicity in numerous tumor sites (45, 51). Also in pelvic gynaecological tumours, the dosimetric superiority of IMRT and IMAT over conformal techniques has been demonstrated. An overview is presented in table 1.1 (18, 52-61). Several studies have demonstrated that this dosimetric superiority also translated into reduced treatment toxicity (13-16, 62, 63). In 2007, IMAT has been implemented clinically in the adjuvant treatment of cervical and endometrial cancer at GUH. The first results on toxicity have been reported in Publication 1: ***Post-operative Intensity-Modulated Arc Therapy for cervical and endometrial cancer: a prospective report on toxicity.***

Table 1.1: Dosimetric comparison of techniques.

	Technique	n	Dose	Significant dosimetric advantage for Intensity Modulated Radiotherapy			
IMRT				Small Bowel	Rectum (+ sigmoid*)	Bladder	Bone Marrow
Definitive treatment							
Forrest et al.(54)[£]	7F-IMRT vs Box	50	50,4Gy	V30; V40; V45; V50	V40*; V45*; V50*	V30; V40; V45; V50	V30; V40; V45; V50
Georg et al.(55)	7F-IMRT vs Box	10	50,4Gy	V50,4	V50,4		
Portelance et al.(18)	9F-IMRT vs APPA	10	45Gy	V45	V45	V45	
	9F-IMRT vs Box	10	45Gy	V45	V45	V45	
Mell et al.(59)	9F-IMRT vs APPA	7	45Gy				V5; V10; V20; V30; V40
	9F-IMRT vs Box	7	45Gy				*-V5; -V10*; V20; V30; V40
Adjuvant treatment							
Ahamad et al.(52)	9F-IMRT vs APPA	10	45 Gy	V30; V40; V45	V30; V40; V45	V30; V40; V45	
	9F-IMRT vs Box	10	45 Gy	V30; V40; V45	V30; V40; V45	V30; V40; V45	
Georg et al.(55)	7F-IMRT vs Box	10	50,4Gy	V47,9; V50,4	V47,9; V50,4		
Heron et al.(56)	7F-IMRT vs Box	10	45Gy	V30	V30	V30	
Lujan et al.(58)	9F-IMRT vs Box	10	45Gy				(V18; V22,5; V27; V36; V45)[$]
Chen et al.(64)	7F-IMRT vs Box	7	45Gy	V15; V45	V45	V45	
Ghent series[α]	7F-IMRT vs Box	10	46Gy	V20; V40; V45	V40*; V45*; V50*	V20; V30; V45	
Definitive and adjuvant treatment							
Roeske et al.(60)	9F-IMRT vs Box	10	45Gy	*-V10*; V20; V40; V45	V30; V40; V45	V30; V40; V45	
ARC							
Definitive treatment							
Hsieh et al.(57)	HT vs Box	10	50,4Gy	mean; V20; V30; V40; V50,4	mean; V30; V40; V50,4	mean; V30; V40; V45; V50,4	V20[$]
Adjuvant treatment							
Wong et al.(61)	IMAT vs APPA	5	45Gy	V45			V30[$]
Ghent series[α]	IMAT vs Box	10	46Gy	V30; V40; V45; V50	V40*; V45*	V20; V30	

- = *advantage conformal technique;* $: only iliac crest; α: not published, no difference between IMRT and IMAT; £: significant lower integral dose with IMRT. xF-IMRT: Intensity Modulated Radiotherapy using "x" beam angles; box: 4-field conventional radiotherapy; APPA: 2-field conventional radiotherapy; HT: Helical Tomotherapy; IMAT: Intensity Modulated Arc Therapy; Vx: Volume of OAR receiving a maximum of xGy; vs: versus.

1.2. Primary treatment of cervical cancer

Early stage cervical cancer (tumours up to FIGO IIA and < 4cm) can be treated with surgery alone or, in case of unfavourable prognostic findings on pathology, with postoperative radiation (with or without chemotherapy). For locally advanced stages (bulky tumours > 4cm and/or FIGO IIB or more) definitive CRT is the treatment of choice. Two meta-analyses including multiple randomized trials show that CRT improves OS and progression-free survival (PFS), whether or not platinum is used, with absolute benefits of 10 and 13%, respectively (3, 65). The standard treatment of locally advanced cervical cancer (LACC) consists of EBRT combined with brachytherapy (BT). However, there is some evidence that the addition of adjuvant surgery might improve local control (66-68). Although no increase in grade 3 or 4 toxicity was shown in the only randomized trial evaluating the effect of an additional hysterectomy (69), a great reluctance to perform post-CRT hysterectomy is present. Indeed, some research groups have reported on excessive toxicity using completion hysterectomy (70). It is our hypothesis that this could be reduced by abandoning the use of conventional treatment fields on the one hand, and by avoiding the dosimetric uncertainty inherent to the combination of two - difficult to add up - RT techniques (EBRT and BT) on the other hand. Delivering a high dose however is important, as there is a clear dose-relationship for cervical cancer (23, 24). This may, however, NOT lead to an extended OTT since the impact of a prolonged OTT with losses of pelvic tumor control from 0.6 to 0.8% per extra day of treatment is well established (28, 30). A SIB, within the timeframe of the pelvic treatment, does not only increase the physical dose to the primary tumour but also increases the dose per fraction, which results in a double advantage. Intensity modulated radiotherapy and IMAT have lead to a significant reduction of toxicity rates (14, 16, 58, 71) and should permit to deliver a SIB to the tumour and affected lymph nodes (as visualized on Magnetic Resonance Imaging (MRI) and 2-deoxy-2-[18] fluoro-D-glucose positron emission tomography (^{18}FDG PET-CT)). The planning procedure, quality control and the clinical implementation of IMAT with image-guided SIB in LACC is described in publication 2: ***Intensity-Modulated Arc Therapy with Simultaneous Integrated Boost in the Treatment of Primary Irresectable Cervical Cancer. Treatment Planning, Quality Control, and Clinical Implementation.***

Intracavitary brachytherapy is still considered as a standard component of radical treatment of cervical cancer. Unfortunately, pooled results from 5 randomized trials (2065 patients) show local recurrence rates (LRR) of 7%, 16% and 26% in stage I, II and III respectively. This is similar with the LRR of 15 to 20% achieved with CRT as described in the meta-analysis performed by Lukka et al. (4). Compared to the conventional BT used in the former series, image guided adaptive BT (IGABT) has lead to a better local control without increasing toxicity (72-74). Despite the fact that complementary hysterectomy could be a treatment option (75) with the aim to remove potentially chemo- and radioresistant foci and hereby seeking better local control rates, adjuvant hysterectomy is not generally used as a randomized study shows no benefit on survival (69). This randomized study however, clearly suggests that patients with tumours measuring 4 to 6 cm, may benefit from extrafascial hysterectomy (69). And moreover (as described before) a great reluctance to perform post-CRT hysterectomy is present due to the fear for an excess in toxicity. Introducing toxicity reducing IMAT with a SIB, which from a technical point of view replaces the brachytherapeutic boost, might open a window for securing the safety of complementary surgery and subsequently improve local control. Whether IMAT with SIB allows post-CRT hysterectomy and the corresponding toxicity and control rates are discussed in publication 3: ***Intensity Modulated Arc Therapy ± Cisplatin as neo-adjuvant treatment for primary irresectable cervical cancer: toxicity, tumour response and outcome.***

Forty percent of our population showed a pathologic complete response (pCR) and did, hypothetically, not need a hysterectomy. Furthermore, hysterectomy is a fair treatment option if residual tumour is present after definitive CRT (67) but, due to fibrosis, its morbidity rate seems to be higher if performed more than 6 weeks after CRT (76). Reliable early assessment of treatment response and local extent after CRT is thus essential and could hypothetically lead to a further patient-individualized approach according to the tumour characteristics during and shortly after CRT. The role of MRI and ^{18}FDG PET-CT in staging and assessment of resectability in (non-treated) cervical cancer is established. Although this was also recognized by the International Federation of Gynaecology and Obstetrics (FIGO), they can't be used for (FIGO) staging purpose due to their limited accessibility. With a negative predictive value of 94-100% for parametrial invasion and its superior soft tissue resolution, MRI is the best for defining the local extent of the tumor (77, 78) as where ^{18}FDG PET-CT is superior for diagnosing lymph node or distant metastasis (78, 79).
More sparse are reports concerning the value of MRI and ^{18}FDG PET-CT in predicting radical resectability of LACC after neo-adjuvant CRT (80, 81). Also the correlation with post-therapy ^{18}FDG uptake and pathology is rarely reported. This was the subject of research and discussion and is presented in publication 4: "***Value of Magnetic Resonance and ^{18}FDG PET-CT in Predicting Tumor Response and Resectability of Primary Locally Advanced Cervical Cancer after Treatment with Intensity-Modulated Arc Therapy. A Prospective Pathology-Matched Study."***

2. Ovarian Cancer

In Belgium, ovarian cancer is the 2nd most frequent gynaecological cancer and the 5th cause of cancer death in females (82). Over 70% of patients with epithelial ovarian cancer (EOC) present with advanced (FIGO stages III and IV) disease. Although the 5-year OS rate for ovarian cancer has improved significantly in the past 30 years, the prognosis for ovarian cancer remains poor and is closely related to the stage at diagnosis, as determined according to the staging system developed by the FIGO. Approximately 60%, 20-30%, and 10-20% of women presenting with FIGO stage II, III, and IV respectively, will survive 5 years (83). For advanced stages, in the '50s, surgery and adjuvant whole abdomino-pelvic radiotherapy (WAPRT) were the dominant treatment modalities (84, 85). However, using conventional techniques, WAPRT was associated with a high rate of severe side effects (particularly SB toxicity and myelosuppression)(86). Whole abdomino-pelvic RT based on conventional technology was not able to deliver adequate radiation doses to the upper abdomen due to OARs tolerance limits (liver, kidney) and was considered ineffective for patients with macroscopic disease after chemotherapy (87, 88). Moreover, platinum-based chemotherapy has dramatically changed the course for these patients and WAPRT has been almost totally excluded from the treatment of EOC. Despite the advances in surgical therapy and expanding choices for adjuvant therapy in advanced EOC, over 70% of women will relapse of whom the tumor is confined to the abdominal cavity in 85% of these (83, 85). For patients with progressive disease after second- or third-line chemotherapy, therapeutic options are very limited and often restricted to the best supportive care. Being the primary cause of hospitalization in palliative setting (89), a difficult problem to palliate is malignant bowel obstruction (MBO) in platinum-resistant patients. Most patients show multiple intestinal levels of obstruction precluding any surgical intent. The mean OS of MBO patients is between 20 and 75 days and the 3- month life expectancy is lower than 25% (83). Palliative RT has shown to relieve most symptoms in 50–80% of patients, with complaints of bleeding and pain responding the best (87, 90). Only 2 reports reported on the palliative effect for patients with MBO (91, 92). In 2003, our research group reported on the feasibility of IMAT

in the treatment planning of WAPRT as palliative treatment of bulky peritoneal relapsed ovarian cancer (17). The first clinical results are presented in publication 5: ***Whole abdominopelvic radiotherapy using intensity-modulated arc therapy in the palliative treatment of chemotherapy-resistant ovarian cancer with bulky peritoneal disease: a single-institution experience.***

REFERENCES

1. King M, McConkey C, Latief TN*, et al.* Improved survival after concurrent weekly cisplatin and radiotherapy for cervical carcinoma with assessment of acute and late side-effects. *Clin Oncol (R Coll Radiol)* 2006;18:38-45.
2. Creutzberg CL, van Putten WL, Koper PC*, et al.* Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet* 2000;355:1404-1411.
3. Green J, Kirwan J, Tierney J*, et al.* Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. *Cochrane Database Syst Rev* 2005:CD002225.
4. Lukka H, Hirte H, Fyles A*, et al.* Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer--a meta-analysis. *Clin Oncol (R Coll Radiol)* 2002;14:203-212.
5. Kong A, Johnson N, Cornes P*, et al.* Adjuvant radiotherapy for stage I endometrial cancer. *Cochrane Database Syst Rev* 2007:CD003916.
6. Kong A, Simera I, Collingwood M*, et al.* Adjuvant radiotherapy for stage I endometrial cancer: systematic review and meta-analysis. *Ann Oncol* 2007;18:1595-1604.
7. Peters WA, 3rd, Liu PY, Barrett RJ, 2nd*, et al.* Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 2000;18:1606-1613.
8. Rotman M, Sedlis A, Piedmonte MR*, et al.* A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. *Int J Radiat Oncol Biol Phys* 2006;65:169-176.
9. Sedlis A, Bundy BN, Rotman MZ*, et al.* A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. *Gynecol Oncol* 1999;73:177-183.
10. Lim K, Small Jr W, Portelance L*, et al.* Consensus Guidelines for Delineation of Clinical Target Volume for Intensity-Modulated Pelvic Radiotherapy for the Definitive Treatment of Cervix Cancer. *Int J Radiat Oncol Biol Phys* 2009;79:348-355.
11. Small W, Jr., Mell LK, Anderson P*, et al.* Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys* 2008;71:428-434.
12. Pinto AE, Pires A, Silva G*, et al.* Ploidy and S-phase fraction as predictive markers of response to radiotherapy in cervical cancer. *Pathology - Research and Practice* 2011;207:623-627.
13. Bouchard M, Nadeau S, Gingras L*, et al.* Clinical outcome of adjuvant treatment of endometrial cancer using aperture-based intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;71:1343-1350.
14. Brixey CJ, Roeske JC, Lujan AE*, et al.* Impact of intensity-modulated radiotherapy on acute hematologic toxicity in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2002;54:1388-1396.
15. Mundt AJ, Lujan AE, Rotmensch J*, et al.* Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2002;52:1330-1337.

16. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys* 2003;56:1354-1360.
17. Duthoy W, De Gersem W, Vergote K*, et al.* Whole abdominopelvic radiotherapy (WAPRT) using intensity-modulated arc therapy (IMAT): first clinical experience. *Int J Radiat Oncol Biol Phys* 2003;57:1019-1032.
18. Portelance L, Chao KS, Grigsby PW*, et al.* Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. *Int J Radiat Oncol Biol Phys* 2001;51:261-266.
19. Duthoy W. Intensity modulated radiation therapy and arc therapy: validation and evolution as applied to tumours of the head and neck, abdominal and pelvic regions. Ph.D. Dissertation. Ghent; 2006.
20. Cozzi L, Dinshaw KA, Shrivastava SK*, et al.* A treatment planning study comparing volumetric arc modulation with RapidArc and fixed field IMRT for cervix uteri radiotherapy. *Radiother Oncol* 2008;89:180-191.
21. Wiesendanger-Wittmer EM, Sijtsema NM, Muijs CT*, et al.* Systematic review of the role of a belly board device in radiotherapy delivery in patients with pelvic malignancies. *Radiother Oncol* 2012;102:325-334.
22. Adli M, Mayr NA, Kaiser HS*, et al.* Does prone positioning reduce small bowel dose in pelvic radiation with intensity-modulated radiotherapy for gynecologic cancer? *Int J Radiat Oncol Biol Phys* 2003;57:230-238.
23. Choy D, Wong LC, Sham J*, et al.* Dose-tumor response of carcinoma of cervix: an analysis of 594 patients treated by radiotherapy. *Gynecol Oncol* 1993;49:311-317.
24. Perez CA, Grigsby PW, Chao KS*, et al.* Tumor size, irradiation dose, and long-term outcome of carcinoma of uterine cervix. *Int J Radiat Oncol Biol Phys* 1998;41:307-317.
25. Chen SW, Liang JA, Yang SN*, et al.* The adverse effect of treatment prolongation in cervical cancer by high-dose-rate intracavitary brachytherapy. *Radiother Oncol* 2003;67:69-76.
26. E C, Dahrouge S, Samant R*, et al.* Radical radiotherapy for cervix cancer: the effect of waiting time on outcome. *Int J Radiat Oncol Biol Phys* 2005;61:1071-1077.
27. Lanciano R. Optimizing radiation treatment for cervical cancer. *Surg Clin North Am* 2001;81:859-870.
28. Perez CA, Grigsby PW, Castro-Vita H*, et al.* Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys* 1995;32:1275-1288.
29. Ahmed RS, Kim RY, Duan J*, et al.* IMRT dose escalation for positive para-aortic lymph nodes in patients with locally advanced cervical cancer while reducing dose to bone marrow and other organs at risk. *Int J Radiat Oncol Biol Phys* 2004;60:505-512.
30. Guerrero M, Li XA, Ma L*, et al.* Simultaneous integrated intensity-modulated radiotherapy boost for locally advanced gynecological cancer: radiobiological and dosimetric considerations. *Int J Radiat Oncol Biol Phys* 2005;62:933-939.
31. Kavanagh BD, Schefter TE, Wu Q*, et al.* Clinical application of intensity-modulated radiotherapy for locally advanced cervical cancer. *Semin Radiat Oncol* 2002;12:260-271.
32. Marnitz S, Stromberger C, Kawgan-Kagan M*, et al.* Helical tomotherapy in cervical cancer patients: simultaneous integrated boost concept: technique and acute toxicity. *Strahlenther Onkol* 2010;186:572-579.

33. Mutic S, Malyapa RS, Grigsby PW*, et al.* PET-guided IMRT for cervical carcinoma with positive para-aortic lymph nodes-a dose-escalation treatment planning study. *Int J Radiat Oncol Biol Phys* 2003;55:28-35.
34. Fonteyne V, De Gersem W, De Neve W*, et al.* Hypofractionated Intensity-Modulated Arc Therapy for lymph node metastasized prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;75:1013-1020.
35. Madani I. Evolution of IMRT for Head and Neck cancer: from organ-sparing to intra-tumor dose painting. Ph.D. Dissertation. Ghent; 2008.
36. Vanderstraeten B, De Gersem W, Duthoy W*, et al.* Implementation of biologically conformal radiation therapy (BCRT) in an algorithmic segmentation-based inverse planning approach. *Phys Med Biol* 2006;51:N277-286.
37. Galvin JM, De Neve W. Intensity modulating and other radiation therapy devices for dose painting. *J Clin Oncol* 2007;25:924-930.
38. Emami B, Lyman J, Brown A*, et al.* Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;21:109-122.
39. Mahantshetty U, Jamema S, Engineer R*, et al.* Whole abdomen radiation therapy in ovarian cancers: a comparison between fixed beam and volumetric arc based intensity modulation. *Radiation Oncology*;5:106.
40. De Neve W, De Wagter C, De Jaeger K*, et al.* Planning and delivering high doses to targets surrounding the spinal cord at the lower neck and upper mediastinal levels: static beam-segmentation technique executed with a multileaf collimator. *Radiother Oncol* 1996;40:271-279.
41. Brahme A, Roos JE, Lax I. Solution of an integral equation encountered in rotation therapy. *Phys Med Biol* 1982;27:1221-1229.
42. De Meerleer G. Multileaf collimation and intensity modulated radiotherapy: initial clinical applications. Ph.D. Dissertation. Ghent; 2000.
43. De Gersem W. IMRT and IMAT engineering the evolution from organ avoidance to dose painting. Ph.D. Dissertation. Ghent; 2008.
44. Fonteyne V. Intensity Modulated Radiotherapy and Arc Therapy for prostate cancer: clinical results and new perspectives. Ph.D. Dissertation. Ghent; 2010.
45. Veldeman L, Madani I, Hulstaert F*, et al.* Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. *Lancet Oncol* 2008;9:367-375.
46. Duthoy W, De Gersem W, Vergote K*, et al.* Clinical implementation of intensity-modulated arc therapy (IMAT) for rectal cancer. *Int J Radiat Oncol Biol Phys* 2004;60:794-806.
47. Duprez F. Modern IMRT for head and neck cancer: a paradoxical paradigm of simultaneous dose-escalation and de-escalation. Ph.D. Dissertation. Ghent; 2010.
48. Vanderstraeten B. Biologically conformal radiation therapy and Monte Carlo dose calculations in the clinic. Ph.D. Dissertation. Ghent; 2007.
49. Kirwan JM, Symonds P, Green JA*, et al.* A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. *Radiother Oncol* 2003;68:217-226.
50. Hogberg T, Signorelli M, de Oliveira CF*, et al.* Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer - Results from two randomised studies. *European Journal of Cancer* 2010;46:2422-2431.
51. Staffurth J. A review of the clinical evidence for intensity-modulated radiotherapy. *Clin Oncol (R Coll Radiol)* 2010;22:643-657.
52. Ahamad A, D'Souza W, Salehpour M*, et al.* Intensity-modulated radiation therapy after hysterectomy: comparison with conventional treatment and sensitivity of the

normal-tissue-sparing effect to margin size. *Int J Radiat Oncol Biol Phys* 2005;62:1117-1124.
53. Chen Q, Izadifar N, King S*, et al.* Comparison of IMRT with 3-D CRT for gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2001;51:332.
54. Forrest J, Presutti J, Davidson M*, et al.* A Dosimetric Planning Study Comparing Intensity-modulated Radiotherapy with Four-field Conformal Pelvic Radiotherapy for the Definitive Treatment of Cervical Carcinoma. *Clinical Oncology* 2011; 24:e63-70.
55. Georg P, Georg D, Hillbrand M*, et al.* Factors influencing bowel sparing in intensity modulated whole pelvic radiotherapy for gynaecological malignancies. *Radiother Oncol* 2006;80:19-26.
56. Heron DE, Gerszten K, Selvaraj RN*, et al.* Conventional 3D conformal versus intensity-modulated radiotherapy for the adjuvant treatment of gynecologic malignancies: a comparative dosimetric study of dose-volume histograms small star, filled. *Gynecol Oncol* 2003;91:39-45.
57. Hsieh CH, Wei MC, Lee HY*, et al.* Whole pelvic helical tomotherapy for locally advanced cervical cancer: technical implementation of IMRT with helical tomotherapy. *Radiat Oncol* 2009;4:62.
58. Lujan AE, Mundt AJ, Yamada SD*, et al.* Intensity-modulated radiotherapy as a means of reducing dose to bone marrow in gynecologic patients receiving whole pelvic radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;57:516-521.
59. Mell LK, Tiryaki H, Ahn KH*, et al.* Dosimetric comparison of bone marrow-sparing intensity-modulated radiotherapy versus conventional techniques for treatment of cervical cancer. *Int J Radiat Oncol Biol Phys* 2008;71:1504-1510.
60. Roeske JC, Lujan A, Rotmensch J*, et al.* Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2000;48:1613-1621.
61. Wong E, D'Souza DP, Chen JZ*, et al.* Intensity-modulated arc therapy for treatment of high-risk endometrial malignancies. *Int J Radiat Oncol Biol Phys* 2005;61:830-841.
62. Du XL, Tao J, Sheng XG*, et al.* Intensity-modulated radiation therapy for advanced cervical cancer: A comparison of dosimetric and clinical outcomes with conventional radiotherapy. *Gynecol Oncol* 2011;125:151-157.
63. Chen MF, Tseng CJ, Tseng CC*, et al.* Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;67:1438-1444.
64. Chen YJ, Liu A, Tsai PT*, et al.* Organ sparing by conformal avoidance intensity-modulated radiation therapy for anal cancer: dosimetric evaluation of coverage of pelvis and inguinal/femoral nodes. *Int J Radiat Oncol Biol Phys* 2005;63:274-281.
65. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 2008;26:5802-5812.
66. Carcopino X, Houvenaeghel G, Buttarelli M*, et al.* Equivalent survival in patients with advanced stage IB-II and III-IVA cervical cancer treated by adjuvant surgery following chemoradiotherapy. *Eur J Surg Oncol* 2008;34:569-575.
67. Houvenaeghel G, Lelievre L, Buttarelli M*, et al.* Contribution of surgery in patients with bulky residual disease after chemoradiation for advanced cervical carcinoma. *Eur J Surg Oncol* 2007;33:498-503.
68. Houvenaeghel G, Lelievre L, Gonzague-Casabianca L*, et al.* Long-term survival after concomitant chemoradiotherapy prior to surgery in advanced cervical carcinoma. *Gynecol Oncol* 2006;100:338-343.

69. Keys HM, Bundy BN, Stehman FB*, et al.* Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. *Gynecol Oncol* 2003;89:343-353.
70. Morice P, Uzan C, Zafrani Y*, et al.* The role of surgery after chemoradiation therapy and brachytherapy for stage IB2/II cervical cancer. *Gynecol Oncol* 2007;107:S122-124.
71. Mundt AJ, Roeske JC, Lujan AE*, et al.* Initial Clinical Experience with Intensity-Modulated Whole-Pelvis Radiation Therapy in Women with Gynecologic Malignancies. *Gynecol Oncol* 2001;82:456-463.
72. Chargari C, Magne N, Dumas I*, et al.* Physics contributions and clinical outcome with 3D-MRI-based pulsed-dose-rate intracavitary brachytherapy in cervical cancer patients. *Int J Radiat Oncol Biol Phys* 2009;74:133-139.
73. Pötter R, Georg P, Dimopoulos JCA*, et al.* Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol* 2011;100:116-123.
74. Tan LT, Coles CE, Hart C*, et al.* Clinical impact of computed tomography-based image-guided brachytherapy for cervix cancer using the tandem-ring applicator - the Addenbrooke's experience. *Clin Oncol (R Coll Radiol)* 2009;21:175-182.
75. Haie-Meder C, Morice P, Castiglione M. Cervical cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2008;19 Suppl 2:ii17-18.
76. Classe JM, Rauch P, Rodier JF*, et al.* Surgery after concurrent chemoradiotherapy and brachytherapy for the treatment of advanced cervical cancer: morbidity and outcome: results of a multicenter study of the GCCLCC (Groupe des Chirurgiens de Centre de Lutte Contre le Cancer). *Gynecol Oncol* 2006;102:523-529.
77. Sahdev A. Cervical tumors. *Semin Ultrasound CT MR* 2010;31:399-413.
78. Liyanage SH, Roberts CA, Rockall AG. MRI and PET scans for primary staging and detection of cervical cancer recurrence. *Womens Health (Lond Engl)* 2010;6:251-267; quiz 268-259.
79. Magne N, Chargari C, Vicenzi L*, et al.* New trends in the evaluation and treatment of cervix cancer: the role of FDG-PET. *Cancer Treat Rev* 2008;34:671-681.
80. Flueckiger F, Ebner F, Poschauko H*, et al.* Cervical cancer: serial MR imaging before and after primary radiation therapy--a 2-year follow-up study. *Radiology* 1992;184:89-93.
81. Vincens E, Balleyguier C, Rey A*, et al.* Accuracy of magnetic resonance imaging in predicting residual disease in patients treated for stage IB2/II cervical carcinoma with chemoradiation therapy : correlation of radiologic findings with surgicopathologic results. *Cancer* 2008;113:2158-2165.
82. Belgian Cancer Registry. Cancer Incidence in Belgium, 2008. Brussels; 2011.
83. Ayhan A, Reed N, Gultekin M*, et al.* Textbook of Gynaecologic Oncology. 2nd ed. Ankara: Hünes Publishing; 2011.
84. Dembo AJ. Abdominopelvic radiotherapy in ovarian cancer. A 10-year experience. *Cancer* 1985;55:2285-2290.
85. Dembo AJ. Epithelial ovarian cancer: the role of radiotherapy. *Int J Radiat Oncol Biol Phys* 1992;22:835-845.
86. Thomas GM, Dembo AJ. Integrating radiation therapy into the management of ovarian cancer. *Cancer* 1993;71:1710-1718.
87. Einhorn N, Lundell M, Nilsson B*, et al.* Is there place for radiotherapy in the treatment of advanced ovarian cancer? *Radiother Oncol* 1999;53:213-218.

88. Sorbe B. Consolidation treatment of advanced (FIGO stage III) ovarian carcinoma in complete surgical remission after induction chemotherapy: a randomized, controlled, clinical trial comparing whole abdominal radiotherapy, chemotherapy, and no further treatment. *Int J Gynecol Cancer* 2003;13:278-286.
89. von Gruenigen VE, Frasure HE, Reidy AM*, et al.* Clinical disease course during the last year in ovarian cancer. *Gynecol Oncol* 2003;90:619-624.
90. Choan E, Quon M, Gallant V*, et al.* Effective palliative radiotherapy for symptomatic recurrent or residual ovarian cancer. *Gynecol Oncol* 2006;102:204-209.
91. May LF, Belinson JL, Roland TA. Palliative benefit of radiation therapy in advanced ovarian cancer. *Gynecol Oncol* 1990;37:408-411.
92. Tinger A, Waldron T, Peluso N*, et al.* Effective palliative radiation therapy in advanced and recurrent ovarian carcinoma. *Int J Radiat Oncol Biol Phys* 2001;51:1256-1263.

Chapter 3

Publication 1:

Post-operative Intensity-Modulated Arc Therapy for cervical and endometrial cancer: a prospective report on toxicity.

Katrien Vandecasteele, M.D.[1], Philippe Tummers, M.D.[2], Amin Makar M.D., Ph.D.[2], Marc van Eijkeren, M.D., Ph.D. [1], Louke Delrue M.D.[3], Hannelore Denys M.D. Ph.D. [4] , Bieke Lambert M.D., Ph.D. [5], Anne-Sophie Beerens M.D. [6], Rudy Van den Broecke, M.D., Ph.D.[2], Kathleen Lambein M.D.[6], Valerie Fonteyne, M.D., Ph.D. [1],Gert De Meerleer M.D., Ph.D[1].

Affiliation:
Department of [1]Radiation Oncology, [2]Gynaecologic Oncology, [3]Radiology, [4]Medical Oncology, [5]Nuclear Medicine and [6]Pathology at Ghent University Hospital, Ghent, Belgium

Int J Radiat Oncol Biol Phys. 2012 Feb 27. [Epub ahead of print]

There is no conflict of interest

Key words: postoperative radiotherapy, IMAT, IMRT, endometrial cancer, cervical cancer.

Summary
A prospective report on toxicity in cervical (n=25) and endometrial (n=41) cancer patients treated with postoperative radiotherapy using intensity modulated arc therapy (IMAT). Apart from 12% grade 3 hematologic toxicity, ≥ grade 3 acute toxicity was very low (2% genito-urinary and no gastro-intestinal). No severe (≥ grade 3) late toxicity was noted. Para-aortic lymph node (PALN) irradiation is feasible when IMAT is used. Concomitant chemotherapy and PALN irradiation influences acute but not late toxicity.

Abstract

Purpose
To report on toxicity after postoperative Intensity-Modulated Arc Therapy (IMAT) for cervical (CC) and endometrial cancer (EC).

Methods and Materials
Twenty-four CC and 41 EC patients were treated with postoperative IMAT. If indicated, para-aortic irradiation (preventive or when affected, PALN) and/or concomitant cisplatin (40 mg/m², weekly) was administered. The prescribed dose for IMAT was 45 Gy (CC, 25 fractions) and 46 Gy (EC, 23 fractions), followed by a brachytherapeutic boost if possible. Radiation related toxicity was assessed on in a prospective way. The effect of concomitant cisplatin and PALN irradiation was evaluated.

Results
Acute toxicity (n=65): Grade 3 and 2 acute gastrointestinal (GI) toxicity was observed in zero and 63% patients (79% CC; 54% EC) respectively. Grade 3 and 2 acute genito-urinary (GU) toxicity was observed in 1 and 18% of patients. Grade 2 (21%) and 3 (12%) hematologic toxicity (n=41) occurred only in CC patients. 17% CC patients and 2% EC patients experienced grade 2 fatigue and skin toxicity respectively. Adding cisplatin lead to an increase in > G2 nausea (57% vs 9%; p=0,01), G2 nocturia (24% vs 4%; p = 0,03), ≥ G2 hematologic toxicity (38% vs nil, p=0,003),≥ G2 leucopenia (33% vs nil, p=0,009) and a strong trend towards more fatigue (14% vs 2%; p=0,05). PALN irradiation lead to an increase of G2 nocturia (31% vs 4%, p=0,008) and a strong trend towards more > G2 nausea (44% vs 18%; p=0,052),
Late toxicity (n=45):
No Grade 3 or 4 late toxicity occurred. Grade 2 GI, GU toxicity and fatigue occurred in 4%, 9% and 1% of the patients. Concomitant cisplatin nor PALN irradiation increased late toxicity rates.

Conclusions
Postoperative IMAT for EC or CC is associated with low acute and late toxicity. Concomitant chemotherapy and PALN irradiation influences acute but not late toxicity.

Introduction

Postoperative pelvic radiotherapy is a standard component of the multimodality treatment in cervical and endometrial cancer (1). Conventionally, opposed fields or a 4-field box technique are used to try to ensure adequate coverage of the target volume leading to large volumes of gastrointestinal and urinary tracts within the treatment field, inevitable leading to important acute and late toxicity. Adding chemotherapy to the postoperative irradiation in cervical cancer has proven superiority by improving overall survival with some studied chemotherapies (1). A similar tendency has been shown in the adjuvant treatment of endometrial cancer (2) and currently the effect of adding chemotherapy to irradiation in the treatment of high-risk endometrial cancers is evaluated in the PORTEC-3 trial (Randomized phase III trial comparing concurrent chemoradiation and adjuvant chemotherapy with pelvic radiation alone in high risk and advanced stage endometrial carcinoma; clinical trials.gov: NCT00411138). Adding chemotherapy leads to a significant twofold increase in acute hematologic and gastro-intestinal acute toxicity, with 8% of chemoradiation patients suffering severe to life threatening adverse events (3). In the recent report of Hogberg et al. 27% of patients were unable to complete their scheduled chemotherapy schema (2). Conventional para-aortic lymph node (PALN) irradiation combined with chemotherapy has proven to be highly toxic with 50% grade 4 bowel-related acute and 34% grade 3 and 4 late toxicity (4).

Evidence of reduced toxicity by the use of Intensity Modulated Radiotherapy (IMRT) is provided for various tumour sites. In gynaecologic malignancies, dosimetric studies have reported reduced volumes of normal tissue irradiated using IMRT when compared to conventional techniques (5). This has been confirmed in the clinical setting (6-10). IMRT generates concave dose distributions to deliver a radical dose to the target volume, while reducing the volume of bladder, small bowel and rectum irradiated. With an increasing inner radius of the target volume, as in gynecologic malignancies, a greater number of beam incidences is needed to combine sufficient coverage of the PTV and sparing of the organs at risk (OAR) (5). Intensity-Modulated Arc Therapy (IMAT) is a fast and easy way to deliver a large number of beam incidences. The theoretical benefits of IMAT have been reported (11). This manuscript reports on the clinical benefits of IMAT (± chemotherapy) concerning acute and late toxicity in the postoperative treatment of cervical and endometrial cancer.

Materials and Methods

This monocentric, prospective study (approved by the local ethical committee), was undertaken between January 2007 and April 2011. Inclusion criteria were: endometrial (EC) or cervical cancer (CC) patients eligible for postoperative pelvic radiation therapy after hysterectomy (with or without lymphadenectomy) or resection of a local recurrence, absence of distant metastases (apart from affected para-aortic lymph nodes); World Health Organization (WHO) score 0-2 (12); absence of any condition hampering compliance with the study protocol and follow-up; ability to understand and sign informed consent.

Patients were assessed on and operated by the referring gynaecologic oncologist. Surgery consisted of hysterectomy ± pelvic lymphadenectomy or resection of the local recurrence; suspicious (clinically or radiographically) pelvic or periaortic lymph nodes were removed. FIGO (International Federation of Gynecology and Obstetrics) 2009 staging (UICC TNM Classification of Malignant Tumours, 7th edition) was assigned on the basis of surgical and pathological findings. Eligibility for postoperative radiotherapy was assessed on in a multidisciplinary consult meeting (gynaecologic oncologists, radiotherapists, medical oncologist, radiologists and pathologists). If indicated, concomitant cisplatin (40 mg/m², weekly) was administered.

Postoperative radiotherapy consisted of IMAT followed by a brachytherapeutic boost (n=58) to the vaginal vault or an external boost if brachytherapy was technically or medically not

feasible (n=2). From 1/2/2009 onwards, if pelvic positive lymph nodes were found in the pathologic specimen of CC patients, preventive PALN irradiation was performed. Para-aortic irradiation was always performed if PALN were affected.

Patients

Twenty-four CC and 41 EC patients were included (n=65). Median age at diagnosis was 65 years (35-83 years); Referred CC patients were significant younger than EC patients (median age: 49 vs 67 years; p<0,001; unpaired 2 sample t-test). Twenty CC patients (83%) received concomitant chemotherapy in comparison with 1 EC patients (2%). The reason for administering cisplatin to this EC patient was the extent of disease (FIGO IIIC1, 5 nodes positive).

Details on patient and tumour characteristics and therapy can be found in table 1 and Figure 1. Reasons for not performing a boost were: refusal by the patient (n=4) or progression of disease (n=1, metastatic disease).

Table 1: patient characteristics

	ALL PATIENTS	CERVIX	ENDOMETRIUM
	n=65	n=24	n=41
Age (yrs) at diagnosis			
median	65	49	67
range	35-83	35-71	50-83
Follow-up in months			
median	18	23	15
range	3-53	5-53	3-51
N+ at diagnosis			
n patients	29 (57%)	17 (74%)	12 (43%)
Chemotherapy			
n	21 (32%)	20 (83%)	1 (2%)
Para-aortic irradiation			
n	16 (25%)	12 (50%)	4 (10%)
Histology			
squamous	17 (71%)	17 (71%)	0
adeno	10 (15%)	6 (25%)	4 (10%)
endometroid adeno	37 (57%)	1 (2%)	36 (88%)
serous papillary	1 (1%)	0	1 (2%)
Grade			
1	14 (22%)	0	14 (34%)
2	23 (35%)	12 (50%)	11 (27%)
3	26 (40%)	11 (46%)	15 (37%)
not reported	2 (3%)	1 (4%)	1 (2%)
FIGO stage (TNM 2009)			
I	28 (43%)	13 (54%)	15 (37%)
II	11 (17%)	5 (21%)	6 (15%)
III	17 (26%)	2 (9%)	15 (36%)
IVA	1 (1%)	1 (4%)	0
IVB	3 (5%)	2 (8%)	1 (2%)
recurrence	5 (8%)	1 (4%)	4 (10%)
Boost			
external	2 (3%)	0	2 (5%)
brachytherapeutic	58 (88%)	22 (92%)	36 (88%)
median dose	17Gy	17,5Gy	17Gy
min-max dose	11-21Gy	11-21Gy	15-20Gy
no boost	5 (8%)	2 (8%)	3 (7%)

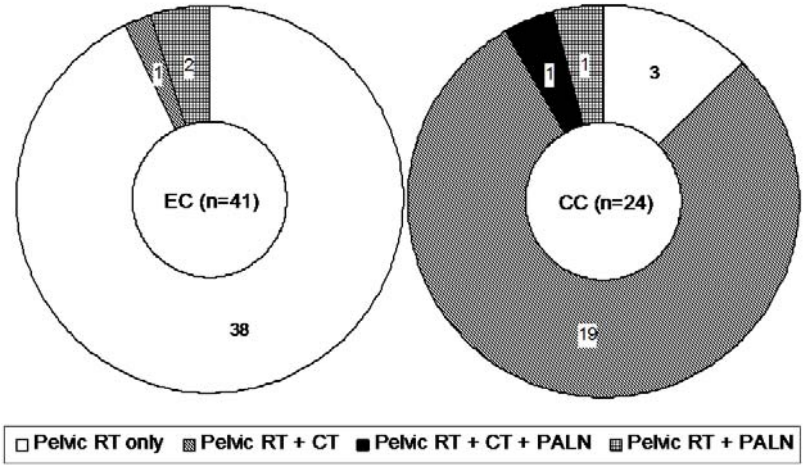

Figure 1:
EC: endometrial cancer; CC: cervical cancer; RT: radiotherapy; CT: Chemotherapy; PALN: Para-aortic Lymph node irradiation.

IMAT

Pre-treatment imaging consisted of CT (Siemens Somatom 4+, Siemens, Erlangen, Germany) performed in treatment position. If distant metastasis still had to be excluded, CT was replaced by ^{18}FDG PET-CT (Gemini, Philips, Eindhoven, The Netherlands). The CT images were considered as the primary image data set. CT slice thickness and interslice distance were 5 mm. No attempts were made to reduce bladder and rectal filling. IV- contrast (Visipaque ^{TM}, GE healthcare, Diegem, Belgium) was used to improve the visibility of the iliac vessels.

Target delineation

The clinical target volume (CTV) was the union of the CTV_T (operation bed, superior third to half of the vagina) and the CTV_N (presacral and obturator region, common, internal and external iliac lymph nodes; para-aortic lymph nodes were included when proven positive or if preventive irradiation was needed). The planning target volume of the CTV_T (PTV_T) was created using a 3-dimensional anisotropic expansion of 10, 7 and 7 mm in the anteroposterior, left-right and supero-inferior direction respectively. Using a 3-dimensional expansion of respectively 5 mm around CTV_N, PTV_N was created. For planning reasons, PTV_N and PTV_T were summed to form the definitive PTV. As from 2008, target delineation was performed in consensus with the guidelines of Small et al. (13). The rectum, sigmoid, small bowel, bladder and cauda equina (in case of PALN irradiation also both kidneys and the spinal cord) were defined as organs at risk.

Dose objectives for planning:

The dose to be received by 98% of the volume (D_{98}) of the PTV was 45 Gy (cervical cancer) and 46 Gy (endometrial cancer) delivered in 25 and 23 fractions respectively. The treatment fractionation was altered to 25 fractions of 1, 8 Gy for the one EC patient who received concomitant cisplatin. Dose objectives/constraints can be found in table 2.

Table 2: Dose objectives and constraints.

Target	dose objectives
PTV_N/T and PTV	D98 ≥ 45 Gy (CC) or 46 Gy (EC) and D02 < 52 Gy (CC) or 53 Gy (EC)
organ at risk	**dose constraints**
rectum	D02 ≤ 66.9 Gy V41 < 84% V50 < 69%
sigmoid	D02 ≤ 66.9 Gy V41 < 84% V50 < 69%
small bowel	D02 ≤ 66 Gy V40 < 30%
bladder	D02 ≤ 69.3 Gy
cauda equina	D02 ≤ 50 Gy
spinal cord	D02 ≤ 50 Gy
kidney	D50 ≤ 18 Gy

PTV_N/T: PTV_N, PTV_T; Dx < z Gy: no more than x% of the volume should receive more than z Gy; Vx < z%: the volume receiving more than x Gy should not exceed z%.

Planning procedure and delivery

The IMAT planning procedure and Quality Assurance has been described previously (14). An example of a dose distribution can be found in figure 2. The arcs for PTV_T were generated using an anatomy based segmentation tool with the rectum as exclusion structure. The arcs for PTV were created using a manually delineated exclusion structure including large parts of the intestinal cavity and bladder (14). All arcs used a 0° couch isocenter rotation and a single isocenter. If PALN were included, a separate 360° arc around this region was created.

All patients were treated in supine position using a knee and ankle fix (Cablon Medical, Leusden, The Netherlands), arms above the head. Treatment was done with 18-MV photons of an Elekta SL18 series Linear Accelerator (SliPlus, Elekta, Crawley, UK) equipped with standard MLC and prototype dynamic control software to deliver IMAT in local service mode. Patient positioning was controlled by electronic portal imaging (14). Brachytherapy (vaginal ovoids) was given within 14 days after the end of external beam RT. The technique used pulsed dose rate with hourly pulses of 0.6 Gy at 0.5 cm from the surface of the applicator, including overnight treatment (microSelectron PDR, Nucletron BV, Veenendaal, the Netherlands or GammamedPlus, Varian Medical Systems Inc., Palo Alto, USA). Doses from 11 to 21 Gy were given.

Follow-up and assessment of disease control

Patients were seen weekly during treatment, 1 and 3 months thereafter. Thereafter, follow-up was scheduled three-monthly (first two years), 6-monthly (year 3-5) and annually.

Endpoints and analysis.

The endpoint of this study was the evaluation of radiation related toxicity (acute and late) for the whole treatment group and both groups separately. The effect of concomitant administration of cisplatin and PALN irradiation was evaluated (within the whole treatment group).

Acute radiation toxicity was scored weekly during IMAT and at 10 days, 1 and 3 months thereafter. *Late radiation toxicity* (toxicity occurring >3 months after IMAT or acute toxicity

lasting longer than 3 months) was scored at every follow-up visit. Used scoring systems can be found in table 3 and 4 (15-17).
For statistical analysis a chi-square test (SPSS 15.0, SPSS, Inc., Chicago, IL) was performed. Statistical significance level was set at $p < 0, 05$.

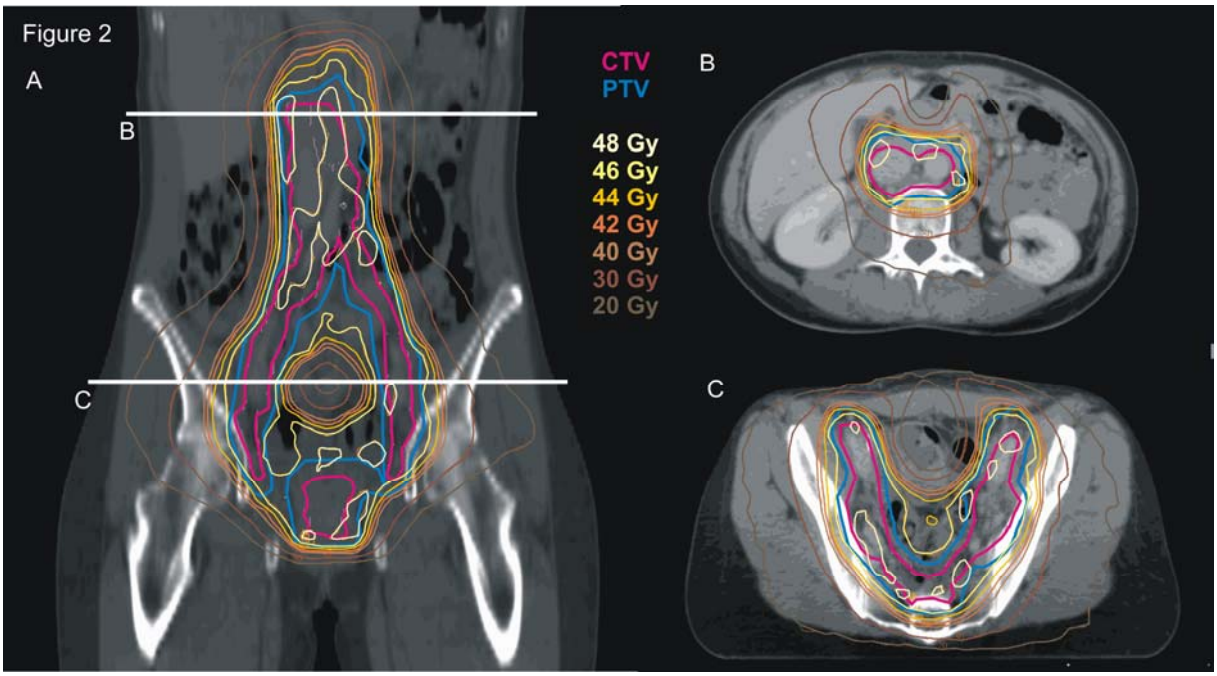

Figure 2: Dose distributions.
Dose distribution through the target volume in a coronal plane (A) and in a transversal plane at the level of the kidneys (B) and the pelvis (C).

Results

Acute and late toxicity was scored in all and 45 (69%) patients respectively.

1. *Acute radiation related toxicity*

Details concerning acute toxicity are presented in table 3.

Gastro-intestinal toxicity

No CC or EC patient experienced Grade 3 or more GI toxicity. One EC patient was operated on for intestinal sub-obstruction within 1 week after ending IMAT. The first signs of sub-obstruction already started after the second fraction of radiotherapy (4Gy). Postoperative anatomopathologic findings demonstrated postoperative adhesions without any sign of radiation-enteritis. The patient is free of GI symptoms 24 months after surgery.
We observed grade 2 toxicity in 19 CC (79%) and 22 EC (54%) patients respectively. The 3 most frequent symptoms for grade 2 toxicity were increased frequency (54%), nausea (50%) and abdominal cramps (17%) in CC patients and frequency (49%), abdominal cramps (22%) and abdominal discomfort (12%) in EC patients.
Adding cisplatin (n=21) lead to a significant increase in ≥ G2 nausea (57% vs 9%, $p < 0,01$). The irradiation of PALN showed a strong trend towards an increase in ≥ G2 nausea (44% vs 18%; p=0,052).

Genito-Urinary toxicity

Only 1 patient (EC) experienced grade 3 pollakisuria. No other Grade 3 GU toxicity was observed. Seven CC (29%) and 5 EC (12%) patients developed grade 2 GU toxicity, with nocturia being the most frequently observed in CC patients (n=6). Adding chemotherapy significantly increased the incidence of grade 2 nocturia (24% vs 4%; $p = 0,03$). The same observation was made if PALN irradiation was added to the treatment (31% vs 4%, p=0,008).

Hematologic toxicity

Hematologic toxicity was scored in 41 patients (CC=24; EC=17). Grade 2 (n=5; 21%) and 3 (n=3; 12%) hematologic toxicity occurred only in CC patients and consisted mainly of leucopenia (G2: n=5; 21% and G3: n=2; 8%) and anaemia (G3: n=1; 4%). PALN irradiation did not influence hematologic toxicity. Grade ≥2 hematologic toxicity (38% vs nil, p=0,003) and more specifically leucopenia (33% vs nil, p=0,009) occurred only and significantly more if IMAT was combined with chemotherapy.

Skin toxicity and fatigue

Four CC patients (17%) experienced grade 2 fatigue whereas 1 EC patient (2%) developed grade 2 skin toxicity.

We observed a strong trend towards more significant fatigue if chemotherapy was included (14% vs 2%; p=0,05).

	ALL (n=65)			CC (n=24)			EC (n=41)		
	G1	**G2**	**G3**	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**
GASTRO-INTESTINAL	**32**	**63**	**0**	**21**	**79**	**0**	**39**	**54**	**0**
Anorexia	17	5	0	29	8	0	10	2	0
Nausea	17	25	0	12	50	0	20	10	0
Frequency	37	51	0	37	54	0	37	49	0
Incontinence	5	1	0	4	0	0	5	2	0
Rectal Blood Loss	6	0	0	5	0	0	8	0	0
Abdominal Cramps	35	20	0	37	17	0	34	22	0
Urgency	31	6	0	32	7	0	29	4	0
Mucus Loss	8	0	0	8	0	0	7	0	0
Anal Pain	6	0	0	12	0	0	2	0	0
Abdominal Discomfort	32	8	0	27	5	0	42	12	0
URINARY	**49**	**18**	**1**	**50**	**29**	**0**	**49**	**12**	**2**
Pollakisuria	34	5	1	42	4	0	29	5	2
Nycturia	38	11	0	29	25	0	44	2	0
Hematuria	1	0	0	0	0	0	1	0	0
Dysuria	32	1	0	33	4	0	32	0	0
Urge	37	3	0	37	0	0	37	5	0
Incontinence	11	1	0	8	0	0	12	2	0
HEMATOLOGIC*	**24**	**12**	**7**	**25**	**21**	**12**	**4**	**0**	**0**
Hemoglobin	15	0	2	25	0	4	0	0	0
White Blood cell Count	22	12	5	21	21	8	24	0	0
Neutrophils	0	0	0	0	0	0	0	0	0
Platelets	2	0	0	4	0	0	0	0	0
FATIGUE	**17**	**6**	**0**	**17**	**17**	**0**	**17**	**0**	**0**
SKIN	**3**	**2**	**0**	**0**	**0**	**0**	**5**	**2**	**0**

Table 3: acute radiation related toxicity

* Hematologic toxicity scoring is based on 41 patients (CC: 24 and EC: 17).

Acute gastro-intestinal (GI) toxicity was scored using a combination of the RTOG scoring system, the scale of GI urgency and incontinence determined by Yeoh et *al.* (17) and an in-house developed scale for rectal blood loss (16). Genitourinary (GU) toxicity was scored using the RTOG scale extended with an in-house developed scale for incontinence (15). Hematologic and skin toxicity was scored according to the RTOG scoring system.

2. Late radiation related toxicity

The median follow-up (range) of all, CC and EC patients was 23 (8-53); 29 (9-53) and 22 (8-51) months respectively. No Grade 3 or 4 toxicity occurred. Adding chemotherapy (n=17) or PALN irradiation (n=14) did not increase late toxicity rates. Details concerning late toxicity can be found in table 4.

Gastro-intestinal (GI) toxicity

Grade 2 GI toxicity occurred in 4% and 5% of EC and CC patients respectively and consisted mainly of a rise in GI frequency in both groups and abdominal cramps in the EC group.

Genitourinary (GU) toxicity

Grade 2 GU toxicity occurred in 5 and 12% of CC and EC patients respectively and consisted mainly of a rise in urinary urge/incontinence in the CC group and urinary incontinence and nocturia in the EC group.

Skin toxicity and fatigue

Grade 2 fatigue occurred in 1 CC patient.

No late skin toxicity occurred.

Table 4: late radiation related toxicity

	ALL (n=45)		CC (n=20)		EC (n=25)	
	G1	G2	G1	G2	G1	G2
GASTRO-INTESTINAL	**29**	**4**	**25**	**5**	**32**	**4**
Anorexia	0	0	0	0	0	0
Nausea	0	0	0	0	0	0
Frequency	18	4	20	5	16	4
Incontinence	0	0	0	0	0	0
Rectal Blood Loss	2	0	0	0	4	0
Abdominal Cramps	9	2	15	0	4	4
Urgency	4	0	5	0	4	0
Mucus Loss	7	0	10	0	4	0
Anal Pain	0	0	0	0	0	0
Abdominal Discomfort	4	0	5	0	4	0
URINARY	**13**	**9**	**0**	**5**	**24**	**12**
Pollakisuria	9	0	5	0	12	0
Nycturia	2	2	5	0	0	4
Hematuria	2	0	5	0	0	0
Dysuria	2	0	0	0	4	0
Urge	4	2	0	5	8	0
Incontinence	7	7	0	5	12	8
FATIGUE	**9**	**2**	**10**	**5**	**8**	**0**
SKIN	**0**	**0**	**0**	**0**	**0**	**0**

Late GI toxicity was scored using the RTOG and Radiation Induced Lower Intestine Toxicity scoring scale (16). Genitourinary (GU) toxicity was scored using the RTOG scale extended with an in-house developed scale for incontinence (15). Hematologic and skin toxicity was scored according to the RTOG scoring system.

Discussion

Conventional 2-field and 4-field postoperative radiation therapy for CC or EC is known to be associated with substantial acute and late side-effects*. This is not surprising considering the large volumes of small intestine, bladder, rectum and sigmoid colon within the concave shaped PTV. With the introduction of IMRT, dosimetrical studies show a significant decrease in dose to the normal tissues (5). This was confirmed clinically by several retrospective studies. In 2002, Mundt et al. (9) reported a significant reduction of overall toxicity and a disappearance of grade 3 toxicity using IMRT (no concomitant chemotherapy) when compared to conventional techniques. Others compared concomitant radiochemotherapy using IMRT or a box technique (6, 7). A significant decrease in grade 1-2 and grade 2 acute GI toxicity of 44% (36% vs 80%) (7) and 31% (60% vs 91%) was noticed (9). Chronic GI toxicity decreased significantly by around 30% (7, 18). Although acute grade 2 GU toxicity is not unequivocally lowered by IMRT (7, 9) late GU toxicity rates were significantly decreased (9% vs 23%) (7). A similar significant reduction (29%) was seen for acute ≥ grade 2 hematologic toxicity (6). Other series reported low toxicity rates but did not compare IMRT with conventional techniques (8, 10). The RTOG 0418 (A Phase II Study of Intensity Modulated Radiation Therapy (IMRT) to the Pelvis +/- Chemotherapy for Post-operative Patients with either Endometrial or Cervical Carcinoma) addressing a similar population reported comparable toxicity rates (19).

To the best of our knowledge, the current study is the first to report on prospectively scored acute and late toxicity using IMAT in the postoperative setting for cervical or endometrial cancer. Our reported toxicity data lie within the spectrum of published data using intensity modulated techniques.

No attempts were made to reduce bladder and rectal filling. In postoperative setting however, a (weak) correlation between rectal filling and position shifts of the target was found (20). This is an ongoing controversy that will be taken into account in our future work.

As mentioned before, adding concomitant chemotherapy lead to superior overall survival above radiation therapy alone in the treatment of cervical cancer (1). However, this survival benefit is accompanied by a twofold increase in acute hematologic and GI toxicity, with 8% of chemoradiation patients suffering severe to life threatening events (3). In our series, no life threatening events were noted. Our acute toxicity data are consistent with the conclusions of Lukka et al. showing a significant increase in overall ≥ grade 2 acute GI toxicity by 25% (56 to 81%) and a two- (white cell count) to three-fold (platelet toxicity) increase in grade 3 toxicity when chemotherapy was added (1). Rather unexpected, adding cisplatin lead to a significant increase of nocturia. A possible explanation could be the effect of hydration (and subsequent dehydration at night) performed when administering chemotherapy. In concordance with Kirwans findings (3) no rise in late toxicity due to the effect of chemotherapy was found.

Prophylactic irradiation of PALN has shown to improve OS en DFS in a subgroup of cervical cancer patients (21). The use of concomitant chemotherapy and the resulting high toxicity rates (4) have lead to the omitment of this prophylactic para-aortic radiotherapy. If, however, prophylactic para-aortic irradiation is performed with modern radiation techniques such as

---

*Remark member of the examination committee: "Substantial acute and late effects: add references."

- Kirwan JM, Symonds P, Green JA, et al. A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. Radiother Oncol 2003;68:217-226.
- Kong A, Simera I, Collingwood M, et al. Adjuvant radiotherapy for stage I endometrial cancer: systematic review and meta-analysis. Ann Oncol 2007;18:1595-1604.
- Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 2010;375:816-823.
- Tan LT, Zahra M. Long-term survival and late toxicity after chemoradiotherapy for cervical cancer--the Addenbrooke's experience. Clin Oncol (R Coll Radiol) 2008;20:358-364.

IMRT (5) or IMAT, toxicity is acceptable and no increase in late toxicity nor life threatening toxicity is observed. We are aware that our data need to be confirmed since the number of patients treated with PALN is limited (n=4). However, it might be of interest to re-investigate the role of preventive PALN radiation with modern techniques in future randomized trials.
Retrospective comparative studies have shown at least comparable outcomes with IMRT compared to conventional techniques (7, 8, 10). Considering the 45 patients of our study with a follow-up longer than 6 months we found no regional failure and 1 local failure thus far. Longer follow-up is definitely warranted and clinical outcomes will be the subject of a separate paper.
It is our believe that conclusions from randomized trials always should be held in the light of the used technology. For instance, although a 72% reduction in pelvic relapse was seen for stage I endometrial cancer treated with external beam therapy, a trend towards survival benefit was shown only in patients with multiple risk factors such a Figo IB or grade 3. Due to an excess in toxicity risk the advise not to give external beam radiotherapy to patients with only 1 risk factor was given (22). Similarly, high GI toxicity rates are contributory to the conclusion of the PORTEC-2 trial (23). However, would this conclusion be the same if grade 3 toxicity was minimal to absent and grade 2 toxicity was halved when IMRT or IMAT were used? Hopefully these trials will be repeated with the use of IMRT or IMAT.
All studies, also the present one, are affected by limitations. The most important one is the lack of direct comparison with conventional techniques. In light of the published results concerning the toxicity comparison between conformal therapy and IMRT, IMAT was the treatment of choice for eligible patients in our treatment centre. The Ethics Committee of our hospital considered the use of conventional techniques not longer as ethical as it would expose our patients to higher toxicity rates.

Conclusion

In our experience, IMAT for endometrial and cervical cancer in the postoperative setting is associated with low acute and late toxicity. Concomitant chemotherapy leads to a significant raise in acute GI and haematological toxicity. Prophylactic para-aortic IMAT is correlated with an increase in acute G2 nocturia. Neither concomitant chemotherapy nor PALN influences late toxicity.

References

1. Lukka H, Hirte H, Fyles A*, et al.* Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer--a meta-analysis. *Clin Oncol (R Coll Radiol)* 2002;14:203-212.
2. Hogberg T, Signorelli M, de Oliveira CF*, et al.* Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer - Results from two randomised studies. *European Journal of Cancer* 2010;46:2422-2431.
3. Kirwan JM, Symonds P, Green JA*, et al.* A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. *Radiother Oncol* 2003;68:217-226.
4. Grigsby PW, Heydon K, Mutch DG*, et al.* Long-term follow-up of RTOG 92-10: cervical cancer with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys* 2001;51:982-987.
5. Portelance L, Chao KS, Grigsby PW*, et al.* Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical

cancer receiving pelvic and para-aortic irradiation. *Int J Radiat Oncol Biol Phys* 2001;51:261-266.
6. Brixey CJ, Roeske JC, Lujan AE*, et al.* Impact of intensity-modulated radiotherapy on acute hematologic toxicity in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2002;54:1388-1396.
7. Chen MF, Tseng CJ, Tseng CC*, et al.* Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;67:1438-1444.
8. Hasselle MD, Rose BS, Kochanski JD*, et al.* Clinical Outcomes of Intensity-Modulated Pelvic Radiation Therapy for Carcinoma of the Cervix. *International Journal of Radiation Oncology*Biology*Physics*;In Press, Corrected Proof.
9. Mundt AJ, Lujan AE, Rotmensch J*, et al.* Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2002;52:1330-1337.
10. Beriwal S, Jain SK, Heron DE*, et al.* Clinical outcome with adjuvant treatment of endometrial carcinoma using intensity-modulated radiation therapy. *Gynecol Oncol* 2006;102:195-199.
11. Cozzi L, Dinshaw KA, Shrivastava SK*, et al.* A treatment planning study comparing volumetric arc modulation with RapidArc and fixed field IMRT for cervix uteri radiotherapy. *Radiotherapy and Oncology* 2008;89:180-191.
12. Oken MM, Creech RH, Tormey DC*, et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-655.
13. Small W, Jr., Mell LK, Anderson P*, et al.* Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys* 2008;71:428-434.
14. Vandecasteele K, De Neve W, De Gersem W*, et al.* Intensity-Modulated Arc Therapy with Simultaneous Integrated Boost in the Treatment of Primary Irresectable Cervical Cancer. *Strahlentherapie Und Onkologie* 2009;185:799-807.
15. De Meerleer G, Vakaet L, Meersschout S*, et al.* Intensity-modulated radiotherapy as primary treatment for prostate cancer: acute toxicity in 114 patients. *Int J Radiat Oncol Biol Phys* 2004;60:777-787.
16. Fonteyne V, De Neve W, Villeirs G*, et al.* Late radiotherapy-induced lower intestinal toxicity (RILIT) of intensity-modulated radiotherapy for prostate cancer: the need for adapting toxicity scales and the appearance of the sigmoid colon as co-responsible organ for lower intestinal toxicity. *Radiother Oncol* 2007;84:156-163.
17. Yeoh EE, Fraser RJ, McGowan RE*, et al.* Evidence for efficacy without increased toxicity of hypofractionated radiotherapy for prostate carcinoma: early results of a Phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2003;55:943-955.
18. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys* 2003;56:1354-1360.
19. Jhingran A, Winter K, Portelance L*, et al.* Efficacy and Safety of IMRT after Surgery in Patients with Endometrial Cancer: RTOG 0418 Phase II Study. *International journal of radiation oncology, biology, physics*;81:S45.
20. Jurgenliemk-Schulz IM, Toet-Bosma MZ, de Kort GA*, et al.* Internal motion of the vagina after hysterectomy for gynaecological cancer. *Radiother Oncol* 2011;98:244-248.

21. Rotman M, Pajak TF, Choi K*, et al.* Prophylactic extended-field irradiation of para-aortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas. Ten-year treatment results of RTOG 79-20. *JAMA* 1995;274:387-393.
22. Kong A, Johnson N, Cornes P*, et al.* Adjuvant radiotherapy for stage I endometrial cancer. *Cochrane Database Syst Rev* 2007:CD003916.
23. Nout RA, Smit VT, Putter H*, et al.* Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet*;375:816-823.

Chapter 4

Publication 2:

Intensity Modulated Arc Therapy with simultaneous integrated boost in the treatment for primary irresectable cervical cancer: treatment planning, quality control and clinical implementation.

Short Title: IMAT for cervical cancer.

Intensitätsmodulierte Strahlentherapie mit dem simultanen integrierten Boost zur Behandlung von primärem, nicht resezierbarem Gebärmutterhalskrebs: Behandlungsplan, Qualitätskontrolle und klinische Umsetzung.

Katrien Vandecasteele, MD[1], Wilfried De Neve MD, PhD[1], Werner De Gersem, Ir., PhD[1], Louke Delrue, MD[2], Leen Paelinck, Lic., PhD[1], Amin Makar, MD, PhD[3], Valérie Fonteyne MD[1], Carlos De Wagter, Ir., PhD[1], Geert Villeirs, MD, PhD[3] and Gert De Meerleer, MD, PhD[1].

Affiliation:
[1] *Department of Radiotherapy, Ghent University Hospital, Ghent, Belgium*
[2] *Department of Radiology, Ghent University Hospital, Ghent, Belgium*
[3] *Department of Gynaecology, Ghent University Hospital, Ghent, Belgium*

Strahlenther Onkol. 2009 Dec;185(12):799-807.

There is no conflict of interest
Key words: IMAT, cervical cancer, SIB, irresectable.
Schlüsselwörter: IMAT, Gebärmutterhalskrebs, SIB.

ABSTRACT

Purpose:

To report on the planning procedure, quality control and clinical implementation of Intensity Modulated Arc Therapy (IMAT) delivering a simultaneous integrated boost (SIB) in patients with primary irresectable cervix carcinoma.

Methods and Materials:

Six patients underwent PET-CT and MRI before treatment planning. Prescription (25 fractions) was:

1. A median dose (D_{50}) of 62, 58 and 56 Gy to the primary tumour (GTV_cervix), primary clinical target volume (CTV_cervix) and its planning target volume (PTV_cervix) respectively.
2. A D_{50} of 60 Gy to the PET-positive lymph nodes (GTV_nodes)
3. A minimal dose (D_{98}) of 45 Gy to the planning target volume of the elective lymph nodes (PTV_nodes).

IMAT-plans were generated using an anatomy-based exclusion tool with the aid of weight and leaf position optimisation. The dosimetrical delivery of IMAT was pre-clinically validated using radiochromic filmdosimetry.

Results:

Five to 9 arcs were needed to create valid IMAT plans. Dose constraints on D_{50} were not met in two patients (both GTV_cervix: 1 Gy and 3 Gy less). D_{98} for PTV_nodes was not met in 3 patients (1 Gy each). Film dosimetry showed excellent gamma-evaluation. There were no treatment interruptions.

Conclusion:

IMAT allows delivering a SIB to the macroscopic tumour without compromising the dose to the elective lymph nodes or the organs at risk. The clinical implementation is feasible.

ZUSAMMENFASSUNG

Ziel:

Bericht über Planung, Qualitätssicherung und klinische Umsetzung einer rotations-intensitätsmodulierten Strahlentherapie (IMAT) mit "Simultanen integrierten Boost" (SIB) bei Patientinnen mit primärem, nicht reserzierbarem Gebärmutterhalskarzinom.

Material und Methodik:

Bei sechs Patientinnen wurde vor der Behandlungsplanung eine PET/CT- und MRI-Untersuchung durchgeführt. Die Dosisverordnung (25 Fraktionen) betrug:

1. Mediane Dosis (D_{50}) von 62, 58 und 56 Gy für Primärtumor (GTV_cervix), primäres klinisches Zielvolumen (CTV_cervix) bzw. Planungszielvolumen (PTV_cervix).
2. Eine D_{50} von 60 Gy für PET-positive Lymphknoten (GTV_nodes)
3. Eine minimale Dosis (D_{98}) von 45 Gy für das Planungszielvolumen der elektiven Lymphknoten (PTV_nodes).

Die IMAT-Pläne wurden mit einem anatomiebasierten Ausschlusswerkzeug mit Hilfe der "Weight-and-Leaf-Position"-Optimierung erstellt. Die Dosimetrie der IMAT wurde vorklinisch anhand radiochromer Filmdosimetrie validiert.

Ergebnisse:

Zur Erzeugung vernünftiger IMAT-Pläne wurden fünf bis neun Rotationsfelder benötigt. In 2 Fällen konnten die Dosisbeschränkungen der $\mathbf{D_{50}}$ nicht eingehalten werden (GTV_cervix: 1 Gy bzw. 3 Gy niedriger**).** In 3 Fällen konnte D_{98} für PTV_nodes nicht erreicht werden (jeweils 1 Gy weniger). Die Filmdosimetrie ergab eine ausgezeichnete Gamma-Bewertung. Keine Behandlungsunterbrechungen.

Schlussfolgerung:
Die IMAT ermöglicht ein SIB-Verfahren bei makroskopischen Tumoren ohne Dosiskompromisse bei den elektiven Lymphknoten oder den Risikoorganen eingehegen zu müssen. Die klinische Umsetzung ist möglich.

Introduction

Based on randomized trials [34, 36, 41, 45, 46, 52] and meta-analyses [19, 30], the standard treatment for irresectable cervical cancer is concurrent cisplatin-based chemoradiation. The survival benefit above radiotherapy alone is 10% [19, 30]. Local recurrence is present in 6-14% and 20-25% of the patients with and without additional hysterectomy respectively [25, 30, 34, 41, 45, 46, 52]. The largest advantage for additional hysterectomy is observed for tumours ≥ 4 cm [25]. The rate of residual tumor in hysterectomy specimens after chemoradiation followed by "conventional" brachytherapy is 45-61% [1, 5, 25, 32, 44]. Residual tumor increases the rate of pelvic recurrence [5, 22, 39] and reduces progression-free survival [25].
With conventional technology, late grade ≥ 3 toxicity is present in up to 23% of the patients[*]. Cisplatin does not increase late toxicity [27, 31], suggesting that radiotherapy is the major determinant. Concerning brachytherapy (after external therapy), image guidance and MRI-guided target volume adaptation have led to acceptable toxicity and better local control [16, 43]. However, efforts to improve the external beam radiotherapy are needed.
Intensity Modulated Radiotherapy (IMRT) results in a better therapeutic ratio concerning pelvic tumours [2, 3, 6, 21, 23, 35, 42, 51]. In case of cervical cancer, the planning target volume (PTV) has a concave shape with a large internal radius (small intestine and bladder are positioned within). In such situations, a large number of intensity-modulated beams are needed to ensure adequate PTV coverage and sufficient sparing of the organs at risk [6, 11].
Intensity Modulated Arc Therapy (IMAT) is a new mean to deliver IMRT and is implemented for several tumor sites [11, 53]. IMAT has an infinite number of beams and is therefore theoretically a good solution to treat locally advanced cervical cancer. We developed a schedule of pre-operative radiochemotherapy that delivers a higher dose the primary tumor and involved lymph nodes without compromising the dose to the rest of the clinical target volume or OAR. This manuscript reports on the planning procedure, prescription levels, quality control and feasibility of IMAT in this indication.

Materials and Methods

This study involves 6 patients with irresectable cervical cancer. Staging and resectability were determined by gynaecological examination and imaging (magnetic resonance imaging (MRI) and ^{18}FDG PET-CT) [10, 20, 40]. If bladder or rectal invasion was suspected, cystoscopy and/or rectoscopy were performed

[*] Remark member of the examination *committee: "late grade ≥ 3 toxicity is up to 23%. This seems a high number, please give a reference and add more series, especially series published after 2006"*
- Kirwan JM, Symonds P, Green JA, et al. A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. Radiother Oncol 2003;68:217-26.
- Maduro JH, Pras E, Willemse PH, et al. Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. Cancer Treat Rev 2003;29:471-88.
- Tseng CJ, Chang CT, Lai CH, et al. A randomized trial of concurrent chemoradiotherapy versus radiotherapy in advanced carcinoma of the uterine cervix. Gynecol Oncol 1997;66:52-58.
Both reviews (Kirwan et al. & Maduro et al). criticise the lack of data on late toxicity. In the series reporting late toxicity 0 to 15% severe (≥ 3) late urologic toxicity and 0-23% severe (≥ 3) total (GI + urologic) toxicity is reported. This article was submitted in 2008, this is the reason why series after 2006 are lacking here. Possible more recent series where less toxicity is described could be:
- Pötter R, Georg P, Dimopoulos JCA, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol 2011;100:116-123.
- Hasselle MD, Rose BS, Kochanski JD, et al. Clinical Outcomes of Intensity-Modulated Pelvic Radiation Therapy for Carcinoma of the Cervix. Int J Radiat Oncol Biol Phys 2011;80:1436-1445.

For planning, an ^{18}FDG PET-CT (Gemini, Philips, Eindhoven, The Netherlands) was performed in treatment position. The CT images were considered as the primary image data set. CT slice thickness and interslice distance were 5 mm. No attempts were made to reduce bladder and rectal filling. IV-contrast (Visipaque™, GE Healthcare, Diegem, Belgium) was used to improve the visibility of the vessels. PET-images were acquired 50-60 minutes after injection of ^{18}FDG. The dose was calculated using the formula: ((body weight/10) +1) x 37 MBq. The PET-images were on-line fused with the CT images. All images were transferred through a local network to the Pinnacle planning system, version 6.2b (Philips Medical Systems, Andover, MA).
MR-images were acquired on a 1.5 Tesla MRI (Magnetom Symphony, Siemens, Erlangen, Germany) using T1-weighted gradient-echo localizer sequences, followed by 4 mm thick transverse, sagittal and coronal T2-weighted turbo spin-echo (TSE) images and T1 TSE images in the transverse plane. Together with a specialized radiologist (GV), the PET-CT and MR images were co-registrated. This method has been previously implemented for prostate cancer [50].

Target volume delineation

A. Primary tumor

The gross tumor volume of the primary tumor (**GTV_cervix)** was defined as the union of the PET-positive cervical lesion and the MRI-defined cervical tumor. The clinical target volume (**CTV_cervix**) was defined as the GTV_cervix, uterus, both parametria and vaginal upper 1/3. In cases with vaginal involvement, the CTV_cervix was caudally extended with 2 cm below the vaginal involvement. The planning target volume of the CTV_cervix (**PTV_cervix**) was created using a 3-dimensional anisotropic expansion of 10, 7 and 7 mm in the anteroposterior, left-right and supero-inferior direction respectively.

B. Lymph nodes.

FDG-avid lymph nodes were considered as malignant and delineated as **GTV_nodes**. The elective lymph node areas (**nodes**) included the common, internal and external iliac nodes, the obturator and presacral region. Using a 3-dimensional expansion of respectively 2 mm and 7 mm around **nodes**, the **CTV_ nodes** and **PTV_ nodes** was created. For planning reasons, PTV_nodes and PTV_cervix were summed: **PTV_all**.

C. Organs at Risk

The rectum, sigmoid, small bowel, bladder and femoral heads were defined as OAR .

D. Optimization Aid Volumes (OAV).

To avoid dose deposit at distance we created 3 OAV [8]:

1. A rim of 3 cm around the PTV_all (**rim3_el**).
2. A rim between 3 and 6 cm away from the PTV_all (**rim6_el**).
3. The tissue between rim6_el and skin: **sur6**.

Constraints for the OAV are presented in Table 1.

Dose objectives for planning

Details are presented in Table 1 and 3. The prescribed median dose (D_{50}) to the GTV_cervix, GTV_ nodes, CTV_cervix and PTV_cervix was 62, 60, 58 and 56 Gy respectively. D_{98} (dose exceeded by 98% of the volume) in the PTV_ nodes was 45 Gy. The treatment was delivered in 25 fractions. Consequently, the GTV_cervix, GTV_ nodes, CTV_cervix and PTV_cervix received 2.48, 2.40, 2.32 and 2.24 Gy per fraction respectively, resulting in a simultaneous integrated boost (SIB).

Physical and dosimetric quality assurance (QA) aspects

We developed an IMAT class solution for rectum carcinoma and whole abdominopelvic radiotherapy [12]. The arcs for PTV_cervix were generated using an anatomy based segmentation tool [7] with the rectum as exclusion structure. The arcs for PTV_all were created using a manually delineated exclusion structure (large parts of the small intestine and bladder). All arcs used a zero couch isocenter rotation and a single isocenter.

3D polymer gel dosimetry as validation method was described elsewhere [9, 49]. Following the strategy outlined in reference 34, (pages 117-128 by De Wagter) further QA was

Table 1: Volume and dose results of the different OAR.

	cc	D98	D50	D02		Dmean	V35 (%)	V40 (%)	V45 (%)	V50 (%)	V35 (cc)	V40 (cc)	V45 (cc)	V50 (cc)
				Constraint	Results									
rectum	37 (33-50)	25 (14-35)	48 (46-52)	65	57 (57-58)	47 (44-49)	92 (84-97)	86 (75-92)	75 (56-88)	58 (39-73)	34 (25-49)	31 (22-45)	28 (17-38)	15 (7-28)
sigmoid	118 (77-202)	1 (0-4)	44 (42-50)	65	57 (56-59)	39 (34-42)	70 (65-71)	57 (43-65)	52 (35-66)	44 (21-63)	80 (66-99)	77 (45-84)	65 (43-72)	50 (33-56)
small intestine	896 (597-1402)	24 (17-29)	51 (50-52)	65	59 (59-60)	47 (45-50)	24 (14-25)	17 (9-20)	11 (5-15)	6 (2-8)	123 (102-201)	88 (73-159)	50 (46-120)	24 (19-66)
bladder	87 (60-97)	29 (19-29)	53 (51-53)	65	59 (59-61)	49 (46-50)	93 (82-94)	86 (76-87)	74 (68-79)	60 (54-66)	81 (57-90)	75 (52-84)	65 (46-76)	50 (37-60)
femoral head	44 (34-51)	24 (20-30)	36 (32-42)	60	49 (43-54)	-	-	-	-	-	-	-	-	-
rim3_el	-	-	-	60	53 (46-56)	-	-	-	-	-	-	-	-	-
rim6_el	-	-	-	45	40 (34-44)	-	-	-	-	-	-	-	-	-
sur6	-	-	-	30	26 (23-27)	-	-	-	-	-	-	-	-	-

The results are presented as median (25^{th} - 75^{th} percentile). V_{35}, V_{40}, V_{45}, V_{50}: volume receiving 35, 40, 45 and 50 Gy expressed as percentage (%) and absolute volume (cc).

Tabelle 1:. Volumen- und Dosisergebnisse der verschiedenen OAR. Die Ergebnisse werden als Medianwerte (25 – 75 Perzentile) wiedergegeben. V_{35}, V_{40}, V_{45}, V_{50}: Volumina die 35, 40, 45 und 50 Gy erhalten, jeweils normiert aufgetragen über dem absoluten Volumen in cm^3.

Table 3: Data on volume, dose objectives and dose results of the target volumes. Results are presented as median

	volume (cc)	D_{98} (Gy)		D_{50} (Gy)		D_{02} (Gy)		Dmean (Gy)
		Dose objectives	Results	Dose objectives	Results	Dose objectives	Results	Results
GTV_cervix	104 (54-121)	58	58 (57-59)	62	62 (61-62)	≤ 64	64 (63-64)	61 (61-62)
GTV_nodes	4 (1-5)	58	60 (58-60)	60	61 (60-61)	≤ 62	61 (61-61)	60 (60-61)
CTV_cervix	201 (186-245)	54	55 (54-56)	58	60 (59-61)	≤ 64	63 (63-64)	60 (59-60)
CTV_nodes	322 (250-397)	46	47 (46-47)	48	53 (52-54)	≤ 62	60 (59-61)	53 (52-54)
PTV_cervix	462 (431-504)	50	50 (48-51)	56	58 (57-59)	≤ 64	63 (63-63)	58 (57-58)
PTV_nodes	693 (604-785)	45	44 (44-45)	47	52 (51-53)	≤ 62	60 (59-60)	52 (51-53)

(25^{th} - 75^{th} percentile). D_{98}, D_{50}, D_{02}: dose received by 98, 50 and 2% of the volume respectively. D_{mean}: mean dose; GTV_cervix, CTV_cervix, PTV_cervix: gross tumor volume, clinical target volume and planning target volume of the primary tumor respectively. GTV_nodes, CTV_ nodes, PTV_ nodes: gross tumor volume, clinical target volume and planning target volume of the lymph nodes.

Tabelle 3: Daten zu Volumen, Dosiszielen und Dosisergebnissen der Zielvolumen. Die Ergebnisse werden als Medianwerte (25 – 75 Perzentile) wiedergegeben. D_{98}, D_{50}, D_{02}: Dosis die in 98%, 50% und 2 % des Volumens absorbiert wurde. D_{mean}: Mittlere Dosis; GTV_cervix, CTV_cervix, PTV_cervix: "Gross Tumor Volume", Klinisches Zielvolumen und Planungszielvolumen des Primärtumors. GTV_nodes, CTV_ nodes, PTV_ nodes: "Gross Tumor Volume", Klinisches Zielvolumen und Planungszielvolumen der Lymphknoten.

streamlined into patient-specific QA by delivering the clinical treatment plan to "CarPet," an anthropomorphic pelvic phantom [18], transversally loaded with one or more radiochromic energy independent EBT films (International Specialty Products Corporation, Wayne, NJ, USA) [38] and by comparing the measured dose distributions to the ones that were computed for CarPet using the Pinnacle treatment planning system. This comparison was done using the gamma evaluation method [29] implemented in a MATLAB environment.

Clinical implementation

All patients were treated in supine position using a knee and ankle fix (Cablon Medical, Leusden, The Netherlands), arms above the head. Treatment was done with 18-MV photons of an Elekta SL18 series Linear Accelerator (SliPlus, Elekta, Crawley, UK) equipped with standard MLC and prototype dynamic control software to deliver IMAT in local service mode [12]. Patient positioning was verified using daily electronic portal imaging (EPI) with online adaptations for the first 4 days. At the 5th treatment day, the mean isocenter correction in all directions was used for patient's setup. If the mean correction was ≤ 2 mm, EPI was repeated weekly. If not, daily EPI was repeated until ≤ 2 mm was reached.

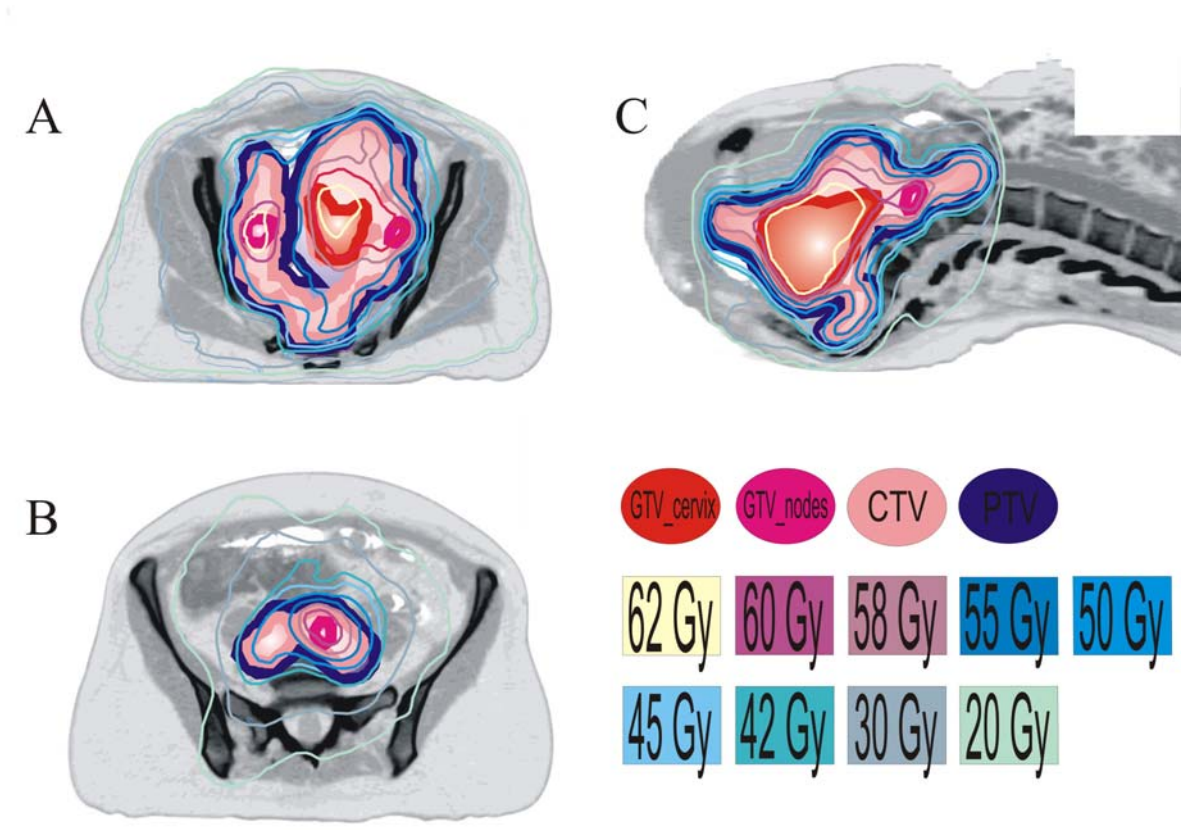

Figure 1: Transversal and Sagittal dose distributions and presentation of the targets/isodoses and their allocated colours. A-B: Transverse dose distribution at the level of the presacral nodes (1A) and common iliac nodes (1B). C: Sagittal dose distribution at the level of the primary tumor, iliac and presacral nodes.
Abbildung 1: Transversale und sagittale Dosisverteilungen und Darstellung der Zielvolumina/Isodosen und ihrer dazugehörigen Farben. A-B: Transversale Dosisverteilung auf Höhe der präsakralen Knoten (1A) und der Lymphknoten der A. iliaca communis (1B). C: Sagittale Dosisverteilung in Höhe des primären Tumors, der Lymphknoten der A. iliaca communis und der präsakralen Lymphknoten.

Results

The patient and tumor characteristics are presented in Table 2. All tumours were FDG-avid. Four to 9 arcs were needed. Figure 1 depicts transverse and sagittal dose distributions of patient 4.

Table 2: Patient, tumor and IMAT characteristics.

Patient #	Age	FIGO	Grade	pathology	PET pos lnn	chemotherapy	GTV_cervix (in cc)	arcs	sum degrees
1	57	IIIA	3	SCC	internal iliac node left	yes	125,32	7	1064
2	72	IIB	3	SCC	external iliac node left	no	26,76	9	1424
3	79	IIB	3	SCC	none	no	101,42	5	560
4	55	IVA	2	SCC	external iliac node left common iliac node left	yes	147,29	8	1088
5	40	IIB	2	AC	none	yes	106,18	4	360
6	52	IIB	3	AC	none	yes	37,71	6	1008

SCC: squamous cell carcinoma; AC: adenocarcinoma; pos: positive; lnn: lymph nodes. Tabelle 2: Patientin, Tumor und IMAT-Eigenschaften. SCC: Plattenepithelkarzinom; AC: Adenokarzinom; pos: positiv; lnn: Lymphknoten.

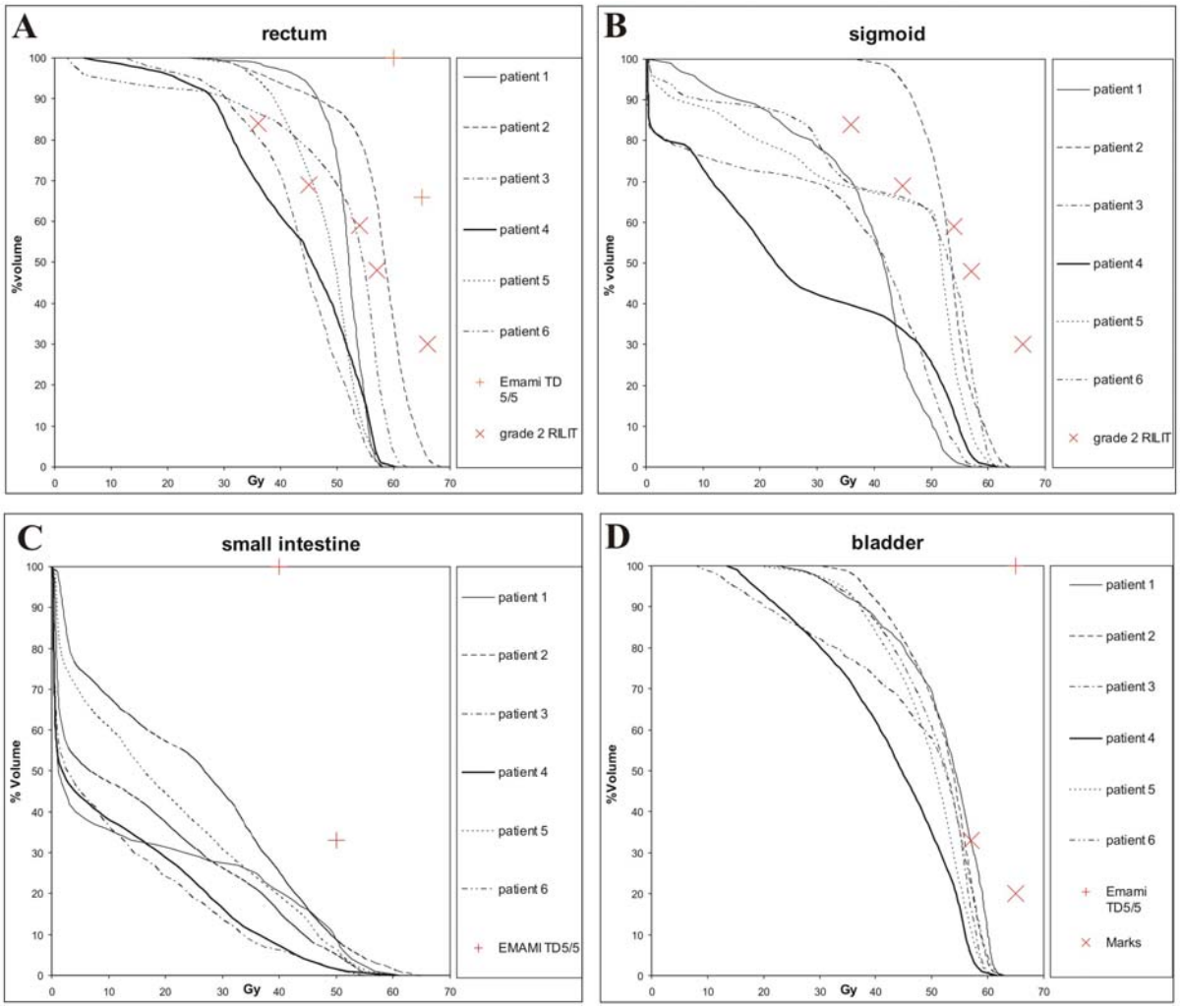

Figure 2: Dose volume histograms for rectum (2A), sigmoid colon (2B), small intestine (2C) and bladder (2D). Figures 2A, 2C and 2D depict also the dose-volume constraints as proposed by Emami [13]. Figures 2A and 2B depict the dose-volume constraints as proposed by Fonteyne [14]. Figure 2D also shows the dose-volume constraints suggested by Marks [33].

Abbildung 2: Dosisvolumenhistogramme für Rektum (2A), Sigma (2B), Dünndarm (2C) und Blase (2D). Die Abbildungen 2A, 2C und 2D zeigen die Dosisvolumenbeschränkungen laut Emami [13]. Die Abbildungen 2A und 2B zeigen die Dosisvolumenbeschränkungen laut Fonteyne [14]. Abbildung 2D zeigt außerdem die Dosisvolumenbeschränkungen laut Marks [33].

Table 3 summarizes the obtained physical doses for the different target volumes. Considering the whole patient group, constraints on D_{50} of the GTV_cervix, GTV_ nodes, PTV_cervix and PTV_nodes were met. On individual patient base, the dose constraints on D_{50} for GTV_cervix were not fulfilled in 2 patients (deviation of 1 and 3 Gy). The constraint on D_{98} of the PTV_ nodes was not met in 3 patients (1 Gy difference).
Table 1 depicts the physical dose-volume data concerning the OAR. For bladder, also D_{20} and D_{33} were considered. The results were 57 Gy (56-57 Gy; 25-75th percentile) and 55 Gy (54-56 Gy; 25-75th percentile) respectively.
Figure 2 depicts the dose-volume histograms for OAR.
Table 4 shows the results of the gamma evaluation of patient 4. For a gamma [3mm, 3%] criterion, 93% of the measured points showed a value <1, >98% showed a gamma value <1.4. For a gamma [3mm, 5%] criterion, the results are 98% and >99% respectively. Figure 3 depicts the results of the radiochromic film dosimetry, Pinnacle calculation and gamma evaluations. This quality control was performed for every patient showing similar results (not shown).

Clinical implementation
All treatments were delivered without discontinuation. Except for one patient, daily delivery time was <15 minutes.

Table 4: Results of the gamma evaluation.

	number of points (%)	
gamma value	3mm, 3%	3mm, 5%
[0-1.0]	92.97	98.35
]1.0-1.2]	3.99	1.01
]1.2-1.4]	1.67	0.31
]1.4-1.6]	0.62	0.10
]1.6-1.8]	0.27	0.02
]1.8-2.0]	0.14	0.01
[2.0-...	0.34	0.20

Column 2 shows the percentage of points per gamma interval for a [3mm, 3%] criterion. Column 3 shows the same for a [3mm, 5%] criterion.
Tabelle 4: Ergebnisse der Gamma-Bewertung. Spalte 2 zeigt den Prozentsatz der Punkte pro Gammaintervall für ein [3 mm, 3 %]-Kriterium. Spalte 3 zeigt das gleiche für ein [3 mm, 5 %]-Kriterium.

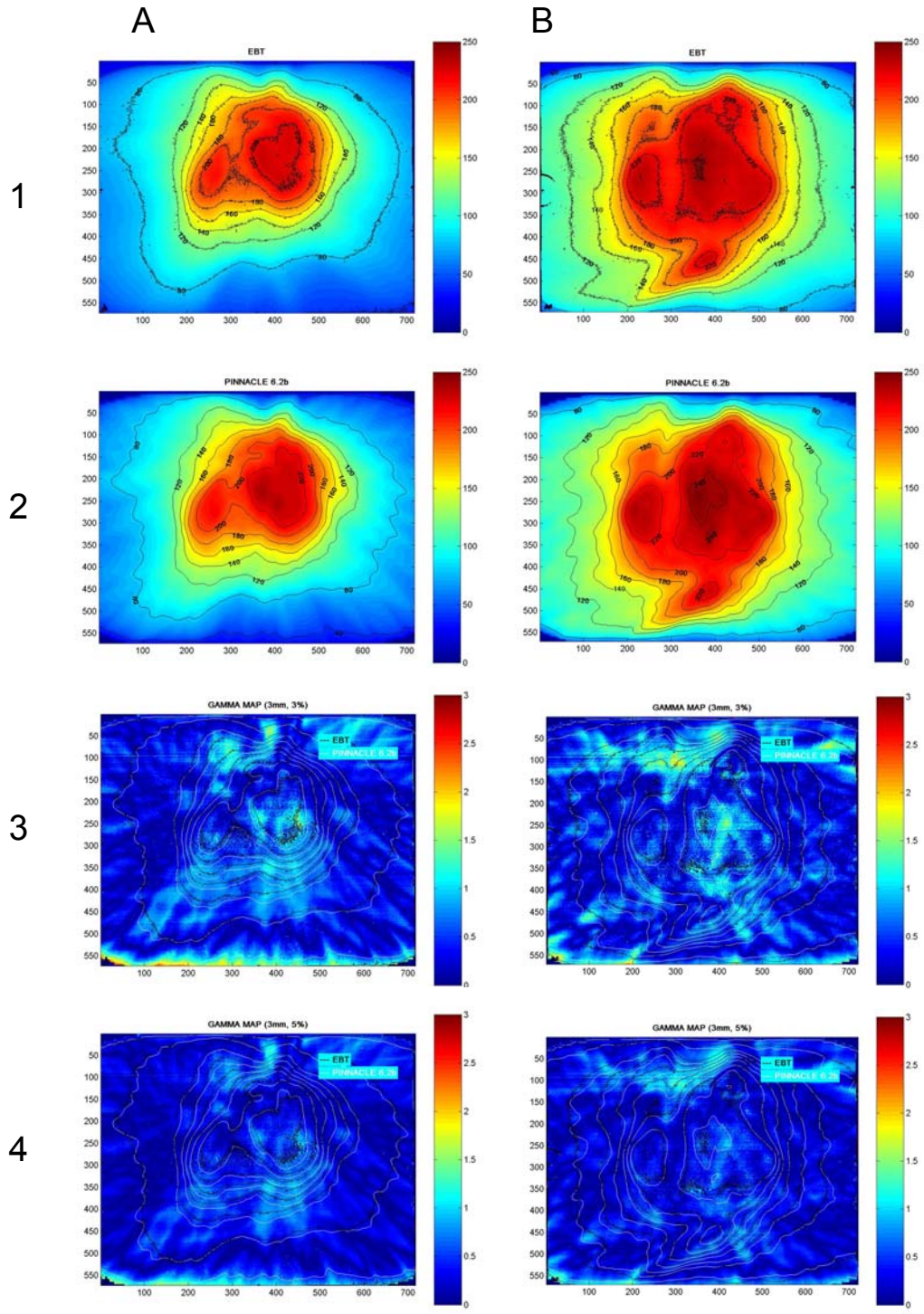

Figure 3: Transverse dose distribution on radiochromic film dosimetry (row 1), Pinnacle (row 2) and gamma evaluations (row 3 and 4) of patient 4, at the level of the common iliac lymph nodes (panel A) and primary tumor (panel B). The gamma maps at rows 3 and 4 show differences between Pinnacle and radiochromic film for a 3 % and 5 % dose gamma criterion respectively. The computed and measured isodoses have been superimposed. Abbildung 3: Transversale Dosisverteilung bei radiochromer Filmdosimetrie (Reihe 1), Pinnacle (Reihe 2) und Gamma-Bewertungen (Reihe 3 und 4) von Patientin 4 in Höhe der Lymphknoten der A. iliaca communis (Bild A) und des primären Tumors (Bild B). Die Gamma-Verteilungen in den Reihen 3 und 4 zeigen Unterschiede zwischen Pinnacle und der Filmdosimetrie für ein 3 %- bzw. 5 %-Gammakriterium. Die berechneten und gemessenen Isodosen wurden übelagert.

Discussion

IMAT is an extension of arc therapy using a combination of rotating gantry and dynamic multileaf collimator. From a treatment planning perspective, IMAT is closer to IMRT wherein the elementary beam segments are designed and sequentially organized to synthesize a number of dynamic arcs. In our approach, each arc is decomposed into multiple segments at 8° intervals. The segment shapes and weights are quasi-simultaneously optimized [7] taking into account the machine and MLC constraints of the SL18 series linear accelerator. IMAT is an excellent solution for pelvic cancers because of the large internal radius of the PTV and the presence of OAR within this concavity [12].

Combined cisplatin-based radiochemotherapy (RCT) is the standard treatment for these tumours [24, 41, 45, 46]. Two meta-analyses expressed concern regarding an excess in acute grade 3-4 toxicity [27, 30], which is due to the cisplatin [45, 47] but also to the conventional radiotherapy technique that was used. To reduce the volume of OAR treated, modern radiotherapy techniques such as IMRT or IMAT are needed [2, 3, 6, 15, 35, 42, 53]. Previous work demonstrated the superiority of IMAT above conventional technology for rectal cancer [11]. Because of the high similarity between the target volume of rectal and cervical cancer, repeating such a comparison would be a waste of time.

IMAT requires an adequate delineation of target volume(s) and OAR. The delineation of the pelvic lymph nodes was done according to the suggestions of other research groups [6, 48].

Several dose-volume constraints have been proposed for the OAR. Concerning **rectum**, data on mean dose ($D_{mean} \leq 44$ Gy), maximal dose ($D_{max} \leq 54$ Gy) and rectal volume receiving 40 Gy (≤ 40%) and 45 Gy (78-85 cc) were proposed [3, 6, 17]. Our D_{mean} and D_{max} are higher because of the higher IMAT prescription dose. In other series, brachytherapy is added to the treatment. Data on the summation of EBRT and brachytherapy doses are unfortunately missing [34, 45, 46]. Intermediate rectal doses are very important in predicting late rectal toxicity [14]. When comparing our data with the ones D'Souza proposed [6], IMAT lowered R_{45} (28 vs. >75 cc). We plotted our IMAT results against the data suggested by Fonteyne and Emami (Figure 2A) [13, 14]. Fonteyne's data were recalculated for 25 fractions. Due to the larger margin in the posterior direction in the present study, the rectal volume receiving an intermediate dose was higher [14]. Emami's constraints were easily met [13].

For **small bowel**, data on D_{max} (≤ 50 Gy), D_{mean} (≤ 33 Gy) and volume receiving 35 Gy ($SB_{35} \leq$ 35%) and 45 Gy ($SB_{45} \leq$ 14% and ≤ 360 cm^3) were proposed [3, 6, 17, 42]. Concerning D_{mean} and D_{max}, the same conclusions as for the rectum can be drawn. Figure 2C shows that the constraint on SB_{35} was easily met as well as Emami's data [13]. Concerning SB_{45}, the 14% that Portelance proposed [42] was not met in 2 patients (positive lymph nodes).

Fonteyne found dose-volume data concerning **sigmoid**. From Figure 2B, it is clear that IMAT generated safe DVH's [14].

Concerning **bladder**, D_{max} and $D_{50} \leq 50$ Gy were proposed [17]. The higher IMAT prescription dose combined with the close vicinity of the bladder and the GTV_cervix explains our higher D_{max}. The dose-volume constraints proposed by Emami [13] and Marks [33] were easily met (Figure 3D). The D_{20} and D_{33} proposed by the latter were 8 Gy and 2 Gy lower in our patients.

Concerning the OAR, we also provided data on real volume (cc) (Table 1).

Whitney suggested that local control might be increased with higher dose. He concluded that radiotherapy failure rate for stage IIB and III was 20-50% and 50-76% [5, 52]. EBRT doses varied from 40.8 to 61 Gy [52]. This dose-response relationship was confirmed by others [4, 28, 37]. To improve local control, EBRT followed by MRI-guided brachytherapy including

adaptive planning is a valid option with local control rates of 90% at 3 years [43][*]. However, local control drops to 80% in case of tumours >5 cm. Secondly, MRI-guided brachytherapy needs specialized logistics and is not possible wheresoever's. With less advanced brachytherapy techniques, 3-years local control of only 65% for tumours >5 cm was achieved. Isn't it therefore worth the effort to look for alternatives such as a radical hysterectomy after chemoradiation?

A postchemoradiation extrafascial hysterectomy was part of the treatment in GOG123 [46], Keys' work [24] and in single-institution studies. The concern that this leads to an excess in toxicity was not confirmed in recent series [5, 25] while a significant benefit towards local control [24, 25, 32], progression-free survival [25] and a favourable trend towards overall survival was suggested [5, 25]. IMAT copes with the "dose-escalation" question and the concern regarding safety of post-RCT hysterectomy. IMAT performs dose escalation by means of a SIB to the GTV_cervix and GTV_nodes. The D_{50} to the GTV_cervix in our study was 62 Gy. Hypothesizing that the α/β ratio of cervix carcinoma is 10 [21], this corresponds to a normalized iso-effective dose of 64 Gy at 2 Gy per fraction. Because a prolongation of overall treatment time worsens disease-free survival [26], we kept the total number of fractions (25) unchanged [21]. Although we consider this SIB boost to be safe as no critical doses are given to the surrounding tissues, we are aware that no late toxicity data are known concerning this regimen. Therefore, toxicity is scored meticulously and will be discussed in a separate paper.

Previously, the gamma evaluation of IMAT showed a high correlation between planning and treatment [12]. In the present study, >98% of the measured points showed a gamma evaluation >98%, independent of the criterion. This feature demonstrates the safety of delivering IMAT clinically. No treatment interruption occurred; this was in contradiction with other reports [26, 32].

This research only involves the IMAT planning procedure, quality control and clinical implementation. It's beyond the scope of the current article to make an evaluation/comparison of the different treatment modalities (IMRT-IMAT-VMAT) available to deliver a SIB or to describe the clinical aspects of this treatment. Both aspects however, are very important and interesting and will be the subject of future papers.

Conclusion

In primary irresectable cervix carcinoma, IMAT is able to create a SIB to the primary tumor and invaded lymph nodes combined with sparing of the OAR. The gamma evaluation shows a high correlation with planning. The clinical delivery is feasible. No treatment interruptions occurred.

[*] Remark member of the examination committee: "The date of *Pötter are cited the wrong way: local control ameliorated from 71% (1998-2000) to 90% (2001-2003) in tumours measuring more than 5 cm. Since, another 5 series reporting LC rates between 90% and 96% are published."*

The reviewer is correct to state that local control in tumours > 5cm is 90% in 2001-2003. Since the Material & Methods section of Pötters series stated that all patients between 1998-2003 were treated with MR-guided BT, we referred to the local control of tumours > 5 cm in the whole group of patients (1998-2003). It was stated that the difference between the two periods was due to a learning curve, though also a learning curve is important information.

REFERENCES

1. Carcopino X, Houvenaeghel G, Buttarelli M, et al. Equivalent survival in patients with advanced stage IB-II and III-IVA cervical cancer treated by adjuvant surgery following chemoradiotherapy. Eur J Surg Oncol 2008;34:569-75.
2. Chan P, Yeo I, Perkins G, et al. Dosimetric comparison of intensity-modulated, conformal, and four-field pelvic radiotherapy boost plans for gynecologic cancer: a retrospective planning study. Radiat Oncol 2006;1:13.
3. Chen MF, Tseng CJ, Tseng CC, et al. Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. Int J Radiat Oncol Biol Phys 2007;67:1438-44.
4. Choy D, Wong LC, Sham J, et al. Dose-tumor response of carcinoma of cervix: an analysis of 594 patients treated by radiotherapy. Gynecol Oncol 1993;49:311-7.
5. Classe JM, Rauch P, Rodier JF, et al. Surgery after concurrent chemoradiotherapy and brachytherapy for the treatment of advanced cervical cancer: morbidity and outcome: results of a multicenter study of the GCCLCC (Groupe des Chirurgiens de Centre de Lutte Contre le Cancer). Gynecol Oncol 2006;102:523-9.
6. D'Souza WD, Ahamad AA, Iyer RB, et al. Feasibility of dose escalation using intensity-modulated radiotherapy in posthysterectomy cervical carcinoma. Int J Radiat Oncol Biol Phys 2005;61:1062-70.
7. De Gersem W, Claus F, De Wagter C, et al. Leaf position optimization for step-and-shoot IMRT. Int J Radiat Oncol Biol Phys 2001;51:1371-88.
8. de Neve W, Duthoy W, Claus F, et al. Dose conformation in IMRT for head and neck tumors: which solution to apply? Cancer Radiother 2002;6 Suppl 1:32s-6s.
9. De Wagter C. QA-QC of IMRT: European Perspective. In: Bortfeld T, Schmidt-Ullrich R, De Neve W, et al., editors. Image-guided IMRT. Berlin: Springer-Verlag; 2005, p. 117-28.
10. Dimopoulos JC, Schirl G, Baldinger A, et al. MRI assessment of cervical cancer for adaptive radiotherapy. Strahlenther Onkol 2009;185:282-7.
11. Duthoy W, De Gersem W, Vergote K, et al. Clinical implementation of intensity-modulated arc therapy (IMAT) for rectal cancer. Int J Radiat Oncol Biol Phys 2004;60:794-806.
12. Duthoy W, De Gersem W, Vergote K, et al. Whole abdominopelvic radiotherapy (WAPRT) using intensity-modulated arc therapy (IMAT): first clinical experience. Int J Radiat Oncol Biol Phys 2003;57:1019-32.
13. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21:109-22.
14. Fonteyne V, De Neve W, Villeirs G, et al. Late radiotherapy-induced lower intestinal toxicity (RILIT) of intensity-modulated radiotherapy for prostate cancer: the need for adapting toxicity scales and the appearance of the sigmoid colon as co-responsible organ for lower intestinal toxicity. Radiother Oncol 2007;84:156-63.
15. Georg D, Georg P, Hillbrand M, et al. Assessment of Improved Organ at Risk Sparing for Advanced Cervix Carcinoma Utilizing Precision Radiotherapy Techniques. Strahlenther Onkol 2008;184:586-91.
16. Georg D, Kirisits C, Hillbrand M, et al. Preliminary results of a comparison between high-tech external beam and high-tech brachytherapy for cervix carcinoma. Strahlenther Onkol 2007;183 Spec No 2:19-20.
17. Gerszten K, Colonello K, Heron DE, et al. Feasibility of concurrent cisplatin and extended field radiation therapy (EFRT) using intensity-modulated radiotherapy (IMRT) for carcinoma of the cervix. Gynecol Oncol 2006;102:182-8.

18. Gillis S, De Wagter C, Bohsung J, et al. An inter-centre quality assurance network for IMRT verification: results of the ESTRO QUASIMODO project. Radiother Oncol 2005;76:340-53.
19. Green J, Kirwan J, Tierney J, et al. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. Cochrane Database Syst Rev 2005:CD002225.
20. Grosu AL, Piert M, Weber WA, et al. Positron emission tomography for radiation treatment planning. Strahlenther Onkol 2005;181:483-99.
21. Guerrero M, Li XA, Ma L, et al. Simultaneous integrated intensity-modulated radiotherapy boost for locally advanced gynecological cancer: radiobiological and dosimetric considerations. Int J Radiat Oncol Biol Phys 2005;62:933-9.
22. Houvenaeghel G, Lelievre L, Buttarelli M, et al. Contribution of surgery in patients with bulky residual disease after chemoradiation for advanced cervical carcinoma. Eur J Surg Oncol 2007;33:498-503.
23. Kavanagh BD, Schefter TE, Wu Q, et al. Clinical application of intensity-modulated radiotherapy for locally advanced cervical cancer. Semin Radiat Oncol 2002;12:260-71.
24. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 1999;340:1154-61.
25. Keys HM, Bundy BN, Stehman FB, et al. Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. Gynecol Oncol 2003;89:343-53.
26. King M, McConkey C, Latief TN, et al. Improved survival after concurrent weekly cisplatin and radiotherapy for cervical carcinoma with assessment of acute and late side-effects. Clin Oncol (R Coll Radiol) 2006;18:38-45.
27. Kirwan JM, Symonds P, Green JA, et al. A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. Radiother Oncol 2003;68:217-26.
28. Lanciano RM, Martz K, Coia LR, et al. Tumor and treatment factors improving outcome in stage III-B cervix cancer. Int J Radiat Oncol Biol Phys 1991;20:95-100.
29. Low DA, Harms WB, Mutic S, et al. A technique for the quantitative evaluation of dose distributions. Med Phys 1998;25:656-61.
30. Lukka H, Hirte H, Fyles A, et al. Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer--a meta-analysis. Clin Oncol (R Coll Radiol) 2002;14:203-12.
31. Maduro JH, Pras E, Willemse PH, et al. Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. Cancer Treat Rev 2003;29:471-88.
32. Mancuso S, Smaniotto D, Benedetti Panici P, et al. Phase I-II trial of preoperative chemoradiation in locally advanced cervical carcinoma. Gynecol Oncol 2000;78:324-8.
33. Marks LB, Carroll PR, Dugan TC, et al. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. Int J Radiat Oncol Biol Phys 1995;31:1257-80.
34. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340:1137-43.
35. Mundt AJ, Lujan AE, Rotmensch J, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. Int J Radiat Oncol Biol Phys 2002;52:1330-7.
36. Nagy V, Coza O, Ordeanu C, et al. Radiotherapy versus Concurrent 5-Day Cisplatin and Radiotherapy in Locally Advanced Cervical Carcinoma : Long-Term Results of a Phase III Randomized Trial. Strahlenther Onkol 2009;185:177-83.

37. Niibe Y, Hayakawa K, Kanai T, et al. Optimal dose for stage IIIB adenocarcinoma of the uterine cervix on the basis of biological effective dose. Eur J Gynaecol Oncol 2006;27:47-9.
38. Paelinck L, De Neve W, De Wagter C. Precautions and strategies in using a commercial flatbed scanner for radiochromic film dosimetry. Phys Med Biol 2007;52:231-42.
39. Paley PJ, Goff BA, Minudri R, et al. The prognostic significance of radiation dose and residual tumor in the treatment of barrel-shaped endophytic cervical carcinoma. Gynecol Oncol 2000;76:373-9.
40. Pandit-Taskar N. Oncologic imaging in gynecologic malignancies. J Nucl Med 2005;46:1842-50.
41. Peters WA, 3rd, Liu PY, Barrett RJ, 2nd, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606-13.
42. Portelance L, Chao KS, Grigsby PW, et al. Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. Int J Radiat Oncol Biol Phys 2001;51:261-6.
43. Potter R, Dimopoulos J, Georg P, et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. Radiother Oncol 2007;83:148-55.
44. Resbeut M, Cowen D, Viens P, et al. Concomitant chemoradiation prior to surgery in the treatment of advanced cervical carcinoma. Gynecol Oncol 1994;54:68-75.
45. Rose PG, Ali S, Watkins E, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:2804-10.
46. Stehman FB, Ali S, Keys HM, et al. Radiation therapy with or without weekly cisplatin for bulky stage 1B cervical carcinoma: follow-up of a Gynecologic Oncology Group trial. Am J Obstet Gynecol 2007;197:503 e1-6.
47. Sterzing F, Grehn C, Dinkel J, et al. Severe reversible toxic encephalopathy induced by cisplatin in a patient with cervical carcinoma receiving combined radiochemotherapy. Strahlenther Onkol 2007;183:487-9.
48. Taylor A, Rockall AG, Reznek RH, et al. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2005;63:1604-12.
49. Vergote K, De Deene Y, Duthoy W, et al. Validation and application of polymer gel dosimetry for the dose verification of an intensity-modulated arc therapy (IMAT) treatment. Phys Med Biol 2004;49:287-305.
50. Villeirs GM, Van Vaerenbergh K, Vakaet L, et al. Interobserver delineation variation using CT versus combined CT + MRI in intensity-modulated radiotherapy for prostate cancer. Strahlenther Onkol 2005;181:424-30.
51. Vorwerk H, Wagner D, Christiansen H, et al. An easy irradiation technique (partial half-beam) to reduce renal dose in radiotherapy of cervical cancer including paraaortic lymph nodes. Strahlenther Onkol 2008;184:473-7.
52. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 1999;17:1339-48.
53. Wong E, D'Souza DP, Chen JZ, et al. Intensity-modulated arc therapy for treatment of high-risk endometrial malignancies. Int J Radiat Oncol Biol Phys 2005;61:830-41.

Chapter 5

Publication 3:

Intensity Modulated Arc Therapy ± Cisplatin as neo-adjuvant treatment for primary irresectable cervical cancer: toxicity, tumour response and outcome.

Intensitätsmodulierte Rotationstherapie mit Cisplatin als neoadjuvante Behandlung bei primärem, inoperabelen Zervixkarzinom: Toxizität, Tumoransprechen und Onkologische Ergebnisse.

Katrien Vandecasteele, M.D.[1], Amin Makar, M.D., Ph.D.[2], Rudy Van den Broecke, M.D., Ph.D.[2], Louke Delrue, M.D.[3], Hannelore Denys, M.D., Ph.D.[4], Kathleen Lambein, M.D.[5], Bie Lambert, M.D., Ph.D.[6], Marc van Eijkeren, M.D., Ph.D.[1], Philippe Tummers, M.D.[2], Gert De Meerleer M.D., Ph.D.[1].

Affiliation:
Department of [1]Radiotherapy, [2]Gynaecology, [3]Radiology, [4]Medical Oncology, [5]Pathology and [6]Nuclear Medicine at Ghent University Hospital, Ghent, Belgium

Strahlenther Onkol. 2012; accepted January 2012.

There is no conflict of interest

Key Words: IMAT; locally advanced cervical cancer; hysterectomy; locoregional control; acute toxicity.
Schlüsselwörter: IMAT; lokal fortgeschrittenes Zervixkarzinom; Hysterektomie, lokal-regionale Kontrolle, akute Toxizität.

Abstract

Background and Purpose

To evaluate the feasibility and outcome of Intensity Modulated Arc Therapy ± cisplatin followed by hysterectomy for locally advanced cervical cancer.

Patients and Methods

Thirty patients participated (table 1). The primary tumour and PET-positive lymph node(s) received a simultaneous integrated boost. Four weeks after IMAT ± C treatment response was evaluated. Resection consisted of hysterectomy ± lymphadenectomy. Tumour response, acute and late radiation toxicity, postoperative morbidity and outcome were evaluated.

Results

All hysterectomy specimens were macroscopically tumor-free with negative resection margins; pathological complete response was 40% (table 2). In 2 patients one resected lymph node was positive. There was no excess in postoperative morbidity (table 3). Apart from two grade 3 hematologic toxicities, no grade 3 or 4 acute radiation toxicity was observed. No grade 3, 1 grade 4 (4%) intestinal and 4 grade 3 (14%) urinary late toxicities were observed (table 4).

Two-year local and regional control rates are 96% and 100% respectively. Two year distant control rate is 92%. Actuarial 2- year progression free survival rate is 89%. Actuarial 1- and 2- year overall survival rates are 96% and 91%, 3-y overall survival is 84%.

Conclusion

Surgery after IMAT ± C is feasible with low postoperative morbidity and radiation toxicity. Local, regional, distant control and survival rates are promising.

Zusammenfassung

Hintergrund und Ziel

Endpunktergebnisse und Machbarkeitsbewertung einer intensitätsmodulierten Rotationstherapie ± Cisplatin vor operativer Entfernung der Gebärmutter bei lokal fortgeschrittenem Zervixkarzinom.

Patienten und Methodik

Es nahmen dreißig Patienten an dem Studie teil (Tabelle 1). Der Primärtumor und die PET-positiven Lymphknoten erhielten simultan einen integrierten Boost. Vier Wochen nach der kombinierten IMAT ± C-Behandlung wurde das Ansprechen bewertet. Die Operation bestand aus Gebärmutter- ± Lymphknotenentfernung. Bewertet wurden das Tumoransprechen, die akute und späte Bestrahlungstoxizität, die postoperative Morbidität und Onkologische Ergebnisse.

Resultate

Alle Hysterektomieproben zeigten sich makroskopisch negativ aus mit negativen Resektionsrändern; das pathologische Gesamtansprechen betrug 40% (Tabelle 2). Bei 2 Patienten hat sich ein resezierter Lymphknoten positiv Befunden. Es wurde keine Übermäßige postoperativer Morbidität festgestellt (Tabelle 3). Es trat keine Grad-3/4-Akuttoxizität auf abgesehen von zwei hämatologischen Grad-3-Toxizitäten. Wohl wurde eine intestinaler Grad-4-Spättoxizität (4%) festgestellt (aber keine Grad-3). Urogenitaler Grad-3-Spättoxizitäten entwickelten 14% der patientinnen (n=4) (Tabelle 4).

Die lokalen und regionären Zwei-Jahres-Kontrollraten waren hoch: 96% bzw. 100%. Die Zwei-Jahres-Fernkontrollrate betrug 92%. Die statistische krankheitsfreies Überleben nach 2 jahren betrug 89%. Die statistische 1- und 2-Jahres-Gesamtüberlebensrate betrug 96% bzw. 91%, die 3-Jahres-Gesamtüberlebensrate 84%.

Schlussfolgerung

Eine Operation nach IMAT ± C ist durchführbar. Es ergibt sich eine niedriger postoperative Morbidität und Bestrahlungstoxizität. Dabei sind Lokal-, Regional- und Fernkontrolle sowie die Überlebensrate vielversprechend.

Introduction

Chemoradiation (CRT) is the standard treatment for locally advanced and/or irresectable cervical cancer [10, 14, 17]. Despite the significant improvement due to the advent of concomitant chemotherapy, local relapse occurs in 15 to 20% [17]. Complementary hysterectomy is a treatment option [2, 8, 13, 19] with the aim to remove potentially chemo- and radioresistant foci. Within the gynaecology and radiotherapy community, however, there is a reticence for post-CRT hysterectomy because of the fear of an increase in treatment-induced toxicity. However, the only randomized trial performed in this setting showed no increase in grade 3 or 4 toxicity [13]. Adding chemotherapy did not show any increase in late toxicity compared to radiotherapy alone [14]. Consequently, radiotherapy seems to be the main contributor in the development of toxicity, certainly when conventional techniques are used.

Novel treatment techniques such as intensity modulated radiotherapy (IMRT) and arc therapy [5, 18, 21] have lead to a significant reduction of toxicity rates [12]. Moreover, IMRT might allow replacing the brachytherapeutic boost by a simultaneous integrated boost (SIB) and consequently reduces treatment time, the latter being strongly correlated with local control and survival [11]. The rationale and clinical implementation of Intensity Modulated Arc Therapy (IMAT) in this setting has been described in detail before [26].

The aim of this prospective study was to evaluate whether IMAT with SIB allows for post-CRT hysterectomy and to evaluate treatment toxicity and outcome.

Materials and Methods

This study (local ethical committee, n° B67020072880) included 30 patients (September 2006 - August 2010). Inclusion criteria were: biopsy-proven locally advanced (FIGO IB2-IVA) cervical carcinoma (LACC); absence of extra-pelvic lymph node(s) and distant metastases on ^{18}FDG PET-CT; WHO score 0-2; absence of any condition potentially hampering compliance with the study protocol/follow-up schedule; ability to understand and sign informed consent.

All patients underwent neo-adjuvant Intensity Modulated Arc Therapy, if possible combined with weekly cisplatin (IMAT ± C) as per the following treatment protocol.

IMAT ± C.

Pre-treatment imaging consisted of MRI (Magnetom Symphony, Siemens, Erlangen, Germany) and ^{18}FDG PET-CT (Gemini, Philips, Eindhoven, The Netherlands) in treatment position [1, 15]. Details concerning the dose prescription and delineation of the primary tumor (GTV_cervix), primary clinical and planning target volume (CTV_cervix and PTV_cervix respectively) and lymph nodes (GTV_nodes and PTV_nodes) were previously reported [26] (Figure 1). From 1/2/2009 onwards, if PET-positive lymph nodes were present, preventive para-aortic lymph node irradiation was performed.

IMAT was performed in supine position using a knee and ankle fix (Cablon Medical, Leusden, The Netherlands), arms positioned above the head. IMAT was delivered using 18-MV photons of an Elekta SL18 series Linear Accelerator (SliPlus, Elekta, Crawley, UK) equipped with a standard MLC and prototype dynamic control software to deliver IMAT in local service mode [7]. The IMAT-plans were generated using an anatomy-based exclusion tool with the aid of weight and leaf position optimisation [7, 26]. Patient positioning was verified online using an electronic portal imaging device (EPID) [26].

If the serum creatine level was lower than 0.96 mg/dl –the cut-off for normal kidney function in our lab- cisplatin 40mg/m² was administered weekly during radiotherapy. Kidney function and Peripheral Blood Count (PBC) were monitored at least twice a week. Haemoglobin levels less than 11 g/dL implicated a blood transfusion.

Surgery.
After IMAT ± C treatment response was evaluated by gynaecologic examination and imaging: ^{18}FDG PET-CT (exclusion of new metastatic spots) and MRI (locoregional response). Surgery consisted of type II hysterectomy ± pelvic lymphadenectomy (if positive pelvic lymph nodes were present on one of the ^{18}FDG PET-CT's).

Follow-up and assessment of disease control
Patients were seen weekly during treatment, 1 and 3 months thereafter. Thereafter, follow-up was scheduled three-monthly (first two years), 6-monthly (year 3-5) and annually. The follow-up was performed at a multidisciplinary consultation (gynaecologist and radiation oncologist). Imaging (^{18}FDG PET-CT and MRI) was performed every 6 months for the first two years and yearly afterwards, unless patients' symptomatology required otherwise.

Analysis
Primary endpoints of the study were the acute and late toxicity (acute/late radiation related toxicity and surgery related morbidity/mortality) and pathologic response at hysterectomy specimen.
Acute radiation toxicity was scored weekly during IMAT ± C and at 10 days, 1 and 3 months thereafter.
Late radiation toxicity (toxicity occurring ≥3 months after IMAT ± C or acute toxicity lasting longer than 3 months) was scored at every follow-up visit.
Surgical morbidity/mortality was evaluated during hospitalization (acute) and at every visit thereafter (late) and was classified according to the Chassagne grading system [3].
Secondary endpoints were local (LC), regional (RC) and distant control (DC), overall survival (OS) and progression free survival (PFS). LC, RC and DC are defined as absence of disease at the primary tumor bed, the regional lymph nodes and distant sites respectively. Time to local relapse, regional relapse and distant relapse were defined as the time elapsed between biopsy and the first event (local, regional or distant relapse) or the last follow-up. PFS and OS were defined as the time elapsed between biopsy and any progression, death or the last follow-up.
For statistical analysis, SPSS (v. 15.0) was used.

Table 1: Patient and clinicopathological characteristics.

Patient characteristics (n=30)	
Age (yrs) at diagnosis	
median	52
range	26-89
Follow-up in months	
median	24
range	8-56
N+ at diagnosis	
n patients	11
1 node +	5
2 node +	5
3 node +	0
4 node +	1
<2 cm (%pCR)	15 (100%)
≥2 cm (%pCR)	4 (50%)
Chemotherapy	
n	25
Para-aortic irradiation	
n	6
Histology	
squamous	25
adeno	4
Grade	
1	2
2	9
3	12
not reported	7
FIGO stage	
IB2 (%pCR)	2 (0)
IIB (%pCR)	20 (45)
IIIA (%pCR)	3 (100)
IIIB (%pCR)	4 (0)
IVA (%pCR)	1 (0)
Tumor size, cm	
<4cm (%pCR)	2 (50)
4-7cm (%pCR)	23 (48)
≥7cm (%pCR)	5 (0)
Tumor Volume, cc	
median	149
range	27-222

pCR= pathologic Complete response = ypT0 or ypN0

Tabelle 1: Patienten- und klinik-pathologische Eigenschaften der Studienpopulation.

pCR= pathologisches Gesamtansprechen = ypT0 oder ypN0

Results

All enrolled patients ended IMAT ± C. Figure 1 shows a dose distribution. Patient characteristics are represented in Table 1. All patients underwent class II radical hysterectomy. In 1 patient, an extrafascial hysterectomy was needed due to fibrosis at both parametria. For 2 patients no data on late radiation or surgery related morbidity are available

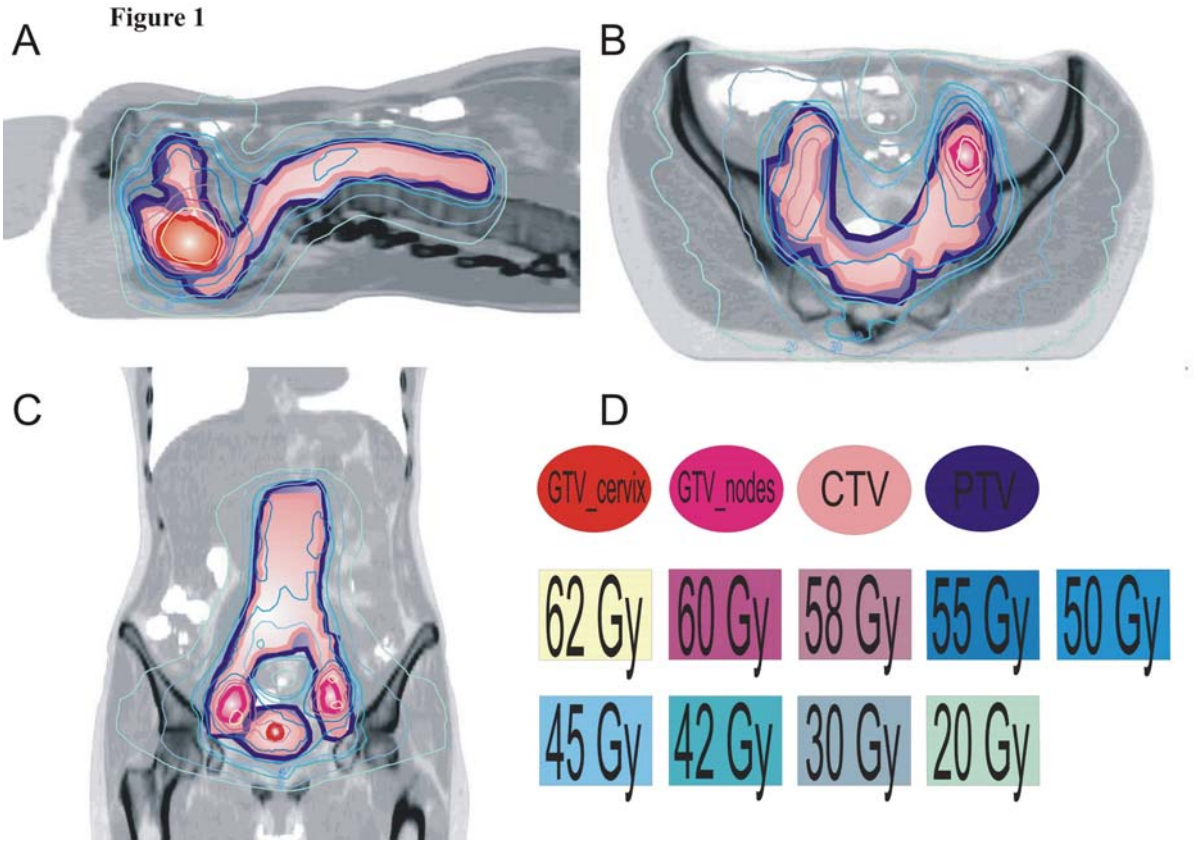

Figure 1: Dose distributions.
Dose distribution through (A) the primary tumor, (B): a PET-positive lymph node (external iliac nodes left), (C): the primary tumor and bilateral PET-positive lymph nodes. D: Targets/isodoses and their allocated colours. The GTV_cervix consisted of all visible tumor on MRI and/or ^{18}FDG PET-CT. The elective lymph node regions consisted of the presacral and common, external and internal iliac lymph nodes and the obturator fossa region (PTV_nodes), delineated following the consensus guidelines of Small *et al.* [25]. PET-positive lymph node(s) were delineated separately (GTV_nodes) [26]. *Dose prescription* (25 fractions) was: D_{50} of 62, 58 and 56 Gy to the GTV_cervix, CTV_cervix and PTV_cervix respectively. D_{50} GTV_nodes: 60 Gy; D_{98} PTV_nodes: 45 Gy.

Abbildung 1: Dosisverteilungen.
Dosisverteilung durch (A) den Primärtumor, (B): einen PET-positiven Lymphknoten (Lymphknoten der A. Iliaca communis), (C): den Primärtumor und bilaterale PET-positive Lymphknoten. D: Zielvolumina/Isodosen und die dazugehörigen Farben. Die GTV_cervix bestand aus einem bei der MRT und/oder der ^{18}FDG PET-CT vollständig sichtbaren Tumor. Die elektiven Lymphknotenregionen bestanden aus den präsakralen Lymphknoten, und der Lymphknoten der A. Iliaca communis, externa und interna und der obturator-fossa-Region (PTV-Knoten), beschrieben nach den Konsensrichtlinien von Small *et al.* [25]. Die PET-positive Lymphknoten wurde getrennt beschrieben (GTV-Knoten) [26]. Die *Dosisverordnung* (25 Fraktionen) verlief nach dem folgendem Muster: D_{50} von 62, 58 und 56 Gy zur GTV_cervix, CTV_cervix bzw. PTV_cervix. D_{50} GTV-Knoten: 60 Gy; D_{98} PTV-Knoten: 45 Gy.

Table 2: Pathological findings per initial FIGO stage.

FIGO	ypT (n)					
	0	1a1	1a2	1b1	1b2	2b
IB2	0	1	1	0	0	0
IIB	9	2	2	5	1	1
IIIA	3	0	0	0	0	0
IIIB	0	2	0	2	0	0
IVA	0	0	0	0	0	1
Total	**12**	**5**	**3**	**7**	**1**	**2**

Tabelle 2: Pathologische Ergebnisse je nach FIGO-Ausgangsstadium.

Pathologic results and postoperative morbidity/mortality.

All operated patients had a clinical complete response (no visible macroscopic tumour rest on pathology specimen) and negative resection margins. Pathologic findings were: ypT0: 40%, ypT1a: 26,65%, ypT1b: 26,65% and ypT2b (solitary tumor cells in parametria) in 6,7%. Pathologic complete response rate per tumor size and FIGO stage can be found in table 1 and 2. Lymphadenectomy was performed in 15 patients (median number of resected nodes: 11, range: 1-28). In 2 patients, one resected lymph node was metastatic invaded (respectively 4 and 22 nodes were removed); both were ^{18}FDG-PET positive and larger than 2 cm on pre-treatment imaging.

Median hospital stay was 8 days (5-137 days). There was neither postoperative mortality nor intra-operative complications. Median blood loss during surgery was 400cc (100cc-2000cc). Four patients needed a blood transfusion. Eleven patients had postoperative urinary retention of which 5 requiring self-catheterization, none persisting longer than 6 months. One patient was diagnosed with hydronephrosis due to large lymphocoeles needing a re-intervention (=hospital stay of 137 consecutive days). An overview of acute and late surgery complications can be found in table 3.

Table 3: Early and late postoperative complications by Chassagne's scoring system

Early postoperative complications (n=30)	
Grade 1	
n (%)	*complication*
2 (7)	Urinary tract infection
1 (3)	Deep venous trombosis
1 (3)	Lymphocoele
Grade 2	
n (%)	*complication*
1 (3)	Urinary tract infection with temporary kidney function impairment
1 (3)	Subobstruction, not requiring surgery
2 (7)	Lymphocoele
1 (3)	Neurological sensory problem with mild functional impairment
5 (17)	Urinary retention requiring self catheterization
Grade 3	
n (%)	*complication*
1 (3)	Lymphocoele causing temporarily inadequate renal function (microsurgery needed)
Late postoperative complications (n=28)	
Grade 1	
n (%)	*complication*
1 (3)	Lymphoedema
Grade 2	
n (%)	*complication*
2 (7)	Lymphoedema
1 (3)	Neurological sensory problem with mild functional impairment
2 (7)	Urinary retention requiring self catheterization (disappeared 6 months postoperative)
Grade 3	
n (%)	*complication*
1 (3)	retroperitoneal fibrosis causing kidney impairment (need for nephrostomy)

Tabelle 3: Frühe und späte postoperative Komplikationen nach dem Chassagne-Punktesystem

Acute radiation related toxicity (n=30)

No grade 4 toxicity occurred. Two patients developed grade 3 hematologic toxicity (white blood cell count ≥1000u/L and < 2000/uL). There was no grade 3 GI, GU or skin toxicity. Four patients received a blood transfusion during or shortly after (before surgery) IMAT-C. There were no treatment interruptions. An overview is given in Table 4. Prophylactic para-aortic irradiation (n=19) did not lead to a significant excess in acute and late radiation related toxicity. The administration of chemotherapy (n=20) was associated with significant more

overall acute GU toxicity (Grade 1: 56%, grade 2: 24% vs grade 1: 0% and grade 2: 20%; p=0,02) and dysuria (Grade 1: 60%, grade 2: 4% vs grade 1: 0% and grade 2: 0%; p=0,03).

Late toxicity (radiation and surgery related) (n=28)

One patient (no para-aortic prevention) needed an intervention due to abdominal cramps (grade 4) caused by perforation of the ileum. The diseased ileal part was resected laparoscopically. Anatomopathologic findings were suggestive for radiation enteritis. She's without any complaint since then. Four patients developed permanent urinary incontinence. Since no pre-treatment incontinence scorings were present, all four of them were scored as grade 3 toxicity. An overview of all surgery and radiation therapy related toxicities is given in Table 3 and 4.

One patient developed retroperitoneal fibrosis leading to ureteral fibrosis needing a permanent nephrostomy (grade 3). No vaginal stenosis (partial nor complete) occurred.

Table 4: Acute and late radiation related toxicity.

	acute toxicity (evaluable: n=30)			late toxicity (evaluable: n=28)			
	G1 (%)	G2 (%)	G3 (%)	G1 (%)	G2 (%)	G3 (%)	G4 (%)
GASTRO-INTESTINAL	**17**	**83**	**0**	**32**	**7**	**0**	**4**
Anorexia	20	10	0	0	4	0	0
Nausea	20	50	0	4	0	0	0
Frequency	17	73	0	11	11	0	0
Incontinence	13	3	0	7	0	0	0
Rectal Blood Loss	3	0	0	4	0	0	0
Abdominal Cramps	47	13	0	7	4	0	4
Urgency	33	7	0	25	4	0	0
Mucus Loss	17	0	0	3	0	0	0
Anal Pain	30	0	0	0	0	0	0
URINARY	**47**	**23**	**0**	**21**	**18**	**14**	**0**
Pollakisuria	33	13	0	4	0	0	0
Nycturia	43	3	0	0	0	0	0
Hematuria	3	3	0	7	4	0	0
Dysuria	50	3	0	0	0	0	0
Urge	37	0	0	14	0	0	0
Incontinence	14	7	0	21	14	14	0
HEMATOLOGIC	**40**	**40**	**7**				
Hemoglobin	43	27	0				
White Blood cell Count	28	24	7				
Neutrophils	13	3	0				
Platelets	10	0	0				
SKIN	**3**	**7**	**0**	**0**	**0**	**0**	**0**

Acute gastro-intestinal (GI) toxicity was scored using a combination of the RTOG scoring system [4], the scale of GI urgency and incontinence determined by Yeoh et *al.* [27] and an in-house developed scale for rectal blood loss [6]. Late GI toxicity was scored using the Radiation Induced Lower Intestine Toxicity scoring scale [9]. Genitourinary (GU) toxicity was scored using the RTOG scale extended with an in-house developed scale for incontinence [6]. Hematologic, and skin toxicity was scored according to the RTOG scoring system [4].

Tabelle 4: Akute und späte bestrahlungsbezogene Toxizität.

Die akute gastrointestinale (GI) Toxizität wurde mittels einer Kombination aus dem RTOG-Punktesystem [4], der von Yeoh et *al.* [27] bestimmten GI-Harndrang- und Inkontinenzskala sowie einer intern entwickelten Skala des rektalen Blutverlusts [6] ermittelt. Die späte GI-Toxizität wurde mittels der Punkteskala für die bestrahlungsinduzierte Toxizität der unteren Darmabschnitte [9] ermittelt. Die genito-urologische (GU)-Toxizität wurde mittels der RTOG-Skala bewertet, die um eine intern entwickelte Inkontinenzskala [6] erweitert wurde. Die hämatologische und die Hauttoxizität wurden gemäß des RTOG-Punktesystems [4] bewertet.

Locoregional control, OS and PFS.

One patient had a local relapse (vaginal cuff) 4 months after surgery and died. No regional relapses occurred. Two patients (8%) developed distant metastasis (1 in lung and 1 in liver) 6 and 7 months after hysterectomy respectively. Both patients died (19 months and shortly after diagnosis of metastases respectively). Actuarial 2-year LC rate is 96%, RC rates are 100%. Actuarial 2- year DC and PFS rates are 92% and 89% respectively. One, 2 and 3- year OS rates are 96%, 91% and 84% respectively.

Discussion

For LACC, chemoradiation is the standard treatment [10, 14, 17]. However, a meta-analysis showed that the benefit of chemoradiation is less pronounced with bulky and Figo III-IVA disease [10]. The only trial randomizing patients (bulky IB tumours) to receive post-RT (including brachytherapy) extrafascial hysterectomy or not showed a significant ($p=0.007$) better overall survival for 4-5 and 6 cm tumours, indicating that these might benefit from extrafascial hysterectomy [13]. Several non-randomized trials addressing the same issue suggest a significant benefit of post-CRT surgery towards local control and a favourable trend towards overall survival [2, 8, 13, 19]. Fear for excess in treatment related toxicity could explain the reserved position towards post-CRT surgery. Keys et al. however could not show any difference in treatment related toxicity [13]. A recent long term analysis of chemoradiation followed by surgery showed an acceptable long-term toxicity profile [8]. Our own preliminary results concerning postoperative morbidity are very promising with 3% grade 3 and no grade 4 postoperative complications and no fistulas so far.

A postoperative urinary retention rate of 30% (during hospitalization) was noted, higher than would be expected after class II radical hysterectomy. It is our hypothesis that this higher rate of postoperative urinary retention is due to (chemo)radiotherapy induced parametrial fibrosis. Also Carcopino et al. found that postoperative morbidity after chemoradiation significantly increases with FIGO stage [2]. Direct comparison with published results is not feasible due to the fact that postoperative morbidity is described differently from one study to another and grade I morbidity is seldom reported. However, since this morbidity is temporarily (5 requiring self-catheterization, none persisting longer than 6 months) we find this morbidity rate acceptable. Further strict follow-up is definitely needed.

The advent of new radiation treatment techniques is an important factor in reducing toxicity. Our study confirmed the ability of IMRT and arc therapy to lower the dose to the organs at risk and to reduce acute toxicity [12, 18]. Apart from 2 patients who developed an acute grade 3 hematologic toxicity during IMAT-C, no other patients suffered grade ≥3 acute toxicity of any kind. This contrasts sharply with literature data, using conventional techniques. Several authors reported grade ≥3 **acute** toxicity, being mainly hematologic and intestinal with grade 3 and 4 toxicity present in 28% and 8% respectively [14]. Four percent **late** grade 4 toxicity and 14% grade 3 urinary incontinences have been noted so far. This compares with literature data on treatment schedules without adjuvant surgery reporting an incidence of late grade 4 toxicity of 2% to 8% and late grade 3 toxicity of 14 to 35%, being mainly intestinal, urinary or development of fistulae [14]. Although the follow-up in our study is not mature, neither fistulas nor grade 3 intestinal toxicities are noted so far. No partial or complete stenosis of the vagina has been observed. This contrasts with the 25% and 3% incidence of grade 2 and 3 vaginal toxicity in series involving brachytherapy [24].

Survival is higher if the post-CRT hysterectomy specimen shows a complete clinical response. In literature this complete clinical response rate varies between 52% and 76% [19]. In our study, **all** patients had a clinical complete response with a complete pathological response in 40%. We hypothesize that the higher biological dose obtained by IMAT is the key factor in this 100% percentage of complete clinical response. Perez et al. [23] already

suggested a positive relation between local control and escalated radiation dose, confirmed by others [20]. Improved local control and survival data using dose escalation in brachytherapy for large (>5cm) locally advanced cervical tumours confirm this clinically [24]. Considering an α/β ratio of 10 for cervical cancer [11], the BED_2 received by the GTV_cervix is 64 Gy, which is substantially higher than the doses described in literature [19], without overall treatment time prolongation resulting in a simultaneous integrated boost [11].
Almost 90% of locoregional recurrences occur within 36 months after treatment with 60% and 80% of them occurring within 1 year and 2 years after treatment [22]. A tendency to develop pelvic recurrence even sooner is seen in patients with high-volume and more advanced disease [22]. With a median follow-up of 24 months, an actuarial 2-years locoregional control and 3-years OS of 96% and 84% respectively is achieved, which is comparable with the data published in six large randomized trials (3 years OS varying between 65 and 87%) [16]. Recently, results concerning dose volume adaptive brachytherapy have published 3-year locoregional control rates of 90%, 3-years OS was 64%. For tumours measuring more than 5 cm, dose escalation lead to an increase of 3-years locoregional control and OS from 71% to 90% and from 28% to 58% respectively [24]. Subgroup analysis of our patients presenting with a tumour >5 cm (n=21; 70%) showed actuarial 2 and 3-years LRC of both 94% and 3 years OS of 80% respectively.
Few data are published concerning the treatment of FDG positive lymph nodes in patients treated with definitive chemoradiation. If no lymphadenectomy is performed, what dose should be given to FDG positive lymph nodes? In our series 100% complete pathological remission is found in FDG-positive lymph nodes < 2 cm with a BED2 of 62Gy. In larger (≥ 2 cm) lymph nodes pCR could be reached in only 50%, suggesting the need for a higher dose in this setting. Further research is indispensible to confirm this finding.
Considering the combination of low toxicity and excellent local control, hysterectomy after IMAT-C should be considered in the multimodality treatment of locally advanced cervical cancer.

Conclusion

IMAT ± cisplatin has low acute and late toxicity and allows post-CRT hysterectomy without excess in surgical morbidity. LC, RC, DC and OS rates are promising.

References

1. Brocker K, Alt C, Eichbaum M, et al. Imaging of female pelvic malignancies regarding MRI, CT, and PET/CT. Strahlentherapie Und Onkologie 2011;187:611-8.
2. Carcopino X, Houvenaeghel G, Buttarelli M, et al. Equivalent survival in patients with advanced stage IB-II and III-IVA cervical cancer treated by adjuvant surgery following chemoradiotherapy. Eur J Surg Oncol 2008;34:569-75.
3. Chassagne D, Sismondi P, Horiot JC, et al. A glossary for reporting complications of treatment in gynecological cancers. Radiother Oncol 1993;26:195-202.
4. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341-6.
5. Cozzi L, Dinshaw KA, Shrivastava SK, et al. A treatment planning study comparing volumetric arc modulation with RapidArc and fixed field IMRT for cervix uteri radiotherapy. Radiotherapy and Oncology 2008;89:180-91.
6. De Meerleer G, Vakaet L, Meersschout S, et al. Intensity-modulated radiotherapy as primary treatment for prostate cancer: acute toxicity in 114 patients. Int J Radiat Oncol Biol Phys 2004;60:777-87.
7. Duthoy W, De Gersem W, Vergote K, et al. Clinical implementation of intensity-modulated arc therapy (IMAT) for rectal cancer. Int J Radiat Oncol Biol Phys 2004;60:794-806.
8. Ferrandina G, Margariti PA, Smaniotto D, et al. Long-term analysis of clinical outcome and complications in locally advanced cervical cancer patients administered concomitant chemoradiation followed by radical surgery. Gynecol Oncol 2010;119:404-10.
9. Fonteyne V, De Neve W, Villeirs G, et al. Late radiotherapy-induced lower intestinal toxicity (RILIT) of intensity-modulated radiotherapy for prostate cancer: the need for adapting toxicity scales and the appearance of the sigmoid colon as co-responsible organ for lower intestinal toxicity. Radiother Oncol 2007;84:156-63.
10. Green J, Kirwan J, Tierney J, et al. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. Cochrane Database Syst Rev 2005:CD002225.
11. Guerrero M, Li XA, Ma L, et al. Simultaneous integrated intensity-modulated radiotherapy boost for locally advanced gynecological cancer: radiobiological and dosimetric considerations. Int J Radiat Oncol Biol Phys 2005;62:933-9.
12. Hasselle MD, Rose BS, Kochanski JD, et al. Clinical Outcomes of Intensity-Modulated Pelvic Radiation Therapy for Carcinoma of the Cervix. Int J Radiat Oncol Biol Phys 2011;80:1436-45.
13. Keys HM, Bundy BN, Stehman FB, et al. Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. Gynecol Oncol 2003;89:343-53.
14. Kirwan JM, Symonds P, Green JA, et al. A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. Radiother Oncol 2003;68:217-26.
15. Lammering G, De Ruysscher D, van Baardwijk A, et al. The use of FDG-PET to target tumors by radiotherapy. Strahlenther Onkol 2010;186:471-81.
16. Loizzi V, Cormio G, Loverro G, et al. Chemoradiation: A new approach for the treatment of cervical cancer. Int J Gynecol Cancer 2003;13:580-6.
17. Lukka H, Hirte H, Fyles A, et al. Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer--a meta-analysis. Clin Oncol (R Coll Radiol) 2002;14:203-12.
18. Marnitz S, Stromberger C, Kawgan-Kagan M, et al. Helical tomotherapy in cervical cancer patients: simultaneous integrated boost concept: technique and acute toxicity. Strahlenther Onkol 2010;186:572-9.

19. Morice P, Uzan C, Zafrani Y, et al. The role of surgery after chemoradiation therapy and brachytherapy for stage IB2/II cervical cancer. Gynecol Oncol 2007;107:S122-4.
20. Niibe Y, Hayakawa K, Kanai T, et al. Optimal dose for stage IIIB adenocarcinoma of the uterine cervix on the basis of biological effective dose. Eur J Gynaecol Oncol 2006;27:47-9.
21. Pasler M, Wirtz H, Lutterbach J. Impact of Gantry Rotation Time on Plan Quality and Dosimetric Verification – Volumetric Modulated Arc Therapy (VMAT) vs. Intensity Modulated Radiotherapy (IMRT). Strahlentherapie Und Onkologie 2011;187:812-9.
22. Perez CA, Breaux S, Madoc-Jones H, et al. Radiation therapy alone in the treatment of carcinoma of uterine cervix. I. Analysis of tumor recurrence. Cancer 1983;51:1393-402.
23. Perez CA, Grigsby PW, Chao KS, et al. Tumor size, irradiation dose, and long-term outcome of carcinoma of uterine cervix. Int J Radiat Oncol Biol Phys 1998;41:307-17.
24. Potter R, Dimopoulos J, Georg P, et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. Radiother Oncol 2007;83:148-55.
25. Small W, Jr., Mell LK, Anderson P, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys 2008;71:428-34.
26. Vandecasteele K, De Neve W, De Gersem W, et al. Intensity-Modulated Arc Therapy with Simultaneous Integrated Boost in the Treatment of Primary Irresectable Cervical Cancer. Strahlentherapie Und Onkologie 2009;185:799-807.
27. Yeoh EE, Fraser RJ, McGowan RE, et al. Evidence for efficacy without increased toxicity of hypofractionated radiotherapy for prostate carcinoma: early results of a Phase III randomized trial. Int J Radiat Oncol Biol Phys 2003;55:943-55.

Chapter 6

Publication 4:

Value of Magnetic Resonance and ^{18}FDG PET-CT in Predicting Tumor Response and Resectability of Primary Locally Advanced Cervical Cancer after Treatment with Intensity-Modulated Arc Therapy. A prospective pathology-matched study.

Katrien Vandecasteele, M.D. (1), Louke Delrue, M.D (2) Bieke Lambert, M.D., Ph.D. (3), Amin Makar, M.D., Ph.D. (4), Kathleen Lambein, M.D. (5), Hannelore Denys, M.D., Ph.D. (6), Philippe Tummers, M.D. (4), Rudy Van den Broecke, M.D., Ph.D. (4), Geert Villeirs, M.D., Ph.D. (2), Gert De Meerleer, M.D., Ph.D. (1).

Affiliation:
(1): Department of Radiation Oncology, (2): Department of Radiology, (3): Department of Nuclear Medicine, (4): Department of Gynaecology, (5): Department of Pathology, (6): Department of Medical Oncology @ Gent University Hospital, Belgium.

Note: The first 2 authors contributed equally to this manuscript.

Int J Gynecol Cancer. 2012 Jan 10. [Epub ahead of print]

There is no conflict of interest
Key words: locally advanced cervical cancer, MRI, ^{18}FDG PET-CT, prediction, tumor response

Abstract

Objective

To report on the value of MRI and ^{18}FDG PET-CT in predicting resectability and pathological response of primary locally advanced cervical cancer following neo-adjuvant intensity-modulated arc therapy (IMAT) ± cisplatin (C).

Methods/materials

Twenty-seven patients with FIGO IB2 – IVA cervical cancer were treated with IMAT-C followed by extrafascial hysterectomy (EH). All patients received MRI and ^{18}FDG PET-CT after IMAT-C. The endpoints of this study were to:

1. Assess the ability of MRI to **predict negative surgical margins (R0).**
2. Assess the sensitivity, specificity, PPV and NPV of MRI in predicting the following situation at the EH specimen: "**no residual disease or minimal microscopically visible residual tumor**".
3. Assess the sensitivity, specificity, PPV and NPV value of ^{18}FDG PET-CT in predicting "**no residual viable tumor cells"** at the EH specimen.

Results

An R0-resection was obtained in all patients. None of the EH specimens contained macroscopically visible tumor. In 13 patients, no viable tumor cells were found, 14 only had residual microscopic disease.

24/27 MRI's were able to correctly predict R0 resection. A negative MRI was 100% predictive for the endpoint "R0 resection".

The specificity and NPV of MRI (endpoint 2) was 74% and 100% respectively. No sensitivity or PPV could be calculated. The sensitivity, specificity, PPV and NPV of ^{18}FDG PET-CT were 29, 62, 44 and 44% respectively (endpoint 3).

Conclusions

A negative MRI post-IMAT-C predicts 100% correctly for "R0 resection". The role of ^{18}FDG PET-CT in predicting viable tumor cells at EH specimen is at least debatable.

Introduction

For FIGO stage IIB – IVA cervical cancer, chemoradiation (CRT) is the standard treatment [(1)]. Brachytherapy increases the dose to the primary tumor [(2)]. A randomized trial showed that hysterectomy post-CRT does not increase toxicity and improves locoregional control [(3)].

Intensity-modulated radiotherapy [(4-8)] and intensity-modulated arc therapy (IMAT) [(9, 10)] lower the dose to the organs at risk and increase the dose to the primary tumor without prolongation of treatment time (which is a determinant of tumor control) [(11-13)]. In stage IB2-IIB disease, brachytherapy is dispensable, provided radical hysterectomy with pelvic lymphadenectomy is performed [(14)].

At Gent University Hospital, combined cisplatin-IMAT (IMAT-C) followed by extrafascial hysterectomy (EH) gives excellent local control of FIGO IIB-IVA cervical cancer [(15)]. The decision about EH is made multidisciplinary and depends on local response diagnosed clinically and by Magnetic Resonance Imaging (MRI) and 2-deoxy-2-[18] fluoro-D-glucose positron emission tomography (^{18}FDG PET-CT) as suggested in the literature [(16-22)].

^{18}FDG PET-CT is superior in detecting lymph nodes to CT alone leading to improved coverage of target volumes and modified radiation fields in 20% of patients [(16, 23)]. The

maximal standardized uptake value (SUV_{max}) at diagnosis predicts disease-free (DFS) and overall survival (OS) [22-24]. Post-therapy FDG-uptake is inversely correlated with cause-specific survival (CSS) and OS [25]. The use of ^{18}FDG PET-CT during radiotherapy to predict outcome is not unequivocally proven [26, 27].
The current paper reports on the value of:
1. MRI in predicting resectability of primary locally advanced cervical cancer (LACC) following IMAT-C.
2. MRI in predicting tumour response as evaluated on EH specimen.
3. ^{18}FDG PET-CT in predicting tumour response as evaluated on EH specimen.

Materials and methods

Between 01/2007 and 01/2010, 27 consecutive patients with primary LACC (bulky IB2 in 1, IIB in 18, IIIA in 2, IIIB in 4 and IVA in 2 patients respectively) were referred for multimodality treatment. Median age was 49 years. The tumor characteristics are presented in Table 1.
The multimodality treatment protocol consisted of IMAT-C followed by EH. Chemotherapy consisted of cisplatin, 40 mg/m^2 weekly. Before starting treatment, all patients received an ^{18}FDG PET-CT and a MRI in radiotherapy treatment position.
MRI was performed on a 1.5 Tesla system using a pelvic phased array body. Scopolamine was administered intravenously to avoid motion artefacts by bowel peristalsis. The MRI consists of fast T2 weighted imaging in 512 matrixes in a sagittal plane and in a plane perpendicular to the cervical axis, and a spin-echo T1 weighted imaging also in a 512 matrix in the transverse plane. Locoregional assessment was made by tumor detection, measuring tumor volume and assessment of stromal, parametrial, pelvic side-wall, bladder and rectal invasion.
Concerning ^{18}FDG PET-CT, patients fasted ≥4 h prior to IV injection of ^{18}FDG (7-12 mCi, administered approximately 60 minutes before scanning). Patients were imaged with a Gemini PET-CT camera (Philips, Cleveland, USA) consisting of a gadolinium oxyorthosilicate full-ring PET scanner with 5 mm spatial resolution and a 16-slice helical CT scanner. A CT without specific breath-holding instructions was performed using IV contrast. Without changing patient position, the PET scan was acquired immediately thereafter. PET images were reconstructed using an iterative 3D-RAMLA (Row Action Maximum Likelihood Algorithm). Low-dose CT data were used for attenuation correction. A region of interest was drawn around the tumour and lymph nodes on the fused images. The SUV_{max} was calculated on the co-registered attenuation corrected PET images.
The primary tumor as visualized on imaging was called “gross tumor volume” (GTV) and treated with 62 Gy. If the PET-CT showed FDG-avid lymph nodes, these were considered as bearing tumor cells and treated with 60 Gy. The clinical target volume (CTV) consisted of the GTV complemented by the cervix, uterus, vagina and parametria and was treated to 58 Gy. The elective pelvic lymph nodes were treated to 45 Gy. All treatments were performed in 25 fractions resulting in a simultaneous integrated boost to the GTV and affected lymph nodes. Details concerning target volume delineation, planning objectives and acute toxicity have been described [9].
All patients underwent gynaecological examination, MRI and ^{18}FDG PET-CT within 24 days after IMAT-C. The clinical examination was performed within 10 days after the MRI. The gynaecologists were blinded to the results of the MRI.

Tumor characteristics												
	Timing: before IMAT-C						Timing: after IMAT-C				Timing: after EH	
	Clinical		Magnetic resonance (MR)		18FDG-PET		MR	18FDG-PET				
	Figo stage	Pathology	Figo stage	T_{prim} volume (cc)	T_{prim} SUV_{max}	Node SUV_{max}	Figo stage	T_{prim} SUV_{max}	Node SUV_{max}	MR-Category	AP-Result	AP-category
Patient 1	IIB	G3 SCC	IIIA	172	4.14	1.39	IB1 (<4 cm)	no	no	2	y pT1B1	2
Patient 2	IIIB	G2 adenoca	IIIB	101	8.13	no	0	no	no	1	y pT1A1	2
Patient 3	IIIB	G2 adenoca	IIB	127	5.62	no	0	no	no	1	y pT1B1	2
Patient 4	IIIA	G3 SCC	IIIA	78	14.3	1.70	0	no	no	1	y pT0	1
Patient 5	IIB	G3 SCC	IIB	179	9.58	no	0	no	no	1	y pT1A2	2
Patient 6	IIB	G3 SCC	IIB	140	10.4	no	IIA	no	no	2	y pT0	1
Patient 7	IIB	G2 adenoca	IIB	17	4.34	no	IIB	5.70	no	3 *	y pT1B1	2
Patient 8	IIB	G3 SCC	IIB	230	3.34	no	0	7.10	no	1	y pT0	1
Patient 9	IVB	G2 SCC	IVB	69	3.06	2.85	0	no	1.23	1	y pT0	1
Patient 10	IIIB	G3 SCC	IIB	66	6.13	2.76	0	no	no	1	y pT1B1	2
Patient 11	IVA	G2 SCC	IVA	48	4.60	1.87	IIIB (HUN)	no	no	2	y pT0	1
Patient 12	IIB	G3 SCC	IIB	79	4.92	no	0	3.20	no	1	y pT0	1
Patient 13	IIB	G2 SCC	IIB	215	7.30	2.70	IB1 (<4 cm)	no	no	2	y pT2b	2
Patient 14	IIB	G1 adenoca	IIB	135	2.50	no	0	no	no	1	y pT1B1	2
Patient 15	IIB	G3 SCC	IIB	83	5.55	no	0	no	no	1	y pT0	1
Patient 16	IIB	G2 SCC	IIB	58	5.18	no	IB1 (<4 cm)	no	no	2	y pT0	1
Patient 17	IIIB	G3 SCC	IVA	154	7.84	4.41	IIIB (HUN)	no	no	2	y pT1B1	2
Patient 18	IIB	G3 SCC	IIB	99	6.37	3.57	0	3.89	2.02	1	y pT0	1
Patient 19	IIIA	G3 SCC	IIIA	27	7.34	no	0	no	no	1	y pT0	1
Patient 20	IIB	G1 SCC	IIB	161	13.89	1.60	0	4.82	no	1	y pT0	1
Patient 21	IIB	G3 SCC	IIB	205	7.49	4.35	0	3.33	3.80	1	y pT1A2	2
Patient 22	IIB	G3 SCC	IIB	48	14.76	no	0	no	no	1	y pT0	1
Patient 23	IIB	G2 SCC	IIB	188	15.85	9.65	0	no	no	1	y pT1B1	2
Patient 24	IB2	G3 SCC	IB2	59	17.63	no	0	5.29	no	1	y pT1A2	2
Patient 25	IIB	G3 SCC	IIB	113	6.50	no	0	no	no	1	y pT1B2	2
Patient 26	IIB	G2 SCC	IIB	82	4.46	no	0	4.39	no	1	y pT0	1
Patient 27	IIB	G3 SCC	IIB	20	8.61	2.68	0	4.37	2.82	1	y pT1B1	2

Table 1: Patient and tumor characteristics at diagnosis, after IMAT-C and after EH.

IMAT-C: Intensity-Modulated Arc Therapy ± cisplatin; MR: magnetic resonance; FDG: fluoro-deoxy glucose; AP: anatomo-pathology; G1, G2, G3: well, moderate or poorly differentiated respectively; N-/N+: node negative – node positive respectively; SCC squamous cell carcinoma; adenoca: adenocarcinoma; HUN: hydro-uretronephrosis. Three patients presented with a urinary derivation due to hydro-uretronephrosis (HUN) causing impairment of renal function. One patient suffered HUN without impairment of renal function. There were two patients with stage IV disease. Patient 9 had a 4 cm large lymph node above the level of the aortic bifurcation (M1 disease), pathologically confirmed (CT-guided biopsy) as lymph node metastasis from a moderately differentiated squamous cell carcinoma. Patient 11 had both on cystoscopy and MRI (vide infra) suspicion of urinary bladder invasion. IMAT-C was delivered in 23 patients, 4 patients received IMAT without chemotherapy (patients 2, 5, 11 and 15). Reasons for omitting were impaired kidney function in 3 and age in 1 patient. Patient 7: *: MRI post-IMAT-C still suggested invasion of the left parametrium because of disruption of the cervical ring at that level. Clinical examination confirmed the left parametrium to be less mobile, but without clear evidence of tumoural invasion. Pathology showed only residual microscopic tumor with an invasion depth of 7 mm (y pT1B1).

Analysis of images

The post-treatment MR images were analyzed by two experienced radiologists (LD – GV), independently. They agreed in all cases. Patients were classified as ***MR-Category 1:*** complete disappearance of the tumor and total restoration of the normal cervix anatomy; ***MR-Category 2:*** residual tumor <4 cm and/or no longer invading parametria, lower vaginal third or adjacent organs or with imaging uncertainties such as radiation-induced fibrosis causing hydro-uretronephrosis (HUN) ("unclassified modifications"); ***MR-Category 3*** with no response to IMAT-C.

The post-treatment ^{18}FDG PET-CT images were analyzed jointly by a radiologist (LD) and nuclearist (BL). In accordance with Schwarz et al. [27] they were classified as ***FDG-Category 1:*** disappearance of FDG uptake in the tumor; ***FDG-Category 2:*** a response >25% in SUV_{max} or ***FDG-Category 3:*** ≤25% response or stable/increased tumor metabolic activity.

Pathology

Extrafascial hysterectomy specimens, including vaginal section margins, were completely sectioned into 3 mm slices and entirely embedded in paraffin blocks. Of each block levels of 3 micrometer each were cut and meticulously evaluated on haematoxylin and eosin stain. In cases of reactive features, these were confirmed by immunohistochemistry broad spectrum cytokeratin. If a lymph node dissection was performed, the different sites were evaluated separately. Residual tumor on the surgical specimen was staged according to FIGO (TNM classification, 5th edition). To indicate that this staging was after neo-adjuvant CRT, all pTN-stages were preceded by "y". The pathologist classified the tumor response in three categories as well: ***AP-Category 1***: no viable tumor cells (ypT0); ***AP-Category 2*** and ***AP-Category 3*** with microscopically and macroscopically visible tumor respectively. The vaginal section margin was considered negative or positive depending on the absence (R0) or presence (R1) of tumor cells at this margin.

The endpoints of this study were to:

1. Assess the ability of MRI to **predict tumor resectability** (R0 resection).
2. Assess the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of MRI in predicting tumor response. MR category 1 & 2 was considered predictive for the endpoint "**no residual disease or minimal microscopically visible residual tumor**" as evaluated on the EH specimen. [21].

1. Assess the sensitivity, specificity, PPV and NPV of ^{18}FDG PET-CT in predicting ypT0 disease as evaluated on the EH specimen. A negative ^{18}FDG PET-CT was considered predictive for the endpoint "**no residual viable tumor cells"**.

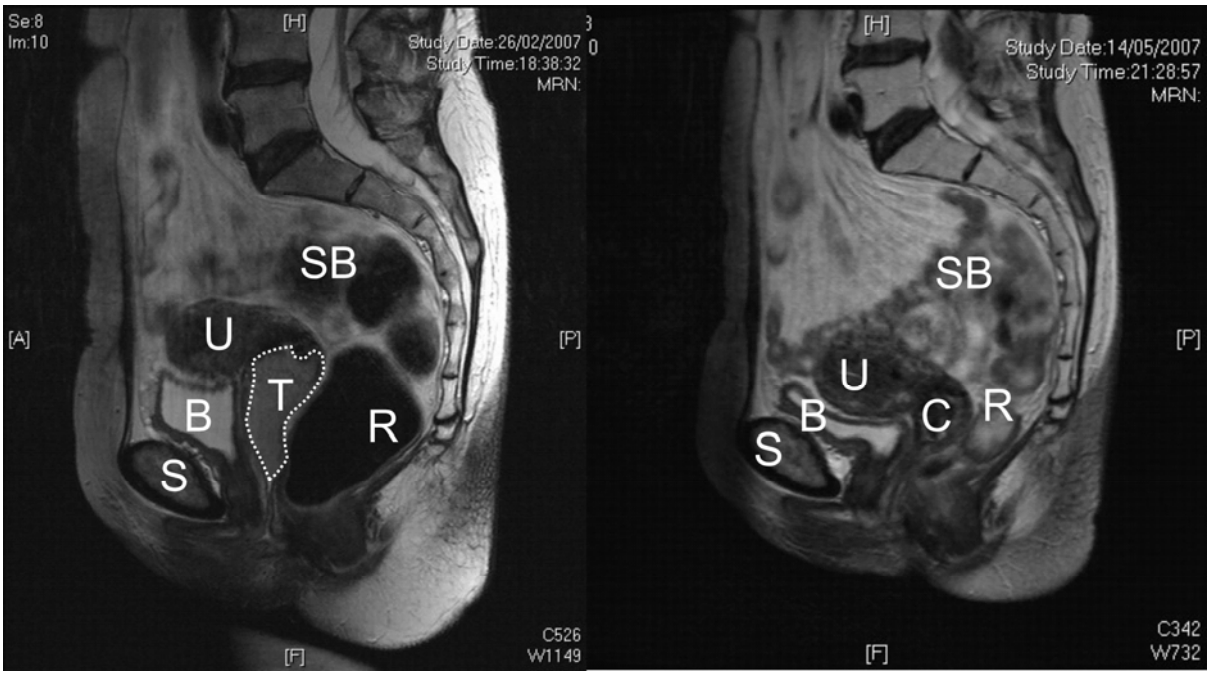

Figure 1. Sagittal MR-image of patient 4 (see Table 1) presenting with a FIGO IIIA disease at initial diagnosis. The left panel shows the tumor as a grey mass invading the vagina. The right panel shows the situation 27 days after the end of IMAT-C: there is no longer tumor present on the MR-image and the cervical anatomy has returned to normal. T: tumor; B: bladder; U: uterus; SB: small bowel; S: symphysis pubis; C: cervix. R: rectum.

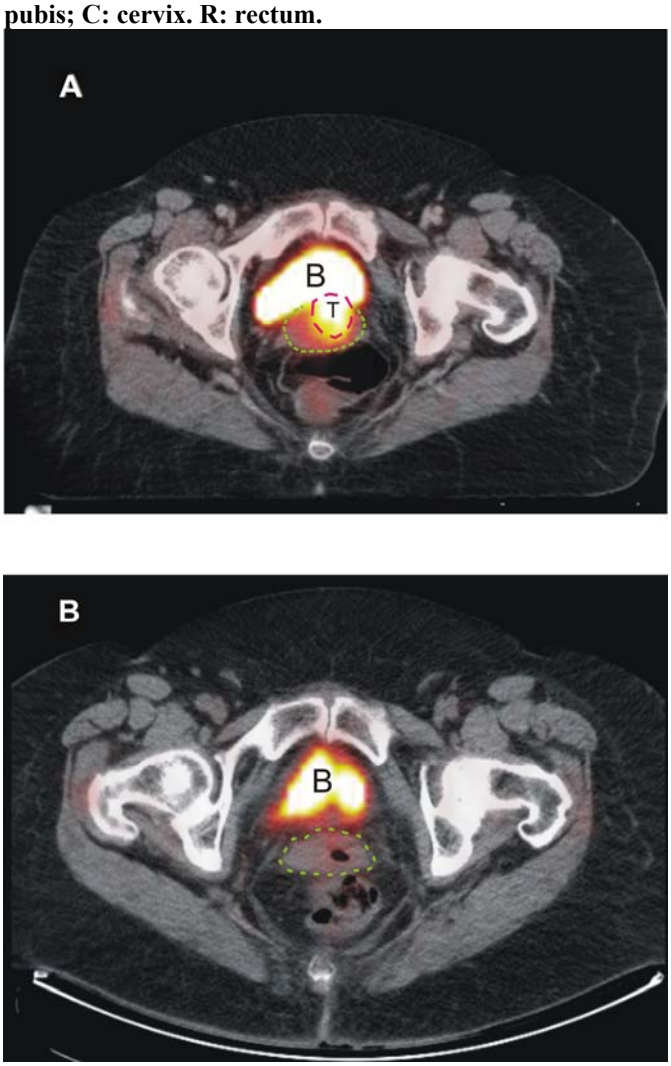

Figure 2. Axial PET-CT images of patient 25 (see Table 1) presenting with a FIGO IIB disease at initial diagnosis. Panel A depicts the pre-treatment PET-CT image showing intense FDG uptake at the primary tumor (T). Panel B depicts the PET-CT image taken 17 days after the end of IMAT-C: there is no longer FDG uptake at the cervix (presented in green). The FDG-PET was false negative; the hysterectomy specimen showed ypT1b2 poorly differentiated SCC with a depth invasion of 8 mm and a diameter exceeding 4 cm. The red dashed line surrounds the tumor; the green dashed line surrounds the cervix.
T: tumor; B: bladder.

Results

Details concerning patient and tumor characteristics and pre-treatment imaging are summarized in Table 1. Pre-treatment ^{18}FDG PET-CT showed uptake in the primary tumor and lymph nodes in all and 12 patients respectively. In the primary tumor, mean (± standard deviation (SD)) and median SUV_{max} was 7.77 (± 4.16) and 6.50. Concerning positive nodes, mean (±SD) and median SUV_{max} was 3.29 (± 2.24) and 2.73. Mean and median pre-treatment MR-derived tumor volume was 109 and 91 cc.

The mean and median time between the end of IMAT-C and imaging post-IMAT-C was 21 and 20 days. The mean and median time between the post-IMAT-C MRI and EH was 27 and 25 days. Imaging of tumor response is presented in Figures 1-3.

None of the ^{18}FDG PET-CT images post-IMAT-C showed evidence of progressive disease at regional lymph nodes or distant sites.

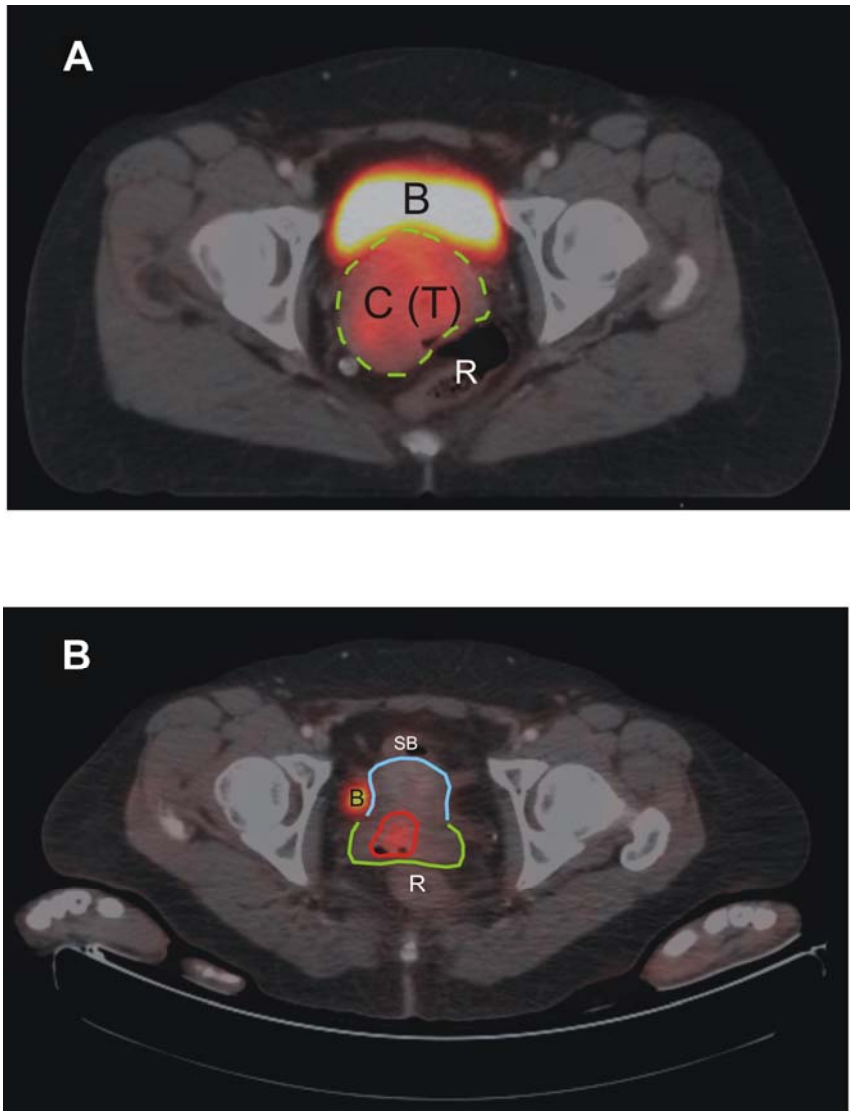

Figure 3. Axial PET-CT images of patient 8 (see Table 1) presenting with a FIGO IIB disease at initial diagnosis. Panel 3.1 depicts the pre-treatment PET-CT image showing FDG uptake at the primary tumor (T). Panel 3.2 depicts the PET-CT image taken 11 days after the end of IMAT-C: there is still FDG uptake at the cervix (presented in red). The FDG-PET was false positive, the hysterectomy specimen showed y pT0 disease. Foamy histiocytes were present abundantly. The cervix is surrounded by a green dotted line (panels A and B), the uterine corpus is surrounded by a blue line (panel B). The remaining FDG-activity is surrounded by a red line (panel B).
C (T): cervix containing primary tumor; B: bladder; R: rectum; SB: small bowel

Results for endpoint 1

All patients received EH. Surgical margins were negative in **all** cases (R0 resection). No EH specimen showed macroscopically visible tumor. In 13 patients, no viable tumor cells were found at pathological examination (AP-category 1). All other patients had residual microscopic disease (AP-category 2). The 2 patients with y pT1A1 disease had solitary tumor cells without measurable invasion depth. The 3 patients with y pT1A2 disease had residual isolated tumor cells with a stromal depth invasion of 3, 3.5 and 5 mm respectively. For the 7 patients with residual y pT1B1 disease, stromal depth invasion was 6, 7 and 11 mm in 2 patients and 10 mm in 1 patient. One patient had y pT1B2 disease with isolated tumor cells spread out over >4 cm. One patient had a residual microscopically tumor focus in the left parametrium and therefore was scored as y pT2B disease.

24/27 MRI's post-IMAT-C correctly predicted R0 resection (true negative rate 89%). A negative MRI post-IMAT-C predicted 100% correctly. Additionally, 3/27 MRI examinations falsely predicted an R1-resection (false positive rate 11 %). In 2 patients, the MRI post-IMAT-C still showed HUN (category 2), leading to the conclusion of MR-stage IIIB. However, at EH specimen, there were no viable tumor cells left in 1 patient and microscopic tumoural nests in the other. In 1 patient, the MRI post-IMAT-C suggested left parametrial invasion. Clinical examination could not confirm this. Pathology showed residual microscopic tumor with an invasion depth of 7 mm (y pT1B1).

Results for endpoint 2

The results are summarized in Table 2. The sensitivity and positive predictive value could not be calculated as there were no events, i.e. macroscopically visible tumor. The specificity and negative predictive values of MRI was 74% and 100% respectively. There were no false negative results.

Table 2: Correlation between MRI and residual tumor as derived from surgical specimen.

Number of patients		
Residual disease at MRI	**Residual disease at surgical specimen**	
	macroscopic rest	**ypT0 - microscopic rest**
Yes	0	7
No	0	20

Results for endpoint 3

a. Primary tumor

There was remaining ^{18}FDG uptake in 9 patients with a mean (± SD) and median SUV_{max} of 5.12 (± 1.17) and 4.84. In 2/9 patients, SUV_{max} after was **higher** than before treatment. In 5/9 patients with remaining ^{18}FDG uptake (mean SUV_{max} of 4.68 (± 1.48), no residual disease was found (y pT0). One of those patients had an increase of SUV_{max} compared to the pre-treatment situation (7.10 vs. 3.34). The 4 other patients with remaining ^{18}FDG uptake (mean SUV_{max} of 4.67 (± 1.05)) had y pT1A2 (n=2) and y pT1b (n=2). In 1 out of those 4 patients, there was an increase in SUV_{max} (5.70 vs. 4.34). The results concerning ^{18}FDG PET-CT are summarized in table 3. Of the 18 patients presenting without ^{18}FDG uptake at the primary tumor after treatment, 10 of them still had persistent tumor at the surgical specimen (y pT1A1: n=2; y pT1A2: n=1; y pT1B1: n=5; y pT1B2: n=1; y pT2B: n=1). The sensitivity,

specificity, positive and negative predictive values of ^{18}FDG PET-CT with regard to remaining tumor at EH specimen were 29, 62, 44 and 44% respectively.

b. Lymph nodes

There was remaining ^{18}FDG uptake in 4 patients with a mean (±SD) and median SUV_{max} of 2.47 (± 1.10) and 2.42 respectively. None of these lymph nodes contained viable tumor cells.

Table 3: Correlation between ^{18}FDG PET-CT and remaining viable tumor cells present on the surgical specimen.

Number of patients		
Residual disease at ^{18}FDG PET-CT	**Viable tumor cells at surgical specimen**	
	Yes	**No**
Yes	4	5
No	10	8

Discussion

In the European Society of Medical Oncology (ESMO) clinical recommendations for treatment of FIGO stage IB2 and IIB-IVA cervical cancer, "external irradiation combined with brachytherapy" is the treatment of choice [2]. Information concerning adjuvant EH is sparse; despite neo-adjuvant chemoradiation followed by EH is emerging as a relevant therapeutic option [14, 28-30]. For tumours >4 cm, there might be a survival benefit in favour of the latter [3]. This ">4 cm"-condition was present in 22 of our patients, which justifies EH certainly in view of the IMAT that was used. IMRT and IMAT have major advantages when compared to conventional radiotherapy. There is proof of improved CSS [13] and significantly reduced dose received by small bowel [8, 31], rectum [8], bladder [8] and bone marrow [32-34]. The implementation of IMAT has been facilitated by incorporating MRI and ^{18}FDG PET-CT in the radiotherapy planning [9, 21].

None of the EH specimens showed residual macroscopic tumor and there was a complete microscopic disappearance of tumor in almost 50% of the patients. This is at least comparable to published data [14, 20, 35].

Although MRI is considered almost as a necessity in modern radiotherapy planning for cervical cancer [36, 37], it's value in staging is only recently been prudently appreciated by the editorial office of the FIGO [38], although accuracy has already been shown to be as high as 90% more than a decade ago [39]. Although the American College of Radiology Imaging Network (ACRIN) Intergroup study recognized the low accuracy of MRI to diagnose minimal parametrial extent [18], this does not apply to our patients as parametrial extent was bulky in all our stage IIB patients.

Reports concerning the value of MRI in predicting radical resectability of primary LACC after neo-adjuvant (C)RT are sparse but not new. Almost 20 years ago, Flueckiger reported the results of serial MR imaging after primary radiotherapy in 28 patients [40]. Although the histopathology in this series was comparable to ours, the tumor volume was clearly smaller (21 cc vs. 109 cc). At MRI performed 1 month after radiotherapy, they noted a complete disappearance of the tumor in 3 patients (11%) compared to 20 patients (74%) in our series

[40]. This difference might have different causes: first of all, the majority of our patients received CRT which improves local control when compared to radiation alone [1]. Secondly, IMAT delivered a higher dose to the tumor. Flueckiger's main conclusion was that MR imaging allowed for accurate assessment of the response of cervical cancer to primary radiation [40]. Recently, Vincens published their experience with MRI performed on 44 patients treated with CRT, brachytherapy and subsequent surgery for FIGO IB2-II cervical cancer. Their results demonstrate that surgery is safe after CRT and that MRI performs excellent in predicting resectability of the tumor. The sensitivity, specificity and NPV for MRI concerning the endpoint "no residual disease or only isolated cells" was 80%, 55% and 83% respectively [20] compared to a specificity and NPV of 74% and 100% in our series. Due to the absence of events we could not calculate sensitivity in our treatment group.

The optimal timing of MRI post IMAT-C is debatable. Most frequently, this MRI is performed within 4 to 6 weeks [20]. In contradiction, Hatano performed MRI 3 months after treatment to optimize accuracy. A major drawback was the correlation between MRI and histopathology being performed on cervical biopsy only [39]. We agree with Vincens [20], who performed an MRI to check for resectability earlier than 3 months. If the time gap is longer, surgery would be jeopardized by an increased risk of fibrosis.

Our data prove that MRI is an excellent imaging modality in predicting radical resectability. All patients showing MR-categories 1 or 2 were operated with pathological R0 resection. This translates in a 100% true negative predictive value. Because of the growing evidence that additional surgery after chemoradiation improves patient's outcome [3, 30, 41-43], a negative MRI after chemoradiation could safely be followed by EH.

More difficult is the "IIIB" situation which implies HUN present on imaging [44]. In our series, 2 patients with HUN at MRI post-IMAT-C were successfully operated, both with R0 resections and with ypT0 and ypT1B1 as remaining disease. The remaining HUN in these patients must be due to radiotherapy induced fibrosis. In both patients, there was no ^{18}FDG avidity anymore. Combining MRI with ^{18}FDG PET-CT might be necessary in this particular situation.

Posttherapy PET using ^{18}FDG has been used to predict outcome after combined chemoradiation. In a retrospective series of 152 patients, persistent or "any new" FDG uptake predicted for an at least 50% drop in CSS and OS, with persistent post-therapy FDG uptake being the most significant predictor for CSS and recurrence-free survival [13, 25, 45]. In our series, 5/9 ^{18}FDG-positive post-treatment PET-CT's were false positive. Histopathology examination revealed no viable tumor cells but chronic inflammation and abundant number of histiocytes and foamy macrophages, 2 types of inflammatory cells that contribute to FDG-PET positivity [46]. The lack of correlation between ^{18}FDG-PET-CT and histology might be the timing of the PET-CT. Our post-treatment PET-CT was performed within 1 month, while the correlation between PET-CT and outcome was demonstrated only when ^{18}FDG PET was done 3 months after treatment [47].

The SUV_{max} as measured on pre-treatment ^{18}FDG PET is associated with local response and OS [13, 22, 23]. Xue defined a SUV_{max} >10.2 as predictive for a 20% decrease in disease-free survival [22]. Kidd demonstrated a significant drop in overall and progression-free survival when SUV_{max} increased from 5.2 to >13.3 [13].

Studies evaluating the changes in imaging during treatment are sparse. Schwarz investigated the correlation between changes in SUV_{max} during radiotherapy with outcome. They defined complete metabolic response as absence of abnormal ^{18}FDG uptake at sites that showed abnormal uptake at the pre-treatment scan. Partial response was defined as a >25% decrease in ^{18}FDG uptake on a scan performed 47 days after treatment start, which corresponds with the timing from our study. Mean SUV_{max} for all patients as measured at the ^{18}FDG PET after IMAT-C was 1.28, a value corresponding well with the SUV_{max} of 1.9 as measured by

Schwarz and a representing a 83% decrease, which is identical at the one measured by Schwarz [27].
Mayr correlated the rate of tumor regression as measured on MRI with treatment outcome. Time of measurements were pre-treatment and after 40-50 Gy of external beam radiotherapy. Tumor regression to <20% was correlated with a significantly lower rate of local recurrence (10 vs. 77%; $p<0.001$) [48]. Although not presented in detail in this paper, all our patients had a tumor regression to <20 % of their initial volume.
Although the number of patients is fairly low, this is to the best of our knowledge the largest series correlating the imaging with surgery-derived pathology. An important clinical conclusion can be drawn from our results: a negative MRI post-treatment has 100% negative predictive value when resectability of primary locally advanced cervical cancer is the endpoint. In view of the 100% locoregional control at 24 months achieved in our patients [15], we consider MRI as a necessity in the modern treatment of primary locally advanced cancer. The role of ^{18}FDG PET-CT in predicting viable tumor cells at EH specimen is at least debatable. Its role in adaptive radiotherapy for cervical cancer should be clearly examined before this could become the standard way of irradiation.

References

[1] Lukka H, Hirte H, Fyles A et al. Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer--a meta-analysis. *Clin Oncol (R Coll Radiol)*. 2002;**14**: 203-12.

[2] Haie-Meder C, Morice P, Castiglione M. Cervical cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol*. 2008;**19 Suppl 2**: ii17-8.

[3] Keys HM, Bundy BN, Stehman FB et al. Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. *Gynecol Oncol*. 2003;**89**: 343-53.

[4] Brixey CJ, Roeske JC, Lujan AE et al. Impact of intensity-modulated radiotherapy on acute hematologic toxicity in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2002;**54**: 1388-96.

[5] Guerrero M, Li XA, Ma L et al. Simultaneous integrated intensity-modulated radiotherapy boost for locally advanced gynecological cancer: radiobiological and dosimetric considerations. *Int J Radiat Oncol Biol Phys*. 2005;**62**: 933-9.

[6] Mell LK, Tiryaki H, Ahn KH et al. Dosimetric comparison of bone marrow-sparing intensity-modulated radiotherapy versus conventional techniques for treatment of cervical cancer. *Int J Radiat Oncol Biol Phys*. 2008;**71**: 1504-10.

[7] Mundt AJ, Lujan AE, Rotmensch J et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2002;**52**: 1330-7.

[8] Portelance L, Chao KS, Grigsby PW et al. Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. *Int J Radiat Oncol Biol Phys*. 2001;**51**: 261-6.

[9] Vandecasteele K, De Neve W, De Gersem W et al. Intensity-Modulated Arc Therapy with Simultaneous Integrated Boost in the Treatment of Primary Irresectable Cervical Cancer. *Strahlentherapie Und Onkologie*. 2009;**185**: 799-807.

[10] Wong E, D'Souza DP, Chen JZ et al. Intensity-modulated arc therapy for treatment of high-risk endometrial malignancies. *Int J Radiat Oncol Biol Phys*. 2005;**61**: 830-41.

[11] Choy D, Wong LC, Sham J et al. Dose-tumor response of carcinoma of cervix: an analysis of 594 patients treated by radiotherapy. *Gynecol Oncol*. 1993;**49**: 311-7.

[12] Girinsky T, Rey A, Roche B et al. Overall treatment time in advanced cervical carcinomas: a critical parameter in treatment outcome. *Int J Radiat Oncol Biol Phys*. 1993;**27**: 1051-6.

[13] Kidd EA, Siegel BA, Dehdashti F et al. Clinical Outcomes of Definitive Intensity-Modulated Radiation Therapy With Fluorodeoxyglucose-Positron Emission Tomography Simulation in Patients With Locally Advanced Cervical Cancer. *International Journal of Radiation Oncology*Biology*Physics*.**77**: 1085-91.

[14] Cetina L, Garcia-Arias A, Candelaria M et al. Brachytherapy versus radical hysterectomy after external beam chemoradiation: a non-randomized matched comparison in IB2-IIB cervical cancer patients. *World J Surg Oncol*. 2009;**7**: 19.

[15] Vandecasteele K, Makar A, Villeirs G et al. Tumour response and resectability after IMAT +/- cisplatin for primary irresectable carcinoma of the cervix. *Radiother Oncol*. 2008;**88** 77.

[16] Gupta T, Beriwal S. PET/CT-guided radiation therapy planning: from present to the future. *Indian J Cancer*.**47**: 126-33.

[17] Harry VN. Novel imaging techniques as response biomarkers in cervical cancer. *Gynecol Oncol*.**116**: 253-61.

[18] Mitchell DG, Snyder B, Coakley F et al. Early invasive cervical cancer: tumor delineation by magnetic resonance imaging, computed tomography, and clinical examination, verified by pathologic results, in the ACRIN 6651/GOG 183 Intergroup Study. *J Clin Oncol*. 2006;**24**: 5687-94.
[19] Smith GE, Gormly KL. Magnetic Resonance Imaging in the staging of cervical carcinoma: a pictorial review. *J Med Imaging Radiat Oncol*. 2008;**52**: 427-33.
[20] Vincens E, Balleyguier C, Rey A et al. Accuracy of magnetic resonance imaging in predicting residual disease in patients treated for stage IB2/II cervical carcinoma with chemoradiation therapy : correlation of radiologic findings with surgicopathologic results. *Cancer*. 2008;**113**: 2158-65.
[21] Wolfson AH. Magnetic resonance imaging and positron-emission tomography imaging in the 21st century as tools for the evaluation and management of patients with invasive cervical carcinoma. *Semin Radiat Oncol*. 2006;**16**: 186-91.
[22] Xue F, Lin LL, Dehdashti F et al. F-18 fluorodeoxyglucose uptake in primary cervical cancer as an indicator of prognosis after radiation therapy. *Gynecol Oncol*. 2006;**101**: 147-51.
[23] Jover R, Lourido D, Gonzalez C et al. Role of PET/CT in the evaluation of cervical cancer. *Gynecol Oncol*. 2008;**110**: S55-9.
[24] Kidd EA, Siegel BA, Dehdashti F, Grigsby PW. The standardized uptake value for F-18 fluorodeoxyglucose is a sensitive predictive biomarker for cervical cancer treatment response and survival. *Cancer*. 2007;**110**: 1738-44.
[25] Grigsby PW, Siegel BA, Dehdashti F et al. Posttherapy [18F] fluorodeoxyglucose positron emission tomography in carcinoma of the cervix: response and outcome. *J Clin Oncol*. 2004;**22**: 2167-71.
[26] Bjurberg M, Kjellen E, Ohlsson T et al. Prediction of patient outcome with 2-deoxy-2-[18F]fluoro-D-glucose-positron emission tomography early during radiotherapy for locally advanced cervical cancer. *Int J Gynecol Cancer*. 2009;**19**: 1600-5.
[27] Schwarz JK, Lin LL, Siegel BA et al. 18-F-fluorodeoxyglucose-positron emission tomography evaluation of early metabolic response during radiation therapy for cervical cancer. *Int J Radiat Oncol Biol Phys*. 2008;**72**: 1502-7.
[28] Benedetti-Panici P, Greggi S, Colombo A et al. Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study. *J Clin Oncol*. 2002;**20**: 179-88.
[29] Ferrandina G, Legge F, Fagotti A et al. Preoperative concomitant chemoradiotherapy in locally advanced cervical cancer: safety, outcome, and prognostic measures. *Gynecol Oncol*. 2007;**107**: S127-32.
[30] Houvenaeghel G, Lelievre L, Buttarelli M et al. Contribution of surgery in patients with bulky residual disease after chemoradiation for advanced cervical carcinoma. *Eur J Surg Oncol*. 2007;**33**: 498-503.
[31] van de Bunt L, van der Heide UA, Ketelaars M et al. Conventional, conformal, and intensity-modulated radiation therapy treatment planning of external beam radiotherapy for cervical cancer: The impact of tumor regression. *Int J Radiat Oncol Biol Phys*. 2006;**64**: 189-96.
[32] Ahmed RS, Kim RY, Duan J et al. IMRT dose escalation for positive para-aortic lymph nodes in patients with locally advanced cervical cancer while reducing dose to bone marrow and other organs at risk. *Int J Radiat Oncol Biol Phys*. 2004;**60**: 505-12.
[33] Hong L, Alektiar K, Chui C et al. IMRT of large fields: whole-abdomen irradiation. *Int J Radiat Oncol Biol Phys*. 2002;**54**: 278-89.
[34] Lujan AE, Mundt AJ, Yamada SD et al. Intensity-modulated radiotherapy as a means of reducing dose to bone marrow in gynecologic patients receiving whole pelvic radiotherapy. *Int J Radiat Oncol Biol Phys*. 2003;**57**: 516-21.

[35] Zannoni GF, Vellone VG, Carbone A. Morphological effects of radiochemotherapy on cervical carcinoma: a morphological study of 50 cases of hysterectomy specimens after neoadjuvant treatment. *Int J Gynecol Pathol*. 2008;**27**: 274-81.
[36] Lim K, Small Jr W, Portelance L et al. Consensus Guidelines for Delineation of Clinical Target Volume for Intensity-Modulated Pelvic Radiotherapy for the Definitive Treatment of Cervix Cancer. *International Journal of Radiation Oncology*Biology*Physics*.**79**: 348-55.
[37] Potter R, Dimopoulos J, Georg P et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. *Radiother Oncol*. 2007;**83**: 148-55.
[38] Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet*. 2009;**105**: 107-8.
[39] Hatano K, Sekiya Y, Araki H et al. Evaluation of the therapeutic effect of radiotherapy on cervical cancer using magnetic resonance imaging. *Int J Radiat Oncol Biol Phys*. 1999;**45**: 639-44.
[40] Flueckiger F, Ebner F, Poschauko H et al. Cervical cancer: serial MR imaging before and after primary radiation therapy--a 2-year follow-up study. *Radiology*. 1992;**184**: 89-93.
[41] Azria E, Morice P, Haie-Meder C et al. Results of hysterectomy in patients with bulky residual disease at the end of chemoradiotherapy for stage IB2/II cervical carcinoma. *Ann Surg Oncol*. 2005;**12**: 332-7.
[42] Keys HM, Bundy BN, Stehman FB et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med*. 1999;**340**: 1154-61.
[43] Morice P, Uzan C, Zafrani Y et al. The role of surgery after chemoradiation therapy and brachytherapy for stage IB2/II cervical cancer. *Gynecol Oncol*. 2007;**107**: S122-4.
[44] Wittekind C, Hutter R, Klimpfinger M, Sobin L. *TNM Atlas: Illustrated guide to the TNM/pTNM classification of malignant tumours. 5Th edition.* 5 ed. Berlin: Springer-Verlag 2005.
[45] Lin LL, Yang Z, Mutic S et al. FDG-PET imaging for the assessment of physiologic volume response during radiotherapy in cervix cancer. *Int J Radiat Oncol Biol Phys*. 2006;**65**: 177-81.
[46] Russell DG, Cardona PJ, Kim MJ et al. Foamy macrophages and the progression of the human tuberculosis granuloma. *Nat Immunol*. 2009;**10**: 943-8.
[47] Schwarz JK, Grigsby PW, Dehdashti F, Delbeke D. The role of 18F-FDG PET in assessing therapy response in cancer of the cervix and ovaries. *J Nucl Med*. 2009;**50 Suppl 1**: 64S-73S.
[48] Mayr NA, Magnotta VA, Ehrhardt JC et al. Usefulness of tumor volumetry by magnetic resonance imaging in assessing response to radiation therapy in carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 1996;**35**: 915-24.

Chapter 7

Publication 5:

Whole abdominopelvic radiotherapy using Intensity Modulated Arc Therapy in the palliative treatment of chemotherapy-resistant ovarian cancer with bulky peritoneal disease: a single institution experience.

Gert De Meerleer, M.D., Ph.D., Katrien Vandecasteele, M.D. (*), Piet Ost, M.D. (*), Louke Delrue, M.D. (°), Hannelore Denys, M.D., Ph.D. (&), Amin Makar, M.D., Ph.D. ($), Bruno Speleers, R.N. (*), Simon Van Belle, M.D., Ph.D. (&), Rudy Van den Broecke, M.D., Ph.D. ($), Valérie Fonteyne, M.D. (*), Wilfried De Neve, M.D., Ph.D. (*).

Affiliation:
(*): Department of Radiotherapy, (°): Department of Radiology, (&): Department of Medical Oncology, ($): Department of Gynaecologic Oncology, Ghent University Hospital.

Int J Radiat Oncol Biol Phys. 2011 Mar 1;79(3):775-81.

This work has been sponsored by a scientific grant of the "Stichting Emmanuel van der Schueren", scientific partner of the "Vlaamse Liga tegen Kanker".

There is no conflict of interest.
Key words: Whole abdominopelvic radiotherapy, WAPRT, intensity-modulated arc therapy, IMAT, ovarian cancer, peritoneal disease.

Abstract

Purpose: To retrospectively review our experience with whole abdominopelvic radiotherapy (WAPRT) using Intensity Modulated Arc Therapy in the palliative treatment of chemotherapy-resistant ovarian cancer with bulky peritoneal disease.

Material and Methods: Between April 2002 and April 2008, 13 patients were treated with WAPRT using intensity modulated arc therapy. We prescribed a dose of 33 Gy to be delivered in 22 fractions of 1.5 Gy to the abdomen and pelvis. All patients had International Federation of Gynecology and Obstetrics stage III or IV ovarian cancer at the initial diagnosis. At referral, the median age was 61 years and patients had been heavily pre-treated with surgery and chemotherapy. All patients had symptoms from their disease: gastro-intestinal (sub)obstruction in 6, minor gastro-intestinal symptoms in 2, pain in 4, ascites in 1, and vaginal bleeding in 2. A complete symptom or biochemical response required complete resolution of the patient's symptoms or cancer antigen125 level. A partial response required ≥ 50% resolution of these parameters. The actuarial survival was calculated from the start of radiation therapy.

Results: The median overall survival was 21 weeks with a 6-month overall survival rate of 45%. The 9 patients who completed treatment obtained a complete symptom response, except for ascites (partial response). The median and mean response duration (all symptoms grouped) was 24 and 37 weeks respectively. Of the 6 patients presenting with obstruction or subobstruction, 4 obtained a complete symptom response (median duration, 16 weeks).

Conclusions: WAPRT delivered using intensity-modulated arc therapy offers important palliation in the case of peritoneal metastatic ovarian cancer. WAPRT resolved intestinal obstruction for a substantial period.

Introduction

Ovarian cancer still is an important cause of death of women in Western countries (1-4). Both the International Federation of Gynecology and Obstetrics (FIGO) stage and the histologic grade are important predictors of overall survival (OS) rates at 5 years, varying from 75% (stage II) to 10% (stage III-IV) (5, 6). For FIGO stages III-IV, the survival rate decreases with increasing grade varying from 38% (grade 1) to 25% (grade 2) and 19% (grade 3) (6). Failure particularly occurs intraperitoneally and can reach 85% in patients with high risk features (4, 7, 8). Secondary cytoreductive surgery is usually insufficient to treat intraperitoneal failure and second-line chemotherapy has been the treatment of choice at most centres. The choice of second-line chemotherapy depends on the recurrence-free period. In the case of platinum-resistance defined as a recurrence-free period of < 6 months after six cycles of platinum, the response rates of topotecan and liposomal doxorubicin have been disappointing with a median progression-free survival < 6 months (3, 7-10) and a 3-year survival rate of about 10% (7). Toxicity of these agents is not negligible (10). When the recurrence free interval is > 6 months, the tumor is considered platinum-sensitive and retreatment with combination of platinum based chemotherapy induce a response in more than one-half of the patients (10).

For patients with progressive disease after second or third-line chemotherapy (including hyperthermic intraperitoneal chemotherapy), the therapeutic options are very limited and often restricted to best supportive care only. Nevertheless, palliative radiotherapy (RT) has been shown to relieve most symptoms in 50-80% of patients, with complaints of bleeding and pain responding the best (3, 8, 11, 12). Most reports on the palliative effect of RT have not included patients with intestinal obstruction (3, 11).

In 2003, our research group reported on the feasibility of intensity-modulated arc therapy (IMAT) in the treatment planning of whole abdominopelvic RT (WAPRT) as palliative treatment for bulky peritoneally relapsed ovarian cancer. (13). The present study reports on the clinical results of WAPRT using IMAT in a platinum-resistant patient cohort. Of special

interest was the presence of a gastro-intestinal obstruction or subobstruction in almost half of the patients.

Material and methods:

Patient characteristics:

The data from all patients who underwent treatment of persistent or recurrent epithelial ovarian cancer with WAPRT using IMAT at Ghent University Hospital between April 2002 and April 2008 were analysed retrospectively. The inclusion criteria to receive WAPRT were histologically proven epithelial ovarian carcinoma, a minimal Karnofsky performance score of 50, evidence of peritoneal relapse after cytoreductive surgery and platinum containing chemotherapy and no previous abdominal or pelvic RT. A total of 13 women were included in the present analysis.

The following information was obtained: cancer antigen-125 (CA-125) level, clinical symptoms, radiological data, Karnofsky score, initial FIGO stage and previous surgical and medical therapies.

The diagnosis of (sub)obstruction was made on the basis of the symptoms reported by patients (at least two of following symptoms: nausea, vomiting, abdominal pain and/or diarrhoea, need of parenteral nutrition) and by the clinical evaluation findings and were confirmed by computed tomography (CT) in all cases. The CT diagnosis of obstruction or subobstruction was determined using previously published criteria (14, 15). Ascites was scored by the number of needed paracenteses needed weekly. Other symptoms were scored as present or absent.

Characteristics and treatment at initial diagnosis.

Figure 1A shows the initial stage and treatment schedules (surgical interventions and chemotherapy regimens) administered before referral. At initial diagnosis, the median age was 57.5 years [range: 30-73]. All patients had advanced stages of ovarian cancer (stage III or IV).

Characteristics at referral for WAPRT.

The median patient age at referral was 61 years [range: 31-75]. The median Karnofsky index was 70 [range: 50-90]. All patients had bulky (>2cm^3) disease and in all but one patient, CA125 serum levels were elevated (median: 343 U/ml; mean: 2159 U/ml; range: 20-13796 U/ml).

The indication for referral was symptomatic progression in all patients and radiologic progression in 12 (documented by abdominopelvic CT findings in all and fluorodeoxyglucose-positron emission tomography CT in 4 patients).

All patients had symptoms due to their disease (Figure 1B). Six patients presented with gastro-intestinal obstruction or subobstruction. Those patients all required parenteral nutrition and presented with a nasogastric tube. Two patients had minor gastro-intestinal symptoms, despite massive tumor bulk threatening gastrointestinal peristalsis. Other symptoms included pain (n=4), ascites requiring therapeutic paracentesis (n=1), and vaginal bleeding (n=2).

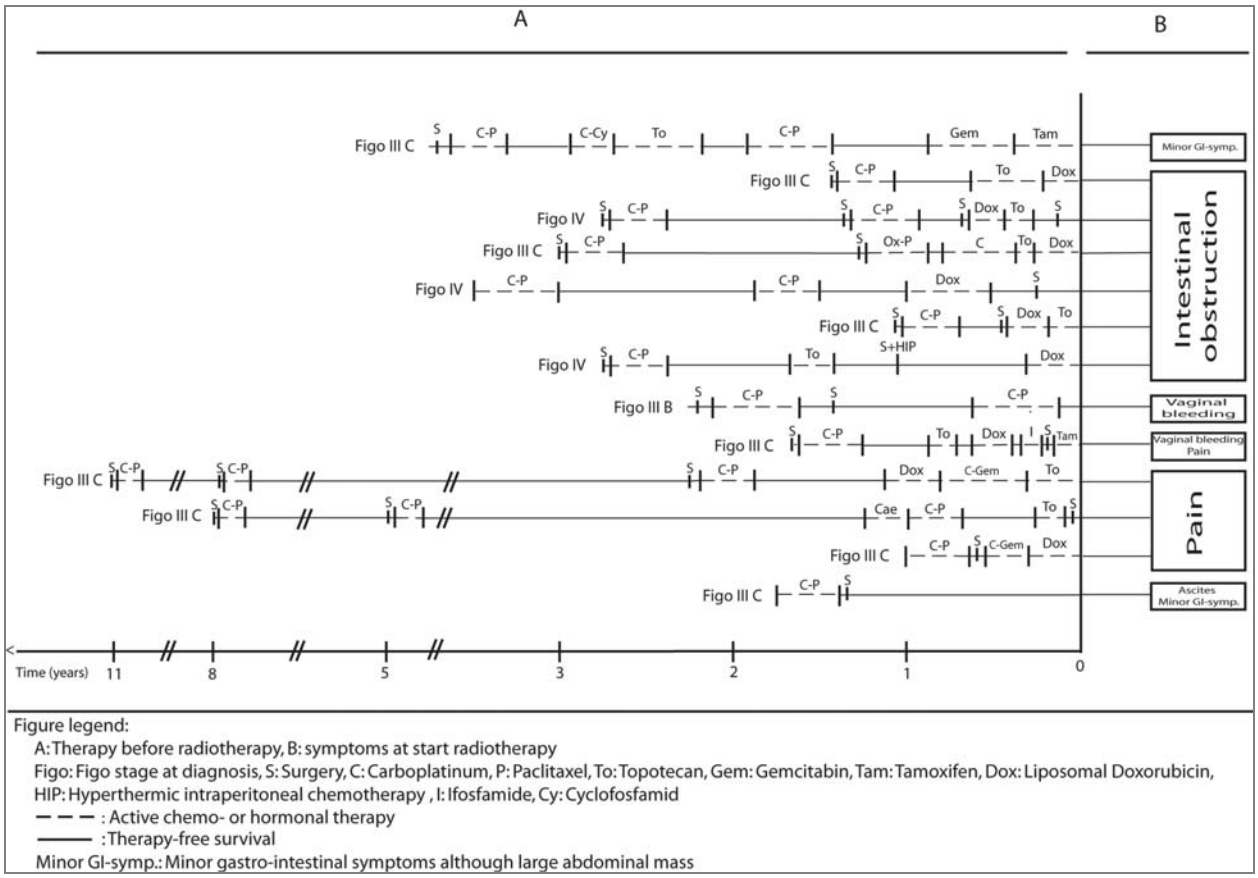

Fig. 1. (A) Overview of therapy administered before whole abdominopelvic radiotherapy and (B) symptoms at referral for whole abdominopelvic radiotherapy for each patient.

WAPRT details

We prescribed a dose of 33 Gy to be delivered in 22 fractions of 1.5 Gy. Treatment was daily except for the weekend. The clinical target volume (CTV) and organs at risk were delineated as described by Duthoy et al. (13). In brief, the CTV was defined as the whole peritoneal cavity, supplemented by the aortocaval and iliac nodes. In the case of extraperitoneal gross disease (e.g. perirectal mass, inguinal lymph nodes), the latter was included in the CTV. To create the planning target volume (PTV), the CTV was expanded with an isotropic margin of 5 mm in all directions. The following organs at risk were delineated: liver, both kidneys and spinal cord. A dose distribution in the transverse and coronal plane is depicted in Fig. 2 and 3 respectively.

Follow-up.

Toxicity and clinical symptoms were scored weekly during treatment, again at the end of treatment, 14 days after treatment, and monthly thereafter. If necessary or if signs of relapse developed, the patient was examined sooner.

Cancer-antigen 125 was measured at end of treatment, 1 month after treatment and at 2-months interval thereafter or when suspicion of relapse was present. At each follow-up visit, the patient was asked whether she was able to consume normal food or liquid food. The number and aspect of stools (diarrhea, blood, mucus loss) was registered. Others symptoms checked included nausea, vomiting, and abdominal cramps. Bowel peristalsis was checked clinically.

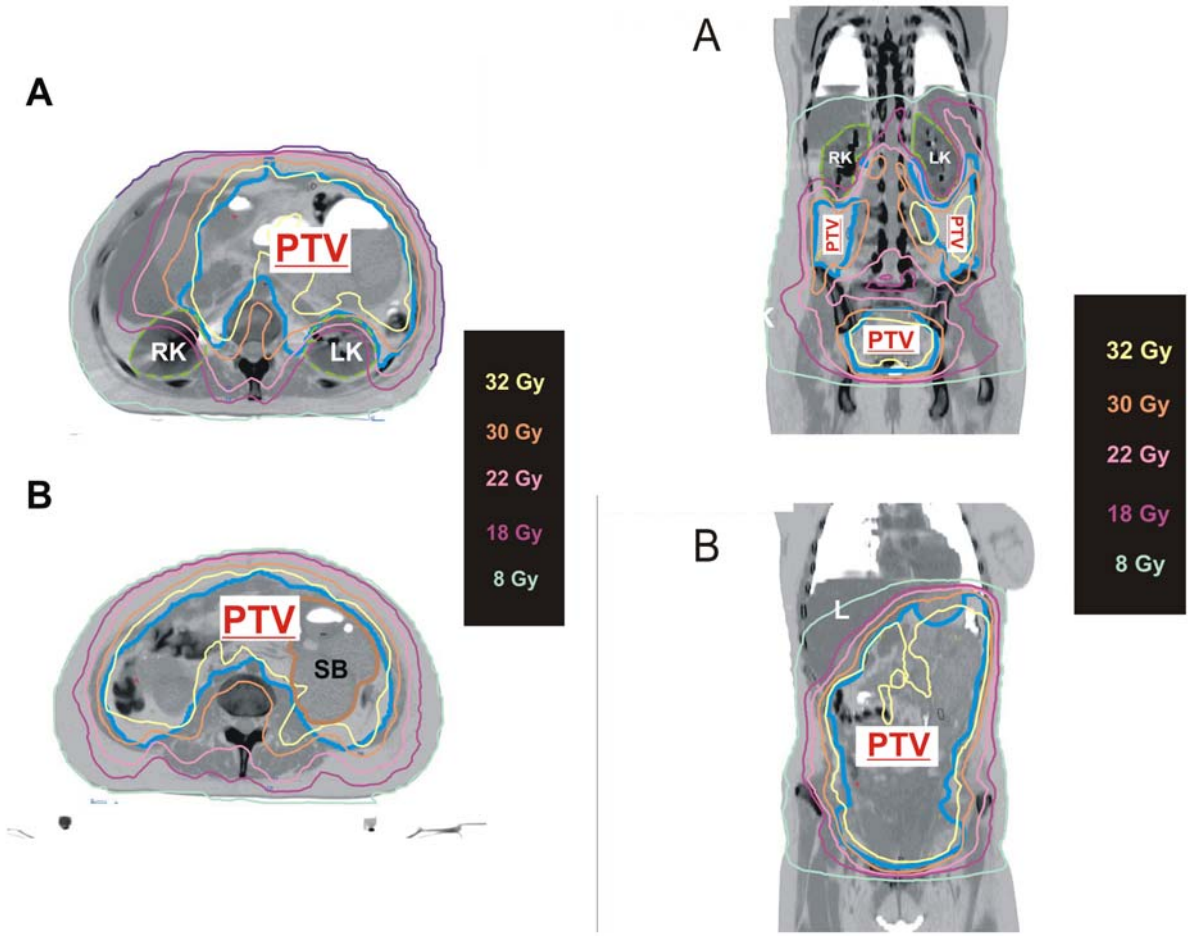

Figure 2 (left): **Transverse dose distribution at the level of (A) both kidneys and (B) umbilicus in patient with intestinal obstruction. Note the combination of the conformal avoidance of kidneys and sufficient coverage of the PTV (A). (B) Inverted axial CT view showing a pathologically distended small bowel loop with air/fluid levels. This patient had a complete intestinal obstruction which completely recovered after whole abdominopelvic radiotherapy. The patient is alive and well 42 weeks after treatment.**
PTV: Planning Target Volume (blue); RK: right kidney; LK: left kidney (green); SB: small bowel (16).
Figure 3 (right): **Coronal dose distribution of the same patient shown in Fig. 2 at the level of both kidneys (A) and intestines (B). Note, combination of the conformal avoidance of kidneys and sufficient coverage of the PTV (A). PTV: Planning Target Volume (blue); RK: right kidney; LK: left kidney (green); L: liver.**

Statistical analysis:

Both the symptom and CA-125 response rates were classified according to the best response obtained by the patient. The response to RT was defined as a complete or partial response, stable disease or disease progression, according to the clinical records for the two parameters. A complete symptom or biochemical response required complete resolution of the patient's symptoms or CA-125 level to within normal laboratory limits (0-35 U/ml). A partial response

was defined as ≥50% reduction of these parameters. Stable Disease was defined as < 50% reduction. Disease progression was defined as an increase in symptoms or an increase in CA-125 serum levels, defined as more than two times the nadir value on two occasions, separated by > 1 week.
The duration of the dominant symptom (Fig. 1B) was defined as the interval from the end of RT to the reappearance or worsening of the symptoms or last follow-up visit or death. OS was defined as the time from the start of RT to death from any cause. Abdominopelvic progression-free survival (APFS) was defined as the time from the start of RT to documented progression (clinical or radiological evidence of abdominopelvic tumor) or death without progression. The OS and APFS distributions were estimated using the Kaplan-Meier method. The log-rank test was used to assess whether APFS or OS differed with respect to Karnofsky (< 70 or ≥ 70), intestinal obstruction and mean CA-125 level (>2159 U/ml or <2159 U/ml), all at referral. A *p*-value <.05 was considered significant.
Acute toxicity was defined as RT induced toxicity during or within 3 months after the end of RT. Late toxicity was defined as an increase of RT induced toxicity starting ≥3 months after RT, or as any acute toxicity that lasted > 3 months. The Common Toxicity Criteria were used to register acute and late genitourinary and gastrointestinal toxicity (17).

Results:

Symptom response:
Figure 4 provides a schematic overview of the symptoms at the start of RT and symptom-free survival in relation to overall survival. All patients who completed or restarted (patient 9 in Fig. 4) treatment obtained a complete response, except for the symptom ascites where only a partial response was reached (need for therapeutic paracentesis reduced by 50%). The median and mean response duration (all symptoms grouped) was 24 and 37 weeks [range: 6-99 weeks], respectively. Of the 6 patients who presented with obstruction or subobstruction, 4 obtained a clinical complete response as determined by the return of peristalsis, normal food intake and normalization of stools (median duration of 16 weeks, range: 6-30). For vaginal bleeding (n=2) and pain (n=4), the complete response rate was 100% and 75% respectively.
Biochemical response:
Only patients completing WAPRT were considered. At the end of WAPRT, 6 patients had a biochemical response with a mean decrease in the CA-125 serum level of 59% [range: 34-75%]. One patient had an increasing CA-125 serum level at the last day of WAPRT, probably because of RT-induced peritoneal inflammation (patient 5 in Fig. 4). The CA-125 serum level was not verified at a later point. One patient had a normal CA-125 level at start and end of RT (patient 11 in Fig. 4).
Correlations among responses:
A significant correlation ($p < .05$; Pearson correlation = .720) was found between the biochemical response and symptom response. Previous platinum-resistant disease (relapse within < 6 months) did not correlate with WAPRT response (p =NS) nor did a previous chemotherapy response (p = NS).
Overall and abdominopelvic progression-free survival:
For the intention-to-treat population, the median OS was 21 weeks, with a 6-month OS rate of 45%. At the present analysis, 2 patients were still alive, respectively 20 and 42 weeks after WAPRT. Of the patients who completed treatment, median OS was 35 weeks with a 6-month OS rate of 60%. Univariate analysis of all patients showed a significant increase in OS for women with a Karnofsky score ≥70 (median OS, 35 vs. 9 weeks; $P < 0.05$) and a CA-125 of <2159 U/ml at referral (median OS, 39 vs. 9 weeks respectively; $P < 0.05$)compared with those with a Karnofsky score <70 and CA-125 >2159 U/mL. Age had no influence on outcome. Median APFS duration was 16 weeks with an estimated 6-month APFS rate of 29%.

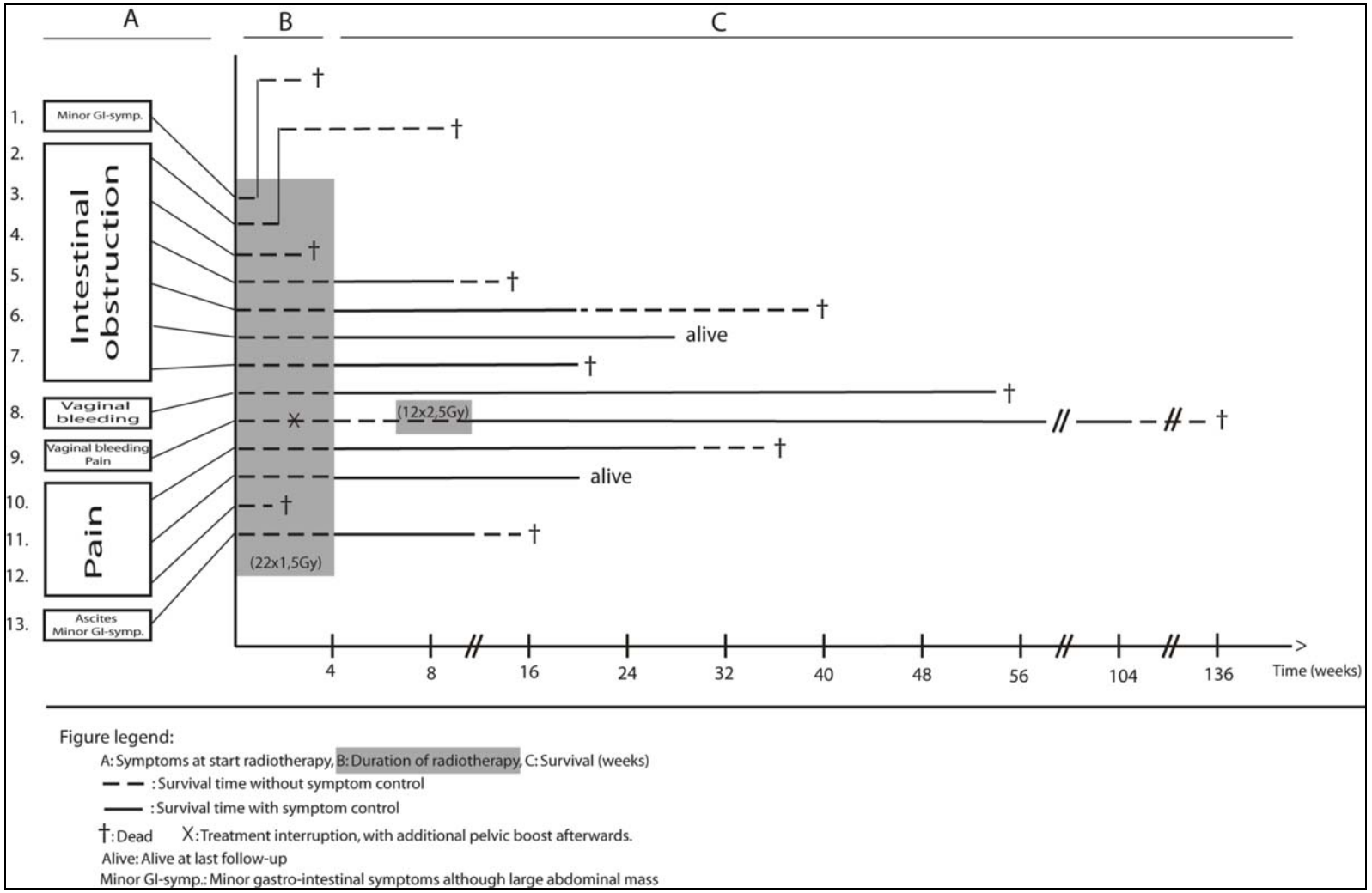

Figure 4: Overview of symptoms at referral (Panel A) and (B) the results of whole abdominopelvic radiotherapy for each patient.

Only Karnofsky performance score of <70 correlated with significantly worse APFS ($P < 0.05$).

Tolerance of WAPRT

Figure 4b depicts the duration of WAPRT and treatment interruptions. The median number of arcs to deliver WAPRT was 7 [range: 4-10]. Eight patients received the treatment objective of 33Gy. One patient was interrupted at 15 fractions because of acute postrenal failure due to obstruction by a tumor mass and underwent additional conventional pelvic irradiation (12 x 2.5Gy) after normalisation of renal function.

Three patients stopped treatment after 6, 12, and 13 fractions respectively because of a worsening of gastrointestinal obstruction that did not respond to conservative treatment. These patients died shortly afterwards (patients 1-3 in Fig. 4). One patient died after developing pneumonia (patient 12). No link was seen between Karnofsky status (< 70 vs. ≥ 70) at referral and treatment continuation (chi-square test).

None of the patients developed genitourinary toxicity. For patients presenting with gastrointestinal symptoms, acute gastrointestinal toxicity was impossible to score. This resulted in 5 patients eligible for the acute gastrointestinal toxicity evaluation. Two patients developed Grade 3 diarrhea –combined with Grade 3 nausea in 1- during WAPRT but with a complete recuperation within 2 weeks afterward. One patient experienced Grade 2 nausea and diarrhea during WAPRT that had resolved within 3 weeks afterward. None of the patients developed late gastrointestinal or genitourinary toxicity.

Discussion

The present study has reported on the palliative effect of WAPRT using IMAT in ovarian cancer patients with progressive peritoneal disease after undergoing treatment with multiple lines of palliative chemotherapy and several surgical interventions. Although the radiosensitivity of ovarian cancer cells has been well established for > 2 decades, WAPRT as adjuvant or palliative treatment has been abandoned in many centers mainly because of 2 reasons.

First, in the case of platinum-resistant disease, second-line chemotherapy using topotecan or liposomal doxorubicin has become the treatment of choice. The response rates have varied from 7 to 25% (18, 19) and the incidence of Grade 4 toxicity (20) has not been negligible (10, 21). The review by Salom et al. included information on new products and ongoing trials but did not, surprisingly enough, mention RT at all (10). Data from the 1980s and 1990s, however, have demonstrated the (even possible curative) role of WAPRT in the treatment of ovarian cancer (22, 23). Some trials have clearly demonstrated a progression-free survival benefit (24, 25) and OS benefit (24) when RT was applied in the treatment of FIGO stage III ovarian cancer. If women with initially advanced ovarian cancer have minimal residual disease after second-look laparotomy, adjuvant WAPRT may be effective with a median progression-free survival of up to 3.5 years (7, 26, 27), 5-10 years overall survival rates of up to 53% (5, 12, 28, 29) and up to 49% respectively (28) and a median survival of 63 months in the case of microscopic disease compared with 9 months if disease was >2 cm (30). In patients for whom second-look laparotomy showed a complete pathologic response after primary treatment, WAPRT significantly improved progression-free survival at 5 years compared to consolidation chemotherapy (25) or intraperitoneal chemotherapy (7).

Secondly, conventional WAPRT has been considered to be too toxic by referring clinicians. WAPRT is a technological challenge because it must combine sufficient coverage of the peritoneal cavity with sparing of the organs at risk such as the kidneys, liver and bone marrow. If conventional technology is used, treatment interruptions because of acute toxicity have been reported in up to 70% of the patients, with myelosuppression and bowel toxicity being the most important (7, 12, 28). Treatment interruptions are inversely correlated with OS

with a decrease of > 2 years and a risk ratio > 2.5 (26). MacGibbon et al. (12) confirmed this by showing that completion of the planned WAPRT was associated with improved survival with a highly significant difference of 37% versus 0%. However, severe late small bowel toxicity still occurs in ≤20% of the patients and is most pronounced in case of a pelvic boost (2, 7, 25, 26, 28, 31, 32). Modern advances in RT such as IMAT will allow us to overcome the shortcomings of conventional techniques (13) and are currently being applied in new phase I-II studies (4).

External beam RT has, however, clearly demonstrated an important palliative effect in platinum-refractory ovarian cancer. Gelblum et al. (33) noted a complete and partial response rate of 70% and 24%, respectively, combined with a good acute tolerance profile. Vaginal bleeding and persistent disease at exploratory laparotomy were the most frequent treatment indications (33).

Our study differs from earlier reports demonstrating the palliative effect of radiotherapy in the treatment of chemotherapy-refractory ovarian cancer in several ways. First, we prescribed an IMAT-generated dose of 33 Gy to be delivered in 20 fractions. Most published data have reported on median WAPRT doses of 19-25 Gy (2, 5, 7, 8, 12, 26, 29, 31) and used conventional technology, leading to suboptimal dose distributions especially at the level of the kidneys (7, 8), (13). Firat et al. (28) prescribed 36 Gy to be delivered in 1 Gy fractions as adjuvant treatment. Radiobiologically, this was almost equal to our prescription (normalized iso-effective dose (NID_2), i.e. the dose recalculated in 2 Gy fractions) of 32 in 2 Gy fractions for an α/β-value of 10). This NID_2 of 32 Gy has been reported to be a threshold to predict for better OS (28). Nevertheless, and because of the palliative setting of our treatment schedule, additional research should emphasize obtaining the least radiation dose that induces important symptom relief. Perhaps 33Gy (at 1,5Gy/fraction) is not needed, and a lower dose might obtain the same palliation as reported in the present study.

Second, our patients were heavily pre-treated with chemotherapy, reflecting aggressive and refractive disease and resulting in suboptimal Karnofsky scores at referral.

Third, all patients had gross disease on imaging (>2 cm^3 in all cases), a feature categorized, by itself, as a "poor-prognostic" finding (5).

Finally, and most important, 6 out of 13 patients presented with intestinal obstruction, which is an often-observed clinical feature associated with recurrent ovarian cancer (34). Survival has ranged from 3 to 12 months, with 20% of the patients surviving >1 year (35)

Although Gelblum et al. (33) described 1 patient with "abdominal discomfort" and Tinger et al. (8) described "obstruction" in 12 out of 72 patients (including ureter, oesophagus and stomach obstruction), to the best of our knowledge, this is the first report showing the possibility of resolving intestinal obstruction with WAPRT for a substantial period (median 4 months). Tinger et al. (8) found relief of "obstruction" in 75% of their patients. However, it was not clear from their study how many patients had ureteral obstruction or how obstruction or obstruction relief was defined. Other reports of the palliative effect of radiotherapy for ovarian cancer did not include patients with intestinal obstruction (3, 11).

Therefore, WAPRT delivered by IMAT deserves a clear and well-defined place in the palliative treatment of recurrent ovarian cancer. The results presented in the present study add to that opinion by providing data on substantial and long-lasting palliation in heavily pre-treated women. Moreover, intestinal obstruction or subobstruction was palliated in 4 of 6 patients for a period of several months, with an impressive improvement in their quality of life and social life. The results of other treatment options such as chemotherapy and palliative surgery have been disappointing in this particular situation (13, 34). Our study had some shortcomings. Its retrospective character made exact comparisons between the clinical symptoms before and after WAPRT less stringent. However, we consider that for food intake and the production of stools, the dichotomy between ''yes'' and ''no'' is of much more

importance, because ‘‘no’’ food intake vs. ‘‘yes’’ food intake and/or ‘‘no’’ production of stools vs. ‘‘yes’’ production of stools have a huge effect on patients’ quality of life. In addition, our study had the disadvantage of being a single-institution study. This was because of the paucity of IMAT availability in Belgium and surrounding countries. Thus, the number of patients was low, and definitive conclusions should be taken prudently. Nevertheless, we consider the clinical message of our results to be of importance to clinical oncologists, certainly in view of the important palliation of intestinal obstruction.

Conclusion

Whole abdominopelvic RT delivered using IMAT offers important palliation in the case of peritoneal metastatic ovarian cancer. WAPRT can resolve intestinal obstruction for a substantial period.

References

1. Berrino F, De Angelis R, Sant M*, et al.* Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study. *Lancet Oncol* 2007;8:773-783.
2. Dusenbery KE, Bellairs EE, Potish RA*, et al.* Twenty-five year outcome of sequential abdominal radiotherapy and melphalan:implications for future management of epithelial carcinoma of the ovary. *Gynecol Oncol* 2005;96:307-313.
3. E C, Quon M, Gallant V*, et al.* Effective palliative radiotherapy for symptomatic recurrent or residual ovarian cancer. *Gynecol Oncol* 2006;102:204-209.
4. Rochet N, Jensen AD, Sterzing F*, et al.* Adjuvant whole abdominal intensity modulated radiotherapy (IMRT) for high risk stage FIGO III patients with ovarian cancer (OVAR-IMRT-01) - Pilot trial of a phase I/II study: study protocol. *BMC Cancer* 2007;7:227.
5. Chapet S, Berger C, Fignon A*, et al.* Abdomino pelvic irradiation after second-look laparotomy for stage III ovarian carcinoma. *Eur J Obstet Gynecol Reprod Biol* 1995;62:43-48.
6. Heintz AP, Odicino F, Maisonneuve P*, et al.* Carcinoma of the ovary. *Int J Gynaecol Obstet* 2003;83 Suppl 1:135-166.
7. Cmelak AJ, Kapp DS. Long-term survival with whole abdominopelvic irradiation in platinum-refractory persistent or recurrent ovarian cancer. *Gynecol Oncol* 1997;65:453-460.
8. Tinger A, Waldron T, Peluso N*, et al.* Effective palliative radiation therapy in advanced and recurrent ovarian carcinoma. *Int J Radiat Oncol Biol Phys* 2001;51:1256-1263.
9. Bukowski RM, Ozols RF, Markman M. The management of recurrent ovarian cancer. *Semin Oncol* 2007;34:S1-15.
10. Salom E, Almeida Z, Mirhashemi R. Management of recurrent ovarian cancer: evidence-based decisions. *Curr Opin Oncol* 2002;14:519-527.
11. Corn BW, Lanciano RM, Boente M*, et al.* Recurrent ovarian cancer. Effective radiotherapeutic palliation after chemotherapy failure. *Cancer* 1994;74:2979-2983.
12. MacGibbon A, Bucci J, MacLeod C*, et al.* Whole abdominal radiotherapy following second-look laparotomy for ovarian carcinoma. *Gynecol Oncol* 1999;75:62-67.
13. Duthoy W, De Gersem W, Vergote K*, et al.* Whole abdominopelvic radiotherapy (WAPRT) using intensity-modulated arc therapy (IMAT): first clinical experience. *Int J Radiat Oncol Biol Phys* 2003;57:1019-1032.
14. Frager D. Intestinal obstruction role of CT. *Gastroenterol Clin North Am* 2002;31:777-799.
15. Mayo-Smith WW, Wittenberg J, Bennett GL*, et al.* The CT small bowel faeces sign: description and clinical significance. *Clin Radiol* 1995;50:765-767.
16. Emami B, Lyman J, Brown A*, et al.* Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;21:109-122.
17. Trotti A, Colevas AD, Setser A*, et al.* CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003;13:176-181.
18. Armstrong DK. Relapsed ovarian cancer: challenges and management strategies for a chronic disease. *Oncologist* 2002;7 Suppl 5:20-28.
19. Herzog TJ. Recurrent ovarian cancer: how important is it to treat to disease progression? *Clin Cancer Res* 2004;10:7439-7449.
20. Kirwan JM, Symonds P, Green JA*, et al.* A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. *Radiother Oncol* 2003;68:217-226.

21. Gordon AN, Fleagle JT, Guthrie D*, et al.* Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol* 2001;19:3312-3322.
22. Dembo AJ. Abdominopelvic radiotherapy in ovarian cancer. A 10-year experience. *Cancer* 1985;55:2285-2290.
23. Dembo AJ. Epithelial ovarian cancer: the role of radiotherapy. *Int J Radiat Oncol Biol Phys* 1992;22:835-845.
24. Pickel H, Lahousen M, Petru E*, et al.* Consolidation radiotherapy after carboplatin-based chemotherapy in radically operated advanced ovarian cancer. *Gynecol Oncol* 1999;72:215-219.
25. Sorbe B. Consolidation treatment of advanced (FIGO stage III) ovarian carcinoma in complete surgical remission after induction chemotherapy: a randomized, controlled, clinical trial comparing whole abdominal radiotherapy, chemotherapy, and no further treatment. *Int J Gynecol Cancer* 2003;13:278-286.
26. Dowdy SC, Metzinger DS, Gebhart JB*, et al.* Salvage whole-abdominal radiation therapy after second-look laparotomy or secondary debulking surgery in patients with ovarian cancer. *Gynecol Oncol* 2005;96:389-394.
27. Einhorn N, Lundell M, Nilsson B*, et al.* Is there place for radiotherapy in the treatment of advanced ovarian cancer? *Radiother Oncol* 1999;53:213-218.
28. Firat S, Murray K, Erickson B. High-dose whole abdominal and pelvic irradiation for treatment of ovarian carcinoma: long-term toxicity and outcomes. *Int J Radiat Oncol Biol Phys* 2003;57:201-207.
29. Petit T, Velten M, d'Hombres A*, et al.* Long-term survival of 106 stage III ovarian cancer patients with minimal residual disease after second-look laparotomy and consolidation radiotherapy. *Gynecol Oncol* 2007;104:104-108.
30. Sedlacek TV, Spyropoulus P, Cifaldi R*, et al.* Whole-abdomen radiation therapy as salvage treatment for epithelial ovarian carcinoma. *Cancer J Sci Am* 1997;3:358-363.
31. Nagai Y, Inamine M, Hirakawa M*, et al.* Postoperative whole abdominal radiotherapy in clear cell adenocarcinoma of the ovary. *Gynecol Oncol* 2007;107:469-473.
32. Randall ME, Barrett RJ, Spirtos NM*, et al.* Chemotherapy, early surgical reassessment, and hyperfractionated abdominal radiotherapy in stage III ovarian cancer: results of a gynecologic oncology group study. *Int J Radiat Oncol Biol Phys* 1996;34:139-147.
33. Gelblum D, Mychalczak B, Almadrones L*, et al.* Palliative benefit of external-beam radiation in the management of platinum refractory epithelial ovarian carcinoma. *Gynecol Oncol* 1998;69:36-41.
34. Pothuri B, Meyer L, Gerardi M*, et al.* Reoperation for palliation of recurrent malignant bowel obstruction in ovarian carcinoma. *Gynecol Oncol* 2004;95:193-195.
35. Feuer DJ, Broadley KE, Shepherd JH*, et al.* Surgery for the resolution of symptoms in malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. *Cochrane Database Syst Rev* 2000:CD002764.

Chapter 8: Discussion and Perspectives.

1. Cervical and endometrial cancer

1.1. Reducing Toxicity

Pelvic RT for gynaecologic malignancies has a long history. The first report on the use of pelvic EBRT was published by Lacassagne et al. in 1932. Since the refinement of this technique by Rutledge and Fletcher in the 50's, the basic treatment technique has not changed significantly (1, 2). Although the introduction of megavoltage machines and cerrobend blocks allowed for better sparing of superficial and deep tissues such as bladder and small bowel, large areas of OARs could only be spared if coverage of lymph node regions was compromised. If target volume coverage was not sacrificed, the delivery of even modest doses of 45–50Gy was accompanied by substantial incidences of severe acute and late toxicity (3-5). With the advent of concomitant chemotherapy severe acute hematologic and gastro-intestinal (GI) toxicity doubled, acute platelet toxicity tripled (3) and life-threatening GI-toxicity even occurred in 8% of the patients (3). This important increase in toxicity has prompted the radiotherapy community to intensively put research efforts in treatment planning improvement. Switching patient positioning from supine to prone and the additional use of a belly board in combination with 3D conformal RT brought a first significant reduction in irradiated SB volume (6). However, SB is not the only OAR. A major improvement was the introduction of IMRT, which significantly reduced volumes of normal tissue irradiated at high dose when compared to conventional techniques (see table 1.1 introduction) (7-17). The resulting lower toxicity has been described in the postoperative (18, 19) as well as in the LACC setting (20, 21), but mostly for a group of patients consisting of both populations (18-24). For rectal cancer treatments, IMRT in supine position significantly decreased GI toxicity when compared to 3D conformal RT in prone position (+ belly board) (25). Although IMRT in prone position + belly board can provide a supplemental reduction in irradiated volume of SB (26), this benefit diminishes (and disappears in low dose regions) when using extended arc techniques (27). Taking into account the unknown effect on the other OARs (27), the potential increased set-up error and internal organ motion (6), we decided to treat our patients with IMAT in supine position.

It is clear from publication 1 that IMAT results in low grade 2 or more acute toxicity when applied in the *postoperative* setting, both for cervical and endometrial cancer. The same is observed when IMAT is applied in the *primary* setting, where the cervix is in loco (publication 3). Our results fit within those reported in literature after IMRT for gynaecologic malignancies, although comparisons should be taken with high caution. Not only has one to take into account the different scoring systems used (e.g. RTOG vs. CTC), most publications contain a rather small number of patients and are very heterogeneous with a mixture of "postoperative" and "primary" setting (22-24), variations in chemotherapy schedules and inclusion of other than cervical or endometrial tumours (20, 22, 23). Although it is impossible to distinguish between acute toxicity rates after postoperative and primary IMRT, they all show the same and often strong trend: compared to conventional pelvic radiotherapy, IMRT significantly decreases acute GI toxicity in all, and acute genito-urinary (GU) toxicity in the majority of the cited reports. The only exception are the results published by Bouchard et al (18), who reported a significant better disease control, but also an increase in acute grade 2 or more GI toxicity. However, reading the paper in detail reveals that in the IMRT group, most patients were treated with an endovaginal boost during EBRT while no patients were treated this way in the conventional RT arm. Moreover, scoring of toxicity differed substantially between IMRT (prospective) and conventional RT (retrospective).

Lukka et al. concluded that adding chemotherapy to radiotherapy lead to a significant increase in overall ≥ grade 2 acute GI toxicity by 25% (56 vs. 81%) and a two- (white cell count) to

three-fold (platelet toxicity) grade 3 toxicity (4). Despite also we demonstrated a chemotherapy-related increased toxicity (publication 1), the toxicity rate after IMAT (publication 1 and 3) was very low and certainly lower than those reported by others using conventional techniques. This supports the hypothesis that IMAT leads to a decreased toxicity.
The rather limited amount of (small-numbered) studies and the lack of long-term follow-up prohibit definitive conclusions regarding toxicity. Only randomized trials comparing conventional with IMRT definitively will solve this question. However, based on all the preliminary results (including ours), one could ask the question whether starting such a trial would be ethical. Our toxicity results re-inforced us to question whether conclusions from randomized trials that used conventional RT would hold true if IMRT or IMAT were used. It is our viewpoint that communications concerning such trials should at least include the note that old fashioned technology was used.

A more controversial issue is the use of prophylactic irradiation of para-aortic lymph nodes (PALN). This approach improved OS en DFS in a subgroup of cervical cancer patients (investigated group: FIGO IB and IIA, > 4cm and FIGO IIB) in the RTOG 79-20 trial (28). No OS benefit was found by Haie et al. (investigated group: node positive and/or all >IIB with lateral parametrial involvement) but they suggested a benefit for those patients with a high probability of local control (29). However, its use has been largely omitted since the advent of concomitant chemotherapy and the resulting high toxicity rates (30, 31). If IMRT(15, 32-36) is used to treat the PALN together with the pelvis (extended field) acute toxicity is acceptable and no increase in severe late or life threatening toxicity is observed. In 10 patients treated this way at our centre (with IMAT and concomitant chemotherapy, if pelvic nodes were present), no ≥ grade 3 toxicity was noticed (publication 1 and 3). Further maturation of data is obviously needed. However, these premature data and the dispersed availability of IMRT and rotational therapy might reinforce the set-up of randomized trials that re-evaluate the important OS and DFS benefit that was demonstrated decades ago.

Future perspectives.
Volumetric modulated arc therapy (VMAT) is an advanced form of IMAT available at GUH. VMAT provides the opportunity of simultaneous but independent variation of the gantry speed, leaf position and dose rate. Currently, planning studies comparing the results of VMAT with IMAT are developed. The tested hypothesis is that VMAT significantly reduces the dose to the organs at risk as compared to IMAT without compromising the dose to the target.

1.2. Does the use of IMAT imply a survival benefit?

Contrary to other sites (37, 38), the use of IMRT or IMAT in pelvic gynaecological tumours has not proven to be advantageous on locoregional control, distant control or survival. Yet, there are some arguments this might change in the future. First, using standard conventional fields, underdosage of elective lymph node regions in 30 to 40 % of patients and geographical misses of gross tumour volumes up to 56% of the cases are described (39). Secondly, Brixey et al. saw that acute hematologic toxicity resulted in missing ≥ 1 chemotherapy cycles in 40% of patients treated with CRT compared to 12,5% in the IMRT group (20). One might also expect a decrease of RT treatment interruptions (40) or chemotherapeutic dose modifications.
Finally, the ability of IMRT to reduce normal tissue toxicity allows for more aggressive locoregional therapy (dose-escalation or SIB) and/or systemic therapy. This in turn has the potential to enhance tumour control and long-term OS.

1.3. Tumour and organ motion

In our work (both the postoperative and primary setting), no attempts were made to control bladder and rectal filling, although this is an ongoing controversy. The relationship between organ motion and organ filling during fractionated pelvic RT is complex. Both bladder and rectal filling show weak correlations with anteroposterior shifts of the target in the primary as well as the postoperative setting (40-43). Bladder filling, however, seems to have more impact on uterine than on cervical movement, certainly in the supero-inferior direction (41-43). With this information the following picture emerges. A full bladder pushes the CTV and GTV towards the rectum. Similarly an increase in rectum volume results in a shift in the anterior direction. In LACC, the orientation of the tumour is also bounded by the orientation of the uterus, and a bladder volume change may change this orientation, provided the vacated volume is not occupied by small bowel. The combination of variation in rectum and bladder volume results in changes in the position and shape that are difficult to describe and as a consequence to influence. Although positional variations might be reduced by counselling patients to have a full bladder during treatment, it is known that even with careful counselling patients may not be able to achieve consistent bladder filling. Consequently efforts to influence bladder or rectal filling have not yet proven to have any impact on the reduction of treatment margins. Treatment with a (comfortably) filled bladder, however, is advocated since it tends to push the intestine out of the pelvis (44, 45) and leads to significant reductions of bladder dose (46).

Future Perspectives

The adoption of IMRT in pelvic gynaecologic oncology, and more specifically LACC, has been limited by the complex organ and tumour motion exhibited in this cancer site. Concerns about tumour movement during treatment and geographic target misses have resulted in the proposal of generous PTV margins (up to 4 cm around the uterine fundus!), which increases the volume of normal tissue irradiated. The inter- and intrafractional uterine and cervical motion and margins to ensure 95% target coverage is presented in table 8.1. As we expect instinctively, expansion of margins leads to significant increases of dose delivered to the OARs, especially in the volumes receiving high doses (7, 47, 48). Finding a solution to cope with the complex motion of the uterus is one of the foremost challenges to reduce further toxicity and ensure adequate target coverage. The answer is certainly not unequivocal and consists most probably out of a combination of multiple little parts.

Three different methods to reduce safety margins and irradiated volume of organs at risk are subject of further research and perspectives:

a. <u>Cone beam CT (CBCT, both postoperative and primary setting)</u>

Daily verification and management of patient movement and internal organ motion is warranted when applying IMAT. Although intra-fractional cervical and uterine motion is smaller than inter-fractional motion, they are still relevant (40, 42, 49, 50), especially at the level of the uterine fundus, where 10mm safety margins are suggested (42) compared to the 5mm needed for the rest of cervix and uterus (42, 47).

Implementation of CBCT and accordingly reduced margins requires a correct interpretation of the CBCT. The inter- and intra-observer variability of interpreting CBCT in both the primary as the postoperative setting will be quantified.

Table 8.1: Inter- and intrafractional uterine and cervical motion and proposed margins to ensure 95% PTV coverage.

	Target	Antero-Posterior (mm)			Latero-Lateral (mm)		Supero-Inferior (mm)			Set-up
		mean ± SD [range]	M	I	mean ± SD [range]	M	mean ± SD [range]	M	I	
Locally Advanced Cervical Cancer										
Haripotepornkul et al. (10)	CTV	4,2 ± 3,5 [0-18]			1,9 ± 1,9 [0-18]		4,1 ± 3,2 [0-18]			daily X-rays (s)
		2,9 ± 2,7 [0-15]			*1,6 ± 2 [0-15]*		*2,6 ± 2,4 [0-15]*			*pre and post RT*
Tyagi et al. (10)	CTV		15	B		15		15		
Collen et al. (10)	Cervix	A: 0,4 ± 10,1	A:17		L: -3,5 ± 4,9	L: 9	S: 2,2 ± 8	S: 15		
		P:-3 ± 6,9	P:12		R: 0,2 ± 4,5	R: 8	I: 0,5 ± 5	I: 9		
	Uterus	A: 3,3 ± 11,9	A:19		L: -3,5 ± 8,1	L: 13	S: 6,1 ± 11,6	S: 20		
		P: 0,3 ± 11,7	P:19		R: -0,6 ± 7,5	R: 13	I: 5 ± 11,2	I: 19		
	Patient	*1,1 ± 1,3*			*-0,3 ± 1,6*		*0,2 ± 2,3*			*pre and post RT*
Lim et al. (20)	GTV	4 ± 4			2 ± 4		3 ± 4			
	Cervix	4 ± 4			1 ± 3		2 ± 4			
	Uterus	6 ± 2			4 ± 2		5 ± 2			
Beadle et al. (16)	cGTV	16 [5,1-25]		B	8,2 [4,4-14]		21 [12-33]		B	
	pCervix	A: 17 [7,8-29]			L: 9,4 [3,9-18]		S: 23 [13-35]			
		P: 18 [7,8-63]			R: 7,6 [2,9-18]		I: 13 [2,5-30]			
van de Bunt et al. (20)	GTV		A:12			L:11		S:4		
			P:14			R: 12		I:8		
	CTV		A:24			L:16		S:11		
			P:17			R: 12		I:8		
Taylor et al. (33)	Cervix	4,1 ± 4,4 [0-19]		R	0,3 ± 0,8 [0-3]		2,7 ± 2,8 [0-12]		B	2 cons. MRI
	Uterus	7± 9 [0-48]		B	0,8 ± 1,3 [0-5]		7,1 ± 6,8 [0-32]		B	
	Vagina	2,6 ± 3 [0-10]		R	0,3 ± 1 [0-5]					
	CTV		15			7		15		
	Nodes		7			7		7		
Chan et al. (20)	Cervix	2,4 [0-11,2]	15			15	1,5 [0-11,3]	15		weekly MRI
		-0,1 [0-10,6]	*5*			*5*	*-0,5 [0-11,2]*	*5*		*6 MRI, every 6'*
	Uterus (C)	4,8 [0-13,1]					5,7 [0-15,7]			
		0,3 [0-11,3]	5			5	*-1,8 [0-12,8]*	*5*		
	Uterus (F)	4,6 [0-14,5]	40	B			7,8 [0-24,4]	40		
		-1,1 [0-12]					*-3,1 [0-18,8]*			
Kaatee et al. (10)	CTV		9,7			8,9		10,8		daily portals (m)
Postoperative										
Jürgenliemk-Schulz et al. (15)	CTV		15	R		15		15		weekly MRI
Harris et al. (22)	CTV	4 ± 3,7 [0-19,3]	12,1		1,2 ± 1 [0-8]	3,1	4± 2,9 [0-15]	9,5		daily MVCT (f)

Intrafractional uterine and cervical motion and proposed margins are in italic. **cGTV: center of GTV; pCTV: perimeter of CTV; C: Canal; F: Fundus; M: proposed margins to encompass 95% of target volume; I: Influence of bladder (B) or rectum (R) on organ motion; MRI= Magnetic Resonance Imaging; MVCT = megavoltage CT: CBCT = Cone Beam CT; s: seeds; m: markers; f: fiducials; cons.: consecutive.**

b. Studying the relation between uterus and CTV (primary setting).

A major contributor to the large margins needed is the uterus and certainly the fundus as it is the most mobile part of the uterus. The uterine body and fundus are connected to the bony pelvis laterally via broad ligaments which, although constraining large lateral motion, permit significant motion in the anterior-posterior (AP) and superior-inferior (SI) directions. Notably, influenced by bladder, bowel and rectal filling, the uterus can tilt from ante-flexed to retro-flexed positions.

We couldn't find unequivocal evidence to support the need to include the whole uterus in the CTV (51). This "dogma" results from the era of conventional treatments without image-guided target volume delineation and image-guided radiotherapy. Excluding non-affected parts of the uterus might lead to significant reductions in bladder and small bowel volumes irradiated to high doses. As a consequence, since the fundus is the most mobile part of the uterus, tighter treatment margins can be used leading to a further sparing of OARs (7).

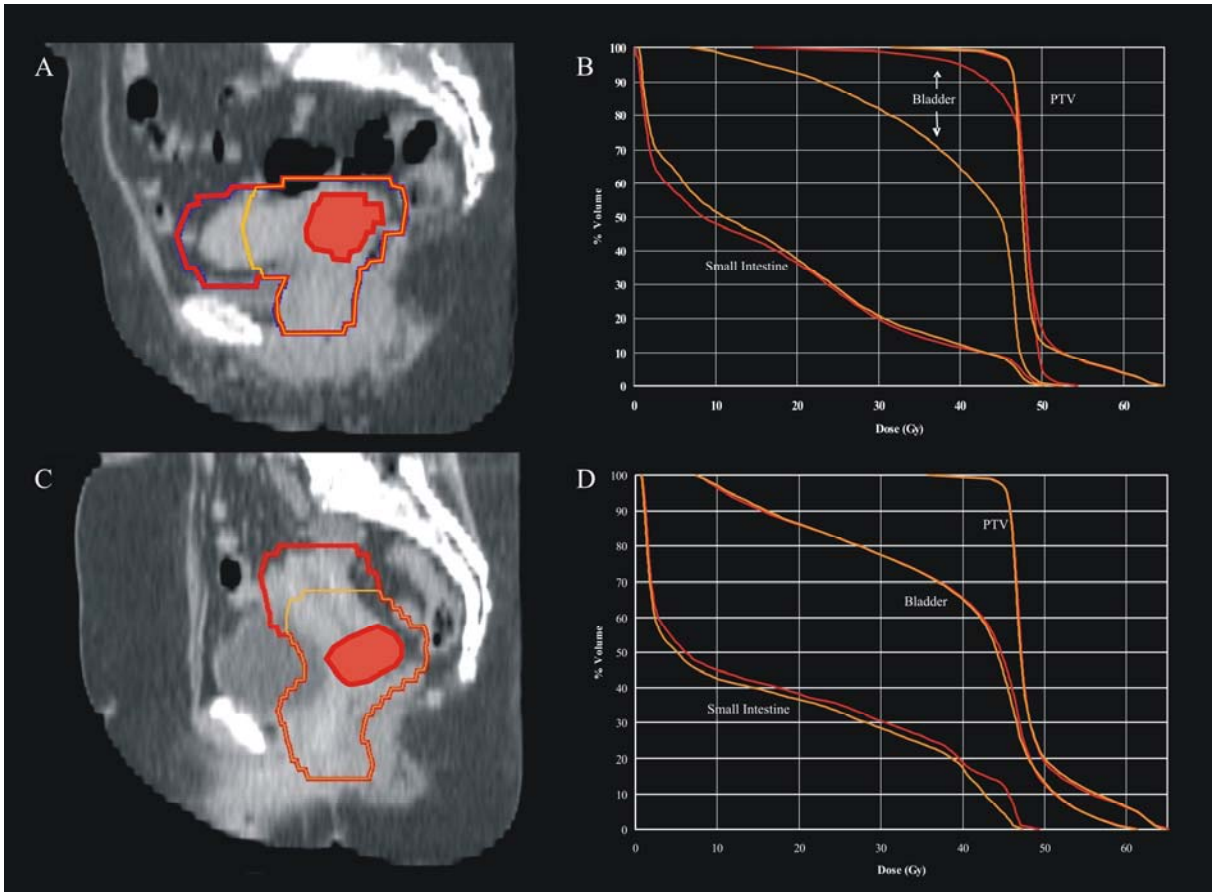

Figure 8.1: Example of Dose Volume Histograms (DVHs) of 2 patients when treated with a partial (yellow) or entire uterus (red) included in the PTV. A and C: red contour = entire uterus included in the PTV; yellow contour = only the parts of the uterus closer than two cm of the GTV (red flooded contour) are included in the PTV. C and D: DVHs of patient A and C respectively; the red DVHs correspond with the red contour (whole uterus); the yellow DVHs correspond with the yellow contour (selected parts of the uterus included in the CTV). The tail towards 62 Gy in the DVH of the PTV corresponds with the SIB given to the GTV.

In the first patient (A) the uterus lies in anteflection causing high doses to the bladder when irradiated entirely. A small reduction of PTV by reducing the amount of uterus included in the PTV causes a huge reduction in dose delivered to the bladder (B). A reduction of the PTV in case of a normal positioned uterus causes mainly a reduction in the irradiated volume of small bowel (D). Due to the large amounts of small bowel delineated, the percentual reduction seems small. In this case the amount of small bowel receiving 45 Gy is reduced with 8% which corresponds with 59cc.

A comparison of treatment plans with the currently used and reduced PTV will allow interpreting and evaluating differences in dose at the OARs. Subsequent a multidisciplinary trial, in which we hypothesize that current modern imaging techniques such as ^{18}FDG-PETCT and dynamic contrast enhanced (DCE) MRI allow accurate definition of the part of the uterus to be irradiated, will be initiated. Since all patients are treated with an adjuvant hysterectomy, stringent pathological examination of the hysterectomy specimen will serve as proof of our hypothesis.

c. Adaptive treatment

Substantial tumour regression over the course of treatment further complicates the issue of organ motion (Figure 8.2). Reduction in the GTV from baseline to the end of EBRT varies from 48 to 96% (41, 52-54). Median time to 50% regression is 20 days (range: 7-34days) (41). A relative reduction of the initial tumour volume of 7%, 24%, 44% and 59% was found after the first, second, third and fourth week respectively (53). Tumour regression induced target volume/position changes necessitate larger margins and lead to movement of OARs into the high dose area. The benefit of adaptive re-planning is therefore two-fold. First, adaptive treatment might allow tighter margins around the target (54), consequently leading to sparing of OARs (7). Secondly, by conforming the high dose area to the regressed tumor adaptive re-planning leads to significant lower doses on OARs (55, 56) as well. The latter is illustrated in figure 8.2, where shrinkage of tumour and uterus leads to a movement of OARs in the initially delineated PTV. If the treatment plan is not adapted at that moment, those OARs will be treated as they were PTV and receive high doses.

Currently, adaptive re-planning - plan of the day - is under investigation. With such complex and interwoven physical changes, simple pointwise assessment of anatomical motion provides incomplete information on target coverage and OAR sparing during treatment. A more accurate appraisal must include volumetric and dosimetric knowledge. Non-rigid image registration might allow us to integrate dose distributions of consecutive treatment plans with acceptable accuracy, merging of changed anatomical and biological imaging data enables us to reduce time-consuming efforts of re-delineation of all targets and OARs.

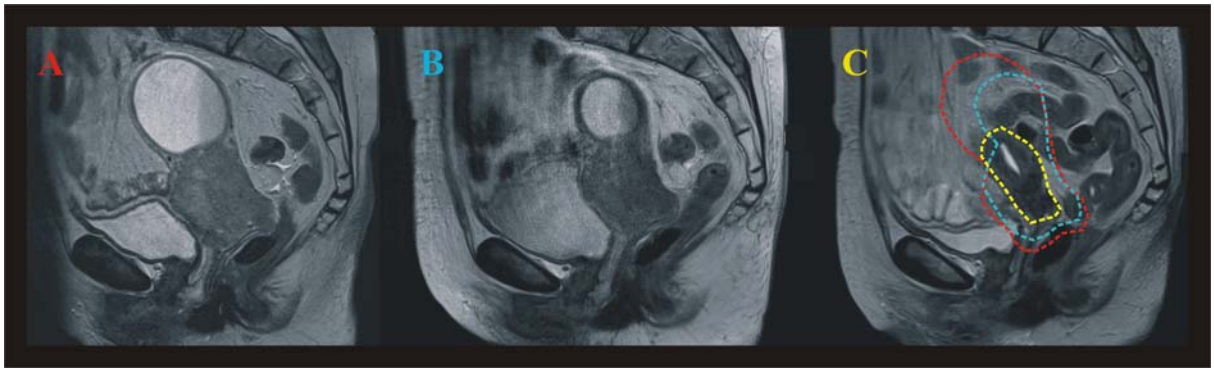

Figure 8.2: MRI imaging of a patient with LACC before (A), after 11 fractions (B) and after CRT (C). The volumes of the CTV before (red), during (blue) and after treatment (yellow) are projected on the post-treatment MRI. As visible in figure C, after shrinkage of the tumour and uterus, the small bowel, rectum and bladder have moved into the high dose area. The volume of the CTV reduced from 349cc before treatment to 213cc (-39%) during and 85cc (-70%) after treatment.

1.4. Primary treatment of locally advanced cervical cancer

1.4.1. Simultaneously Integrated Boost

Obtaining a maximal reduction of tumour is of utmost importance since negative resection margins are necessary to obtain local control (57) and the complication rate after surgery is correlated with the extent of tumour (58). Local control and escalated radiation dose are closely linked (59-62). At least of equal importance is the relationship between OTT and local control with an estimated loss of 0,6% to 1% for each additional treatment day (63-68). Escalation of the dose without increasing the number of fractions (SIB) should therefore theoretically result in a double advantage. The feasibility of performing a SIB using IMRT without compromising the dose to surrounding tissues has been proven before (69, 70). We demonstrated that IMAT easily succeeded in performing SIB (publication 2). The result of delivering a higher dose was described in publication 3. None of the patients had macroscopically visible tumour on the hysterectomy specimen. This compares favourable with literature data from series concerning EBRT + ICBT. In these series macroscopically visible rest tumours in 23-50% (60Gy) (57, 58, 71, 72) and 16% (75Gy) (73) of the cases are described. Although further maturation of our data is warranted, we hypothesize that this difference in macroscopic response rates endorses the double advantage of performing a SIB.

Another area of interest is the use of a SIB to deliver higher than conventional doses in women with documented pelvic or even para-aortic macroscopic lymph node involvement (^{18}FDG-PETCT). Results on the use of SIB on enlarged PALN, extended field IMRT and concurrent cisplatin are very encouraging with good loco-regional control and a significant lowering of morbidity when compared to conventional techniques (32, 34, 74). In our population, a SIB on the affected pelvic lymph nodes (up to 4) of 60 Gy was delivered while maintaining a dose of 45 Gy to the remaining elective lymph nodes. There was no increased toxicity (publication 1 and 3). Because all suspicious lymph nodes as visible on pre- and/or post treatment ^{18}FDG-PETCT were removed during surgery, assessment of local lymph node failure rate after lymph node SIB (without surgery) was impossible. This combined approach however leads to a 100% 2-year regional control rate (publication 3). Few data are published concerning the dose required to adequately treat FDG-positive lymph nodes. In our series 100% complete pathological remission (pCR) is found in FDG-positive lymph nodes < 2 cm with a NID_2 of 62Gy. In lymph nodes ≥ 2 cm pCR was only achieved in 50% of the nodes, suggesting the need for a higher dose in this setting. An obvious radiobiological explanation of this finding is that the number of tumour clonogens increases with tumour volume. Cell kill by radiotherapy increases roughly exponential with dose and is modelled using the linear-quadratic formulation (75). The resulting dose-response curves demonstrate that for a given dose increment always the same fraction of cells is killed. However, the number of cells killed depends on the absolute number of cancer cells and/or volume of the tumour. Consequently, the dose of irradiation to eradicate a certain volume of cancer (clonogen) cells increases with increasing volume. The effect of tumour volume on tumour control probability is less unequivocal than expected from a simple proportionate increase in tumour clonogen number with tumour volume. Other biologic events such as hypoxia or tumour characteristics such as tumour grade influence radioresistancy as have been proven in several tumour types (76). Further research is indispensible and will be executed to confirm this hypothesis.

At this moment ^{18}FDG-PETCT and MRI are used to delineate the primary tumour and affected lymph nodes which are to receive a SIB. This planning strategy is also known as dose painting by contours. Both imaging modalities could also provide biological data which have proven to be correlated with outcome. Kidd et al. showed that increased pre-treatment SUVmax is significantly associated with persistent abnormal ^{18}FDG uptake in the cervix at 3 months, higher pelvic recurrence and worse survival (77). SUVmax has also shown to be

correlated with histology and tumour proliferation rate, reflecting tumor aggressiveness (78). The cause of a higher FDG uptake in these more aggressive tumours remains uncertain, although there might be a role for glucose transporter gene expression (GLUT-1) (78), whose expression is enhanced by the hypoxia driven hypoxia-inducible factor 1- α (HIF 1-α) (79). By increasing the number of glucose transporters on the tumoural cell surface, HIF-1α enhances FDG-uptake leading to a high SUVmax. HIF-1α (a factor also playing an important role in other tumours such as renal cell carcinoma) drives tumour growth and progression, for instance by promoting neo-angiogenesis (80), resulting in a strong negative correlation with prognosis (81). This leads to the assumption that a high SUVmax is correlated with intra-tumour hypoxic radio-resistant foci which might need a more aggressive treatment, a hypothesis supported by the observation of Schütze et al. By using human FaDu head and neck squamous cell carcinomas in nude mice, they observed a greater effect on local control by increasing the radiation dose in tumours with higher FDG-uptake, where the dose-response relationship appears to be steep, than in tumours with a low FDG-uptake (82). Mayr et al. evaluated several parameters of DCE-MRI studies before and during combined CRT. They found that the degree of very-low-dynamic contrast-enhancement regions within the tumour, represented by the lowest relative signal intensity (RSI), correlated with tumour recurrence. Patients with a 10^{th} percentile RSI of 2.5 or less had a significantly higher tumour recurrence rate (88%) compared with patients with a 10^{th} percentile RSI higher than 2.5 (0%). If a 10th percentile RSI of 2.0 was used as a threshold value, all tumour recurrences could be predicted. They proposed that regions of very-low dynamic contrast enhancement are correlated with therapy-resistant hypoxic tumour cells (83). The use of both imaging modalities could allow detecting those intra-tumoural hypoxic radio-resistant foci in need for a more aggressive treatment to higher doses.

Planning and optimization tools for dose painting which enable to integrate intensities of any (biological) image type are developed at GUH (84, 85) and integration of biological information into the treatment planning (dose painting by numbers) has shown to be feasible and promising (86). Initial results of the integration of biological imaging in prostate cancer, using dose painting by contours, suggest a significant improvement in disease control (87).

Future perspective:

We hypothesize that further integration of biological information will lead to higher complete pathological response rates which are correlated with better outcome (71, 72). A multidisciplinary phase I-II dose-escalation trial using dose painting by numbers will be initiated. The continuous tumoural changes (biological AND volumetric) imply that this should be closely connected with gained insights in adaptive treatment planning.

1.4.2. Hysterectomy or not?

Whether a hysterectomy should be performed after CRT or not has been a source of controversy for several years. There are some clear arguments in favour of this approach.

At first, pCR rates after definitive CRT are only in the range of 39 to 55%. Macroscopic tumour rest is found in 16 to 50% of the cases (57, 58, 71-73, 88-90) and these rates increase with tumour stage (57). In our series we found pCR in 40% of the cases. Additional therapy thus might be beneficial, as residual tumour is known to be associated with a higher rate of pelvic recurrence (57, 60, 71) and appears to be the major cause of treatment failure (91, 92). This is reflected in overall LRR of 15 to 26% (4, 93). Moreover, the risk for technical unsuccessful intracavitary BT insertions (up to 10%) (94), increases with tumour stage (95) and results in incomplete treatments and higher risk of pelvic recurrence. Adjuvant hysterectomy removes potential chemo- and radioresistant foci, which might improve local

control. Moreover, detailed evaluation of pathological response after CRT can only be achieved on the hysterectomy specimen.
Yet, there is huge reticence towards hysterectomy, based on the fear of an increase in treatment-induced toxicity on the one hand and the absence of hard data on an OS benefit on the other hand.
The fear of increased treatment-induced toxicity results mainly from small single institution retrospective studies reporting high rates of late bowel and GU toxicity after using conventional radiation technology. However, the only randomized trial performed in this setting showed no increase in grade 3 or 4 toxicity (89) nor did two non-randomized retrospective comparative trials (73, 88). Surgical complications consisted mainly out of lymphocoeles, fistulae and hydronephrosis. A higher frequency of GI toxicity such as proctitis was observed after high dose brachytherapy (88). It is our hypothesis that the incorporation of new radiation techniques such as IMAT will lower the surgical complication rate. This is supported by our preliminary results concerning postoperative morbidity: there were only 3% grade 3 and no grade 4 postoperative complications so far (publication 3). Probably, the absence of macroscopic disease could be one of the reasons, as surgical morbidity is significantly correlated with residual disease > 1 cm (58).
Thorough evaluation of complications should also take into patients' quality of life (QOL). In this context scoring of vaginal/sexual morbidity is indispensible. Even with MRI guided adapted brachytherapy vaginal toxicity is described in 84% of the patients, with at least 30% grade 2 or more (adhesions, telangiectasia, dyspareunia). Although our study was not meant to score sexual morbidity and follow-up is not mature, neither fistulas nor partial or complete vaginal stenosis have been observed (publication 3).
In a randomized trial Keys et al. evaluated the benefits of adjuvant hysterectomy in 256 patients with bulky stage IB2 disease compared to RT alone (89). The exact conclusion was (citation): *"Overall, there was no clinically important benefit with the use of extrafascial hysterectomy. However, there is good evidence to suggest that patients with 4-, 5-, and 6-cm tumours may have benefitted from extrafascial hysterectomy (URR of progression; 0.58; URR of death, 0.60)."* While the OS rate was not significantly different in both groups, after adjusting for age, performance status and tumour size they reported a 5-year disease free survival (DFS) rate of 62% after surgery versus 53% in the control group (RR: 0,72; p=0,04). This benefit was mainly due to a reduced local recurrence rate (15% versus 27% respectively). In addition, a significant correlation was found concerning OS, favouring hysterectomy in increasing tumour size (p = 0,007). This indicates that patients with tumours measuring 4 to 6 cm on the hysterectomy regimen had a lower risk of death than the radiation-alone patients (RR:0,6).
Additionally, although this study was a keystone in abandoning adjuvant surgery (even in FIGO stages not studied), some other issues force us to caution the reader. At first, the publication included only 78% of the deaths targeted for final analysis of OS (sufficient to detect a 39% reduction in death rate with 80% statistical power). Secondly, this study only included patients with stage IB2 tumours (89).
In absence of randomized or non-randomized prospective comparative trials, our answers must be found in single-institution retrospective series. Several retrospective studies demonstrate that surgery is feasible and may be beneficial in terms of removing residual disease (57, 71-73, 88, 90, 96, 97) when compared to the results from 2 meta-analyses (including patients with stage II or more is), in which the LRR present in 17% to 25% (4, 93). Local recurrence rates for the same population in our single-institution series was 4% (publication 3) and was never more than 12% in others (57, 88, 97, 98). We hypothesize that these lower LRR will result in an OS benefit, certainly in more advanced stages. Carcopino et al. showed equivalent survival in patients with advanced stage IB-II and III-IVA cervical

cancer treated by adjuvant surgery following CRT (57). Three groups published 5-year OS rates for stage III and IV disease 60 to 69% (57, 71, 72) after adjuvant hysterectomy. With advanced brachytherapy techniques, these **3y**-OS rates are maximal 45% (99).
This is not a plea against brachytherapy. In the last decades, major developments in BT with image-guided brachytherapy allowing contour-based conformal BT planning as well as adaptive treatment allowed dose-escalation without increase in toxicity. Results concerning IGABT are promising. Mono-institutional experience using MR (100-102) or CT-based IGABT (103, 104) reported a favourable outcome with increased local control. The largest single-institution series by Pötter et al. (FIGO IB –IVA, 156 patients) reports 3-year locoregional control (LRC) and OS rates of 90% and 64% respectively. For tumours measuring more than 5 cm, dose escalation lead to an increase of 3-years LRC and OS rates from 71% to 90% and from 28% to 58% respectively. Additionally, morbidity using adaptive therapy has significantly decreased (62, 99). To confirm these results, a prospective collaborative international observational study on the parameters and the effects of MRI guided brachytherapy in locally advanced cervical cancer (EMBRACE) was initiated. However, we should be aware that these highly effective but specialized techniques are certainly not widely spread. Nevertheless we support a plea NOT to abandon adjuvant hysterectomy from the treatment options, to agree that hysterectomy could be performed without an excess in morbidity in this subset of patients and to be open minded in order to recognize adjuvant hysterectomy as a treatment option for patients with LACC.

Future perspectives:
- Further maturation of the study including multidisciplinary and stringent follow-up.
- Assessment of sexual morbidity (and subsidiary to this: QOL) in patients treated with adjuvant hysterectomy and comparison with a similar group of patients treated with exclusive CRT and BT.
- The true clinical role of adjuvant surgery remains to be verified, ideally in a prospective randomized multi-institutional study. Being aware that this will most probably never happen, pooling our data with those from other hysterectomy performing centres is a first step forward.

2. Ovarian Cancer

2.1. The role of radiotherapy in the palliative care of Epithelial Ovarian Cancer.

2.1.1. Update of publication 5

Radiotherapy has been used effectively to relieve symptoms of patients with EOC (105, 106). The results presented in publication 5 add to that evidence by providing data on substantial and long-lasting palliation with WAPRT in heavily pre-treated women. Conclusions, however, were presented prudently because of the low patient number. Since the publication of these data, 29 additional patients with the same inclusion criteria have been treated likewise and the analysis, including 42 patients, has been updated (unpublished data). From here on, all data refer to the updated patient series. Patient characteristics are presented in table 8.2.

Table 8.2: Patient Characteristics

Characteristic	All patients	Complete treatment	Incomplete treatment
	n=42	n=30	n=12
Age (start WAPRT)			
median	59	59	61
range	31-76	31-76	39-75
KPS (start WAPRT)			
median	80	80	60
range	40-90	60-90	40-80
≥ 80 (n)	22	**21**	**1**
< 80 (n)	20	**9**	**11**
≥ 70 (n)	31	**27**	**4**
< 70 (n)	11	**3**	**8**
Platinum-S (1st relapse)			
yes	25	19	6
no	13	9	4
refractory	4	2	2
FIGO (diagnosis)			
I	4	3	1
II	0	0	0
III	33	25	8
IV	5	2	3
CA 125 (at start)			
median (U/ml)	421	345	2263
range	6-13769	6-8636	60-13769
"x" lines chemotherapy			
median	4	3	5
range	1-8	1-7	1-8
"x" laparatomies			
median	2	2	2
range	0-5	0-5	1-4
Post WAPRT chemotherapy			
n	16	15	1

WAPRT: Whole abdomino-pelvic radiotherapy; KPS: Karnofsky Performance Status; Platinum-S: platinum sensitive; "x": number of; numbers in bold: significant difference (p<0,05)

2.1.1.1. *Symptom response*

Patients were treated for one (or multiple) of the following indications: pain, palpable mass, (sub)obstruction, ascites and vaginal bleeding. Table 8.3 lists the indications and the corresponding response rates. Consistent with our first publication and literature (105, 107), a high overall response rate was achieved for all symptoms with ascites as least responding symptom. More specifically a complete clinical response in 69% of patients with malignant bowel obstruction (that ended treatment) was noted (table 8.2). The median symptom response duration (all symptoms grouped) was 16 weeks (range: 0–139). Patients with a Karnofsky Performance status (KPS) ≥ 70 had a significantly longer median response duration compared to those with KPS < 70: 22 (range: 0-139) vs 5 weeks (range: 2-8) (p<0,02).

Table 8.3: Response rate per symptom (%) for all patients that completed treatment (n=30).

Symptom	n	CR	PR	SD	PD	ORR
Palpable Mass	7	43	43	1	0	100
Pain	16	75	0	12,5	12,5	87
(Sub)Obstruction	13	69	23	0	8	92
Ascites	7	14	57	0	29	71
Bleeding	2	100	0	0	0	100

CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Overall Response Rate.

2.1.1.2.Overall Survival and abdominal progression free survival (aPFS).

After multivariate analysis (Cox regression model with co-variates: age, KPS and CA125 at start WAPRT; Cisplatin sensitivity after the first cycle and FIGO stage at diagnosis) only KPS was significantly correlated with OS and aPFS. Median OS and aPFS for the intention to treat population was 4 months (range: 0-32) and 11 weeks (range: 0-142). Both were significantly longer for patients with KPS ≥ 70 compared with KPS < 70: 8 months (range: 1-32) vs 1 month (range: 0-5), (p < 0,001) and 18 weeks (range: 0-142) vs 3 weeks (range: 1-21), (p < 0,001) respectively. Median OS and aPFS for the patients that ended the treatment was 8 months (range: 2-32) and 17 weeks (range: 4-142). Again, both were significantly longer for patients with KPS ≥ 70 compared with KPS < 70: 11 months (range: 2-32) vs 3 months (2-4), (p < 0,001) and 21 weeks (range: 4-142) vs 10 weeks (range: 8-14), (p < 0,001) respectively. Overall survival and aPFS rates are visualised in figure 8.3

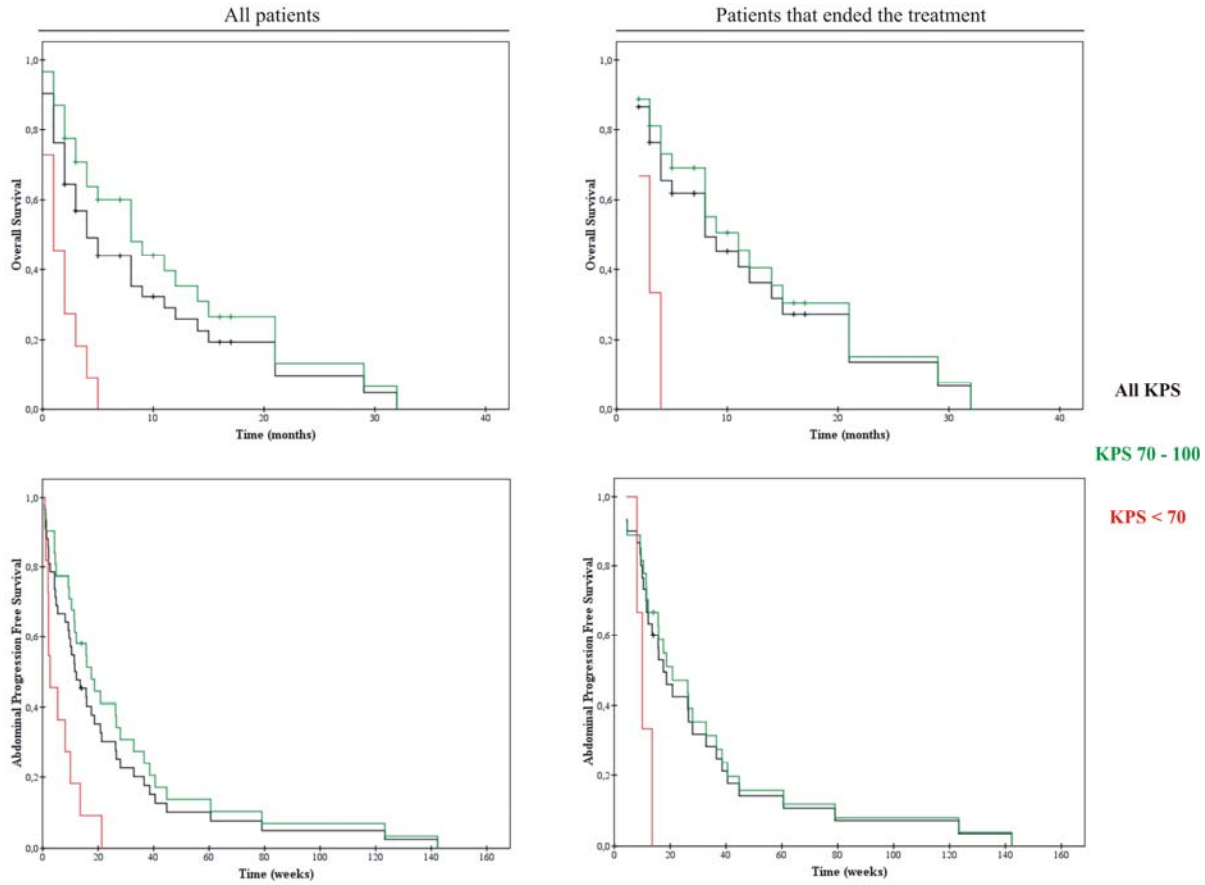

Figure 8.3: Kaplan-Meier curves representing overall survival and abdominal progression free survival for all patients (intention to treat population; n=42) and the patients that ended treatment (n=30). Patients with a Karnofsky score (KPS) less than 70 are represented in red, with a KPS of 70 or more in green and the whole population in black.

2.1.1.3.Tolerance of WAPRT

Twelve patients did not end treatment, mostly due to disease progression before any palliation could be started (median fractions delivered: 6 (range: 2-13)). One patient died of cerebral bleeding (grade 5 trombopenia). Acute toxicity was assessed in 24 patients. As expected, grade ≥ 3 acute GI toxicity was most frequent. Details concerning acute toxicity are presented in table 8.4. Only in 2 patients diarrhoea persisted more than 3 months (both grade 2 late toxicity).

Table 8.4: Acute toxicity in %.

Acute toxicity				
	G 2	G 3	G 4	G 5
Intestinal	46	29	4	0
Vomiting	33	8	4	0
Diarrhoea	50	25	0	0
Urinary	0	0	0	0
Hematological	4	4	8	4
Fatigue	12	0	0	0

G: Grade

2.1.2. The role of radiotherapy in the palliative setting.

The role of RT in the palliative treatment of EOC has been studied before (105, 107-113). Despite the heterogeneity of patient populations and treatment schemes in these studies, 3 global conclusions could be drawn.

1. Excellent response rates for bleeding (71 -100%), pain (51-100%) and (GU or GI) obstruction (up to 75%), respectively are described. (105, 107-109, 111, 112). Other sites of metastasis that appear to benefit from palliative irradiation include brain metastasis, lymph nodes and bone (105, 112).
2. Even heavily pre-treated women respond well
3. Ascites and lymph oedema respond less (105, 107).

Our data confirm all three above conclusions. Our study differs however from the earlier reports in target volume. Except for 24/109 in Tinger's series (107) and 1 patient in Geldblum's (111) all patients were treated locally. Malignant bowel obstruction is mostly present at multiple intestinal levels, precluding any surgical intent, in those mostly heavily pre-treated patients. By using WAPRT, patients with peritoneal carcinomatosis can be palliated. Our series is the first to show the ability of WAPRT to relieve intestinal obstruction caused by peritoneal carcinomatosis. Therefore, WAPRT should be considered as one of the possible treatments in those patients. Patient selection is, however, very important. Only patients with KPS > 70 benefit (update publication 5).

2.2. The role of WAPRT in the adjuvant or salvage setting.

The prognosis for patients with advanced EOC remains poor despite the use of aggressive surgical debulking and platinum-based multi-agent chemotherapy. The median time to recurrence is less than 2 years, with a 5-years OS rate of 20-25% (114). Recurrence of disease occurs mostly intra-peritoneal. Treatment of patients after debulking and chemotherapy is considered as the adjuvant setting; once the patient recurred she's treated in a salvage setting.

The use of WAPRT might sterilize small residual tumour deposits – mostly exclusive – in the peritoneal cavity. This approach is not new. Already in the 80's postoperative WAPRT *(adjuvant setting)* has shown to be curative in certain subsets of patients with optimal disease (Table 8.4) (115).

Table 8.4: "Optimal disease" in the adjuvant treatment for EOC as defined by Dembo et al. (115).

Stage	T rest	S + C	M + E	S + C + U
		G1	G: All	>G1
I	<2cm*			
II	0			
II	<2cm*			
III	0			
III	<2cm*			

Optimal disease = white cells. T rest: residual disease after debulking, largest diameter; * preferably. S: serous; C: clear cell; M: mucinous; E: endometroid; U: undifferentiated or unclassified.

With the advent of chemotherapy, WAPRT has been increasingly abandoned. The relative effectiveness of surgery, chemotherapy and radiation (when given as monotherapy) enforced the hypothesis that combining those therapies could offer a treatment advantage. Many reports have appeared in literature since then, mostly single-arm (116). Three additional randomized

trials of consolidation WAPRT have been performed. Two trials were supportive of its use over chemotherapy or observation (117, 118), one trial found no difference between radiotherapy or chemotherapy (119). Sorbe et al. randomly assigned patients with a pCR after second-look laparatomy to treatment with WAPRT, chemotherapy or only observation. Patients with a complete clinical, but not pathologic response were randomly assigned to receive WAPRT or chemotherapy, without an observation protocol. Patients with macroscopic disease were excluded for randomization. For those with microscopic disease, the 5-years PFS and OS did not differ between WAPRT and chemotherapy. For the patients with a complete pathologic response, the 5-year PFS was 56% in the WAPRT cohort and 36% for both the chemotherapy and observation group (p = 0,03).(118). These observations made the authors conclude that WAPRT should be considered as consolidation therapy in advanced EOC patients who had a pCR after chemotherapy (120). The only (small) series of WAPRT for patients with clinical complete response after adjuvant chemotherapy (carboplatin/paclitaxel) supported this (121).
However, when conventional RT is used as consolidation after combined surgery-chemotherapy, complication rates are high. In the acute phase GI toxicity, which can be severe in 6% and present in around 70%, is the predominant toxicity. Hematologic toxicity, however, should not be underestimated Treatment interruptions or failures to finish WAPRT due to myelosuppression up to 36% are reported, with thrombocytopenia being the predominant reason (116, 121-123). Although several authors comment on increased incidence of bone marrow toxicity in patients who received chemotherapy prior to WAPRT, no objective correlation with bone marrow toxicity could be found (106). Also late toxicity constitutes mainly of GI toxicity, with small bowel obstruction (4 to 10 %) being the most important one (116, 122, 123). Bowel complication rates seems to be correlated with increasing number of prior laparotomies, higher radiation doses (>45Gy) to the pelvis (106) and the used radiation technique (122). Whole-abdominopelvic radiotherapy does not compromise the use of chemotherapy afterwards (121).
Despite improved tumour response rates to newer chemotherapeutic regimens, the majority of patients with advanced EOC will recur with ultimately platinum resistant or refractory disease (*salvage setting).* The choice of second-line treatment depends on the recurrence-free period. For platinum sensitive relapsed patients, platinum based chemotherapy will be restarted with secondary debulking in selected cases. Response rates range from 27% to 72% and PFS rates from 8 to 12 months (114). In platinum resistant or refractory relapse, response rates and survival are poor, with median PFS rates ranging from 2 to 7 months (114). Several studies have evaluated the efficacy and toxicity of WAPRT in those patients with persistent disease. Again, OS rates were highly correlated with the amount of tumour prior to WAPRT. Overall, a response rate to salvage RT of 30 to 50% in patients with microscopic residual disease after chemotherapy versus a response rate of less than 10% for patients with evidence of gross disease are reported and a long-term OS of approximately 35% is described (124, 125). Results for patients with platinum-refractory/resistant disease are not different from the platinum-sensitive patients (126).

Future direction:
- Dose-response curves suggest that 30 to 40 Gy can eradicate 60 to 90% of subclinical (less than 1 cm) tumours (117, 127). However, using conventional techniques, renal and hepatic tolerance levels will lead to severe underdosage in some peritoneal regions (128) and especially hematologic toxicity often makes treatment interruptions or definitive treatment stop necessary, which is a predictor for worse outcome (116).We hypothesize that modern radiation such as IMAT-based WAPRT will reduce hematologic toxicity and consequently lower the rate of treatment interruptions or definitive treatment stops. Moreover, the

peritoneal cavity would be treated to higher and more homogeneous doses. A randomized trial using modern RT techniques should be initiated to reaffirm the role of consolidation WAPRT in the multimodality treatment of advanced ovarian cancer.
- In salvage setting, the response rate after WAPRT is substantial and OS is more than satisfactory in patients with minimal disease. Especially in platinum refractory/resistant patients with disappointing response rates on second-line chemotherapy, this approach merits further investigation.
- For patients with >2 cm persistent or recurrent disease, WAPRT didn't show any results of importance thus far. This is not surprising since a radiation dose around 30 Gy is not able to eradicate macroscopic tumour (117, 127). Using IMAT for WAPRT, targeted dose escalation to macroscopic tumour areas is feasible. This possible chance of increased local control could open a new window of opportunities.

3. Conclusion

Capable of creating steep dose gradients, IMAT allows a challenging combination of reducing dose at the surrounding tissues while intensifying the radiation dose to the tumour at the same time. And so, introducing IMAT and its opportunities in the multimodality treatment of gynaecological tumours caused a chain of changes and a true paradigm shift. Performing IMAT with a SIB in locally advanced cervical cancer lead to low radiation related toxicity rates and allows a safe adjuvant hysterectomy. The resulting local, locoregional and OS rates are very promising. Low toxicities in the postoperative treatment of endometrial and early stage cervical cancer are achieved and open a new window for opportunities such as preventive radiation to the para-aortic nodes. Finally, in ovarian cancer, IMAT allowed a revival of WAPRT in the palliative setting with more than satisfactory symptom palliation and response rates that allow re-introducing WAPRT in more early stages of the treatment.
A lot of work remains to be done. Multiple hypotheses described in this thesis are to be tested and should lead to further reduced toxicity and dose-intensification on radio-resistant foci within the tumour. The hardest challenge however, lies in convincing the radiotherapeutic community to embrace the opportunities created by new radiation techniques and to rethink the existing dogmas.

REFERENCES

1. Lacassagne A. Results of the Treatment of Cancer of the Cervix Uteri. *Br Med J* 1932;2:912-913.
2. Rutledge FN, Fletcher GH. Transperitoneal pelvic lymphadenectomy following supervoltage irradiation for squamouscell carcinoma of the cervix. *Am J Obstet Gynecol* 1958;76:321-334.
3. Kirwan JM, Symonds P, Green JA*, et al.* A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. *Radiother Oncol* 2003;68:217-226.
4. Lukka H, Hirte H, Fyles A*, et al.* Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer--a meta-analysis. *Clin Oncol (R Coll Radiol)* 2002;14:203-212.
5. Maduro JH, Pras E, Willemse PH*, et al.* Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. *Cancer Treat Rev* 2003;29:471-488.
6. Wiesendanger-Wittmer EM, Sijtsema NM, Muijs CT*, et al.* Systematic review of the role of a belly board device in radiotherapy delivery in patients with pelvic malignancies. *Radiother Oncol* 2012;102:325-334.
7. Ahamad A, D'Souza W, Salehpour M*, et al.* Intensity-modulated radiation therapy after hysterectomy: comparison with conventional treatment and sensitivity of the normal-tissue-sparing effect to margin size. *Int J Radiat Oncol Biol Phys* 2005;62:1117-1124.
8. Chen Q, Izadifar N, King S*, et al.* Comparison of IMRT with 3-D CRT for gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2001;51:332.
9. Forrest J, Presutti J, Davidson M*, et al.* A Dosimetric Planning Study Comparing Intensity-modulated Radiotherapy with Four-field Conformal Pelvic Radiotherapy for the Definitive Treatment of Cervical Carcinoma. *Clinical Oncology* 2012;24:e63-70.
10. Georg P, Georg D, Hillbrand M*, et al.* Factors influencing bowel sparing in intensity modulated whole pelvic radiotherapy for gynaecological malignancies. *Radiother Oncol* 2006;80:19-26.
11. Heron DE, Gerszten K, Selvaraj RN*, et al.* Conventional 3D conformal versus intensity-modulated radiotherapy for the adjuvant treatment of gynecologic malignancies: a comparative dosimetric study of dose-volume histograms small star, filled. *Gynecol Oncol* 2003;91:39-45.
12. Hsieh CH, Wei MC, Lee HY*, et al.* Whole pelvic helical tomotherapy for locally advanced cervical cancer: technical implementation of IMRT with helical tomotherapy. *Radiat Oncol* 2009;4:62.
13. Lujan AE, Mundt AJ, Yamada SD*, et al.* Intensity-modulated radiotherapy as a means of reducing dose to bone marrow in gynecologic patients receiving whole pelvic radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;57:516-521.
14. Mell LK, Tiryaki H, Ahn KH*, et al.* Dosimetric comparison of bone marrow-sparing intensity-modulated radiotherapy versus conventional techniques for treatment of cervical cancer. *Int J Radiat Oncol Biol Phys* 2008;71:1504-1510.
15. Portelance L, Chao KS, Grigsby PW*, et al.* Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. *Int J Radiat Oncol Biol Phys* 2001;51:261-266.
16. Roeske JC, Lujan A, Rotmensch J*, et al.* Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2000;48:1613-1621.

17. Wong E, D'Souza DP, Chen JZ*, et al.* Intensity-modulated arc therapy for treatment of high-risk endometrial malignancies. *Int J Radiat Oncol Biol Phys* 2005;61:830-841.
18. Bouchard M, Nadeau S, Gingras L*, et al.* Clinical outcome of adjuvant treatment of endometrial cancer using aperture-based intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;71:1343-1350.
19. Chen MF, Tseng CJ, Tseng CC*, et al.* Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;67:1438-1444.
20. Brixey CJ, Roeske JC, Lujan AE*, et al.* Impact of intensity-modulated radiotherapy on acute hematologic toxicity in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2002;54:1388-1396.
21. Du XL, Tao J, Sheng XG*, et al.* Intensity-modulated radiation therapy for advanced cervical cancer: A comparison of dosimetric and clinical outcomes with conventional radiotherapy. *Gynecol Oncol* 2012;125:151-157.
22. Mundt AJ, Lujan AE, Rotmensch J*, et al.* Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2002;52:1330-1337.
23. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys* 2003;56:1354-1360.
24. Hasselle MD, Rose BS, Kochanski JD*, et al.* Clinical Outcomes of Intensity-Modulated Pelvic Radiation Therapy for Carcinoma of the Cervix. *Int J Radiat Oncol Biol Phys* 2011;80:1436-1445.
25. Samuelian JM, Callister MD, Ashman JB*, et al.* Reduced acute bowel toxicity in patients treated with intensity-modulated radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2011;82:1981-1987.
26. Stromberger C, Kom Y, Kawgan-Kagan M*, et al.* Intensity-modulated radiotherapy in patients with cervical cancer. An intra-individual comparison of prone and supine positioning. *Radiat Oncol* 2010;5:63.
27. Adli M, Mayr NA, Kaiser HS*, et al.* Does prone positioning reduce small bowel dose in pelvic radiation with intensity-modulated radiotherapy for gynecologic cancer? *Int J Radiat Oncol Biol Phys* 2003;57:230-238.
28. Rotman M, Pajak TF, Choi K*, et al.* Prophylactic extended-field irradiation of para-aortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas. Ten-year treatment results of RTOG 79-20. *JAMA* 1995;274:387-393.
29. Haie C, Pejovic MH, Gerbaulet A*, et al.* Is prophylactic para-aortic irradiation worthwhile in the treatment of advanced cervical carcinoma? Results of a controlled clinical trial of the EORTC radiotherapy group. *Radiother Oncol* 1988;11:101-112.
30. Grigsby PW, Heydon K, Mutch DG*, et al.* Long-term follow-up of RTOG 92-10: cervical cancer with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys* 2001;51:982-987.
31. Small W, Jr., Winter K, Levenback C*, et al.* Extended-Field Irradiation and Intracavitary Brachytherapy Combined With Cisplatin and Amifostine for Cervical Cancer With Positive Para-Aortic or High Common Iliac Lymph Nodes: Results of Arm II of Radiation Therapy Oncology Group (RTOG) 0116. *International Journal of Gynecological Cancer* 2011;21:1266-1275.
32. Salama JK, Mundt AJ, Roeske J*, et al.* Preliminary outcome and toxicity report of extended-field, intensity-modulated radiation therapy for gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2006;65:1170-1176.

33. Ahmed RS, Kim RY, Duan J*, et al.* IMRT dose escalation for positive para-aortic lymph nodes in patients with locally advanced cervical cancer while reducing dose to bone marrow and other organs at risk. *Int J Radiat Oncol Biol Phys* 2004;60:505-512.
34. Esthappan J, Mutic S, Malyapa RS*, et al.* Treatment planning guidelines regarding the use of CT/PET-guided IMRT for cervical carcinoma with positive paraaortic lymph nodes. *Int J Radiat Oncol Biol Phys* 2004;58:1289-1297.
35. Gerszten K, Colonello K, Heron DE*, et al.* Feasibility of concurrent cisplatin and extended field radiation therapy (EFRT) using intensity-modulated radiotherapy (IMRT) for carcinoma of the cervix. *Gynecol Oncol* 2006;102:182-188.
36. Salama JK, Mundt AJ, Roeske J*, et al.* Preliminary outcome and toxicity report of extended-field, intensity-modulated radiation therapy for gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2006;65:1170-1176.
37. Veldeman L, Madani I, Hulstaert F*, et al.* Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. *Lancet Oncol* 2008;9:367-375.
38. Staffurth J. A review of the clinical evidence for intensity-modulated radiotherapy. *Clin Oncol (R Coll Radiol)* 2010;22:643-657.
39. Taylor A, Powell MEB. Conformal and Intensity-modulated Radiotherapy for Cervical Cancer. *Clinical Oncology* 2008;20:417-425.
40. Haripotepornkul NH, Nath SK, Scanderbeg D*, et al.* Evaluation of intra- and inter-fraction movement of the cervix during intensity modulated radiation therapy. *Radiother Oncol* 2011;98:347-351.
41. Beadle BM, Jhingran A, Salehpour M*, et al.* Cervix Regression and Motion During the Course of External Beam Chemoradiation for Cervical Cancer. *Int J Radiat Oncol Biol Phys* 2009;73:235-241.
42. Chan P, Dinniwell R, Haider MA*, et al.* Inter- and intrafractional tumor and organ movement in patients with cervical cancer undergoing radiotherapy: a cinematic-MRI point-of-interest study. *Int J Radiat Oncol Biol Phys* 2008;70:1507-1515.
43. Taylor A, Powell ME. An assessment of interfractional uterine and cervical motion: implications for radiotherapy target volume definition in gynaecological cancer. *Radiother Oncol* 2008;88:250-257.
44. Han Y, Shin EH, Huh SJ*, et al.* Interfractional dose variation during intensity-modulated radiation therapy for cervical cancer assessed by weekly CT evaluation. *Int J Radiat Oncol Biol Phys* 2006;65:617-623.
45. Gerstner N, Wachter S, Knocke TH*, et al.* The benefit of Beam's eye view based 3D treatment planning for cervical cancer. *Radiother Oncol* 1999;51:71-78.
46. Buchali A, Koswig S, Dinges S*, et al.* Impact of the filling status of the bladder and rectum on their integral dose distribution and the movement of the uterus in the treatment planning of gynaecological cancer. *Radiother Oncol* 1999;52:29-34.
47. Lim K, Kelly V, Stewart J*, et al.* Pelvic radiotherapy for cancer of the cervix: is what you plan actually what you deliver? *Int J Radiat Oncol Biol Phys* 2009;74:304-312.
48. Roeske JC, Bonta D, Mell LK*, et al.* A dosimetric analysis of acute gastrointestinal toxicity in women receiving intensity-modulated whole-pelvic radiation therapy. *Radiother Oncol* 2003;69:201-207.
49. Collen C, Engels B, Duchateau M*, et al.* Volumetric imaging by megavoltage computed tomography for assessment of internal organ motion during radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2010;77:1590-1595.
50. Lee JE, Han Y, Huh SJ*, et al.* Interfractional variation of uterine position during radical RT: weekly CT evaluation. *Gynecol Oncol* 2007;104:145-151.

51. Lim K, Small Jr W, Portelance L*, et al.* Consensus Guidelines for Delineation of Clinical Target Volume for Intensity-Modulated Pelvic Radiotherapy for the Definitive Treatment of Cervix Cancer. *Int J Radiat Oncol Biol Phys* 2009;79:348-355.
52. Tyagi N, Lewis JH, Yashar CM*, et al.* Daily online cone beam computed tomography to assess interfractional motion in patients with intact cervical cancer. *Int J Radiat Oncol Biol Phys* 2011;80:273-280.
53. van de Bunt L, Jurgenliemk-Schulz IM, de Kort GA*, et al.* Motion and deformation of the target volumes during IMRT for cervical cancer: what margins do we need? *Radiother Oncol* 2008;88:233-240.
54. Stewart J, Lim K, Kelly V*, et al.* Automated weekly replanning for intensity-modulated radiotherapy of cervix cancer. *Int J Radiat Oncol Biol Phys* 2010;78:350-358.
55. van de Bunt L, van der Heide UA, Ketelaars M*, et al.* Conventional, conformal, and intensity-modulated radiation therapy treatment planning of external beam radiotherapy for cervical cancer: The impact of tumor regression. *Int J Radiat Oncol Biol Phys* 2006;64:189-196.
56. Kerkhof EM, Raaymakers BW, van der Heide UA*, et al.* Online MRI guidance for healthy tissue sparing in patients with cervical cancer: An IMRT planning study. *Radiother Oncol* 2008.
57. Carcopino X, Houvenaeghel G, Buttarelli M*, et al.* Equivalent survival in patients with advanced stage IB-II and III-IVA cervical cancer treated by adjuvant surgery following chemoradiotherapy. *Eur J Surg Oncol* 2008;34:569-575.
58. Touboul C, Uzan C, Mauguen A*, et al.* Prognostic factors and morbidities after completion surgery in patients undergoing initial chemoradiation therapy for locally advanced cervical cancer. *Oncologist* 2010;15:405-415.
59. Choy D, Wong LC, Sham J*, et al.* Dose-tumor response of carcinoma of cervix: an analysis of 594 patients treated by radiotherapy. *Gynecol Oncol* 1993;49:311-317.
60. Paley PJ, Goff BA, Minudri R*, et al.* The prognostic significance of radiation dose and residual tumor in the treatment of barrel-shaped endophytic cervical carcinoma. *Gynecol Oncol* 2000;76:373-379.
61. Perez CA, Grigsby PW, Chao KS*, et al.* Tumor size, irradiation dose, and long-term outcome of carcinoma of uterine cervix. *Int J Radiat Oncol Biol Phys* 1998;41:307-317.
62. Potter R, Dimopoulos J, Georg P*, et al.* Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. *Radiother Oncol* 2007;83:148-155.
63. Bese NS, Hendry J, Jeremic B. Effects of prolongation of overall treatment time due to unplanned interruptions during radiotherapy of different tumor sites and practical methods for compensation. *Int J Radiat Oncol Biol Phys* 2007;68:654-661.
64. Chen SW, Liang JA, Yang SN*, et al.* The adverse effect of treatment prolongation in cervical cancer by high-dose-rate intracavitary brachytherapy. *Radiother Oncol* 2003;67:69-76.
65. Girinsky T, Rey A, Roche B*, et al.* Overall treatment time in advanced cervical carcinomas: a critical parameter in treatment outcome. *Int J Radiat Oncol Biol Phys* 1993;27:1051-1056.
66. Hill RP, Fyles W, Milosevic M*, et al.* Is there a relationship between repopulation and hypoxia/reoxygenation? Results from human carcinoma of the cervix. *Int J Radiat Biol* 2003;79:487-494.

67. Lanciano R. Optimizing radiation treatment for cervical cancer. *Surg Clin North Am* 2001;81:859-870.
68. Perez CA, Grigsby PW, Castro-Vita H*, et al.* Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys* 1995;32:1275-1288.
69. Guerrero M, Li XA, Ma L*, et al.* Simultaneous integrated intensity-modulated radiotherapy boost for locally advanced gynecological cancer: radiobiological and dosimetric considerations. *Int J Radiat Oncol Biol Phys* 2005;62:933-939.
70. Mutic S, Malyapa RS, Grigsby PW*, et al.* PET-guided IMRT for cervical carcinoma with positive para-aortic lymph nodes-a dose-escalation treatment planning study. *Int J Radiat Oncol Biol Phys* 2003;55:28-35.
71. Classe JM, Rauch P, Rodier JF*, et al.* Surgery after concurrent chemoradiotherapy and brachytherapy for the treatment of advanced cervical cancer: morbidity and outcome: results of a multicenter study of the GCCLCC (Groupe des Chirurgiens de Centre de Lutte Contre le Cancer). *Gynecol Oncol* 2006;102:523-529.
72. Ferrandina G, Legge F, Fagotti A*, et al.* Preoperative concomitant chemoradiotherapy in locally advanced cervical cancer: safety, outcome, and prognostic measures. *Gynecol Oncol* 2007;107:S127-132.
73. Darus CJ, Callahan MB, Nguyen QN*, et al.* Chemoradiation with and without adjuvant extrafascial hysterectomy for IB2 cervical carcinoma. *Int J Gynecol Cancer* 2008;18:730-735.
74. Kavanagh BD, Schefter TE, Wu Q*, et al.* Clinical application of intensity-modulated radiotherapy for locally advanced cervical cancer. *Semin Radiat Oncol* 2002;12:260-271.
75. Joiner M, van der Kogel A. Basic Clinical Radiobiology. Vol 4. London: Amazon; 2009.
76. Bentzen SM, Thames HD. Tumor volume and local control probability: Clinical data and radiobiological interpretations. *Int J Radiat Oncol Biol Phys* 1996;36:247-251.
77. Kidd EA, Siegel BA, Dehdashti F*, et al.* The standardized uptake value for F-18 fluorodeoxyglucose is a sensitive predictive biomarker for cervical cancer treatment response and survival. *Cancer* 2007;110:1738-1744.
78. Kidd EA, Spencer CR, Huettner PC*, et al.* Cervical cancer histology and tumor differentiation affect 18F-fluorodeoxyglucose uptake. *Cancer* 2009;115:3548-3554.
79. Zhao S, Kuge Y, Mochizuki T*, et al.* Biologic Correlates of Intratumoral Heterogeneity in 18F-FDG Distribution with Regional Expression of Glucose Transporters and Hexokinase-II in Experimental Tumor. *Journal of Nuclear Medicine* 2005;46:675-682.
80. Keith B, Johnson RS, Simon MC. HIF1alpha and HIF2alpha: sibling rivalry in hypoxic tumour growth and progression. *Nat Rev Cancer* 2011;12:9-22.
81. Birner P, Schindl M, Obermair A*, et al.* Overexpression of hypoxia-inducible factor 1alpha is a marker for an unfavorable prognosis in early-stage invasive cervical cancer. *Cancer Res* 2000;60:4693-4696.
82. Schütze C, Bergmann R, Yaromina A*, et al.* Effect of increase of radiation dose on local control relates to pre-treatment FDG uptake in FaDu tumours in nude mice. *Radiotherapy and Oncology* 2007;83:311-315.
83. Mayr NA, Yuh WT, Arnholt JC*, et al.* Pixel analysis of MR perfusion imaging in predicting radiation therapy outcome in cervical cancer. *J Magn Reson Imaging* 2000;12:1027-1033.
84. De Gersem W. IMRT and IMAT engineering the evolution from organ avoidance to dose painting. Ph.D. Dissertation. Ghent; 2008.

85. Vanderstraeten B. Biologically conformal radiation therapy and Monte Carlo dose calculations in the clinic. Ph.D. Dissertation. Ghent; 2007.
86. Duprez F. Modern IMRT for head and neck cancer: a paradoxical paradigm of simultaneous dose-escalation and de-escalation. Ph.D. Dissertation. Ghent; 2010.
87. Fonteyne V, Villeirs G, Speleers B*, et al.* Intensity-modulated radiotherapy as primary therapy for prostate cancer: report on acute toxicity after dose escalation with simultaneous integrated boost to intraprostatic lesion. *Int J Radiat Oncol Biol Phys* 2008;72:799-807.
88. Cetina L, Garcia-Arias A, Candelaria M*, et al.* Brachytherapy versus radical hysterectomy after external beam chemoradiation: a non-randomized matched comparison in IB2-IIB cervical cancer patients. *World J Surg Oncol* 2009;7:19.
89. Keys HM, Bundy BN, Stehman FB*, et al.* Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. *Gynecol Oncol* 2003;89:343-353.
90. Morice P, Uzan C, Zafrani Y*, et al.* The role of surgery after chemoradiation therapy and brachytherapy for stage IB2/II cervical cancer. *Gynecol Oncol* 2007;107:S122-124.
91. Perez CA, Breaux S, Madoc-Jones H*, et al.* Radiation therapy alone in the treatment of carcinoma of uterine cervix. I. Analysis of tumor recurrence. *Cancer* 1983;51:1393-1402.
92. Perez CA, Kuske RR, Camel HM*, et al.* Analysis of pelvic tumor control and impact on survival in carcinoma of the uterine cervix treated with radiation therapy alone. *Int J Radiat Oncol Biol Phys* 1988;14:613-621.
93. Viani G, Manta G, Stefano E*, et al.* Brachytherapy for cervix cancer: low-dose rate or high-dose rate brachytherapy - a meta-analysis of clinical trials. *Journal of Experimental & Clinical Cancer Research* 2009;28:47.
94. Walji N, Chue AL, Yap C*, et al.* Is There a Role for Adjuvant Hysterectomy after Suboptimal Concurrent Chemoradiation in Cervical Carcinoma? *Clinical Oncology* 2010;22:140-146.
95. Houvenaeghel G, Lelievre L, Buttarelli M*, et al.* Contribution of surgery in patients with bulky residual disease after chemoradiation for advanced cervical carcinoma. *Eur J Surg Oncol* 2007;33:498-503.
96. Azria E, Morice P, Haie-Meder C*, et al.* Results of hysterectomy in patients with bulky residual disease at the end of chemoradiotherapy for stage IB2/II cervical carcinoma. *Ann Surg Oncol* 2005;12:332-337.
97. Houvenaeghel G, Lelievre L, Gonzague-Casabianca L*, et al.* Long-term survival after concomitant chemoradiotherapy prior to surgery in advanced cervical carcinoma. *Gynecol Oncol* 2006;100:338-343.
98. Ferrandina G, Margariti PA, Smaniotto D*, et al.* Long-term analysis of clinical outcome and complications in locally advanced cervical cancer patients administered concomitant chemoradiation followed by radical surgery. *Gynecol Oncol* 2010;119:404-410.
99. Pötter R, Georg P, Dimopoulos JCA*, et al.* Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol* 2011;100:116-123.
100. Chargari C, Magne N, Dumas I*, et al.* Physics contributions and clinical outcome with 3D-MRI-based pulsed-dose-rate intracavitary brachytherapy in cervical cancer patients. *Int J Radiat Oncol Biol Phys* 2009;74:133-139.

101. Mahantshetty U, Swamidas J, Khanna N*, et al.* Magnetic resonance image-based dose volume parameters and clinical outcome with high dose rate brachytherapy in cervical cancers--a validation of GYN GEC-ESTRO brachytherapy recommendations. *Clin Oncol (R Coll Radiol)* 2011;23:376-377.
102. Mahantshetty U, Swamidas J, Khanna N*, et al.* Reporting and Validation of Gynaecological Groupe Euopeen de Curietherapie European Society for Therapeutic Radiology and Oncology (ESTRO) Brachytherapy Recommendations for MR Image-Based Dose Volume Parameters and Clinical Outcome With High Dose-Rate Brachytherapy in Cervical Cancers: A Single-Institution Initial Experience. *International Journal of Gynecological Cancer* 2011;21:1110-1116
103. Beriwal S, Bhatnagar A, Heron DE*, et al.* High-dose-rate interstitial brachytherapy for gynecologic malignancies. *Brachytherapy* 2006;5:218-222.
104. Tan LT, Coles CE, Hart C*, et al.* Clinical impact of computed tomography-based image-guided brachytherapy for cervix cancer using the tandem-ring applicator - the Addenbrooke's experience. *Clin Oncol (R Coll Radiol)* 2009;21:175-182.
105. Choan E, Quon M, Gallant V*, et al.* Effective palliative radiotherapy for symptomatic recurrent or residual ovarian cancer. *Gynecol Oncol* 2006;102:204-209.
106. Einhorn N, Lundell M, Nilsson B*, et al.* Is there place for radiotherapy in the treatment of advanced ovarian cancer? *Radiother Oncol* 1999;53:213-218.
107. Tinger A, Waldron T, Peluso N*, et al.* Effective palliative radiation therapy in advanced and recurrent ovarian carcinoma. *Int J Radiat Oncol Biol Phys* 2001;51:1256-1263.
108. Adelson MD, Wharton JT, Delclos L*, et al.* Palliative radiotherapy for ovarian cancer. *Int J Radiat Oncol Biol Phys* 1987;13:17-21.
109. Corn BW, Lanciano RM, Boente M*, et al.* Recurrent ovarian cancer. Effective radiotherapeutic palliation after chemotherapy failure. *Cancer* 1994;74:2979-2983.
110. Firat S, Murray K, Erickson B. High-dose whole abdominal and pelvic irradiation for treatment of ovarian carcinoma: long-term toxicity and outcomes. *Int J Radiat Oncol Biol Phys* 2003;57:201-207.
111. Gelblum D, Mychalczak B, Almadrones L*, et al.* Palliative benefit of external-beam radiation in the management of platinum refractory epithelial ovarian carcinoma. *Gynecol Oncol* 1998;69:36-41.
112. May LF, Belinson JL, Roland TA. Palliative benefit of radiation therapy in advanced ovarian cancer. *Gynecol Oncol* 1990;37:408-411.
113. Fujiwara K, Suzuki S, Yoden E*, et al.* Local radiation therapy for localized relapsed or refractory ovarian cancer patients with or without symptoms after chemotherapy. *Int J Gynecol Cancer* 2002;12:250-256.
114. Ayhan A, Reed N, Gultekin M*, et al.* Textbook of Gynaecologic Oncology. 2nd ed. Ankara: Hünes Publishing; 2011.
115. Dembo AJ. Abdominopelvic radiotherapy in ovarian cancer. A 10-year experience. *Cancer* 1985;55:2285-2290.
116. Thomas GM. Is there a role for consolidation or salvage radiotherapy after chemotherapy in advanced epithelial ovarian cancer? *Gynecol Oncol* 1993;51:97-103.
117. Pickel H, Lahousen M, Petru E*, et al.* Consolidation radiotherapy after carboplatin-based chemotherapy in radically operated advanced ovarian cancer. *Gynecol Oncol* 1999;72:215-219.
118. Sorbe B. Consolidation treatment of advanced (FIGO stage III) ovarian carcinoma in complete surgical remission after induction chemotherapy: a randomized, controlled, clinical trial comparing whole abdominal radiotherapy, chemotherapy, and no further treatment. *Int J Gynecol Cancer* 2003;13:278-286.

119. Lambert HE, Rustin GJ, Gregory WM*, et al.* A randomized trial comparing single-agent carboplatin with carboplatin followed by radiotherapy for advanced ovarian cancer: a North Thames Ovary Group study. *J Clin Oncol* 1993;11:440-448.
120. Einhorn N, Trope C, Ridderheim M*, et al.* A systematic overview of radiation therapy effects in ovarian cancer. *Acta Oncol* 2003;42:562-566.
121. Dinniwell R, Lock M, Pintilie M*, et al.* Consolidative abdominopelvic radiotherapy after surgery and carboplatin/paclitaxel chemotherapy for epithelial ovarian cancer. *Int J Radiat Oncol Biol Phys* 2005;62:104-110.
122. Fyles AW, Dembo AJ, Bush RS*, et al.* Analysis of complications in patients treated with abdomino-pelvic radiation therapy for ovarian carcinoma. *Int J Radiat Oncol Biol Phys* 1992;22:847-851.
123. Whelan TJ, Dembo AJ, Bush RS*, et al.* Complications of whole abdominal and pelvic radiotherapy following chemotherapy for advanced ovarian cancer. *Int J Radiat Oncol Biol Phys* 1992;22:853-858.
124. Mychalczak BR, Fuks Z. The current role of radiotherapy in the management of ovarian cancer. *Hematol Oncol Clin North Am* 1992;6:895-913.
125. Cardenes H, Randall ME. Radiotherapy in epithelial ovarian cancer: state of the art. *Forum (Genova)* 2000;10:335-352.
126. Cmelak AJ, Kapp DS. Long-term survival with whole abdominopelvic irradiation in platinum-refractory persistent or recurrent ovarian cancer. *Gynecol Oncol* 1997;65:453-460.
127. Fletcher GH. Lucy Wortham James Lecture. Subclinical disease. *Cancer* 1984;53:1274-1284.
128. Duthoy W, De Gersem W, Vergote K*, et al.* Whole abdominopelvic radiotherapy (WAPRT) using intensity-modulated arc therapy (IMAT): first clinical experience. *Int J Radiat Oncol Biol Phys* 2003;57:1019-1032.