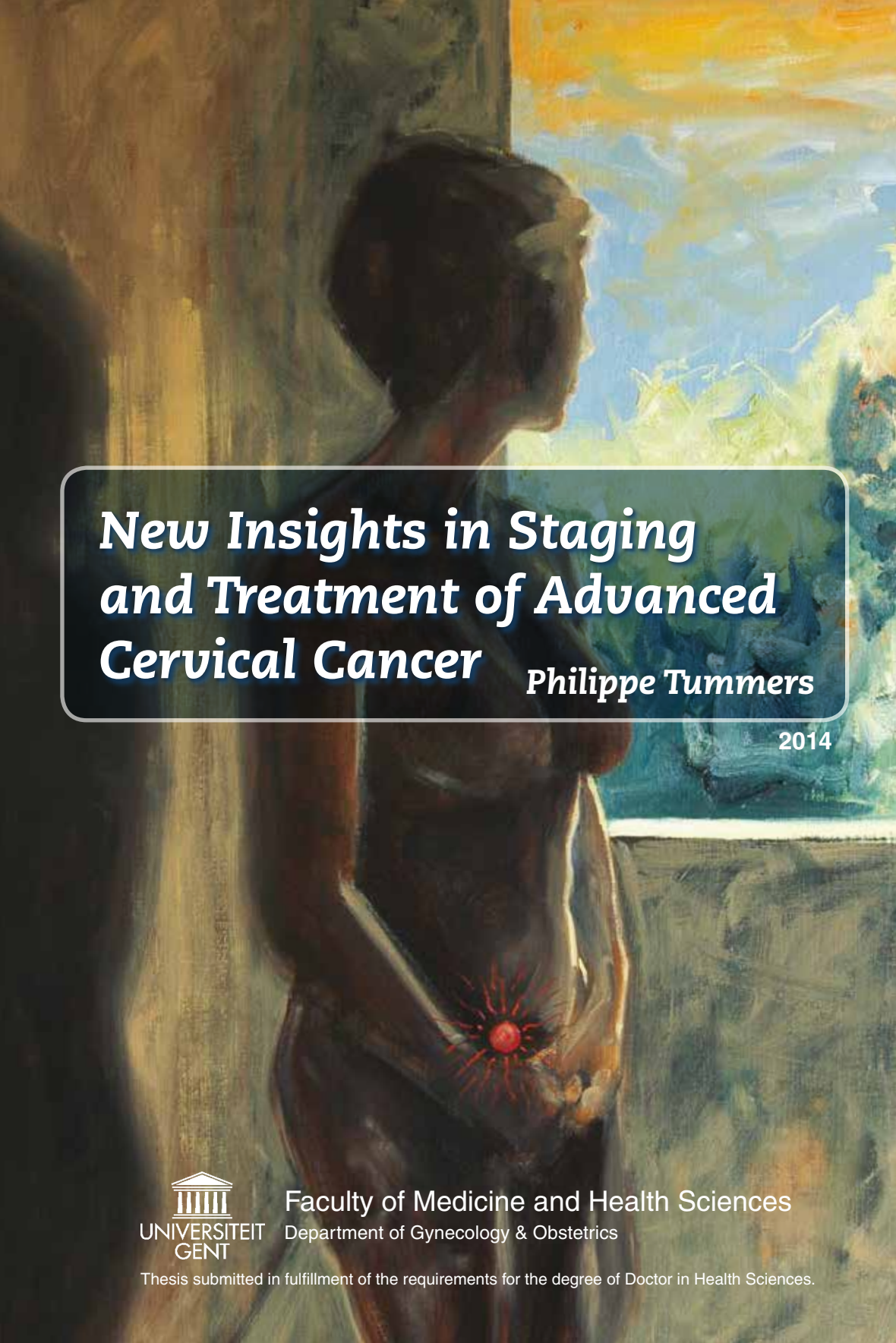

New Insights in Staging and Treatment of Advanced Cervical Cancer

Philippe Tummers

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Thesis submitted in fulfillment of the requirements for the degree of Doctor in Health Sciences.

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New Insights in Staging and Treatment of Advanced Cervical Cancer.

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Abbreviations

BMI	Body Mass Index
BT	Brachytherapy
CA 125	Cancer Antigen 125
CRT	Chemo Radiotherapy
CT	Computer Tomography
EBRT	External Beam Radiotherapy
EBCRT	External Beam Chemo Radiotherapy
EUA	Examination Under Anesthesia
^{18}FDG-PET	2-deoxy-2-18 Fluoro-D-Glucose Positron Emission Tomography
FIGO	International Federation of Gynecology and Obstetrics
HDR	High-Dose Rate
HIV	Human Immunodeficiency
HPV	Human Papillomavirus Virus
IMAT	Intensity-Modulated Arc Therapy
IMAT+C	Intensity-Modulated Arc Therapy with/without concomitant Chemotherapy
IMRT	Intensity-Modulated Radiation Therapy
IOA	Inter Observer Agreement
LACC	Locally Advanced Cervical Cancer
LDR	Low-Dose Rate
LVI	Lymph Vascular Invasion
MRI	Magnetic Resonance Imaging
OARs	Organs At Risk
OS	Overall Survival
OSC	Overall Survival in Complete responses
OSP	Overall Survival in Partial responses
PDR	Pulsed-Dose Rate
PET	Positron Emission Tomography
PFS	Progression Free Survival
PTV	Planning Target Volume
QOL	Quality of Life
RD	Residual disease
RT	Radiotherapy
SCC(-ag)	Squamous Cell Carcinoma antigen
WHO	World Health Organization

Chapter 1: *Summary*

Over the past decades cervical cancer has become significantly less common in those countries where screening has been introduced, nevertheless it is still the second most common cancer in developing countries. Worldwide it is responsible for about 266,000 deaths each year. The International Federation of Gynecology and Obstetrics (FIGO)-staging system is the principal instrument in the staging of cervical cancer. Although it is used for almost a century no data on the accuracy of this staging system are available. Therefore, in order to investigate its reliability and reproducibility, we performed a prospective study to evaluate the interobserver agreement of the examination under anesthesia on which FIGO staging mainly is based. In addition we evaluated possible confounding factors of FIGO staging. The interobserver agreement among experienced investigators is only moderate. This could indicate possible limitations for sharing and comparing results based on this staging system. Our data demonstrated a significant better agreement between experienced investigators compared to the agreement between an experienced and an inexperienced investigator. This implies that clinical gynecological examination is a skill that can be improved by training. A close look to the disagreement patterns on FIGO stage showed that in case of discrepancy the inexperienced investigator tended to underestimate the disease stage (by rating the FIGO stage lower than the rating of the experienced examiner) and consequently recommended surgery in patients that were considered inoperable by the experienced examiner. This could result in a suboptimal treatment with an increased risk of morbidity and higher medical costs. Multivariate analysis could not demonstrate any patient or tumor related characteristics with a significant impact on the interobserver agreement of FIGO staging. In conclusion we could say that our data, demonstrating the importance of experience of the investigators in staging of cervical malignancies, are strong additional arguments for centralization of care in cervical cancer patients.

Since the addition of chemotherapy to radiotherapy, the survival rates of locally advanced cervical cancer (LACC) have improved but are still disappointing. Therefore, the idea of surgery after chemoradiation in case of LACC or bulky disease was adopted. The rationale for this idea is to obtain a better local control that might translate into a better overall survival. One of the concerns regarding surgery following chemoradiotherapy is surgery-related morbidity. The implementation of advanced radiotherapy techniques with a higher radiation dose on the target volume and less damage to the organs at risk creates opportunities to safely perform radical hysterectomy and a tailored lymphadenectomy. Our data demonstrated complication rates of type II hysterectomy after intensity modulated arc therapy (IMAT) with concomitant chemotherapy to be acceptable and comparable to complication rates of radical surgery for low-stage cervical cancer.

In order to reduce the overall toxicity of the treatment in patients with LACC it would be opportune to be able to select patients with residual disease after the initial chemo radiation therapy that would benefit adjuvant treatment. Consequently this would mean that one would be able to avoid additional brachytherapy and/or surgery in patients without residual disease. This could minimalize the treatment toxicity without deteriorating the prognosis. We evaluated the value of cervical biopsy in predicting residual disease after initial chemo radiation therapy. Only in half of the patients with residual disease (sensitivity of 50%) cervical biopsies could prove malignancy. This indicates it is not reliable for evaluating treatment response. We therefore can not recommend routine application of this technique for selecting LACC patients for additional treatment.

Chapter 1: *Samenvatting*

De voorbije decennia is in landen waar een screening naar cervixafwijkingen werd geïntroduceerd de incidentie van baarmoederhalskanker aanzienlijk gedaald. In ontwikkelingslanden daarentegen is cervixcarcinoom echter nog steeds de tweede meest voorkomende kanker bij vrouwen. Wereldwijd is baarmoederhalskanker jaarlijks verantwoordelijk voor ongeveer 266,000 sterftegevallen. De stagering van het cervixcarcinoom gebeurt volgens de richtlijnen van de Internationale Federatie voor Gynaecologie en Verloskunde (FIGO). Hoewel deze reeds bijna een eeuw gebruikt worden, zijn er geen gegevens bekend over de nauwkeurigheid ervan. Wij onderzochten daarom de betrouwbaarheid en reproduceerbaarheid van de FIGO classificatie aan de hand van de hoeveelheid "eensgezindheid" tussen de verschillende onderzoekers bij het bepalen van het FIGO stadium. Bij ervaren onderzoekers was de eensgezindheid betreffende het FIGO stadium matig. Dit kan duiden op eventuele beperkingen van de FIGO classificatie in de bruikbaarheid bij het uitwisselen en vergelijken van resultaten. Uit onze gegevens blijkt daarenboven dat er een significant betere eensgezindheid is betreffende het FIGO stadium tussen ervaren onderzoekers in vergelijking met de eensgezindheid tussen een ervaren en een onervaren onderzoeker. Dit impliceert dat het klinisch gynaecologische onderzoek een vaardigheid is die kan aangeleerd worden. In het geval van onenigheid tussen een ervaren en een onervaren onderzoeker bleek dat de onervaren onderzoeker systematisch de uitgebreidheid van de ziekte onderschatte. Bijgevolg adviseerde deze dan ook vaker heelkunde in gevallen waar de ervaren onderzoeker voor chemo radiotherapie opteerde. Dit kan leiden tot een suboptimale behandeling met een verhoogd risico op morbiditeit en hogere medische kosten. Er konden via multivariate analyse geen tumor of patiënt gerelateerde kenmerken weerhouden worden die de klinische stadiëring van baarmoederhalskanker zouden beïnvloeden. Samenvattend kunnen we stellen dat deze gegevens, die het belang van de ervaring bij stagering van cervixcarcinoom aantonen, sterke aanvullende argumenten zijn voor centralisatie van zorg bij deze patiënten.

De toevoeging van chemotherapie aan radiotherapie zorgde voor een aanzienlijke verbetering in overlevingskansen van patiënten met een lokaal gevorderd cervixcarcinoom. Toch blijven de overlevingskansen teleurstellend. Daarom opperden een aantal onderzoeksgroepen het idee om na de behandeling met chemo radiotherapie een aanvullende hysterectomie te verrichten. De rationale hierachter is dat door het verwijderen van de initiële tumorlokalisatie de potentieel radiotherapie resistente tumorcellen verwijderd worden waardoor een betere lokale controle kan bekomen worden die dan zou kunnen resulteren in betere overlevingskansen. De vrees voor bijkomende toxiciteit ten gevolge van de heelkunde is de voornaamste reden voor de terughoudendheid ten aanzien van deze behandeling. De introductie van geavanceerde radiotherapie, met een hogere stralingsdosis op het doelvolume en minder schade aan de omliggende organen, opent nieuwe perspectieven voor aanvullende heelkunde. Onze data toonden aan dat het aantal complicaties ten gevolge van type II hysterectomie na een initiële behandeling met intensiteit gemoduleerde boog therapie (IMAT) met concomitante chemotherapie aanvaardbaar is en zelfs vergelijkbaar is met deze van radicale chirurgie bij een primair laag stadium cervixcarcinoom.

Teneinde de totale toxiciteit van de behandeling bij patiënten met lokaal geavanceerde ziekte te reduceren zou het opportuun zijn indien we de aanwezigheid van residuele ziekte na de initiële behandeling correct konden inschatten. Patiënten met residuele ziekte zouden dan een aanvullende behandeling kunnen krijgen middels heelkunde of brachytherapy. De patiënten met een complete respons op de initiële behandeling zouden dan gespaard kunnen worden van een nabehandeling. In dit kader onderzochten we de mogelijkheid om door middel van een cervix biopsie een uitspraak te doen over de aanwezigheid van residuele ziekte na de initiële behandeling. De betrouwbaarheid hiervan bleek onvoldoende (sensitiviteit van 50) voor het selecteren van patiënten.

Chapter 2: *Introduction*

2.1 Background information on cervical cancer

Cancer of the cervix is the fourth most common cancer in women worldwide. In 2012, about 528,000 new cases and 266,000 deaths were estimated (7.5% of all female cancer deaths). A large majority of the global burden (around 85%) occurs in the less developed regions, where it accounts for almost 12% of all female cancers. High-risk regions include Melanesia and Southern, Eastern and Middle Africa (in the last two it remains the most common cancer). Rates are lowest in Australia/New Zealand and Western Asia. Worldwide, the mortality rate from cervical cancer is around 50%[1] Global incidence and mortality rates depend upon the presence of screening programs for cervical pre-cancerous lesions[2,3] and of human papillomavirus vaccination[4], which are most likely to be available in developed countries. Due to these interventions, a 75% decrease in incidence and mortality of cervical cancer has been noticed in industrialised countries over the past 50 years. Hence it is not surprising that almost nine out of ten (87%) cervical cancer deaths nowadays occur in the less developed regions.[1]

	INCIDENCE			DEATHS		
	NUMBER	%	RANKING	NUMBER	%	RANKING
World	527624	8,8	4	265653	7,5	4
Europe	33679	2,8	8	13117	2,3	12
Belgium	639	2,3	9	219	2,3	15

TABLE 2.1: cervical cancer Incidence and Deaths (based on GLOBOCAN 2012 reports).[1]

Human papillomavirus (HPV) is the key factor behind the development of cervical neoplasia and cervical cancers and a persistent infection by an oncogenic HPV type is a condition sine qua non[5,6,7,8]. The presence of HPV in virtually all cervical cancers (worldwide HPV prevalence in cervical carcinomas is 99.7%) implies the highest worldwide attributable fraction for a specific cause of cancer.

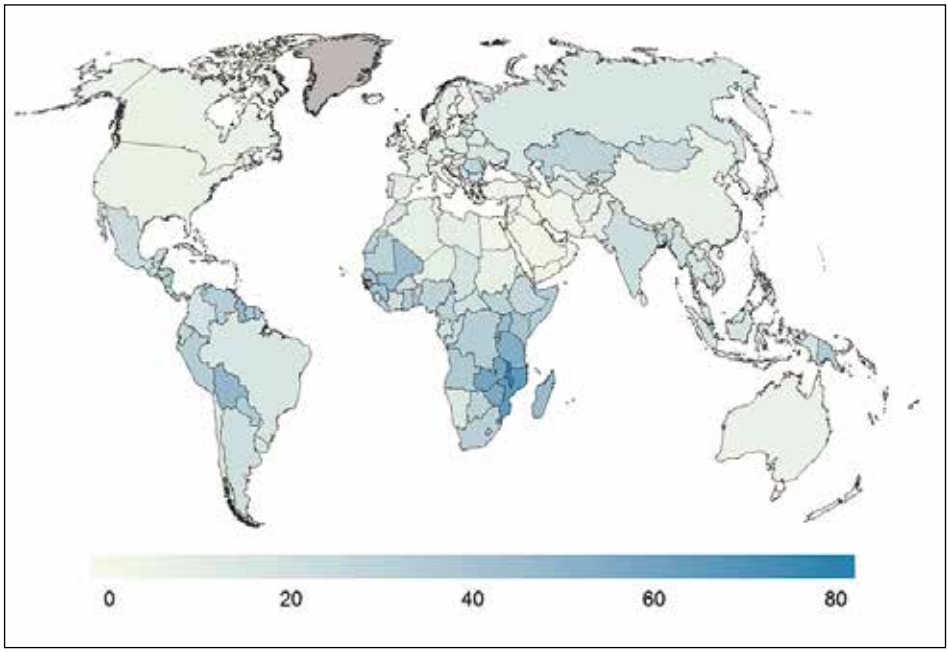

FIGURE 2.1: Estimated Cervical Cancer incidence worldwide in 2012 (GLOBOCAN 2012). [1]

Target zone for infection is the epithelial transformation zone. Genital HPV types (over 40 subtypes) are subdivided into groups based on their oncogenic potential. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 are considered to be of high oncogenic risk (High Risk HPV)[9]. The first two, HPV types 16 and 18 account for approximately 50% and 20% of all cervical cancers[10,11]. The two available vaccines against HPV 16 and 18 (®Gardasil (Merck) and ®Cervarix (GlaxoSmithKline)) were evaluated in large randomized controlled trials and both were found nearly 100% effective in preventing new infections in previously unaffected women[12,13,14] and thereby have the potential to reduce the risk on cervical cancer by more than 70%[4]. However, affordable pricing is the most critical factor to facilitate the introduction of HPV vaccines in low- and medium-resource countries in the short term[15]. In addition in these regions the vast majority of women infected with human immunodeficiency virus (HIV) will be co-infected with human papillomavirus (HPV). The interaction between the two sexually transmitted infections appears to be related to the alteration in cell-mediated immunity in HIV infected persons, increased susceptibility, and possibly reactivation of a latent HPV infection.[16]

Over three-quarters of cervical cancer cases occur in 25-64 year olds. There are two peaks in the age-specific incidence rates: the first in women aged 45-49 and the second in women aged 75-79. The first peak is related to many women becoming sexually active in their late teens/early 20s, giving rise to an increase in HPV infections. The second peak is due to increasing cancer incidence with age and increased altered relationships during midlife.

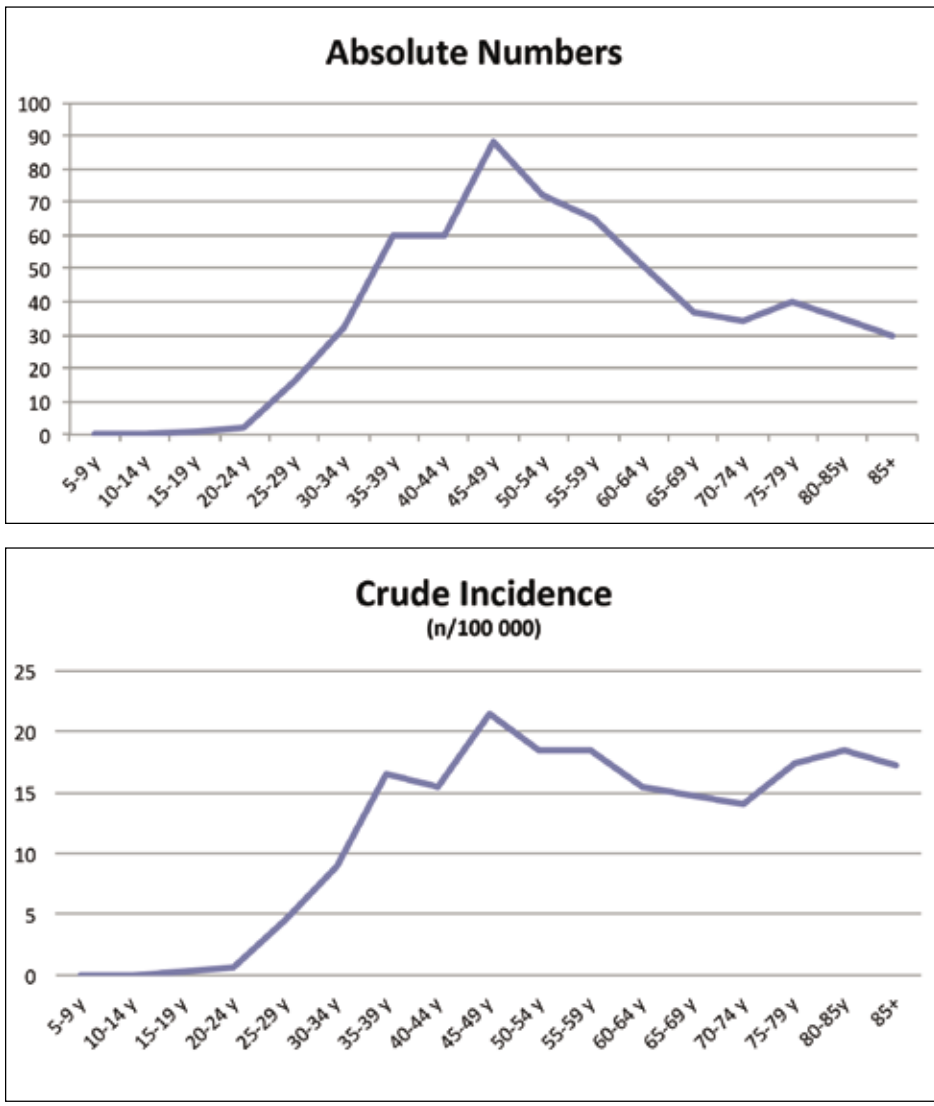

FIGURE 2.2: Age distribution of absolute numbers (a) and crude incidence (b) of cervical cancer in Belgium (based on data 2011).[17]

The most common histologic types of cervical cancer are squamous cell carcinoma and adenocarcinoma, accounting for approximately 70% and 25% each. The other 3 to 5% consist of neuroendocrine (predominantly small cell carcinoma) and other rare cell types (the WHO histological classification is shown in TABLE 2.2).

WHO histological classification of tumours of the uterine cervix
Epithelial tumours
Squamous tumours and precursors
Squamous cell carcinoma, not otherwise specified
Early invasive (microinvasive) squamous cell carcinoma
Squamous intraepithelial neoplasia
Benign squamous cell lesions
Glandular tumours and precursors
Adenocarcinoma
Mucinous adenocarcinoma
Endometrioid adenocarcinoma
Clear cell adenocarcinoma
Serous adenocarcinoma
Mesonephric adenocarcinoma
Adenosquamous carcinoma
Neuroendocrine tumours
Undifferentiated carcinoma
Mesenchymal tumours and tumour-like conditions
Leiomyosarcoma
Endometrioid stromal sarcoma, low grade
Undifferentiated endocervical sarcoma
Mixed epithelial and mesenchymal tumours
Carcinosarcoma (malignant müllerian mixed tumour)
Adenosarcoma
Melanocytic tumours
Malignant melanoma
Blue naevus
Miscellaneous tumours
Tumours of germ cell type
Lymphoid and haematopoetic
Malignant lymphoma (specify type)
Leukaemia (specify type)
Secondary tumours

TABLE 2.2: *WHO Classification of Histological types cervical cancer (short version).*[23] *For the complete version see http://screening.iarc.fr/atlasclassifwho.php?lang=1*

The incidence of invasive cervical adenocarcinoma has increased dramatically over the past few decades[18,19,20]. Several causative factors have been proposed explaining this trend: 1) increasing prevalence of specific HPV variants that are associated more with adenocarcinoma[6], 2) exposure to exogenous (e.g. hormonal contraception, hormonal substitution therapy) [21,22] and endogenous (e.g. obesity) oestrogens.

2.2 Staging of cervical cancer

Cancer staging is one of the fundamental activities in oncology and is of pivotal importance to modern management of cancer patients. The purpose of cancer staging is to reach an uniform/unified terminology that is able to provide appropriate prognosis to the patients, to enhance the exchange of information among health professionals, to compare outcome between centres and to create a common language to facilitate making diagnoses and treatment plan. To achieve this objective, staging systems should be evidence-based, reproducible and user-friendly.

Over the years, most staging systems for gynaecological malignancies have shifted from a clinical to a surgical-pathological basis. In contrast to other gynecological cancers, cervical cancer staging remains mainly a clinical staging. This is because the majority of cervical cancers take place in low resource countries where additional staging tools are not generally available.

Cervical cancer staging is the oldest staging system in the literature, dating back to 1928 when, for the first time, physicians grouped cancer of the cervix uteri into different stages according to the extent of tumor growth. Since then, the International Federation of Gynecology and Obstetrics (FIGO) has developed a widely accepted staging system for cervical cancer[24]. A latest update of the FIGO staging system was published in 2009 by Pecorelli et al.[25]. The FIGO stage is assigned at the time of diagnose. Stages are defined by tumor size and extension of disease beyond the cervix to adjacent tissues including vagina, parametria, sacrouterine ligaments, pelvic sidewalls, bladder, or rectum. In this staging system,

Primary tumor (T)		
TNM	**FIGO**	**Surgical-Pathologic Findings**
TX		Primary tumor can not be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ (pre-invasive carcinoma)
T1	I	Cervical carcinoma confined to the cervix (disregard extension to the corpus)
T1a	IA	Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less; vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion ≤ 3.0 mm in depth and ≤ 7.0 mm in horizontal spread
T1a2	IA2	Measured stromal invasion > 3.0 mm and ≤ 5.0 mm with a horizontal spread ≤ 7.0 mm
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T1b2	IB2	Clinically visible lesion > 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T2a2	IIA2	Clinically visible lesion > 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or non-functional kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or non-functional kidney
T4	IV	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis
T4a	IVA	Tumor invades mucosa of bladder or rectum
T4b	IVB	Tumor extends beyond true pelvis
Regional lymph nodes (N)		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
Distant metastasis (M)		
M0	No distant metastasis	
M1	Distant metastasis (including peritoneal spread; involvement of supra-clavicular, mediastinal, or para-aortic lymph nodes; and lung, liver, or bone)	

TABLE 2.3: TNM and FIGO classification of cervical cancer.

cervical cancer is staged predominantly by physical pelvic examination. This pelvic examination is ideally performed under anaesthesia (EUA), which allows optimal clinical evaluation. Some additional examinations are allowed: hysteroscopy, cystoscopy, proctoscopy, abdominal ultrasound, intravenous pyelogram, and imaging with a plain radiograph of the lungs and skeleton. These additional tests are not mandatory for every patient but when performed results can help in staging. Findings of optional examinations, e.g. laparoscopy, ultrasound, Computer Tomography (CT) scan, Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) scan are of value for planning therapy but, because these are not generally available and the interpretation of results is variable, the findings of such studies should not be the basis for changing the FIGO staging.

The limitations of FIGO staging are well appreciated. The most important being lymph node status, which, although an important prognostic parameter, is not incorporated.[26]

The clinical assessment of parametrial and sidewall invasion can be difficult. These limitations can lead to under- or overstaging of some patients. Clinical staging appears to perform best for early or late stage disease, but less well for stages that depend largely upon assessment of tumor size or local spread. For these reasons, additional testing modalities (MRI, CT, PET-CT) are used (when available) to evaluate cervical cancer. The results of these tests are used for planning treatment.[27, 28]

Although FIGO staging is often reported in treatment planning, the International Federation of Gynecology and Obstetrics has always maintained that staging is intended for comparison purposes only and not specifically as guide for therapy.

The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) created a TNM classification system that is parallel to the FIGO system[29]. If a case was treated surgically, the pathologic TNM nomenclature (pTNM) is appropriate to report the pathological extent of the disease and

it can help in decision-making on adjuvant treatment and in reporting prognosis to patients. It should, however, not be used to alter the initial (clinical) FIGO staging.

FIGO Stage	Number	Average age
I	257	48,7
II	53	57,7
III	96	57,4
IV	63	65,4
Unknown stage	154	60,5
Total number cervical cancers	623	55,4
Carcinoma in situ of cervix uteri	2926	36,6

TABLE 2.4: Number of new diagnoses of cervical cancer and average age per stadium in Belgium [30].

Although used for almost a century as the principal instrument in staging (and indirect in decision making) of cervical cancer no data on the accuracy of FIGO staging are available. Therefore, in order to investigate its reliability and reproducibility, we performed a prospective study (see chapter 4) to investigate the interobserver agreement of the examination under anesthesia (EUA) on which FIGO staging (mainly) is based. In addition we evaluated it on possible confounding factors.

2.3 Prognosis of cervical cancer

Worldwide the five-year overall survival (OS) rate is estimated to be 65%, in Belgium it is 69,8%. These OS rates depend on the extent of the disease: in small tumors, limited to the cervix, the five-year survival rate is 93%. As shown in TABLE 2.5, the 5y-OS decreases dramatically in case of disease extension beyond the pelvis or distant metastases.[31] In Belgium, as in most industrialized countries, the disease is diagnosed in the majority of cases at an early stage. This explains the relative high 5y-OS rate. Research by the Organization for Economic Cooperation and Development shows that this relative 5y-OS in Belgium is similar to that in other European countries. Based on data for the period 2002-2004 the survival in Norway is significantly better than in Belgium, while that of the

United Kingdom and Ireland is worse[32]. The EUROCARE study, which is based on patients who were diagnosed between 1995 and 1999 and were followed until December 2003, reports similar findings[33].

FIGO Stage	5-Year Observed Survival Rate
IA	93%
IB	80%
IIA	63%
IIB	58%
IIIA	35%
IIIB	32%
IVA	16%
IVB	15%

TABLE 2.5: The 5-year observed survival rates based on the 7th edition of the AJCC staging manual from data collected by the National Cancer Data Base, based on people diagnosed between 2000 and 2002.

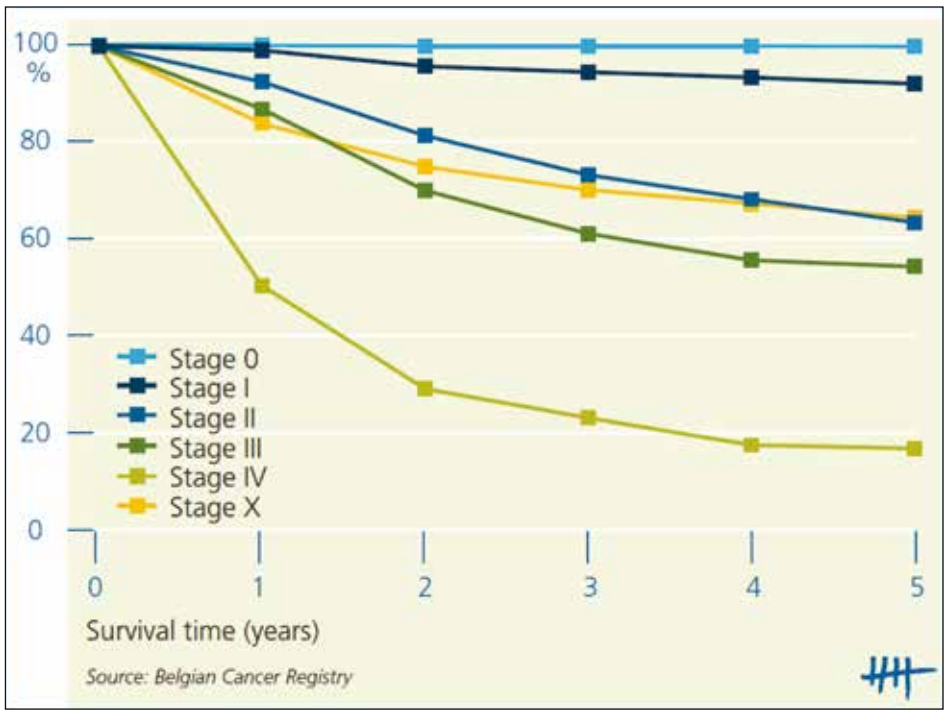

FIGURE 2.3: Five-year survival for in situ and invasive cervical cancer in Belgium (2004-2008), per stage 30.

The stage at diagnosis and survival after diagnosis are strongly influenced by the socio-economic status. Women who live in areas with more poverty are 20% more likely to be diagnosed with late-stage cervical cancer than those in a richer area. Regardless of the stage at which they are diagnosed, women who live in poorer areas have a lower 5y-OS (about 7%).[34]

2.4 Treatment of primary cervical cancer

Cervical cancer treatment depends on disease stage and tumor size. In non-bulky tumors (<4cm) confined to the cervix or with minimal extension to the proximal vagina (early stage cervical cancer), (radical) surgery is usually primary opted for. Radiotherapy in combination with chemotherapy (CRT) is the treatment of choice in all other, non-metastasized patients (locally advanced cervical cancer). Palliative chemotherapy and palliative radiation therapy are usually the choice in case of metastatic setting (stage IVB).[35, 36]

2.4.1 Treatment of early stage cervical cancer

The extent of the hysterectomy depends on the size and characteristics of the disease. Tumors of limited size without aggressive characteristics (FIGO IA1or IA2 without lymph vascular invasion (LVI)) can be treated by conisation in order to conserve fertility or by simple hysterectomy in case of completed family planning. Tumors with a diameter larger than 7mm or with an infiltration depth of more than 5 mm confined to the cervix or with minimal extension to the proximal vagina are mainly treated with radical (Wertheim) surgery when there is no desire to conceive. The first large series (500 patients) of radical hysterectomy in the treatment of cervical cancer was reported by Ernst Wertheim in 1912.[37] Since then there have been several variations in the surgical technique of hysterectomy. The radical hysterectomy today is commonly categorized by amount of parametria resected. These variations are, based on their extent, traditionally divided in five classes as described by Piver et al. in 1974 (called Piver classes).[38] The first three classes are used in the primary treatment of cervical carcinoma.

Piver class I hysterectomy is a slight extension of a simple hysterectomy with removal of a small part of the parametrium. The Piver class II hysterectomy removes a more generous part of the vaginal cuff, ligates the uterine artery on the medial side of the ureter (but does not dissect it from the vesico-uterine ligament), and removes the inner one third of the cardial ligament. The Piver class III operation with removal of all of the parametrium and para-vaginal tissue in addition to the pelvic lymph nodes is considered the classic Wertheim-Meigs procedure. Landoni et al.[39] demonstrated that Class II and class III radical hysterectomies are equally effective in surgical treatment of cervical carcinoma, but class II is associated with a lesser degree of late complications. The last two classes (Piver IV and V) are more extensive procedures, generally reserved for patients with recurrent disease.[38]

Surgical advances in the last decades have put attention on quality of life (QOL) of patients. This has led to a growing trend for nerve sparing surgery in order to decrease urologic and gastrointestinal morbidities.[40] In addition, fertility conserving surgery with trachelectomy seems to be safe in certain subsets of patients.[41]

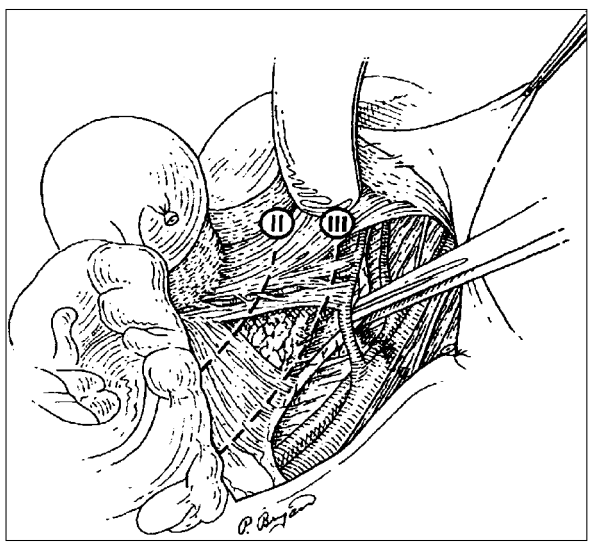

FIGURE 2.4: Piver class II and III radical hysterectomy – image from the right side wall (Piver MS, 1974) .[38]

The description and specification of anatomic landmarks in Piver's classification does not allow for precise reproducibility. As a consequence, the extent of parametrial resection may vary substantially across institutions and surgeons, even if the same terminology is used. Therefore Querleu and Morrow[42] published a classification system proposal (slightly adapted in 2011 by Cibula[43]) describing four types of radical hysterectomy (A-D), which can be precisely defined on a three-dimensional anatomical template and includes nerve-sparing procedures. This new system is more and more promoted to become the new standard.

Recent data indicate non-radical surgery (simple hysterectomy + pelvic lymphadenectomy) for the treatment of early stage cervical cancer (max IB1 (< 2cm)) seems to be a safe and reasonable option in well-selected patients who have favorable prognostic factors. This approach reduces operative morbidity[44] (Bouchard-Fortier GO 2014). We are waiting for the results of three large prospective trials (SHAPE[45], GOG-0278[46]; ConCerv[47]) on this topic.

New Classification System	Corresponding Historical Types
A	Extrafascial hysterectomy
B	Piver Type II radical hysterectomy
C1	Nerve-sparing radical hysterectomy
C2	Piver Type III radical hysterectomy
D	Laterally extended parametrectomy

TABLE 2.6: Proposed classification system and corresponding historical types of radical hysterectomy.[48]

2.4.2 Treatment of bulky and locally advanced cervical cancer

It was the discovery of radium more than a century ago that revolutionized the management of cervical cancer. Before the 20th century, inoperable equated to untreatable. By the early 1920s, the combination of both external beam deep x-ray treatment and brachytherapy had become the standard. Over the next 80 years or so, this basic treatment paradigm was

never improved. It was not until 1999 that the outcome of cervix cancer radiotherapy chanced significantly. Since the meta-analysis of Green et al in The Lancet in 2001[49] the combination of radiotherapy (RT, unless mentioned otherwise this equals always external beam radiotherapy) and chemotherapy followed by brachytherapy has been recommended as standard treatment for bulky (>4 cm) IB and locally advanced cervical cancer (LACC) up to stage IVA. The additional effect of chemotherapy, when added to radiotherapy, was evaluated again in 2005 by Green et al.[50] in a Cochrane review of 24 trials concerning 4921 patients. The review strongly suggests that chemoradiation (CRT) improves OS and progression free survival (PFS), whether or not platinum was used, with absolute benefits of 10% and 13% respectively. Chemoradiation also showed significant benefit for local recurrence and a suggestion of a benefit for distant recurrence. This puts forward the hypothesis that concomitant chemotherapy may afford radio-sensitisation and systemic cytotoxic effects. Acute haematological and gastrointestinal toxicity was significantly greater in the concomitant CRT group.

Conventional pelvic RT uses bony landmarks as seen on planar X-rays to define the target volume. Treatment is delivered either with anterior and posterior opposed fields or with a 4-field box technique, which reduces the volume of the small bowel in the treated volume. Conventional RT, while highly effective, delivers ionizing radiation not only to the target tumor volume but also to significant areas of adjacent normal tissue, accounting for many of the observed acute (diarrhea, cystitis) and late (small bowel obstruction from luminal narrowing and fibrosis, chronic proctitis, sigmoid strictures, ureteral stricture, chronic hemorrhagic cystitis) tissue toxicities.[51, 52] These potential complications limit the total radiation dose that can be safely delivered.

In an attempt to increase the ratio of prescribed radiation dose given to the tumor (Planning Target Volume (PTV)) as opposed to the Organs At Risk (OARs), novel RT techniques have been developed. At first, the use

of cerrobend blocks and multileaf collimators allowed the beams to match or conform the outline of the target (conformal radiotherapy). Intensity-modulated radiotherapy (IMRT) is an extension of this principle. By varying the intensity within the radiation beam, it allows dose diversity within the same beam angle leading to the possibility of dose intensification or more accurate shaping (even around concavities). Hence, dose distribution with IMRT fits more precisely to the target volume, producing a concave shape at the posterior aspect of the PTV, reducing dose to the rectum, and also anteriorly, curving around the lateral lymph node target volume while sparing more of the central bladder and bowel[53] resulting in reduced toxicities.[51] In cervical cancer, where the target volume has a concave shape with the bladder and small intestine positioned within, a large number of intensity-modulated beams are needed to ensure an adequate target coverage and sufficient sparing of the OARs. Intensity-modulated arc therapy (IMAT), with an infinite number of beams, is a new means to deliver IMRT. It is a fast and easy way to deliver a large number of beam incidences achieving beam intensity modulation by superimposing multiple arcs or by regulating the dose rate and the multileaf collimator movement dynamically and relatively to the speed of the rotating gantry.

The addition of brachytherapy during or following EBRT is still considered as a standard component of radical treatment of LACC.[35, 36] Brachytherapy involves the application of a radioactive source inside or in close proximity to the tumor which allows very localized irradiation resulting in a high dose to the tumor with relative sparing of the surrounding normal structures. Brachytherapy for cervical cancer can be performed using an intracavitary (placing the radioactive source into a cavity of the body, in this case the vagina, uterus or cervix) or interstitial approach (placing needles or catheters in/around tumor using a transperineal and/or vaginal approach). The choice of technique depends primarily on disease extent, anatomy and the experience in the department. In brachytherapy for cervical cancer different dose regimens are used, referring to the level with which the radiation is delivered (expressed in Grays per hour (Gy/h)): 1)

Low-dose rate (LDR) brachytherapy involves implanting radiation sources that emit radiation at a rate of up to 2 Gy/h. 2) High-dose rate (HDR) brachytherapy is when the rate of dose delivery exceeds 12 Gy/h. Most HDR treatments are performed on an outpatient basis. 3) Pulsed-dose rate (PDR) brachytherapy involves short pulses of radiation, typically once an hour, to simulate the overall rate and effectiveness of LDR treatment. Overall clinical outcomes and toxicities are felt to be similar between LDR, HDR and PDR.[54] However, a key advantage of HDR treatment is that each dose can be delivered on an outpatient basis with a short administration time providing greater convenience for many patients.

Over the last decade dramatic advances have been made in brachytherapy for cervical cancer. Treatment planning has evolved from two-dimensional to three-dimensional, incorporating magnetic resonance imaging and/or computed tomography into the treatment paradigm. This allows for better delineation and coverage of the tumor, as well as improved avoidance of surrounding organs. Consequently, image guided adaptive brachytherapy can achieve better local control with a reduction in morbidity to adjacent organs such as bladder, rectum and sigmoid.[55]

The advantages of brachytherapy come at the expense of requiring an invasive procedure to be carried out, and the benefits must be balanced against possible complications. Overall, in the era of image-guided brachytherapy, later grade ≥3 rectal, bowel, and bladder toxicity rates are typically in the 10% range.[56] The probability of severe vaginal morbidity (grade ≥3) was around 4%. However, mild and moderate vaginal symptoms were still pronounced frequently (grade ≥1 around 90%; grade ≥2 around 30%).[57]

2.4.3. Ghent treatment protocol for bulky and locally advanced cervical cancer

Since the meta-analysis of Green et al[49], the combination of external beam radiotherapy and chemotherapy followed by brachytherapy has been

recommended as standard treatment for bulky IB and LACC up to stage IVA. Nevertheless, the meta-analysis showed a rather limited survival benefit for LACC in the group with FIGO stages III–IVA[49, 50]. Therefore, some groups adopted the idea of performing completion surgery after CRT. The rationale for performing surgery following CRT in locally advanced or bulky cervical cancer is to obtain a better local control by resecting potential radiation therapy-resistant tumor foci. The improved local control might then be translated into better OS. In addition, complementary surgery permits the assessment of the pathological response. The concern for surgery-related morbidity such as fistulas and bowel or bladder injuries, however, has made completion surgery not widespread. The introduction of advanced radiation therapy techniques such as IMAT has shown to result in a better therapeutic ratio concerning pelvic tumors[51, 58, 59].

This creates new opportunities for completion surgery. We developed a schedule of preoperative CRT that delivers a higher dose to the primary tumor and involved lymph nodes without compromising the dose to the rest of the clinical target volume or organs at risk.

The treatment protocol was approved by the local ethics committee (referred to as n° B67020072880). Clinical staging was obtained by pelvic examination by an experienced gynecologic oncologist and a radiation oncologist. In addition, all patients were staged by total body ^{18}FDG PET-CT and pelvic magnetic resonance imaging (MRI). A panel of experienced radiologists and nuclear medicine physicians reviewed all images. All patients were thoroughly discussed multidisciplinary before inclusion.

After diagnosis, patients underwent neoadjuvant IMAT, if possible combined with weekly cisplatin (40 mg/m^2) administration (IMAT ± C).[60]

After completing IMAT ± C, the possibility to perform adjuvant surgery was evaluated based on imaging (^{18}FDG PET-CT and MRI) and gynecologic examination. All results were multidisciplinary discussed. If considered

not resectable, additional brachytherapy was administered. If considered resectable, type II Wertheim hysterectomy ± pelvic lymphadenectomy was performed 4 to 6 weeks after completing IMAT ± C. Pelvic lymphadenectomy was performed whenever there were positive lymph nodes present on one of the ^{18}FDG PET-CTs. From August 2008 onward, lymph node dissection was limited to the lymph node regions that were positive on one of the ^{18}FDG PET-CTs. The reason for this change was 3-fold: first, pelvic lymphadenectomy after IMAT ± C only revealed histologically positive lymph nodes in 8.8% of the patients; second, these positive lymph nodes were always found in the lymph node region that was positive on the pre-treatment PET-CT; third, some patients developed severe lymphocoeles and lymph edema after extensive pelvic lymphadenectomy.

In a prospective study we investigated the surgery-related morbidity after neo-adjuvant IMAT CRT. In addition we analyzed the value of a core biopsy to predict residual disease after the initial treatment.

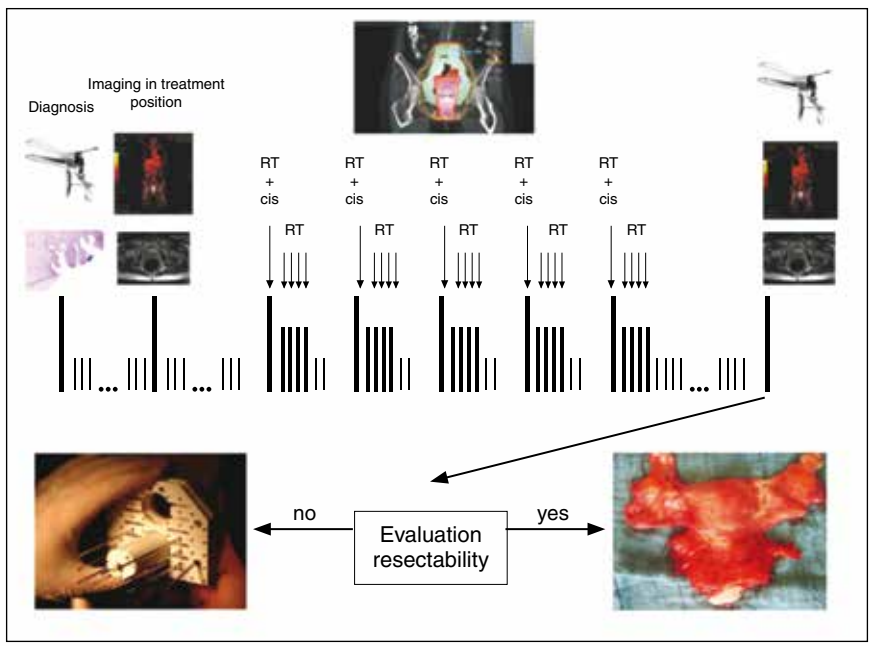

FIGURE 2.5: Schematic representation of the treatment protocol (Figure courtesy K. Vandecasteele).

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Chapter 3: *Relevance of the work*

The introduction of new techniques in staging and treatment of cervical cancer raises questions on their overall applicability. Although advanced imaging techniques have proven their value in assessing the extent of local disease and distant spread including lymph node invasion, results can not be included in a staging system as long as these tools are not widely accessible. The inclusion of its results would imbalance the staging system resulting in an incomparability of the obtained results. The success of the International Federation of Gynecology and Obstetrics (FIGO) clinical-based staging system of cervical cancer is due to the fact that it can be used worldwide without necessity of advanced imaging techniques or surgical interventions. Nevertheless from an ideal staging system to be used in comparing treatment results and prognosis, it is expected to be reliable and reproducible. Although used for almost a century no data on the accuracy of FIGO staging are available. We looked at this topic by investigating two main questions:

- **How reliable is clinical FIGO staging in cervical cancer?**

  In a prospective study we were the first to examine the interobserver agreement of the examination under anesthesia on which FIGO staging is based, in order to investigate its reliability and reproducibility **(publication 1**).

- **Are there patient, tumor or investigator related characteristics that influence the reliability of clinical FIGO staging in cervical cancer?**

  We examined the impact of the experience of the investigator and patient specific or tumor related characteristics on the reliability of the FIGO staging (**publication 2**). Our conclusions could help to optimize staging in cervical cancer.

The standard treatment of bulky and locally advanced cervical cancer consists of external beam chemo-radiotherapy followed by brachytherapy. Results of this treatment stay disappointing. To obtain a better local control that might be translated into a better overall survival some groups had adopted the idea of performing completion surgery after chemo radiotherapy. Nevertheless there has been a lot of concern regarding morbidity in case of complementary surgery. The introduction of advanced radiation therapy techniques (such as IMAT) significantly lowered grades 3 and 4 radiotherapy-related toxicity and reduced the radiation dose to the suspensory ligaments of the uterus. This created new opportunities for completion surgery. Concerning this topic we investigated following questions:

- **What is the induced per- and postoperative morbidity of completion surgery after IMAT±C for bulky and LACC patients? (chapter 5, publication 3).**
- **How reliable is a core biopsy in predicting residual disease after the initial treatment with IMAT±C for bulky and LACC patients? (chapter 5, publication 4).**

The first author contributed to the concept and the design of the studies, patient selection and acquisition, analysis and interpretation of the obtained data. He prepared and edited all papers.

Chapter 4: *FIGO Staging*

4.1: Publication 1: Interobserver Variability of the International Federation of Gynecology and Obstetrics Staging in Cervical Cancer

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The authors declare no conflicts of interest.

Keywords: FIGO staging; Cervical cancer; Interobserver variability; Examination under anesthesia

ABSTRACT

Objective

The objective of this study was to assess the interobserver variability of pelvic examination under anesthesia (EUA) in cervical cancer.

Methods

Subsequent patients undergoing a staging procedure under anesthesia for primary cervical cancer were enrolled in the study. All clinicians assessed "blinded" tumor size, and the involvement of vagina, parametria, sacro uterine ligaments, pelvic sidewalls, bladder, and/or rectum. Items were scored varying from 1 ("certainly no involvement"), 2 ("not sure about involvement"), to 3 ("involvement"). Each individual decided on the International Federation of Gynecology and Obstetrics (FIGO) stage; also, the urge for imaging and treatment proposal were accounted for. Final FIGO staging was obtained by consensus of the team. Investigators were classified as experienced after more than 50 EUAs. All others were classified less experienced. The free-marginal κ values between experienced and less experienced investigators were calculated for all previously mentioned items.

Results

Between February 2009 and December 2010, a total of 86 patients were enrolled. Among experienced investigators, a moderate interobserver agreement was found with regard to FIGO stage (free-marginal κ value of 0.49) and an excellent interobserver agreement on their proposed therapy (free-marginal κ value of 0.84). A lower level of agreement was found when comparing experienced with less experienced investigators: only a slight level of agreement on FIGO stage and a substantial agreement on their therapy proposal (free-marginal κ values of 0.03 and 0.66).

Conclusions

We describe only a moderate interobserver agreement on clinical staging

of patients with cervical cancer. The interobserver agreement increases in the group of experienced doctors, indicating that EUA can be learned.

INTRODUCTION

Cancer of the uterine cervix is the second most common cancer in women worldwide, and 80% of new cases are diagnosed in developing countries.[1] Patients with cervical cancer are staged at the time of diagnosis. Cervical cancer staging is the oldest staging in the literature, dating back to 1928 when, for the first time, physicians grouped cancer of the cervix uteri into different stages according to the extent of tumor growth. Since then, the International Federation of Gynecology and Obstetrics (FIGO) has developed a widely accepted staging system for cervical cancer. The FIGO stages are defined by tumor size and extension of disease beyond the cervix to adjacent tissues including vagina, parametria, sacro uterine ligaments, pelvic sidewalls, bladder, or rectum*.[2] In this staging system, cervical cancer is staged predominantly by physical pelvic examination. Pelvic examination is ideally performed under anesthesia (EUA), which allows optimal clinical evaluation. Some additional examinations for establishing the stage of cervical cancer are allowed: hysteroscopy, cystoscopy, proctoscopy, abdominal ultrasound, intravenous pyelogram, and imaging with a plain radiograph of the lungs and skeleton. These additional tests are not mandatory for every patient.

Results of other possible investigations such as magnetic resonance imaging (MRI) and positron emission tomography (PET) are not taken into account for FIGO staging because these imaging techniques are not widely available.

Although widely used, the reliability and reproducibility of this staging system are unclear. We therefore assessed the interobserver variability of EUA in cervical cancer. To our knowledge, this is the first article addressing this topic.

* Addition on advise of a member of the examination committee: Clinical examination, even in ideal circumstances, can be difficult. Tumor oedema, inflammatory changes, remnants of previous surgery or a recent biopsy can make it difficult to determine the exact tumor size or to evaluate parametrial and sidewall invasion.

MATERIALS AND METHODS

Subsequent patients with pathological proof of cervical cancer underwent an EUA. During this examination, all patients were evaluated by a team of gynecologist-oncologists and radiotherapists. We classified doctors as experienced in this evaluation after more than 50 EUAs. All others were classified as less experienced. All involved clinicians assessed individually the tumor size (in centimeters) and the involvement of vagina, parametria, sacro uterine ligaments, pelvic sidewalls, bladder, and rectum. An involvement of these different items was scored, varying from 1 ("no involvement"), 2 ("not sure about involvement") and 3 ("involvement"). Each individual decided on the FIGO stage and need for additional imaging, as well as treatment proposal. All patients were examined by at least 3 investigators, including at least 2 experienced investigators. Final FIGO staging was obtained by consensus of the team. We calculated the level of agreement for all previously mentioned items, first between experienced investigators and second between both less experienced investigators and experienced investigators. The free-marginal κ values were calculated to obtain the level of agreement on the different topics. For interpretation of free-marginal κ, see TABLE 1.[3]

κ	Level of Agreement
<0	Less than chance agreement
0.01-0.20	Slight agreement
0.21-0.40	Fair agreement
0.41-0.60	Moderate agreement
0.61-0.80	Substantial agreement
0.81-0.99	Almost perfect agreement

TABLE 1: Interpretation of free-marginal.κ[3]

RESULTS

Between February 2009 and December 2010, a total of 86 patients with cervical cancer were enrolled in this study. The mean age of investigated patients was 48 years; their mean body mass index (BMI) was 26 kg/m2. Squamous cell carcinoma was the predominant histology (76.5%). A large majority of patients were

at advanced stage of disease (>IB1) at the time of diagnosis (69%). Patient characteristics are summarized in TABLE 2.

An analysis of the calculated free-marginal κ results demonstrate only a fair to moderate agreement between experienced investigators on tumor involvement of vagina, sacrouterine ligaments, and parametria. The agreement on tumor size is also moderate. Consequently, these findings result in a moderate level of agreement on FIGO stage. Nevertheless, these rather disappointing agreement levels do not reflect on the agreement on the choice of therapy, where we found an almost perfect level of agreement (TABLE 3).

When calculating the agreement between an experienced investigator and a less experienced investigator, we found lower κ values, indicating less agreement. This is reflected in the fact that this comparison showed only a slight level of agreement on FIGO stage. The κ value on the proposed therapy is 0.66, meaning a substantial agreement (TABLE 4).

Patient Characteristics	n = 86 (100%)
Age, mean (range), y	48 (28-88)
Mean BMI (range), kg/m^2	26 (17-40)
Tumor type, % Squamous cell carcinoma (SCC) Adenocarcinoma	 76.5 23.5
Tumor markers For squamous cell carcinoma SCC, mean (range), mg/L SCC > 2 mg/L, % For adenocarcinoma CA-125, mean (range), U/mL CA-125 > 35 U/mL, %	 3.6 (0.1-233) 31 17 (9-625) 23.5
FIGO stage (consensus), % Stage IA1 Stage IA2 Stage IB1 Stage IB2 Stage IIA1 Stage IIA2 Stage IIB Stage IIIIA Stage IIIB Stage IVA Stage IVB	 0 1.2 29.1 7 3.5 1.2 45.4 0 8.1 4.5 0

TABLE 2: Patients characteristics.

	Free-Marginal κ	*p*	Interpretation of κ: Level of Agreement
Size of the tumor	0.42	0.07	Moderate
Vaginal < ½ involvement	0.57	< 0.01	Moderate
Vaginal > ½ involvement	0.47	0.01	Moderate
Sacrouterine ligament right < ½ involvement	0.32	0.01	Fair
Sacrouterine ligament right ≥ ½ involvement	0.46	0.02	Moderate
Sacrouterine ligament left < ½ involvement	0.38	< 0.01	Fair
Sacrouterine ligament left ≥ ½ involvement	0.25	0.05	Fair
Parametrium right < ½ involvement	0.43	< 0.01	Moderate
Parametrium right ≥ ½ involvement	0.42	< 0.01	Moderate
Parametrium left < ½ involvement	0.38	< 0.01	Fair
Parametrium left ≥ ½ involvement	0.31	< 0.01	Fair
Rectum involvement	1	0.08	Perfect
FIGO stage	0.49	< 0.01	Moderate
Proposed therapy	0.84	< 0.01	Almost perfect
Request for additional imaging test (MRI)	0.84	< 0.01	Almost perfect

TABLE 3: Free κ value on all different scored items of the EUA when the results of 3 experienced investigators were compared.

	Free-Marginal κ	*p*	Interpretation of κ: Level of Agreement
FIGO stage	0.03	< 0.01	Slight agreement
Proposed therapy	0.66	< 0.01	Substantial agreement

TABLE 4: Agreement on EUA by experienced investigator versus nonexperienced investigator.

Of all patients considered suitable for primary surgery, 21 patients were operated on (24% of all patients). In 14 patients (66.7%), pathological results were similar to FIGO staging (consensus FIGO stage), and no involved pelvic lymph nodes were detected. In 7 patients (33. 3%), there was either a tumoral involvement of the parametrium or sacrouterine ligaments (2 patients) or an involvement of lymph nodes (3 patients) or both (2 patients). This means that, first, in 4 of these 21

patients (19%), the tumor spread beyond cervix and uterus was not predicted by clinical staging and, second, that in 5 (24%) of these operated patients, positive lymph nodes were detected (FIGURE 1). Characteristics of patients operated on with positive lymph nodes are summarized in TABLE 5.

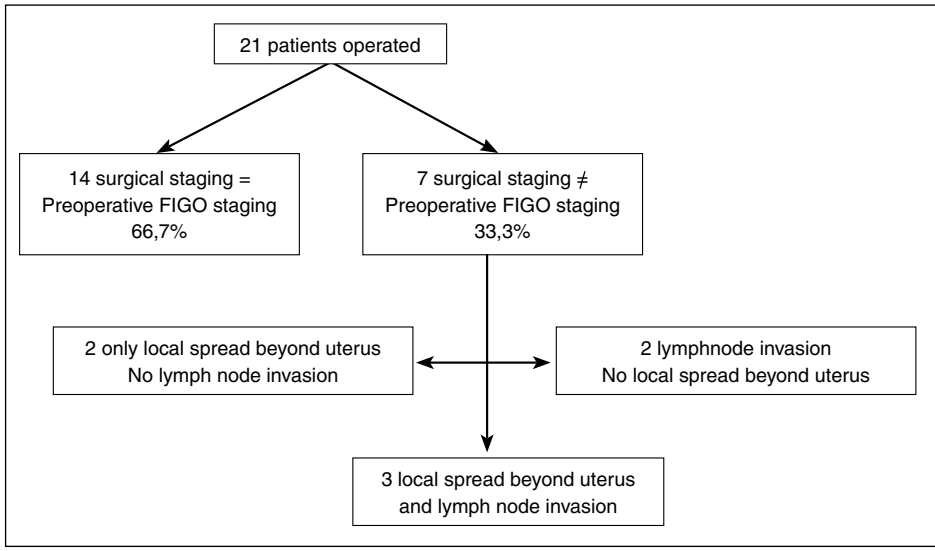

FIGURE 1: Results of patients operated on.

	FIGO Stage	Preoperative Imaging	No. Removed Lymph Nodes	No. Positive Lymph Nodes	Localization of the Positive Lymph Nodes	Maximal Size of Metastasis
Patient 1	IB1	No	57	2	Right obturator fossa (1) Left common iliac artery (1)	4 mm
Patient 2	IB1	No	20	2	Right external iliac artery (1) Left internal iliac artery (1)	Not reported
Patient 3	IB1	No	28	1	Left obturator fossa (1)	Micro metastasis
Patient 4	IB1	No	34	5	Right common iliac artery (2) Right external iliac artery (2) Left obturator fossa (1)	Not reported
Patient 5	IB1	No	37	1	Right external iliac artery (1)	5 mm

TABLE 5: Characteristics of operated patients with positive lymph nodes.

DISCUSSION

The success of clinical-based cervical cancer FIGO staging is mainly built on the fact that it can be used worldwide to stage new patients without necessity of advanced imaging techniques or surgical interventions. This is particularly important because 80% of new cervical cancers are diagnosed in low resource countries.[1] Cervical cancer FIGO staging aids in treatment decisions, can be used to assess the response to treatment, gives information about prognosis, and is at present the uniform format for the description of disease to exchange and compare information. Although limitations of FIGO clinical staging are also well appreciated, to our knowledge this is the first article addressing its reliability and reproducibility. Tumor size, parametrial invasion, and sidewall invasion can be difficult to assess accurately by clinical examination or by FIGO-approved additional tests. These findings are reflected in the level of agreement of experienced investigators on these items as calculated in our study. The low κ values indicate a fair to moderate agreement on these items. In literature, it stays controversial whether additional imaging techniques (MRI, computed tomography [CT]) are more accurate than clinical examination alone to assess tumor size or local spread.[4,5] In a recent meta-analysis by Thomeer et al,[6] imaging is shown to be superior to EUA to assess tumor status*.

Nevertheless, we see that when available additional testing modalities are frequently used to evaluate women with cervical cancer. The results of these tests are used for planning treatment but do not influence FIGO stage.

The disagreement on local spread logically results in a moderate level on agreement of FIGO stage, although this has little effect on the choice of therapy where an almost perfect agreement was found. This can be explained by the fact that at present in the most standard treatment protocols[7,8] of cervical cancer there are few therapeutic options: (1) surgery is typically reserved for lower-stage disease and smaller lesions, such as stages IA, IB1, and selected IIA1; (2) concurrent chemoradiation is the primary treatment of choice for stages IB2-IVA; it can also be used

* Change on advise of a member of the examination committee: change “tumor status” to “tumor volume”.

for patients who are not candidates for surgery; (3) those patients with widely metastatic disease (stage IVB) are typically treated with full-dose chemotherapy alone or in addition with palliative radiation to reduce bleeding and pain. Future new insights in the pathology and evolutions in treatment of cervical cancer (such as additional hyperthermia,[9,10] neoadjuvant chemotherapy,[11] and advanced radiotherapy techniques[12]) could result in a wider spread of treatment options, making precise staging more important to decide on individualized therapy.

Some patient or tumor characteristics (such as BMI and size of the tumor) could influence the interobserver variability of an EUA. A much larger study population is needed to distinguish influencing characteristics.

The clinical staging system for cervical cancer is limited to the specified set of examinations and does not assess the full extent of disease in all women. This leads to understaging of some patients, resulting in suboptimal treatment. In our series of all patients operated on, 33% were understaged by clinical-based FIGO staging.

In FIGO staging, no consideration is taken to lymph node metastasis, although it is associated with a worse prognosis.[13] Because of the lack of screening programs and health care facilities, the vast majority of cervical cancers in developing countries are diagnosed at an advanced stage. Therefore, the lymph node assessment could be considered less important, because they more likely to be positive in advanced stages and of less impact on therapy choices and prognosis. In industrialized countries with better organized health care systems, cervical cancer often is diagnosed in earlier stages. Lymph node invasion has an impact on therapeutic decision making. Historically, surgery with lymphadenectomy was required to evaluate for lymph node metastases; nowadays, options for evaluating for lymph node metastases include also imaging studies (CT, PET, or PET-CT).[14] Malignant lymph node involvement was detected in 24% of patients who were operated on in our study. No PET or PET-CT was performed before surgery in these cases.

The FIGO staging system is largely based on physical examination. Our data show a better interobserver agreement between experienced investigators when compared with less experienced doctors. This indicates that there is a learning process for EUA, and therefore an examination by an experienced examiner is more reliable. In addition, the learning time of an EUA is very much dependent on availability of patients, whereas nowadays the tumor assessment by imaging techniques can be trained on reproducible examples.

CONCLUSIONS

In our study, a moderate interobserver agreement on clinical staging of patients with cervical cancer is described. Examination under anesthesia can be learned, because interobserver variability decreases in the group of experienced doctors.

REMARK: The text is identical to the one published in the journal.

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4.2: Publication 2: Study of confounding factors of the Inter-observer variability of FIGO staging in cervical cancer

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Keywords: cancer staging, cervical cancer, inter-observer agreement, examination under anaesthesia.

ABSTRACT

Background

The International Federation of Gynecology and Obstetrics (FIGO) Cervical cancer staging system is based on a clinical gynecological examination. Although widely used, no data are available on its reliability and reproducibility. We investigated the inter observer agreement (IOA) of this staging system and its confounding factors.

Methods

From February 2009 to October 2012 patients undergoing clinical cervical cancer staging were included. Patients were examined by 2 experienced (and often 1 inexperienced) investigators independently. Each investigator assessed the FIGO stage and defined a treatment proposal. The inter-observer agreement was operationalized through the unweighted Cohen's κ coefficient. A multivariate analysis was used to evaluate the impact of patient and tumor characteristics on the IOA of FIGO staging.

Findings

155 patients were enrolled. Among experienced investigators, a moderate IOA was found with regard to FIGO stage (κ = 0.64 (0.052)) and an excellent IOA on their proposed therapy (κ = 0.87 (0.042)). No significant impact of BMI, age, tumor type or level of tumor markers on the IOA could be demonstrated. The IOA between 2 experienced investigators differed from the IOA among experienced and inexperienced investigators concerning stage of disease (*significant*) and choice of therapy (*almost significant*).

Conclusions

The IOA on clinical cervical cancer staging is moderate. On the contrary the IOA for choice of treatment is excellent. The IOA on tumor stage and choice of therapy was best among experienced investigators, indicating the importance of centralization of care. No confounding patient or tumor related characteristics were demonstrated.

INTRODUCTION

Cancer of the cervix uteri is the fourth most common malignancy to affect women. In 2012 528,000 new cases of cervical cancer were reported worldwide with an estimated 266,000 deaths, representing 7.5% of all female cancer deaths. About 85% of the global burden occurs in less developed countries, where it accounts for almost 12% of all female cancers[1]. The limited access to cytological screening in these countries results in delayed diagnosis and more advanced stage diseases. In addition, prospects for treatment of advanced disease are poor, resulting in a high rate of death from cervical cancer.[2,3]

Determination of optimal treatment in cervical cancer patients is mainly based on an accurate assessment of the extension of the disease. The extension of cervical cancer at time of diagnosis is expressed following the definitions adopted by the International Federation of Gynecology and Obstetrics (FIGO) originated in the work of the cancer commission of the Health Organization of the League of Nations first published in 1920.[4] This classification was designed to mimic the natural history of the disease where the different stages represent the progressive growth of the tumor. Over the years the FIGO Committee on Gynecologic Oncology has made several modifications to the classification system of cervical cancer but it is still mainly based on the clinical gynecological examination evaluating the anatomic extent of the disease. FIGO stages are defined by tumor size and extension of disease beyond the cervix (vagina, parametria, sacro - uterine ligaments, pelvic side walls, bladder, rectum or distant metastasis). The last classification revision dates from 2009.[5] According to the current FIGO staging guidelines, findings on clinical examination (ideally performed under anesthesia) can be supplemented by few diagnostic tools: hysteroscopy, cystoscopy, proctoscopy, abdominal ultrasound, intravenous pyelogram (IVP) and imaging with a plain radiograph of the lungs and skeleton. Results of more advanced radiologic techniques as Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) are not taken in account for staging. This is because of the limited accessibility to such techniques in developing countries where most cases of cervical cancer are diagnosed nowadays.

One of the major purposes of cancer staging is to offer a classification of a cancer's extent in order to provide a method for comparing treatment results. To achieve this objective the quality, reliability and reproducibility of the staging system is crucial.

In a previous preliminary report we addressed the interobserver variability of the examination under anesthesia (EUA) in cervical cancer.[6] We documented only a moderate interobserver agreement in clinical staging of cervical cancer when results of independent experienced clinicians were compared.

In the present report, based on a larger sample we investigated the influence of multiple characteristics (experience of the investigator and patient or disease related characteristics) on the interobserver agreement of the clinical FIGO staging of cervical cancer. To our knowledge this is the first study addressing this topic.

MATERIALS AND METHODS

All subsequent patients with primary cervical cancer diagnosed and staged at the Erasmus MC Cancer Institute (Rotterdam, The Netherlands) between February 2009 and October 2012 were included in the study. The clinical staging was performed under general anaesthesia. Patient's characteristics were prospectively documented. During the procedure all patients were examined independently by at least 2 experienced investigators. When present, patients were also examined by an inexperienced practitioner. Investigators were classified as experienced after more than 50 Examinations Under Anesthesia (EUA). All clinicians scored the examination independently on different staging related topics: tumor size and the involvement of vagina, parametria, sacro - uterine ligaments, pelvic side walls, bladder, and / or rectum. All items were scored on a 3-point scale varying from 1 "certainly no involvement", 2: "not sure about involvement" and 3:"involvement". Finally each investigator was asked to appoint the FIGO stage and to propose a therapy (1: surgery, 2: (chemo) radiotherapy or 3: other treatment). For statistical evaluation FIGO stages were grouped in 5 categories (I, IIA, IIB, III, IV)

STATISTICAL METHODS

Results were expressed as means (standard deviations) for quantitative variables, while frequencies and proportions (%) were used for categorical variables.

The inter-observer agreement on each item was calculated through the unweighted Cohen's κ coefficient using a Bayesian multilevel approach. Cohen's κ coefficient was chosen instead of a weighted kappa coefficient to reflect the practice reality that all disagreements are of equal importance. The maximum likelihood estimator of Cohen's kappa coefficient was not appropriate since a random pair of practitioners, differing from patient to patient, examined each patient. Therefore, the practitioners have to be considered as random rather than fixed. The method described in Vanbelle et al. (2012)[7] was therefore used. We assumed non-informative priors, which express that we do not have prior information on the parameters. For the regression coefficients, vague independent priors were assumed to follow a normal distribution with mean 0 and large variance, i.e. N(0,100). The prior distribution for all the standard deviations of the observer random effects was taken as uniform [0,100]. Three parallel Markov-Chain Monte Carlo (MCMC) chains were run, each for 30000 iterations for all the models with a burn in period of 2500 iterations. The convergence of these MCMC was checked using the CODA package in R. In particular, we used the Gelman and Rubin's diagnostics measure R and this value was close to 1 for all the parameters, which means there was no evidence against convergence. The same method was used to study the effect of the practitioner's experience on the agreement level by comparing the agreement level between the two experienced examiners with the agreement level between inexperienced and experienced practitioners. Finally, we studied the influence of patient and tumor characteristics on the agreement level between the two experienced investigators. Before performing a multivariate analysis, the influence of each characteristic was considered separately. Documented characteristics were age and BMI of the patient, tumor histology (squamous cell carcinoma or adeno carcinoma) and level of specific tumor marker (Squamous Cell Carcinoma antigen (SCC-ag) (ng/mL) in squamous cell carcinoma, Cancer Antigen 125 (CA125) (U/ml) in adeno carcinoma).

Calculations were always carried out on the maximum number of data available. Missing data were not replaced. The posterior distribution of the κ coefficient was summarized using a 95% credibility interval (95% CI). Data analysis was carried out using R (version 3.0.2 for Windows) and Winbugs statistical packages.

RESULTS

Between February 2009 and October 2012 a total 155 subsequent patients with cervical cancer undergoing an EUA were enrolled in this study. Average age was 52.7 (SD: 15.1) years with a mean BMI of 26.2 (SD: 5.1) kg/m². The histology was predominantly squamous cell carcinoma (79.4%), followed by adenocarcinoma (20.6%). The vast majority of patients (71.7 %) were diagnosed with an advanced stage of disease (> FIGO IB1), as agreed on by consensus between investigators. Patient characteristics are summarised in TABLE 1.

Patients characteristics	n	Frequency (%)
Age (years)	155	52.7 (15.1) [27-88]
BMI (kg/m²)	146	26.2 (5.1) [17-41]
Tumor type	155	
Sqamous cell carcinoma	123	79.4 %
Adenocarcinoma	32	20.6 %
Tumor markers	126	
For squamous cell carcinoma		
SCC, mean (range), mg/L		2.9 (0.1 - 233)
SCC > 1,9 mg/L %		61.6 %
For adenocarcinoma		
CA-125, mean (range), U/mL		25 (9 - 625)
CA-125 > 35 U/mL, %		23.1 %
FIGO Stage (consensus), %		
Stage IA1	0	0 %
Stage IA2	1	0.6 %
Stage IB1	43	27.7 %
Stage IB2	10	6.5 %
Stage IIA1	7	4.5 %
Stage IIA2	2	1.3 %
Stage IIB	69	44.6 %
Stage IIIA	3	1.9 %
Stage IIIB	8	5.2 %
Stage IVA	11	7.1 %
Stage IVB	1	0.6 %

TABLE 1: Patients characteristics. Results are expressed as Mean (SD) [range] for quantitative variables and frequency (%) for qualitative variables. SCC > 1.9 or CA 125 > 35 are indicative for imaging in clinically low stage disease

The agreement level between the two experienced examiners on staging related topics is given in TABLE 2. Cohen's κ coefficient was the largest on tumor size and therapy. Agreement was less satisfactory regarding tumor involvement of sacro uterine ligaments and parametria. Finally, the agreement level on rectal invasion was not larger than chance due to the large asymptotic standard error (ASE). Note that 97% of the patients were negative for rectal invasion. Despite a moderate level of agreement on FIGO stage, the agreement on the proposed therapy was almost perfect.

	Sample size	κ	95% CI
size of the tumor	144	0.72 (0.048)	0.62-0.81
vaginal involvement	154	0.54 (0.061)	0.41-0.65
sacro uterine ligament right involvement	155	0.29 (0.092)	0.092-0.46
sacro uterine ligament left involvement	155	0.40 (0.072)	0.24-0.53
parametrium right involvement	155	0.42 (0.072)	0.28-0.56
parametrium left involvement	155	0.43 (0.069)	0.29-0.56
rectum involvement*	155	0.36 (0.41)	-0.69-0.82
FIGO STAGE (5 categories**)	155	0.64 (0.052)	0.53-0.74
proposed therapy	155	0.87 (0.042)	0.77-0.93

TABLE 2: Posterior distribution of the Cohen's kappa coefficient, (mean SD) and 95% credibility interval between pairs of experienced investigators

*97% of the patients are negative.

** Stage I, IIA, IIB, III, IV

A subset of 111 patients was examined by one inexperienced and two experienced investigators. The agreement level between inexperienced and experienced examiners on the FIGO staging was significantly lower compared to the agreement level between two experienced examiners (0.34 (95% CI: 0.23-0.44) versus 0.59 (95% CI: 0.46-0.71)). The disagreements between the inexperienced and the experienced examiners were mainly situated in cases where the inexperienced practitioner rated the FIGO stage to be lower than the experienced examiner. There was no such particular disagreement pattern between the two experienced examiners. The agreement level between an inexperienced and an experienced examiner on the therapy was lower than the agreement level between two expe-

rienced examiners (0.58 (95% CI: 0.45-0.69) versus 0.81 (95% CI: 0.66-0.91)). Most of the disagreements between the inexperienced and the experienced examiners occurred when the inexperienced examiner recommended surgery while the experienced examiner recommended (chemo) radiotherapy. There was no disagreement pattern between the two experienced examiners.

Univariate and multivariate regression analysis showed no effect of patient and tumor characteristics on the agreement level amongst the two experienced examiners. The results were similar for the univariate and multivariate approach. Results are presented in TABLE 3.

Variable	Means (SD) (P2.5-P97.5)	Means (SD) (P2.5-P97.5)
Model for the marginals*		
Intercept 1	0.32 (0.39) (-0.44-1.07)	0.82 (0.51) (-0.16-1.86)
Intercept 2	0.47 (0.39) (-0.30-1.22)	0.99 (0.51) (0.0081-2.01)
Intercept 3	1.84 (0.41) (1.04-2.62)	2.41 (0.53) (1.39-3.47)
Intercept 4	2.42 (0.42) (1.59-3.22)	3.20 (0.54) (2.15-4.28)
Age	0.020 (0.0046) (0.011-0.029)	0.019 (0.0051) (0.0084-0.029)
BMI	-0.021 (0.012) (-0.044-0.0023)	-0.0075 (0.016) (-0.039-0.024)
Marker(1)		
<=2 normal values	-	0.80 (0.23) (0.35-1.25)
>2 normal values	-	0.81 (0.16) (0.49-1.13)
Histology (2)		
SCC	0.32 (0.17) (-0.0078-0.66)	-
s^2	0.017 (0.026) (0.00-0.087)	0.013 (0.025) (0.00-0.083)
Cohen's kappa coefficient**		
Intercept	0.45 (0.61) (-0.67-1.67)	0.55 (0.65) (-0.74-1.82)
Age	0.00061 (0.0061) (-0.011-0.013)	0.0015 (0.0066) (-0.011-0.014)
BMI	0.0021 (0.018) (-0.033-0.038)	0.0078 (0.020) (-0.031-0.048)
Marker(1)		
<=2 normal values	-	-0.15 (0.31) (-0.75-0.49)
>2 normal values	-	-0.29 (0.23) (-0.74-0.15)
Histology (2)		
SCC	0.22 (0.22) (-0.23-0.65)	-

TABLE 3: Summary of the posterior distribution of the model parameters (mean (SD) (95%CI)) corresponding to the marginal and kappa model when histology of the tumor (left) of the level of the tumor (right) is included in the model

*The model for the marginal is $Probit\left(P(Y_{i,r})\right) = \alpha_j - \beta_1 AGE - \beta_2 BMI - \beta_3 HISTOLOGY - \eta_r$ (j=1,…,4) where η_r is a random effect normally distributed with mean 0 and variance relative to the examiners (r=1,…,21).

** The model for Cohen's kappa coefficient is: $\frac{1}{2} ln\left(\frac{1+\kappa}{1-\kappa}\right) = \gamma_0 + \gamma_1 AGE + \gamma_2 BMI + \gamma_3 HISTOLOGY$

(1) Normal value is taken as reference category

(2) Adenorcarcinoma is taken as reference category

Patients with a consensus FIGO stage < IIB and < 4 cm, with normal tumor markers and (if performed) normal imaging were evaluated for surgery. Of all patients, thirty-five were operated on (22,6% of all patients). In 77.1% (n= 27) of surgically treated patients the preoperative FIGO stage was comparable with the postoperative pathological TNM classification (pTNM). In eight patients (22.9%) the FIGO differed from the pTNM. In five patients the pT was upstaged (14.3%), in 6 patients (17.2%) malignant lymph nodes were present. Findings of operated patients are documented in FIGURE 1.

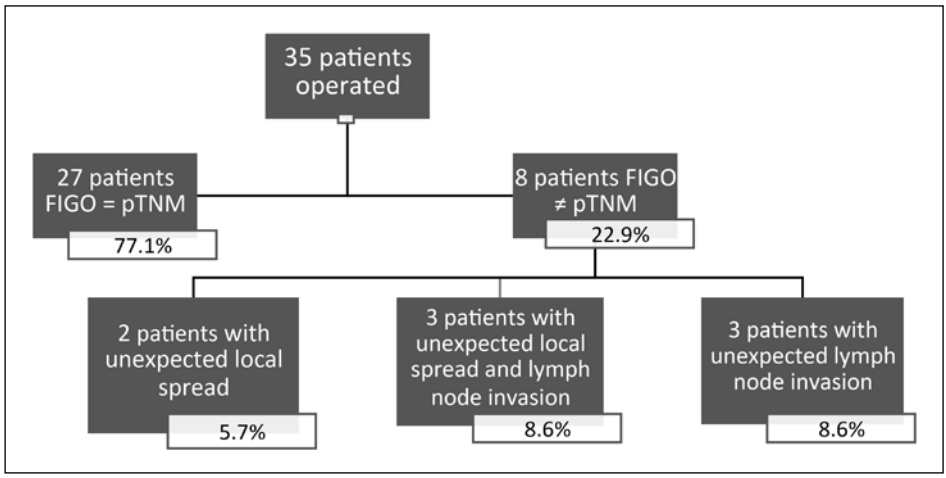

FIGURE 1: Results of patients operated on.

DISCUSSION

Prognosis and treatment decisions in cervical cancer patients are based on size and extent of the disease mainly estimated by clinical examination and classified according to FIGO staging system.[8] This staging system can also be seen as a common international language for information sharing and results comparing. Since supplementary information from advanced radiologic techniques are not permitted in the current cervical cancer FIGO staging[5], the clinical gynecological examination on which FIGO staging is based, needs proof of reliability and reproducibility. To our knowledge we are the first to address these issues by investigating its IOA.

Our results showed a moderate inter-observer agreement between two experienced investigators on the FIGO stage indicating a possible limitation for sharing and comparing results based on this staging system.

At present time the therapeutic impact of the moderate agreement on FIGO stage seems to be limited since we found an almost perfect inter-observer agreement between two experienced examiners on treatment proposal. This can be explained by the fact that currently only few therapeutic options are considered as standard treatment[9,10]: 1) surgery as primary option for early stage non-bulky disease and 2) chemo radiation for more advanced disease. Future therapeutic options based on surgical evolutions (f.e. applicability of sentinel node procedure, a tailored extension of radical surgery, fertility preserving treatment…), progress in systemic treatment (f.e. chemotherapy in advanced cervical cancer…) and the introduction of advanced radiotherapeutic tools will result in a more differentiated and individualized care. It is possible that with an increase in therapeutic options, the level of agreement on treatment proposal based on a clinical gynecological examination would decrease and become comparable to the level of agreement on FIGO stage.

In this study multivariate analysis showed no significant impact of BMI, age, tumor histology or level of the specific tumor markers on the IOA of FIGO stage. It is important to stress that all exams were performed under general anesthesia. These findings implicate that BMI has no major impact on accuracy of clinical staging when it is performed by experienced gynecologic / radiotherapeutic oncologist under optimal condition including general anesthesia.

Not only is an EUA used for clinical staging of cervical cancer but it also provides an opportunity for obtaining an adequate biopsy of the tumor for further pathological typing and it facilitates the introduction of radiological markers to delineate the tumor which can help in radiotherapy planning.

We demonstrated a significant better agreement concerning FIGO stage between experienced investigators when compared with an experienced and an

inexperienced investigator. This implicates that clinical examination is a matter of training that is normally available within high volume hospitals. Besides, one could stipulate that at least one experienced clinician should stage patients in order to obtain the best possible clinical staging.

A close look on the disagreements patterns on FIGO stage between the inexperienced and the experienced examiners showed that in case of discrepancy the inexperienced investigator tended to underestimate the disease stage (by rating the FIGO stage to be lower than the rating of the experienced examiner). No such disagreement pattern between the two experienced examiners was found.

Our results also showed that the underestimation of disease stage by the inexperienced compared to the experienced examiner resulted consequently in a lower level of agreement concerning the choice of therapy that almost reached a significant value. Most of the disagreements between the inexperienced and experienced examiner occurred when the inexperienced examiner recommended surgery in patients with more advanced stage that were considered inoperable by the experienced examiner. This implies a potential risk of suboptimal surgeries, with positive surgical margins and subsequent indications for adjuvant radiotherapy. Overall resulting in a suboptimal treatment with an increased risk of morbidity and higher medical costs.[11,12] We found no such disagreement pattern between the two experienced examiners.

The differences in agreement among experienced versus inexperienced and among experienced investigators concerning stage of disease and choice of therapy are important arguments favoring centralization of care, also in low resource countries.

* Addition on advise of a member of the examination committee: Our data on operated patients (figure 1) demonstrate that of the 35 patients that were estimated eligible for Wertheim surgery, in 27 the postoperative pathological classification (pTNM) was comparable to the preoperative FIGO-classification. In more than 1/5 patients additional pre-operative staging techniques (such as MRI, PET-CT) could have adjusted the treatment directly towards chemoradiotherapy.

CONCLUSIONS

We found a moderate inter observer agreement on the clinical staging of cervical cancer. We were unable to demonstrate any patient or tumor related characteristics that have an impact on the inter observer agreement of this clinical staging. We found differences in agreement between experienced versus inexperienced and two experienced investigators concerning stage of disease (significant difference) and choice of therapy (almost significant difference), indicating the importance of centralization of cervical cancer care.

REMARK: the text is identical to the one submitted to the journal.

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Chapter 5:
Treatment of LACC

5.1. Publication 3: Completion Surgery After Intensity-Modulated Arc Therapy in the Treatment of Locally Advanced Cervical Cancer: Feasibility, Surgical Outcome, and Oncologic Results

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ABSTRACT

Introduction

Since the addition of chemotherapy to radiotherapy, the survival rates of locally advanced cervical cancer (LACC) have improved but are still disappointing. Therefore, the idea of surgery after chemoradiation in case of LACC or bulky disease was adopted. One of the concerns regarding surgery following chemoradiotherapy is surgery-related morbidity.

Aim

The objectives of this study were to investigate the feasibility of surgery after advanced radiotherapy techniques such as intensity-modulated arc therapy (IMAT) and to describe the morbidity.

Methods

This was a prospective study of primary inoperable LACC patients primary treated with IMAT, in most cases combined with weekly cisplatin. Then the resectability was reevaluated. If resectable patients were treated with Wertheim type 2 surgery ± pelvic lymphadenectomy (on positron emission tomography–computed tomography indication). If tumor was not resectable, patients were treated with brachytherapy.

Results

Since 2006, 41 consecutive patients were included. After neoadjuvant IMAT, 34 were considered resectable and underwent surgery, whereas 7 proceeded with brachytherapy. The operative mortality rate was nil. There were no major perioperative complications. No ureter, bladder, or bowel injuries occurred. No postoperative urinary/digestive fistulae or stenoses were noted. Eleven patients had postoperatively urinary retention problems. At the time of discharge, 5 patients still needed self-catheterization. All problems resolved within 3 months. In 4 cases, we saw significant lymphoceles. In all patients intended to treat, overall survival and disease-free survival at 3 years were 63% and 74%. In the Wertheim group, overall survival and disease-free survival at 3 years were 81% and 91%.

Conclusions

Completing surgery after chemoradiation therapy (with IMAT) for LACC or bulky disease is feasible, and complication rates are comparable with those of primary surgery for cervical cancer.

INTRODUCTION

Cancer of the uterine cervix is the second most common cancer in women worldwide, and 80% of new cases are diagnosed in developing countries. Although the incidence of invasive cervical cancer has decreased in industrialized countries because of screening programs and management of intraepithelial lesions, 60% of cases are already at advanced stages at the time of diagnosis. This incidence is even higher in developing countries.[1] Management of patients with cervical cancer depends on the stage of disease at diagnosis, based on the International Federation of Gynecology and Obstetrics (FIGO) staging system. Since the meta-analysis of Green et al,[2] the combination of external beam radiotherapy (EBRT) and chemotherapy (CRT) followed by intracavitary brachytherapy has been recommended as standard treatment for bulky IB and locally advanced cervical cancer (LACC) up to stage IVA. Nevertheless, the meta-analysis showed a rather limited survival benefit for LACC in the group with FIGO stages III–IVA and remained disappointing. Therefore, some groups adopted the idea of performing completion surgery after chemoradiation. The rationale for performing surgery following chemoradiation in locally advanced or bulky cervical cancer is to obtain a better local control that might translate into better overall survival (OS), because surgery allows the removal of potential radiation therapy–resistant tumor foci.

In addition, it permits the assessment of the pathological response. The concern for surgery-related morbidity such as fistulas and bowel and bladder injuries, however, has made completion surgery not widespread. Advanced radiation therapy such as intensity-modulated radiotherapy has shown to result in a better therapeutic ratio concerning pelvic tumors.[3,4] Intensity-modulated arc therapy (IMAT), with an infinite number of beams, is a new means to deliver IMRT. In cervical cancer, where the target volume has a concave shape with the bladder and

small intestine positioned within, a large number of intensity-modulated beams are needed to ensure an adequate target coverage and sufficient sparing of organs at risk.

The introduction of these advanced radiotherapy techniques creates new opportunities for completion surgery. We developed a schedule of preoperative CRT that delivers a higher dose to the primary tumor and involved lymph nodes without compromising the dose to the rest of the clinical target volume or organs at risk. We previously reported on the rationale, feasibility, toxicity, and oncologic results of neoadjuvant IMAT followed by hysterectomy in the treatment of FIGO IB2 (bulky)–IVA tumors.[4,5] This report evaluates the surgical morbidity on this multimodality treatment.

MATERIALS AND METHODS

This prospective study was approved by the local ethics committee, referred to as n° B67020072880. Inclusion criteria were biopsy-proven locally advanced (FIGO IB2-IVA) cervical cancer (LACC), absence of distant metastases and extrapelvic lymph node(s) as diagnosed on fluorine 18 fluorodeoxyglucose (^{18}FDG) positron emission tomography–computed tomography (PET-CT), World Health Organization score 0–2; ability to understand and sign informed consent, and absence of any condition potentially obstructing compliance with the follow-up schedule and study protocol.

Clinical staging was obtained by pelvic examination by an experienced gynecologic oncologist and a radiation oncologist. In addition, all patients were staged by total body ^{18}FDG PET-CT and pelvic magnetic resonance imaging (MRI). A panel of experienced radiologists and nuclear medicine physicians reviewed all images. All patients were thoroughly discussed multidisciplinary before inclusion. Patient characteristics are summarized in TABLE 1.

	Overall	Operated	Not Operated
No. (%) patients	41	34 (82.9%)	7 (17.1%)
Mean age (range), y	53 (26-80)	52 (26-80)	57 (45-80)
Karnovsky score, % (n) 70 80 90 100	 4.9 (2) 14.6 (6) 56.1 (23) 24.4 (10)	 2.9 (1) 11.8 (4) 58.8 (20) 26.5 9)	 14.3 (1) 28.6 (2) 42.8 (3) 14.3 (1)
Histology, % (n) Squamous cell carcinoma Adenocarcinoma	 90.2 (37) 9.8 (4)	 88.2 (30) 11.8 (4)	 100 (7) 0 (0)
FIGO, % (n) IB2 IIB IIIA IIIB IVA IVB	 7.3 (3) 58.6 (24) 9.8 (4) 14.6 (6) 7.3 (3) 2.4% (1)	 8.8 (3) 64.6 (22) 8.8 (3) 11.8% (4) 2.9 (1) 2.9 (1)	 0 (0) 28.5 (2) 14.5 (1) 28.5 (2) 28.5 (2) 0 (0)
Grade, % (n) Grade 1 Grade 2 Grade 3	 4.9 (2) 51.2 (21) 43.9 (18)	 5.8 (2) 47.1 (16) 47.1 (16)	 0 (0) 71.4 (5) 28.6 (2)
Average diameter (range), cm	5.5 (2.3 -7.5)	5.3 (2.3 - 7.5)	5.8 (5.0-7.5)
PET + ln, % (n)	39.0 (16/41)	38.2 (13/34)	42.8 (3/7)
Chemotherapy associated with radiotherapy, % (n)	82.9	85.3 (29)	71.4 (5)
Clinical complete response to IMAT + C, % (n)	80.5 (33)	97.1 (33/34)	0 (0/7)

TABLE 1: Patients characteristics.

After diagnosis, patients underwent neoadjuvant IMAT, if possible combined with weekly cisplatin administration (IMAT ± C). Details concerning delineation, dose description, planning, and delivery of IMAT were previously reported.[4]

After completing IMAT ± C, the possibility to perform adjuvant surgery was evaluated based on imaging (^{18}FDG PET-CT and MRI) and gynecologic examination. All results were multidisciplinary discussed. If considered resectable, type II Wertheim hysterectomy ± pelvic lymphadenectomy was performed 4 to 6 weeks after completing IMAT ± C. Pelvic lymphadenectomy was performed whenever there were positive lymph nodes present on one of the ^{18}FDG PET-CTs. From August 2008 onward, lymph node dissection was limited to the lymph node regions that

were positive on one of the ^{18}FDG PET-CTs. The reason for this change was 3-fold: first, pelvic lymphadenectomy after IMAT ± C only revealed histologically positive lymph nodes in 8.8% of the patients; second, these positive lymph nodes were always found in the lymph node region that was positive on the pretreatment PET-CT; third, some patients developed severe lymphoceles and lymph edema after extensive pelvic lymphadenectomy.

The protocol excluded the following patients from adjuvant hysterectomy:
(1) evidence of local progression,
(2) insufficient response on clinical examination and MRI
(defined as tumor shrinkage by <50%),
(3) development of distant metastasis (PET-CT),
(4) insufficient general condition to undergo hysterectomy, or
(5) patient's refusal.

These patients with a poor prognosis would benefit only from large (exenteration) surgery and therefore, taking into account their quality of life, were treated with an additional brachytherapy.

Postoperative morbidity was prospectively examined and registered. A standard postoperative schema was used to register complains and morbidity. Postoperative period was defined as up to 6 weeks' postsurgical intervention.

Registration of Surgical Morbidity

Surgical morbidity/mortality was evaluated and registered during hospitalization (acute) and at every visit thereafter (late) and was classified according to the Chassagne grading system.[6] The postoperative period was considered as up to 6 weeks' postsurgical intervention.

After patients were discharged from the hospital, the first follow-up at the outpatient clinic was scheduled 6 weeks after surgery. Thereafter, follow-up was scheduled 3-monthly for the first 2 years after treatment and from then 6-monthly. The

follow-up was performed at a multidisciplinary consultation (by both a gynecologic oncologist and a radiation oncologist). Local and distant control was evaluated at every visit by gynecologic and general clinical examination. Imaging (^{18}FDG PET-CT and MRI) was performed every 6 months for the first 2 years and yearly thereafter, or on symptoms.

RESULTS

Patients

Between September 2006 and August 2011, 41 consecutive patients with LACC were included in this study. Patient characteristics are summarized TABLE 1. The mean age at diagnosis was 53 years (range, 26–80 years). Squamous cell carcinoma was the predominant histology (90.2%). All enrolled patients completed IMAT, and 34 patients received weekly cisplatin (40 mg/m^2) as a radio sensitizer.

Following CRT, all patients were evaluated for surgery. Seven patients were found to be inoperable. Indications for inoperability were progressive disease in 2, insufficient tumor response in 3, poor general conditions in 1 patient, and the refusal of surgery by 1 patient. These patients underwent consolidation brachytherapy. Thirty-four patients were assigned for surgery.

Surgery

Radical hysterectomy was performed 4 to 6 weeks after completion of CRT. Surgery consisted of type 2 Wertheim hysterectomy including resection of the uterosacral and vesicouterine ligaments, unroofing, and mobilizing of the ureter to the lateral side, permitting a transection of the parametria and paracervical tissue at the level of the ureteral tunnel. At least 15 to 20 mm of the vagina from the cervix or tumor was resected. To reduce potential risk of ureteric fistulas, the ureters were not stripped. Consequently, the surrounding mesoureter with its underlying blood vessels remained unharmed.

Eighteen patients underwent a (limited) pelvic lymphadenectomy. A mean number of 11 lymph nodes (range, 1–31) were resected.

The mean operative time was 116 minutes (range, 60–235 minutes). The mean estimated blood loss was 500 mL. Six patients required a postoperative blood transfusion. No ureter, bladder, or bowel injuries occurred.

The operative mortality rate was nil. The median duration of hospital stay was 8 days (range, 5–137 days). No urinary/digestive fistulae or stenoses were noted. One patient developed a paralytic ileus, and another had an intestinal subobstruction. Both patients were successfully treated conservatively.

Three patients were diagnosed with a postoperative urinary infection. Eleven patients (32%) had problems with urinary retention when the bladder catheter was removed. At the time of hospital discharge, 5 of these patients required self-catheterization. All urinary retention problems resolved spontaneously within 3 months after the procedure.

In 4 cases, clinically significant lymphoceles occurred. One of these patients stayed hospitalized for more than 4 months because of a massive lymphocele producing more than 1 L lymph fluid a day. Her treatment was complicated by a surinfection with methicillin-resistant Staphylococcus aureus. In TABLE 2, the results concerning perioperative and postoperative complications are summarized.

Tumor resection margins were free of disease in all 34 cases. Complete pathological response was observed in 14 patients (41, 2%). Residual tumor was present in pelvic lymph nodes in 16% of patients with positive lymph nodes on pretreatment ^{18}FDG PET-CT. In TABLE 3, the results on pathology are summarized.

	Radical Hysterectomy
No. patients	34
With (elective) lymphadenectomy, n Complete lymphadenectomy Elective or directed lymphadenectomy	18 8 10
No lymphadenectomy, n	16
Mean (range) operative time, min	116 (60-235)
Intraoperative complications, n (%) Hemorrhage (> 1000 mL) Urinary injury Bowel injury Other injury	3 (8.8) 3 (8.8) 0 (0) 0 (0) 0 (0)
Mean (range) intraoperative blood loss, mL	500 mL (100-2000)
Postoperative mortality, n (%)	0 (0)
Postoperative reintervention, n (%)	0 (0)
Wound infection, n (%)	0 (0)
Pelvic infections, n (%)	0 (0)
Hemorrhage, n (%)	0 (0)
Postoperative blood transfusion, n (%)	6 (17.6)
Urinary infection, n (%)	3 (8.8)
Urinary retention, n (%) Grade 1 Grade 2	11 (32.3) 6 (17.4%) 5 (14.5)
Urinary fistulae, n (%)	0 (0)
Urinary stenosis, n (%)	0 (0)
Digestive fistulae, n (%)	0 (0)
Ileus, n (%)	1 (2.9)
Bowel subobstruction, n (%)	1 (2.9)
Pulmonary embolism, n (%)	0 (0)
Symptomatic lymph cysts, n (%) Grade 1 Grade 2	4 (11.7) 2 (5.8) 2 (5.8)
Other complications, n (%)	0 (0)
Mean (range) hospital stay, d	8 (5-137)

TABLE 2: perioperative and postoperative complications.

	Abdominal Hysterectomy
Type of resection, n (%) R0 R1 of 2	 34 (100) 0 (0)
Pathological response to IMAT (C) RT (n=34), % (n) Complete response Tumor rest <5 mm Tumor rest >5 and <10 mm Tumor rest >10 mm	 41.2 (14/34) 20.6 (7/34) 17.6 (6/34) 20.6 (7/34)
Pathological response of PET + LN to (C)RT	18 patients had (elective) lymphadenectomy (18/34 = 52.9%)
yN03	15 (15/18 = 83.3% or 15/34=44.1%)
yN1	3 (3/18=16.6% or 3/34=8.8%)

TABLE 3: pathological results of operated patients.

Follow-up and Assessment of Disease Control in the Surgery Group

In the group of operated patients, 1 patient had a local relapse (vaginal top) within 6 months after surgery. There was 1 pelvic lymph node relapse. Two patients developed distant metastasis (1 in the liver and a lung, respectively) within the first year after hysterectomy. Both patients died within 18 months after surgery. In the Wertheim group, OS and disease-free survival (DFS) at 3 years were 81% and 91%. In all patients intended to treat, OS and DFS at 3 years were 63% and 74% (TABLE 4).

	Intention to Treat (n=41)	Surgery Only (n=34)
OS		
1 y	90%	97%
2 y	73%	87%
3 y	63%	81%
Estim 5 y	63%	81%
DFS		
1 y	80%	91%
2 y	74%	91%
3 y	74%	91%
Estim 5 y	74%	91%
Disease-specific survival		
1 y	90%	97%
2 y	77%	93%
3 y	67%	87%
Estim 5 y	67%	87%
Local relapse-free survival		
Local relapses	8	1
1 y	76%	97%
2 y	76%	97%
3 y	76%	97%
Estim 5 y	76%	97%
Follow-up, mo		
Median	24	28
Min	7.67	12
Max	63.67	63.67

TABLE 4: follow up results.

DISCUSSION

Completion surgery after CRT is controversial as there is until now no randomized study showing a survival benefit. In addition, there are concerns regarding morbidity of surgery following CRT. Keys et al[7] included 256 eligible patients with bulky exophytic or "barrel"-shaped IB tumors. These patients were randomized to either EBRT and intracavitary irradiation (n = 124) or EBRT followed by extrafascial hysterectomy (n = 132). They reported complete pathological response rates

in 48% of patients. There was macroscopically persistent disease in 12% of the patients. Interestingly, patients with bulky IB2 disease who underwent adjuvant hysterectomy had an improved 5-year DFS of 62% compared with 53% in the group without complementary surgery. This improvement was mostly related to a decrease in the rate of local recurrences after hysterectomy (15% vs 27%). Unfortunately, this improvement in DFS did not translate into an improved OS. Reasons for lacking survival benefit could be a relatively limited number of patients in each arm and the absence of effective adjuvant therapy for patients at risk of having systemic metastases. Another reason might be the lack of number of patients with locally advanced disease who are at risk of having persisting disease following CRT, as Green et al[2] showed in their meta-analysis. Nevertheless, a subgroup analysis showed a significant survival benefit in favor of complementary hysterectomy in patients with tumors measuring 4 to 6 cm. Houvenaeghel et al[8] confirmed that adjuvant surgery could improve the outcome of patients with bulky residual tumor (≥2 cm) after CRT for LACC. In addition, they stated that even if survival was not improved, complementary surgery resulted in a better quality of life before metastatic spread, as local recurrence is a source of chronic pelvic pain.

Because only a randomized trial could adequately determine whether completion surgery would be therapeutically beneficial, the GYNECO 02 study was started in 2002.[9] This multicenter phase III trial comparing hysterectomy with no hysterectomy in patients with a clinical and radiological complete response after CRT for stage IB2 or II cervical cancer was closed after 3 years because of insufficient accrual. A major reason for this poor accrual was the preference of the participating physicians toward hysterectomy. Nevertheless, 61 patients were included and were investigated. Although the study was underpowered, some interesting results were observed. Nearly one third of the patients undergoing adjuvant hysterectomy with a complete clinical and radiological response still had residual disease on histopathology.

In literature, the rate of residual cancer after chemoradiotherapy on surgical specimen ranges from 32% and 59%, depending on the study or FIGO stage.[5,7,11] As for our study, we report a residual disease of 59% (38% with residual disease <1 cm,

21% with residual ≥1 cm). An explanation for this high percentage of residual disease when compared with literature could be 3-fold: (1) surgery was performed after CRT without brachytherapy; (2) surgery consisted of Wertheim type 2 compared with simple hysterectomy in all referred articles; (3) surgery was performed 4 to 6 weeks after ending IMAT, whereas the effect of radiotherapy tends to last longer.

There is a lot of concern regarding morbidity in case of complementary hysterectomy after CRT. This concern might be legitimated in cases where conventional radiation technology was applied. However, as shown previously, the introduction of IMAT significantly lowered grades 3 and 4 radiotherapy-related toxicity.[5] In addition, IMAT also reduces the dose to what we call "supportive" tissues, making complementary surgery easier, certainly from a technical point of view, and making it possible to perform a radical hysterectomy (type II Wertheim) to remove also the parametria and a vaginal manchet of approximately 2 cm. Although out of the operated patients in our study 27% were more than FIGO stage III* we achieved an R0 resection in all cases (100%).

In 2 patients, the residual tumor was mainly found in the parametrium and would have been missed or ended in a transection of the tumor when surgery would have been limited to simple hysterectomy. The 3 year OS and DFS in this group were, respectively, 81% and 91%.

Generally, stage IV is considerate inoperable. We think a selected subgroup of patients with a satisfying response to CRT could benefit from complementary surgery. Our study included 2 patients with stage IV disease. The first had pathologically proven bladder invasion that regressed completely following CRT. Therefore, bladder-conserving surgery could be performed. Tumor-free resection margins were obtained.

* Correction on advise of a member of the examination committee: "FIGO stage III" should be "FIGO stage IIB"

The second patient had PET-positive pelvic and para-aortic nodal spread. She obtained complete remission on PET-CT scan following CRT with therapeutic pelvic and para-aortic field. Therefore, she was considerate to be operable, and Wertheim type II with selective pelvic and para-aortic lymph node dissection were performed. No residual disease was found on pathological examination of pelvic and para-aortic lymph nodes. Only residual disease (6 mm) was encountered in the cervix. Obtained resection margins were free of tumor.

Performing completion surgery after CRT also remains the only method to correctly assess the extent of residual disease, which is, after all, the most important prognostic factor. This allows determining a personalized postsurgical updated risk profile, which could be largely different than at initial diagnosis.[12]

Although lymph node status is one of the principal prognostic factors of cervical cancer, it is not included in the current FIGO classification. After CRT treatment, about 16% of patients are left with positive pelvic lymph nodes. This rate increases if the primary tumor is radioresistant.[13,14] Initially, a pelvic lymphadenectomy was performed in all our patients. However, because the number of positive lymph nodes was limited, and all positive lymph nodes were located at the initial positive PET-CT location, this policy was changed, and only the PET-CT–positive lymph nodes were removed. It is nevertheless important to remember that complications after pelvic lymphadenectomy following IMAT were not negligible: 2 patients had persisting lymphoceles that needed prolonged hospitalization for repeated evacuation, and even in 1 patient a lymphatic microanastomosis was performed. In contradiction, after adapting the lymph node dissection protocol as described previously, no significant lymphoceles developed.

The arguments against adjuvant surgery are mainly related to the fear of surgical morbidity after CRT. The risk of surgical complications depends on the radicality of the surgical procedure. In the series of Keys et al,[7,15] grades 3 and 4 morbidity was not altered by hysterectomy after radiotherapy if compared with nonoperated patients (10% in each group). These findings were confirmed by Ferrandina et al,[16] who observed a low percentage of intraoperative and postoperative complications.

In those series, simple hysterectomy was the type of surgery, whereas in our series a more extensive surgery (Wertheim type II ± lymphadenectomy) was performed. Nevertheless, we found low operative and postoperative complications. When compared with the surgical morbidity data after hysterectomy for low-stage cervical cancer, presented in the overview article by Trimbos et al,[17] the rates of surgical morbidity from our series were comparable: (1) postoperative mortality less than 1% versus 0%; (2) urinary tract infection: 42% versus 9%; (3) deep venous thrombosis: 3% versus 3%; and (4) fistula: 2% versus 0%. These favorable operative and postoperative findings differ from previous reports described by Resbeut et al[18] and Jurado and Martínez-Monge[11] possibly because of (1) the use of additional brachytherapy or intraoperative radiotherapy in their series and (2) the use of IMAT radiotherapy in our series, which allows more precise targeting of tumor and relative sparing of surrounding normal organs and tissues.

In addition, surgical complication rates should be weighed against adverse effects such as the higher frequency of chronic proctitis and vaginal stenosis with decreased sexual function that are observed when patients receive brachytherapy as a standard treatment.

CONCLUSIONS

We believe that the implementation of advanced radiotherapy techniques with a higher radiation dose on the target volume and less damage to the organs at risk creates opportunities to safely perform radical hysterectomy and a tailored lymphadenectomy. Complication rates of type II hysterectomy after IMAT + C are acceptable and comparable to complication rates of radical surgery for low-stage cervical cancer.

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5.2: Publication 4:
Value of cervical biopsy in predicting tumor response of primary locally advanced cervical cancer after treatment with intensity-modulated arc therapy: a prospective pathology-matched pilot study

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ABSTRACT

Objective

In this study we evaluated the value of cervical biopsies in predicting residual disease after initial (chemo) radiotherapy in the treatment of local advanced cervical cancer (LACC).

Materials and Methods

Since August 2012 all consecutive patients with LACC, treated with a multimodality treatment protocol consisting of Intensity Modulated Arc Therapy and concomitant chemotherapy (IMAT-C) followed by Wertheim type 2 surgery, were included in the study. All patients underwent cervical biopsies at the time of surgery using the ©Spirotome Cervicore device. At least 4 biopsies per case were performed. Pathology results of the biopsies were compared with the results of the resection specimen obtained through surgery.

Results

Ten consecutive patients were included. The mean age of patients was 66 years. The majority presented with squamous cell carcinoma (70%), 30% of patients had an adenocarcinoma. At the time of diagnosis all but two patients were classified FIGO stage IIB, the two other patients were staged FIGO IIIB. In 4 patients, no viable tumor cells were found. Six patients had residual disease. Only in 3 out of all cases with residual disease (n=6) the biopsies were able to predict persisting disease. The sensitivity, specificity, negative and positive predictive value for the biopsy result in predicting the presence of residual tumor was 50%, 100%, 57% and 100% respectively.

Conclusions

Only in half of the patients with residual disease (sensitivity of 50%) cervical biopsies could prove malignancy. This indicates it is not reliable for evaluating treatment response. We therefore can not recommend routine application of this technique for selecting LACC patients for hysterectomy following (chemo) radiotherapy.

INTRODUCTION

With an estimated 528,000 new cases in 2012 worldwide, cervical cancer is the fourth most common malignancy to affect women. It accounts for 7.5% of all female cancer deaths (266,000 in 2012). Around 85% occurs in the less developed regions.[1] Management of patients with cervical cancer depends on the stage of disease at time of diagnosis. The staging of cervical cancer is based on the International Federation of Gynecology and Obstetrics (FIGO) staging system. Since the meta-analysis of Green et al[2], based on 8 randomized trials, the combination of external beam radiotherapy (EBRT) and cisplatin-based chemotherapy (EBRT-C) followed by intracavitary brachytherapy is considered to be the standard treatment for bulky IB and locally advanced cervical cancer (LACC) up to stage IVA. The acute and long- term toxicity of this treatment is however not neglectable3. A valuable alternative is performing a (Wertheim or extrafascial) hysterectomy after C-EBRT. Our group has demonstrated the feasibility, safety and therapeutic power of such an approach, with very promising (early) results.4,5 These results are confirmed in a recent paper by Sun at al.6 Technical evolutions in radiotherapy planning and delivery such as intensity-modulated radiotherapy (IMRT) and intensity-modulated arc therapy (IMAT) are being implemented successfully thanks to the use of multimodality imaging for treatment planning and image-guided radiotherapy for treatment delivery.7 As a result, the combination of delivering a higher dose to the target volume and meanwhile lowering the dose to the small intestine, bone marrow, bladder and rectum has become perfectly feasible7. The ultimate goal is in an increase in the therapeutic ratio, which is the result of a higher disease control and a lower toxicity rate.

In cases with complete clinical response and negative cervical biopsies after the C-EBRT an additional treatment (such as brachytherapy) might not be necessary and consequently, treatment toxicity could be further reduced. However, it is not clear whether the combination of a complete clinical response and negative cervical biopsies corresponds with a complete pathological response (so-called ypT0 disease).

This study emphasizes on the value of cervical biopsies in predicting residual disease after initial IMAT-C. To the best of our knowledge, this has never been studied before.

MATERIALS AND METHODS

Since 2007, patients referred to our centre with biopsy proven LACC are treated with a multimodality treatment protocol consisting of IMAT-C (IMAT and 40 mg/m2 cisplatin weekly) followed by Wertheim type 2 surgery3, 4. According to the study protocol (n° B67020072880) surgery was performed 4 to 6 weeks after finishing IMAT-C. Prior to surgery all patients were evaluated on treatment response by clinical examination, magnetic resonance imaging (MRI) and 18FDG PET-CT.

Since August 2012 all patients underwent cervical biopsies at the time of surgery using the ©Spirotome Cervicore device (®Medinvents, Hasselt, Belgium). At least 4 biopsies per case were performed. Biopsies were guided by clinical findings. In case of lack of macroscopic residual disease biopsies were randomly taken in the four cervical quadrants (3-6-9-12 o'clock). Pathology results of the biopsies were compared with the results of the resection specimen obtained through surgery. Of the Wertheim hysterectomy specimens, the cervix was sectioned into 3-mm slices and entirely embedded in paraffin blocks. Hematoxylin and eosin slides were meticulously evaluated for residual tumor. Lack of residual tumor was confirmed by immunohistochemistry broad-spectrum cytokeratin stains. Residual tumor on the surgical specimen was staged according to TNM classification (5th edition). To indicate that this staging was after neoadjuvant CRT, all pTN stages were preceded by "y".

RESULTS

By December 2013 ten consecutive patients were included. Patients' characteristics are summarized in TABLE 1.The mean age of patients was 66 years. The vast majority presented with squamous cell carcinoma (70%), while 30% presented with adenocarcinoma. At the time of diagnosis all but two patients were classified FIGO stage IIB. The two other patients were staged FIGO IIIB.

Pathological examination was performed on all Wertheim hysterectomy specimens. Surgical margins were negative in all cases (R0 resection). In 4 patients, no viable tumor cells were found (ypT0). Six patients had residual disease.

Patients characteristics	n=10
Age, mean (range), y	66 (47 - 80)
Tumor type, % (n) Sqamous cell carcinoma Adenocarcinoma	 70 (7) 30 (3)
FIGO Stage (consensus), % (n) FIGO IIB FIGO IIIB	 80 (8) 20 (2)
Pathological complete Response % (n) complete response residual disease	 40 (4) 60 (6)
Response by stage (n) complete response FIGO IIB complete response FIGO IIIB	 2 (2 out of 8) 2 (2 out of 2)

TABLE 1: Patients characteristics.

One patient was pathologically staged as ypT1a2 (6mm residual disease (RD)), 3 as ypT1B1 (10, 11 and 30 mm RD respectively) and 2 as ypT2a1 (9 an 30 mm RD respectively). Details on pathological results are shown in TABLE 2. Only in 3 out of 6 cases with RD the biopsies were able to predict persisting disease, resulting in a sensitivity of 50%. All cases where there was a discrepancy between core biopsy and Wertheim specimen were squamous cell carcinoma. The sensitivity, specificity, negative and positive predictive value for the biopsy result in predicting the presence of viable tumor at the hysterectomy specimen was 50%, 100%, 57% and 100% respectively. The accuracy was 70%.

Patient	Tumor type	Residual disease (RD)	Max. size residual disease (cm)	Pathological staging post IMAT (ypT)	Biopsy
1	SCC	no RD	0	ypT0	no RD
2	SCC	RD	0.6	ypT1a2	no RD
3	AC	RD	3	ypt1b1	RD
4	SCC	RD	0.9	ypT2a1	no RD
5	SCC	RD	1.1	ypT1b1	no RD
6	AC	RD	3	ypT2a1	RD
7	AC	no RD	0	ypT0	no RD
8	SCC	RD	1	ypt1b1	RD
9	SCC	no RD	0	ypT0	no RD
10	SCC	no RD	0	ypT0	no RD

TABLE 2: Pathological results.
SCC: squamous cell carcinoma - AC: adeno carcinoma - RD: residual disease

DISCUSSION

The standard recommendation for treatment of FIGO stages IB2 and IIB-IVA cervical cancer is C-EBRT followed by brachytherapy2, 8. Completion surgery after (C)RT is controversial as there is until now no randomized study showing a survival benefit so far. In addition, there are concerns regarding morbidity of surgery following (C)RT, certainly if conventional EBRT techniques are used. 9

However the implementation of IMAT allowed delivering a higher radiation dose on the target volume while lowering the dose to the organs at risk creates, hereby creating the opportunity to safely perform a radical hysterectomy and a tailored lymphadenectomy with surgical complication rates comparable to these of radical surgery for low-stage cervical cancer5. In this study we evaluated the value of cervical biopsies in predicting therapy response after IMAT-C.

We used the ®Spirotome Cervicore system consisting of a cutting helix combined with a cutting cannula. This device was developed specifically for cervical disease that needs a representative and high quality diagnostic biopsy from both the mucosa and submucosal structures. A high quality sample with a penetration depth of 20 mm can be obtained, which is larger and penetrates deeper than when classical biopsy instruments are used. This deep penetration is useful in evaluating treatment response, since (chemo) radiation therapy induces diffuse ulceration and erosion of the tumor with, often, residual disease beyond the surface of the cervix.

In literature, the rate of residual cancer after CRT on surgical specimen ranges from 32% to 59%, depending on the study or FIGO stage5,10,11,12. In a previous report based on a larger subset of patients treated with the same treatment protocol, we documented residual disease in 59% of patients. In this smaller subset of patients we found residual disease in 60%, showing this smaller group to be representative for the study population. Although this number is at the upper edge of the reported literature data, it can be easily explained. At first, we omitted brachytherapy from the treatment protocol and delivered a simultaneous boost to the tumor using IMAT alone. Secondly surgery consisted of Wertheim type 2

hysterectomy while in most referred articles, the authors used a simple hysterectomy. Thirdly surgery was performed 4 to 6 weeks after ending IMAT, whereas the effect of radiotherapy tends to last longer. Finally, but probably very important, is the fact that the median initial diameter of the tumor in our study population was substantially larger than in comparable trials5.

Only in half of the patients with residual disease (sensitivity of 50%) cervical biopsies showed malignancy. Although we performed multiple cervical biopsies (4 each patient) using an advanced biopsy device (resulting in larger and deeper biopsies) these results should be considered disappointing. Not surprisingly, as shown in TABLE 2, the smaller the residual tumor, the higher risk of obtaining a false negative biopsy. These data are based on a small set of patients and further data on this topic are being collected.

CONCLUSIONS

Based on a small subset of patients it seems that cervical biopsies after EBRT has only a sensitivity of 50% to predict residual disease. The residual disease load was inversely related to the predictive value of the biopsy. These preliminary disappointing results of cervical biopsies post (chemo) radiotherapy for LACC strongly suggest that completion surgery should not be omitted in our treatment protocol.

REMARK: the text is identical to the one submitted to the journal

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Chapter 6: *Discussion*

6.1 Is there need for a FIGO face-lift?

Cervical cancer is a global health crisis that is still responsible for more than 266.000 female deaths annually worldwide[1]. More than 80% of cervical cancer cases occur in low resource countries. The "epidemic" of cervical cancer in the sub Sahara countries is a reflection of the dramatic gap in health care between industrialized and underdeveloped countries in all its aspects from prevention, through screening and ending with management.[2,3,4] The limited health care facilities in low resource countries result in retarded diagnosis with as consequence often an advanced stage of disease, associated with a poor overall prognosis.

Recent introduction in industrialized countries of advanced imaging techniques have proven their value in assessing the extent of local disease (mainly MRI)[5,6] and distant spread including lymph node invasion[7] (CT and PET (CT)). Lymph node invasion is not included in the conventional FIGO staging system, but requires early detection and treatment and is an important prognostic factor. The most reliable diagnostic and therapeutic option is a systematic lymph node dissection. However this approach has a risk for (post)operative complications and therefore non invasive methods for detection of lymph node metastasis are required. In a large prospective study on the value of FDG-PET/CT for detecting pelvic lymph node invasion in 120 cervical cancer patients with $\geq$ Ib, Loft et al.[8] found a sensitivity of 75%, specificity of 96%, positive predictive value of 75% and a negative predictive value of 96%. These values were 100%, 99%, 94% and 100% for detection of para-aortic lymph node invasion and 100%,94%, 63% and 100 % for the detection of distant metastasis.

MRI and PET/CT are not accessible in low resource countries and the inclusion of its results in FIGO staging would imbalance the staging system resulting in incomparability of the obtained results. The success of FIGO staging is therefore

mainly based on the fact that it can be used worldwide. Nevertheless from being an ideal staging system to be used in comparing treatment results and prognosis, it is expected to be reliable and reproducible. Although used for almost a century no data on the accuracy of FIGO staging are available. In a prospective study (see chapter 4)[9] we examined the interobserver agreement of the examination under anaesthesia (EUA) on which FIGO staging mainly is based, in order to investigate its reliability and reproducibility. Our data demonstrated only a moderate inter observer agreement (IOA) on the FIGO stage among experienced investigators. These results should be considered disappointing and could indicate possible limitations for sharing and comparing results based on this staging system. At present time the therapeutic impact of the moderate agreement on FIGO stage seems limited since we found an almost perfect IOA between experienced examiners on their treatment proposal. This can be explained by the fact that currently only few therapeutic options are considered as standard treatment[10,11] : 1) surgery as primary option for early stage non-bulky disease and 2) chemo radiation for more advanced disease.

Our data demonstrated a significant better agreement concerning FIGO stage between experienced investigators than between an experienced and an inexperienced investigator. This resulted consequently in a lower level of agreement concerning the choice of therapy between experienced and inexperienced investigators. This implies that clinical gynecological examination is a skill that can be improved by training. Additionally it stipulates that patients should be staged by at least one experienced clinician in order to obtain the best possible clinical staging. A close look to the disagreement patterns on FIGO stage showed that in case of discrepancy the inexperienced investigator tended to underestimate the disease stage (by rating the FIGO stage to be lower than the rating of the experienced examiner) and consequently recommended surgery in patients that were considered inoperable by the experienced examiner. This could implicate a potential risk of suboptimal surgeries, with positive surgical resection margins and consequently need for adjuvant radiotherapy (RT). Overall this would result in a suboptimal treatment with an increased risk of morbidity[12] and higher medical costs.

In order to evaluate possible confounding factors of the clinical cervical cancer FIGO staging we investigated the impact on the IOA of some patient or tumor related characteristics. Multivariate analysis could not demonstrate a significant impact on the IOA of any of the investigated characteristics. It is important to stress that all exams were performed under general anaesthesia. This could explain why for example Body Mass Index (BMI), in these optimal conditions, had no major impact on the clinical staging of cervical cancer.

For gynecological cancers there has been tremendous movement over the last decade toward centralization of care into specialized centres. This comes from the recognition that multidisciplinary care, including access to opinions from gynecologic, medical, and radiation oncologists, can improve patient outcomes[13,14]. In addition to this input, it is important to have access to subspecialty pathology, diagnostic radiology, oncology nursing, and other disciplines as necessary. We think that the demonstrated impact of the experience of the practitioner on the reliability of cervical cancer staging is an important additional argument for further centralization of care in cervical cancer. In addition centralization in high volume hospitals would facilitate an optimal training in cancer staging and management. In low resource countries, where optimal conditions and additional imaging is often not available, the experience of the investigator is probably even more important. In these countries, in addition to an organized screening[15] and an adjusted vaccination program[2,3,4], the specialized training of the practitioners is a top priority that could result in a significant improvement on the overall prognosis of cervical cancer patients.

While for the coming decennia in low resource countries FIGO staging based on clinical examination will stay the corner stone in the management of cervical cancer, its significance in industrialized countries will be challenged by the evolution in imaging technology. Therefore the latest revision of the FIGO staging in 2009[16] remarked that advanced imaging techniques are useful (and even advisable when available) in therapeutic decision-making, but should not be used to alter the FIGO stage. This remark is a reflection of the reality in developed countries where the use of advanced imaging is more standard than exception in treatment

planning[17,18]. Recently advanced imaging techniques have been included by the National Comprehensive Cancer Network among the procedures for pretreatment work-up of cervical cancer.[19] This evolution in imaging techniques together with innovations in radiation therapy created new therapeutic approaches that permit a more tumor delineated treatment, associated with less morbidity, better quality of life (QOL) and hopeful survival results. This is most needed in advanced disease (bulky disease and LACC) where survival rates still stay disappointing. Therefore the ethical issue arises whether one should stick to a clinical based staging system of cervical cancer in order to be able to compare results of outcome of treatment and thereby ignoring the advantages of new diagnostic tools is more important than allowing improvement in cervical cancer care through a tailored approach based on these new diagnostic tools. Exclusion of advanced techniques could slow down research for new treatment modalities, predictive markers and prognostic factors.

In conclusion we think that in the present global health care situation there is no possibility to introduce a general applicable new "face-lifted" FIGO staging system. Nevertheless, in industrialized countries the availability of advanced imaging techniques creates opportunities for a makeover in treatment planning and in individualization of management that will be at least associated with better QOL. However the application of these advanced techniques in the management of cervical cancer can hamper comparison of different treatments outcomes unless included within a standardized framework.

6.2 The (re)introduction of completion surgery in the treatment of LACC in an era of advanced radiotherapy

Since the publication by Green et al.[20] in 2001 of a meta-analysis demonstrating the additional effect of chemotherapy when added to RT in the treatment of LACC, external beam radiotherapy (EBRT) with cisplatin based concomitant chemotherapy followed by brachytherapy (BT) is considered standard treatment for bulky IB and locally advanced cervical cancer (LACC) up to stage IVA[21,22,23,24].

A Cochrane review in 2005[25] confirmed these findings: chemo radiation (CRT), when compared to RT alone, improves overall survival (OS) and progression free survival (PFS) with absolute benefits of 10% and 13% respectively. It also showed a significant benefit for local recurrence and a benefit of distant recurrence of borderline significance. These findings have suggested the hypothesis that concomitant chemotherapy may afford radio-sensitization and systemic cytotoxic effects[26]. Nevertheless, the meta-analysis of Green[20] showed a rather limited survival benefit for LACC in the group with FIGO stages III–IVA. In order to obtain better results some groups adopted the idea of performing completion surgery after CRT[27,28,29,30]. The rationale for this idea is to obtain a better local control that might translate into a better OS.

6.2.1 Favouring arguments for completion surgery

The rationale for completion surgery is double. Firstly it allows the removal of potential radiation therapy–resistant tumor foci[29,31] and secondly it permits the assessment of the pathological response to the initial treatment. The presence and size of residual disease (RD) is a strong prognostic factor for future recurrence[31,32,33,34]. Depending on the study or FIGO stage, the rate of RD after CRT on the surgical specimen ranges from 45% to 70% [27,29,31,35,36]. The chance of RD after primary CRT is dependent on initial stage of disease.[37] We reported a RD of 59% (publication 3)[38] (38% with RD <1 cm, 21% with RD ≥1 cm) and 60% (publication 4)[39]. The incidence of RD in our series is rather high because of 3 main reasons. A) We omitted BT from the treatment protocol and delivered a simultaneous boost to the tumor using IMAT alone. B) We performed Wertheim type 2 extended hysterectomy that included parametrial and vaginal wall resections while simple hysterectomy was performed in most previous publications[27,29,31]. The parametrium or the vaginal-cuff was the only site of RD in 5.8 % of our patients. Sun et al.[40] reported an overall RD of 12% in parametria and 4.2% in the top of the vagina were reported. With a simple hysterectomy this RD would not have been detected. C) Surgery was performed 4 to 6 weeks after RT, whereas the effect of RT tends to last longer. The timing of surgery has an impact on RD rates (see TABLE 6.2). D) Last but not least the average initial diameter of the tumor in

our study population was substantially larger (5.3 cm) than in comparable trials. (See TABLE 6.2)

Since patients with RD are at risk for an early recurrence there is an urge for an additional treatment in order to improve their prognosis.

6.2.2 Concerns regarding the morbidity of completion surgery

Ever since the option of completion surgery was proposed there has been a lot of concern regarding its morbidity[32]. Intra- and postoperative complication rates of completion surgery depend, as in primary surgery, mainly on the extent of the procedure. More complications are seen when surgery consists of Piver[41] III or IV and in case of extended (pelvic and/or para-aortic) lymph node dissections[42,43,44,45]. In a recent paper by Ferrandina[44] et al. 25.7 % of patients experienced any grade postoperative complications, 16.6 % had ≥ grade 2 complications and grade 3-4 complications occurred in 5.8 % of patients. In this study 86.5 % of patients underwent type III-IV radical hysterectomy. Adopting class II radical hysterectomy we showed low operative and postoperative complications even though surgery was performed after CRT. Our complication rates are comparable to these reported after primary surgery for low-stage disease[46,47].

	Pahisa[47]	Trimbos[46]	Tummers[38]
Mortality	0%	< 1%	0%
Venous thromboembolism	8.7%	3%	3%
Bowel injury	0%	NA	0%
Bladder injury	8.7%	NA	0%
Ureter injury	4.3%	NA	0%
Urinairy tract infection	NA	42%	9%
Postoperative transfusion	26.1%	32%	17.6%
Fistula	NA	2.1%	0%

TABLE 6.1: peri-operive complications. Pahisa and Trimbos: primary Wertheim surgery, Tummers: Wertheim post chemo radiotherapy. (NA= data not available)

The low morbidity rates in our series can also be explained by the fact that: all of our patients were primarily treated by Intensity Modulated Arc Therapy (IMAT) which permits more precise targeting of the tumor and relative sparing of surrounding/ normal organs and tissues. We are convinced that the concern about serious operative morbidity might be more legitimated in cases where conventional radiation technology is applied. It is known that the introduction of advanced RT techniques such as intensity-modulated radiotherapy (IMRT) and IMAT is associated with a better therapeutic ratio and a significant decrease in grade 3 and 4 RT-related toxicity[30,48]. In addition it also reduces the radiation dose to what we call uterine suspensory ligaments. This creates new opportunities for completion surgery. It makes complementary surgery easier, certainly from a technical point of view, and makes it possible to perform a more radical hysterectomy to remove also the parametria and the upper 2 cm of the vagina. Another explanation for our morbidity rates might be the fact that all patients have been operated on by experienced gynecologic oncologists (first and second authors).

The use of additional brachytherapy or intraoperative radiotherapy in previous reports could have a negative impact on the complication rates. In our series we avoided brachytherapy by performing surgery. Omitting brachytherapy is associated with lesser frequency of chronic proctitis and vaginal stenosis (with decreased sexual function). These adverse effects are not neglectable and can have a significant impact on the QOL certainly when taking into account most women with cervical cancer are diagnosed before the age of 50.

After CRT treatment, about 16% of patients are left with positive pelvic lymph nodes. This rate increases if the primary tumor is radio-resistant [49,50]. Initially, a pelvic lymphadenectomy was performed in all our patients during completion surgery. However, because the number of positive lymph nodes was limited, and all positive lymph nodes were located at the initial positive ^{18}FDG PET-CT location, our policy was changed, and only the PET-CT–positive lymph nodes (or lymph node areas) were removed. It is nevertheless important to remember that complications after pelvic lymphadenectomy following CRT are not negligible. In our series 2 patients had persisting lymphocoeles that needed prolonged hospitalization

for repeated evacuation, and even in 1 patient a lymphatic micro-anastomosis was performed. In contradiction, after modification of the lymph node dissection protocol no significant lymphoceles developed.

6.2.3 Impact of completion surgery on survival rates

Until now no data are available from a large prospective randomized controlled trial proving a benefit in OS of patients with bulky IB and locally advanced cervical cancer (LACC) up to stage IVA treated with (C)RT followed by (radical) hysterectomy in comparison with patients managed by standard treatment ((C)RT + brachytherapy).

Few papers were published regarding completion surgery after CRT. Comparison of the results of different institutions hampered by heterogeneity of different confounding factors including disease stage, dose of RT, modalities or chemotherapy, achievement of brachytherapy and type of surgery. Analysis of the outcome of completion surgery is therefore infeasible. In TABLE 2 we tried to highlight some specific issues.

	# patients	FIGO stage	mean initial size (cm)	Piver	time window for surgery (weeks)	residual disease %	survival (%)
Keys et al. 1999[20]	132	IB2	NA	I	2-6 weeks	52.0%	5-year DFS = 62%
Houvenaeghel al. 2005[28]	35	IB2-IVA	NA	I-IV	4-10 weeks	54.2%	10-year DFS = 66.4% 10-year OS = 57.7%
Classe et al. 2006[30]	175	IB2-IVA	NA	I-IV	4-6 weeks	61.1%	5-year OSC=89% 5-year OSP=54%
Huguet et al. 2008[32]	92	IB-IIA-IIB	4.9 cm	II	3-14 weeks	45.5%	2-year DFS = 80.4% 2-year OS= 93.8% 5-year DFS = 72.2% 5-year OS= 78%
Ferrandina et al. 2010[50]	174	IB2-IVA	NA	III	4-14 weeks	56.3%	5-year DFS = 75.5% 5-year OS= 77.4%
Tummers et al. 2013[37]	31	IB2-IVA	5.3 cm	II	4-6 weeks	58.8%	3-year DFS= 91% 3-year OS = 81%
Wang et al. 2014[35]	119	IIB	4.5 cm	ns	2-3 weeks	68.9%	3-year DFS= 91% 3-year OS= 94.9%

TABLE 2 : Illustration of the diversity of reported data on OS and DFS in completion surgery for bulky and locally advanced cervical cancer. (DFS= disease free survival, OS= overall survival, OSC= overall survival in case of complete response, OSP= overall survival in case of partial response)

Keys et al[21] included 256 eligible patients with bulky exophytic or "barrel"-shaped IB tumors. These patients were randomized to either RT plus brachytherapy (n = 124) or RT followed by extrafascial hysterectomy (n = 132). They reported complete pathological response rates in 48% of patients. There was macroscopically RD in 12% of the patients. Interestingly, patients with bulky IB2 disease who underwent adjuvant hysterectomy had an improved 5-year DFS of 62% compared with 53% in the group without complementary surgery (p=0.09). The difference reached significance (p=0.04) when comparisons were adjusted for tumor size, performance status and age. This improvement was mainly related to reduced local recurrence rate after hysterectomy (15% versus 27%). Unfortunately, this improvement in DFS was not translated into significantly improved OS. Reasons for lacking survival benefit could be a relatively limited number of patients in each arm and the absence of effective adjuvant therapy for patients at risk of having systemic metastases (those with RD after CRT). Another reason might be the lack of number of patients with LACC who are at risk of having RD following CRT as shown by meta-analysis of Green et al[20]. Nevertheless, a subgroup analysis showed a significant survival benefit in favor of complementary hysterectomy in patients with tumors measuring 4 to 6 cm. In addition, the authors stated that even if survival was not improved, complementary surgery resulted in a better QOL before metastatic spread, as local recurrence is a source of chronic pelvic pain.

In a recently published prospective trial Wang et al.[36] compared two groups of patients with FIGO stage IIB cervical carcinoma treated either with RT followed by radical surgery (n = 119) or with RT followed by brachytherapy (n = 121). This report is however not a randomized trial since patient's preference decided on treatment modality. They showed a 3-year OS benefit of 10.3 % (94.9% versus 84.6%, p=0.011) and a 3-year PFS benefit of 9.2% (91.0 versus 81.8%, p=0.049) in favour of patients that received completion surgery. The results of this trial are very promising.

Because only a randomized controlled trial could adequately determine whether completion surgery would be therapeutically beneficial, the GYNECO 02 study[35] was started in 2002. This multicentre phase III trial comparing hysterectomy with

no hysterectomy in patients with a clinical and radiological complete response after CRT for stage IB2 or II cervical cancer was stopped after 3 years because of insufficient accrual. Nevertheless, 61 patients were included and were investigated (arm A with surgery: 30 patients, arm B without surgery: 31 patients). Although the study was underpowered, results seem to suggest that completion surgery had no impact in these patients. A major reason for the poor accrual was the preference of the participating physicians toward hysterectomy and patients insisting on having the "initial site" of the tumor removed. Possible positive psychological effect of the procedure is seldom reported in the literature. This study is one of the few that looked more carefully to this particular aspect and observed that patients submitted to the adjuvant procedure are highly satisfied. A number of women referred to subjective sense of relief, enhanced feeling of cancer cure, and improved self-esteem after extirpation of the affected organ. Further research on the QOL after completion surgery is required.

The promising results from the first two trials and the fact that the only randomized controlled trial (RCT) was closed early because patients and practitioners favored completion surgery and therefore did not want to be randomized, urges for a new international multicentre RCT on this topic.

6.2.4 How to select patients for completion surgery

In order to reduce the overall toxicity of the treatment in patients with LACC it would be opportune if we could select patients with RD after initial RT treatment that would benefit adjuvant treatment. Consequently this would mean that we would be able to avoid additional brachytherapy and/or surgery (or other treatment modalities) in patients without RD. This could minimalize the treatment toxicity without deteriorating the prognosis.

In a pilot study we used the ®Spirotome Cervicore system to evaluate the value of cervical biopsies in predicting therapy response after CRT (using IMAT). This device was developed specifically for cervical disease that needs a representative and high quality diagnostic biopsy from both the mucosa and submucosal

structures. A high quality sample with a penetration depth of 20 mm can be obtained, which is larger and penetrates deeper than when classical biopsy instruments are used. This deep penetration is useful in evaluating treatment response, since (chemo) radiation therapy induces diffuse ulceration and erosion of the tumor with, often, RD beyond the surface of the cervix. Only in half of the patients with RD (sensitivity of 50%) cervical biopsies were contributory and showed malignancy. Although we performed multiple cervical biopsies (4 each patient) using this advanced biopsy device, false negative results were observed in 50% of patients. Based on these disappointing results we can conclude that cervical biopsy is not valuable in predicting pathological response in patients with LACC after an initial IMAT±C treatment because of its low sensitivity. As demonstrated in Morice et al.[35], patients with a clinical and radiological (MRI and PET-CT) complete response to initial CRT + brachytherapy still showed in more than 30% of cases residual disease on pathological examination of hysterectomy specimen after surgery, demonstrating the poor reliability of preoperative clinical and radiological evaluation in predicting RD after CRT. In a study by Fanfani et al.[52] 2013 cone biopsies were used to predict the treatment response in FIGO IB2-IIB cervical cancer patients to neo-adjuvant CRT. Results showed cone biopsies accurately identified patients with complete and microscopic partial pathological response. The negative predictive value (NPV) of cone biopsy was 100%. In their series the NPV of MRI and PET-CT was 79% and 79%. A close look to the presented data showed that: 1) In 25% of patients the intended cone biopsy was omitted because of stenosis of the top of the vagina or because of the complete cervical tissue retraction. 2) The cone biopsy was performed at the time of surgery, while when to use it in order to predict response to initial treatment it should be performed prior to surgery. After a cone biopsy it is advisable to wait several (on average 6) weeks before performing (radical) hysterectomy in order to avoid additional complications. This would delay surgery beyond the ideal time window (4-6 weeks after CRT) concerning radiotherapy related fibrosis. Overall we think these data on cone biopsy are encouraging but a larger study to verify the safety, real life feasibility (cone biopsy prior to surgery) and oncological efficacy are needed before it should be considered a valid option for the pathological response evaluation of LACC patients undergoing neo-adjuvant CRT.

6.3 Future perspectives on …

(FIGO) staging

- The experience of the investigator is an important confounding factor in the reliability of FIGO staging of cervical cancer. In low resource countries where there is no/limited access to (advanced) imaging techniques, this experience is probably even more crucial, since treatment planning relies (completely) on clinical FIGO staging. Centralization of care in high volume hospitals would optimize staging and treatment conditions and would facilitate better training opportunities. It is obvious that this change towards centralization in management of cervical cancer care needs a global approach driven by an institution such as the World Health Organization. Our research on this topic could help to put this item on their agenda. Ideally it should be part of a master plan covering also sex-education, screening, adapted HPV vaccination programs and HIV prevention and treatment.

- In a sequel to our study on the reliability of clinical FIGO staging, we want to add in all patients the information of MRI and PET-CT to the data in order to investigate on which indications their input in staging is required/favourable.

- The application of advanced imaging techniques in the management of cervical cancer in industrialized countries can hamper comparison of different treatments outcomes. Therefore there is a need for a standardized framework in treatment planning.

Treatment of LACC

- A prospective randomized trial comparing 1) complementary surgery following CRT with 2) standard treatment (EBCRT + BT) in patients with bulky and locally advanced cervical cancer is required. The design of this study should take consideration to all different aspects such as survival benefit and QOL (including sexuality).

- A prediction model could help us in the selection of patients without RD after initial CRT treatment that can be saved unnecessary additional treatment such as complementary surgery or brachytherapy. We plan to investigate if the combination of information obtained by clinical examination, tumor markers, cone/core biopsies, MRI and PET-CT could lead to an accurate prediction model of RD.

- Patients with persisting disease after CRT are at high risk of disease recurrence and distant metastases. An additional effective consolidation therapy is urgently required in this subcategory as no efficient chemotherapy is available. Further investigations within field of targeted therapy or therapeutic vaccination are needed.

6.4 Conclusions

FIGO staging

- We describe a moderate interobserver agreement on clinical staging of patients with cervical cancer. These results should be considered disappointing and could indicate possible limitations for sharing and comparing results based on this staging system.

- In order to obtain an optimal clinical staging of cervical cancer it should be performed by an experienced investigator and under optimal conditions including general anesthesia.

- Staging by an inexperienced investigator is associated with a significant higher risk of under staging. This might result in unnecessary surgeries, more need for adjuvant therapy and can result in increased morbidity and costs.

- The skill of clinical staging of cervical cancer can be improved by training within a centralized cancer care.

Treatment of LACC

- Type II Wertheim surgery after initial CRT with IMAT for bulky or locally advanced cervical cancer is feasible and is associated with low morbidity.

- Our data regarding completion surgery following primary CRT with IMAT for bulky/locally advanced cervical cancer are promising. These findings urge for a large international prospective randomized trial.

- Cervical biopsy has low sensitivity in predicting pathological response in patients with LACC after an initial IMAT$\pm$C treatment.

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"Genieten van het leven zoveel je kan… dat is wijsheid"

G. De Clercq-Colle

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