

# How to prevent the iatrogenic diffusion of gynecological malignant tumors?

X. Tianmin, C. Weiqin, C. Manhua, L. Yang, S. Lihui, J. Shan

*Department of Obstetrics and Gynecology, the Second Hospital of Jilin University, Changchun City (China)*

## Summary

An analysis of the causes for iatrogenic diffusion of gynecological malignant tumors during their diagnosis and treatment, through clinical experience and a comprehensive review of both Chinese and international literatures was carried out. When a curettage, hysteroscopy or laparoscopy is performed, an iatrogenic diffusion of malignant tumors can be caused. Therefore this phenomenon needs to be prevented and reduced during the diagnosis and treatment of gynecological malignant tumors, and to improve the curative effect and survival times of tumor patients.

*Key words:* Gynecological tumors; Iatrogenic diffusion; Prevention.

## Introduction

The iatrogenic diffusion of tumors refers to improper or inaccurate treatment at some point during the diagnosis and treatment of malignant tumors [1]. As early as the 19<sup>th</sup> century, some reports state that surgery might promote the diffusion of cancer cells. Nowadays, the incidence of gynecological malignant tumors increases year after year and the metastasis and diffusion of them is one of the main causes of death in tumor patients. The attempt to analyze the causes for possible iatrogenic diffusion during the diagnosis and treatment of gynecological tumor patients formulates the preventive measures so as to reduce the diffusion itself, enhance the survival rate among patients, improve the prognosis, and reduce the death rate as much as possible.

### *Iatrogenic diffusion in diagnosis of gynecological tumors*

*Diagnostic curettage.* Although diagnostic curettage is the routine diagnostic method to diagnose vaginal bleeding, it may promote the diffusion of cancer cells of patients with endometrial cancer [2]. This is mainly due to the scratching of the tissues during curettage that may cause metastasis through lymphatic vessels or blood vessels for the pressure exerted on the muscular layer; the larger the surface area is, the more possible the diffusion is [3]. If it is necessary to expand the neck of uterus because the orifice of uterus is too tight, cervical injury is most likely, causing the diffusion of tumor cells. Therefore, avoiding uterine neck expansion as much as possible, the curettage force will be adequate, and no blind or invasive curettage will occur; when the sample amount is sufficient or the scraped matter is suspicious, surgery should be stopped in order to avoid repeated curettage of

the tumor area [4]. Targeted curettage may be carried out under ultrasound guidance. Before curettage, the surgeon must be aware of the thickness of the endometrioid mucosa with suspicion of cancer. In the case of fractional curettage, the cervical mucosa may be scraped before the endocavitary mucosa in order to diagnose the site of the tumor.

### *Hysteroscopy*

At present, hysteroscopy has been widely utilized in the etiologic diagnosis for irregular vaginal bleeding, intrauterine abnormal echo, sterility, etc. Its main advantages include: direct viewing of changes of the uterine cavity and well-targeted indication of biopsy; however, as to whether the patients with endometrial cancer should be examined with hysteroscopy, there is much dispute at present, and the main focus is whether hysteroscopy promotes the diffusion of cancer cells or not. Since hysteroscopy requires medium distention, and when the distention pressure exceeds a certain range [5], the endometrial cancer cells may enter the abdominal cavity through uterine tube together with distention medium. Some researchers find that: after carrying out hysteroscopy on endometrial cancer, a collection of the abdominal lavage cell examination results in a positive rate for cancer in 9.7%, while after examining the abdominal cancer cells of patients with clinical phase I endometrial cancer, but without conducting hysteroscopy, the positive rate is 12.7%, and the abdominal cytologic positive rate of operation phase I is 7.3% [6]; there is no statistical significance in their comparisons. However, Zerbe conducted a retrospective research on 222 cases with endometrial cancer; among them, 64 cases had carried out hysteroscopy before surgery and 158 cases in the control group had not. According to the results of cytologic examination of abdominal lavage in the hysteroscopy group, the positive patients account for 17.2%, higher than 6.3% of the control group, and there is sig-

Revised manuscript accepted for publication August 14, 2012

nificance with this difference [7, 8]. The author suggests: (1) for patients diagnosed with endometrial cancer, hysteroscopy only should not be performed to clarify the clinic staging; (2) while carrying out hysteroscopy in patients with suspect endometrial cancer, the distention pressure should not be excessive in order to prevent the cancer cells from spreading to the pelvic cavity through uterine tube; (3) hysteroscopy duration should be decreased as much as possible; (4) the endometrium should be accurately scrape at suspicious locations according to hysteroscopic observations, therefore avoiding full curettage; (5) after examination, if diagnosed with endometrial cancer, surgical treatment should be performed as soon as possible [9, 10].

#### *Iatrogenic diffusion during gynecological tumor therapy*

Iatrogenic diffusion during gynecological tumor therapy may cause the implantation of tumor cells at the cutting location, as well as the diffusion and implantation of tumor cells in the pelvic and abdominal cavity; this may occur during laparotomy and laparoscopy.

#### *Laparoscopic surgery*

The rapid development of minimally-invasive surgery, as laparoscopy, is very useful for surgical-pathological staging and surgical treatment of the gynecological malignant tumors. On the other hand, there is the risk of celiac tumor diffusion, port site metastasis (PSM), etc [11]. Some researchers think that the frequent changes of devices during the laparoscopic surgery increases the incidence rate of implantation in the area of entry. Other researchers think that performing pneumoperitoneum may cause a large amount of tumor cells to fall-off with gas from the sleeve side and cause PSM. Although laparoscopic surgery of malignant gynecological tumors has been carried out for over 20 years [12], its advantages and disadvantages in the therapy of malignant tumors are still under exploration and disputed. According to a retrospective analysis of 2,593 patients with gynecological malignant tumors conducting laparoscopic surgery in 1991-2003 by Nadeem, the incidence rate of PSM was 0.97%, often connected to the wide abdominal diffusion and isolated PSMs were rare. Fu Chun, *et al.* [13, 14] carried out the tumor cytological examination on the abdominal lavage, CO<sub>2</sub> filtered liquid, surgical instrument lavage obtained from patients with cervical cancer or endometrial cancer conducting the laparoscopy, excision of full uterus, plus pelvic lymphadenectomy, and also detected the E-cadherin,  $\beta$ -catenin, P-selectin, MMP-2, VEGF proteins; he discovered that there were no tumor cells found in the abdominal lavage, CO<sub>2</sub> filtered liquid, surgical instrument lavage before and after surgeries of all patients, in comparison to the laparotomy and there was no statistical difference. Laparoscopy in the management of women with borderline ovarian tumors or ovarian cancer remains controversial [15, 16]. The current literature defining the role of laparoscopy in

the diagnosis and treatment of ovarian cancer is limited to case reports, case series, and cohort studies Liu *et al.* reported equal efficacy of laparoscopy compared with laparotomy in both early and advanced-stage ovarian cancer. Fauvet reported that laparoscopic management of borderline ovarian tumors is associated with a higher rate of cyst rupture and incomplete staging [17].

Although there is proof that laparoscopy can change the biological behaviors of gynecological malignant tumors, there are no consistent results about the diffusion, PSM incidence, and mechanism after the laparoscopic surgery of malignant tumors; however, the following points must be recommended: (1) perfect the normalized preoperative examination and routine diagnostic programs, and grasp the indication for laparoscopy of gynecological malignant tumors; (2) surgeries should be performed by skilled doctors; (3) during surgery, special attention should be paid to the following: shorten the CO<sub>2</sub> pneumoperitoneum duration as much as possible; avoid repeated punctures to reduce the tissue injuries; reduce the times of instruments entering into and out of the sleeve holes during surgery as much as possible; maintain the CO<sub>2</sub> pneumoperitoneum pressure stable during surgery and use heated and wetted CO<sub>2</sub> to reduce the aerosolized state of tumor cells; place the uterine manipulator under laparoscopy to avoid piercing through the uterus; before surgery of endometrial cancer, clamp the gorge section of uterine tube with Ti clamps to avoid the diffusion of tumor cells while cutting off the tumor tissues; avoid breakage or direct operations on the tumor; before removing the cut tissue, place it into the sample bag to avoid polluting the wounds; while completing surgery, exhaust the gas inside the abdominal cavity, and then pull out the sleeve to avoid the chimney effect, causing diffusion of tumor cells after the laparoscopic surgery; close the peritoneum, fascia, and skin layers of the wound carefully and completely; cutting off the tissues around the port site may reduce the implantation and metastasis at the puncture locations; rinsing of wound surfaces and puncture holes at the pelvic and abdominal cavity with the diluents of drugs such as tauridine, povidone iodine, fluorouracil, amethopterin, etc., may reduce the peritoneal diffusion and incisional implantation and metastasis; (4) if indicated, selecting gasless laparoscopy may reduce the incidence of implantation and metastasis [18, 19].

#### *Laparotomy*

The scalpel is a kind of double-edged sword while the doctors resect tumors boldly and resolutely. Carelessness or inaccuracies during surgery often increase the iatrogenic diffusion of tumor cells. As early as 1954, researchers presented the notion regarding tumor-free operation technique during surgery. The so-called tumor-free surgical technique refers to a series of measures taken during surgery of malignant tumors in order to reduce or prevent the fall-off, implantation, and spread of tumor cells. Its purpose is to prevent the metastasis and

diffusion of tumor cells through the blood or lymph, as well as prevent the abdominal spreading and implantation of tumor cells. Nowadays, a large amount of local and international research has proved that the tumor-free surgical technique can effectively reduce local relapse and remote metastasis of tumor after radical surgery, improving patient prognosis and extending the patient's tumor-free survival time [20].

Tumor metastasis due to laparotomy, mainly occurs in the following cases: (1) during surgery of malignant ovarian tumors, in some benign tumors (such as ovarian mucinous cystadenoma) and borderline tumors, if the tumor size is big or heavily adhered to surrounding tissues and with unclear border, during dissection or its removal [21], the liquid inside the tumor may leak, causing the tumor cell to implant in the incisional and surgical fields, i.e., the tumor cell implantation in the incision and abdominal cavity occurs; (2) for tumor patients with ascites, during surgery, if there are no incision protective measures, too many ascites, untimely treatment, or improper treatment, incision implantation may occur postoperatively; (3) while performing radical surgery of endometrial or cervical cancers, the cancer cells may fall off in the vagina, causing vaginal implantation and relapse [22]; (4) less invasive treatment concept prompts many doctors to select small incisions during surgery; however, while performing the surgery of malignant tumors, small incisions suffer multiple defects, such as insufficient exposure of surgical field, difficult removal the tumor, and celiac implantation caused by tumor breakage during removal [23].

For these reasons, the tumor-free technique during surgery should be adopted: (1) for malignant tumors, small incisions should be limited as much as possible, and the surgical field should be sufficiently exposed to reduce the stimulation and pulling towards tumors, as well as facilitate the handling of fortuitous events such as bleeding during surgery, etc; (2) suturing the peritoneum protective tissue to the peritoneum on both sides, and then securely suturing the peritoneum protective tissue to the upper and lower corners of incision, to protect the peritoneum and incision; (3) during surgery, the tumor should be detected from far to near, it should be gently treated and not squeezed, and special attention should be paid when adhesion is extensive. The touching and squeezing of tumor will increase the fall-off phenomenon and implantation of cancer cells into the abdominal cavity [24]; (4) avoid re-using polluted instruments by tumor as much as possible; if the surgical instruments cannot be changed, they should be dipped into distilled water for five min before use; some reports say that after being dipped with normal saline solution, the tumor cells can still maintain certain activities; (5) for tumor patients with a large amount of ascites, a small incision should be opened on the peritoneum, the liquid should be aspirated in order to maintain the same as dry as possible by patiently absorbing the peritoneum as much as possible, and then carry out surgery to avoid in this way the overflow of the peritoneum and tumor cell implantation; (6)

during tumor excision, protect the serosal surface of tumor as much as possible; if the tumor has invaded the serosal layer, apply sealant glue for cancer serosal layer on the serosal surface, or dress and separate with gauze or surgical towel [25]; (7) before resecting off the tumor, treat the tumor blood vessels first, to reduce the probability of spreading of tumor cells along with blood; (8) while carrying out endometrial cancer surgery, it is advisable to perform the eight-shaped suture of the orifice of uterus or fill gauze into the fornix of vagina first, then clamp the side of uterus, and then detect the pelvic cavity and touch the uterus, to avoid the fall-off of tumor cells, causing vaginal and pelvic implantations and metastasis along the vessel; (9) during surgery, use an electric scalpel as much as possible, since it does not only reduce bleeding, but can also cauterize small lymphatic vessels or blood vessels, reducing the probability of cancer cells entering the vessel system [26]; (10) surgical toilette after resecting the tumor plays an important role in the prevention of infection and residue of tumor cells, as well as in the prevention of tumor cell implantation and spreading. During surgical toilette of the various gaps of wound surface, wait for 3-5min before absorbing the lavage; carry out the rinsing twice or thrice; absorb the liquid completely with absorber, and do not use gauze to wipe and absorb, in order to avoid tumor cell implantation [27, 28]. Before closing the abdominal cavity, both gloves and instruments should be substituted; after closing the abdominal cavity, dip the incision with distilled water or rinse it with normal saline solution repeatedly, to avoid incisional implantation of tumor cells.

Whether the iatrogenic diffusion during diagnosis and treatment of gynecological tumors can be reduced, as well as the curative effect and survival time of tumor patients improved, are dependent to a considerable degree on the specialist's sense of responsibility, knowledge, surgical normalization, and skill [29]. The tumor-free operation is the fundamental principle the authors advocate and it should be followed during the whole process of diagnosis and treatment. Iatrogenic tumor diffusion caused by abnormal acts of medical treatment is contrary to the ethical service directed to the patient, and the recognition and regard of this issue should be considered.

### Acknowledgments

The authors are thankful for financial support from the National Natural Science Foundation of China (30973187) and Jilin Science and Technology Funds (200705203, 20080134, and 200905146) and Basic Scientific Research of Jilin University Funds and Ministry of Education for Young Teacher Foundation of China (20110061120084).

### References

- [1] M. Ying, B. Ping: "Iatrogenic implantation". *J. Chin. J. Clin. Oncol.*, 2008, 35, 117.
- [2] Miller C.E.: "Training in minimally invasive surgery - you say you want a revolution". *J. Minim. Invasive Gynecol.*, 2009, 16, 113. doi: 10.1016/j.jmig.2009.01.001.

- [3] Eltabbakh G.H., Shamonki M.I., Moody J.M., Garafano L.L.: "Hysterectomy for obese women with endometrial cancer: laparoscopy or laparotomy?". *Gynecol. Oncol.*, 2000, 78, 329.
- [4] Wang X., Zhang H., Di W., Li W.: "Clinical factors affecting the diagnostic accuracy of assessing dilation and curettage vs frozen section specimens for histologic grade and depth of myometrial invasion in endometrial carcinoma". *Am. J. Obstet. Gynecol.*, 2009, 201, 194. Epub 2009, Jun. 28.
- [5] Canis M., Botchorishvili R., Wattiez A., Pouly J.L., Mage G., Manhes H., Bruhat M.A.: "Cancer and laparoscopy, experimental studies: a review". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2000, 91, 1.
- [6] Taner C.E., Oztekin M., Mun S., Sehirali S., Büyüksosun C., Basogul O.: "Borderline ovarian tumors: A study of 100 cases". ASCO Meeting Abstracts, 2006, 24, 15069.
- [7] Desfeux P., Bats A.S., Bensaid C., Chatellier G., Blanc B., Querleu D., Lecuru F.: "Impact of the surgical route on staging and outcome of early borderline ovarian tumors". *Gynecol. Obstet. Fertil.*, 2007, 35, 193.
- [8] Kornblith A.B., Huang H.Q., Walker J.L., Spirtos N.M., Rotmensch J., Cella D.: "Quality of life of patients with endometrial cancer undergoing laparoscopic international federation of gynecology and obstetrics staging compared with laparotomy: A gynecologic oncology group study". *J. Clin. Oncol.*, 2009, 27, 5337.
- [9] Bijen C.B., de Bock G.H., ten Hoor K.A., Nijman H W., Hollema H., Mourits M.J.: "Role of endocervical curettage in the preoperative staging of endometrial carcinoma". *Gynecol. Oncol.*, 2009, 112, 521.
- [10] Oonk M.H., van de Nieuwenhof H.P., de Hullu J.A., van der Zee A.G.: "The role of sentinel node biopsy in gynecological cancer: a review". *Curr. Opin. Oncol.*, 2009, 21, 425.
- [11] Fait V.: "Sentinel node biopsy and possibilities of use in current surgical oncology". *Klin. Onkol.*, 2008, 21, 5.
- [12] Wood N.J., Munot S., Sheridan E., Duffy S.R.: "Does a 'one-stop' gynecology screening clinic for women in hereditary nonpolyposis colorectal cancer families have an impact on their psychological morbidity and perception of health?". *Int. J. Gynecol. Cancer*, 2008, 18, 279.
- [13] Fu Chun, Li Guangyi, Liu Fengying, Lin Qihua, Fang Xiaoling: "Influence of laparoscopic surgery of endometrial cancer under CO<sub>2</sub> pneumoperitoneum upon implantation and metastasis of cancer cells". *J. J. Central South Univ. (Medical Sciences)*, 2008, 33, 130. (In Chinese).
- [14] Fu Chun, Li Guangyi, Liu Fengying: "Influence of laparoscopic surgery of early cervical cancer under CO<sub>2</sub> pneumoperitoneum upon Implantation and metastasis of cancer cells". *J. Chin. J. Clin. Oncol.*, 2008, 35, 697. (In Chinese)
- [15] Ghezzi F., Cromi A., Uccella S., Bergamini V., Tomera S., Franchi M., Bolis P.: "Laparoscopy versus laparotomy for the surgical management of apparent early stage ovarian cancer". *Gynecol. Oncol.*, 2007, 105, 409.
- [16] Park J.Y., Kim D.Y., Suh D.S., Kim J.H., Kim Y.M., Kim Y.T., Nam J.H.: "Comparison of laparoscopy and laparotomy in surgical staging of early stage ovarian and fallopian tubal cancer". *Ann. Surg. Oncol.*, 2008, 15, 2012.
- [17] Heitz F., Ognjenovic D., Harter P., Kommos S., Ewald-Riegler N., Haberstroh M. *et al.*: "Abdominal wall metastases in patients with ovarian cancer after laparoscopic surgery: incidence, risk factors, and complications". *Int. J. Gynecol. Cancer*, 2010, 20, 41.
- [18] Degaard E., Staff A.C., Langebrekke A., Engh V., Onsrud M.: "Surgery of borderline tumors of the ovary: retrospective comparison of short term outcome after laparoscopy or laparotomy". *Acta Obstet. Gynecol. Scand.*, 2007, 86, 620.
- [19] Nowak M., Szpakowski M., Malinowski A., Romanowicz H., Wiczorek A., Szpakowski A. *et al.*: "Laparoscopy and laparotomy in the operative treatment of ovarian cysts". *Ginekol. Pol.*, 2000, 71, 1173.
- [20] Van Dam P.A., De Cloedt J., Tjalma W.A., Buytaert P., Becquart D., Vergote I.B.: "Trocar implantation metastasis after laparoscopy in patients with advanced ovarian cancer: can the risk be reduced?". *Am. J. Obstet. Gynecol.*, 1999, 181, 536.
- [21] Volz J., Köster S., Spacek Z., Paweletz N.: "The influence of pneumoperitoneum used in laparoscopic surgery on an intraabdominal tumor growth". *Cancer*, 1999, 86, 770.
- [22] Morice P., Camatte S., Larregain-Fournier D., Thoury A., Duvillard P., Castaigne D.: "Port-site implantation after laparoscopic treatment of borderline ovarian tumors". *Obstet. Gynecol.*, 2004, 104, 1167.
- [23] Liu C.S., Nagarsheth N.P., Nezhat F.R.: "Laparoscopy and ovarian cancer: a paradigm change in the management of ovarian cancer?". *J. Minim. Invasive Gynecol.*, 2009 16, 250.
- [24] Fauvet R., Boccara J., Dufournet C., Poncelet C., Daraï E.: "Laparoscopic management of borderline ovarian tumors: results of a French multicenter study". *Ann. Onc.*, 16, 403.
- [25] Santi A., Kuhn A., Gyr T., Eberhard M., Johann S., Gunther A.R., Mueller M.D.: "Laparoscopy or laparotomy? A comparison of 240 patients with early-stage endometrial cancer". *Surg. Endosc.*, 2010, 24, 939.
- [26] Ikechebeli J.I., Okeke K.A.: "Improving the safety of room air pneumoperitoneum for diagnostic laparoscopy". *Niger J. Clin. Pract.*, 2008, 11, 127.
- [27] Langmar Z., Szabo I.: "Role of laparoscopy in the treatment of early endometrial cancer". *Orv. Hetil.*, 2010, 151, 1748.
- [28] Tenney M., Walker J.L.: "Role of laparoscopic surgery in the management of endometrial cancer". *J. Natl. Compr. Canc. Netw.*, 2009, 7, 559.
- [29] Zanvettor P.H., Filho D.F., Neves A.R., Amorim M.J., Medeiros S.M., Laranjeiras L.C. *et al.*: "Laparoscopic surgical staging of locally advanced cervix cancer (IB2 to IVA): initial experience". *Gynecol. Oncol.*, 2011, 120, 358.

Address reprint requests to:  
 C. MANHUA, M.D.  
 Department of Obstetrics and Gynecology  
 The Second Hospital of Jilin University  
 218 Ziqiang Street  
 Nangan district, Changchun City  
 130041 Jilin Province (China)  
 e-mail: manhuacui@126.com