MINI REVIEW

Unsuspected Genital Tract Malignancy Discovered During or After Gynecologic Surgery

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Abstract

   Preoperative counseling is a fundamental process in surgical practice. Although uncommon, discordance between preoperative and postoperative diagnoses has been observed in surgical practice. This would be a major concern if a serious condition such as malignant disease is noted incidentally. Encountering unexpected cancers during or after an operation may result in suboptimal treatment performed because of the potential of failure to follow standard treatment guidelines for such cancer. In addition, failing to prepare patients for a possibility of unsuspected cancer is an extremely difficult situation and may complicate the relationship with the surgeon. This article focused on the incidence and major causes of unsuspected genital tract malignancies found during or after gynecologic surgery.

Keywords: Unsuspected malignancy - genital tract - chance finding at surgery

Introduction

   Preoperative counseling is a fundamental process if good surgical practice is to be established. Surgeons have to provide an adequate time to explain and to discuss with patients and their supporters about clinical diagnoses, treatment options, planned surgical procedures if necessary, and possible perioperative risks.

   Following the operation, detailed information including intraoperative findings, surgical procedures carried out, postoperative diagnoses, and further management planning should be recorded and given to patients and their relations in a timely fashion.

   Although uncommon, the discordance between preoperative and postoperative diagnoses has been observed in surgical practice. These would be a major concern if a serious condition such as malignant disease is noted incidentally. Discovering unexpected cancers during or after an operation may result in suboptimal treatment performed because of the potential of failure to follow standard treatment guidelines for such cancer. In addition, failing to prepare patients for a possibility of unsuspected cancer is an extremely difficult situation and may complicate the relationship between the surgeon and patient. Therefore, an accurate preoperative diagnoses and adequate preoperative counseling about the possibility of unsuspected cancers found during or after operation are mandatory.

   This article focuses on the incidence and major causes of unsuspected genital tract malignancy found during or after gynecologic surgery.

Cervical cancer

   Due to the lack of a well-organized prevention program, cervical cancer remains a major health problem in many of the developing countries including Thailand. The incidence of cervical cancer in Thailand is continuously rising. The highest incidence is in Chiang Mai with an aged-standardized incidence rate (ASR) of approximately 30 per 100000 women (Moore et al., 2010). Based on the high incidence of cervical cancer in Thailand, the possibility of unexpected cervical cancer should be kept in mind during preoperative evaluation for every woman requiring a hysterectomy.

   The most important management for reducing the possibility of unsuspected cervical cancer in women undergoing hysterectomy is an extensive evaluation of the uterine cervix. Cervical screening history and its results should be assessed. Cervical screening should be carried out prior to the operation if the uterine cervix is normal in appearance. Colposcopy is recommended in women with a previous history of abnormal cervical pathology, history of abnormal vaginal bleeding, particularly postcoital bleeding, and those women who are found to have an unusual-appearing cervix (Bender 2002).

   Reasons for inappropriate simple hysterectomy in women with invasive cervical cancer
   Annually, approximately 10-15 women with unexpected cervical cancers diagnosed from hysterectomy specimens who were considered to receive an improper simple hysterectomy, or the so-called "inadvertent

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hysterectomy", were referred to Chiang Mai University Hospital. An inadvertent hysterectomy is generally defined as performing a simple hysterectomy in women who have frankly invasive cervical cancer (stage IA2 or higher). In women with frankly invasive cervical cancer, type 2 or type 3 hysterectomies with bilateral pelvic lymphadenectomy is considered to be the standard surgical treatment.

In a series of 70 women with unsuspected invasive cervical cancer who were referred to Chiang Mai University Hospitals during January 1991 and December 1998 because of an inadvertent hysterectomy revealed that an incomplete evaluation of abnormal cervical cytology or microinvasive cervical cancer was the most common cause of an inadvertent hysterectomy which accounted for approximately one-third of such women, followed by a lack of preoperative cervical screening (23%), and false-negative result of cervical cytology (18.6%) (Srisomboon et al., 2000)

Roman et al (1992) reported that major causes of an inappropriate simple hysterectomy among 148 women with unsuspected cervical cancer included an inadequate evaluation of an abnormal Pap smear or cervical biopsy (21%), failure to perform an indicated cervical conization (12%), intended hysterectomy for grossly invasive cervical cancer (11%), lack of preoperative cervical screening (7%), and conization margin positive or not evaluated (7%).

Behtash et al (2003) demonstrated major reasons for inadvertent hysterectomy among 62 women who found to have invasive cervical cancer which were as follows: lack of preoperative cervical smears (29%), deliberate hysterectomy for biopsy-proven cancer (25.8%), inadequate evaluation of abnormal Pap smears (6.5%), and failure to perform an indicated cervical conization (3.2%).

The absence of preoperative cervical screening and inadequate evaluation of abnormal cervical cytology were also noted as major causes of suboptimal management of cervical cancer by simple hysterectomy in a study of Rodolakis et al (1999)

Based on the findings mentioned earlier, almost all leading causes of inappropriate hysterectomy in women who have invasive cervical cancer therefore could be preventable by performing preoperative cervical screening and strict adherence to the well-established management guidelines for women with an abnormal cervical screening.

Interestingly, a considerably high proportion of women who had undergone inadvertent hysterectomy (50-70%) in aforementioned studies had preexisting abnormal vaginal bleeding (Behtash et al., 2003; Rodolakis et al., 1999; Roman et al., 1992; Srisomboon et al., 2000). This finding supports the necessity of an extensive evaluation of the uterine cervix i.e. preoperative colposcopy with cervical biopsy in order to exclude unexpected invasive cervical cancer before undergoing hysterectomy in women who have abnormal vaginal bleeding.

Management of preoperative cervical smear abnormality

The principal aim for evaluating abnormal cervical screening results among women who planned to undergo a simple hysterectomy is to exclude the possibility of finding frankly invasive cervical lesion. Thus, colposcopy with cervical biopsy is strongly recommended.

In Chiang Mai University Hospital, colposcopy with colposcopically-directed biopsy (CDB) is carried out in all women who have abnormal preoperative cervical cytology regardless of the severity of smear interpretation due in part to the fact that the incidence of invasive cervical cancer among women with an abnormal cervical smear in Chiang Mai University Hospital is extraordinarily high compared to previous reports from the areas with low incidence of cervical cancer. In addition, this unique finding is consistently noted across all grade of cervical smear abnormality (Table 1) (Kantathavorn et al., 2008; Kiatiyosnusorn et al., 2010 ; Kietpeerakool et al., 2008; Sawangsang et al., 2010).

Diagnostic cervical conization is generally indicated if one of the following criteria has been met: (1) biopsy revealing microinvasion or adenocarinoma in situ; (2) biopsy revealing cervical intraepithelial neoplasia (CIN) 1 or lesser in women with preceding cytology revealing high-grade smear abnormalities including high-grade squamous intraepithelial lesion (HSIL), suspected invasive lesion on cytology, high-grade glandular cell abnormality (atypical glandular cell favor neoplasia, AGC-FN; adenocarcinoma in situ, AIS); (3) having high-grade smear abnormality i.e. HSIL and unsatisfactory colposcopic examination, and (4) having history of recurrent smear abnormality (Wright et al., 2007).

Management of cervical conization margin involvement

As mentioned earlier, hysterectomy among women whose conization margins are involved is one of common causes of receiving an inadvertent hysterectomy. This would be due to the fact that when conization margins are positive, there is a risk of having residual high-grade lesions, and it is sometimes a frankly invasive cervical cancer. Repeat diagnostic excision as per the American Society for Colposcopy and Cervical Pathology (ASCCP) 2006 guidelines (Wright et al., 2007), therefore should be carried out in order to attain clear conization margins, and then the severity of cervical pathology could be

Table 1. Histopathologic Findings among Women with Abnormal Cervical Cytology attending Colposcopy Clinic, Chiang Mai University Hospital

Cytology	Histopathologic results, n (%)				
	No lesion	CIN 1	CIN 2-3	AIS	Cancer
ASC-US (208)	153 (73.6)	5 (2.4)	21 (10.1)	3 (1.4)	5 (2.4)
ASC-H (85)	20 (23.5)	6 (7.1)	52 (61.2)	0 (0.0)	7 (8.2)
LSIL (208)	79 (38.0)	62 (29.8)	63 (30.3)	0 (0.0)	4 (1.9)
HSIL (282)	18 (6.4)	9 (3.2)	195 (69.2)	3 (1.1)	57 (20.2)
SCCA (48)	0 (0.0)	1 (2.1)	31 (64.6)	0 (0.0)	15 (31.3)
AGC* (63)	49 (77.8)	0 (0.0)	5 (7.9)	3 (4.8)	2 (3.2)

*4 cases had endometrial hyperplasia (1) and endometrial carcinoma (3); CIN, cervical intraepithelial neoplasia; AIS, adenocarcinoma in situ; ASC-US, atypical squamous cell of undetermined significance; ASC-H, atypical squamous cell cannot exclude HSIL; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCCA, squamous cell carcinoma; AGC; atypical glandular cells

determined with confidence.

In real practice, repeat diagnostic excision however might not be possible to perform in all cases. In Chiang Mai University Hospital, repeat diagnostic excision is technically impossible in approximately one-third (38%) of women with conization margin involvement (Kietpeerakool et al., 2007). Hysterectomy therefore is inevitable and risk of inadvertent hysterectomy is subsequently expected.

In a previous study at Chiang Mai University undertaken to evaluate risk and types of residual disease among 85 women with CIN 2-3 on loop electrosurgical excision procedure (LEEP) specimens, in whom the endocervical LEEP margins were involved, invasive cervical cancer was noted in six women (7.1%) including stage IA1 (5) and IB1 (1). The risk of inadvertent hysterectomy therefore was approximately 1.7 % if a simple hysterectomy was carried out in such women (Kietpeerakool et al., 2007).

Another study from Chiang Mai University Hospital was conducted to evaluate an independent predictor of having a residual invasive lesion in women with microinvasive squamous cervical cancer and positive cone margins. In this study, the majority of women (85.3%) underwent LEEP. Cone margin involvement for an invasive lesion was noted to be a significant independent predictor for having residual invasive lesions detected in subsequent surgery. Residual frankly invasive lesion was noted in 1.6% of such women (Phongnarisorn et al., 2006).

In our practice, women with CIN 2-3 or microinvasion (presumed stage IA1) on conization specimens whose conization margin are involved and repeat diagnostic excision is not technically feasible, will be informed that the risk of having frankly invasive cancer found in hysterectomy specimens or receiving inadvertent hysterectomy was approximately 2 % (Phongnarisorn et al., 2006; Kietpeerakool et al., 2007)

Ovarian cancer

Unexpected ovarian cancer found during or after a planned surgery for benign ovarian mass is expected to be low if multimodalities of investigations i.e. detailed ultrasonography, tumor marker measurement are carried out. From an extensive literature review regarding the unexpected ovarian malignancy found during operative laparoscopy by Muzii et al (2005), premenopausal women with a benign appearing ovarian cyst had less than 1% risk of unexpected ovarian cancer while noted in approximately 3% of postmenopausal women. Unilocular ovarian cyst is associated with less than 1% risk of malignancy compared to 13% to 40% risk in predominately multiloculated and/or solid-cystic masses (Granberg et al., 1989).

Malignancy in women presenting with adnexal torsion
Adnexal torsion represents approximately 3% of all gynecologic emergencies and the major leading site of torsion is an ovarian mass (Oelsner and Shashar 2006) Although common histologies of ovarian masses causing torsion are benign tumors including corpus luteum, mature teratoma, follicular cyst, and epithelial cystadenoma

(Oelsner and Shashar 2006), the risks of encountering ovarian malignancy is still of major concern.

In literature, there are some patients and tumor characteristics that would be useful for predicting the risk of malignant lesion in a twisted ovary. Eitan et al (2007) reported that postmenopausal women with adnexal torsion carried a higher risk of having ovarian malignancy compared to a premenopausal group (22% vs. 0%, respectively).

In the recent study from Yen et al (2009) which was undertaken to evaluate the risk of discovering malignancy for adnexal torsion during pregnancy, the incidence of ovarian malignancy was 2.3%. Large tumor diameter (≥10 cm) measured at initial diagnosis and rapid tumor growth (≥ 3.5 cm per week) have been noted as significant independent factors for predicting malignant disease on a twisted ovary. Large tumors were more likely to be malignant compared to smaller sizes (8.77% vs. 0.85%, respectively). Tumors with a history of rapid growth carried a higher risk of malignancy versus a lower rate (8.33% vs. 0.88%, respectively). This information should be taken into account during preoperative counseling.

Malignancy of sonographically detected unilocular ovarian cyst in postmenopausal women
A simple unilocular ovarian cyst is sonographically defined as a sonolucent thin-walled (<3 mm) cyst without septation or solid component or papillary projection of any site.(Castillo et al., 2004) The risk of malignancy of unilocular ovarian cyst in the general population is notably low (less than 1%). However, the most important question is whether the low risk of malignancy of unilocular adnexal cyst shown in general women is still the same or not when occurring in postmenopausal women. The incidence of a simple unilocular adnexal cyst in postmenopausal women varies from 2.5% to 18% (Castillo et al., 2004; Modesitt et al., 2003; Wolf et al., 1991).

Historically, the management of adnexal cyst diagnosed in postmenopausal women has been treated surgically in order to exclude a risk of malignancy even in an asymptomatic unilocular cyst. Because of the advancement of ultrasound technology, a wide usage of modern ultrasound equipments in clinical practice, and natural history of sonographically- detected unilocular ovarian cyst has been increasingly acknowledged, therefore, a routine surgical approach should be reconsidered.

Modesitt et al (2003) reported that 18% of 15,106 women aged 50 years or older who participated in the ovarian cancer surveillance study using serial transvaginal ultrasound with Doppler flow assessment and CA 125 measurement, were found to have unilocular ovarian cyst. The majority of women (69%) had a cyst with a maximum diameter of less than 3 cm. The remaining women had a lesion size ranging from 3-10 cm. In approximately 6.3 years of the follow-up period, two-thirds (69.4%) of these ovarian cysts resolved spontaneously. Ten cases of ovarian cancer were diagnosed but all were observed among women who developed another morphological abnormality, experienced resolution of an unilocular cyst before developing cancer, or developed cancer in

the contralateral ovary. The authors concluded that the incidence of cancer in unilocular-appearing adnexal cyst less than 10 cm was less than 0.1%.

The incidence of sonographically detected unilocular adnexal cyst was 2.5 % in a cohort of 8794 asymptomatic postmenopausal women in Spain (Castillo et al., 2004). Eighty-eight percent of these cystic lesions have not been recognized at the initial pelvic examination. At the median follow-up time of 27 months, the incidence of ovarian cancer was 0.6% of all the unilocular cysts included in this study. In cancer case, serum CA 125 concentration was elevated indicating a requirement of surgical intervention. The probability of spontaneous resolution was significantly higher when occurring in women with shorter menopausal time (<10 years) compared to women with a longer time (54% vs. 29%, respectively)(Castillo et al., 2004). Nardo et al (2003) reported that no ovarian malignancy was observed in all women with persistent unchanged unilocular cysts.

The above studies have confirmed that routine surgical treatment is unwarranted in asymptomatic postmenopausal women with unilocular ovarian cyst of less than 10 cm. in diameter because of its' low incidence of malignancy (<0.1%), particularly in women with a shorter menopausal period. Surgery should be reserved for women who have an elevated serum CA 125 concentration or in whom the sonographically characteristics have progressed (Castillo et al., 2004; Dikensoy et al., 2007; Modesitt et al., 2003; Nardo et al., 2003). Any association between unilocular adnexal cyst formation and hormonal replacement therapy is inconclusive (Modesitt et al., 2003; Wolf et al., 1991).

Metastatic ovarian malignancy

Generally, malignancy by nature of metastatic ovarian tumor is easily recognized because the majority of the cases have symptoms indicating an advanced disease and further investigations i.e. ultrasound findings (tumor size, bilaterality, solid or papillary structure) and tumor marker assays are frequently suggestive for malignant condition. The most important problem becomes whether this tumor is a primary or metastatic lesion and is the location of the primary site, if clinically suggested for metastatic tumor.

In the literature, the distribution of a primary site has been noted to be accordingly associated with the common cancers reported in each area. In Chiang Mai University Hospital, 30% of metastatic ovarian tumors are from nongyneoclogic organs. The five most common primary sites were as follows: (1) large intestine, 31%; (2) stomach, 14%; (3) intrahepatic bile duct, 10%; (4) breast, 9%; and (5) extrahepatic bile duct/gall bladder, 7% (Khunamornpong et al., 2006).

Uterine cancer

In order to exclude unexpected uterine cancer, women who are scheduled for hysterectomy should be assessed for the signs and symptoms related to an unexpected uterine cancer. In women with abnormal vaginal bleeding, having cervicovaginal smear suggesting glandular abnormality in origin, and women aged 40 years or older with endometrial cells on smears regardless of the degree of cellular

abnormality, should undergo an endometrial evaluation before operation.

Coexisting endometrial cancer in women with a preoperative diagnosis of atypical endometrial hyperplasia

Endometrial hyperplasia, an abnormal proliferation of endometrium, is traditionally classified as simple or complex, with or without atypia depending on the architectural features and degree of cellular atypia. For a more practical approach, however, Ronnett and Kurman stated that "it is reasonable to classify noninvasive proliferative lesion of the endometrium as either hyperplasia without atypia or atypical hyperplasia". This purpose is based on the facts that in the neoplastic process, cellular atypia and architecture have been simultaneously changed. Therefore, the majority of atypical endometrial hyperplasias (AEH) are found to have a complex structure resulting in the rarity of atypical simple hyperplasia. Additionally, there is no clear evidence regarding the clinical benefits gained from the differentiation between simple and complex AEH (Ronnett and Kurman 2001).

It is well established that women with AEH have a significantly increased risk of having unexpected coexisting endometrial carcinoma and risk of progression to an invasive stage(Bilgin et al., 2004; Karamursel et al., 2005; Merisio et al., 2005; Shutter and Wright 2005; Suh-Burgmann et al., 2009; Wang et al., 2005; Widra et al., 1995). An increased risk of unrecognized endometrial cancer in women with AEH on preoperative diagnoses is secondary to the subjectivity by nature of histological differentiation between AEH and well differentiated endometrial cancer on endometrial specimens (Trimble et al., 2006). This has raised the most important question in that whether a simple hysterectomy is appropriate for such women because it would be a suboptimal surgery if endometrial cancer is noted incidentally. In the literature, the rate of concurrent endometrial cancer found in hysterectomy specimens among women with preoperative diagnoses of AEH varies widely, ranging from 20-60% depending on the characteristics of population which have been studied, endometrial evaluation methods i.e. curettage or biopsy, and expertise of pathologists (Bilgin et al., 2004; Karamursel et al., 2005; Merisio et al., 2005; Shutter & Wright, 2005; Suh-Burgmann et al., 2009; Widra et al., 1995).

In the recent retrospective cohort study by Suh-Burgmann et al (2009), age was noted to be a significant predictor of the risk of unexpected cancer, deep myometrial invasion, and grade III lesion found on subsequent hysterectomy specimens among women with AEH. In comparison to women aged 50 years or lesser, risk of unexpected cancer was significant associated with every decade of increased age. Due to the lower the risk of overtreatment, the author suggests incorporating patients' age as a factor in consideration of surgical staging.

In several previous reports, the risk of having unrecognized endometrial cancer in hysterectomy specimens among women undergoing endometrial curettage and biopsy is still inconclusive because of a considerably small number of study samples (Bilgin et al., 2004; Merisio et al., 2005; Shutter and Wright, 2005).

However, the association between the risk of unexpected endometrial cancer and methods of endometrial evaluation leading to the preoperative diagnoses of AEH were recently evaluated among the largest cohort of women with AEH (824 women). Interestingly, endometrial biopsy was associated with a significantly higher risk of encountering unexpected endometrial cancer compared with curettage (45% vs. 30%, respectively). Additionally, after adjusting for age, women undergoing endometrial biopsy were two times more likely to be diagnosed with endometrial cancer compared with biopsy group (adjusted odds ratio, 2.0; 95% confidence interval, 1.4-2.9). The author concludes that despite selective bias, endometrial curettage lowered the risk of unexpected cancer compared with biopsy, but continues to be unreliable to confidently exclude coexisting endometrial cancer (Suh-Burgmann et al., 2009).

In real practice while unexpected endometrial cancer in women with preoperative diagnoses of AEH could not be confidently excluded, detailed information involving the rate of unexpected endometrial cancer, the possible benefits of complete surgical staging, and procedures' related morbidity should be clearly given during preoperative counseling.

Unexpected cancer in women with presumed myoma uteri

Uterine myoma is the most common benign tumor of the uterus. Conservative management comprising an interval follow-up to monitor the size of the tumor and associated symptoms is the most appropriate approach for asymptomatic cases at initial diagnosis. Surgical treatment is preserved for symptomatic cases. The risk of unexpected uterine sarcoma in women undergoing surgery for symptomatic myoma uteri is extremely low at less than 0.23%. Furthermore, this notably low risk was also noted in women having a clinical diagnosis of rapid enlargement (0.27%) (Parker et al., 1994).

Primary Fallopian Tube Cancer

Primary fallopian tube cancer (PFTC) is a rare disease, accounting for less than 0.5 % of female genital tract malignancy found in Chiang Mai University each year (Kietpeerakool et al., 2005). Although there are typical presenting symptoms of women with PFCT including pelvic mass, pelvic pain, and profuse watery vaginal discharge, or the so-called "hydrops tubae profluens", the full range of this symptom complex however is infrequently encountered. Additionally, abnormal gross appearances of the fallopian tube found during operation including hydrosalpinx, hematosalpinx, pyosalpinx, and tubal mass are observed in only less than 50% of the cases (Daskalakis et al., 1998; Kietpeerakool et al., 2005; Kurjak et al., 1998; Piura and Rabinovich, 2000). Because of the rarity of this disease, silent natural course, and the low level of suspicion, almost all of PFTC cases therefore are diagnosed postoperatively (Kurjak et al., 1998).

PFTC is generally recognized as a disease of women in perimenopausal and postmenopausal periods. Therefore, is should be considered in the differential diagnoses in perimenopausal and postmenopausal women who have the following conditions: (1) unexplained vaginal bleeding; (2) unexplained vaginal discharge; (3) complicated pelvic inflammatory disease; and (4) abnormal glandular cells on cervicovaginal smears but having no significant lesions detected on endocervical and endometrial evaluation (Kietpeerakool et al., 2005).

Other Female Genital Tract Malignancies

Vulvar and vaginal cancers are uncommon. In Chiang Mai University Hospital, these two malignant diseases represent less than 5% of the cases of female genital tract cancers. In Thailand, where regular examination including per vaginal examination is not widely popular, particularly in older women who are at a high risk group of developing vulvar and vaginal neoplasia. Almost all of the cases therefore are diagnosed after developing gross lesions.

Common preexisting symptoms of early stage of vulvar and vaginal cancers include multiple episodes of abnormal bleeding, abnormal discharge and chronic vulvovaginal itching. Women with these symptoms should undergo meticulous assessment of the lower genital tract to exclude occult cancers of the cervix, vagina, and vulva, particularly when postmenopausal. With suspicious occult lesions, vulvoscopy and/or colposcopy might be helpful to define the most appropriate biopsy site.

Bartholin's gland carcinoma is an extremely uncommon malignancy. However, encountering Bartholin's gland abscess or painless lump in posterior half of vulva in postmenopausal women should intensify the concerns of this condition and histological examination is strongly needed (Cardosi et al., 2001; Lopez-Varela et al., 2007; Obermair et al., 2001)

Conclusion

In the literature, only few reports regarding unsuspected gynecologic malignancy discovered during or after gynecologic surgery are available. Therefore, the magnitude of this problem is still questionable but probably has been underestimated. Theoretically, the incidence of unexpected cancers at gynecologic surgery varies between the settings depending on various factors i.e. the experience of attending physicians, an availability of laboratory investigations, and the complexity of patients' conditions. However, major discordance between preoperative and postoperative diagnoses such as encountering an unsuspected cancer should be considered as one of the issues in the process of medical audit if qualified surgical practice is to be achieve. Obviously, preoperative counseling about the risks of encountering unexpected cancer at surgery is of paramount important in everyday surgical practice.

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