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INDICATIONS FOR LAPAROSCOPY IN GYNAECOLOGIC ONCOLOGIC SURGERY

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Abstract: *Minimally invasive surgery has been used in obstetrics and gynaecology since 1949 when culdoscopy was introduced for the first time as an exploration tool. Along with the progress of laparoscopic instruments, laparoscopic hysterectomy was first performed in 1989 by Reich et al. In 1993 Nicols used laparoscopy to perform a pelvic lymphadenectomy in patients with cervical cancer. Indications of laparoscopy in gynaecological oncologic surgery widened as new retrospective studies and case studies have demonstrated efficacy, safety and feasibility comparable to conventional surgery on increasingly more advanced stages of disease in patients of increasing age. Nowadays, minimally invasive surgery is about to be implemented routinely to treat patients with uterine cancer, cervical or ovarian cancer.*

Key words: *Cervical cancer, Early-stage ovarian cancer, Endometrial cancer, Laparoscopic staging, Fertility-sparing, Second look.*

1. Laparoscopy in cervical cancer

Most patients with cervical cancer are suitable to minimally invasive approach. Typically, radical hysterectomy with bilateral pelvic lymphadenectomy is practiced for stages IA2 /IB1 but also for high-risk IA1 like lymphovascular invasion.

Studies on the use of laparoscopy in cervical cancer almost unanimously stated that although surgery duration is often longer, the intraoperative bleeding is diminished, there are fewer transfusions and also shorter hospitalization times [8].

A systematic study published in 2012, which included data from 21 studies on 1339 patients operated laparoscopically, suggests that the number of lymph nodes resected, vaginal and parametrial resection margins are equivalent to conventional surgery [18].

In 2008 The Scottish Intercollegiate Guidelines Network said that radical transvaginal hysterectomy using laparoscopic surgery is a safe and effective alternative to radical hysterectomy using conventional abdominal surgery for cervical cancer FIGO stage IB1.[43] In the 2010 guide, National Institute of Health and Clinical Excellence in the UK described sufficient evidence of the effectiveness of laparoscopic guided radical hysterectomy in treatment of cervical cancer at an early stage to encourage this method [38]. The new

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German Guide -s3 states that laparoscopic guided radical hysterectomy can be an alternative procedure to radical hysterectomy using open abdominal surgery [30].

1.1. The principles of staging and surgery

Depending on the stage there is either the conservative approach with fertility preservation, or the classical one.

The possibility of less radical surgery may be appropriate not only for patients who want to preserve fertility but also for those with low risk of cervical cancer. Therapeutic options are conization with or without sentinel lymph node biopsy and pelvic lymphadenectomy, simple trachelectomy and simple hysterectomy.

The criteria that define this low risk include: squamous cell carcinoma, adenocarcinoma, adenoscuamos carcinoma, less than 2 cm tumor, stromal invasion less than 10 mm and no lymphovascular invasion.

The approaches that preserve fertility must be used in carefully selected patients who were counseled carefully about the risk of disease and pre- and perinatal issues.

Retrospective studies suggest that there may be a subset of patients with early-stage cervical cancers are unnecessarily exposed to radical procedures such as radical hysterectomy or radical trahelectomy.

The most important criterion in these cases is the lack of parametrial invasion. There have been studies to highlight risk factors for invasive tumors:

Wright and colleagues [48] aimed to determine the predictors of parametrial spread of the tumor and to define a subset of patients with low risk for parametrial involvement. A total of 594 patients with invasive cervical cancer who received hysterectomy were studied retrospectively. Parametrial metastases were documented in 64 patients (10.8%). The factors associated with parametrial involvement were: histopathological examination suggestive of high risk, high degree, deep cervical invasion, lymphovascular invasion, large tumor, late stage, uterine or vaginal involvement, and metastasis of pelvic or para-aortic lymph nodes. It was observed that in women with negative lymph nodes, without lympho-vascular invasion and tumors less than 2 cm in size, the parametrial involvement is 0.4%.

Frumovitz et al. [17] conducted a similar study in which parametrial involvement rate was determined in 350 patients who received radical hysterectomy. The parametrial involvement rate in patients with low risk criteria (n = 125): adenocarcinoma, squamous cell carcinoma, adeno-scuamos carcinoma, tumor less than 2 cm and without lympho-vascular damage was zero.

Selection of patients performed by appropriate preoperative evaluation is an important process before choosing the use of conservative techniques. The extension of lesions is of great importance, the lesion having to be small and limited to the cervix without parametrial or uterine invasion. A 19% relapse rate was reported in patients with lesions larger than 2 cm and 25% in those with lesions larger than 2 cm and 1 cm deep invasion. [33].

1.2. The management of stage IA1

Conization and laparoscopic pelvic lymphadenectomy

FIGO **IA1 micro invasive disease without lympho-vascular involvement** is associated with extremely low incidence of lymphatic metastases (<1%), and conservative treatment with conization is an option. The aim is the block removal the endocervix and endocervical canal. The shape of the piece has to be tailored

depending on the size, type and location of the lesion. Scalpel excision is preferred but the loop electrocoagulation is also accepted as long as the piece will not fragment, will have adequate margins and proper orientation, and no artifacts will occur by thermal effect [25]. Conization seems safe for stage IA1. In most studies, no differences occur in the survival rate between this approach and hysterectomy [22].

In **IA1 stage with lymphovascular tumoral involvement** conization is a resonable conservative approach with safety margins and pelvic lymphadenectomy with sentinel lymph node biopsy.

For patients without lymphovascular invasion and negative margins after conization who are suitable for surgery and don't want to preserve fertility, extrafascial simple hysterectomy is recommended. In patients with positive margins radical hysterectomy with pelvic lymph node dissection is recommended [2].

1.3. The management of stages IA2, IB, IIA

Radical Hysterectomy / trachelectomy, with bilateral pelvic lymphadenectomy +/- sentinel node biopsy.

Recommendations for stage IA2 depend on the desire to preserve fertility and tumor operability. For patients seeking fertility preservation the recommendation is radical trachelectomy and pelvic lymphadenectomy with or without paraaortic sentinel node biopsy. The recommended option for those who don't want to preserve fertility is radical hysterectomy and bilateral pelvic lymphadenectomy with or without sentinel lymph node biopsy [37].

Radical hysterectomy with pelvic lymphadenectomy is the preferred treatment for FIGO **stages IA2, IB, IIA** when fertility preservation is not desired.

Radical hysterectomy is defined by much broader resection margins than simple hysterectomy, including removal of parts of the utero-sacral and cardinal ligaments and 1-2 cm from the upper vagina; In addition pelvic and sometimes paraaortic lymph nodes are removed.

Fertility preservation techniques are recommended only in selected IB1 patients, with tumors less than 2 cm and the practice is bilateral pelvic lymphadenectomy and radical trahelectomy with or without sentinel lymph node biopsy [15], [32], [41].

1.3.1. Sentinel node biopsy

Laparoscopic sentinel node identification can be considered the symbol of the trend towards minimizing surgical trauma in the staging of gynaecological malignancies using the possibilities of laparoscopic surgery at an optimal level. Evaluation of lymph nodes by detecting sentinel lymph node was recently suggested. The sensitivity and specificity of detecting lymph node metastases is 91 and 100% respectively.

Recent data suggest that sentinel node biopsy can be useful for decreasing the need to perform pelvic lymphadenectomy in patients with early-stage cervical cancer. [13, 29] Prospective studies support the feasibility of sentinel node detection in patients with early cancer and suggest that lymphadenectomy can be avoided safely in a significant proportion of cases [6], [12].

1.3.2. Radical trachelectomy

Can provide an option for patients with stage **IA-2 or IB-1** that have lesions less than or equal to 2 cm in diameter confined to the cervix and stromal infiltration under 10 mm. The cervix, the upper edge of vagina and the supporting ligaments are removed leaving the bottom and the body

of the uterus intact. This is not recommended for small-cell carcinoma sarcoma [42].

Laparoscopic radical trachelectomy has all the advantages of abdominal open approach and the benefits of minimally invasive surgery.

Approximately 60% of patients receiving trachelectomy do not have residual disease at histo-pathologic examination after diagnosis conization and less than 1% have parametrial involvement [11]. Studies have found that patients with early-stage cervical cancer with low risk can be treated with simple trachelectomy [24], [40], [47].

2. Laparoscopy in endometrial cancer:

After several years of debate and discussion, minimally invasive techniques have been integrated into the management of endometrial cancer as a standard of care. The techniques used in the initial treatment of endometrial carcinoma include laparoscopic assisted vaginal hysterectomy, laparoscopic assisted hysterectomy and robotic hysterectomy with pelvic and para-aortic lymph node dissection for staging. Minimally invasive staging techniques include assessing transperitoneal and extraperitoneal lymph nodes and can be performed either during a hysterectomy or later to re-stage a patient after an incomplete surgical staging [5].

2.1. The evaluation and surgical staging for endometrial cancer

The staging of endometrial carcinoma is surgical and must be achieved through the collaboration of experts in imaging and histo-pathology. The maneuvers absolutely necessary for a proper staging are taking peritoneal fluid or washing fluid cytology for evaluation, careful exploration of the entire abdominal cavity including pelvic and para-aortic lymph nodes and a total hysterectomy with bilateral salpingo-oophorectomy. In high risk cases retroperitoneal lymphadenectomy and omentectomy is often recommended (for serous carcinomas), although these maneuvers' influence on survival is controversial [4].

2.1.1. Laparoscopic lymphadenectomy and sentinel node technique

Studies say it is as safe as conventional procedure for lymphadenectomy [20], [45]. Most studies have not found differences in the number of lymph nodes resected. Both pelvic and periaortic lymphadenectomy can be performed with proper oncological outcome. The morbidity associated with the procedure can be reduced by using the concept of sentinel node in patients with tumors less than 2 cm [3]. By using technetium tracer and blue dye markers a sensitivity of 93.5% and a negative predictive value of 99.1% have been observed. False negative rate may be reduced by using ultra-staging by histology and immunohistochemistry [23].

Recently published studies support laparoscopic surgery for endometrial cancer.

In the year 2012 LAP2 study data was published, performed on 2616 women with uterine cancer. It confirmed that the classical approach and complete minimally invasive technique for staging cervical cancer are equivalent in terms of survival and curative treatment [46].

Mori K. M. and Nikki L., in a study that includes recent years of research on the increasingly use of laparoscopy in onco-gynaecology, summarizes that the use of laparoscopy in endometrial cancer appears to bring significant peri- and post-operative benefits without sacrificing the expected results in terms of oncology [35].

Berchuck, in a 2012 study, refers to intraoperative tumor cell dissemination

problem which if proven would be a contraindication of laparoscopy, at least for certain histologic subtypes of cancer. Although the LAP 2 study did not identify differences on relapse rate between the two surgical approaches, it has not enough power to exclude the possibility that relapse may depend largely on histology, for example the one with high risk for peritoneal implantation as the serous type. The issue of tumor dissemination should be further studied analyzing the high risk histological subtypes and defining recurrence incidence in relation to hysterectomy technique [7].

Soliman H.O. conducted a study in 2011 on 20 patients with early stage endometrial cancer operated upon by laparoscopic radical hysterectomy and pelvic lymphadenectomy.

The selection criteria were determined as follows: estimated uterine upper margin was not beyond the midpoint between the umbilicus and the symphysis pubis, no preexisting cardiopulmonary dysfunction or poor control of systemic diseases, bimanual pelvic examination confirming good mobility of an enlarged uterus, fractional curettage revealing no tumor extension in the endo cervical canal, preoperative work up revealed no extra-uterine metastatic disease, all tumors were endometrial carcinomas stages GI–II. Hussein finds that laparoscopic total hysterectomy with pelvic lymphadenectomy approach is safe and effective in the treatment of early endometrial carcinoma. It is observed from this study that laparoscopy is indicated exclusively in early stage patients without comorbidities, after fractionated curettage excluded tumor extension at uterine cervix [44].

Acholonu U.C. co. [1] conducted a study based on PubMed and MEDLINE including articles on the management of endometrial cancer between 1950 and 2011. After a thorough analysis they concluded that laparoscopy should be the standard for early endometrial cancer surgery.

3. Laparoscopy in ovarian cancer

According to guidelines developed by the American College of Obstetricians and Gynecologists laparoscopy can be used as a part of the initial treatment of epithelial ovarian cancer in cases with early stage cancer when tumoral lesions are not found outside the ovary. The use of laparoscopy in more advanced disease, when spread is visible outside the ovary, is limited by the fact that a cytoreductive surgery is required and by the possibility of recurrence on the abdominal wall. Laparoscopy also has a role in the second-look inspection and in staging of early stage cancer discovered incidentally during another intervention. NCCN 2011 states that minimally invasive surgery may be considered in patients with stage I [37].

In one of the largest studies, clinical evidence indicated that laparoscopic staging of ovarian cancer was complete and feasible without jeopardizing survival, supporting the use of laparoscopy in the management of early ovarian cancer [39].

On the other hand there are still controversies about metastasis appeared at the entry point, tumor cell dissemination due to carbon dioxide pressure, tumor rupture and inadequate staging. In particular, concerns are turning especially to the metastases at the entry point that are now reported with an incidence varying between 1% and 16% from one study to another [31].

As noted in FIGO guidelines, complete surgical staging includes full assessment of all visceral and parietal areas of the peritoneal cavity, total hysterectomy, bilateral salpingo-oophorectomy, bilateral para-aortic and pelvic lymph node excision, omentectomy, peritoneal

biopsies, multiple biopsies from the abdominal peritoneum, including sub diaphragmatic and intestinal region, and maximal debulking effort with the intent of leaving "no visible and no palpable disease."[26].

Unlike uterine and cervical cancers, indications of minimally invasive surgery for women with ovarian cancer remains controversial, because the goal of surgery is complete cytoreduction at a microscopic level. For women with stage III and IV there are firm believes that optimal cytoreduction surgery can only be achieved through vertical midline laparotomy [14].

In the year 2014 Yu Jin Koo et al. conducted a study on patients who underwent surgical treatment for early-stage ovarian cancer between 2006 and 2012. They identified 77 patients who had undergone surgery: 24 patients - laparoscopic surgery and 53 patients – laparotomy, and the conclusion was that the laparoscopic approach seems to be appropriate and feasible for the treatment of early-stage ovarian cancer with comparable results with laparotomy in terms of oncological safety and postoperative results [26].

A recent publication from the UK presented the largest prospective study to date [9]. The study included 35 patients with early stage ovarian cancer operated by laparoscopy. The total rate of complications was 14% and the percentage of conversion to laparotomy was 6%; After follow up for a median of 18 months (range 3-59) the disease free survival rate was 94% and overall survival rate was 100%. The authors concluded that laparoscopy is a safe technique, acceptable in terms of oncology.

An Italian study group [34] came to the same conclusions in a retrospective analysis of data of 19 patients with early stage ovarian cancer or fallopian tube cancer stage IA-IC who underwent either primary treatment or completion staging by laparoscopy. After the follow up at (an average) 30 months, overall survival and disease-free survival were 100% and 84%, respectively. Total number of pelvic and para-aortic lymph nodes excised was 17 and 14.

Lazar N. made an analysis of modern options and trends on the role of laparoscopic surgery in staging and treatment of ovarian cancer stage I and II and concluded that it is equal and has even more advantages than conventional surgery if performed by gynaecologists with adequate oncologic skill and experience in laparoscopic surgery [28].

3.1 Fertility sparing surgery in ovarian cancer

Fertility sparing surgery is an established treatment in young patients with borderline ovarian tumor and malignant germ cell tumor; however acceptance of fertility sparing surgery for invasive epithelial ovarian cancer treatment came later. Although there has been no prospective trial to evaluate the role of fertility preservation surgery on invasive epithelial ovarian cancer, current information suggests that it is a safe procedure in carefully selected women with early ovarian epithelial cancer [21], [36].

Ditto and co. presented in 2014 the study „ Fertility sparing surgery in early stage epithelial ovarian cancer". Inclusion criteria were: women who were strongly wishing to preserve fertility under the age of 40 after proper advice on the risks and benefits; signed informed consent, precise and comprehensive staging, apparently one healthy ovary.

Patients were submitted to laparoscopic unilateral salpingo-oophorectomy and complete peritoneal staging (washing; random multiple peritoneal biopsies;

omentectomy) and systematic bilateral pelvic and para-aortic lymphadenectomy with preservation of uterus and one ovary.

The data of this study suggest that fertility sparing surgery in early stage epithelial ovarian cancer who underwent a comprehensive surgical staging could be considered safe with oncological results comparable to radical surgery group. Moreover a good obstetrical outcome could be achieved [16].

In a meta-analysis conducted on several medical databases between 1990 and 2011, Lawrie TA et al. did not find enough evidence to quantify the risks and benefits of laparoscopic management for early ovarian cancer as routine practice [27].

3.2. Second-look laparoscopy

The second look represents surgical and histopathologic systematic evaluation of pelvi-abdominal cavity in patients without evidence of disease. In advanced ovarian cancer it has lost its popularity. However the model has allowed us to establish the practical value of laparoscopic evaluation of the peritoneal cavity. Husain et al. reported that the rate of negative evaluation and recurrence rate in patients with negative second look are equivalent to those described in studies where the procedure was done by laparotomy. However, there is the possibility that the procedure is sometimes hampered by the presence of adhesions and has suboptimal results [19].

After the abdominal cavity is entered, the abdominal and the pelvic cavities are inspected for visible metastases and peritoneal washings are collected. A biopsy specimen is taken of suspicious lesion and sent for frozen section.

If no malignant lesions are found, multiple peritoneal biopsies are taken including from all adhesions. Generally, multiple specimen biopsies are taken from the peritoneum including the cul-de-sac, the bladder, paracolic gutters, rectum, abdominal wall, and infundibulopelvic and round ligaments.

If biopsies were not taken from lymph nodes and omentectomy was not performed on another occasion, they are now done during the second look.

Approximately 20-30 fragments should be taken to minimize the chances of missing an occult metastasis [10].

4. Conclusions

The benefits of minimally invasive surgery are also a support for oncological indications of laparoscopy. The winner among these benefits is low perioperative morbidity. Equally important are the decreased length of hospitalization and blood loss.

Laparoscopic radical hysterectomy is a well established alternative to traditional surgery, indicated for surgical treatment of early cervical cancer with the same oncologic results. The benefits are shorter hospitalization and lower intraoperative bleeding. A recently proved great success are the fertility sparing techniques where laparoscopy has an important role.

Based on the data gathered so far we can say that the use of laparoscopic surgery is supported by the international recommendations and guidelines for the treatment of early-stage endometrial cancer. Laparoscopy is safe and feasible for oncological pelvic lymphadenectomy and sentinel lymph node biopsy.

The indication for the use of laparoscopy in ovarian cancer is still highly debated but the results of recent studies are in favor of laparoscopic staging showing similar data to classic surgery when speaking of disease free survival and the number of dissected lymph nodes.

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