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Personalized approach in gynecology

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Index	I
List of abbreviations	III
Content	IV
1. Prologue	1
2. Introduction	1
2.1.1 Patient-oriented gynecology: walking the walk	1
2.2 Tailoring approaches for benign disorders	3
2.2.1 Myo-Clip	3
2.2.2 VITOM	5
2.2.3 Objective signs	7
2.3 Tailoring approaches for malignant disorders	9
2.3.1 Early stage cervical cancer	9
2.3.2 Pregnancy and cancer	10
2.4 Objectives	11
3. Results of selected original papers	12
3.1 Patient-tailored diagnosis and treatment of benign gynecological diseases	12
3.1.1 Hemorrhage preventing surgery in patients with uterine fibroids	12
3.1.2 Tissue sparing excisional therapy of Cervical Intraepithelial Neoplasia	20
3.1.3 Clinical significance of objective colposcopic signs to diagnose Cervical Intraepithelial Neoplasia 2 and 3	29
3.2 Patient-tailored treatment of malignant gynecological diseases	39
3.2.1 Laparoscopic lymph node staging in the treatment of early stage cervical cancer	39
3.2.2. Laparoscopic lymphadenectomy in pregnant patients with cervical cancer	48
4 Discussion	58
4.1 Sartorial management of benign gynecological pathologies	58
4.1.1 The role and use of vascular clips in laparoscopic myomectomy	58
4.1.2 The role of magnification in the excisional treatment of Cervical Intraepithelial Neoplasia 2 and 3	59

4.1.3	The role of objective colposcopic signs in the management of Cervical Intraepithelial Neoplasia 2 and 3	61
4.2	Sartorial management of malignant gynecological pathologies	64
4.2.1	Benchmark definition to avoid double treatment in patients with early stage cervical cancer	64
4.2.2	The role of laparoscopic staging in pregnant patients with cervical cancer	65
5	Summary	66
6	References	68
7	Acknowledgments	112
8	Declaration	114

List of abbreviations

cc ³	Cubic centimeter
CC	Cervical cancer
CIN	Cervical Intraepithelial Neoplasia
CIN 2+	Cervical Intraepithelial Neoplasia 2 and 3
cm	Centimeter
DCV	Direct colposcopic vision
DF	Disease-free
dl	Deciliter
DSS	Disease free survival
ESCC	Early stage cervical cancer
F-up	Follow-up
g	Gram
G3	Grading 3
GW	Gestational week
Hb	Haemoglobin
HD	High Definition
HPV	Human Papilloma Virus
IFCPC	International Federation of Cervical Pathology and Colposcopy
LACC	Locally advanced cervical cancer
LEEP	Loop electrosurgical excisional procedure
LGTD	Lower Genital Tract Disease
LLETZ	Large loop excision of the transformation zone
LMWH	Low molecular weight heparin
LNE	Lymphadenectomy
MRI	Magnetic Resonance Imaging
LR	Likelihood Ratio
LR -	Negative likelihood ratio
LR +	Positive likelihood ratio
LVSI	Lymph – and hemovascular space invasion
NACT	Neoadjuvant chemotherapy
NCI	National Cancer Institute
NPV	Negative predictive value
OS	Overall survival
PAP test	Papanicolau test
PI	Pulsatility index
pN0	Absence of lymph node metastases
pN1	Presence of lymph node metastases
PPV	Positive predictive value
PL	Preterm Labour
PPROM	Preterm premature rupture of membranes
QoL	Quality of life
RH	Radical hysterectomy
RI	Resistance index
RS	Radical surgery
RT	Radiotherapy
RTr	Radical trachelectomy
R0	Complete resection
R1	Positive resection margins
Rx	Unknown resection margins
RCT	Chemoradiation
TZ	Transformation zone
WHO	World Health Organization

Personalized approach in gynecology

*To my beloved dad, prematurely passed away,
innocent victim of a doctor's culpable mistake*

1. Prologue

„Primum nil nocere, secundum cavere, tertium sanare“, i.e. “first do not harm, second be careful, third cure“. This translated Latin proverbial precept attributed to Hyppocrates is of paramount importance and every doctor should daily bear it in mind (1).

In the last decades the world has witnessed an astounding increase in technology, to everybody’s benefit, in almost all fields of life, medicine being no exception; likewise there has been a steady acceleration of our lifestyles. These undeniable changes carry a major intrinsic, yet hidden diddle: people are no longer used to waiting. Similarly doctors are now less prone to think, and even less to ponder if an action not just is the right thing to do, but most importantly if it can be more harmful than helpful. Physicians sometimes seem to forget their role of care givers, and often culpably cross the thin red line separating help from damage. The Institute of Medicine report "To Err Is Human" in 1999 depicted a gloomy scenario with an estimated 98.000 deaths per year in the USA because of preventable hospital mistakes (2). Recent updates consider this number to be two to four times higher, thus making medical errors the third-leading cause of death in the USA, behind heart disease and cancer, and roughly accounting for one-sixth of all deceases in the USA yearly (3 - 5). Serious harm, not so thoroughly reported and hence more difficult to be precisely evaluated, could be 10 to 20 fold more common (4).

Aware of the capital responsibility that physicians have when treating every single patient, simple weighing the possible remedies is no longer sufficient. Doctors should always try to offer sartorial cures, and make them more patient-oriented. Just like a custom-made suit fits perfectly as opposed to a mass-product, taking time to think about all viable therapy options and to recommend patients, singularly, in a personalized way, the best current treatment represents a big advantage for them and reduces the number of unintended, often undetected, and long lasting harm (6 - 14).

2. Introduction

2.1 Patient-oriented gynecology: walking the walk

“... The best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, union of forces is necessary ...” (Dr. William James Mayo in a speech to the graduating class of Rush Medical College 1910).

In the USA Gynecology originated as a separate specialty from general surgery at the end of the nineteenth century, mainly due to the outstanding work of Dr. H.A. Kelly, a pioneer in understanding the etiopathogenesis of the diseases and developing new surgical approaches for female pathologies (15 -19).

One century and counting gynecology has seen the birth of a number of subspecialties, leading to more precise diagnoses and successful cures, as well as growing specialist collaboration.

Additionally due to longer overall life expectancy, and better social welfare in the more developed countries doctors are constantly looking for new and more personalized treatment options for many gynecologic disorders.

Moreover lifestyle changes have generated a new subset of patients with conflicting interests: physicians are faced with previously unknown and challenging tasks, i.e. the combination of optimal treatments with adequate satisfaction of patient's new expectations and needs (21, 22).

Lately focus on quality of life (QoL) has steadily been gaining importance at the expense of the mere treatment of the disease (23 – 33). Increased awareness on this subject in the gynecological literature is in its turn prompting a raising request from patient's side. As a result over the last decade the widespread availability of an almost unlimited and partly scientific piece of information in the internet has caused an unprecedented and fast rising demand from the patients themselves and their relatives for more personalized and less traumatic remedies (34).

Consequently improved teamwork among doctors, both in the gynecological field and in other specialties, has expanded to cope with the augmented difficulty to otherwise offer patients efficient yet customized treatments in the absence of this much needed inter- or multi-disciplinary cooperation (35). The necessity to develop new, more tailored, and patient-friendlier therapies, both for benign and malignant diseases, is constantly getting more consideration, highlighting and underlying the significance of this subject in modern times.

To this augmented QoL consciousness and reduction of avoidable iatrogenic damage evidently belongs not only the implementation of minimally invasive surgery, when technically and medically possible, but also a critical reevaluation of the need for operations overall. Medical treatment of abortion started almost three decades ago, and in England is overtaking the leadership of the classical surgical curettage; likewise not only laparoscopic surgery is long since the established standard of care

for extrauterine pregnancy, but initial cases are been increasingly handled conservatively with methotrexate (36- 44). Similarly the surgical conservative management of uterine fibroids, i.e. myomectomy could become obsolete before long (45 – 46).

Studies measuring QoL and postoperative happiness have clearly demonstrated that increased patient involvement in therapeutic decisions has outstanding psychological repercussions and diminishes post-treatment stress and delayed medical advice (47 – 48).

This change in mentality has created a virtuous circle in every aspect of gynecology, shifting from doctor's offer to patient's request and is now part of gynecological practice, spanning from university hospitals to private offices.

Finally this new approach to gynecological pathologies will further push physicians to tailor therapies in a quest to define the ultimate sartorial cure for each single patient so to minimize iatrogenicity (49). This is already becoming the case in some oncological patients, in whom recurrences are specifically treated, within studies, in a very targeted way (50 – 52).

Non uno die Roma aedificata est: obviously medicine and gynecology as well are not evolving suddenly, by leaps and bounces, but with little steady steps. Many studies are still needed, to help find and define the best personalized therapies for each specific pathology, as well time is necessary before the medical community as a whole recognizes the subject, accepts the suggested solutions and, which is more, implements them in daily practice.

2.2 Tailoring approaches for benign disorders

2.2.1 Myo-Clip

Uterine fibroids, also called leiomyomata or myomas, are the most common benign tumor of the female reproductive system (53 -55). On average 40% of Caucasian women 35 years old have leiomyomata, and this rate raises further with increasing age until the menopause (56). In African women their incidence is even higher and menopause does not seem to affect their regression. Fibroids often asymptomatic, and undiagnosed should not be treated prophylactically (57 – 59). Typically myomas cause abnormal uterine bleeding, i.e. heavy and prolonged or irregular blood loss which is the main reason for gynecologic consultation in women in the fifth decade of life (58). Other discomforts include lower abdominal pains, bladder urgency or urine incontinence or retention, feeling of pelvic pressure, and infertility or miscarriage. The

severity of the symptoms, the age of the patient, the wish to fulfill motherhood, as well as the number and location of leiomyomata, or the association with adenomyosis should guide a patient-oriented, thus friendlier treatment.

Current remedies are multiple and span from conservative drug-based approaches to minimally invasive surgery, yet studies examining the effectiveness of these strategies are lacking (60, 61). In addition significant risks associated with long term medical therapy including GnRH analogues, selective estrogen or progesterone receptor modulators, mifepristone, ulipristal acetate, very often limit the duration and the role of these options to a sheer pre-surgical step to reduce the size of the myomas and the bleeding, in order to increase hemoglobin level (62 – 65). Minimally invasive techniques including uterine artery embolization, magnetic resonance-guided focused ultrasound surgery have limited applications either due to the high rate of post procedural complications and further need for re-operation, or to low eligibility inclusion criteria (66 – 71). More recently ultrasound-guided ablation seems to offer promising results (72 – 76).

Possibly in a near future better understanding of the pathophysiology of uterine fibroids will revolutionize their treatment and likely culminate in disease prevention (77)

Notwithstanding surgery, either conservative or demolitive, depending on patient age, preferences and wish to fulfill her reproductive planning remains the primary treatment of myomas. Fibroids and menorrhagie are the leading cause of hysterectomy, the second most common surgery in women of reproductive age, after cesarean section, and account for about 38% of all this kind of operations (58, 78 - 81).

In developed countries women are putting off their childbearing potential until the fourth decade of life, when the incidence of leiomyomata increases, thus conservative surgery is mandatory (82 -86). Since its introduction in the last decades of the 20th century endoscopy has slowly yet steadily substituted open gynecological surgery both for benign and malignant diseases, with the exception of ovarian cancer. Laparoscopy of severe endometriosis, early stage cervical cancer (ESCC), or endometrial cancer is now standard of care: laparotomy has become obsolete and has been almost abandoned for these indications (87 - 91). The same does not apply to fibroids: the role of laparoscopic myomectomy to treat symptomatic myomas in women wishing to preserve their fertility remains very debated and many advocate

the use of laparotomy (92, 93). Due to technical challenges, such as the position, the number, the dimensions of leiomyomata, and to the related heavy intraoperative bleeding, coelioscopic myomectomy remains a relatively high operator-dependent technique (80). Uterine perfusion is guaranteed by a number of vessels and is responsible for the marked anatomical changes culminating in its ten fold weight increase at the end of gestation; similarly in case of numerous or isolated big myomas the volume and weight of this organ can even outgrow a uterus a full term pregnancy. Blood supply in these instances is highly augmented: thus hemorrhagic risks sharply rise in case of surgery.

Vasoconstrictor agents are effective, yet their use is not devoid of dangers or complications, both intra and postoperative (94 - 99).

Despite some reassuring obstetric reports with inconspicuous gravidities after ligation of hypogastric vessels, an efficacious emergency management of massive bleeding in pregnancy, definitive coagulation of uterine vessels should be avoided during laparoscopic myomectomy in patients of childbearing age to zero the risk of possible and not completely predictable side events during gestation (100 – 103).

For this reason it is important to develop safer and more reproducible techniques to reversibly curb blood loss during endoscopic myomectomy, and to tailor their use to the single patient, on account of the fibroids characteristics.

2.2.2 VITOM

Approximately 3 ‰ to 1-2 % of women each year have cervical intraepithelial neoplasia 2 and 3 (CIN2+), premalignant lesions and natural precursors of cervical cancer (CC) (104 - 106). If untreated 20% of CIN 2 will progress to CIN 3 and less than 5% to invasive CC (107 - 110).

The incidence of CC, the third most common gynecological malignancy in the world, has sharply fallen in Western Europe and USA due to improvements in secondary prevention, and management of cervical intraepithelial neoplasia (CIN) (111 - 116).

Prof Zur Hausen who was awarded the Nobel Prize for medicine in 2008 for his milestone work on Human Papilloma Virus (HPV) opened a new era in understanding the pathophysiology of CC and eventually in its prevention: 10 years ago a vaccination was successfully introduced for the primary prevention of the disease (117 – 121). HPV testing, recently associated with cytology in screening programs, has won increasingly acceptance and could before long substitute it, at least in women \geq 29 years of age (106, 122 – 134).

Likewise the surgical treatment of CC has been living exciting decades: endoscopy has become the “standard of care”, whereas technical innovations, such as robotic assistance are ongoing being evaluated (135 -152). Fertility sparing techniques are consolidated options for patients with CC < 2 cm seeking parenthood; in addition recently articles exploring possible new frontiers in such patients with cancers > 2 cm are sprouting (153 – 161).

The treatment of CIN experienced his latest spring in the late '80 with the advent of electro-surgical excision, either called LEEP (loop electro-surgical excisional procedure) in the USA or LLETZ (large loop excision of the transformation zone) in the UK (162– 167). This surgery which rapidly gained popularity, and within a decade substituted both cold knife and laser conisation, is worldwide the treatment of choice of CIN 2+ (168 – 174). Its peculiarity, i.e. the cheapness of the equipment and its limited maintenance's cost, the possibility to treat all cases of CIN, in an outpatient setting and under see and treat conditions, its high effectiveness, along with the possibility to provide a specimen for pathological evaluation, and the simplicity to learn the technique have contributed to its diffusion (175 – 179). At the same time the majority of these aspects, together with the premalignant nature of CIN have sometimes culpably led to increased morbidity: overtreatment both germane to indication for surgery and to the extension of the procedure, and the loss of standardization of the technique have increasingly happened (108, 179 - 185).

Just as important and certainly negative is the fact that scientific production has stagnated. The World Health Organization (WHO) and Cochrane regret the lack of randomized controlled trials, the best way to verify treatment results: hence the majority of recommendations are poorly scientifically supported and further research is needed (105, 168, 186)

In the last decades in the most developed countries postponement of childbearing has overlapped and overcome the peak incidence of CIN 2+, which is 25 to 29 years of age; yet the clinical course of CIN 2 and CIN 3 varies and is and not uniform (187 - 189). This may explain the sometimes antithetic strategies of various authors: some consider CIN 2 and CIN 3 a unity, hence treat them alike, others suggest different therapies (109, 171, 190 – 198). Possibly in a near future biomarkers will play a decisive role in further tailoring the best treatment both of CIN 2 and CIN 3 (199 - 202).

In addition recently systematic reviews have cast light on and made the scientific community aware of the increased obstetrical morbidity following excisional surgery for CIN 2 +: therefore doctors are oftener and oftener confronted with a previously unknown and challenging scenario and are requested to combine effective treatment of CIN, i.e. prevention of CC, with a limited removal of healthy cervical tissue, to contain possible future gestational pathology (203 – 214). The pathogenesis of preterm premature rupture of membranes (PPROM) and preterm labor (PL) is not completely understood, and is probably multifactorial: nonetheless it is undeniable that the excised volume of both cervical and endocervical tissue plays a key role in their onset in this subset of patients (215 – 219).

Hence a tissue sparing surgery may be preferable and though suggested in the first description of the technique, over the years the loss of standardization has led many doctors to neglect the use of colposcopic assistance during LEEP/LLETZ, thus infringing a basic rule of this procedure. Recently Prendiville himself has underlined the need to perform the excision under direct colposcopic vision (DCV) and to tailor the quantity of removed cervical tissue (220, 221).

2.2.3 Objective signs

Milestone moments marked the centennial fight against CC: the first was the onset of a surgical therapy, i.e. radical hysterectomy (RH) in 1898, followed by the possibility of early detection, with the development of colposcopy in 1925 (222 -226). When in 1938 Prof. Hinselmann introduced the acetic acid test, for the first time patients with smaller cancers or preinvasive cervical lesions could be diagnosed (225, 226). The PAP smear developed in 1941 represented the first preventive strategy, whereas the researches of Prof zur Hausen in 1976 shed light on the pathogenesis of CC, and opened the way to primary prophylaxis with the advent of vaccination in 2004 (117 – 121, 227 – 229). A wave of enthusiasm had risen after the implementation of each of these diagnostic measures. Obviously primary prevention, i.e. herd immunization is the key to defeat CC, nonetheless this moment is yet far away and secondary prevention, i.e. PAP test, colposcopy, and more recently HPV typing and biomarkers remains the principal weapon against CC (104, 106, 113 – 115, 173, 186, 199 - 202). PAP test, the real begin of secondary prophylaxes of CC, had a dramatic impact on modifying its natural history: the paramount difference in frequency and mortality for CC, as well as incidence and morbidity for CIN in developed and developing countries worldwide clearly reflects its effectiveness (111, 114). These excellent

results favoured the rapid spread of PAP screening; at the same time its thriving diffusion coincided with the almost overnight abandonment of colposcopy, for the first time falling into disgrace.

In the '80 the development of LEEP / LLETZ contributed to a new surge from rags to riches of colposcopy, which was deemed to be absolutely necessary to guide LEEP/LLETZ (162, 163).

Yet this marriage was not supposed to last long. LEEP / LLETZ diffusion was almost sudden and overcame any expectations due to its main features, cheapness, simplicity and good surgical and pathological results: this turned to be counterproductive to colposcopy, whose assistance during surgery was rapidly considered redundant and useless (175 - 178, 183, 185, 230). For the second time colposcopy was downed by its own intrinsic characteristic, specificity, and operator dependency, whereas simplicity was the key peculiarity of both PAP test and LEEP / LLETZ, the reason for the spreading and the success of screening programs everywhere in developed countries. Lately the introduction of HPV typing in secondary prevention has further contributed to cornering colposcopy (103, 128 – 131, 231, 232).

Historically this swinging confidence in colposcopy and its alternating use, i.e. false expectations and subsequently disappointing results, have led to throw the baby out with the bath water, i.e. to abandon colposcopy, and to consider it inadequate. Obviously colposcopy is not a screening tool, but it's a very effective diagnostic instrument to diagnose CIN 2+, due to its capability to precisely and correctly identify the atypical transformation zone (TZ), hence it is a fantastic instrument to guide its surgical management (233 - 237).

However colposcopy could possibly see a new spring someday soon, and a new chapter in its tidal destiny could be written before long (171, 220, 221, 238 – 241).

New evidence is highlighting the need to reconsider the currently often forgotten or deliberately neglected colposcopic assistance, both to tailor destructive techniques for low grade lesions seemingly having no pregnancy-related morbidity, and to allow a sartorial removal of CIN 2+ in patients seeking future parenthood, to diminish iatrogenic obstetric damage, secondary to the quantity of removed cervical volume (241, 206 - 214, 220, 221).

Finally colposcopy should be the cornerstone for conservative personalized follow-up (F-up) of CIN 2 in young women, as well as F-up of CIN 2+ in pregnancy, and to

monitor the response to neoadjuvant chemotherapy (NACT) in patients with big volume ESCC strongly wishing to preserve their fertility. Prerequisite is the mastery of colposcopy, since magnification alone without its knowledge is useless (162, 235 - 237, 239).

2.3 Tailoring approaches for malignant disorders

2.3.1 Early stage cervical cancer

At the end of the 19th century surgery was the only therapy for CC: death and morbidity rates were extremely high, although only 50 % of patients were operable (242). A decade after Prof. Wertheim, thanks to a better understanding of the spread of CC, after extensive anatomic study of the cervix and its vascular and lymphatic system developed his RH, in which the parametrium was the main goal of the operation. In addition “It was a priori clear”, Wertheim wrote, “that methodical treatment of the ureters was indispensable to a so-called extended operation” (222 - 224). Initially deceases were exceeding 35%, twice as low as the prevailing rates of 80% typical for these operations, yet within two lustra, through tireless work and strong commitment Wertheim reduced these figures to 10% (243). At the same time radiotherapy (RT), introduced shortly after the announcement of Marie and Pierre Curie on their researches on radioactivity in 1898, showed to be effective in treating CC and improved overall survival (OS) (243).

Nowadays with enhanced surgical, antiseptic, anesthesiologic and medical know-how mortality is no more a matter of concern: radical surgery (RS), either RH or radical trachelectomy (RTr), combined with pelvic lymphadenectomy (LNE) is the standard surgical treatment for patients with ESCC, (136, 138, 139, 143, 144, 149, 153 – 161). Over the years risk factors for recurrence, thus requiring adjuvant therapy, have been identified by milestones histopathologic studies and divided into high and intermediate hazard groups (244 - 246). To the former belong positive lymph nodes (pN1), involved or unclear resection margins (R1, Rx), and parametria invasion; the latter group comprises both increasing tumor volume, depth of stromal invasion and lymph – and hemovascular space invasion (LVSI), described by Delgado et al in GOG study 49, and grading 3 (G3) and young age of GOG study 92 (247 – 261).

Cure rates for stage IB CC are approximately equal using primary RT or RH (262 - 266). 15 years ago with the National Cancer Institute (NCI) Clinical Announcement, exclusive concomitant chemoradiation (RCT) has become the standard treatment for locally advanced cervical cancer (LACC), as opposed to exclusive RT (244, 267 –

273). Subsequently therapy improvements have led to longer disease-free survival (DFS), to OS exceeding 70%, and a growing population of long-term healed patients (25, 262). This in turn has shifted the focus of research and care from sheer OS to previously unknown subjects, such as QoL and life after cancer (23 - 33, 274 - 278). Combination of RH followed by RCT has more adverse effects than either modality alone (245, 258, 262, 264, 279 - 286). Similarly the general surgeons have clearly demonstrated that iatrogenic morbidity after two different therapies of rectal cancer with comparable OS can significantly vary, hence the most tolerable and personalized treatment should be chosen (287). For this reason it is extremely important to avoid unnecessary treatment: indications for both postoperative RCT, as well as pre-RCT RS should be carefully balanced to avoid a useless and potentially harmful therapy.

2.3.2 Pregnancy and cancer

CC is the third commonest cancer in women, the fourth deadliest female malignancy worldwide, with more than 270.000 deaths yearly, due to late diagnosis, mostly in developing countries, and its only second to testicular malignancy in males as for number of years of life lost from this kind of disease (111, 288 – 292). The epidemiologic picture is extremely different in the various world regions. The number of survivors in developed countries has sharply increased and more than 70% of CC patients will be cured, due to better prevention, earlier detection and more effective treatment programs: many of them return to their normal life, live many years after the primary diagnosis, and some may even develop a second malignancy (244, 293 - 295). Studies have shown that after cancer diagnosis patients may experience long term distress, which can reduce their QoL (296 – 302). In addition due to a relatively new trend, and yet widespread in richer countries, i.e. delaying the age at childbearing the number of women in whom CC is detected in the course of a gestation has steadily risen (189, 303 - 307). These patients do experience the worst possible nightmare: they normally cannot even concentrate on their cancer, since in many cases their treatment could collide with the interest of the baby in their womb, whereas their survival or the way to reach it may often coincide with the suppression of their unborn child (21). Despite their partner's and family's support the patient in the end is "left alone", on the horns of a dilemma, and regardless of her choice she could possibly be confronted with it the rest of her life. A multidisciplinary approach, to individually evaluate every single patient, and even more tailored therapies, which

unfortunately and despicably are still very much uncommon, are mandatory: treatments have to be evidence based, or at least supported by data, and not to be fruit of emotional decisions of single physicians (308, 309). Doctor's suggestions in expectant patients with CC have a double impact and affect simultaneously two different individuals, mother and son. It is absolutely necessary to always bear that in mind, since unwarranted and careless cures may carry lifelong consequences for the patients or cause avoidable pregnancy interruptions. Some patients choosing to undergo cancer treatment and subsequently gravidity termination will be thereafter indefinite haunted by that decision; others courageously opting for pregnancy continuation may pay their generosity with their lives, at the same time creating distress in their partners, who most often will privilege the woman's healing at the expense of the foetus destiny.

2.4 Objectives

The two questions raised and answered in this work are:

Is it possible to implement in daily clinical activities new, more tailored and patient-friendlier therapies, thus diminishing avoidable iatrogenicity?

What is the impact of sartorial treatments on women of childbearing age with benign or malignant diseases?

Eventually and more specifically:

Can a prophylactic, transient and reversible chocking of uterine vessels with vascular clips during laparoscopic myomectomy lead to an efficient, reversible and safe control of intraoperative blood loss, to the advantage of patient's wellbeing?

Is it feasible to combine a successful removal of CIN 2+ with its sartorial excision?

Can specific colposcopic signs be defined to help master the technique, so to tailor surgical treatment of CIN 2+?

Is it possible to define and implement preoperative criteria to reduce and customize the number of multimodality therapy in patients with ESCC?

Can pregnant patients with CC be offered a safe, yet mother- and baby-friendly therapy?

3. Results of selected original papers

3.1 Patient-tailored diagnosis and treatment of benign gynecologic diseases

3.1.1 Haemorrhage preventing surgery in patients with uterine fibroids

Aim of this randomized controlled multicentric trial was to verify the feasibility and safety of bilateral temporary occlusion of uterine arteries during laparoscopic myomectomy, by special vascular clamps, and its effect on blood loss. The clips, called after their inventor, Prof. Yaşargil, a neurosurgeon who developed and first used them in the mid '60 to operate cranial aneurisms, are cross-action light titanium narrow-based spring clips. They can be left in place for indefinite time, being absolutely inert and in neurosurgery they are now the gold standard for the treatment of vascular aneurisms.

These clips have an utterly smooth, atraumatic surface and strong and reproducible closing pressure: their placement on and removal from uterine vessels during a laparoscopic myomectomy is easy and safe.

A total of 166 symptomatic patients, aged 18 to 50 years, with a minimum uterine fibroid diameter of ≥ 4 cm and no coagulation pathologies were enrolled in this multicentric randomized study.

A 1:1 computer generated randomization either to study group (80 pat) , with clips, or to control group (86 pat), without, took place the day before surgery, subsequently performed by twelve expert laparoscopic surgeons, in two university settings and one public hospital. Preoperatively all patients had sonographic count and location of the myomas. The two groups were comparable before surgery: the maximum fibroids diameter was 14 cm and 15 cm, whereas the average weight was 144 g and 147 g in the study and control group, respectively. The mean time for bilateral clipping of the uterine arteries was 15 minutes. No complications occurred either during positioning or removal of the clips, which was performed before the fibroids morcellation, to avoid a delayed unnoticed bleeding. No blood transfusion, no conversion to laparotomy were needed. The main intraoperative data comprised the number, location, size and weight of the leiomyomas. Blood loss, myomas characteristics, blood transfusions, intra- and post-operative complications and flow indexes, i.e. pulsatility index (PI) and resistance index (RI) of the uterine vessels prior to and after surgery were evaluated. To test a difference in blood loss between the two groups hemoglobin levels were determined the third day after the myomectomy, whereas its intraoperative evaluation was not chosen, being imprecise. PI and RI of the uterine arteries evaluated before

and after the operations showed no difference. Despite thrombotic prophylaxes one patient in each group developed an embolic complication, which anyway could be managed conservatively with a therapeutic dosage of low molecular weight heparin (LMWH). All in all mean hemoglobin (Hb) drop was 1.2 g / dl in the study group and 1.45 g / dl in the control group (P: < 0.05), this difference being statistically significant. In addition in the clip group we observed a trend towards reduced blood loss in patients with either fibroids > 6 cm or multiple myomas. In conclusion minor, and easily learnable technical improvements, allow a safe laparoscopic myomectomy, provided a previous individualized patient selection.

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Laparoscopic temporary clipping of uterine artery
during laparoscopic myomectomy
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3.1.2 Tissue sparing excisional therapy of Cervical Intraepithelial Neoplasia

This randomized multicentric controlled trial compares the efficacy and the safety of LEEP/LLETZ of CIN 2+ under colposcopic guidance or exoscope assistance, to provide an alternative in the treatment of this pathology.

Two distinct and equally important reasons, one concerning the physicians directly, the other pertaining the patients, have led to the formulation of this study, taking into account the diagnostic comparability of traditional colposcope and exoscope.

First, despite clear guide lines, the excellent results, and the simplicity to perform LEEP/LLETZ under colposcopic guidance, unfortunately and regrettably in many instances, and still a relatively widespread habit in Germany, this surgery is performed with the naked eye, at a superficial analysis just as valid and effective as an operation under DCV.

Second, in western societies in the last two decades increasingly often remarkable changes in family planning habits have occurred, the first and more outstanding consequence of women's postponement of the age at childbearing being the augmented rate of CIN 2+ patients still seeking parenthood.

Prior to LEEP all 300 patients, randomized 1:1 had a histologically proven CIN 2+, except 8 patients who had a CIN 1 persistent >1 year.

The most important evaluated parameters were intra and post-operative bleeding, resection margins and excised volume; not surprisingly, even though obviously not previously known, results in the two groups were comparable and no technique showed to have the upper hand over the other. A clinically not relevant bleeding either intraoperative or postoperative happened in 2% of patients. The percentage of R1, Rx < 10% in both groups, was higher and showed a significant association in the multivariate analysis with just one parameter, i.e. TZ3, as defined by the International Federation for Cervical Pathology and Colposcopy (IFCPC) (P = 0.01). The addition of a so called top-hat procedure, a second deeper central and more limited excision, helped to correctly identify merely an additional 3% of patients who otherwise would have gone undetected, and labeled as complete resection (R0). The excised cervical volume, intraoperatively measured according to Archimede's principle was < 1.3 cc³ in both groups, thus very low. At a 6 month F-up < 2% in each group had recurrence / persistence of CIN 2+ and no patient developed dysmenorrhea, cervical stenosis or pains. Finally this study showed the equivalence of two different magnification systems for effective, safe and tailored removal of CIN 2+, whereas the exoscope

could be preferably used by gynecologist not so familiar with colposcopic assisted surgery.

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A multicentric randomized study comparing two techniques of magnification assisted loop excision of high-grade cervical intraepithelial neoplasia: video exoscopy and colposcopy

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3.1.3 Clinical significance of objective colposcopic signs to diagnose Cervical Intraepithelial Neoplasia 2 and 3

The purpose of this study was to evaluate the colposcopic accuracy of objective signs to predict CIN 2+ using an exoscope.

335/389 patients without a history of hysterectomy or previous radiation or TZ3, defined according to the criteria of the IFCPC, referred to two different university and one hospital settings for the diagnoses of lower genital tract diseases (LGTD), were enrolled for evaluation; patients with invasive cancer were also excluded, since this was not the aim of this investigation.

All patients had a video exoscopy, which had shown to be comparable for the diagnose of CIN 2+ to colposcope, while edging the classical examination for two reasons: the possibility to record full high definition (HD) and to storage data for later reanalysis. Two expert senior colposcopists blinded to any patient piece of information except age, independently evaluated colposcopic videos, under standard study conditions to increase reproducibility of results. In addition all videos were not edited and had been previously recorded during daily outpatient activity, thus were fully representative of day-to-day routine.

All video exoscopies were specifically checked for the presence of three objective colposcopic signs, the ridge sign, the inner border sign, and the rag sign, of which two had been accepted in the new 2011 IFCPC nomenclature.

The ridge sign is an opaque lesion resembling a mountain crest directly adjacent to the squamocolumnar junction. The inner border sign is an oyster white area, within a less opaque acetic white area, in its turn demarcated by normal squamous epithelium. The rag sign, an opaque area at the squamocolumnar junction, results from mechanical abrasion of cervical cells during either HPV testing or performing colposcopy with Lugol solution and / or acetic acid. All biopsies and LEEP / LLETZ were colposcopically guided: patients underwent one (85%) or two (15%) biopsies and 48% of them had subsequent LEEP / LLETZ.

The presence of the above mentioned objective signs was evaluated in three groups of patients differing for age, i.e., < 25 years, < 35 years, > 35 years: ridge sign was the only objective criterion to show a correlation with this parameter ($P < .05$), being significantly less common in women > 35 years.

The diagnostic test performance of all three colposcopic signs was significantly improved in the two groups of women > 25 years, compared with women < 25 years.

The likelihood ratios (LR) of each objective sign, single and combined were calculated. The likelihood ratios both positive (LR +) and negative (LR -) describe the different probability that an event, in this instance CIN 2+, exists in presence or absence of a particular situation, in this case the objective colposcopic signs. Relevant was that a single objective criterion was present in almost 80% CIN 2+ patient, with a specificity for CIN 2+ of 93%, thus much improving the diagnose of CIN2 +, and even more that LR + was 11.2, i.e. the presence of a single objective sign was correlated with a strong likelihood of disease.

Objective signs significantly associated with CIN 2+, allow its reliable colposcopic identification. This in turn is very useful to target and tailor cervical destruction of persistent CIN1 or excision of CIN 2+.

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Validity of the Colposcopic Criteria Inner Border Sign, Ridge Sign, and Rag Sign for Detection of High-Grade Cervical Intraepithelial Neoplasia

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3.2 Patient-tailored treatment of malignant gynecological diseases

3.2.1 Laparoscopic lymph node staging in the treatment of early stage cervical cancer

Aim of this retrospective study was to establish a diagnostic and therapeutic strategy in patients with ESCC to minimize the rate of unnecessary adjuvant therapy after RS. 448 patients with invasive CC stage IA1L1 to IIA underwent laparoscopic staging in our department over a 7 year period: only patients with local disease, i.e. pN0 at frozen section evaluation, without LVSI combination, and without neuroendocrine tumor (n = 394) got either RH (n = 228), or RTr (n = 166). Mean age of patients was 39 years. Squamous epithelial cancer and adenocarcinoma were the prevailing histotypes, accounting for 95% of all cancer, i.e. 62.5% and 32.7% respectively. Postoperatively a tumor board decided the need for adjuvant therapy on account of the presence of either at least one major criterium, i.e. category one, or at least two softer criteria, i.e. category two. The former were pN1, parametrial involvement as well as R1 / Rx. The latter criteria comprised LVSI, deep stromal involvement, large tumor size, grading 3 (G3) and young age. Ten percent of patients (39/394) needed adjuvant RCT due to either category one risk factor (25/39) or category two (14/39). Many patients had a combination of category one and two risk factors. 3% of patients (n = 11) had undetected pN1 at the time of the frozen section during LNE, 3 % of patients (n = 12) had microscopic parametrial infiltration, 1.3% (n = 5) had either R1 or Rx. 31% of patients had G3 tumors, 32% had a separate presence of LVSI, whereas this piece of info was missing in 19% of patients, thus emphasizing the need for increased cooperation between pathologists and gynecologists. In conclusion careful and tailored selection of patients with ESCC needing adjuvant treatment after RS, can be easily implemented in oncological units, and which is more, allows an effective reduction of the burden of unnecessary long-term morbidity after multimodality therapy.

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Validity of Laparoscopic Staging to Avoid
Adjuvant Chemoradiation following Radical
Surgery in Patients with Early Cervical Cancer

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3.2.2 Laparoscopic lymphadenectomy in pregnant patients with cervical cancer

Aim of this study was to evaluate the oncological safety as well as to describe a standardized technique of pelvic LNE in pregnant patients with CC, allowing a tailored and individualized cancer treatment.

Data of 32 expectant patients in the first and second trimester of gestation with ESCC have prospectively been collected, including some which had been previously reported in a smaller series. On account of the uterus dimensions, for the sake of a precise description of the surgical technique, patients were divided in two groups, < and > 16 gestational weeks (GW) in singleton pregnancy, since the procedure is performed slightly differently. Two patients had twin pregnancies.

LNE was performed by experienced surgeons: no complications happened and no conversion to laparotomy was necessary. There was no intraoperative bleeding: the mean blood loss was 5 ml, and just in a single patient reached 50 ml. The mean number of harvested lymph nodes, regardless of GW, was 14, hence comparable to other series of not pregnant patients with analogous malignancies. 14 patients pN0 with additional risk factors, i.e. R1 in cone, G3, LVSI (+), histotype and bigger cancer dimensions were given low dose platin-based neoadjuvant chemotherapy (NACT) (20 mg / m²) over three days every three weeks for two to four cycles, according to tumor response, evaluated at three week intervals after each NACT, by means of colposcopy and magnetic resonance imaging (MRI). Histologic data of these patients showed tumor persistence (Nr. = 5), but no tumor progression. Additionally one patient with one single hazard factor, and maximal security expectation received NACT. A total of 5 patients had postoperative complications, of whom one had to undergo surgery for a symptomatic lymphocele which could not be managed in a less invasive way, and one patient developed a deep vein thrombosis. This patient, later diagnosed with a thrombophilia was subsequently given LMWH throughout her pregnancy, otherwise unremarkable. The median time between LNE and final treatment spanned from 7 to 32 GW and was on average 16 GW. Four pN1 patients and a total of five patients, i.e. also one with pN0 status who changed her mind after laparoscopy, interrupted the pregnancy.

With the exception of this above mentioned patient, this tailored treatment allowed safe gestation protraction in all pN0 patients, of whom 14, due to concomitant risk factors were given low dose NACT.

F-up data were available for all patients, but for oncological evaluation a minimum threshold of 12 months was set: 23/32 patients were alive and disease-free (DF) at a mean of 3.5 years. 29 healthy new born babies, with subsequent inconspicuous neurological development, and always delivered per cesarean section were born from 27 pN0 patients at a mean 34 GW. To finish with, a standardized LNE in pregnant women with ESCC is feasible, safe, allows the currently best individualized, tailored, both mother- and baby-friendly patient selection before cancer treatment, and is accompanied by good oncological and obstetrical results.

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Laparoscopic Pelvic Lymphadenectomy in 32 Pregnant Patients With Cervical Cancer

Rationale, Description of the Technique, and Outcome

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4. Discussion

In the last decades medicine has rapidly progressed in many sectors. Improved and more efficient treatments have been the focus of research: therapies are oftener less invasive, and better results have been reached. Yet also in the richest countries relevant medical decisions are not always evidence based, they are not necessarily in the interest of the patients, and which is worst sometimes it may take years before mistakes are discovered (9, 12, 310 - 315).

Lately growing attention to the subject of overtreatment has become a hot and very relevant topic (316 - 324). Moreover the need for more patient-oriented cures, strictly depending on doctor's precise knowledge of each single patient is overwhelming emerging, even in palliative situations or at the end of life, in which supportive options are limited (289, 325 - 328).

Notwithstanding scanty attention has yet been paid to the consequences of therapies, and originally just in an attempt to limit the financial costs and not to minimize the human burden of adverse events and complications after any kind of cure (329 - 331).

4.1 Sartorial management of benign gynecological pathologies

4.1.1 The role and use of vascular clips in laparoscopic myomectomy

This study shows that minor, safe, and easily learnable technical improvements, may greatly impact laparoscopic myomectomy.

Medicine, alike every scientific domain is constantly evolving: indications and contraindications rapidly change or even become obsolete.

A higher than expected rate of malignant pathology following morcellation of uterine fibroids has recently led to clear statements against the use of laparoscopic myomectomy for the treatment of leiomyomata, the "morcellement" being no more acceptable (332 - 335).

Yet it is unlikely that laparoscopy will disappear completely for the treatment of all kinds of myomas; probably more effective and reliable preoperative imaging technique will be developed to minimize the risk of misdiagnosing uterine sarcoma, and other safer method of morcellation will be developed (336). One of the keys to the spread of laparoscopy has been the usually very limited intraoperative blood loss, due to the possibility of preventive coagulation (337). In case of multiple or very big fibroids blood perfusion is highly increased: consequently hemorrhagic risks sharply raise in case of surgery (338). As of today the main obstacle to the diffusion of

laparoscopic myomectomy is the not marginal threat of heavy intraoperative bleeding generally higher than in other kind of technically more demanding endoscopic surgery (87 – 91, 339 – 343). Vasoconstrictor agents like misoprostol, vasopressin, are effective in reducing blood loss (95, 96). However severe complications may arise; additionally since their action may outlast the duration of the procedure, sometimes postoperative hemorrhage may happen (97 – 99, 344, 345). Just as the ligation of hypogastric vessels to control massive bleeding in pregnancy is often very efficacious in emergency situations, the laparoscopic vascular ligation of uterine arteries or peri-cervical tourniquet during myomectomy successfully reduces intraoperative morbidity; yet this could result in increased obstetrical jeopardies in women subsequently seeking parenthood, leading to PL and postpartum hemorrhage (346 - 349). In the mid '60 Prof. Yaşargil a neurosurgeon to prevent massive intraoperative bleeding and to safely operate vascular brain anomalies invented and successfully used titanium clips; similarly vascular surgeons temporarily reduce blood perfusions to organs, constrictions being intermittent or continuous during surgery (350, 351). Exact knowledge of the vascular anatomy of the pelvic organs is a fundamental prerequisite to safely intraoperatively reduce the blood supply to the uterus. Some technical problems and the initial limited experience in clinical trials, despite the randomized study design, have partly limited the evidence of the positive effect of the use of vascular clips in the surgery of uterine fibroids (unpublished data). A significant difference in blood loss in the two groups of patients was noted, yet its clinical relevance was limited. Nonetheless in a subgroup of patients with larger or multiple myomas a completely different intraoperative sensation arose, in that the clipping of the uterine vessels resulted in a markedly reduced blood loss, and which is more allowed the surgeons to operate safely and without stress very voluminous fibroids.

A transient clipping of the uterine vessels causing a controlled and reversible blood flow reduction to the uterus, curbing intraoperative blood loss, allows a safe and tailored laparoscopic myomectomy of multiple or big leiomyomata.

4.1.2 The role of magnification in the excisional treatment of Cervical Intraepithelial Neoplasia 2 and 3

This study shows that effective removal of CIN 2+ can be equally achieved with two distinct magnification systems, thus the major message is not the definition of the best instrument, whether the colposcope or the exoscope, but the superiority of

magnification assistance over naked eye operations. No difference was found in the two randomized groups of patients in term of postoperative complications, R1 - Rx and excised cervical volume.

Successful secondary prevention of CC has led to a sharp decrease of mortality for CC in developed countries (111, 112, 115, 227). Since its introduction in the '80 LEEP/LLETZ rapidly became the most used treatment for CIN: its main characteristics, i.e. cheapness, simplicity and effectiveness made it the ideal choice of the majority of physicians (168 – 179).

Prior to the '80 surgery for CIN caused a heavy load of consequences, both in terms of extension of the operation, i.e. hysterectomy, or complications, like intra and postoperative bleeding, stenosis, or pathological events in subsequent pregnancies, mainly due to cold knife conisations (352 – 356). Prediville in its first description of the technique underlined the need to perform LEEP/LLETZ under DCV (162). Many years on, encouraging and positive data on CIN treatment have generated a common, though not general, lowering of the guard, an unconscious downgrading of the real significance of CIN (179). In an attempt to reassure patients about the not malignant nature of CIN, along with its simple and minimal, usually outpatient treatment, doctors have paradoxically reduced CIN in the patient and their own imagination to the equivalent of a high-grade cytological lesion. The two major consequences have been both an uncontrolled and unjustified overtreatment of lesions with extremely little evolution potential, and the abandonment of magnification guidance during their surgery (182, 185). Yet the therapy of CIN is not devoid of complications, mainly in case of a subsequent pregnancy (354, 355). Probably one of the most remarkable and fastest social changes in developed countries is the rising postponement of childbearing age (189, 303, 305). Very lately this trend has even been sponsored directly by companies: Facebook and Apple are now offering egg freezing for female employees, thus further supporting the tendency to put off the age at gestation (357). Year in year out women postpone their first pregnancy, which in many western countries nowadays happens around the 30th anniversary; finally recent reports also in the news quoted that 20% of women in Germany deliver their first baby after age 35, thus clearly after the peak incidence of CIN, which is 25 - 29 years (187, 188, 352, 358). This unprecedented situation has confronted doctors with previously unknown needs and demands from the patients themselves, since excisional cervical treatments are associated with increased PL and PPROM (206 -

211). The two major prerequisite for a patient-oriented treatment of CIN 2+ are a correct therapy indication and the use of the right technique, i.e. magnification assistance (162, 171, 359).

A limitation of this multicentric investigation is the lack of obstetrical data to support that the very limited, sartorial excised, directly intraoperatively measured removed cervical volume, comparable with few authors could positively affect future gestations: yet obviously no randomized studies will ever be ethically possible to evaluate the effect on subsequent pregnancies of two techniques removing clearly different quantities of cervical tissues (166).

The best interest of the patient through a friendlier and more personalized therapy is the real goal of doctor's efforts, regardless of the technique: for this reason this study is not sponsoring a change of habits for gynecologists already using the colposcope during LEEP/LLETZ, rather suggests the ones performing naked eye surgery to do away with their habit and to turn to other magnification techniques.

4.1.3 The role of objective colposcopic signs in the management of Cervical Intraepithelial Neoplasia 2 and 3

This study shows that objective colposcopic signs are significantly associated with CIN 2+. Their knowledge can help tailoring colposcopic assisted loop excision of CIN 2+, or allow precise destruction of persistent CIN 1.

"...What we need are many young doctors, who are taught colposcopy the right way...": pronouncing these words, Prof. Hinselmann, inventor of colposcopy in 1925, underlined the absolute need to skillfully command the technique to obtain the expected results (360). Some years after Stafl stated: "...The significance of adequate training and expertise cannot be overemphasized..." and "...Without proper training it is impossible to obtain adequate results..." (237,361). Both statements share and point out the need for expertise to master colposcopy (236, 360, 362 - 364).

Colposcopy precisely identifying the atypical TZ, i.e. the area where CIN develops, and defining the grade of the underlying lesion, is of the pivotal value to target biopsy in case of CIN 2+ (364). On account of these two features subsequently Prendiville underlined its essential role to guide the surgical excision of CIN 2+ (162, 359).

Many authors in the past, when other diagnostic possibilities were not yet available, had reached excellent results with the colposcope (234, 235, 361, 363 - 366). However more recently with the introduction of PAP test first, and HPV typing lately,

these has been an undeniable diagnostic trend worsening (231, 367 - 369). The evolution of medicine has often coincided with the advent of faster, easier examinations, to the disadvantage of prior knowhow, including semeiotic. Skillful learning of colposcopy, unlike PAP test reading and newly HPV testing, both of which can be relatively easily picked up, needs adequate training (237, 361).

Quam tangere ut non potuit, discedens ait: "Nondum matura est; nolo acerbam sumere." (370). Though thousand-years old these words are just as relevant nowadays: they could well have been pronounced by the growing number of authors who probably can't corner for toffee, who claim the diagnostic superiority of random tissue sampling and who advocate to abandon colposcopy due to lack of results, to the advantage of naked eye evaluation (371 - 375).

Other authors try to better define the current role of colposcopy in the constantly evolving diagnostic and therapeutic scenario of CIN, to select the appropriate individual surgical treatment of CIN 2+, to guide both ablative and excisional procedures thus limiting unnecessary iatrogenic culpable damage or removal of healthy cervical tissue while reducing the rate of R1 - Rx (171, 238, 376)

Finally industry is experimenting new alternatives to the colposcope, to try to fill up the learning gap of many gynecologists in traditional colposcopy, by offering a more modern version of this magnification system i.e. the exoscope (377, 378).

Let's not walk out the door and throw away the key: despite a relatively limited role, colposcopy remains irreplaceable in the management of patient with persistent atypical cytology or HPV infection and in the treatment of CIN 2+ (238, 239). Since the most prominent colposcopic changes do not always coincide with the area of greatest histologic abnormality, objective colposcopic signs could play a decisive role in these regards with undeniable direct repercussion on patient's health (364, 379).

Notwithstanding operator dependency is still the main flaw of colposcopy, most of all due to the high subjectivity of its diagnoses and its poor specificity (234, 380, 381). Improvements in these figures could significantly increase the diagnostic power of colposcopy (379).

Clearly the possibility to drastically, efficiently and easily improve the diagnosis of CIN 2+ has undeniable direct repercussion on patient's health.

It is of paramount importance to tell CIN 1 from CIN 2+ to avoid overtreatment, with possible negative impact on future childbearing, or oversee progression to CC, with ominous consequences.

Because of the known high regression rate of CIN 2 in women < 25 years as well as the much more frequent histological downgrading of cervical biopsies in final histologic specimens, and the significant difference of the acetic white reaction in women < 35 years, different age cutoffs were set and the association of objective signs in various patients groups was analyzed (109, 171, 382 – 386). The ridge sign was significantly less common in women > 35 years, and was the only objective criterion to show a correlation with age (P.05). Due to the high specialization of the diagnostic settings taking part to the investigation, the prevalence of CIN 2+ in the study population was high: hence to avoid a possible bias, i.e. its confounding influence over positive predictive value (PPV) and negative predictive value (NPV) the LR of each objective sign, single and combined were calculated.

Objective colposcopic findings, easily detectable, learnable and highly specific for CIN 2+ improve colposcopic accuracy (381). This allows more precise and secure detection of CIN 2+ in an atypical TZ, and makes a guess strategy unnecessary. Objective signs could represent the renaissance of colposcopy: in 2011 the IFCCP addressing the diagnosis of major change lesions, i.e. CIN 2+, added to the long known graduating criteria two objective signs, i.e. inner border sign and ridge sign (387 - 389). Lately the group of Cibula has described another objective sign, thus highlighting the ongoing quest to minimize subjectivity in colposcopy (390).

Most importantly objective criteria are either present or absent, and the colposcopist does not have to grade them. The main shortcomings of this study are the retrospective nature and the “specialized” analysis made just by senior colposcopist.

The mastery of colposcopy is essential to perform a sartorial destruction of persistent CIN 1, or to tailor the extension of LEEP/LLETZ, which is and should be the goal of any treatment for CIN 2+, even though randomized studies versus abundant tissue resections will never be ethically possible.

In addition colposcopy can monitor the course of CIN 2 in patients < 25 years, as well as the evolution of CIN 2+ during pregnancy (193, 362, 382).

In these regards the newly developed exoscope has some decisive strengths allowing HD image storage and their subsequent reanalysis, extremely important in case of F-up of lesions, and more recently to evaluate the tumor regression in patients with bulky ESCC undergoing NACT to downsize their malignancy, prior to fertility sparing surgery (158, 160). Finally it allows a much more active patient involvement during the examination, with positive effects on their understanding the

underlying problem, the suggested therapy, and most of all on reducing anxiety (391 – 395).

4.2 Sartorial management of malignant gynecological pathologies

4.2.1 Benchmark definition to avoid double treatment in patients with early stage cervical cancer

This study shows that careful and tailored selection of CC patients needing adjuvant therapy after RS is possible and can be easily implemented in oncological units. The discovery of tumor remains psychologically a very hard blow for the patient; however over the decades and for many gynecological malignancies prognosis has significantly improved (25, 244, 262, 270). Progress in diagnosis and treatment in an aging population are changing cancer from a big killer to a chronic disease, at least in the eyes of the physicians (396 – 398). OS is now 70% for CC, all stages included, opening new, previously unknown scenarios at any level, for patients, for doctors, for society: long survival, QoL and cost of care after malignance survival are emerging aspects in oncology (23 – 26, 28 - 32, 274 – 279, 284 – 286, 399, 400). Literature describing QoL after gynecological tumors is sprouting, yet it remains limited to the tip of an iceberg of patients usually treated in university settings. Tailoring therapy trying first to not harm is the prerequisite to improve QoL after a diagnosis of cancer. For instance it is relatively recent knowledge that 1/3 of all LNE in early stage endometrial cancer could be safely omitted and should not be performed (401, 402). Even newer is the analysis in these patients of the long term effects on QoL of lower extremity lymphedema, a direct consequence of LNE, though the extension of the phenomenon is not yet well quantified (403 – 405). Many studies have shown comparable results in OS in patients with ESCC, treated with RS or RCT, as well an increase in adverse events after combined therapy (244, 280, 406). Studies evaluating QoL after female cancer have focused on sexual function, postactinic cystitis or proctitis (23 – 33, 285, 406 - 408). Notwithstanding doctors' and patients' perception of disease, or definition of disease and of QoL differ substantially (409 – 414). Hence the burden of late events and ailing population after cancer therapy is by far bigger than currently known, i.e physicians know the adverse events and side effects of a treatment, but not the exact amount of patient suffering from it. On average still 1/3 of patients receives adjuvant RCT after RS for ESCC (415). This study shows that on a relatively mixed cohort of 400 patients 10% of RCT following RS is a more justified, reasonable, yet "reachable" target. Aiming at reducing the

number of unnecessary adjuvant RCT, offering more patient-centered and tailored therapies, should become the goal of all oncologists to the advantage of patient QoL and wellbeing. The parameters used to evaluate the need for adjuvant therapy have long been known, but frequently little attention is initially paid to them when taking care of the patient, often leading to an overtreatment, culpably harmful (244, 284). Thus preoperatively it is very important to request the pathologist to evaluate LVSI status, grading and depth of stromal invasion. Until equally reliable and yet less invasive modalities will allow lymph node status evaluation, LNE remains the last diagnostic step to easily and precisely triage a ESCC patient to either RS or primary RCT (416 – 423). This personalized approach limits the unnecessary, harmful, double therapy and life long adverse effects in many patients.

4.2.2 The role of laparoscopic staging in pregnant patients with cervical cancer

This study shows that LNE in pregnant patients with CC is feasible, safe, allows an individualized treatment, both mother- and baby-friendly, and is accompanied by good oncological and obstetrical results (424 – 432). A pregnant patient is by definition one of a kind: the treatment has always to take into consideration two individuals, i.e. the mother and the unborn baby. Sometimes pregnant mothers and sons, despite being a unity may have colliding interests (21, 424). Of course many pregnant patients may share the same disease, yet the psychological repercussions and the reactions to the suggested treatments and to their potential effects are absolutely individual and seldom predictable.

Traditionally there is a tendency to favor the expectant woman at the expenses of the unborn baby. For many decades and still nowadays many doctors have been suggesting termination of pregnancy for ESCC diagnosed in the first, and often also in the second term of gestation (433 – 438). Tailoring therapies combining scientific though scanty data with emotional support for the patient and her close family members is imperative (432, 433, 439, 440). Hippocrates tenet first to not harm and the need for multimodal approach with many different specialists is in these patients as relevant as ever. It all boils down to the assessment of disease extension with LNE to allow safe pregnancy continuation in case of local illness (158, 160, 433, 441, 442). In addition despite limited numbers, there is sufficient evidence to support when necessary the use of low dose NACT in expectant patients with ESCC with no harm to the baby (440, 442 – 447).

Finally it should be kept in mind that also the standardization of the steps of LNE is of pivotal importance to safely operate pregnant patients with CC, provided that a careful, multidisciplinary and individualized analysis has taken place to allow a sartorial, hence patient-oriented treatment.

5. Summary

Medicine has much evolved in the last decades and improved therapies have significantly augmented cure rates for some diseases: as a consequence attention has shifted from the mere healing to offering more individualized remedies, aiming at reducing the rate of adverse effects after treatment. However this process is still in a budding stage.

Hippocrates is credited with a cornerstone medical tenet: “Primum nil nocere, secundum cavere, tertium sanare“(1). The current free translation could be: “First do not harm, and tailor your therapy so to maximize its benefit and to limit the number and the extent of adverse events”. Furthermore medical progress, secondary to advancing specialization, has led to increased complexity, which in turn often requires tighter and more intense cooperation among specialists.

Finally changes in society have created new and challenging tasks for doctors, forcing them to thoroughly reconsider consolidated strategies, and to steadily offer patients more customized, hence friendlier treatments.

This work describes a safe and tailored laparoscopic myomectomy with the use of vascular clips, invented and firstly used in neurosurgery, therefore highlighting the advantages of multidisciplinary exchange of knowhow.

Additionally it illustrates the effect of the positive feedback, on the gynecological community, of obstetricians with regards to patients who had undergone excisional therapy of CIN 2+, highlighting the need to reconsider and tailor the extension of the removed volume, a known risk factor for increasing obstetrical pathology (206 - 215). At present gynecologists are more and more eyeing this subject: new reports are emphasizing an original, yet regrettably forgotten principle of LEEP/LLETZ, i.e. the need for magnification assistance. As a natural complement it also illustrates the importance of regaining hold of the much underrated, and neglected colposcopy, relegated in a rear corner by the simplicity of PAP test and HPV typing in the diagnosis, and the speed and success of LEEP/LLETZ in the management of CIN 2+, with culpable and potentially very serious obstetrical repercussions (206 - 214). Skillful command of colposcopy is essential for the correct CIN identification and is a

cardinal prerequisite both for LEEP/LLETZ and destructive therapies (236, 358, 360 - 362).

As for malignant diseases, i.e. ESCC, this work describes the role of LNE to evaluate the local or metastatic stage of disease to help individualizing treatment, thus being a patient-oriented strategy.

Patients undergoing RS for ESCC do definitively benefit from more careful selection before CC treatment: LNE is an important, yet not the sole parameter to be considered to reach this goal and to avoid redundant and harmful multimodality therapy.

Similarly LNE is of incommensurable value to triage pregnant patients with ESCC in high and low risk groups, allowing the latter ones to safely carry on their pregnancy, provided that a personalized, multidisciplinary approach has taken place. This in turn will limit iatrogenicity, and permit to successfully overcome the devastating piece of news of malignancy during gestation, turning it under these circumstance from a lose-win situation to a win-win situation, with undoubtedly improvement of QoL and positive life-long psychological repercussions. Cancer defeat is no longer associated with the guilty and selfish patient's sensation of prioritizing one's own life to the expense of that of the unborn baby.

Finally while doctor's basic principle and duty when taking care of patients is to avoid to culpably hurt them, regardless of the underlying good intentions, it is mandatory to look for individualized, patient-centered therapies, to evaluate the need for a multidisciplinary approach, and to always bear in mind the potential intrinsic harm of every kind of therapy.

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Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

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