"Clinical outcomes of therapies for early-stage invasive uterine cervical cancer: a single-institution retrospective study"

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von

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Abreviations

AIS	Adenocarcinoma in situ
AE	Adverse event
A-RT	Adjuvant RT
A-CHT	Adjuvant chemotherapy
A-CCRT	Adjuvant concurrent chemoradiotherapy
CIN	Cervical intraepithelial neoplasia
CHT	Chemotherapy
CKC	Cold-knife conization
CT	Computerized tomography
CCRT	Concurrent chemoradiotherapy
LEEP	Loop electrosurgical excisional procedure
LLETZ	Large Loop Excision of the Transformation Zone
LSIL	Low-grade
LVSI	Lymphovascular space invasion
HSIL	High-grade
HPV	Human papilloma virus
FIGO	International Federation of Gynecology and Obstetrics
MRI	Magnetic resonance imaging
NA-CHT	Neoadjuvant chemotherapy
NA-CCRT	Neoadjuvant chemoradiotherapy
PET-CT	Positron emission tomography
RT	Radiotherapy
SAE	Serious adverse event
SCJ	Squamous columnar junction
SIL	Squamous intraepithelial lesion
Sg	Surgery
UCC	Uterine cervical cancer

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Abstract

Introduction: Late detection of cervical cancer is a serious health concern among adult women worldwide. It is influenced by the tumor's pathobiology itself as well as by failures in regular screening and follow-up testing. Options for the treatment of tumors include surgery, radiotherapy, chemotherapy or a combination, either sequentially or concurrently. Intrinsic tumoral factors, side effects, inherent toxicities of therapies, and therapy adherence influence treatment success and prognosis. However, there is limited or inconclusive evidence about treatment-related adverse events in patients with clinical diagnosis of early invasive cervical cancer.

Objective: To describe the clinical outcomes of therapies for patients with clinical diagnosis of early uterine cervical cancer, stages IA to IIB, who were treated at the University Clinic of Gynecology and Gynecological Cancer of Pius Hospital Oldenburg during 2009-2013.

Methods: Retrospective, descriptive analysis of treatment outcomes of women with clinical diagnosis of early uterine cervical cancer, FIGO stages IA2 to IIB. Changes of the initial disease stage after staging procedures were identified. Complications and serious adverse event frequencies, as well as recurrence and survival rates were estimated. For quantitative or numerical variables central tendency and dispersion measures were used. Values are presented as mean number of patients or percentage. The 5-years survival rate curve was estimated by means of the Kaplan and Meier method

Results: Clinical records of 60 women (mean age 50 years) were reviewed. In 25% of patients the initial stage increased and in 5% it decreased, identifying one case with disease stage IA1, 23 with B1, 6 with IB2, 12 with IIA, 15 with IIB, 1 with III and 2 with IVA. 75% had a squamous epithelial cancer and 23% an adenocarcinoma. Most patients presented with more than two high-risk factors of recurrence. 32% of patients underwent surgery alone, 31% adjuvant therapies, 25% neoadjuvant therapy, 4% chemoradiation, 2% radiotherapy and 2% chemotherapy. 57% of patients who received neoadjuvant therapy achieved complete tumor reduction prior to surgery. Most complications and toxicities occurred in patients who received adjuvant or neo-adjuvant chemoradiation, such as anemia (64%), hematological, renal or electrolytic toxicities (25%), urinary infections (18%) and ureteral stenosis (9%). Three ureter ligations occurred during surgery. Recurrence affected 25% of all patients, mainly after neoadjuvant chemoradiation. All deaths (N=13) occurred within the first three years following treatment, mostly in patients with recurrent disease, yielding a 5-years overall survival rate of 78%.

Conclusion: This study highlights the importance of staging as a crucial step in the treatment decision-making process when attending patients with a clinical diagnosis of uterine cervical cancer. By the other hand, radical surgery and concurrent chemo-radiation are effective for tumor size reduction, but an important number of adverse events are induced by these therapies. More research in regard to adverse events and tumoral behavior after different therapies for cervical cancer is needed.

Key Words: Cervical cancer; locally advanced; Adjuvant chemotherapy; Neoadjuvant chemotherapy; Gynecological cancer centers.

Zusammenfassung

Einführung: Die späte Diagnose eines Zervixkarzinoms ist ein weltweites ernsthaftes Gesundheitsproblem erwachsener Frauen. Sie wird beeinflusst durch die Pathobiologie des Tumors sowie durch Versagen regelmäßiger Screening- und Nachsorgeuntersuchungen. Die Therapieoptionen beinhalten die sequentielle oder zeitgleiche Anwendung von Chirurgie, Strahlentherapie und Chemotherapie sowohl einzeln als auch in Kombination. Innerliche Tumorfaktoren, Nebenwirkungen, inhärente Therapietoxizitäten und Therapieadhärenz beeinflussen den therapeutischen Erfolg und die Prognose. Nichtdestotrotz besteht eine eingeschränkte oder unschlüssige wissenschaftliche Evidenz über behandlungsabhängige unerwünschte Ereignisse in Patienten mit der Diagnose eines frühen invasiven Zervixkarzinoms.

Studienziel: Beschreibung der klinischen Ergebnisse der Therapien von Patienten mit der Diagnose eines frühen Zervixkarzinoms der Stadien IA bis IIB, welche zwischen den Jahren 2009 bis 2013 in der Gynäkologischen Universitätsklinik am Pius-Hospital in Oldenburg behandelt wurden.

Methoden: Retrospektive und deskriptive Analyse der Behandlungsergebnisse von Frauen mit klinischer Diagnose eines frühen Zervixkarzinoms im Stadium FIGO IA2 bis IIB. Änderungen des Tumorstagings nach Stagingdiagnostik wurden identifiziert. Es wurden die Häufigkeit von Komplikationen und Nebenwirkungen sowie Rezidiv- und Überlebensraten berechnet. Für quantitative oder numerische Variablen wurden zentrale Tendenz und Streuung berechnet. Die Angabe erfolgt als mittlere Patientenzahl oder prozentual. Die 5-Jahre-Überlebensrate wird in einer Kurve nach Kaplan und Meier dargestellt.

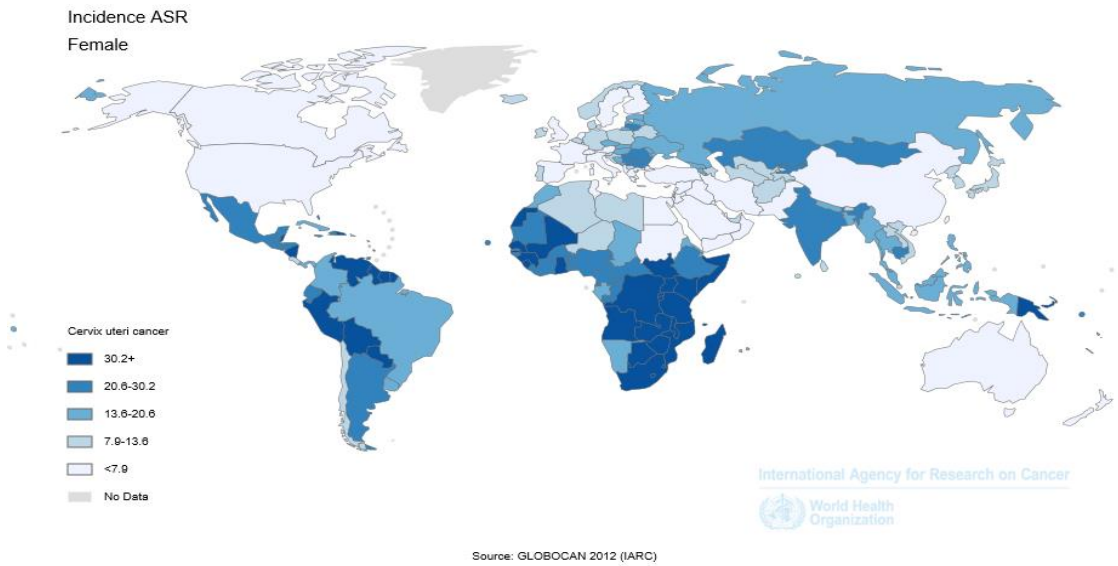
Ergebnisse: Es wurden Krankenakten von 60 Frauen (Durchschnittalter 50 Jahre) untersucht. Das initiale Tumorstadium wurde in 25% der Patientinnen hochgestuft und in 5% runtergestuft. Wir identifizierten einen Fall im Stadium IA1, 23 in IB1, 6 in IB2, 12 in IIA, 15 in IIB, einen in III und 2 in IVA. In 75% lag ein Plattenepithelkarzinom und in 23% ein Adenokarzinom vor. Die meisten Patientinnen wiesen mehr als zwei Hochrisikofaktoren für ein Rezidiv auf. 32% der Patientinnen erhielten nur radikal Chirurgie, 31% adjuvante Therapien, 25% neoadjuvante Therapie, 4% Radiochemotherapie, 2% Strahlentherapie und 2% Chemotherapie. 57% der Patientinnen mit neoadjuvanter Therapie erreichten eine komplette Tumorreduktion vor Operation. Die meisten Komplikationen und Toxizitäten traten in Patientinnen mit adjuvanten oder neoadjuvanten Therapien auf. Hierzu zählten Anämie (64%), hämatologische, renale oder elektrolytische Toxizitäten (25%), Harnwegsinfekte (18%) und Harnröhrenstenosen (9%). In drei Fällen erfolgte eine intraoperative Ureterligatur. Ein Rezidiv trat in 25% aller Patientinnen auf, überwiegend nach neoadjuvanter Radiochemotherapie. 13 Patientinnen verstarben und zwar alle innerhalb der ersten drei Jahre nach Behandlung, die meisten mit einem Rezidiv. Die 5-Jahres-Überlebensrate betrug 78%.

Schlussfolgerungen:Diese Untersuchung bekräftigt die entscheidende Bedeutung des Tumorstaging für die Versorgung von Patientinnen mit klinischer Diagnose eines Zervixkarzinoms, wegen seiner Auswirkung auf den Therapiefindungsprozess. Andererseits, Radikale Tumorchirurgie und zeitgleiche Radiochemotherapie reduzieren die Tumorgröße effektiv, induzieren aber auch eine wichtige Anzahl von unerwünschten

Ereignissen. Weitere Untersuchungen von Nebenwirkungen und Tumorverhalten nach unterschiedlichen Therapien des Zervixkarzinoms sind notwendig.

1. Introduction

Uterine cervical cancer (UCC) is one of the most common malignancies worldwide, with 500,000 new cases appearing yearly. In Germany during 2012, it is ranked tenth among all cancers (2.8%), and is the second most common gynecological cancer, with 4,995 new cases (Incidence rate 9.8/100,000), and 1,566 deaths during 2012 among women (mortality rate 2.4/100,000) (Figure 1) [1]. A 73% reduction rate (incidence rate 36/100,000) has been observed since the introduction of the Pap smear as part of the national health guidelines in 1971 as an effective early detection method for this disease [2].



ASR: Age-Standardized Rate per 100.000 – Reproduced with permission from IARC, 2012 [1].

Figure 1. Estimated Global Cervical Cancer Incidence Rates

Performed by a decentralized organization renowned for its level of high quality and the exclusive involvement of gynecologists and pathologists, screening is offered to all women over the age of 20 free of charge [2]. However, only 79% of all eligible women, in particular younger women, married women, and those with a higher degree of education, are effectively reached, [3]. Women with a lack of awareness derived from insufficient knowledge regarding the risks and benefits of the Pap smear, appear to be a

key-contributing factor for the emergence of new cases of advanced UCC. In 2012, 62% of the reported cases in Germany were diagnosed in initial stages and 39% in advanced stages of the disease, resulting in decreased options for more conservative or fertility sparing interventions [4]. In the University Clinic of Gynecology at Pius Hospital of Oldenburg, a leading center for gynecological oncology and a reference center for the Weser-Ems region of Germany, 96 women were treated for UCC during the period 2009-2013. 15% of them exhibiting a microinvasive disease IA, 63% an early invasive disease IB-IIB, and 26% an advanced disease stages III-IV. Those patients with clinical diagnosis stages IA2 to IIB (N=60) constituted the population of the present study (Figure 2b) [Data provided by Pius Hospital´s Tumor Documentation Bureau] (Figure 2).

Fig. 2a. All referred cases
N= 96

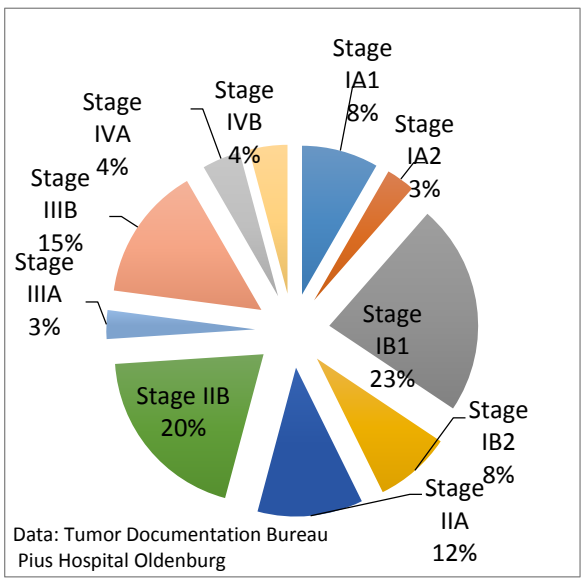


Fig. 2b. Study population
N= 60

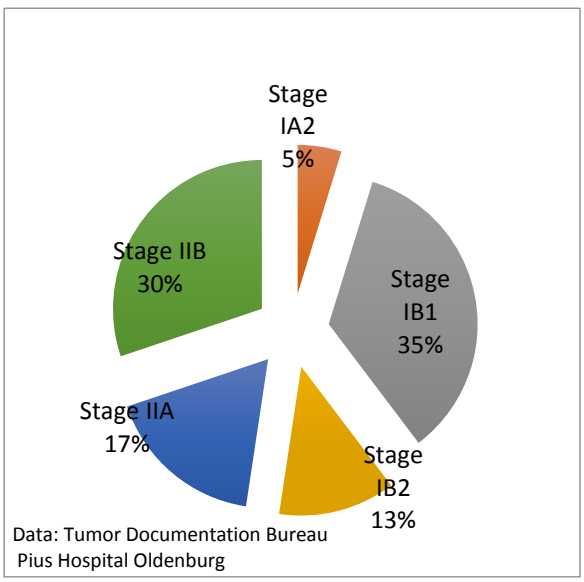


Figure 2. Cases of cervical cancer and study population attended at the University Clinic of Gynecology, Pius Hospital of Oldenburg. 2009-2013

The main risk factor for UCC is infection of the cervix with Human Papilloma Virus (HPV). Other risk factors are early sexual activity, multiple sexual partners, and cigarette smoking [5]. Therefore, emphasizing preventive measures and vaccination against HPV can help to decline the incidence and mortality rates related to UCC [6]. Evidence based guidelines are periodically updated globally as well as in Germany, in order to improve the quality of care that is provided to patients. This in turn impacts the

accuracy of diagnosis, recurrence, and survival rates among this population [5].

Guidelines recommend that the treatment of UCC cases should be managed by an expert interdisciplinary team and should be based on the initial spread of the disease, the woman´s clinical condition, the patient's choice, and availability of resources. Successful treatment includes the destruction of abnormal tissue and control of the disease. In metastatic stages, recommended treatment includes providing specialized medical and support care. Once an abnormal Pap smear is detected, a subsequent colposcopy is performed to confirm the diagnosis. When a pre-invasive neoplastic lesion is found, destruction of the affected cervical epithelium or resection of the uterine cervix could be the definitive treatment. For early invasive and advanced UCC the options include a broad spectrum of single, sequential, or concurrent therapies; surgery (Sg), radiotherapy (RT), chemotherapy (CHT), or concurrent chemoradiotherapy (CCRT). Support and best care practices include the management of co-morbidities related with tumor dissemination, pain control, and psychosocial support.

Intrinsic tumoral factors, side effects, intrinsic toxicities of therapies, and therapy adherence influence treatment success and prognosis. Intrinsic tumoral factors include histologic type and immunohistochemistry, staging at diagnosis (TNM stage), infiltration of stromal nerves, venules, and lymph vessels, lymph node involvement, and compromised resected borders after initial surgery [5, 7]. In German women, the worst survival rates are observed in those patients with advanced TNM stage at diagnosis and histology of adenocarcinoma (Table 1) [7].

Table 1: Relative 5-year survival rates of German women with uterine cervical cancer, according to TNM stage

Histologic type	TNM stage of disease				
	0	I	II	III	IV
Squamous cell	100	83%	62%	42%	18%
Adenocarcinoma	100	51%	44%	17%	0%
UCC= uterine cervical cancer T= tumor size N= lymph node involvement M= metastasis		UCC 0 = TIS N0 M0; in situ. UCC I = T1 N0 M0; UCC II = T2 N0 M0; UCC III = T3 N0 M0 or T1-3 N1 M0; UCC IV = T4 N0 M0 or T4 N1 M0 or any T of any N M			
Font: Based on Port, 2011[7].					

Moreover, side effects and intrinsic toxicities of therapies influence the patient's adherence to treatment. Complications are related to the extension of the procedure, the surgical technique or the combination of therapies. Physical and psychosocial factors, such as anxiety, depression, pelvic organs dysfunction, and sexual dysfunction are also linked to complications among women [8,9]. Complication rates are related to treatment methods; treatments of dysplastic lesions and micro-invasive disease have very-low complication rates. Invasive disease cases that require minimal aggressive surgery exhibit low rates of acute complications including decreased blood loss, reduced postsurgical pain, short hospitalization, improved cosmetic results, and a faster recovery [10].

Radical procedures and RT are associated with anorectal dysfunction, urinary symptoms, vaginal dryness, short vagina, dyspareunia, and lymphedema. CHT can induce hematologic, renal, and neurological toxicities [11]. Furthermore, few studies have been conducted evaluating the side effects and sequela of the combined chemoradiation for patients with early invasive disease [4,12,13]. Thus, better knowledge of the disease and effects of available therapies is needed.

1.1. Scientific rationale and significance

The advancement in cancer screening and treatment methods allows women with UCC to have better prognoses now than even before. Nevertheless, the cancer itself, its management, and treatment related complications significantly affect the woman´s quality of life. Therefore, the scientific community is determined not only to improve the recurrence and survival rates of patients with UCC [5,9], but to improve the quality of care that physicians give their patients with UCC [8, 9,14].

With the intention of adding to the knowledge within the international community and to help our patients affected by UCC in the decision-making process related to their therapy and subsequent self-care, we conducted a retrospective study to describe the clinical outcomes of therapies provided to patients with clinical diagnosis of early uterine cervical cancer who were treated at the University Clinic of Gynecology and Gynecological Cancer of Pius Hospital Oldenburg between 2009 and 2013. In addition, the first two sections of this paper present a comprehensive literature review

regarding the physiopathology, diagnosis, and treatment of UCC in order to give an overview of the disease and the current state of its diagnosis and treatment.

Part I.

2. Physiopathology and diagnosis of uterine cervical cancer

2.1 Anatomy

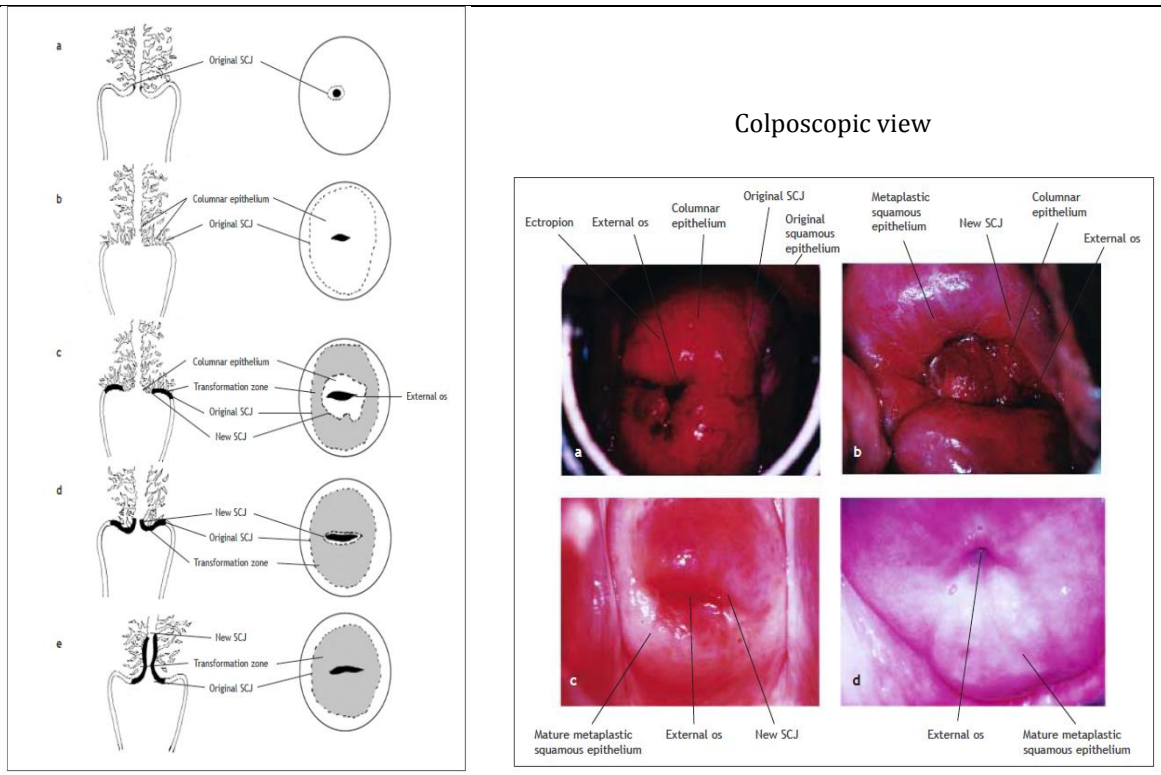
The uterine cervix is a unique structure within the woman's body due to its localization, cell architecture, hormonal susceptibility, surrounding environment, and function. It constitutes the most inferior portion of the uterus, protruding slightly angled into de upper vagina (exocervix), and is connected to the uterine isthmus through an internal canal (endocervix) [15]. Its size and form depend of the woman´s reproductive stage, usually 2.5-4.0 cm in length x 2.5 cm in diameter in the adult null-gravida [16]. Moreover, the cervix is relatively insensitive, with innervation limited to the endocervix and peripheral exocervix [15].

The main functions of the cervix become very important during the woman´s reproductive years, facilitating the migration and transport of sperm from the vagina to the uterine cavity with the purpose of fertilization; acting as a sphincter to retain the fetus and membranes during pregnancy; and as the channel to permit the birth of the fetus [15]. It may be used to support some contraceptive devices such as cervical caps, diaphragms, and female condoms [17]. Additionally, the intrinsic relations of the cervix with other pelvic organs have been postulated to play an important supportive and sexual role, helping to support the pelvic floor to prevent bladder and genital prolapse; and improving sexual sensations during intercourse, however this evidence is still controversial [18, 19].

The descending branches of the uterine arteries supply the cervix with blood, while the parallel venous plexus system communicates with vessels of the urinary bladder's neck. Its mucosal and stromal lymphatic drainage collects into four nodal regions: external iliac and obturator nodes, hypogastric and common iliac nodes, sacral nodes, and nodes found in the posterior wall of the urinary bladder [15]. Menstrual cycle, pregnancy, and labor induce the most dramatic changes in cervix's morphologic and histologic characteristics.

The cervix is composed of fibrous, muscular, and elastic tissue and is covered by mucosae. The exocervix is coated by a three layer non-queratinized squamous glycogen-containing epithelium, while a single layer of columnar epithelium covers the

endocervix; the line where both epithelia converge is called the squamous-columnar junction. This squamous-columnar junction is very sensitive to estrogen levels, vaginal pH and infections, moving from the exocervix during the reproductive years into the cervical canal after menopause. The continuous exposure of the endocervix to the acidic vaginal environment during the reproductive years and pregnancy, or in response to infections, leads to the development of a new squamous metaplastic epithelium, which in turn transforms into a mature squamous metaplastic epithelium [15,16]. The area where the endocervical mucosae is or has been replaced by new metaplastic squamous epithelium is denominated the transformation zone (Figure 3).



(a) Original squamous columnar junction (SCJ) in a young woman in the early reproductive age group. The SCJ is located far away from the external os. Note the presence of everted columnar epithelium occupying a large portion of the exocervix producing ectropion.
(b) The new SCJ has moved much closer to the external os in a woman in her 30s. The SCJ is visible as a distinct white line after the application of 5% acetic acid due to the presence of immature squamous metaplastic epithelium adjacent to the new SCJ.
(c) The new SCJ is at the external os in a perimenopausal woman.
(d) The new SCJ is not visible and has receded into the endocervix in a postmenopausal woman. Mature metaplastic squamous epithelium occupies most of the exocervix.
(e) SCJ in a postmenopausal woman.

Source: Based on Sellors, JW, and Sankaranarayanan R. 2003 [16].

Figure 3. The Squamous-columnar junction and transformation zone

These metaplastic changes are irreversible and may progress to dysplasia or anaplasia or further invasive cancer if an uncontrolled proliferation and expansion of the abdominal cells occur (Figure 4) [16].

Source: Own design, based on Sellors, JW, 2003.

Figure 4. Mechanisms of cervix metaplasia

Additionally, the cervix may be affected by non-malignant abnormalities that are of mandatory recognition during the differential diagnosis of the cervical cancer.

2.2 Benign diseases of the uterine cervix

There is a broad spectrum of benign uterine cervical diseases, including congenital anomalies, anatomical variations, inflammatory diseases, non-malignant tumors, and pre-malignant lesions (Table 2). Anatomical anomalies in particular may not be recognized until the onset of puberty or reproductive years, when girls and women are examined due to primary amenorrhea, infertility or recurrent abortions [20]. Likewise, an elongated cervix could be the cause of dyspareunia, while cervix stenosis is associated with dysmenorrhea and infertility [21]. The presence of cervical myomata or other nodules could impair the fertilization or effacement during labor [22]. The postoperative spindle cell nodule is a reactive benign lesion that develops several weeks to months at the site of a recent cervix operation [23].

Acute and chronic diseases produced by bacterial, protozoan, viral or fungal microorganisms could produce signs and symptoms of inflammation such as vaginal discharge, pelvic pain, abnormal bleeding, or lymph node enlargement. However, the inflammatory changes induced by these infections are usually not limited to the transformation zone and could also lead to the obstruction of mucosa glands, with the subsequent appearance of petechiae, erosions, vesicles, condylomata, cysts, or mucosal polyps [16].

Table 2. Benign diseases of the uterine cervix

Type	Diseases
Congenital anomalies	Duplex cervix
	Septate cervix
	Cervical atresia
	Cervical aplasia
Anatomical variants	Cervix elongate
	Cervical stenosis
Inflammatory diseases	Cervicitis due to bacterial, protozoan, viral or fungal infections
	Condylomata
	Aseptic cervicitis related to intrauterine devices (IUD)
	Cervicitis induced by chemical irritants or foreign bodies (spermicides, tampons)
Benign tumors	Naboth cysts,
	Polyps
	Myoma
	Lipoma
	Hemangioma
	Postoperative spindle cell nodule
Pre-invasive lesions	Dysplasia
	Cervical intraepithelial neoplasia (CIN 1; CIN2; CIN3)

Own design

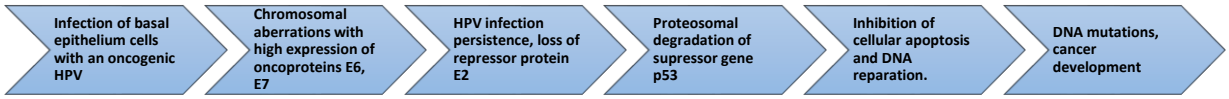
On the other hand, the presence of an inert or a hormonal intrauterine device (IUD) is characterized by an increased number of inflammatory cells in the mucosa layer like CD4+ T cells, macrophages, neutrophils, and NK cells, but without bacterial invasion or symptomatology [17,24]. Furthermore, infections play a key role in the development of permanent metaplasia of mucosal cells with a subsequent risk of developing premalignant and invasive lesions, especially those related with the HPV.

2.3 The role of the human papilloma virus in uterine cervical cancer

Premalignant and malignant lesions related to HPV are the result of a persistent infection of the immature basal squamous metaplastic epithelium [16]. Cervical HPV infection can be identified by the molecular detection of viral DNA by polymerase chain reaction (PCR), or Hybrid Capture 2 (HC2), though neither test can identify whether a woman is infected with a specific type of HPV [25]. Therefore, this test is not recommended prior to vaccination.

The persistent infection of cervical cells by oncogenic types of the HPV (16, 18, 45, 31, 33, 58, 52, 35, 59, 56, 6, 51, 68, 39, 82, 73, 66 and 70) [5] has been determined to

be a required factor in the initiation and progression of cervical cancer, as well of some vulvar, vaginal, and anal cancers. The oncogenesis induced by HPV initiates with a high expression of integrated oncoproteins E6 and E7 in the basal epithelium in combination with an elevated ratio of integrated-to-episomal viral DNA [26]. The infection of basal cells results in an excessive accumulation of chromosomal instability with concomitant loss of the repressor protein E2 and binding of E6 to the tumor suppressor gene product p53, promoting its proteosomal degradation. Therefore, cellular apoptosis is inhibited, integration of HPV episomes into the host genome occurs, and DNA damages are not repaired prior to cellular replication; consequently, carcinogenesis is initiated (Figure 5) [27].



Source: Own design, based on Habbous S, 2012 [26].

Figure 5. Oncogenetic mechanisms induced by HPV

Although in initial phases of the process an episomal clearance could occur through the repressor E2, via dependent- and independent p-53 pathways, which leads to cellular apoptosis and final regression to normal epithelium. Moreover, host genetic factors play a decisive role in the reduction of HPV load and spontaneous clearance of the infection during the transformation of normal tissue to dysplastic lesions, or during the progression of a dysplastic lesion toward cancer [26, 27]. For example, pre-invasive lesions tend to reappear in immunocompromised patients [27]; and women who exhibit a polymorphism in the p53 Arginine allele (p53Arg72Pro), that is a P-53 polymorphism on codon 72, whereby a point mutation of an Arginine into a proline occurs, seem to be more susceptible to develop invasive cervical cancer when exposed to HPV [OR 1.37; 95% CI, 1.15–1.62; $p< 0.001$] [26].

Granted that most persistent HPV infections involve only one HPV type, vaccination is considered a high cost-benefit public health intervention geared towards reducing morbidity, mortality, and the cost associated with screening, diagnoses, and

treatment of pre-invasive- and invasive HPV related lesions [25]. If no previous exposure has occurred, vaccination against some HPV oncogenic types 6, 11,16,18, 31, 33, 45, 52 and 58 induced a systematic humoral response making women resistant to infection by virus types contained in the vaccine but has little impact on existing infections [26]. With the introduction of the HPV DNA detection test and vaccination, modifications of screening programs are expected, as well as a decline in the prevalence of high-grade cervical intraepithelial neoplasia (CIN) and cervical cancer [28].

2.4 Risk factors of cervical cancer

Well-known risk factors for UCC are early initiation of sexual activity, multiple sexual partners, cigarette smoking, malnutrition, HIV infection, immunosuppression, multiparity, use of oral contraceptives, low level of education, history of high-grade CIN, and lack of access to UCC screening programs [5,29]. Around the world, delay of medical consultation is related to ethnical, geographical, socio-economic disparities as well as personal reasons. African American, Hispanic and women living in geographical areas with limited access to medical services exhibit advanced stages of the disease at diagnosis [30]. Key personal reasons for not seeking medical care are lack of recognition of symptoms as abnormal, infrequent care, and fear of cancer [31]. In younger women, reasons to not seek medical care include feeling too-embarrassed, difficulties to get an appointment or not wanting to waste the physician's time [32].

Additionally, some women are not aware of their risks of developing cervical cancer. Specifically in Germany, it is reported that 12% of women know at least one risk factor; almost 70% are insufficiently informed about the disease, 18% do not know how cervical cancer could be diagnosed early, and 21% do not get a regular Pap smear exam [3]. These reasons compounded by the barriers encountered in accessing health care are pervasive within educational and screening cancer programs.

2.5 Malignant diseases of the uterine cervix

All cell types found in cervical histology are susceptible to developing cancer, the epithelial keratinizing-and non-keratinizing squamous (80%), and columnar (10%) cells are the most frequent**;** sometimes a squamous neoplasia can coexist with an adenocarcinoma [29,33]. Each cellular type varies in its growth pattern, histological

characteristics, and degree of differentiation [23]. Keratinizing and non-keratinizing squamous carcinomas differ in that the former has intracellular keratin pearls that are pathognomonic. Verrucous squamous carcinoma has a tendency to recur locally after excision but does not metastasize. Papillary tumors are usually positive for HPV-16. Lymphoepithelioma-like carcinoma is biologically similar to its nasopharyngeal homolog and seems to be linked to the Epstein Barr Virus [23].

Endometrioide adenocarcinoma, which constitutes 30% of all columnar carcinomas, usually has endophytic growth and should be differentiated from adenocarcinoma of endometrial origin. Clear-cell adenocarcinoma is associated with in-utero exposure to diethylstilbestrol. Mesonephric adenocarcinoma initiates from mesonephric remnants and usually presents as an intramural lesion of the lateral and posterior wall of the cervix. A rare tumor, the adenosquamous carcinoma of the glassy cell variant (1-2% of all cervix cancers) grows rapidly and is resistant to radiotherapy [23].

Mesenchymal tumors are rare and could initiate in the smooth muscle, skeletal muscle, blood vessels or nerves; 0.5% of cervical cancers are sarcomas. Mixed epithelial and mesenchymal tumors are composed of a mixture of benign and malignant elements of epithelial and mesenchymal components. Melanotic, germ cell and lymphoid carcinomas are very rare and non-specific in appearance [23].

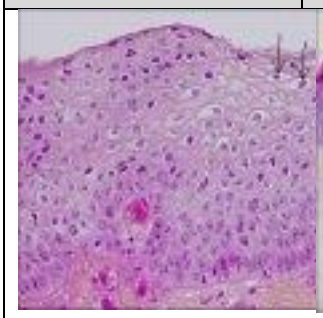
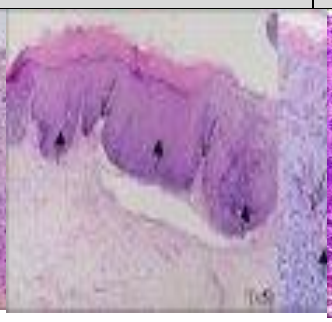
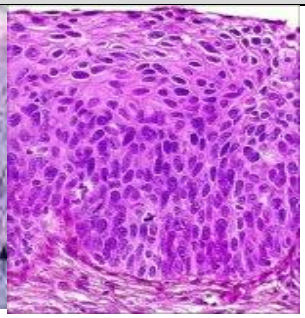
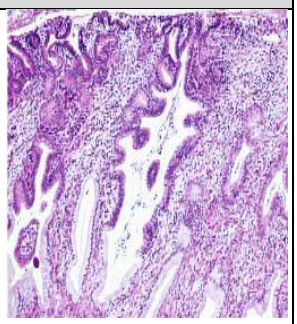
Melanomas are pigmented polypoid masses but also could be amelanotic and non-specific in appearance and have poor prognosis. Secondary tumors of the cervix are distinguished because they exhibit a submucosal localization with a normal superficial epithelium; the prognosis depends on the underlying disease [23].

In addition, the cervix is susceptible to secondary tumors as part of the dissemination of a primary lesion originated in other genital organ (vagina, adnexa), endometrium (mostly high grade endometrial carcinoma), breast (mostly lobular carcinoma), or extra genital organs (stomach or large bowel) [23].

2.6 Pre-invasive lesions of the uterine cervix

The histologic description of the pre-invasive stage of the disease is referred as

Cervical Intraepithelial Neoplasia (CIN), and is graded 1, 2 or 3 according to the degree and extension of cellular abnormality (Figure 6); CIN-1 being located in the basal third of the mucosal layer and CIN-3 is a full-thickness neoplasia [16, 34]. When unspecific changes are seen in the endocervix they are referred to as atypical glandular cells (AGC), and adenocarcinoma in situ is used when anaplastic cells are seen (AIS).

CIN 1	CIN 2	CIN 3	AIS
			
Dysplastic cells are confined to the lower third of the epithelium. Koilocytes are mostly in the upper layers of the epithelium (x20).	Dysplastic cells are mostly in the lower two-thirds of the epithelium. Stretched out capillaries are observed the stromal papillae (x40).	Dysplastic cells are distributed in the full thickness of the epithelium with loss of cell polarity (x40).	Anaplastic cells show loss of polarity, increased cell and nuclear size, nuclear hyperchromasia, mitotic activity, reduction of cytoplasmic mucin expression, and cellular stratification (x10).

CIN = Cervical Intraepithelial Neoplasia; AIS = Adenocarcinoma in situ.
Source: Modified from Sellors JW and Sankaranarayanan R, 2003 [16].

Figure 6. Histopathology of cervical epithelial lesions

CIN lesions induce pro-inflammatory and potentially cytotoxic and immunosuppressive local responses; therefore, the development of an invasive lesion is determined by the cytotoxic immune response of the local mucosa, which is particularly critical in HPV clearance and disease progression. Under normal conditions, the local immune microenvironment of the cervix is composed of B cells, T cells, macrophages, mast cells, neutrophils, NK cells, and IFN-γ–expressing cells and a specific group of resident intraepithelial lymphocytes CD8+ T. When an HPV infection occurs, an intense Th1 response with a high production of IFN-γ and regulatory cytokines initiates the control and eradication of the infection, indicating a protective role of the local CD4 -T cells. However, initial infection by HPV is characterized by an evasion of local and systemic immune response, facilitating its integration to the DNA of mucosal cells, where it can persist for years [26, 27].

CIN 2 and CIN 3 lesions exhibit complex infiltrates of immune cells from both the acquired and the innate arms of the immune response, including activated CD4+ and stromal CD8+T cells, and immunosuppressive regulatory T-like cells. In turn, the production of IFN-γ and regulatory cytokines TGF- β and IL-10 are impaired and, in addition, inflammatory cells exhibit an excessive secretion of matrix metalloprotease-9, favoring neovascularization and disease progression [27]. Nonetheless, spontaneous regression of pre-invasive lesions usually occurs in a short period of time in 57% of CIN-1; 43% of CIN 2; 32% of CIN-3 and 68% of AGC; but 5-10% of affected women will have persistent infection [5].

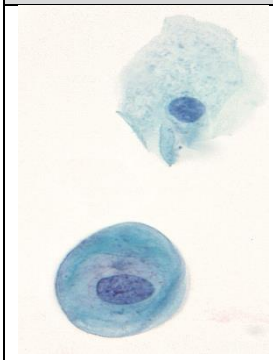
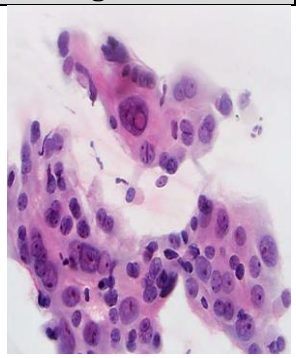
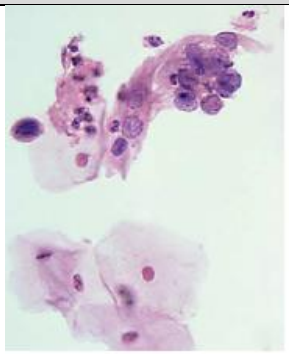
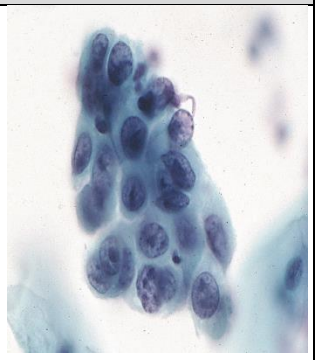
Granted that 1% of CIN-1; 1.5% of CIN-2; 12% of CIN-3 and 0,3% of AIS lesions could transform into an invasive lesion, women with CIN-1 should be followed and those with CIN-2 and CIN-3 should be treated in order to reduce the risk of invasive cervical cancer, especially in women with known cofactors for disease progression, like smoking and immunosuppression [29]. Particularly, follow-up by means of Pap smear and colposcopy are corner stones in the diagnosis of carcinomas in pre-invasive stages, because over 50% of invasive disease is not recognized during simple visual gynecological examination [35].

2.7 Screening of uterine cervical cancer

The Pap smear consists of the microscopic analysis of exfoliating cells from the transformation zone. The aim of the cytology is to identify pathognomonic changes of dysplastic and anaplastic cells, such as altered nuclear to cytoplasm ratio, nuclei pleomorphysm, presence of vacuoles, etc. When a dysplasia of the squamous epithelium is seen, it is called a squamous intraepithelial lesion (SIL), and is reported as Low-grade (LSIL), High-grade (HSIL), atypical squamous cells, or possibly cancerous (malignant) (Figure 7).

Cytology remains the preferred screening method due to its sensitivity (51%), and specificity (98%) and a good cost/effectiveness balance; helping to reduce 82% of deaths associated to UCC in developed countries [36]. Its relative low sensitivity however is associated with failures during sample acquisition, fixation, processing or

interpretation of histological findings; leading to unnecessary diagnostic colposcopy, psychological stress, and extra costs [37].

Normal endocervical cells	Atypical squamous cells of undetermined significance	High-grade squamous intraepithelial lesion	Adenocarcinoma
			
Normal intermediate and parabasal cells. Parabasal cells have larger nuclei (~50 µm2) and less cytoplasm than intermediate cells.	Cells are arranged in a 2-dimensional sheet with abundant cytoplasm. Nuclei exhibit pleomorphysm of size and shape, and some cells have multiple nuclei. Most nuclei have prominent nucleoli.	Abnormal, naked nuclei and a single, hyperchromatic High-grade squamous intraepithelial lesion cell with a high nuclear to cytoplasm ratio.	Glandular cells with vesicular chromatin, irregular chromatin distribution, and macro nucleoli arranged in a syncytial cluster.

Source: Based on Nayar R et al, 2015; American Society of Pathology, 2015 [39]

Figure 7. Cytological appearance of cervical epithelial lesions.

Thus, the quality of the report is decisive for accurate diagnosis, treatment, and follow-up [38]. The cytological examination report is given according to a system first released in 1988, by the National Cancer Institute of the United States of America, the Bethesda System [39], which allowed for an international unification of the clinical management of women with abnormal cervical cytology. Later, this system was subjected to multiple modifications as a result of cumulative evidence in regards to the management of unsatisfactory cytology, minor anomalies, pre-invasive lesions, HPV-genotyping test, and management of special populations [37, 40].

The introduction of liquid cytology and viral DNA detection of oncogenic types of HPV increased the negative predictive value of the cytology up to 100%, helps to detect more women at high-risk of UCC or with precursor lesions (RR 1.23, 95% CI 0.91-1.67),

and could reduce the risk of death related to UCC (RR 0.59, 95% CI 0.39-0.91) [5, 36, 39]. In 2008, Germany updated its own guidelines and reporting system, referred to as the Munich Nomenclature III (Appendix 1) [41,42], which contains more subgroups in order to improve the communication of cytology reports among pathologists and gynecologists to avoid unnecessary follow-up examinations, and, finally, to improve the quality of care of women with precursor lesions or cancer [5].

As part of an organized public health effort, the vast evidence regarding the advantages and utility of the Pap smear (Evidence level II, grade of recommendation C), and HPV-DNA test (Evidence level II, grade of recommendation B) supports its endorsement as a good practice that saves lives [36, 43]. Screening frequency varies according to each country's health policies, but in general is performed every 2-5 years, with specific recommendations for special populations (Table 3).

Table 3. Screening frequency for special populations without previous cervical cytology abnormalities

Population	Frequency of screening	Quality of evidence
Women living with VIH or immunocompromised	1st year each 6 months if negative, then annually, or 2 year-intervals with negative HPV test.	Evidence level II Grade of recommendation C
Pregnant woman	Same as general population.	Evidence level III Grade of recommendation B
Women having sex with women	Same as general population.	Evidence level II Grade of recommendation B
Women with previous total hysterectomy	Same as general population if reason was a pre-invasive carcinoma or with unknown reasons, up to 10 years of follow up.	Evidence level III Grade of recommendation C
Women who received HPV vaccination	Same as general population.	Evidence level III Grade of recommendation C
Women (30-64 years), who had a co-testing with normal cytology and negative HPV test.	5-years intervals	Evidence level II Grade of recommendation B
Young women (18- 30 years)	3-year intervals	Evidence level II Grade of recommendation B

Own design based on INC, 2007; Massad et al, 2012; Griesser H et al, 2013 [36, 40, 41].

The screening is recommended to women between 25 - 65 years of age by means of a Pap smear or combined with HPV-DNA test, including those who received HPV-vaccination during adolescence and women with subtotal hysterectomy. After total

hysterectomy, only HPV positive women should continue with the screening schedule [5]. Women with a suspected HSIL or cancer are referred to colposcopy.

2.8 Early diagnosis of uterine cervical cancer

Colposcopy and punch biopsy allow for the definitive diagnosis when an abnormality was reported through cytology or was seen at simple inspection (**Table 4**). The procedure has a high sensitivity (85%), but a low specificity (69%) for high-grade lesions because it is dependent on the person practicing the procedure, which leads to a high rate of false-positive diagnosis [44]. The colposcope allows a magnified visualization of the cervix mucosa, the entire squamous columnar junction, and the transformation zone and allows describing and defining the extension of the lesion. Furthermore, it facilitates the collection of a directed biopsy of suspicious areas or treats the local lesions [45].

Table 4. Indications for colposcopy according to the International Agency for Research on Cancer

Clinical condition
Suspicious-looking cervix (leukoplakia or hyperkeratosis)
Invasive carcinoma on cytology
CIN-2 or CIN-3 on cytology
Persistent low-grade (CIN-1) abnormalities on cytology (for more than 12-18 months).
CIN-1 on cytology
Persistently unsatisfactory quality on cytology
Infection with oncogenic human papillomaviruses (HPV)
Acetopositivity on visual inspection with acetic acid (VIA)
Acetopositivity on visual inspection with acetic acid using magnification (VIAM)
Positive on visual inspection with Lugol's iodine (VILI)
Source: Reproduced from Sellors JW et al, 2003 [16].

At colposcopy, benign conditions at the congenital transformation zone, immature squamous metaplasia, inflammation, and regenerative epithelium appear as an acetowhite lesion. CIN-1 lesions exhibit a thin, smooth acetowhite area with well–defined but irregular or angular margins. CIN 2 appears as thick, dense, dull, opaque, or greyish-white acetowhite areas with well-defined regular margins, which could be raised and rolled-out, and extend into the endocervical canal. CIN-3 usually appears as a

less smooth, irregular, and nodular acetowhite area, or as an acetowhite lesion with varying color intensity, or with more than one border [16].

Direct punch biopsies should be taken from abnormal areas, especially those closest to the squamous columnar junction, to confirm the presence of a pre-invasive or invasive lesion. Nevertheless, the sensitivity of a guided biopsy to detect pre-invasive lesions in women with abnormal cytology does not exceed 70%, leading to false positive diagnosis [46]. Endocervical curettage is always desirable, even if no abnormal area is found, because a hidden lesion of invasive cancer could exist. Excision of the endocervix is recommended when an acetowhite lesion penetrates the canal, with exception of pregnant women due to the risks of complications with the pregnancy.

The management of visualized lesions, including application of cryotherapy or realization of a loop electrosurgical excision procedure for high-risk lesions, can be performed the same day, a procedure known as the "See-and-treat management", or in a second visit, referred to as the "Two-step management". In contrast, the American Society for Colposcopy and Cervical Pathology [40], and the European Federation for Colposcopy and Pathology of the Lower Genital Tract [46] recommend taking a biopsy prior to definitive treatment. In favor of the "See-and-treat management" are the lower pooled overtreatment rates in women with suspected high-grade lesions, at both cytology and colposcopy. However, it is not recommended in cases of pregnant or young women aged 21 – 24 years old (Table 5). Moreover, the "See-and-treat management" results in higher patient compliance, lower cost of attention, and reduced patient psychological stress for women referred to a colposcopy because of a suspected CIN [47].

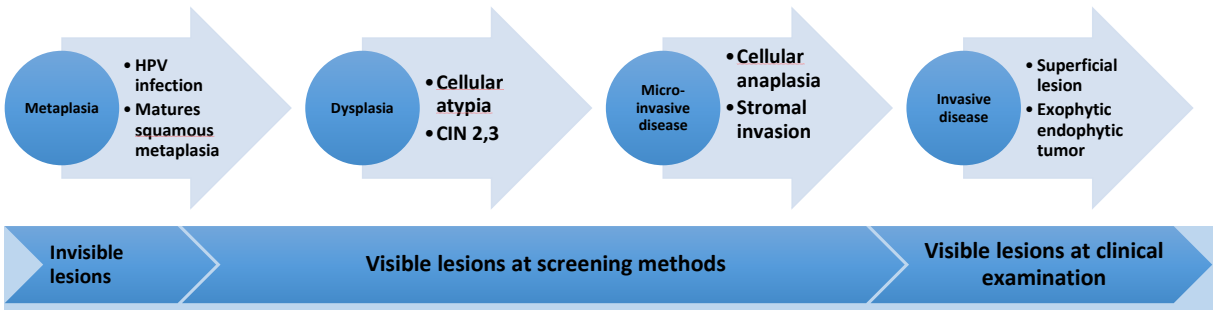
Table 5. Overtreatment rates of "See –and –Treat management" for CIN

Cytology and colposcopy grade **Meta-analysis 13 studies; n=4611**	**Overtreatment rate** **(%)**	**Incidence** **95% IC**
Low-grade cytology and low-grade colposcopy	72,9	68,1 – 77,7
Low-grade cytology and high-grade colposcopy	46,4	15,7 – 77,1
High-grade cytology and low-grade colposcopy	29,3	16,7 – 41,9
High-grade cervical cytology and high-grade colposcopy	11.6	7,8 – 15,3
Source: Own design based on Ebisch RMF et al, 2015 [47].		

Although more details about colposcopy are out of the scope of this paper, it is important to mention that non-invasive lesions diagnosed in the first trimester of pregnancy should be reviewed at 28 weeks of gestation and at six weeks post-partum. An invasive cancer requires a conization, preferably in the second trimester [16]. It is also encouraged that a multidisciplinary team, including a cytologist, a pathologist, and a colposcopist, lead the proper treatment of cases with glandular lesions, cancer, or in cases of discrepancy between the abnormalities described at cytology, colposcopy and histology. In the interest of preserving the uterus and/or fertility of women with pre-invasive or micro-invasive lesions, conservative treatments are recommended to very young women and select patients [48]. That is to say, that women must adhere highly to follow-up scheduling and the existing lesion should meet standard criteria for uterine preserving therapies (this means, a satisfactory colposcopy, fully visualized lesions, no endocervical disease, and the absence of glandular dysplasia) [40, 49].

2.9 Micro invasive and invasive lesions

The oncogenic process in cervix cells usually takes a long time, even years, before the destruction of the mucosal basal membrane and stromal invasion by neoplastic cells with further progression from a micro invasion until a tumoral mass occurs (Figure 8). Early phases of invasion are usually asymptomatic and invisible at simple examination, but a routine Pap smear, colposcopy, and histology could detect anaplastic cells.



Source: Own design based on Sellors JW et al, 2003; Saslow D et al, 2012 [16, 29].

Figure 8. Invasive lesions pathway

The micro invasive disease is defined as an invasion into the underlying stroma no more than 5 mm deep and 7 mm wide, characterized by a tiny bud of anaplastic cells accompanied by a localized lymphocytic collection, or loosening of surrounding stroma

[16, 29]. Further progression of cancer includes the destruction of supportive structures of the cervix and surrounding organs, becoming clinically symptomatic or visible at speculum examination. Initial clinical signs of an invasive disease are rough, reddish, and granular areas that bleed upon touch, while advanced stages are easily identified as a tumoral lesion confined to the cervix or extended to pelvic organs.

Tumors can display an exophytic, endophytic or both types of growth (Figure 9). Exophytic tumors are usually superficially invasive, growing into the upper vaginal lumen as a mushroom or as a cauliflower-like bulk with polypoid or papillary excrescences. Endophytic tumors extend mainly into the endocervix with a clear disturbance of the squamous epithelium, usually when the tumor reaches 5-6 cm, and include a characteristically extensive stroma infiltration that distorts the cervix, giving it a barrel-shaped appearance with the largest part of the tumor not easily visible [16, 29].

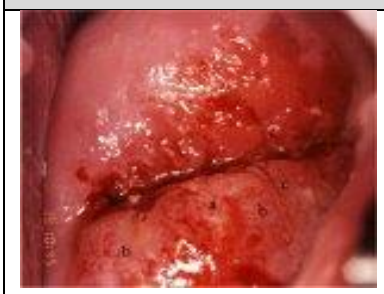
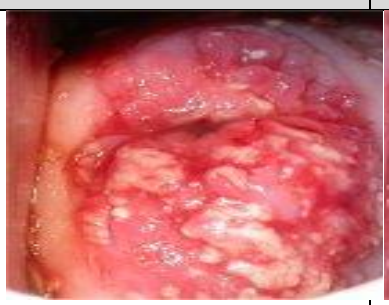
Early invasive cancer	Exophytic tumor	Adenocarcinoma
		
Raised irregular mosaics with umbilication (a), breaking mosaics (b), surface irregularity and the atypical vessels (c) after the application of 5% acetic acid.	There is a proliferative growth on the cervix, which becomes dense, chalky white after the application of acetic acid. Bleeding partly obliterates the acetowhitening areas.	Elevated lesions with an irregular acetowhite surface, enlarged and hypertrophied villi, papillary patterns (a), and atypical vessels (b), overlying the columnar epithelium.
Source: Based on Sellors JW and Sankaranarayanan R, 2003 [16].		

Figure 9. Appearance of invasive cervical cancer at colposcopy

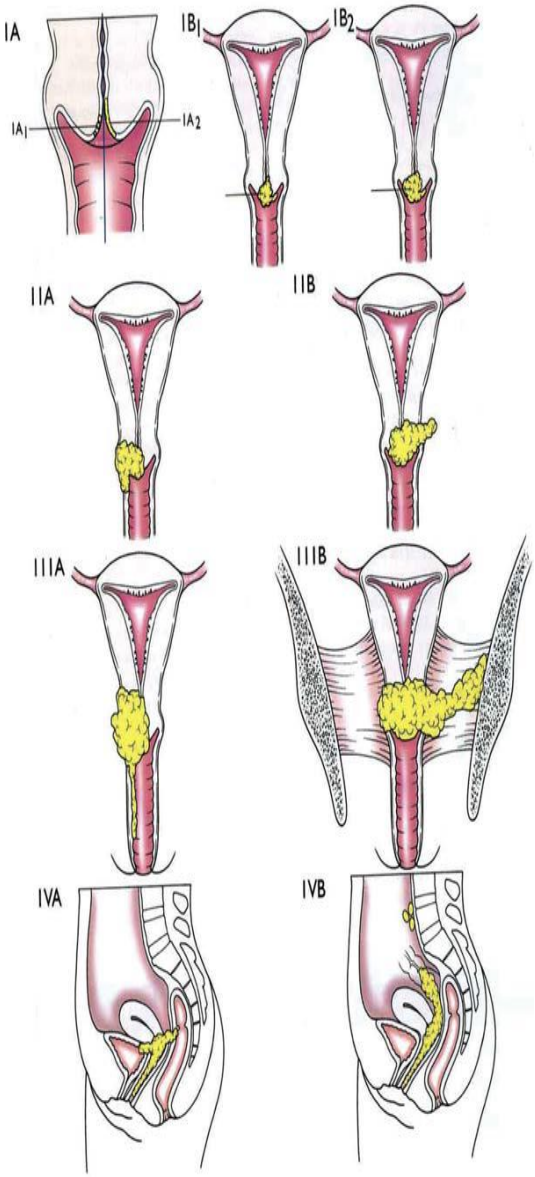
Extension of the disease to adjacent and distant organs may occur in three ways: 1) by continuity to distal vagina, parametrium, uterine corpus, adnexa, pelvic sidewall, bladder, and rectum; 2) by lymphatic dissemination into pelvic and aortic lymph nodes, vertebrae, and nerve roots; 3) by haematogenous spread to lungs, liver, peritoneum, bone, brain, and other organs [29]. The clinical findings at first diagnosis determine the initial staging, treatment, and prognosis of the disease.

2.10 Clinical manifestations of invasive disease

Early clinical manifestations of an invasive cervical cancer are vague and usually longstanding. Symptomatic women seek medical consultation due to postcoital vaginal bleeding, vaginal discharge, dyspareunia, intermenstrual bleeding, chronic abdominal pain, serosanguinous foul smelling or backache [50]. In a recent study of British women diagnosed with UCC via symptomatic presentation, the median duration of symptoms from first symptom to diagnosis was 29.6 months (IQR 15.4–87.1 months); 80% patients aged <25 years and 60% of patients aged 25–29 years were diagnosed with an early local invasive cancer stage 1b at first examination [32]. Late symptomatology and late consultation are contributing factors for apparition of new cases of invasive uterine cervix cancer worldwide.

2.11 Staging of invasive cervical cancer

Tumor size and extension of the disease at the patient's first consult are the basis for disease staging, which is mainly defined according to the International Federation of Gynecology and Obstetrics classification (FIGO system) (Figure 10). Staging is intended for both therapy planning and post-therapy follow-up, from Stage-I tumors confined to the cervix to Stage-IV metastatic disease [51]. In addition to the vaginal and rectal examination, an accurate staging is completed through different diagnostic methods including imaging studies like ultrasonography, intravenous urogram, chest and skeletal X-Rays, computerized tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET-CT); as well as through invasive procedures such as cystoscopy, recto-sigmoidoscopy, and laparoscopy [52, 53]. Neither lymph node metastases nor histological typing are included in the FIGO staging system. The histological report adds to the anatomical findings, allows the identification of individual prognostic factors, such as cellular type (Appendix 2) [23], stromal invasion, lymphovascular space invasion (LVSI), tumor volume, tumor extension, and lymph node involvement. The regional lymph nodes usually affected are the paracervical, parametrial, internal iliac, obturator, hypogastric common, external iliac, pre-sacral and lateral sacral nodes. Distal nodes affected are the aortal and aorto-caval nodes, which are considered the most important prognostic survival factor.

Schematic representation	Stage	Localization
	**I:** The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded). IA: Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5mm* and wider <7 mm. IA1: Measured invasion of stroma <3 mm in depth and <7 mm width. IA2: Measured invasion of stroma >3 mm and >5 mm in depth and >7 mm width.	
	IB: Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA. IB1: Clinical lesions no greater than 4 cm in size. IB2: Clinical lesions greater than 4 cm in size.	
	II: The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or to the lower third of vagina. IIA: Involvement of up to the upper two-third of the vagina. No obvious parametrial involvement. IIA1: Clinically visible lesion < 4 cm IIA2: Clinically visible lesion >4 cm IIB: Obvious parametrial involvement but not onto the pelvic sidewall.	
	III: The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall. The tumor involves the lower third of the vagina. All cases of hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes. IIIA: Involvement of the lower vagina but no extension onto pelvic sidewall. IIIB: Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney	
	IV: The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum. IVA: Spread to adjacent pelvic organs. IVB: Spread to distant organs.	

*The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface of glandular, from which it originates. Vascular space invasion should not alter the staging. Based on Camisão CC et al., 2007 [52], with permission to reproduce the figure..

Figure 10. FIGO - Uterine cervix carcinoma staging system

Clinical examination allows us to appreciate the extension of the tumor into the vagina, to determine parametrial involvement, to estimate uterine size and presence of adnexal masses. However, it is reported that 17% – 32% of patients with disease FIGO IB – II A and up to 65 % with FIGO II –IV are erroneously diagnosed at physical examination, as the method could under or –overestimate the extent of the tumor to the endocervix, parametria, and is not appropriate to evaluate lymph node and distant metastases [53].

Transvaginal and transrectal ultrasound are not part of the routine staging but are helpful methods in the evaluation of regional tumoral extension, due to their high sensitivity for detecting parametrial involvement (83%). Transvaginal ultrasound has a low sensitivity (23%), but a high positive predictive value (71%) for detecting compromised lymph nodes [54, 55]. Adding 3D imaging or Doppler at ultrasound evaluation improves the accuracy of the bimanual examination. It is reported that color signal at Doppler increases the probability of lymph node metastasis detection (Sensitivity 80%; specificity 57%), parametrial involvement detection (Sensitivity 91 %, specificity 57), as well as allows assessment of tumor angiogenesis [54]. In addition, it is observed that vascularization decreases during radiotherapy, which is associated with tumor response; while persistence of high vascularity is associated with a poor response. The inherited subjectivity as well as the inter- and intra-observer variability of a Doppler evaluation limits its use during cancer evaluation, treatment, and follow-up [54]; hence, it is not considered a standardized method for staging.

Given the limitations of clinical examination and ultrasound in the evaluation of parametrial lymph node involvement and distant disease, and according to FIGO recommendations, high resource settings have introduced new imaging techniques as first–line methods for clinical staging of malignancies, such as computed tomography (CT), magnetic resonance imaging (MRI), and combined positron emission tomography and computed tomography (PET-CT) [50]. New MRI equipment provided with turbo sequences and phased-array coils permit an accurate evaluation of disease extension, thus avoiding the need for other staging studies such as urography, cystoscopy, and rectosigmoidoscopy [53].

MRI permits multiplanar images with high contrast and spatial resolution of

pelvic tissue and organs, and in particular yields an accurate evaluation of the parametrial musculotendinous structures [52, 53]. Pre-invasive lesions are not detected on T2-weighed images; they can be seen as areas of noticeable early impregnation in the arterial phase of MRI dynamic studies.

Malignant tumors appear in MRI as slightly hyper intense areas, while normal cervical stroma exhibit low-density signals. Tumors that extend to the pelvic wall show partial or complete loss of the normal hyposignal of the pelvic musculature. Vaginal involvement is seen as a segmental interruption of the normal hypointense signal of the vaginal wall. Bladder invasion is observed as a hyperintense signal of its muscle and mucosa. Rectum involvement exhibits a focal thickening or segmental interruption of the hypointense signal of the rectal wall.

MRI T2-weighted sequences with suppression of the adipose tissue surrounding the lymph nodes allow the differentiation between the hypointense images of vessels and musculature and the slightly hyperintense images of affected nodes; while lymph node necrosis exhibits a signal intensity similar to the tumor [52, 56]. MRI detects suspicious lymph nodes up to 7 mm in the internal iliac chain; 9 mm in the common iliac chain; and 10 mm in the external iliac chain. PET-scan is more specific for detecting regional adenomegalies [52]; and CT does not detect normal sized lymph node metastases [50].

The reported accuracy for parametrial evaluation is higher with MRI (92 - 100%) than clinical examination (78%) and CT (70%) [52]. For assessment of bladder involvement, MRI has a high sensitivity (83%) and specificity (100%) [52]. The accuracy of the MRI provides us with a non-surgical staging uterine cancer that correlates to the FIGO classification (Table 6) [56]. The information provided by the MRI is useful for radiotherapy planning and patient follow-up, and it also offers the possibility to detect fistulous tracts, which is why the MRI is now proposed as the gold standard for clinical staging of cervical cancer. However, when compared to laparoscopic surgical staging, CT, MRI, and PET-CT images have lower sensitivity for detecting para-aortic lymph node metastasis in patients with cervical cancer (MRI 38%; PET-CT 36%; CT 67%), [57].

Table 6. MRI findings in correlation to FIGO staging of uterine cervix cancer

FIGO Stage	MRI Stage
IA	No tumor evidence
IB	Hyperintense tumor T2-wighted sequence in contrast with hypointense signal from cervical stroma.
IB1 IB2	Tumor partially or completely replacing the hypointense cervical stroma, not surpassing the parametrial interface represented by a hypointense halo.
IIA	Segmental interruption of hypointense signal on the upper third of the vaginal wall.
IIB	Hyperintense tumor interrupting hypointense halo of the interface between cervical stroma and parametrium.
IIIA	Segmental interruption of the hypointense signal of the lower vaginal third.
IIIB	Tumor extending to the musculature (obturator muscle, piriform muscle o elevator ani muscle of causing hydroureter.
IVA	Loss of hypointense signal of the internal wall (mucosa) of the bladder rectum.
IVB	Distant metastasis
Source: Reproduced with permission from Okamoto Y et al, 2003[56].	

Surgical staging, which is para-aortic lymph node dissection, could be used during the lymph node status evaluation, prior to radiation or chemotherapy, in order to provide patients with adequate adjuvant treatment, particularly extension-field and volume of radiation. Extra peritoneal retrieval of these lymph nodes, either by laparoscopic or robotic methods, is the preferred approach, because transperitoneal surgery is associated with secondary bowel complications when surgery is followed by radiation, with a 30% complication rate compared to 2% with the extraperitoneal approach [58]. It is reported that surgical staging after PET-CT evaluation leads to radiation field modifications in 18 -44% of cases, after some negative para-aortic nodes at PET-CT were found positive on histopathologic examination (false negative PET-CT) [57].

Surgical staging could therefore avoid suboptimal therapies and improve survival rates of patients in stages IB2 – IVA of the disease (Category 2B of recommendation) [59]; especially if PET-CT reports positive pelvic nodes and negative para-aortic lymph nodes, which could have micrometastasic disease. However, a there is a lack of evidence

to whether surgical staging improves outcomes and progression-free survival of patients with micrometastasic disease [57, 58, 60].

Sentinel node mapping is another resource recently introduced to avoid the long-term sequela of pelvic lymphadenectomy, mainly lymphedema (10–15%), and lymph cyst formation (up to 20%) [61]. This test has a detection rate of 97.5% - 100% (73.3% bilaterally), with a specificity value of 100%, a false-negative predictive value of 0%, and a negative predictive value of 100% in stages IA2–IB1 cervical cancer, with no adverse reactions. It is recommended a) To avoid complete pelvic lymphadenectomy, with a less radical parametrial resection for small tumor volume, when the test is negative; b) To identify and remove alternative lymphatic node sites, as cervical drainage is complex; c) To identify nodal metastases in patients with apparent normal nodes at ultrasound or MRI, thus is up to 16% of cases with tumors less than 2 cm and 15-31% of cases with tumors stage 1B have micrometastasic disease; and d) To avoid radical surgeries in young women receiving a fertility-sparing radical trachelectomy [61]. In this case, when a sentinel node shows metastasis on frozen section, radical surgery is omitted, and the patient undergoes radio-chemotherapy [50].

The recommended technique for sentinel node evaluation is the preoperative injection of technetium-nanocolloids in all four quadrants of the cervical sub mucosae. If at least one sentinel node is not apparent on each side of the preoperative scintigram, then blue dye is injected in all four quadrants once the patient is under anesthesia. If a positive node is detected, a complete lymphadenectomy should be performed [61]. In the near future, it is expected that this mapping will become a standard practice in the management of patients with early-stage UCC if resources are available.

Part II:

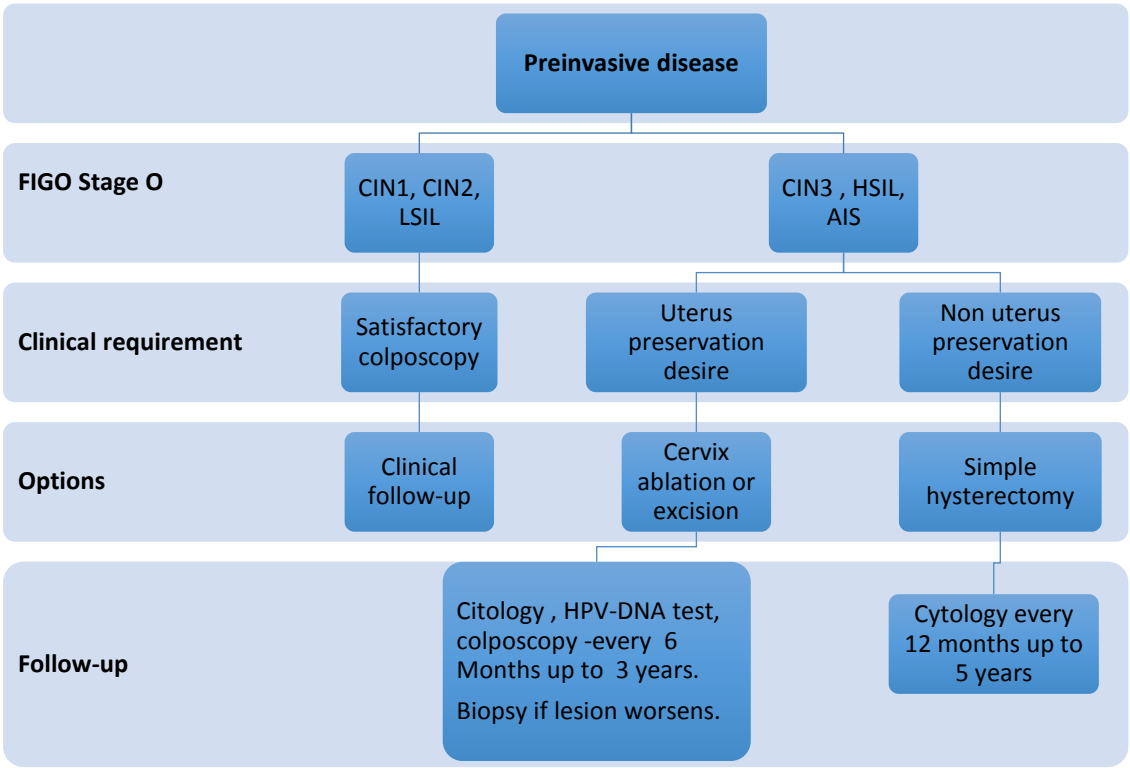
3. Management of the uterine cervical cancer

The foundation of cervical cancer management is to avoid the risk of disease progression through effective treatment of preinvasive and invasive lesions. Conservative treatments are appropriate for women with pre-invasive or microinvasive lesions that desire to preserve their fertility or their uterus; less radical management is suitable for women with early-stage disease IA1-IB1. Radical surgery, radiotherapy or the concurrent administration of radiotherapy and chemotherapy are the choices for advanced stage IIB-IVA disease. Adapted palliative measures are appropriate for untreatable metastatic disease stage IVB. In addition to good pre-treatment assessment and appropriate management, close follow-up, nutritional- and psychosocial support and access to supportive medicine are needed to achieve effective disease control. Most women of all ages will enter into remission with the provided management; however, success is influenced by the availability of resources, accessibility to health care facilities, the quality of care, and therapy compliance. [62]

3.1 Preinvasive and microinvasive disease management

Based on the high regression rates and uncommon progression of the preinvasive lesions CIN-1 and CIN-2, observation is recommended for women with a desire to preserve fertility or their uterus, who are younger than 25 years of age or pregnant; with a satisfactory colposcopy. These patients need a close follow-up that includes cytology and a colposcopy every 6 months, with re-biopsy if the lesion persists or worsens [63]. In the presence of persistent disease or microinvasive disease CIN-3 or AIS which might progress to invasive cervical cancer if left untreated, a simple hysterectomy or less invasive treatment could be recommended, practicing local ablative or excisional methods if the patient wishes to retain fertility (Figure 11) [5, 64].

According to the extent of the disease, the ablation of the affected epithelium could be accomplished the application of trichloroacetic acid, laser or cryotherapy on the cervix surface. Ablation is also appropriate for low-grade CIN with satisfactory colposcopy for women over 25, but not over 40, because older women have deeper glands and usually have disease extending further into the canal [63]. Women with HGSL, extensive or persistent stage IA1 lesions, recurrent CIN2 or CIN-3 lesions or positive endocervical curettage are eligible for an excisional method.



Own design based on Wiebe E et al., 2012; AWMF, 2014

Figure 11. Management of preinvasive uterine cervical lesions

Excision should be performed using a technique that does not result in cauterized margins, allowing the histological examination of the surgical margins. This procedure includes the excision of a cone-shaped portion of the exo-and endocervix and the transformation zone, known as conization. This procedure may be performed by cold-knife, laser or loop electrosurgical techniques. Conization can be performed at the same time as the patient's colposcopy with a high-grade smear, except in the case of pregnancy or women younger than 25 years [65]. This see-and treat or single visit treatment has demonstrated a reduction in the lifetime risk of UCC by 30% when it is provided to women between the ages 35-45 years [66].

Ablation with topical 85%-trichloroacetic acid is also used for the treatment of other premalignant lesions, such as condylomata acuminate, anal intraepithelial neoplasia and vaginal intraepithelial neoplasia [67,68]. This acid causes protein denaturation and cell death, favoring the clearance of HPV and remission of CIN.

Specifically, high rates of clearance of HPV type 16 (73.5%; 95% CI, 62.5–81.3), and HPV type 18 (75.0%; 95% CI 46.2–95.0), as well as histologic regression of HSIL (87.7%; 95% CI, 82.0–92.1), and LSIL (82.3%; 95% CI, 70.5–90.8) have been reported eight weeks following a single application [68]. Side effects such as low abdominal pain during application (VAS-scale 3), vaginal discharge or short post treatment bleeding were rare (1–2% of cases). Besides its effectiveness, 85%-trichloroacetic acid is inexpensive, well tolerated, has no systemic side effects, and is safe during pregnancy [67, 68]. Therefore, it constitutes a good non-surgical approach for precursor lesions, especially in low-resource settings.

Laser vaporization of the cervix is indicated for lesions with visible margins. It is performed by means of a specialized probe that can deliver laser energy to the whole cervical circumference with a mean density of 100 J/cm2, producing necrosis of the irradiated tissue. Up to 4% of cases display postoperative bleeding [63]. To avoid extensive damage to the normal tissue; photosensitizing substances can be used to distinguish between affected and normal cells. For example, Photofrin, a strongly colored substance, mostly metabolized by the liver, is injected into the patient intravenously 48 hours prior to vaporization; then colored lesions are irradiated with a pulsed excimer dye laser at a wavelength of 630 nm [69]. The day after vaporization the necrotic tissue and hardened mucus around the cervix should be removed. Laser therapy is associated with a low rate of complications, less of 4% of cases exhibit postoperative bleeding [63] yet reveal low cure rates (17%) [70].

Cryotherapy uses a compressed refrigerant CO2 (freezing point of –65°C), or liquid nitrous oxide (freezing point of –89°C), which result in cellular death at -20°C and destruction of abnormal tissue. By lowering the temperature, hypothermic conditions are generated crystallizing intra and extra cellular water, obstructing capillary, and leading to further cryonecrosis of transformation zone cells and the surrounding tissue. [71]. This method is effective at eliminating lesions extending into the endocervical glands by means of a double-freeze cycle; it consists of freezing the transformation zone for 3 min, thawing for 5 min, and refreezing again for another 3 min. Leading to tissue necrosis up to 4–5 mm depth, with some difference between the anterior (mean 5.2 mm) and posterior lip (mean 4.9 mm). Depths of 3.5 mm eradicate 95% of CIN-3 cases and depths of 4.8 mm eradicate more than 99% of CIN-3 cases [63, 71].

As part of the see-and treat strategy, cryotherapy produced a 25% reduction on UCC incidence and 35% in mortality rate of Indian women, compared to controls receiving the same therapy during a later visit [72]. Cryotherapy has a low rate of complications (< 1·5% of cervical stenosis; >1·0% of infections) and could also be performed by trained nurses or midwives; but should be avoided during pregnancy [70]. In addition, this therapy is not appropriate for lesions beyond the cryo-tip scope such as lesions covering more than 75% of the exocervix or extending into the cervical canal or big lesions on the posterior lip; consequently, these types require excisional techniques to be eliminated [63, 73].

Cold-knife conization (CKC) is a surgical excisional treatment performed using a scalpel that allows the modification of the width and depth of the excision. This procedure has a lower proportion of non-negative surgical margins, which is especially useful in patients more than 45 years old who are more likely to have lesions located in the endocervical canal (28.6% of women older than 50 years old), compared with younger women (10%). [74, 75]. The disadvantages of CKC are the costs of general anesthesia and potential complications, such as postoperative bleeding (RR 3.91; 95% CI 1.02–1 5.04), infection (RR 2.34; 95% CI 0.13–43.18) or damage to other organs requiring surgery (RR 1.46; 95% CI 0.77–2.76) [76]. Subsequently, loop electrosurgical excisional procedure (LEEP), or also Large Loop Excision of the Transformation Zone (LLETZ) and laser excision are the preferred methods for the management of squamous and glandular intraepithelial neoplasia. However, CKC should be offered when no other method is available [77,78].

LLEP/LLETZ and laser conization are indicated in women presenting any of the following: HGSIL cytology, large lesions (>3 quadrants), high grade appearing lesions on colposcopy, unsatisfactory colposcopy, positive endocervical curettage, or with post-treatment recurrence of CIN-2 and CIN-3. Laser conization uses a highly focused laser spot to achieve the cone excision and by defocusing the laser beam, coagulation is achieved. The beam permits the operator to obtain the desired cone size specimen with less tissue trauma and blood loss than CKC [40]. LLEP/LLETZ uses a wire loop electrode on the end of an insulated handle powered by an electrosurgical unit to provide a concurrent cutting and coagulation effect without causing thermal artifacts. Its ease of

use provides reliable specimens for histology examination, and has high success rates (91-98%), and low morbidity (<2% of post-operative bleeding).

Laser and loop excisions are key procedures in the See-and-Treat strategy because both provide reliable specimens for histology examination, have high success rates (91-98%), and low morbidity (<2% of post-operative bleeding) [40, 73, 79]. In comparison to loop excision, laser conization is more expensive, requires more extensive training and operative times, and produces more perioperative pain and thermal damage of margins [79].

Long-term complications after treatment of pre-and microinvasive diseases are related to the technique and amount of cervical tissue removed, including stenosis or decreased volume of cervical mucus, shorter mid-trimester cervical lengths, cervical incompetence and secondary obstetrical morbidity; being higher for excision than for ablation. A meta-analysis of obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth [80] found that cone depth and risk of preterm birth are directly related, increasing the risk from 7.1% when depth is ≤10-12 mm (95% IC 1.54 -2.18), to 10.2% when it is ≥20 mm (95% IC 2.06 - 11.68). The same study reported that the relative risks for delivery at <37 weeks were 2.70 (2.14 - 3.40) for CKC, 2.11 (95% IC 1.26 - 3.54) for laser conization, 2.02 (95% IC 1.60 - 2.55) for LLETZ, and 1.46 (95% IC 1.27 - 1.66) for ablation not otherwise specified. In addition, the risk of preterm birth was higher in women who had undergone more than one treatment (13.2%; 95% IC 3.78 -5.39).

Moreover, having a LLEP/LLETZ before the age of 25 increases the risk of extreme preterm labor [73, 81], without differences in the outcomes for nulliparous and parous women [82]. Different mechanisms for the adverse outcomes in subsequent pregnancies have been hypothesized, such as alteration of the antimicrobial and mucus secretion from endocervical glands, disruption of the local immunomodulation related to HPV infection, and other genetic, viral, and microbial factors or the pre-cancer lesion itself [82] which result in an acquired “mechanical weakness” of cervical tissue.

In regard to the risk of residual disease or persistent disease after local treatment for preinvasive and early invasive cervical diseases, several studies showed no

statistically significant differences between the described excisional approaches (laser ablation vs. cryotherapy: RR 2.75, 95% CI 0.68 - 11.11); cervical stenosis (laser ablation and cryotherapy: RR 1.45, 95% CI 0.45 - 4.73), or success of treatment of CIN-3 lesions (all approaches: 77% -93%), [79]. However, 12-month recurrence rates tend to be lower after CKC than after LEEP (RR 0.53; 95% CI 0.14–1.98), and cryotherapy exhibits higher failure rates than those of other methods, especially in women over the age of 40 (up to 34%) [76]. Independently of the approach, lesions occupying more than two-thirds of the cervix are 19 times more likely to be persistent; and recurrence is higher in women older than 30 (RR 2.61; 95% CI 1.3 – 5.3), with positivity for HPV-16 or HPV-18 (RR 2.02 95% CI 1.1 – 3.8), or with previous treatment for CIN-3 (RR 2.6; 95% CI 1.3 – 5.4) [70, 75].

Despite the efficacy of the local treatments, 10% of cases could progress to a higher grade or invasive lesion; thus, women with pre and microinvasive lesions should be monitored through repeat cytology, colposcopy, and HPV test after 6 months post-treatment, with re-biopsy if the lesion persists or worsens [63, 83].

3.2 Invasive disease IA2-IIA1 management

Tumor size, LVS involvement and presence of risk factors of recurrence, uterus preservation or desire to conserve fertility determine the type of therapy of the microinvasive and early invasive disease IA-IB1, being surgical resection the ancillary therapy which could be complemented with radiotherapy (RT) or/and chemotherapy (CHT) (Table 7 and 8) [5].

Lymph node assessment prior to therapy, either by means of images (PET-CT), or surgery (laparoscopic or open), is not yet a FIGO standard for invasive disease, but guidelines in Germany recommend a surgical assessment of pelvic and para-aortic lymph nodes for stages IA1 with ≥2 risk factors of recurrence, lesions IA2 with ≥1 risk factors of recurrence and for all IB-IIB disease [5].

Table 7. Management of microinvasive uterine cervical cancer

FIGO Risk factor	Clinical condition	Procedures
IA1 One risk factor of recurrence	Non uterus preservation desire Non fertility desire Completed family planning Biopsy with lymphovascular involvement HPV –persistence Recurrent PAP abnormalities Restricted or abolished cervix access	Total Hysterectomy
	Fertility desire	Conization plus cervix curettage
	Uterus preservation desire and easy follow-up	Trachelectomy
	Cone biopsy with positive margins or lymphovascular involvement	RE-conization Trachelectomy plus permanent cerclage
IA1 ≥2 risk factors of recurrence **IA2** One risk factor of recurrence Negative pelvic lymph node involvement	Completed family planning Non uterus preservation desire HPV –persistence Recurrent PAP abnormalities Restricted or abolished cervix access	Hysterectomy
	Fertility desire	Conization plus cervix curettage Trachelectomy plus permanent cerclage
	Premenopausal	Hysterectomy and ovarian suspension
IA1 ≥2 risk factors of recurrence **IA2** ≥2 risk factors of recurrence Positive lymph node involvement	Any clinical condition	Postoperative Chemoradiotherapy
IA2 ≥2 risk factors of recurrence	Negative pelvic lymph node involvement + any clinical condition	Radical hysterectomy with bilateral adnexectomy and resection of parametria
	Positive sentinel or pelvic lymph node involvement at surgical staging	Radical hysterectomy with bilateral adnexectomy, resection of parametria, pelvic and para-aortic lymphadenectomy followed by Chemoradiotherapy
	Premenopause	Radical hysterectomy with Ovariopexy and resection of parametria
	Macroscopic pelvic or para-aortic lymph node metastasis	Pelvic and para-aortic lymphadenectomy followed by chemoradiotherapy

Table 8. Management of invasive uterine cervical cancer IB1 -IIA1

FIGO	Clinical condition	Options
IB1 -IIA1	Negative pelvic lymph node involvement at surgical staging Postmenopause	Radical hysterectomy Piver II with bilateral adnexectomy plus tumor-free resection of the vaginal cuff.
	Fertility desire and tumor size <2cm without risk factors	Radical hysterectomy Piver II
	Completed family planning Premenopause	Radical hysterectomy Piver II with ovariopexy, plus tumor-free resection of the vaginal cuff.
	Premenopause	Hysterectomy Piver II and ovariopexy.
	Positive sentinel or pelvic lymph node involvement at surgical staging	Radical hysterectomy Piver II and pelvic and para-aortic lymphadenectomy followed by chemoradiotherapy
	Macroscopic pelvic or para-aortic lymph node metastasis	Pelvic and para-aortic lymphadenectomy followed by chemoradiotherapy (further surgery).
	Inoperability Patient decision	Chemoradiotherapy
Piver refers to the extension of the procedure; please see Table 9. Own design based on AWMF, 2014 [5]		

The surgery, a modified radical- or radical hysterectomy, plus pelvic and/or aortic lymph node dissection permits accurate staging information, removal of the tumor and suspicious lymph nodes; also facilitates the achievement of an adequate loco-regional tumor control. Exceptions for radical hysterectomy are young women with IA2 or 1B1- IIA1 disease desiring to preserve their fertility, who are not eligible for a radical trachelectomy plus pelvic lymphadenectomy and prophylactic cerclage [5]. Hysterectomy is also suitable for microinvasive lesions IA1 with positive postsurgical margins or lymphovascular involvement confirmed at histology [59, 64]. Radiotherapy alone is reserved for women with stage IA2 – IB1 lesions who refuse or are not eligible for surgery [59, 64]. Surgical management is also recommended for selected cases of persistent disease after radiotherapy [84].

The extension of *radical surgery* is determined by the stage of the disease and is classified in five types or Piver classes (Table 9). In Germany, abdominal washing, multiple biopsies of peritoneal surfaces and infracolic omentectomy are also recommended prior to the excision in bloc of the uterus and surrounding structures [5]. Radical hysterectomy may be performed laparoscopically, robotically or by laparotomy. Laparoscopic and robotic approaches are associated with less nerve fiber damage, less intraoperative bleeding and shorter hospital stays [4, 85, 86].

Table 9. Classification of the radical hysterectomy

Piver Class	Designation	Extension of the procedure
I	Extrafascial hysterectomy	• The fascia of the cervix and lower uterine segments are removed in bloc with the uterus.
II	Modified radical hysterectomy	• The uterine artery is ligated where it crosses over the ureter. • The ureters are prepared without removal of the pubovesical ligament. • The uterosacral and cardinal ligaments are divided midway towards their attachment to the sacrum and pelvic sidewall, respectively. • Resection of parametria medial of ureter. • Resection of the upper one-third of the vagina.
III	Radical hysterectomy	• The uterine artery is ligated at its origin from the superior vesical artery or internal iliac artery. • The ureters are prepared up to where they join to the bladder, while preserving a small lateral portion of the pubovesical ligament. • Uterosacral and cardinal ligaments are resected at their attachments to the sacrum and pelvic sidewall, respectively. • Resection of the upper one-half of the vagina.
IV	Extended radical hysterectomy	• The uterine artery is ligated at its origin from the superior vesical artery or internal iliac artery. • The ureter is completely dissected from the vesicouterine ligament; the superior vesical artery is sacrificed. • Uterosacral and cardinal ligaments are resected at their attachments to the sacrum and pelvic sidewall, respectively. • Resection of the upper three-fourths of the vagina.
V	Extended radical hysterectomy	• Like Piver III, with additional resection of a portion of the bladder or distal ureter with ureteral reimplantation.
Own design based on AWMF, 2014 [5]		

The laceration of the autonomic nerve fibers during parametrial excision affects bladder and bowel function as well sexual response, especially in older patients or if a large diameter tumor has been removed [85, 87]. A study involving 8,199 American

women with invasive cervical cancer concluded that patients over 70 at the time of surgery exhibit higher all-cause morbidity rates than those less than 50 (22.1% vs. 34,9%; p<0.0001); specifically intraoperative complications (9.9% vs. 19.5%; p<0.0001), surgical site complications (10.9% vs. 17.5%; p<0.0001), and medical complications (9.9% vs. 19.5%; p<0.0001). Additionally, older women require more postoperative nursing facility services (0.5% vs. 12.3%; p<0.0001) [87].

Lymphadenectomy refers to the dissection of lymph nodes that could be affected by tumoral cells, which have migrated from the tumor to different levels of regional lymph nodes (Table 10) [88]. The affected nodes can be detected prior to selected primary therapy -that is surgery, radiation, or chemotherapy- by means of a surgical sentinel node assessment, which has a sensitivity of 92% to detect metastatic disease [88]. Additionally, para-aortic lymph node sampling is recommended for the identification of cases of stages IA – IB1 needing radical lymphadenectomy; for cases of tumors ≥2 cm plus middle-third stromal cervix invasion with lymphovascular space invasion; and for tumors ≥4 cm with deep or middle-third stromal invasion without lymphovascular space invasion [59; 84]. However, sentinel node assessment is not a standard procedure [64]. This test also allows for accurate radiation extension planning when nodes are affected, while further removal of enlarged nodes reduces the required radiation dose and increases the efficacy of the treatment [85, 89]. Long-term complications related to radical lymphadenectomy are lymphocele and lymphedema.

Table 10. Levels of lymph node dissection

Level	Lymph node region
1	Internal and external iliac lymph nodes
2	Level 1 plus common iliac and pre-sacral lymph nodes
3	Level 2 plus aortic inframesenteric lymph nodes
4	Level 3 plus aortic infrarenal lymph

Own design based on [Filippeschi M et al., 2012 [88].

Trachelectomy is the removal of the cervix with the contiguous parametria plus the upper vaginal cuff and is performed vaginally or abdominally by laparotomic, laparoscopic or robotic techniques. It may be offered as a treatment for epidermoid,

squamous or adenocarcinomas confined to the cervix (tumor size <2 cm confirmed by MRI), with cervical stromal invasion less than 50%, and without signs of lymphatic invasion. The procedure is also suitable for cases with IA1 lesions with stromal lymphovascular space involvement [64, 90], but cases with small cell neuroendocrine carcinomas are excluded as they have been documented to have a high mitotic rate, extensive necrosis, lymphovascular space invasion and aggressive spread pattern [91]. Vaginal and laparoscopic approaches are associated with less bleeding, shorter hospital stays and better postoperative recovery compared to open abdominal surgery [92].

Another fertility sparing option for patients with stage IB1 disease includes primary pelvic lymphadenectomy followed by CHT, using a combination of paclitaxel–ifosfamide–carboplatin or a combination of paclitaxel–carboplatin followed by large conization. In a retrospective analysis of 11 patients who received this modality, 64% of cases had complete reduction of tumor, and underwent conization; 20% of them exhibited residual disease at histology and 67% achieved a pregnancy. All cases with residual and progressive disease underwent radical surgery. One recurrence presented, requiring adjuvant radiation. No deaths were reported at the 58-month follow-up [93].

After trachelectomy, cervical stenosis and incompetence are the most frequent long-term complications. They manifest with abnormal uterine bleeding, dysmenorrhea, haematometra, subfertility or complications in a subsequent pregnancy; specifically, the risk for premature delivery is 2 to 3 times higher when compared to women with an intact cervix [94, 95]. Cervical stenosis is observed in up to 73 % of cases but no statistical differences have been reported by type of technique or whether postoperative cerclage was performed or not. In contrast, the utilization of post-surgical anti-stenosis tools, such as catheters or intrauterine devices, reduces the risk of stenosis from 12.7% to 4.6% ($p< 0.001$) [95].

Regarding obstetrics outcomes, in a cohort of 123 women post radical vaginal trachelectomy the following outcomes were reported: 52% cumulative probability of conception at 5 years, 12% of second trimester miscarriages, 61.5% of preterm premature rupture of membranes and 47.6% of preterm deliveries [96]. When results are classified by type of approach in patients with tumors larger than 2 cm, the global pregnancy rate is 16% after abdominal trachelectomy, 24% after vaginal trachelectomy

and 31% after neoadjuvant chemotherapy (NA-CHT) followed by surgery [97]. Recurrence and death rates after 5-years post radical trachelectomy are overall low (3% - 6%) and (2% - 5%) respectively [90]. Differentiated by approach in patients with tumors larger than 2 cm, recurrence rates are 4% - 6% after abdominal or vaginal trachelectomy and 8% after NA-CHT followed by surgery [97].

The presence of residual disease or high-risk factors for recurrence after radical surgery for local invasive UCC is indicator for further therapies. Risk factors include: adenocarcinoma or adenosquamous histology, a pathological specimen with involvement of parametria lymph nodes, cervical lymphovascular space invasion, and outer third cervical stromal invasion [12, 98]. An intermediate risk of recurrence is present in patients with tumors smaller than 4 cm, LVI, or invasion depth less than half of the tumor. Patients with one or more of the following parameters: larger tumor size, parametrial invasion, positive margins, lymph node involvement, or distant metastasis, are at high-risk of recurrence and have low survival rates. In addition, there is a direct correlation between the number of risk factors and adjuvant treatment failure. Higher recurrence rates are observed in the high-risk group defined as having more than one risk factor (25%), than in an intermediate risk group (11%) [99].

Adjuvant RT (A-RT) consists of external pelvic radiation provided 4-6 weeks after surgery and usually given in a dose range of 45 - 50.4 Gy at 25-28 fractions divided in 180–200 cGy per fraction, 5 fractions per week. In the presence of gross unresected metastatic lymph nodes or positive vaginal or parametria resection margins, an additional 10–15 Gy boost of external or intracavitary RT, with an accumulated total dose of 60 Gy to 75 Gy is recommended [64, 100]. Brachytherapy refers to the administration of intracavitary radiation in the cervix or vagina cuff by using ovoids with an iridium-192 source. It is usually given in a dose range of 10-32,4 Gy divided in 2-6 fractions at 3-10 Gy per fraction, 1-5 days a week [64, 85, 99, 101, 102]. This boosting has shown to have the same local control rates and survival rates as patients with negative vaginal margins (49% - 82%) [102]. An adequate adherence to an RT schedule is associated with better prognosis; women completing RT within 56 days had significantly lower rates of treatment failure than those who completed the treatment after 9-10 weeks [64].

In order to improve the radiation dose distribution and to minimize the radiation damage to normal tissues, radiotherapy is provided after a CT or MRT-planning imaging. The images are used to calculate the clinical target volume and to contour the nearby normal organs. Volume is calculated based upon the overall tumor, pelvic organs and parametria size plus elective pelvic and paraaortic lymph nodes. Organs to be protected are bladder, rectum, sigmoid, bowels, and the femoral head [103]. After therapy, a new MRI should be performed after 1-2 months to evaluate the tumor response [102].

For patients with a high-risk of recurrence, a combination of RT with sensitizer CHT, namely *concurrent chemoradiotherapy (CCRT)* is preferred over RT alone, as the addition of CHT avoids the radio-resistance of the new cancer clones that are developed during the progression of the cancer [64]. It increases the sensitivity of tumoral cells to radiation thus increasing the tumor cell-death by direct cell toxicity, tumor cell cycle disturbance and inhibition of cell repair [104]. Sensitizer CHT is given weekly for 4-6 cycles. [105]. However, the addition of CHT increases the risk of severe complications like acute neutropenia, renal- and gastrointestinal toxicity [104]. For CHT, different drugs are used alone or in combination, such as cisplatin, paclitaxel, vinblastine, bleomycin, ifosfamide, vincristine, mitomycin-C or methotrexate, with platinum-based CHT being the most commonly used.

Studies of CCRT in early stages of UCC with high-risk of recurrence showed that this postsurgical therapy has better outcomes in terms of progression-free survival rates (80% vs. 63%; p=0.003), and overall survival rates (81% vs. 71%; p=0.007) than adjuvant RT (HR= 0.81; p <0 .001) [64, 106]. There is an equal survival benefit for both platinum-based (HR=0.83; p=0.17), and non-platinum based CCRT (HR=0.77; p=0.009). Moreover, only a modest benefit of CCRT on both local (OR 0.61; p<0·0001) and distant metastases (OR 0.57; p<0.0001) has been observed [107].

Evidence from several meta-analysis studies reported that low-risk patients with a diagnosis of early cervical cancer treated with adjuvant therapies, either RT or CCRT, after surgical intervention, did not show improvement in clinical outcomes-complication, recurrence, and survival rates and quality of life [12, 13]. In contrast, patients with intermediate-risk benefit more from A-RT, exhibiting high progression-

free survival and 5-years survival rates, at 90% and 97.5% respectively [99]. Particularly in cases with isolated deep stroma invasion, A-RT has a higher 5-years progression–free survival in comparison to A-CHT (92% vs. 48%; long rank p=0.014) [108]. However, the evidence is still unclear whether cisplatin-based adjuvant therapies are associated with additional toxicity risks or survival benefits in the long term for patients with low and intermediate risks [13].

After therapy, patients should be evaluated every 3 months within the first 2 years, biannually for 3-5 years after surgery, and annually thereafter. Monitoring must be conducted via Pap test, colposcopy, and clinical examination, including transvaginal and transabdominal ultrasound allowing the detection of small abnormalities and extra-pelvic implants. When a recurrence is suspected, it is mandatory to confirm the diagnosis through a colposcopy-guided biopsy, and look for metastasis through pelvic MRI, cystoscopy, proctoscopy, TAC of thorax and abdomen [4, 5, 11].

3.3 Invasive disease stages IB2-III management

CCRT plus surgery is the standard management of patients with disease stages IB2 – IIA2, and CCRT alone for stage IIB and III, although the management could vary according to availability of resources, tumor size and patient's condition.

Table 11. Personal performance status according to the Eastern Cooperative Oncology Group

Grade	Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light-house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

At time of diagnosis, between 35-80% of patients with UCC stages IB – IIA have pelvic node metastases, and 12 - 25% of patients with UCC stages >IB2 have para-aortic lymph node metastases; then operative staging could lead to upstaging in up to 33% of cases, without delays of primary CCRT [89]. Particularly, patients with a poor

performance status (Table 11 and 12), or co-morbidities should receive radical RT alone, especially those with poor renal function [109, 62].

Table 12. Management of invasive uterine cervical cancer IB2-III

FIGO	Clinical condition	Procedures
IB2 **IIA2**	Negative pelvic lymph node involvement at surgical staging Postmenopause Premenopause with adenocarcinoma	CCRT followed by radical hysterectomy with bilateral adnexectomy, Piver III, plus tumor-free resection of the vaginal cuff.
	Positive sentinel pelvic node or para-aortic lymph node involvement at surgical staging	CCRT followed by radical hysterectomy Piver III (with bilateral adnexectomy,), pelvic and para-aortic lymphadenectomy plus tumor-free resection of the vaginal cuff.
	Macroscopic pelvic or para-aortic lymph node metastasis	Pelvic and para-aortic lymphadenectomy followed by o CCRT and radical hysterectomy
	Involvement of the vagina	CCRT followed by partial radical vaginectomy plus tumor-free resection of the vaginal cuff.
	Premenopause with squamous epithelial carcinoma	Ovarian suspension followed by and to CCRT and radical hysterectomy Piver III, plus tumor-free resection of the vaginal cuff.
	Inoperability Poor performance status Patient desire	Surgical staging prior to CCRT or RT
IIB - III	Macroscopic pelvic or para-aortic lymph node metastasis	Pelvic and para-aortic lymphadenectomy followed by o CCRT
	Negative pelvic lymph node involvement at surgical staging	CCRT
Own design based on AWMF, 2014 [5]		

When CHT alone is provided prior to surgery, it is called *neoadjuvant chemotherapy* (NA-CHT) and is usually cisplatin-based. The NA-CHT allows reduction of tumor size, facilitating the radical surgery and improving the prognosis in up to 86% of

patients with stage IB2 – IIB disease, but only in the half of cases in stage IIIB. This approach provides a 62% - 73%, 5- years progression-free survival rate and a 75% - 78%, 5-years survival rate. Recurrence occurs in one third of patients, mainly in those with lymph node metastasis prior to NA-CHT (HR 34.88) and in non-responders (HR 30.58) [105, 110]. In comparison to radical surgery alone, NA-CHT exhibits better disease-free survival rates (HR 0.76, p=0.001) [107]. Compared with radical RT, NA-CHT is associated with a lower risk of death (HR 0.71; 95% CI 0.55 to 0.93; I2= 0%); but there is no difference in disease progression and recurrence rates (RR 0.75, 95% CI 0.53 to 1.0; I2= 20%) in women with locally advanced cervical cancer [111]. However, in patients with IB-IIB disease NA-CHT has no significant difference in comparison to CCRT in terms of loco-regional control (90% vs. 93%), progression free survival (76% vs. 74%), or overall survival rates (92% vs. 85%) [111].

Neoadjuvant chemoradiotherapy (NA-CCRT), which consists of CCRT prior to radical hysterectomy, is also offered for disease stage IB2–IIB with the aim of tumor size reduction to improve operative curability and reduction of distant metastasis [64]. However, it does not modify the radical nature of the surgical management, which is based on the initial FIGO stage of the disease [88]. Prior to therapy it is recommended anemia (Hb <11.2 g/dL) be treated, as hypoxia related to anemia decreases tumor sensitivity to radiation and antineoplastic drugs [5]. Anemia is present in 12.3% - 25% of patients with locally advanced cervical cancer, significantly correlating it with tumor size, advanced clinical stage, and parametrial invasion (R2=-0.46, $p < 0.001$) [112]. In addition, anemia is an independent poor prognostic factor for recurrence, disease free survival and overall survival. However, increase in tumor oxygenation following transfusion is seen in only 50% of cases with large size tumors [113].

After completion of NA-CCRT, 30-65% of patients exhibit residual tumors at MRI follow-up. Patients with residual tumor less than 2 cm are better candidates for surgery [98]. During NA-CCRT, 4% to 30% of all cases display signs of hematologic, genitourinary, gastrointestinal, or renal toxicity. While these conditions are manageable with supportive therapy, they lead to therapy interruption in up to 15% of patients thus increasing the risk of disease progression or recurrence [102, 113]. Specifically, the use of multifractionated low-fraction dose-brachytherapy increases the therapeutic effect on the tumor and reduces damage to normal tissues, which are repaired at different

times than tumor cells. Furthermore, this technique offers similar quality of dose distribution, similar treatment procedure and disease control as continuous high-dose brachytherapy [114].

Recurrences after NA-CCRT appear in 81% to 88% of cases within 2 years after therapy (a mean of 17 months), influenced by disease stage, initial lymph node involvement, initial tumor size, clinical response to NA-CCRT, and positive surgical margins or positive squamous cell carcinoma antigen after NA-CCRT [102, 105, 113].

Recurrence and 5-years survival rates after treatment of a local advanced disease differs according to FIGO-stage at diagnosis (Table 13). For patients with bulky tumors stages IB2-IIB who underwent RT alone or RT plus hysterectomy the risk of death or disease progression showed no differences (HR 0.89; 95% CI 0.61 to 1.29), with a high 5- years survival rate (70% to 85%). However, 52% of cases show recurrence within 2.3 years after initial RT, especially among cases with a high-risk of recurrence [43, 62, 64, 98, 115]. Recurrence appears usually within the first 2 years after diagnosis in up to 70% of cases of local advanced disease, 20%-30% of cases within the radiation field, and 50%-60% present with distant metastasis [59, 115, 116].

Table 13. Risk of recurrence and survival rates of local advanced disease

FIGO stage	Risk of recurrence	5-years survival rate
IB1-IIA	10% - 17%	85% -100%
IIB	23%	64% - 80%
III,	42%	37% - 53%
IVA	74%	9% - 33%

3.4 Advanced disease stages IVA - IVB management

Primary palliative cisplatin-topotecan based CCRT plus brachytherapy is the standard of care for patients with stages IVA – IVB of the disease. Some select patients in stage IVA could benefit from a pelvic exenteration (Table 14). Palliative combined CHT may be considered for women with very low performance status, grade 1-2 [64]. Type,

doses, and duration of treatment vary according to the availability of resources, the patient´s desires and clinical conditions.

Table 14. Management of invasive uterine cervical cancer IV

FIGO	Clinical condition	Options
IVA	All cases	CCRT
	Selected cases	Pelvic exenteration followed by CCRT
	Very low performance status	Palliative CHT Best supportive care
IVB	According to symptomatology	Management of morbidities Best supportive care Palliative CHT Palliative RT
Own design based on AWMF, 2014		

CCRT is associated with a 5-year survival rate of 22% in stage IVA and 3% in stage IVB, but without treatment most patients die within 7 months of diagnosis [64]. However, these therapies are associated with deterioration of quality of life because most patients with advanced regional and metastatic disease are medically debilitated or have very low health status. They usually develop anemia, malnutrition, diminished marrow reserves, tumor- and radiations -related hydronephrosis, or have renal insufficiency due to hydronephrosis or previous CHT or RT and are also at increased risk for pelvic fistula. The best support-care includes optimization of treatment for medical comorbidities, pain relief management, placement of ureteral stents or percutaneous nephrostomies, other specific surgical procedures for symptoms release and psychosocial support [5].

Regarding the prognosis of local advanced disease, it is expected that 40% -60% of patients present loco-regional recurrence, 20% – 40% develop distant metastasis, and 10%-20% develop both local and distant metastasis [4, 5].

3.5 Management of persistent and recurrent disease

The approach for persistent and recurrent cancer depends on initial treatment, recurrent tumor- or metastasis localization, and the patient´s clinical conditions and desire (Table 15). For example, patients with previous cisplatin-based CHT generally exhibit acquired resistance to cisplatin [59]. Treatment options include surgery and new cycles of RT or CHT with the addition of antiangiogenesis therapy to overlap the systemic toxicities of the chemo-and radiation therapies provided previously [5, 117].

Table 15. Management of recurrent uterine cervical cancer

Initial treatment	Central recurrence	Lateral recurrence
Trachelectomy	Radical hysterectomy Pelvic exenteration RT or CCRT	RT or CCRT ev. LEER
Radical hysterectomy	RT or CCRT Pelvic exenteration	RT or CCRT LEER
Surgery plus RT/CHT	Pelvic exenteration	LEER Palliative CHT
RT or CCRT	Pelvic exenteration Radical hysterectomy	LEER Palliative CHT
LEER = laterally extended endopelvic resection. Based on AWMF, 2014		

A*ntiangiogenesis therapy* provides the greatest benefit among patients with at least four of the following conditions: low performance status, pelvic disease, African-American ancestry, a disease-free interval less than one year, and prior platinum exposure [118]. Bevacizumab is a monoclonal antibody with antiangiogenesis properties that exhibits a synergistic effect with chemotherapeutic agents. It prevents tumor neovascularization via inhibition of vascular endothelial growth factor expression, normalizing the vasculature to a more typical phenotype and enhancing tumor susceptibility to chemotherapy or radiation [119].

Side effects of bevacizumab are observed in 20% of patients. These include: fatigue, anorexia, hyperglycemia, hypomagnesaemia, headaches, weight loss, and urinary tract infections [118, 119]. Major toxicities include gastrointestinal–vaginal fistula (8.6%), gastrointestinal perforation (3%), thromboembolism (8%), and easily managed hypertension (25%) [118, 119). In addition, an analysis of the health quality of life comparing cisplatin versus bevacizumab plus cisplatin reported that there is no significant impact on patient quality of health between groups (-1 to -2 points; 98·75%

CI -4·1 to 1·7; p=0·30), or complaining of pain (OR 0.96; 95% CI: 0.39 to 1.52; p=0.78), except that patients receiving bevacizumab are less likely to report neurotoxicity (overall OR: 0.58; 98.75% CI: 0.17 to 0.98; p=0.01) [120].

The addition of bevacizumab improves the disease-free survival rates (8.2 vs. 5.9 m; HR 0.67, 95 % CI 0.54–0.82) and overall survival time (17m; HR 0.71, 97 % CI 0.54–0.94) of patients with recurrent and metastatic disease, in comparison to cisplatin alone [118]. Moreover, cumulative evidence shows that cisplatin-paclitaxel-bevacizumab is most likely to prolong overall survival times (68%; median rank 1; CrI, 1-4) than other regimens including topotecan-paclitaxel-bevacizumab (7%; median rank 3; CrI, 1-8), paclitaxel-carboplatin (3.6%; median rank 4; CrI,1-10), topotecan-paclitaxel (0.2%; median rank 6; CrI, -11), and cisplatin-topotecan (0.2%; median rank 8; CrI,3-10) [121].

Compartmentalized surgery, pelvic exenteration and laterally extended endopelvic resection are considered useful for patients with a high probability of achieving a complete extirpation of the affected pelvic compartment with a metrically defined circumferential margin of tissue microscopically free of tumor cells. Compartmentalized surgery, pelvic exenteration, and laterally extended endopelvic resection are based on the theory that the ontogenetic-stage field determines the infiltration of the tumor tissue compartment (Table 16) [122].

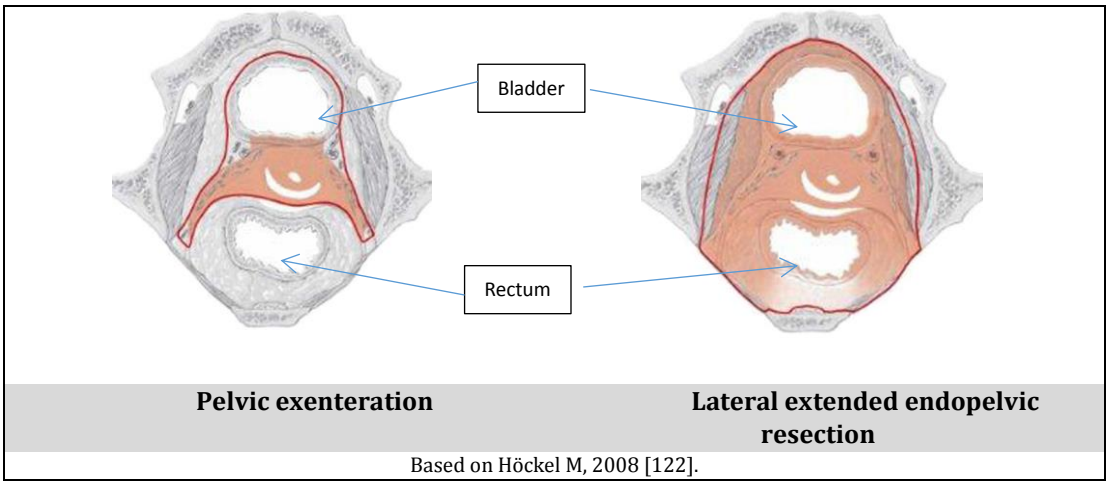
Prior to surgery patients should have an examination under anesthesia, site-directed core biopsies, and imaging evaluation by means of imaging procedures to exclude distant metastases. Despite their utility for planning surgery, these evaluations provide limited information about the extent of the disease leading to the cancelation of procedures in 30-50% of cases after intraoperative assessment of resectability [122, 123].

The surgical resection of the affected compartment grants preservation of non-involved tissues, low treatment-related morbidities, and better loco-regional cancer control [122]. The topographic-oriented approach and the excision of one of the morphogenetic anatomic units en-bloc with the afferent viscera (uterus, bladder, rectum, vagina), is called radical compartmentalized surgery.

Table 16. Ontogenetic staging of cervical carcinoma

oT stage	Cancer field	First-line lymph node Regions
1	Cervical stroma	Mesometrium External iliac Paravisceral · Supraobturator · Infraobturator · Internal iliac · Inferior gluteal
2	Müllerian compartment · Fallopian tubes, mesosalpinx · corpus, paracorpus · cervix, paracervix · Proximal vagina/paracolpos	Mesometrium External iliac Paravisceral Infundibulopelvic Perimesenteric Periaortic Infrarenal periaortic
3	Genital metacompartment · Gonadal compartments · Infundibulopelvic and ovarian · ligaments · Genital peritoneum · Müllerian compartment · Mesometrium · Dorsal bladder wall · Distal vagina · Urethra	Mesometrium External iliac Paravisceral Bladder mesentery Common iliac Superior gluteal Presacral Infundibulopelvic Perimesenteric Periaortic Infrarenal periaortic
4	Urogenital ridge metacompartment · Peritoneum · Retroperitoneum · Kidneys and ureters · Round ligament · Complete genital tract including · vulvar vestibulum · Bladder and urethra · Rectovaginal septum · Rectum and mesorectum	Mesometrium External iliac Paravisceral Bladder mesentery Common iliac Superior gluteal Presacral Mesorectal Mesureteric Infundibulopelvic Aortic bifurcation Perimesenteric Periaortic Infrarenal periaortic
Based on Höckel M. 2008 [122].		

Removing two or more units constitutes an ultraradical compartmentalized surgery or pelvic exenteration and both are performed for a recurrence that affects ontogenetic stage 3 (Figure 12). Recurrences with ontogenetic stage 4 require a wider excision, referred as extended endopelvic resection that includes the affected ontogenetic field, the pelvic floor, the infundibulopelvic ligaments, the wall muscles, the internal iliac vessel system, the urogenital mesentery, and its first-line lymph node regions [122].



Based on Höckel M, 2008 [122].

Figure 12. Limits of the radical compartmentalized surgery

Radical and ultra-radical compartmentalized surgeries are considered curative options for all-age patients with central recurrence and absence of sidewall involvement such as external iliac vessels, sciatic foramen and obturator nerve or bone invasion. Minor complications occur in 50% of cases, 22% develop major complications and 0%-5.5% die during the postoperative period. The 5-year survival rate after exenteration is not affected by age but by residual disease, it being 20%-50% for free resection margins and 10%-20% for positive ones [123].

Extended endopelvic resection is suitable for patients with tumors affixed to the lower pelvic sidewall, up to the level of the sciatic nerve and excluding the sciatic foramen, which also involves the pelvic sub- and retroperitoneum. In 97% of well-selected cases it is possible to achieve a R0 resection, with a low postoperative mortality (2%), and a 55% 5-year survival rate. Compared to partial exenteration, extended endopelvic resection has a higher postoperative morbidity rate (70%), a stronger

impact on body image, social functioning, and attitude towards the disease. Especially in women older than 60, who exhibited significantly worse scores for physical functioning, dyspnea, and sexual activity, but a better score for daily functioning [123].

3.6 Follow-up

Closer clinical follow-up is needed for an early detection of persistent and recurrent disease and should be performed every 3 months in the first year, then every 6 months subsequently for 2 more years post treatment (Table 17).

Table 17. Post-therapeutically follow-up interventions

Anamnesis	General, respiratory, gastrointestinal, urologic symptoms Lymphedema Sexual function Psychological status Personal performance status Familiar and social support
Physical examination	Palpation of abdomen, lymph nodes, septum rectovaginal, parametria. Visual examination of vagina, colposcopy.
Imaging examination	Pelvic, renal, abdominal ultrasound Chest X-ray, CT or MRI* Cysto-rectoscopy*
Biopsy*	Iodine guided biopsy Biopsy of tumoral masses
Tumor marker*	SCC in squamous epithelial carcinoma CEA and CA 125 in adenocarcinoma
* When patient presents with suspicious symptomatology. Based on Wiebe E et al., 2012; AWMF, 2014 [5, 64]	

The anamnesis includes questions regarding the physical, psychological, and social factors associated with women, such as: fatigue, alopecia, diarrhea, vaginal dryness, constipation, dysuria, rectal and vaginal bleeding, lymphedema, depression, familiar dysfunction, daily physical and social functionality. Visual and bimanual pelvic examinations are mandatory to evaluate the presence of burns, vaginal mucosae inflammation, vaginal synechiae, tumor or adenomegalies. Specific imaging and histologic and tumor marker examinations should be performed in cases with previous lymph or peritoneal metastasis, or when patients develop suspicious symptomatology of ureteral stenosis, persistent, recurrent, or metastatic disease [5, 64].

3.7 Supportive and rehabilitation therapies

Planning for the first treatment of invasive uterine cancer should also address the prophylaxis and management of acute- and long-term adverse effects of the recommended therapies, because these effects could lead to therapy toxicities, early withdrawal of treatment, and decline of the woman´s quality of life (Table 18).

Table 18. Indications of supportive and rehabilitation therapies

Prophylaxis of acute adverse effects	Nausea and emesis Diarrhea, enteritis, and constipation Anemia Renal dysfunction Mucosae and skin burns Psychological stress Partner and Familiar stress Drop of performance status
Management of long-term effects	Mucositis Proctitis Vaginitis Leg and vulvar lymphedema Vaginal dryness Vaginal stenosis Vaginal fibrosis Urinary and anal incontinence Sexual dysfunction
Own design	

More specifically, relationships (social, intimate, and familiar) may be affected by a deterioration of the patient's self-esteem, body image, coping skills functioning, and vaginal health [9]. Therefore, physicians should discuss these issues with their patients and suggest the best support and rehabilitation therapies in accordance to the woman's needs and clinical condition.

Important routine measures include psychological support to overcome the stress related to cancer diagnosis and fear of death, physical activity, and massage to control lymphedema, pelvic floor training to improve anal and urinary incontinence, the use of emollient substances to alleviate mucositis and skin burns due to radiation, as well as vaginal dilatators to prevent vaginal stenosis and dyspareunia [5]. However, it

was observed that only 20% of patients are prescribed dilatators, and non-sexually active women do not discuss these issues related with their physicians; mainly because patients are not interested (52 %), fear relapse or infections (41%), or present fatigue or other physical problems [9]. The use of complementary medicine is not strongly recommended due to lack of solid evidence concerning its efficacy and safety.

3.8 New genetic and immune-based agents

Additional research is exploring the role of new antiangiogenesis, as well as genetic and immune-based treatments for the management of advanced and metastatic cervical cancer (Table 19). These agents act upon and interrupt different molecular pathways that are involved in mutation and neoplastic cell transformation, cell growth, proliferation and survival, tumor angiogenesis, tumor progression, or host-immune tolerance [117, 124, 125].

A phase II study with temsirolimus in patients with metastatic and/or locally advanced and recurrent carcinoma of the cervix reported a response rate of 60% (20/33), and 28% of progression-free survival rate at six months after therapy. The phase II study of ADXS11-001 in patients with recurrent cervical cancer previously treated with CHT, RT or CCRT reports a 11% (12/110) response rate and 28% (31/110) progression-free survival rate at 18-month after immunotherapy [117]. The incoming evidence will determine the potential benefit on recurrence, overall survival rates (OS), and also the impact of these new options on the quality of health of patients with advanced, progressive or recurrent disease [126].

Table 19. New genetic and immune-based agents for the management of advanced and metastatic cervical cancer

	Mechanism of action	Effect
Antiangiogenesis agents		
Notch and VEGF blockers: Cetuximab, matuzumab, gefitinib, erolotinib	Interruption of the delta-like 4 transmembrane signaling and disruption of pericyte coverage of endothelial cells.	
Antiangiogenesis dual inhibitor: Brivanib	Dual inhibition of VEGFR-2 and fibroblast growth factor receptor-1 (FGR1).	Blood vessel regression Endothelial cell apoptosis Cytoskeletal changes
Tyrosine kinase inhibitor: Sunitinib.	Inhibition of VEGFR-1, -2, -3, platelet-derived growth factor α and β, and inhibition of related tyrosine kinase receptors.	Abnormal protein folding Endothelial cell damage Angiogenesis suppression Vascular resistance
Vascular disrupter: Combretastatin A-4 phosphate	Binding β-tubulin subunits to prevent microtubule formation.	Reduced tumor blood flow Central tumor necrosis
Non–VEGF-dependent antiangiogenesis: Trebananib	Disrupt signaling in the angiopoietin axis.	
Heat shock protein 90: Geldanamycin	Block interactions between client proteins receptor and their downstream substrates.	
Genetic agents		
mTOR inhibitor: Temsirolimus	Inhibition of TSC2degradation via PI3K/AKT/mTOR pathway related to HPV-E6 expression.	Squamous cell mutations. Cell apoptosis
Histone deacetylase inhibitors: Valproic acid, hydralazine	Remotion of acetyl groups of histone proteins inhibiting deacetylase activity and hyperacetylated histones.	Gene expression suppression Cell growth arrest
Nuclear kinase WEE1 inhibitors: MK1775, PD0166285	Arrest of the transition G_2–M cancer cell phase.	Mitotic failure Cell apoptosis
Poly ADP ribose polymerase PARP inhibitors: Olaparib, veliparib	Creation of single stand breaks in DNA, and further double strand breaks (DSBs) at cellular replication forks.	Tumor-selective lethality
Immune agents		
Live attenuated L. monocytogenes protein: ADXS11-001	Secretion of a HPV-16 E7 fusion protein.	Cellular expression of L1 and L2 capsid antigens. Increased T-cell immune response
Adoptive T-cells: Tumor-infiltrating lymphocytes	Secretion of a HPV E6 and E7 fusion protein.	
Antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4): Ipilimumab	Attenuation of the early activation of naïve and memory T cells.	Reawakening of silenced immune responses
Antibody against PD-1: Nivolumab	Negative regulation of T-cell ligands, PD-L1 and PD-L2.	Modulation of T-cell activity in peripheral tissues

Own design based on Tewari KS et al., 2014; van Meir H et al., 2014; Eskander RN et al., 2014 [117, 124, 125]

Part III.

4. Methodology and results of the retrospective study

4.1 Primary objective

The objective of this study is to describe the clinical outcomes of therapies provided to patients with a clinical diagnosis of early uterine cervical cancer, stages IA to IIB, who were treated at the University Clinic of Gynecology and Gynecological Cancer of Pius Hospital Oldenburg between 2009 and 2013.

4.2 Secondary Objectives

1. To describe the patients´ clinical characteristics at diagnosis.
    - Values are presented as mean number of patients (%), standard deviation (SD), or median (range).
2. To describe the high-risk factors of recurrence at diagnosis.
    - Values are presented as mean number of patients (%).
3. To identify the changes of FIGO-clinical diagnosis after staging procedures.
    - Values are presented as mean number of patients (%).
4. To identify the type of treatment received according to disease stage.
    - Values are presented as mean number of patients (%).
5. To identify the therapy compliance at initial management.
    - Values are presented as mean number of patients (%)
6. To estimate the mean size of residual tumor after neoadjuvant concurrent chemoradiotherapy.
    - Values are presented as mean number of patients (%) and median (range).
7. To estimate the complications and adverse events frequency according to provided treatment.
    - Values are presented as number of patients (%).
8. To identify the type of treatment for recurrent disease according to site of recurrence.
    - Values are presented as mean number of patients (%).
9. To estimate the recurrence rate according to type of treatment.
    - Values are presented as mean number of patients (%).
10. To estimate the recurrence rate according to stage of disease.

- Values are presented as mean number of patients (%).

11. To calculate the mortality rate according to type of treatment.
    - Values are presented as a rate or proportion.
12. To estimate the overall survival (OS) rate according to type of treatment.
    - Values are presented as survival curve by Kaplan Meier method.
13. To estimate the pregnancy frequency after conservative fertility sparing surgery.
    - Values are presented as number of patients (%).

4.3 Study design

Longitudinal, retrospective, descriptive study

4.4 Statistical analysis

For quantitative or numerical variables, the central tendency measures (mean, median, mode), and the dispersion measures (standard deviation, or ranges) were used. Arithmetic mean (%) was used for qualitative variables. The Kaplan-Meier method was used to estimate the overall survival.

To avoid potential sources of bias, mainly related to frequency of complication, any type of adverse event reported in the patient´s clinical chart was registered in the study´s database.

4.5 Definition of variables

- Clinical stage refers to the stage of cancer based on physical examination, imaging tests, laboratory tests, and biopsies carried out prior to staging [127].
- Early stage cancer refers to a cancer that is in the beginnings of its growth, which may not have spread to other parts of the body [127].
- Stage of disease refers to the tumor extension according to the FIGO classification. Here, the initial FIGO stage refers to the clinical stage and FIGO final refers to the confirmed extension of tumor, which was used for the measurements.
- Risk factors of recurrence are tumor characteristics that are well known to be associated with a high risk of recurrence or poor chance of disease survival.
- Neoadjuvant (NA-) therapy was defined as complementary treatment administered prior to surgical management of cancer.

- Adjuvant therapy (A-) was defined as a complementary treatment administered posterior to surgical management of cancer.
- Type of treatment was defined as the initial management with curative purposes:
    - Sg= surgery
    - NA-CCRT= concurrent chemoradiotherapy followed by surgery
    - A-RT= surgery followed by radiotherapy
    - A-CHT= surgery followed by chemotherapy
    - A-CCRT= surgery followed by concurrent chemoradiotherapy
    - CCRT= concurrent chemoradiotherapy
    - CHT= chemotherapy
    - RT= radiotherapy
- Therapy compliance is the act of following the therapeutically recommendations given by the multidisciplinary team correctly and consistently [127].
- Complication was defined as any event directly related to the administered treatment and in relation to its time of apparition:
    - Short-term complications: appear shortly after therapy initiation and resolve within the next 60 days.
    - Long-term complications: appear or persist beyond day 60 after therapy.
- An adverse event (AE) was defined as an unexpected medical problem that happens during treatment with a drug or therapy [127].
- A serious adverse event was defined as any event that results in any of the following outcomes: a life-threatening adverse event; inpatient hospitalization or prolongation of existing hospitalization; a significant, persistent, or permanent damage or disruption in the patient's body function, structure, physical activities, or quality of life; persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; death [128]
- Toxicity grade refers to the severity of the AE, from Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline [128]:
    - Grade 1 Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2 Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
    - Grade 3 Severe: medically significant but not immediately life-threatening;

hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
    - Grade 4 Life-threatening consequences; urgent intervention indicated.
    - Grade 5: Death related to AE.
- Residual tumor was defined as a macro- or microscopic tumor identified following an initial therapy administered with the aim of tumor size reduction.
- Recurrent disease refers to any tumor that has reappeared after a period of time during which the cancer could not be detected. The cancer may come back to the same place as the original (primary) tumor or to another place in the body [127].
- Central pelvic recurrence was defined as a cancer that develops from the cervix and vagina after primary radiotherapy or from the vaginal cuff and central scar after radical hysterectomy [127].
- Recurrence rate was defined as the time between the date of diagnosis and the first date of disease recurrence.
- Overall 5-years survival (OS) was defined as percentage of patients still living after 5 years from the date of diagnosis.
- Conservative fertility sparing surgery was a surgical approach performed to preserve the corpus uteri but not the cervix:
    - Conization
    - Trachelectomy.

4.6 Population

A list of 60 cases was obtained from a master list of 96 female patients with uterine cervical cancer (UCC) who were attended to in the University Clinic of Gynecology and Gynecological Cancer during 2009 - 2013. The Tumor Documentation Bureau of Pius Hospital provided the data.

Criteria for inclusion were a confirmed diagnosis of invasive UCC stages IA2, IB1, IB2, IIA or IIB and primary treatment of the condition in the Hospital. Cases with other stages of disease or different treatments as well as patients treated outside of the proposed time-range were excluded. The patient´s clinical information was accessed through the hospital´s intranet (Orbis Database), and all variables of interest were

translated anonymously into an SPSS-database. All 60 clinical records were followed over 5 years or until patient´s death.

4.7 Ethical approval

Prior to data collection, approval by the Documentation Office of Pius hospital, permission from the Hospital's Director and consent from Ethics Committee of Carl von Ossietzky University were obtained (No.134/2016).

4.8 Results

Study population and patient's characteristics are summarized in Figure 13 and Table 20. Most cases were postmenopausal women with a mean age of 50 years (26 -84 years) 5% of them with a clinical diagnosis of microinvasive disease (stage IA), and 95% with local invasive disease (IB 52%; II 43%) (Figure 13).

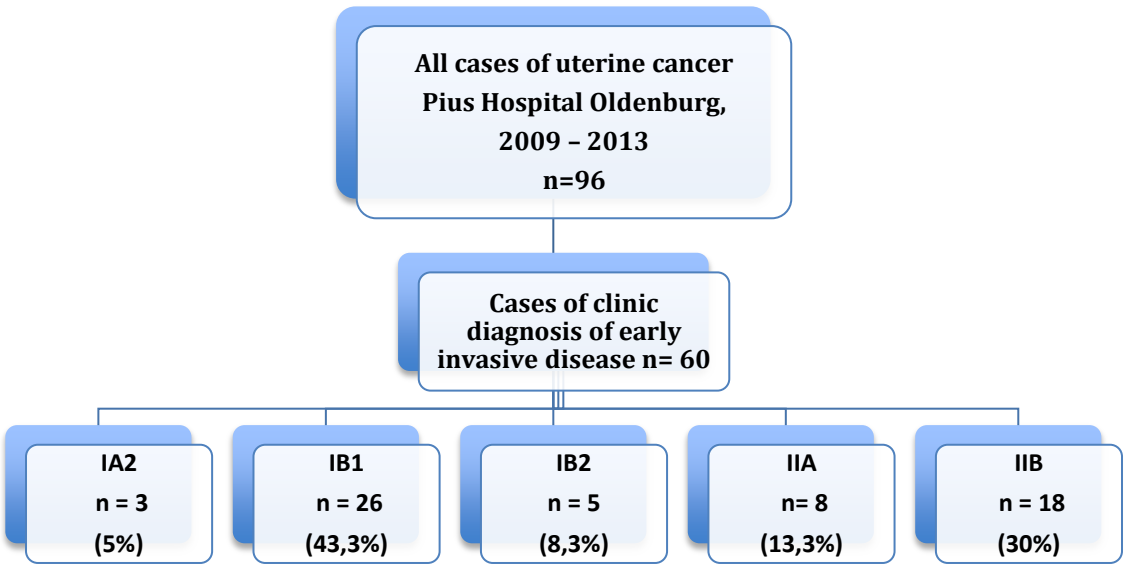


Figure 13. Selection of cases

The clinical diagnosis was made by means of physical examination, pelvic ultrasound and conization or pouch biopsies, which were performed mainly by external colposcopist. 75% of cases had a squamous epithelial cancer and 23% a glandular carcinoma, with mean tumor size of 39 mm, accompanied by hydronephrosis in 8% of

cases. Most of patients reported no familiar history of UCC and previous negative cytological results more than two years prior to diagnosis. HPV-DNA status was registered in less than 10% of cases (Table 20).

Table 20. Clinical characteristics of patients at diagnosis

Characteristics	Total (N=60)	%	Mean	SD
Age (years)			50.7	±13.5*
Menopause status				
Positive	35	58%		
Negative	25	42%		
Smoking				
Positive	10	18%		
Negative	50	82%		
Family history of UCC				
Positive	5	8%		
Negative	55	92%		
Previous abnormal Pap smear (> 2 year)				
Positive	6	10%		
Negative	54	90%		
Cancer detection				
Conization	29	48%		
Pouch biopsy	31	51%		
Histology				
Squamous tumors	45	75%		
Glandular tumors	14	23%		
Müllerian papilloma	1	2%		
Tumor size at diagnosis (mm)			39.0	±23.6*
Presence of hydronephrosis				
Positive	5	8%		
Negative	55	92%		

At admission, and in compliance with the German guidelines, all patients underwent a staging procedure that allowed the interdisciplinary group to perform an individualized risk- benefit analysis of therapies. Staging procedures to evaluate the tumor size, disease extension, and presence of metastasis included: physical examination, common hematological and biochemical tests, histological examination, and imaging studies. Abdominal and pelvic ultrasound and CT were performed in all

cases; here, the radiologists' reports described the localization and quantity of abnormal nodes as they were seen in CT, MRI or PET-CT scans. However, lacked details regarding used criteria to classify a lymph node as abnormally enlarged.

Seven patients with clinical stage IB disease and with enlarged pelvic- and paraaortic lymph nodes at CT underwent a complementary abdominal MRI examination. Six of these cases were also interpreted as positive at MRI; therefore they underwent surgical-sentinel lymph node assessment, resulting in five cases of negative nodes and one case of positive paraaortic lymph node involvement. Staging also allowed the detection of three cases of advanced regional disease stages III and IVA. PET –CT was used later in these three cases to evaluate the presence of distant metastasis. After staging, 25% (n=15) of patients had an increased initial clinical stage and for 5% (n=3) of them it was reduced (Table 21).

Table 21: FIGO classification after staging procedures

	IA1	**IB1**	**IB2**	**IIA**	**IIB**	**III**	**IVA**
Initial	3 (5%)	26 (43.3 %)	5 (8.3%)	8 (13.3%)	18 (30%)	0 (0%)	0 (0%)
Final	1 (2%)	23 (38%)	6 (10%)	12 (20%)	15 (25%)	1 (2%)	2 (3%)

An additional important step in the multidisciplinary team's decision-making process was the assessment of high risk factors for local recurrence. These were decisive parameters for whether to use more radical approaches. 58% of the patients had more than two high risk factors of recurrence at diagnosis. Four patients did not have any risk factors, 21 had one factor, 16 had two factors, 5 had three factors, 14 had four factors and none presented more than five risk factors (Table 22).

Of the possible high risk factors, the most frequent were large tumor size, deep stromal invasion, and lymph node or parametria involvement. Almost one fourth of patients had an adenocarcinoma, a type of cervical cancer that exhibits endophytic growth resulting in bulky tumors associated with late symptomatology and diagnosis.

Table 22. High-risk factors of recurrence at diagnosis

Risk factor	Total N=60	%
Tumor size > 4 cm	46	77%
Deep cervical stromal invasion	29	48%
Involvement of lymph nodes	25	42%
Involvement of parametria	23	38%
Glandular tumors	14	23%
Lymphovascular invasion	2	3%
Number of risk factors	**Total N=60**	**%**
0	4	7%
1	21	35%
2	16	27%
3	5	8%
4	14	23%

In addition to the final FIGO-stage, several criteria were used by the interdisciplinary group to establish the best treatment for each case such as: a) the medical reports on the health and performance status of the patient, b) the surgeons' reports on the findings at surgical intervention, including visible tumoral extension and palpable enlarged lymph nodes, c) the radiologists' reports regarding the presence, localization, and size of tumoral- and enlarged lymph nodes, d) the findings provided by pathologists in regards to histological type and presence of risk factors for local recurrence and e) the recommendations of the German guidelines[1],mainly radical surgery with lymphadenectomy for stage IB and II disease; adjuvant or neo-adjuvant therapies for patients with stage IB and II who presented high risk factors of recurrence; CCRT alone for stage III disease, and an individualized management for stage IV disease. Consequently, not all patients in the same FIGO stage underwent the same management (Table 23).

One third of cases, mainly patients with tumors less than 4 cm (stages IA-IB1), were treated with surgery alone; 64% of cases received an adjuvant or neoadjuvant therapy, CCRT being provided in almost half of cases (Table 23). Cisplatin was the primary chemotherapeutical agent used. No fertility preserving surgery was performed. Eight from 15 cases who underwent NA-CCRT, that is 57% of this group, presented a complete tumor reduction before surgery.

[1] For detailed information, please refer to Table 12 and 14 of this manuscript or to reference AWMF, 2014 [5].

Table 23. Initial treatment according to FIGO stage

Treatment	IA2 N=1	IB1 N=23	IB2 N=6	IIA N=12	IIB N=15	IIIB N=1	IVA N=2	Total N=60
Sg	1	15	1	2	0	0	0	19 (32%)
A-CCRT	0	3	4	5	3	0	0	15 (25%)
NA-CCRT	0	2	1	3	6	1	1	14 (23%)
A-RT	0	3	0	1	0	0	0	4 (7%)
A-CHT	0	0	0	0	2	0	0	2 (3%)
CCRT	0	0	0	1	3	0	0	4 (7%)
RT	0	0	0	0	1	0	0	1 (2%)
CHT	0	0	0	0	0	0	1	1 (2%)

Prior to therapy initiation, each patient received a counseling session regarding her therapeutic options, associated complications, adverse events, toxicities and prognosis. Subsequently, an informed consent was signed. In accordance with the interdisciplinary group reports, in 7 cases (5%) the extension of surgery or chemotherapy cycles were adapted to the patient´s clinical conditions. One patient (3%) with IVA- disease stage refused to receive the recommended concomitant radiotherapy, resulting in a 97% rate of therapy compliance.

According to the available information regarding complications, adverse events and toxicities of therapies (Table 24), almost half of patients complained of general symptoms like pain, nausea, vomiting or depression. Depressed patients received at least one consultation by the hospital´s psychotherapist. Wound healing problems were present in 52% of patients (N=32), being most frequent in those who underwent some type of adjuvant therapy in comparison to radical surgery alone (18 vs. 14 cases, respectively). Urinary infection was present in 30% of cases and was the cause of fever in one third of cases.

A total of 115 AE of different toxicities [128][2] were reported mostly hematological with 15 of them occurring after surgery, (Table 24). Patients who

[2] For detailed information, please refer to reference NCI, 2017 [128].

received some type of chemotherapy (A-CCRT, NA-CCRT, A-CHT or CHT) presented toxicities more frequently than those who received adjuvant RT, but the patient who received RT alone had none of these events.

Table 24. Adverse events according to treatment approach

Adverse event	Sg N=19	A-CCRT N=15	NA_CCRT N=14	A-RT N=4	A-CHT N=2	CCRT N=4	RT N=1	CHT N=1	Total N=60 (%)
Pain	14	11	13	4	2	3	0	1	48 (80%)
Wound healing problems	14	4	9	2	2	0	0	1	32 (53%)
Depression	9	6	8	1	2	2	0	1	29 (48%)
Nausea and vomiting	3	6	5	0	2	2	0	1	19 (32%)
Urinary infection	3	6	4	3	1	1	0	0	18 (30%)
Fever	7	2	4	0	0	2	0	1	16 (26%)
Anemia	7	13	10	3	2	4	0	1	40 (67%)
Neutropenia	2	12	8	1	0	2	0	1	26 (43%)
Thrombocytopenia	2	9	7	0	2	3	0	1	24 (40%)
Renal /Electrolyte dysfunction	4	10	7	0	1	2	0	1	25 (42%)
*Some events were simultaneously presented									

According to toxicity grade, 48% of these AE were Grade-1 (56 events), 33% Grade-2 (38 events), 16% Grade-3 (18 events), and 3% Grade-4 (3 events). Only one

event of Grade-5 (Death) due to sepsis developed after the first cycle of chemotherapy occurred (Table 25).

Table 25. Frequency of toxicities during adjuvant therapies, according to National Cancer Institute Common Toxicity Criteria

Adverse Event*	Toxicity Grade 1	Toxicity Grade 2	Toxicity Grade 3	Toxicity Grade 4
Anemia (Hb)	>10.0 g/dL	8.0 -10.0 g/dL	6.5 - <8.0 g/dL	<6.5 g/dL
N= 40 (%)	8 (20.5%)	24 (59%)	8 (20.5%)	0
Neutropenia	<LLN -3000/mm^3	2000 -<3000/mm^3	1000 - <2000/mm^3	<1000/mm^3
N= 26 (%)	9 (35%)	11 (42%)	5 (19%)	1 (4%)
Thrombocytopenia	<LLN -75.000/mm^3	50.000 -75.000/mm^3	10.000 -50.000/mm^3	<10.000/mm^3
N= 24 (%)	20 (84%)	2 (8%)	1 (4%)	1 (4%)
Hypokalemia	<LLN - 3.0 mmol/L	2.0 – 2.5 mmol/L	2.5 - <3.0 mmol/L	<2.5 mmol/L
N= 2 (%)	2 (100%)	0	0	0
Hypernatremia	>ULN - 150 mmol/L	150 - 155 mmol/L	155 - 160 mmol/L	>160 mmol/L
N= 2 (%)	2 (100%)	0	0	0
Hyponatremia	<LLN - 130 mmol/L	(no range)	130 - 120 mmol/L	<120 mmol/L;
N= 14 (%)	9 (64%)	-	4 (29%)	1 (7%)
Creatinine above baseline	1.5 x- 2.0x above	2 x- 3x above	3x- 6x above	> 6x above
N= 6 (%)	5 (83%)	1 (17%)	0	0
Proteinuria	0.15 - 1.0 g/24h	1.0 – 3.5 g/24h	>3.5 g/24h	Nephritic syndrome
N= 1 (%)	1 (100%)	0	0	0
Total Events N=115	56 (48%)	38 (33%)	18 (16%)	3 (3%)
*Some events were simultaneously present				

In addition, 32 serious adverse events (SAE) were reported (Table 26), 24 cases of them presented with abdominal pain that required surgery. Ureter ligation (N=3), ascites (N=4) and peritoneal adhesions (N=2) were the most frequent SAE after radical surgery. On third of the SAE were reported in those patients who received A-CCRT (11 events), including ureteral stenosis (N=2), neurotoxicity (N=2), ileus small bowel stenosis (N=1), hemoperitoneum (N=1), and peritonitis (N=1). No SAE were reported in

the patients that underwent CHT alone. Acute severe toxicities related to radiation were ureteral stenosis (N=4), three of them bilateral and one case of small-bowel obstruction. These patients underwent surgical correction of the lesions by the correspondent specialized team, including partial resection of small-bowel and re-anastomosis or reimplantation of ureters, respectively.

Table 26. Serious adverse events according to treatment approach

Serious adverse event*	**Sg N=19**	**A-CCRT N=15**	**NA_CCRT N=14**	**A-RT N=4**	**A-CHT N=2**	**CCRT N=4**	**RT N=1**	**CHT N=1**	**Total**
Sepsis	0	0	0	0	0	0	0	1	1
Thrombo-embolism	0	1	0	0	0	1	0	1	3
Hemo-peritoneum	0	1	1	0	0	2	0	1	5
Ureter rupture	0	0	0	1	0	0	0	0	1
Urinoma	0	1	0	0	0	0	0	0	1
Peritonitis	0	1	0	0	0	0	0	0	1
Ileus	0	1	0	0	0	0	0	0	1
Ureter ligation	3	0	0	0	0	0	0	0	3
Adhesions	2	0	0	0	0	0	0	0	2
Ascites	0	1	3	0	0	0	0	0	4
Adnexal torsion	0	0	1	0	0	0	0	0	1
Pelvic lymphocele	1	0	0	0	0	0	0	0	1
Ureteral stenosis	0	2	1	0	0	0	1	0	4
Small bowel stenosis	0	1	0	0	0	0	0	0	1
Neurotoxicity	0	2	0	0	0	0	0	0	2
Peritoneal metastasis	0	0	0	0	0	1	0	0	1
TOTAL	7	11	6	1	0	4	1	3	**32**
*Some events were simultaneously present									

After finalization of therapy, all patients were counseled to attend a follow- up visit quarterly during the first year, every six months the second- and third years, and then annually. Physical examination, laboratory analysis, imaging controls and complementary therapies were performed according to guidelines and clinical

symptomatology. These included lymph drainage or physiotherapy for chronic pain and lymphedema, and psychotherapy for patients with depression.

Less than half of patients presented a long-term adverse event or reported a chronic symptom; lymphedema, chronic pelvic pain and fatigue being those most frequently reported. Although 63% of all cases received some type of RT (alone, adjuvant or concurrent) a small proportion of them presented actinic mucositis, either urinary (18%) or anal (13%). Urinary incontinence and vaginal symptoms like stenosis or prolapse were reported by 5% of patients. Five patients developed a vaginal fistula, with three of them being previously re-operated due to ureter ligation (Table 27).

Table 27. Long-term adverse events according to treatment approach

Complication	Sg N=19	A-CCRT N=15	NA_CCRT N=14	A-RT N=4	A-CHT N=2	CCRT N=4	RT N=1	CHT N=1	Total N=60
Chronic pelvic pain	7	7	8	1	1	2	0	0	26 (43%)
Fatigue	3	8	8	1	2	3	0	0	24 (40%)
Lymphedema (Legs)	2	4	4	1	1	1	0	0	13 (22%)
Actinic cystitis	0	6	3	1	0	2	0	0	12 (18%)
Actinic proctitis	0	4	3	0	0	1	0	0	8 (13%)
Lymphocele	1	4	1	0	0	0	0	0	6 (10%)
Vaginal fistula	2	1	1	0	1	0	0	0	5 (8%)
Urinary incontinence*	0	1	2	0	0	0	0	0	3 (5%)
Vaginal stenosis*	0	0	1	1	0	1	0	0	3 (5%)
Vaginal prolapse*	0	0	1	0	0	0	0	1	2 (3%)
Total	15	35	32	5	5	10	0	1	
Some events were simultaneously present									

During the 5-year follow-up, 25% (N=15) of patients presented a recurrent disease within the three years after initial treatment. Half the cases appeared during the

first year, predominantly in patients with local advanced disease stages IIA-IIB (Table 28). In accordance to number of high-risk factor of recurrence, five cases had one factor; five had two factors; two had three factors and three had four factors.

Table 28. Recurrence time interval according to FIGO stage

Recurrence interval	1A2 N=1	IB1 N=23	IB2 N= 6	IIA N=12	IIB N=15	IIIB N=1	IVA N=2	Total N=60
< 12 months	0	1	0	2	3	1	0	7 (11%)
13 - 24 months	0	2	0	1	1	0	1	5 (8%)
25 - 36 months	0	1	0	0	2	0	0	3 (5%)
36 - 48 months	0	0	0	0	0	0	0	0
49 - 60 months	0	0	0	0	0	0	0	0
Total recurrences	0	4 (17%)	0	3 (25%)	6 (40%)	1 (100%)	1 (100%)	15 (25%)

With respect to treatment approach (Table 29), more cases of recurrent disease developed in the NA-CCRT group (N=6), than in patients who received surgery as a primary approach. According to time of recurrence, they appeared equally along treatment groups. Worthy of mention is that from the three recurrent cases in the surgery group, all were in patients with initial tumor size less than 4 cm.

Table 29. 5-years recurrence rate according to treatment approach

Time	Sg N=19	A-CCRT N=15	NA-CCRT N=14	A-RT N=4	A-CHT N=2	CCRT N=4	RT N=1	CHT N=1*
1 year	1	2	2	0	1	1	0	-
2 years	1	0	2	1	0	1	1	-
3 years	1	0	2	0	0	0	0	-
4 years	0	0	0	0	0	0	0	-
5 years	0	0	0	0	0	0	0	-
Total	3 (16%)	2 (13%)	6 (43%)	1 (25%)	1 (50%)	1 (50%)	0	

*Excluded of analysis because of death at 2nd month.

With regard to site of presentation (Table 30), central pelvic recurrence presented mostly at the vagina. It is noteworthy that 72% of these patients exhibited a second site of tumoral involvement, mainly abdominal peritoneum, and distant metastasis occurred in 54% of recurrent disease.

Additional therapies for recurrent disease were discussed within the interdisciplinary group and administered with the aim of tumor control or palliation, in accordance with patient clinical condition and consent. One patient declined the proposed management. Combined chemotherapy schema was delivered to the rest of patients. It included the administration of cisplatin with another agent such as paclitaxel, carboplatin or topotecan, and concomitant administration of bevacizumab, an antiangiogenesis agent. Four patients (40%) received concurrent radiotherapy.

Table 30: Treatments for recurrent disease

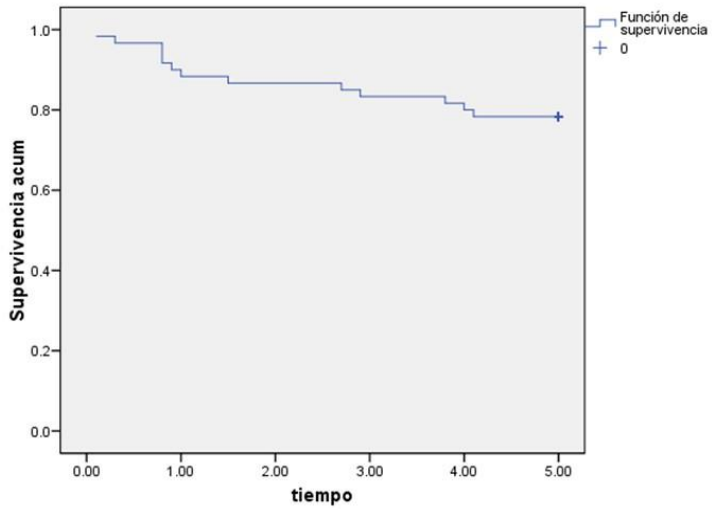
Site of recurrence	None	Sg	Combined CHT *	CCRT*	Total
Vagina	0	0	4	2	6
Abdominal peritoneum	1	1	2	2	6
Uteri	0	0	0	1	1
Lever	0	0	3	0	3
Lungs	0	0	3	0	3
Chemotherapy included two medicaments plus an antiangiogenesis agent.					

At the end of the 5-years follow-up period, 13 (22%) patients died, most of them within the first three years after treatment. Eight (61%) were patients who received an adjuvant or neo-adjuvant therapy (Table 31).

Table 31. Overall mortality rate according to treatment approach

	Sg N=19	A-CCRT N =15	NA_CCRT N =14	A-RT N =4	A-CHT N =2	CCRT N=4	RT N=1	CHT N=1
Total N=13 (22%)	2 (10%)	2 (13%)	4 (28%)	1 (25%)	1 (50%)	1 (25%)	1 (100%)	1 (100%)

Mortality was lower in patients with disease stages IB1 –IB2 (30%; N=4), than in those with stages IIA to IVA (70%; N=9) with an overall survival rate of 78% by the 5Th year (Figure 14). One patient who received CHT who had an initial tumor size of 10 cm died two months after therapy initiation.



Time (year)	0-1	1-2	2-3	3-4	4-5
Total	60	54	52	50	49
Deaths	6	2	2	1	2
Survival	0.90	0.87	0.83	0.82	0.78

Calculated by Kaplan Meier method

Figure 14. Overall 5-years survival rate

4.9 Discussion

The incidence and mortality rates of UCC have been declining worldwide as a result of better health service networks committed to its prevention and attention. An accurate diagnosis and appropriate treatment require integral public health programs allow an effective articulation of sexual and reproductive health services with higher complexity health facilities [129]. This includes prevention of the HPV-related oncogenic process by means of a) sexual education and vaccination of naïve adolescents; b) invitations to attend regular Pap smear examinations c) educational material to increase women´s awareness on UCC [62], d) detection of the disease in preinvasive stages by means of regular screening methods, including cervical cytology and HPV-DNA tests; an e) providing the best quality of care to affected women in accordance with clinical

guidelines. However, most programs worldwide are not fulfilling public health expectations in regard to increasing women´s awareness of UCC and encouraging them to undergo screening [62]. Consequently, new cases of advanced cervical cancer are still frequently diagnosed, increasing the probability of treatment-related morbidities that negatively impact the quality of health of surviving women and increase the costs to health care systems [8, 9].

In Germany, women have guaranteed access to screening, vaccination, and treatment. UCC management is usually provided in certified centers that have been created in the last ten years to assure women have access to high quality health care facilities. Through a guidelines-based interdisciplinary approach, individualized treatments and close follow-up of patients, these centers are committed to achieving a reduction in the recurrence intervals and to increasing the survival rates of affected women [AWMF, 2014]. Compared to Germany, where 61% of UCC cases are early stage I at diagnosis, while 39% are advanced stage (25% in stage II, 14% in stages III-IV) [130], in USA, 50% of cases are diagnosed at advanced stages (46% in stage I, 36% in stage II and 14% in stages III-IV) [131].These numbers imply that those structured measures are effective, but more efforts are needed to continuing reducing the incidence of UCC.

The present analysis shows the treatment outcomes of 60 patients referred with a diagnosis of UCC stages I-II. The mean age of patients (50y) was similar to those reported in both Germany (53y) and USA (49y) [129, 130]. It was observed that all patients were managed in strict compliance with the German quality of care criteria for cancer centers [5, 132]. Prior to therapy initiation, a staging procedure evaluating the extent of the disease and risk factors of recurrence was performed, including a sentinel node assessment, when needed; therapeutic options were analyzed within a multidisciplinary cancer team following the national guidelines; when necessary, cisplatin-based chemotherapy was the first line of treatment; and finally therapies were discussed with patients before their informed consent was obtained. With reference to sentinel node assessment, it is not a FIGO standard, however it is recommended by the German guidelines when enlarged pelvic or para-aortal lymph nodes are observed in CT and MRT scans to establish if an adjuvant or extended-field RT is further needed once a micro-metastatic disease in those nodes is confirmed [AWMF, 2014]. As a result, patients underwent individualized therapies adjusted to their clinical conditions and

their own decisions, which in turn, resulted in a high therapy compliance rate, which made a close follow-up of treated patients possible.

After staging, the initial clinical FIGO stage of one third of all patients had either been increased or reduced, with more than half of the patients exhibiting more than two high-risk factors of recurrence. Therefore staging procedures allowed referred patients to have a more accurate assessment of disease extent.

Close follow-up of patients is an additional important issue, because treatment outcomes and intrinsic toxicities of therapies influence therapy compliance, treatment success, and prognosis [8, 9]. Regarding therapy outcomes, it is well known that combined and concurrent therapies for cancer increase the risk of complications and AE [107]. Moreover, complications, AE, and toxicities related to cancer management are frequently scattered or are partially reported [13, 110]. In the present study, all morbidities were considered for analysis. Here it was observed that physicians frequently did not systematically reported complications and adverse events in terms of international grading standards. Similar frequency of short- term AE between therapies was found, but toxicities and SAE were present in a higher proportion in those who underwent CCRT than RT alone. These results are in accordance with a recent meta analysis of eight RCTs and three cohort studies comparing CCRT vs. RT in 2130 subjects with high-risk cervical carcinoma, where toxicities are significantly enhanced in those who underwent CCRT (OR =3.13, 95% CI: 2.37-4.13) [133]. In the same way, different trials showed that radical surgery has been associated with a higher morbidity, especially in elderly women, from 22.1% in women less than 50 years of age to 34.9% in women more than 70 years of age ($P<0.0001$) [87]. In addition, A-CCRT is associated with a higher risk of toxicities than A-RT (RR 5.66, 95% CI 2.14 to 14.98) [134]. Other studies report that NA-CCRT is associated with hematological and gastrointestinal toxicities, but there is no difference ($P > 0.05$) in long-term SAE or toxicities between NA-CCRT and RT [110]; although, severe toxicities occurred significantly more frequently with NA-CCRT (RR= 6.26, 95% CI 2.50 to 15.67) [13].

The aim of the NA-CCRT is to achieve a tumor size reduction, thereby making less radical subsequent surgery necessary and minimizing the necessity of postoperative adjuvant therapies [135]. More than half of the cases considered in this

study exhibited a complete tumor reduction after NA-CCRT. These results are similar to those from a retrospective multicenter analysis examining 159 patients with locally advanced UCC (stages IB-IVA), where 55% of cases exhibited complete tumor reduction prior to surgery. Although, the results of the present study differ from those of a prospective study of141 women with stage IB disease, where only 11% of cases achieved complete response and 70% of cases exhibited a tumor reduction up to 50% of its initial size [136].

In relation to recurrence and survival rates, a quarter of patients observed in this study presented a recurrent disease, mainly in those with a local advanced disease IIB-IVA, or with one or two high-risk factors of recurrence. These findings might be explained by the fact that these patients had a tumor bigger than four centimeters, which is a well-recognized risk factor that has a significant prognostic impact on recurrence and OS; despite most of them exhibiting a complete tumor reduction after NA-CCRT [137]. An OS rate of 78% was calculated by the 5th year, predominantly in patients with disease stages IB1 –IB2. Deaths occurred similarly between therapies, mostly in patients with local advanced stages who received an adjuvant or neo-adjuvant therapy and between those with recurrent disease.

Hence, our study design does not permit the establishment of statistically significant differences between therapies. Evidence from meta analysis show that platinum-based CCRT reduces the risk of death (HR= 0.56, 95% CI: 0.36 to 0.87), and decreases the risk of disease progression in early disease stages (HR = 0.47, 95% CI 0.30 to 0.74), with no heterogeneity between trials (I^2 = 0% for both meta-analyses) [131]. When compared to RT, CCRT is associated with higher OS rates (HR=0.68; CI 95% 0.57 to 0.80) and DFS rates (HR=0.63; CI 95% 0.50 to 0.76) [132]. However, there is a lack of evidence on local and distant recurrence after NA-CCRT and survival comparisons stratified by tumor response after non-cisplatin based CCRT regimens [132]. This is an important issue that should be addressed in future trials to evaluate which are the safer and more effective antineoplastic combinations for the management of early invasive UCC.

4.10 Implications for future research and clinical practice

Our study revealed that women with early invasive disease lose the opportunity to receive conservative therapies; therefore, we emphasize the importance of early cancer detection. Later, staging-based disease management is mandatory prior to any treatment to provide the best possible care for the patient. Finally, a systematical monitoring of treatment-outcomes and reporting according international criteria should be performed during oncological follow-up that guarantees the early recognition of tumor response and complications, especially after radical surgery and CCRT.

Transparent and accurate reporting in relation to treatment-outcomes and other critical aspects of UCC management after NA-CCRT and new therapies are required, including suitable population, adverse events, long-term toxicities, predictor factors of tumor response, as well as their impact on a woman´s quality of life.

4.11 Strengths and limitations

This is the first time that an analysis regarding the quality of care in respect to treatment-outcomes for patients with early invasive UCC has been carried out in Pius Hospital. Similar to other retrospective studies, this study has some limitations as a result of data availability. Specifically, medical reports reflect the differences between physicians in relation to the questions addressed to patients during follow-up interviews and the way patients express their symptoms elicited over time. Nevertheless, and considering the high proportion of patients who underwent staging procedures and CCRT, these results add to the international knowledge on the clinical outcomes of these interventions.

4.12 Conclusion

This study highlights the importance of staging as a crucial step during the attention of patients with clinical diagnosis of cervical cancer due to its repercussion on the treatment decision-making process. Specifically, radical surgery and concurrent chemo-radiation are effective for tumor size reduction, but an important number of complications, adverse events and toxicities are induced by these suitable therapies. Such topics should be considered by the multidisciplinary team and discussed with patients prior to treatment initiation, moreover should be actively assessed during

follow-up sessions. Furthermore, treatment-outcomes related to tumor response and adverse events are not usually reported in clinical trials. Therefore, we encourage investigators to report their clinical results beyond recurrence and survival rates to improve the knowledge in relation to tumoral behavior and adverse events related to available and incoming therapies for cervical cancer.

5. Disclosures

There are no conflicts of interest to be reported by the author. Professor De Wilde supervised this study, and his comments have been incorporated. The views and opinions expressed herein are those of the author and tutor and do not necessarily reflect those of the Pius Hospital Oldenburg.

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Appendixes

Appendix 1. : Munich nomenclature III and Bethesda reporting system.

Tabelle 1

Gruppe	Definition	Korrelat im Bethesda System
0	**Unzureichendes Material** → *Abstrichwiederholung*	Unsatisfactory for evaluation
I	**Unauffällige und unverdächtige Befunde** → *Abstrich im Vorsorgeintervall*	NILM
II-a	**Unauffällige Befunde** bei auffälliger Anamnese → *ggf. zytologische Kontrolle wegen auffälliger Anamnese (zytologischer/histologischer/kolposkopischer/klinischer Befund)*	NILM
II	**Befunde mit eingeschränkt protektivem Wert**	
II-p	Plattenepithelzellen mit geringergradigen Kernveränderungen als bei CIN 1, auch mit koilozytärem Zytoplasma/Parakeratose → *ggf. zytologische Kontrolle unter Berücksichtigung von Anamnese und klinischem Befund (evtl. nach Entzündungsbehandlung und/oder hormoneller Aufhellung; in besonderen Fällen additive Methoden und/oder Kolposkopie)*	ASC-US
II-g	Zervikale Drüsenzellen mit Anomalien, die über das Spektrum reaktiver Veränderungen hinausreichen → *ggf. zytologische Kontrolle in Abhängigkeit von Anamnese und klinischem Befund (evtl. nach Entzündungsbehandlung; in besonderen Fällen additive Methoden und/oder Kolposkopie)*	AGC endocervical NOS
II-e	Endometriumzellen bei Frauen > 40. Lebensjahr in der zweiten Zyklushälfte → *Klinische Kontrolle unter Berücksichtigung von Anamnese und klinischem Befund*	Endometrial cells
III	**Unklare bzw. zweifelhafte Befunde**	
III-p	CIN 2/CIN 3/Plattenepithelkarzinom nicht auszuschließen → *Differentialkolposkopie, ggf. additive Methoden, evtl. kurzfristige zytologische Kontrolle nach Entzündungsbehandlung und/oder hormoneller Aufhellung*	ASC-H
III-g	Ausgeprägte Atypien des Drüsenepithels, Adenocarcinoma in situ/invasives Adenokarzinom nicht auszuschließen → *Differentialkolposkopie, ggf. additive Methoden*	AGC endocervical favor neoplastic
III-e	Abnorme endometriale Zellen (insbesondere postmenopausal) → *Weiterführende klinische Diagnostik, ggf. mit histologischer Klärung*	AGC endometrial
III-x	Zweifelhafte Drüsenzellen ungewissen Ursprungs → *Weiterführende Diagnostik (zum Beispiel fraktionierte Abrasio; ggf. additive Methoden/Differentialkolposkopie)*	AGC favor neoplastic
IIID	**Dysplasiebefunde mit größerer Regressionsneigung**	
IIID1	Zellbild einer leichten Dysplasie analog CIN 1 → *Zytologische Kontrolle in sechs Monaten, bei Persistenz > ein Jahr: ggf. additive Methoden/Differentialkolposkopie*	LSIL
IIID2	Zellbild einer mäßigen Dysplasie analog CIN 2 → *Zytologische Kontrolle in drei Monaten, bei Persistenz > sechs Monate: Differentialkolposkopie, ggf. additive Methoden*	HSIL
IV	**Unmittelbare Vorstadien des Zervixkarzinoms** → *Differentialkolposkopie und Therapie*	
IVa-p	Zellbild einer schweren Dysplasie/eines Carcinoma in situ analog CIN 3	HSIL
IVa-g	Zellbild eines Adenocarcinoma in situ	AIS
IVb-p	Zellbild einer CIN 3, Invasion nicht auszuschließen	HSIL with features suspicious for invasion
IVb-g	Zellbild eines Adenocarcinoma in situ, Invasion nicht auszuschließen	AIS with features suspicious for invasion
V	**Malignome** → *Weiterführende Diagnostik mit Histologie und Therapie*	
V-p	Plattenepithelkarzinom	Squamous cell carcinoma
V-g	Endozervikales Adenokarzinom	Endocervical adenocarcinoma
V-e	Endometriales Adenokarzinom	Endometrial adenocarcinoma
V-x	Andere Malignome, auch unklaren Ursprungs	Other malignant neoplasms

Source: [41,42]Griesser H, Breinl H, Jordan B. (Munich nomenclature III. Gynecological dysplasias are clearly assigned). Deutsch Aerzteblatt 2014; 111: A640/B-550/C-530. Available from: URL: http://www.zytologie.org/media/data/Broschuere-Muenchner-Nomenklatur-III-fuer-die-gynaeko.pdf . German.

Appendix 2: WHO histological classification of tumours of the uterine cervix

Epithelial tumours	ICD-10
Squamous tumours and precursors	
Squamous cell carcinoma, not otherwise specified	8070/3
Keratinizing	8071/3
Non-keratinizing	8072/3
Basaloid	8083/3
Verrucous	8051/3
Warty	8051/3
Papillary	8052/3
Lymphoepithelioma-like	8082/3
Squamotransitional	8120/3
Early invasive (microinvasive) squamous cell carcima	8076/3
Squamous intraepithelial neoplasia	
Cervical intraepithelial neoplasia (CIN 3)	8077/2
Squamous cell carcinoma in situ	8070/2
Benign squamous cell lesions	
Condyloma acuminatum	
Squamous papilloma	8052/0
Fibroepithelial polyp	
Glandular tumours and precursors	
Adenocarcinoma	8140/3
Mucinous adenocarcinoma	8480/3
Endocervical	8482/3
Intestinal	8144/3
Signet-ring cell	8490/3
Minimal deviation	8480/3
Villoglandular	8262/3
Endometrioid adenocarcinoma	8380/3
Clear cell adenocarcinoma	8310/3
Serous adenocarcinoma	8441/3

Mesonephric adenocarcinoma	9110/3
Early invasive adenocarcinoma	8140/3
Adenocarcinoma in situ	8140/2
Glandular dysplasia	
Benign glandular lesions	
Müllerian papilloma	8560/3
Endocervical polyp	8015/3
Other epithelial tumours	8015/3
Adenosquamous carcinoma	
Glassy cell carcinoma variant	
Adenoid cystic carcinoma	8200/3
Adenoid basal carcinoma	8098/3
Neuroendocrine tumours	
Carcinoid	8240/3
Atypical carcinoid	8249/3
Small cell carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Undifferentiated carcinoma	8020/3
Mesenchymal tumours and tumour-like conditions	
Leiomyosarcoma	8890/3
Endometrioid stromal sarcoma, low grade	8931/3
Undifferentiated endocervical sarcoma	8805/3
Sarcoma botryoides	8910/3
Alveolar soft part sarcoma	9581/3
Angiosarcoma	9120/3
Malignant peripheral nerve sheath tumour	9540/3
Leiomyoma	8890/0
Genital Rhabdomyoma	8905/0
Postoperative spindle cell nodule	

Mixed epithelial and mesenchymal tumours	
Carcinosarcoma (malignant müllerian mixed tumour)	8980/3
Adenosarcoma	8933/3
Wilms tumour	8960/3
Adenofibroma	9013/0
Adenomyoma	8932/0
Melanocytic tumours	
Malignant melanoma	8720/3
Blue naevus	8780/0
Miscellaneous tumours	
Tumours of germ cell type	
Yolk sac tumour	9071/3
Dermoid cyst	9084/0
Mature cystic teratoma	9080/0
Lymphoid and haematopoetic	
Malignant lymphoma (specify type)	
Leukaemia (specify type)	
Secondary tumours (specify type)	

Source: [23] WHO, IARC (World Health Organization, International Agency for Research on Cancer). Classification of tumours of female reproductive organs. In: Kurman, RJ, Carcangiu ML, Herrington CS, Young RH editors. WHO histological classification of tumours of the uterine cervix. 4th ed. Paris: IARC; 2014 [cited 2017 Apr 30]:[307 screens]. p. 259-289. Available from: URL: https://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb4/bb4-chap5.pdf