Chapter 12

An Outlook on Uterine Neoplasms: From Hormonal and DNA Damaging to Cervical and Endometrial Cancer Development and Minimally Invasive Management

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Abstract

Uterine neoplasms are common tumors, formed by endometrial and cervical cancers; endometrial cancer is the fourth most frequently diagnosed cancer in developed countries and the eighth leading cause of cancer death in women, and cervical cancer is the second most common cancer in women worldwide and is a leading cause of cancer-related death in women in underdeveloped countries.

Cervical cancer arises by HPV DNA damaging; in fact cervical cancer starts in the cells on the surface of the cervix, exposed to viral infective agents, as HPV, founded in 80% of patients affected by cervical cancer. Thus, more than 99% of cervical uterine cancer cases show HPV presence.

Nevertheless, Endometrial cancer involves cancerous growth of the endometrium, and increasing evidence indicates that different biological and genetic factors play relevant roles its onset so as carcinogenesis generally develops by hormonal modifications.

Both tumors can be safely and feasibly managed from minimally invasive surgical techniques till to endoscopic radical operations, such as hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy for surgical treatment.

The authors reviewed several excellent reviews and studies in the area of hormonal, viral and genetical risk factors associated with endometrial and cervical cancer risk and development, analyzing the area of biologic markers, all papers dealing with serum and plasma markers involved in uterine cancer detection, development, progression and minimally invasive treatment.

Keywords: Endometrial cancer, cervical cancer, DNA, HPV, cancerogenesis, minimally invasive treatment, laparoscopy, endoscopy

Introduction

Endometrial Cancer involves cancerous growth of the endometrium, the lining of the uterus. EC is one of the most common invasive gynaecologic malignancy and it represents the fourth most frequent diagnosed cancer among women (1); Europe and North America are the countries with the major incidence of this tumor, while is lowest in Africa, Central and South America and Asia (2).

The cancer is typically one of post-menopausal age, with a main age-related incidence between 50 and 70 years. Increasing evidence indicates that different biological and genetic factors play relevant roles its onset and are parameters that can be used as indicators of pathological progression.

The endometrial carcinomas was classified into two pathogenetic groups: the Type I, that occur most commonly in pre- and peri-menopausal women, often with a history of unopposed estrogen exposure and/or endometrial hyperplasia, of the low-grade endometrioid type, and carry a good prognosis; the Type II, that occur in older, post-menopausal women, more common in African-Americans, not associated with increased exposure to estrogen, typically of the high-grade endometrioid, papillary serous or clear cell types, and carry a generally

poor prognosis, not associated with hyper estrogenic factors and accounts for 20% of the cases (3).

General risk factors for endometrial cancer include: age at menarche, age at menopause, history of infertility, obesity, diabetes, oestrogen therapy, polycystic ovarian syndrome, prior pelvic radiation therapy, hereditary non-polyposis colon cancer (HPNCC) and westernisation of lifestyle. (2,3)

Worldwide, cervical cancer is the second most common cancer in women worldwide and is a leading cause of cancer-related death in women in underdeveloped countries. (4)

Worldwide, approximately 500,000 cases of cervical cancer are diagnosed each year: approximately 13,000 cases of invasive cervical cancer and 50,000 cases of cervical carcinoma in situ (i.e., localized cancer) are diagnosed yearly in USA (5); over the next 40 years, the death rate from cervical cancer decreased by more than 70% because preinvasive lesions and cervical cancers were detected at an earlier stage.

Cervical cancer starts in the cells on the surface of the cervix: it develops in the lining of the cervix, and is always associated to HPV infection, since carcinogenic human papillomavirus (HPV) infection is necessary for the development of cervical cancer (6).

More than 99% of cervical uterine cancer cases show HPV presence, with more than 100 HPV types identified, and types 16 and 18 being found in approximately 70 percent of cases.

But infection alone is not sufficient to cause cervical cancer, since infections become undetectable within 1–2 years (6).

Cervical cancer risk seems to be influenced by other variables too, like smoking, while other factors, like alcohol consumption and diet, don't seem to have any influence. Infection with other sexually transmitted viruses seems to act as a cofactor in the development of cervical cancer (7)

In this article, the authors will focus on the area of hormonal, viral and genetical risk factors associated with endometrial and cervical cancer risk and development; they analyze the area of hormonal cancerogenesis, particularly on molecular mechanisms involved in endometrial cancer of type I, and the area of the molecular mechanisms involved in the onset of the cervical carcinoma.

Finally, it will focus the possible minimally invasive surgery in cervical and endometrial tumors, as an appropriate, if not preferred, alternative in many wide ranging surgical procedures, till to radical endoscopic treatments, such as hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy for surgical treatment.

Endometrial Cancer and Hormonal Carcinogenesis

Approximately 95% of uterine cancers are of endometrial origin, while the remaining 5% include carcinosarcoma, leiomyosarcoma, stromal sarcoma, and adenosarcoma.

As said, the endometrial adenocarcinomas were divided into two pathogenetic groups, and the more common Type I, is associated with a history of estrogen exposure and this is now considered the most important etiological factor.

Type 1 endometrial cancer mimics the endometrium and is usually the endometrioid cell type; it is most common in obese peri-menopausal and post-menopausal women, or in women taking unopposed estrogen, and arises on the basis of endometrial hyperplasia.

Estrogens exert their effects by binding to specific receptors (ERα and ERβ); this action that can be blocked by some drugs called selective estrogens receptor modulators (SERMs), such as tamoxifen, which is associated with a strong anti-estrogenic activity in breast cancer, but an increased risk of endometrial cancer. Tamoxifen and estrogens have a distinctive but overlapping target gene profile, PAX2 (paired box 2 gene), which can promote the onset of endometrial cancer (8).

Exogenous estrogen sources, substances without progestins, increase the risk of endometrial cancer, while combined therapy actually decreases the risk of cancer (9).

Genetic and allelic polymorphisms of genes involved in estrogen metabolism may contribute to inter-individual differences that can lead to an increased or decreased endometrial cancer risk (10).

The HSD17B1 (17β-hydroxysteroid dehydrogenase type 1) gene produces the enzyme that catalyzes the final step of estradiol biosynthesis; single nucleotide polymorphisms (SNPs) within the gene have nor been shown to be associated with endometrial cancer risk, although a significant increase in the level of estradiol was present in lean postmenopausal women carriers of the +1954A/A genotype (Ser312Gly) (10).

Studying the correlation between the use of estrogen replacement therapy and the risk of endometrial cancer, other authors found a higher risk for women carriers of the CYP17 (17α-hydroxylase/17,20-lyase) alleles A1/A1 (11).

Berstein et al compared CYP17 and CYP19 aromatase gene polymorphisms in patients with endometrial cancer and controls, reporting that genotypes with the longest alleles of CYP19 (A6 or A7) were over-represented and the A2/A2 CYP17 genotype under-represented in endometrial cancer patients (12); they demonstrated that the intra-tumoral aromatase activity of patients with the A2/A2 genotype was significantly lower than in carriers of the A1/A1 genotype, while in carriers with the longest CYP19 alleles aromatase activity was higher than in carriers of all other CYP19 allele variants, suggesting a more rapid breakdown metabolism in these patients compared to others. This results, on the contrary, has not be confirmed in other studies (13-15) and the precise mechanisms leading to the association between CYP SNPs and endometrial cancer are not clear, even if all these findings could indicate that certain polymorphisms of the CYP17 and CYP19 genes may increase the risk of endometrial cancer.

Another evidence is that Cytochrome P450 1B1 (CYP1B1) catalyzes the conversion of 17β-estradiol to 4-hydroxyestradiol (4-OH-E2) and 2-hydroxyestradiol (2-OH-E2); in the Syrian hamster, 4-OH-E2 has been shown to induce tumours (16,17); the glucuronidation of 2-OH-E2, by preventing the formation of 2-MeO-E2, that exhibits anti-tumorigenic and anti-angiogenic effects (18), results in an increased cancer risk and specific polymorphisms in UDP-glucurosyltransferase gene (UGT) may lead to an altered risk of endometrial cancer (19,20).

Several alleles of CYP1B1 have been described by the Human Cytochrome P450 (CYP) Allele Nomenclature Committee, but only certain combinations have a significant effect on cancer susceptibility.

Progesterone, a hormone involved in endometrial control, acts in reverse to the tumorigenic effect of estrogens and its effects are dependent on the progesterone receptor (PR).

A single gene encodes for two proteins, termed progesterone receptor A (PRA) and progesterone receptor B (PRB) (21), with a different sub-cellular localization in endometrial cancer cells (22,23).

Many studies have been focused on elucidating the precise role of these two isoforms in endometrial carcinogenesis and it is clear that differential expression of the two isoforms can represent an important prognostic factor (24).

An author reported reduced PR expression levels in tumours compared with normal glands and areas of complex atypical hyperplasia within the same specimen: a predominance of PR isoforms in hyperplasia and in higher grade tumours and an inverse correlation between PR expression and clinical grade (25).

The expression of the PR isoforms was investigated by immunohistochemical analysis in 141 tissue samples of endometrial carcinoma of endometrioid type, since the expression of both progesterone receptors (A and B) decreases with the increasing of the tumor growth (26).

The PRB appeared to have a crucial role as a prognostic indicator of endometrial adenocarcinoma of type I and an inverse correlation with clinical pathological prognostic factors, including myometrial invasion and lymph-vascular space involvement and the FIGO (International Federation of Gynecology and Obstetrics) stage, while the PRA was only inversely correlated with myometrial invasion and, in addition, the expression of both isoforms was significantly lower in hyperplasia and in poorly differentiated adenocarcinoma than in endometrial carcinomas (26).

It has been suggested that genetic polymorphisms in PR genes could affect their expression.

A promoter region polymorphism +331G/A appears to result in a unique transcriptional start site and the +331A form seemed to favour the production of PRB expression in an endometrial cancer cell, suggesting an association between the +331G/A SNP and endometrial cancer risk (27).

Another PR polymorphism, known as PROGINS, has recently been identified (28,29): an author showed that in the presence of PR expression, PROGINS was significantly predictive of the risk of recurrence (30) and that this polymorphism seemed to be associated with an increased risk of endometrial cancer (31).

The PRB is inactivated by methylation of the CpG dinucleotides, whereas the PRA was un-methylated in all of the cell lines studied (32); low levels of DNA methylation in the promoter region are correlated with active expression, whereas high levels of methylation are associated with gene silencing.

A recent study showed that sixty-two of 83 endometrial cancer samples had only methylated bands of PRB and were all negative on immuno-histochemical analysis of PRB (33) and an aberrant methylation status of the PR gene in endometrial cancer is supported by others reports (34, 35).

It was demonstrated a hypermethylation of the first exon of the gene in two cancer cell lines; the gene expression was restored by a combination of 5-aza-20-deoxycytidine and trichostatin A (34); ADC is an inhibitor of DNA methyltransferase, the enzyme responsible for the methylation of CpG residues; trichostatin acts by blocking the enzyme histone

deacetylase and the use of these two agents has been proposed as a powerful therapy for the treatment of cancer by restoring the normal functions of many genes (35) and by promoting cell-cycle and apoptosis-related protein expression (36).

Finally, in hormonal carcinogenesis, also androgens have a crucial role in endometrial cancer risk and polymorphisms in androgen receptor gene are found in the cancer (37).

The first exon of the androgen receptor gene contains two polymorphic short tandem repeats of GGC and CAG, highly polymorphic in length, that influence its activity (38,39).

Endometrial cancer patients had longer CAG and GGC alleles than healthy subjects (40), while an association between short alleles and a more favourable prognosis was reported in another research (41).

In contrast, an author demonstrated an inverse association with increased androgen receptor CAG repeat length and endometrial cancer risk (42) and no correlation with age at the time of diagnosis of endometrial cancer was found in a study involving 43 patients (43).

Endometrial Hyperplasia: A Possible Pre-Cancer

Endometrial hyperplasia is generally considered a precursor to endometrial cancer.

The presence of unopposed estrogen, for example, may result from exogenous estrogen therapy, anovulatory cycles, polycystic ovary syndrome, or obesity may lead to endometrial hyperplasia, and, successively, to endometrial cancer (44).

As said, by histopathology, endometrial cancer is usually an endometrioid adenocarcinoma: it appears on a background of endometrial hyperplasia.

In endometrial hyperplasia, the tumor cells are atypical and form irregular glands, with multiple lumens, pluristratification, the stroma is reduced, producing the "*back to back*" aspect and, with evolution of the disease, the myometrium is infiltrated.

Endometrial hyperplasia must be ruled out particularly in patients older than 35 years of age who present with these conditions; the most common method used to diagnose hyperplasia and cancer is endometrial aspiration with a pippelle, also known as an endometrial biopsy (45).

The important consideration when dealing specifically with the treatment of endometrial hyperplasia is the classification of the type of hyperplasia that is present; endometrial hyperplasia is defined as a proliferation of glands of irregular size and shape with an increase in the glands/stroma ratio (46).

By pathologists, there are 4 types of hyperplasia: simple, complex, simple with atypia, and complex with atypia (47); carcinoma developed in 25 percent of patients with atypia as opposed to less than 2 percent of those without atypia (48).

In fact, it is well established that obesity, weight change and body size are associated with an increased risk of endometrial cancer, as more than the 40% of its incidence can be attributed to excess body weight, in affluent societies.

This can be explained by the fact that excess weight results in increased estrogens concentrations from peripheral conversion of androgens (mainly A) to estrogens (mainly E1) in adipose tissue by aromatase enzyme (49).

Another important risk factor for the development of endometrial cancer by endometrial hyperplasia, among pre- and post-menopausal women, seems to be chronic hyperinsulinemia, as this condition appears to be associated with the development of hyperandrogenism, and so progesterone deficiency and with a reduction of IGFBP-1 (Insulin Growth factor Binding Protein-1) levels also an increasing of IGF-I (Insulin Growth Factor-I) levels, mediated by insulin, that then acts as a growth factor for the tumour mass (50).

IGF-1 and IGF-2 are also involved in the regulation of endometrial growth as well as the interactions between the epithelial and stromal compartments of the endometrium (51).

Plasma levels of IGFBP-3 were significantly lower in women with endometrial cancer than in control subjects, demonstrating an inverse relationship between the plasma level of IGFBP-3 and the risk of developing endometrial cancer. In contrast to other solid tumor sites, they have found lower levels of IGF-1 in the endometrial cancer cases as compared to the controls (52).

Although there is a very high rate of spontaneous regression (80% in cases without atypia and over 50% in complex with atypia), therapy should be instituted since some patients will progress to cancer nonetheless; for patients who present with cellular atypia, the general recommendation is to strictly follow up the patients, for the high risk to develop an endometrial cancer (53).

Several recent studies have suggested that the distinguishing feature of endometrial hyperplasia and cancer is the presence or absence of cytologic atypia, since endometrial hyperplasia and endometrial cancer are two different entities (54).

A series of studies has provided a correlation between genomics, endogenous and exogenous estrogens and development of endometrial cancer from endometrial hyperplasia.

Mutations in DNA-mismatch repair (MMR) genes and microsatellite instability (MSI) are strongly associated with the onset of hyperplasia and many studies have proved their involvement in the endometrial cancer process.

An author examined the association between MMR genes and the increased risk of endometrial cancer: they showed that the two common variant alleles of the *MLH1* and *MSH2* genes give a significant contribution to endometrial cancer incidence (55).

Genetic and allelic polymorphisms of the genes involved in the oestrogen metabolism may contribute to predisposition to EC: the *HSD17B1* produces the enzyme that catalyzes the final step of estradiol biosynthesis and it has been observed that three common SNPs (single nucleotide polymorphisms) within the gene were not associated with endometrial cancer risk (56).

Beiner et al. compared *CYP17* (17α-hydroxylase/17,20-lyase) and *CYP19* (aromatase) gene polymorphisms in patients with EC respect to controls; they reported that genotypes with longest alleles of *CYP19* (A6 or A7) were over-represented and A2/A2 *CYP17* genotype was under-represented in patients as compared to controls (57).

Minimally Invasive Surgical Treatment of Endometrial Hyperplasia

In women affected by excess body weight, with a Body Mass Index (BMI) >29 kg/m^2, particularly during the perimenopausal period (age 40-50 years), with chronic

hyperinsulinemia, hyperandrogenism, progesterone deficiency, with a reduction of IGFBP-1 (Insulin Growth factor Binding Protein-1) and IGFBP-3 levels, an increasing of IGF-I (Insulin Growth Factor-I) levels, the endometrial hyperplasia development and the successive cancer development is at very high risk.

In add, the presence of DNA-mismatch repair (MMR) genes and micro satellite instability (MSI) strongly associated with the onset of EC, so as the two common variant alleles of the *MLH1* and *MSH2* genes and the inactivation of the progesterone receptors (PR) isoforms, PR-B, in patients with endometrial hyperplasia with cellular atypia, should lead to a minimally invasive surgical treatment to avoid endometrial cancer (58).

The minimally invasive treatment of high risk endometrial pathologies is hysteroscopy, by biopsy or by endometrial removing by ablation; endometrial ablation has traditionally been done using an operative hysteroscope, the resectoscope, inserted through the cervix, after a dilation of the cervix, always done in an operating room.

Minor procedures can be done under local anesthesia, but most women prefer general anesthesia; the resectoscope has a built in wire loop that uses high-frequency electrical energy to cut or coagulate tissue (59).

This instrument has the advantage of being able to remove polyps and some fibroids at the time of ablation; in results reported to the FDA where resectoscopic endometrial ablation was done by experts, the success rate was approximately 95%, with 40% of women having no bleeding whatsoever in 1 year (60).

The resectoscope is far more efficient at removing tissue than conventional instruments; although the resectoscope provides excellent results in experienced hands, the technique is difficult to master: resection of the endometrium is superior to destructive techniques because it provides tissue for pathologic evaluation (61) and endometrial carcinoma after hysteroscopic endometrial ablation is still a possibility even when strict selection criteria are applied (62,63).

An other method of ablation, FDA approved, was the Thermachoice balloon: this device uses a balloon placed in the uterine cavity through the cervix and hot water is circulated inside the balloon to destroy the endometrium.

Some experts are concerned about the balloon's ability to reach the cornual areas of the uterus, although the balloon's "success" rate in FDA studies was reasonable: it had a much lower rate of amenorrhea the other currently available device (only 13%), but it was seen some disadvantages connected to it's use (64).

The Hydrothermablator also uses hot water, but allows it to circulate freely in the endometrial cavity; it is done under direct vision through a hysteroscope [123]: once the proper temperature is reached, the hot water circulates for 10 minutes; there's the possibility of fluid leaking out the fallopian tubes and burning intestines and, although this did not happen in clinical studies, a case of an intestinal burn is being reviewed by the FDA (65).

After endometrial ablation, most women are able to go home within an hour after the an endometrial ablation and there may be mild cramping, which can usually be relieved by ibuprofen (66).

It is normal to be tired for a few days, but most women are able to return to most normal activities in a day or two; intercourse and very strenuous activity is usually restricted for 2

weeks; it is possible to have a increased discharge for 2 to 4 weeks afterward, as the lining is shedding (66).

After endometrial removing or biopsy, if the histological exam is positive for cancer, it is indicated to remove uterus with ovaries.

Minimally Invasive Surgical Treatment of Endometrial Cancer

Generally, the majority of patients with endometrial cancer are diagnosed with early stage disease with a favorable 5 year prognosis, therefore any new surgical approach must be carefully validated to assure that the technique is at least equivalent.

Minimally invasive hysterectomy can be performed in some ways: total laparoscopic hysterectomy (TLH), laparoscopic assisted vaginal hysterectomy (LAVH) and vaginal hysterectomy (VH).

A LAVH or LH is often less invasive than an abdominal hysterectomy, but more invasive than a vaginal hysterectomy, that is performed more quickly but without direct vision of the pelvis and the abdomen, and without the possibility to remove lymph nodes (67).

As we said, hysterectomy can be done vaginally, and there are no data showing that LAVH is superior to vaginal hysterectomy (68).

Whether a patient is well staged by pre-surgical assessment and via laparoscopy, the oncologic procedure should be performed by endoscopy.

Normally a surgical treatment of an endometrial cancer should consist of, at least, cytological sampling of the peritoneal fluid, pelvic-abdominal exploration, palpation and biopsy of suspicious lymph nodes, hysterectomy and bilateral salpingo-ophorectomy (BSO); these findings cannot be done by vaginal approach or by laparoscopic helping.

In case of advanced endometrial cancer, an hysterectomy, bilateral-salpingo oophorectomy, pelvic and para-aortic lymph node sampling vs lymphadenectomy is performed, also by endoscopy.

Lymphadenectomy, or removal of pelvic and para-aortic lymph nodes, is performed for tumors that have high risk features, such as pathologic grade 3 serous or clear-cell tumors, invasion of more than 1/2 the myometrium, or extension to the cervix or adnexa.

In advanced cases, removal of the omentum is also performed (69).

With the appropriate treatment, the 5-year survival rate for endometrial cancer is: 75% to 95% for stage 1, 50% for stage 2, 30% for stage 3 and less than 5% for stage 4 (70).

A prospective German study compared laparoscopy to laparotomy in a randomized trial of 70 patients: 37 patients were treated in the laparoscopic versus 33 patients in the laparotomy group, the blood loss and transfusion rates were significantly lower in the laparoscopic group, yield of pelvic and para-aortic lymph nodes, duration of surgery, and incidence of postoperative complications were similar for both groups and overall and recurrence-free survival did not differ significantly for both groups (71).

In another study, these same investigators reported their experience with 650 pelvic and para-aortic lymphadenectomies performed for gynecologic malignancies, 112 of which were for endometrial cancer; after a learning period of approximately 20 procedures, a constant number of pelvic lymph nodes (16.9-21.9) were removed, the number of removed para-aortic

lymph nodes increased over time, from 5.5 to 18.5 and the number of removed lymph nodes was independent of the body mass index (BMI).

Duration of pelvic lymphadenectomy was independent of BMI, but right-sided paraaortic lymphadenectomy lasted significantly longer in obese women (35 vs. 41 min, P = 0.011), while the overall complication rate was 8.7% with 2.9% intraoperative (vessel or bowel injury) and 5.8% postoperative complications (72).

A case series of 203 patients demonstrated success with laparoscopic staging. the conversion rate was 8% for adhesions or poor exposure; the mean hospital stay was 2.8 days, one recent report showed a significant increase in the use of laparoscopy over a 12 year period at a single institution involving 1312 patients (73).

An Italian study showed that laparoscopy provides equivalent lymph node yield compared to laparotomy: this retrospective study identified 110 patients with apparent early-stage endometrial cancer, 55 (50%) were treated by laparoscopic-assisted vaginal hysterectomy (LAVH) and 55 (50%) by total abdominal hysterectomy (TAH).

All patients underwent pelvic lymphadenectomy: the mean number of lymph nodes removed was 17 for the LAVH group and 18.5 for the TAH group (p = 0.294).

Compared with TAH, LAVH required a significantly longer operating time (220 vs. 175 min; p < 0.01), but shorter hospital stay (4 vs. 8.5 days; p < 0.001) and less estimated blood loss (177 cm3 vs. 285 cm3; p = 0.02).

Overall, there were fewer post-operative complications in the LAVH group (6 vs. 11 cases; p < 0.001); the conclusion of this study is limited by the biases inherent in retrospective analysis, and lack of complete staging (74).

The Gynecologic Oncology Group (GOG) has completed a phase III randomized study (LAP 2) comparing laparoscopy vs. laparotomy in endometrial cancer: laparoscopic surgical staging could be performed in 76.3% of cases.

No difference in stage, positive cytology, or lymphatic metastasis could be attributed to the laparoscopic approach: quality of life and physical functioning are improved 6 weeks post-operatively following laparoscopy, but these differences were not significant by 6 months; while laparoscopic staging may be a technically feasible option for surgical management, long-term data regarding recurrence and survival have yet to be characterized (75,76).

The Laparoscopic Approach to Cancer of the Endometrium (LACE) is a randomized controlled trial comparing total abdominal hysterectomy to total laparoscopic hysterectomy in stage 1 endometrial cancer patients, the study is ongoing and expected to be completed in 2009 and will report on quality of life and disease free survival in these two groups; survival outcomes with minimally invasive surgery have also been reported (77).

A prospective randomized study demonstrated comparable survival at a median follow-up of 44 months between laparoscopy and laparotomy: among 122 patients, the overall survival for the laparoscopy vs. laparotomy group, respectively, was 82.7% and 86.5%, and these data are consistent with reported retrospective data demonstrating equivalent survival between these two groups (78,79).

The only question is the impact of laparoscopy on the incidence of positive cytology, that is controversial; some investigators report a significantly higher incidence of positive peritoneal cytology in patients undergoing laparoscopy for endometrial cancer.

This may be due to the retrograde dissemination of cancer cells into the peritoneal cavity during uterine manipulation, the clinical significance of these findings is not clear and should be individualized based upon uterine pathology and lymph node status (80,81).

Finally, there are potential economic advantages to minimally invasive surgery; a retrospective report suggested that for early-stage endometrial cancer, patients treated with laparoscopy had significantly shorter hospitalization and fewer complications, resulting in less overall hospital charges when compared to patients treated via laparotomy (82-85).

Cervical Tumors and HPV Correlation

Invasive cervical cancer is more common in women middle aged and older and in women of poor socioeconomic status, who are less likely to receive regular screening and early treatment.

There is also a higher rate of incidence among African American, Hispanic, and Native American women.

The etiological role of HPV in large part of cervical tumors is well consolidated, since more than 99% of cervical uterine cancer cases show HPV presence, with more than 100 HPV types identified and, of these, up to 40 different types are able to infect the ano-genital tract.

Low-risk types are frequently connected to genital warts (condyloma acuminata), while types with a medium and high oncogenic risk are occasionally or commonly found in patients with high degree lesions and cervical invasive cancer (86).

The HPV (Human Papilloma Virus) is a virus responsible for many female and male genital tract diseases, especially in uterine cervix; these clinical conditions, from simple feet and hands warts to genital cancer, can be classified in mucosal and cutaneous viruses: within each of these groups, HPV types are divided into low-risk, intermediate risk and high-risk types on the basis of their association with benign or malignant lesions (87).

The cervix, usually, has HPV lesions with a flat aspect that are not visible to the naked eye, often require colposcopy for detection and are often associated to dysplastic lesions; cervical dysplasia describes the presence of abnormal, precancerous cells on the surface of the cervix or its canal and, about the number of diagnosis for year, between 250,000 and 1 million women in the United States are diagnosed with cervical dysplasia (88).

While it can occur at any age, the peak incidence is in women between the ages of 25 to 35; most of dysplasia cases can be cured with proper treatment and follow-up: without treatment, from 30% to 50% may progress to invasive cancer, even if it can take 10 years or longer for cervical dysplasia to develop into cancer (6).

Generally, the literature recognize two types of dysplasia: low-grade squamous intraepithelial lesions (LGSIL) and high-grade squamous intraepithelial lesions (HGSIL).

The Bethesda 2001 system classifies squamous cell abnormalities in four categories: first type or ASC (atypical squamous cells), second type or LSIL (low-grade squamous intraepithelial lesions), third type or HSIL (high-grade squamous intraepithelial lesions), fourth type or cervical squamous cell carcinoma (89); the ASC category contains two

subcategories: ASC-US (atypical squamous cells of undetermined significance) and ASC-H (atypical squamous cells cannot exclude HSIL) (90).

The abnormal cells present in LGSIL usually return to normal on their own within 18 to 24 months, but the HGSIL cells, if not treated, can progress to cancer of the cervix, and, to detect these changes early, it is essential to have regular Pap smears (91).

Genomic Detection of HPV by DNA Chips: A New Frontier

Since tumors develop as a result of accumulated molecular genetic or genomic alterations including amplification, deletion, point mutation, and translocation and the studies of these are critical to understand the molecular basis of cancer and provide potential diagnostic/outcome markers and therapeutic targets for cancer patients.

But gene expression is dynamic and this is the reason why it is difficult to discover new oncogenes and tumor suppressors.

The introduction of the DNA chips use have resulted in an era of genome-wide approaches to prognostication and outcome prediction in patients with cancer because the traditional clinicopathological parameters such as tumor size, involvement of axillary lymph nodes (LNs), histological grade, nuclear grade, have some limits, considering also the molecular-genetic heterogeneity and the large number of genes involved in controlling cell proliferation, apoptosis and differentiation (92).

DNA sensors and DNA chips evolve from the combination of the principle of nucleic acid hybridization with the sensitivity of optical, electrochemical or gravimetric transducers and have many applications including medical diagnostic and genetic screening.

A DNA microarray consists of a collection of thousands of microscopic spots of DNA to hybridize a cDNA or cRNA sample (a fluorophore-labeled targets) under high-stringency conditions: this hybridization is usually detected and quantified by fluorescence with the aim to determine changes in expression levels or to detect single nucleotide polymorphisms (SNPs) in the target.

DNA microarrays can be used to detect DNA (as in comparative genomic hybridization), or RNA (most commonly as cDNA after reverse transcription) that may or may not be translated into proteins.

The fluorescence, electrochemical, optical, electrical or microgravimetric signal analyzes DNA concentrations as small as $10-18$ μ, typically required for medical diagnostic applications; in standard microarrays, the probes are attached to a solid surface by a covalent bond to a chemical matrix (via epoxy-silane, amino-silane, lysine, polyacrylamide or others).

So, it is possible to speak of *DNA chip* (also called *genome chip*, *gene chip* or *gene array*) when the solid surface is glass, plastic or silicon chip.

Finally, DNA chips consist of immobilized biomolecules, often PCR products or oligonucleotides, on planar surfaces, and, after viral DNA extraction, the amplification products obtained with a primer set designed for specific viral ORF are hybridized to microarrays prepared with specific probes to discriminate different genotypes.

These DNA chips are the new frontiers of HPV study, since so many researches are conducted in these field since the viral genome consists of a single circular DNA molecule, containing about 7900 basepairs (bp) associated with histonic proteins.

By the genomic side, the HPV genome is functionally distinct in three regions: the first of these is a noncoding region or URR (Upstream Regulatory Region), also known as LCR (Long Control Region), that it is about 400-1000 basepair long, and it contains the promoter p97 along with enhancer and silencer sequences, that regulate transcription of the ORFs (Open Reading Frame).

The second region is the early region or ER (ORF E1, E2, E4, E5, E6 and E7), is about 4000 bp long and encodes non-structural proteins involved in viral replication and oncogenesis.

In particular, the E1 and E2 proteins start viral replication by binding to particular motifs in the replication origin; furthermore, the products of these two ORFs insure a correct division of the viral genome during cell replication, with different strategies for each type (93).

The E2 protein encoded by HPV 16 show a stronger transcriptional activity and a DNA binding affinity that E2 encoded by other virus types.

The third region is the late region that encodes the two structural proteins of the viral capside, L1 and L2.

Vázquez-Ortíz et al. used, in 2005, a cDNA array (ULTRArray Advantage System array blots, Ambion Inc.) to evaluate expression of 8400 genes in cellular lines derived by human cervical cancer and control cell lines, with the aim to identify new genes involved in cervical cancer biology. Five genes were found to be consistently high in all malignant cells and tissues (94).

Currently in the diagnostic field, many microarray systems are already available for HPV genotyping and, at the present, the challenge for researchers is to compare these systems to standard genotyping methods for validation purposes (95).

Detection of HPV DNA is generally based on immunochemical or fluorescent methods, by using of biotinylated or fluorescent primers: the E6, E7 and L1 ORF have been extensively used to diagnose and to genotype HPVs (96), allowing the simultaneous discrimination of 53 different genotypes (97).

Mechanisms of Pathogenesis of Cervical Tumors by HPV

One of the key events in HPV induced carcinogenesis is viral integration into the host genome.

Molecular basis for the malignant potential of these viruses has been determined in the dysregulation of the cell cycle by the viral oncogenes E6 and E7.

After viral integration, expression of the E6 and E7 genes is maintained, whereas the interruption of the circular viral genome in the E2 region leads to a loss of its specific repressor function and to an increased stability of HPV 16 E6 and E7 mRNA (98).

The E6 gene is one of the most variable regions of the HPV-16 genome and some studies suggested a relationship between E6 variants and the clinical manifestation of viral infection.

Viral integration in the host genome occurs at preferred sites, causing changes in the expression of surrounding genes, likely contributing to tumor development. (99).

The E7 protein binds to the retinoblastoma protein (pRB) and inhibits its ability to modulate the function of E2F transcription factors, while the E6 protein forms a ternary complex with p53 activity and E6-AP, leading to degradation of p53 and, in addition, the E6 and E7 proteins play important roles in the episomale maintenance viral genome (100).

In normal cells, the function of the Rb protein is regulated by the cyclin/cyclin-dependent kinase (CDK) complexes.

Inhibitors, such as p16^{INK4a}, prevent the phosphorylation of Rb; in HPV positive cervical cancer a good correlation was found between cervical lesions and p16^{INK4a} expression, as a result of the inactivation of pRb by the HPV-E7 protein (101); in addition, overexpression of p16^{INK4a} seems to be connected to the viral type, being higher with genotypes associated with high degree lesions (102).

The expression of these proteins occurs with a different mechanism based on cervical lesion types, with a marked expression of both proteins in CIN3 and carcinoma cases (103).

In cervical cancer cells with mutations of *p53*, genomic instability is detected: mutations in the p53 gene are frequently associated with gynecological malignances (104).

The molecular mechanisms involved in the onset of the cervical carcinoma are well defined and they are mainly associated to the ability of the proteins E6 and E7 to neutralize the activity of p53 and the pRB respectively.

Minimally Invasive Surgical Treatment of Benign Cervical Pathologies

Because of the HGSIL pathologies and cervical neoplasia "*in situ*", if not treated, can progress to cancer of the cervix; it is clear that HGSIL dysplasia and, specially if HPV positive, must be treat by minimally invasive surgical options.

Cryotherapy, or freezing, is done by placing a probe against the cervix which cools the cervix to sub-zero temperatures: the cells damaged by freezing are shed over the next month in a heavy watery discharge (105).

The main advantages of freezing are that it is simple to do and uses inexpensive equipment but one problem with freezing is that the depth cannot be precisely controlled, so abnormal cells may be left behind and this is less of a problem with small areas of mild to moderate dysplasia, and more of a problem with severe dysplasia and carcinoma-in-situ (106).

Cryotherapy has a high failure rate for treating large areas of dysplasia and dysplasia that extends into the cervical canal, so other methods are preferable when they are available (107).

It is possible to obtain the target zone cervix resection also by laser treatment; laser technology (LASER – Light Amplification by Stimulated Emission of Radiation) is one of the most rapidly medical areas and, since many years, laser technology is applied in endoscopical gynaecology (108).

In laser surgery basically are applied Er-YAG, Nd-YAG and CO_2 lasers; among them the special place occupies the CO_2 laser because of its unique properties (depth of penetration 20-50 microns., zone of damage – maximal 300 microns), of a universality and its versatility in gynaecology (107,108).

The CO_2 laser uses a tiny beam of light to vaporize the abnormal cells, in the medical office with no or very little discomfort, with laser directed through the colposcope so that the area and depth of treatment can be controlled precisely (109).

Healing after laser treatment is much faster than after freezing because dead tissue is not left behind; studies using the latest techniques of laser treatment are showing lower failure rates with the laser than with freezing (110).

An important advantage is that the cervix usually heals with the squamo-columnar junction visible, so that future evaluation is easily carried out, but the major disadvantage of the laser over the cryo is that it requires sophisticated equipment, and most gynecologists do not have a laser in their office, also if laser is much more expensive to do laser if it has to be done in the hospital (110).

Also known as "LLETZ" or "LEEP", loop excision uses a fine wire loop with electrical energy flowing through it to remove the abnormal area of the cervix: the tissue removed is sent to the laboratory for examination (111).

LEEP, therefore, can often treat and diagnose the problem at the same time, it is commonly done under local anesthesia and usually causes little discomfort and it can often be used as a substitute for cone biopsy; the advantage of LEEP is that the problem is treated at the time of diagnosis, so it is not necessary to wait for lab results before treatment: at other times, a tiny sample may be taken at the time of the initial evaluation (112).

A cone biopsy removes a cone-shaped or cylinder-shaped piece of the cervix, it is usually done in an operating room and it can be done with a laser or with conventional surgical instruments (cold-cone).

A cone biopsy may be done for diagnosis or for treatment, although a diagnostic cone may treat the problem at the same time; although laser vaporization and cryotherapy are effective treatments for dysplasia, they are not suitable for invasive cancer; a cone biopsy may also be selected as treatment of dysplasia or carcinoma-in-situ: this treatment has a high success rate, but a "cold-cone" has a higher complication rate than a laser cone, cryo, or loop.

In a small percentage of cases, a cone biopsy may interfere with childbearing; actually, many cases requiring cold cone biopsy in the past can be treated, with the laser or with the loop, with a lower chance of complications (113).

Cervical Cancer and Endoscopic Surgical Treatments

The development of cervical cancer is very slow, since one of the key events in HPV induced carcinogenesis is viral integration into the host genome; as said, normal cervical cells may gradually undergo changes to become precancerous and then cancerous, by cervical dysplasia.

The treatment options for early and advanced cervical cancer are surgical and include:

- LEEP
- Cryotherapy
- Laser therapy
- Radical Trachelectomy
- Radical Hysterectomy

About the first tree options we discussed before, but on the last two options we have to explain more in details, because traditionally radical hysterectomy has formed the mainstay of treatment for early stage cervical carcinoma.

Because of cervical cancer occurs frequently in young women who would like to preserve their childbearing potential, since 10 years radical trachelectomy and laparoscopic lymphadenectomy have been introduced to allow preservation of fertility in early stage invasive lesions (114): this is a new complicate approach to fertility-sparing surgery that preserves the functions of the uterus, the technique is similar to a standard radical hysterectomy and lymphadenectomy, combines laparoscopic (for pelvic lymphadenectomy) and transvaginal approaches, the ovarian vessels are not ligated and, following lymphadenectomy and skeletonisation of the uterine arteries, the cervix, parametrium and vaginal cuff are excised (115).

The residuum of the cervix is then sutured to the vagina and the uterine arteries re-anastomosed; the mean duration of the radical hysterectomy, for laparoscopic and vaginal steps, is more than two hours and half.

In young patients affected by early invasive cervical carcinoma, radical trachelectomy does not appear to increase the rate of cancer recurrence; it carries a relative risk of infertility and late miscarriage but makes it possible for some patients to become pregnant and give birth to normal newborns (115).

Thus, it seems reasonable to offer this procedure in selected cases, provided that each patient is fully informed and the surgeon properly trained.

However, in more advanced disease, a radical hysterectomy may be performed (4, 116).

Generally, radical hysterectomy is performed, in the large part of General Hospital, in laparotomy; the history of radical hysterectomy is very interesting and it began in the beginning of the last century.

In 1898, Wertheim, a Viennese physician, developed the radical total hysterectomy with removal of the pelvic lymph nodes and the parametrium; in 1905, Wertheim reported the outcomes of his first 270 patients: the operative mortality rate was 18%, and the major morbidity rate was 31%.

In 1901, Schauta described the radical vaginal hysterectomy and reported a lower operative mortality rate than the abdominal approach; than, in the late 20th century, radiation therapy became the favored approach because of the high mortality and morbidity of the surgical approach.

In 1944, Meigs repopularized the surgical approach when he developed a modified Wertheim operation with removal of all pelvic nodes and he reported a survival rate of 75% for patients with stage I disease and demonstrated an operative mortality rate of 1% when these procedures were performed by a specially trained gynecologist.

Throughout the remainder of the 20th century, various modifications have been made for this radical procedure, especially in light of improvements in the areas of anesthesia, intensive care, antibiotics, and blood product transfusion science (113-115).

This type of hysterectomy removes the uterus, ovaries and much of the surrounding tissues, including internal lymph nodes and upper part of the vagina and it was initially developed as a surgical treatment for cervical cancer due to the absence of other modalities for treatment (116).

The pelvic lymphadenectomy is performed in a systematic fashion; the anatomy of this procedure involves stripping all fatty tissue from the mid portion of the common iliac vessels and the internal and external iliac vessels to the level of the circumflex iliac vein distally, with preservation of the genitofemoral nerve on the psoas muscle.

The nodal tissue in the obturator fossa is removed from above the obturator nerve to the external iliac vein superiorly and laterally to the pelvic sidewall.

Care must be taken in the obturator fossa to avoid injury to the obturator nerve or to an accessory obturator vein, which is present in approximately 20% of patients (4,116)

It is very important to stage cervical cancer initially by International Federation of Obstetric & Gynaecology (FIGO) classification.

This classification of CC is as follows:

- Stage I: Cervical carcinoma is confined to the uterus.
- Stage IA1: Invasive carcinoma is diagnosable only by microscopy. Stromal invasion is 3 mm deep or less and 7 mm or less in horizontal dimension.
- Stage IA2: The microscopic depth of invasion is greater than 3 mm and less than 5 mm. Horizontal spread is 7 mm or less.
- Stage IB1: The lesion is grossly visible and less than 4 cm in diameter. The microscopic lesion has a depth of invasion greater than 5 mm or a horizontal spread greater than 7 mm.
- Stage IB2: The lesion is grossly visible and greater than 4 cm in diameter.
- Stage II: Cervical carcinoma invades beyond the uterus but not to the pelvic sidewall or to the lower third of the vagina.
- Stage IIA: Cervical carcinoma extends down the vagina but does not exceed two thirds of the vaginal length.
- Stage IIB: Cervical carcinoma extends out into the parametrium but does not extend all the way to the pelvic sidewall.
- Stage III: Cervical carcinoma extends out to the pelvic sidewall, and/or involves the distal third of the vagina, or causes hydronephrosis or a nonfunctioning kidney.
- Stage IIIA: Cervical carcinoma involves the lower third of the vagina without extension to the pelvic wall.
- Stage IIIB: Cervical carcinoma extends out to the pelvic sidewall or causes hydronephrosis or a nonfunctioning kidney.
- Stage IVA: Tumor invades the bladder or rectal mucosa and/or extends beyond the true pelvis.
- Stage IVB: Distant metastasis is present

For patients with stage IA1 lesions, an extrafascial hysterectomy or cold-knife cone with adequate negative margins may be performed if future fertility is an issue. In these patients, the risk of having tumor in the pelvic lymph nodes is 0.5-1.5%.

Radical hysterectomy is indicated for patients with FIGO stage IA2-IIA cervical cancer who are medically fit enough to tolerate an aggressive surgical approach and wish to avoid the long-term adverse effects of radiation therapy. Prospective randomized trials have validated equal curative rates from radical surgery and radiotherapy (overall survival similar at 83%).

Currently, with stage IB patients, approximately 54% of patients with tumors size 4 cm or less (stage IB1) and 84% with tumors greater than 4 cm (stage IB2) will require postoperative adjuvant radiotherapy (117).

Recent encouraging data for improved outcomes with combined chemo-radiation therapy and the increased morbidity noted with the combined surgical and adjuvant radiotherapy has brought into question the role of radical surgery with stage IB2 and stage IIA.

In the setting of recurrence, radical hysterectomy has been performed for very small, centrally recurrent or persistent cancers after radiation therapy.

Current evidence on the safety and efficacy of laparoscopic radical hysterectomy confirm that laparoscopic radical hysterectomy can be used to treat stage I (cervical cancer confined to the cervix) and stage IIA (cancer spread to the top of the vagina, but not into the uterus).

Laparoscopic radical hysterectomy involves surgical removal of the uterus, the supporting ligaments and the upper vagina, together with removal of the pelvic lymph nodes and sometimes the para-aortic lymph nodes (4,116).

Radical hysterectomy is also indicated for other disease processes that involve the cervix (eg, primary upper vaginal carcinoma, endometrial cancer with involvement of the lower uterine segment or cervix).

Intraoperative complications include damage to surrounding structures during the intended procedure. Injury may occur to the bladder, bowel, ureters, pelvic vessels, and nerves (118).

Large-volume blood loss and subsequent need for transfusion may occur; as with any abdominopelvic operation for cancer, these patients are at an extremely high risk for deep venous thrombosis and subsequent embolism.

Because the upper 2 cm of the vagina are removed, some patients may note vaginal shortening, particularly if even more vagina was removed because of stage IIA disease or in the event that postoperative adjuvant radiation therapy was administered (119).

Postoperative complications include wound complications that lead to wound skin separation, wound abscess, and wound dehiscence (eg, seroma, hematoma), while postoperative issues involving the ureter, which may be significantly devitalized during the dissection, include ureteral stricture and fistula. Vesicovaginal fistulae may occur in the postoperative period.

Patients with bulky tumors (>4 cm) are at a higher risk for both nodal metastasis and pelvic recurrence and patients with deep stromal invasion, positive vaginal margins, or positive parametrial margins are at increased risk for recurrence.

Cervical Cancer and Vaccine

The demonstrated effectiveness of HPV prophylactic vaccination opens a new era of hope for both health professionals and women.

In June of 2006, the Food and Drug Administration (FDA) approved a cervical cancer vaccine for girls and women between the ages of 9 and 26, which prevents infection against the two types of HPV responsible for the majority of cervical cancer cases.

These vaccine (Gardasil, Cervarix) has been shown to protect against the HPV (120).

Studies have shown that the vaccine appears to prevent early-stage cervical cancer and precancerous lesions (121).

The HPV vaccines are the first vaccines presented as an anti-cancer immunization; indeed, these prophylactic vaccines, to protect against precancerous and cancerous lesions associated with HPV, shall save lives, reduce costly treatment interventions, and have an individual and collective benefit that should not be neglected.

The clinical studies of vaccines against papillomavirus based on the use of viral like particles (VLPs), constituted of the major protein L1 of the capsid of the virus, without any viral genetic material — immunogenic while not infectious and non-transforming — demonstrated their remarkable efficacy in preventing cervical precancers and cancers, as proven for the quadrivalent [against HPV types 6,11,16,18] and the bivalent [against HPV types 16,18] vaccines (122).

Their level of clinical efficacy in the ''per-protocol'' analysis (consisting of women who were naive to vaccine targeted HPV types at baseline as determined by serology testing for the presence of HPV type-specific antibodies or polymerase chain reaction (PCR) testing of genital samples for the presence of HPV DNA) is unprecedented in the history of vaccination: close to 100% (123).

The highest efficacy is demonstrated in young women naive to the virus types associated to the vaccines, whom seem to have no therapeutic effect on existing lesions or on the course of viral infections already carried by healthy individuals (121-123).

Four large trials of either a HPV 16 monovalent vaccine or the quadrivalent HPV vaccine demonstrated a vaccine efficacy of 44% for preventing HPV 16/18 associated CIN 2,3 or AIS in the ''intent-to-treat'' population (consisting of all women who were enrolled into the trial) after a mean follow-up of 3 years (124).

Results with a limited benefit have been reported for the bivalent HPV 16 and 18 vaccine: the vaccines also have been shown to not accelerate clearance of infections in women already infected with HPV 16 and 18 (125).

In practice the effectiveness of HPV vaccines are limited by two factors: all genital cancers and precancerous lesions are not induced exclusively by HPV types 16 or 18, and the optimal benefit is demonstrated in adolescents and young women before they have encountered these viruses (126).

The question of vaccination before or after sexual debut is controversial, and depends on the concept of individual or collective benefits and arguments of effectiveness over efficacy.

Regardless, continued and regular screening with a Pap Test for all vaccinated and unvaccinated populations effectively lowers the risk for developing invasive cervical cancer, by detecting precancerous changes in cervical cells; women who do not receive regular Pap smears have a higher risk for the condition.

Conclusions

Endometrial cancer is one of the most common invasive gynaecologic malignancies, its incidence can be attributed to obesity, weight change and body size in affluent societies, because these conditions result in increased estrogen concentrations.

The endogenous and exogenous estrogen hyper-stimulation, along with cancer biomarkers, may play an important role in the early detection, progression and survival after the diagnosis of endometrial cancer.

In add, the interaction between polymorphisms in genes coding for metabolism and biosynthesis of estrogens, androgens and progesterone and endometrial cancer risk is of particular interest because different data support that the cancer development could be driven by different allelic variants.

Increasing our understanding of the role of DNA damaging in the aetiology and the course of endometrial cancer and combining the genomic data with known risk factors have a great potential to facilitate the development of new early detection and treatment modalities for this challenging disease.

On the other side, persistent cervical infections by approximately 15 carcinogenic genotypes of human papillomavirus (HPV) cause virtually all cases of cervical cancer and its immediate precancerous precursor, cervical intraepithelial neoplasia grade 3 or carcinoma in situ.

Two standard laboratory methods have been used in epidemiology studies to identify HPV infection: HPV DNA detection and serum antibody detection.

Type specific HPV DNA is identified in exfoliated cells sampled from the cervix or vagina by PCR consensus primers or occasionally performed after detection with a cocktail probe of multiple HPV types.

To HPV detection, new diagnostic systems, such as DNA microarrays, can detect viral genotypes in a sensitive and rapid way, since DNA-chips have the ability to determine rare genotypes, variants and multiple infections with different viral types of HPV, giving to this method excellent prospects both for research and diagnostic applications.

In fact, molecular biology and biomicrotechnology have promising tools for the early detection and disease monitoring of HPV and endometrial DNA modifications, but future studies in this area should concentrate on examining the longitudinal changes in endometrial and cervical cells and in serum concentrations of these biomarkers and investigating their associations with tumor treatment response, relapse, complications and survival.

After the tumor development, minimally invasive and laparoscopic treatment of cervical and endometrial tumors are an appropriate and reasonable therapeutic option for young women with low-stage disease who wish to preserve their childbearing potential.

Finally, minimally invasive gynecological surgery should only be considered if the benefits of removing pre-cancerous lesions from a patient outweigh the risks of the tumor advancing.

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