advanced stages with unresectable diseases. On the other hand, the TC regimen may now be considered for listing as a standard treatment useful for recurrent cases as a remission induction therapy having minimal side effects, and for patients in Stage I/II with risk factors requiring an adjuvant therapy. We firmly believe that GOG #209 and JGOG #2043 studies will provide strong evidence supporting our findings and our proposals.

Details of ethics approval All patients provided written informed consent before the treatment commenced. This study was approved by the Institutional Review Board of Osaka Medical Center for Cancer and Cardiovascular Diseases (#1006145029, June 14, 2010) and the Ethics Committee of Osaka University Graduate School of Medicine (#117, July 2, 2001).

Acknowledgments We would like to thank Dr. G. S. Buzard, CDCP, for his constructive editing of our manuscript. We are also grateful to Ms. S. Sugiyama and Ms. K. Nakano for their dedicated and excellent bioinformatics work extracting patient data from our medical records.

Conflict of interest The authors have no conflicts of interest to declare.

References

1. DiSaia PJ, Creasman WT (2002) Clinical Gynecologic Oncology, 6th edn. Mosby, St. Louis
2. Berek JS (2002) Novak's Gynecology, 13th edn. William and Wilkins, Baltimore
3. Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, Thigpen JT, Benda JA, Gynecologic Oncology Group Study (2006) Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: A Gynecologic Oncology Group Study. J Clin Oncol 24:36–44
4. Muss HB (1994) Chemotherapy of metastatic endometrial cancer. Semin Oncol 21:107–113
5. Thigpen JT, Brady MF, Homesley HD, Malfetano J, DuBeshter B, Burger RA, Liao S (2004) Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynecologic oncology group study. J Clin Oncol 22:3902–3908
6. Ball HG, Blessing JA, Lentz SS, Mutch DG (1996) A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol 62:278–281
7. Lissoni A, Zanetta G, Losa G, Gabriele A, Parma G, Mangioni C (1996) Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. Ann Oncol 7:861–863
8. Fleming GF, Brunetto VL, Cella D, Look KY, Reid GC, Munkarah AR, Kline R, Burger RA, Goodman A, Burks RT (2004) Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 22:2159–2166
9. Lissoni A, Gabriele A, Gorga G, Tumolo S, Landoni F, Mangioni C, Sessa C (1997) Cisplatin-, epirubicin- and paclitaxel-containing chemotherapy in uterine adenocarcinoma. Ann Oncol 8:969–972
10. Papadimitriou CA, Bafaloukos D, Bozas G, Kalofonos H, Kosmidis P, Aravantinos G, Fountzilas G, Dimopoulos MA, Hellenic Co-operative Oncology Group (2008) Paclitaxel, epirubicin, and carboplatin in advanced or recurrent endometrial carcinoma: a Hellenic Co-operative Oncology Group (HeCOG) study. Gynecol Oncol 110:87–92
11. Sovak MA, DuPont J, Hensley ML, Ishill N, Gerst S, Abu-Rustum N, Anderson S, Barakat R, Konner J, Poyner E, Sabbatini P, Spriggs DR, Aghajanian C (2007) Paclitaxel and carboplatin in the treatment of advanced or recurrent endometrial cancer: a large retrospective study. Int J Gynecol Cancer 17:197–203
12. Pectasides D, Xiros N, Papaxoinis G, Pectasides E, Sykiotis C, Koumarianou A, Psyrri A, Gaglia A, Kassanos D, Gouveris P, Panayiotidis J, Fountzilas G, Economopoulos T (2008) Carboplatin and paclitaxel in advanced or metastatic endometrial cancer. Gynecol Oncol 109:250–254
13. Vandenput I, Vergote I, Leunen K, Berteloot P, Neven P, Amant F (2009) Leuven dose-dense paclitaxel/carboplatin regimen in patients with primary advanced or recurrent endometrial carcinoma. Int J Gynecol Cancer 19:1147–1151
14. Ueno Y, Enomoto T, Otsuki Y, Sugita N, Nakashima R, Yoshino K, Kuragaki C, Ueda Y, Aki T, Ikegami H, Yamazaki M, Ito K, Nagamatsu M, Nishizaki T, Asada M, Kameda T, Wakimoto A, Mizutani T, Yamada T, Murata Y (2006) Prognostic significance of p53 mutation in suboptimally resected advanced ovarian carcinoma treated with the combination chemotherapy of paclitaxel and carboplatin. Cancer Lett 241:289–300
15. World Health Organization (1979) Handbook of Reporting Results of Cancer Treatment No. 48. WHO Offset Publication, Geneva
16. Pectasides D, Xiros N, Papaxoinis G, Pectasides E, Sykiotis C, Koumarianou A, Psyrri A, Gaglia A, Kassanos D, Gouveris P, Panayiotidis J, Fountzilas G, Economopoulos T (2008) Carboplatin and paclitaxel in advanced or metastatic endometrial cancer. Gynecol Oncol 109:250–254
17. du Bois A, Lück HJ, Meier W, Adams HP, Möbus V, Costa S, Bauknecht T, Richter B, Warm M, Schröder W, Olbricht S, Nitz U, Jackisch C, Emons G, Wagner U, Kuhn W, Pfisterer J, Arbeitsgemeinschaft Gynäkologische Onkologie Ovarian Cancer Study Group (2003) A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 95:1320–1329
18. Egawa-Takata T, Ueda Y, Kuragaki C, Miyake T, Miyatake T, Fujita M, Yoshino K, Nakashima R, Okazawa M, Tsutsui T, Morishige K, Kimura T, Yamasaki M, Nishizaki T, Nagamatsu M, Ito K, Asada M, Ogita K, Wakimoto A, Yamamoto T, Nishio Y, Enomoto T (2011) Chemotherapy for endometrial carcinoma (GOGO-EM1 study): TEC (paclitaxel, epirubicin, and carboplatin) is an effective remission-induction and adjuvant therapy. Cancer Chemother Pharmacol 68:1603–1610

Int J Clin Oncol (2012) 17:407–411
DOI 10.1007/s10147-011-0313-4

CASE REPORT

Primary retroperitoneal mucinous cystadenocarcinoma with mural nodules: a case report and literature review

Tomoko Kanayama · Kiyoshi Yoshino · Takayuki Enomoto · Hiroshi Ohashi · Masami Fujita · Yutaka Ueda · Toshihiro Kimura · Eiji Kobayashi · Eiichi Morii · Tadashi Kimura

Received: 16 June 2011 / Accepted: 22 August 2011 / Published online: 17 September 2011

Abstract A primary retroperitoneal mucinous cystadenocarcinoma (PRMC) is an extremely rare lesion. To date, only 49 cases have been reported. The presence of mural nodules in a PRMC may indicate a worse prognosis. We report the case of a 40-year-old Japanese woman with a PRMC with mural nodules. Microscopic examination revealed that the stromal cells of the nodules were spindle-shaped and varied in size. The nodules were immunoreactive for vimentin but negative for cytokeratin and EMA, and the nuclei of the stromal cells were pleomorphic and strongly Ki-67 immunoreactive. The nodules were diagnosed as true sarcoma. To the best of our knowledge, this is 11th published case report of a PRMC with mural nodules.

Keywords Retroperitoneal mucinous cystadenocarcinoma · Mural nodule · Sarcoma

Introduction

Primary retroperitoneal mucinous tumors (PRMTs) are uncommon neoplasms. Similar to mucinous tumors of the ovary, PRMTs are divided into three categories: mucinous cystadenomas, mucinous borderline tumors (tumors of low malignant potential), and mucinous adenocarcinomas. Here, we report the case of a 40-year-old Japanese woman with a primary retroperitoneal mucinous cystadenocarcinoma (PRMC) with mural nodules. We also review the literature of similar rare cases.

T. Kanayama · K. Yoshino (✉) · T. Enomoto · M. Fujita · Y. Ueda · T. Kimura · E. Kobayashi · T. Kimura
Department of Obstetrics and Gynecology, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
e-mail: yoshino@gyne.med.osaka-u.ac.jp

H. Ohashi · E. Morii
Department of Pathology, Graduate School of Medicine, Osaka University, Suita, Japan

The case

A 40-year-old Japanese woman, gravida 0, with no previous medical history of any significance, was admitted to our hospital because of a progressive abdominal distension of a 2-year duration. On physical examination, her abdomen was markedly distended with a palpable mass the size of a man's head. Pelvic examination and transvaginal ultrasound showed that the uterus and left ovary were normal and that the the tumor seemed to arise from the right ovary. Magnetic resonance imaging (MRI) revealed a unilocular large cyst with solid mural nodules (Fig. 1a). Laboratory evaluations, including those for carcinoembryonic antigen (CEA) and carbohydrate antigen 125 (CA125), were within normal limits. A laparotomy was performed, revealing the presence of a large cystic tumor in the retroperitoneal space of the right iliac fossa. Although the tumor was close to the right ovary, there was no direct connection between them. The uterus, fallopian tubes, and ovaries appeared bilaterally normal (Fig. 1b). The cyst wall, having no apparent connection with any organs and showing no evidence of abdominal spread, was completely excised without rupture. A right salpingo-oophorectomy was subsequently performed. Since the intra-operative frozen section diagnosis could not rule out the possibility of malignancy, both a right pelvic and right paraaortic lymphadenectomy were performed. The uterus and the left ovary were preserved because the patient wished to remain fertile. Following the surgery the patient recovered without

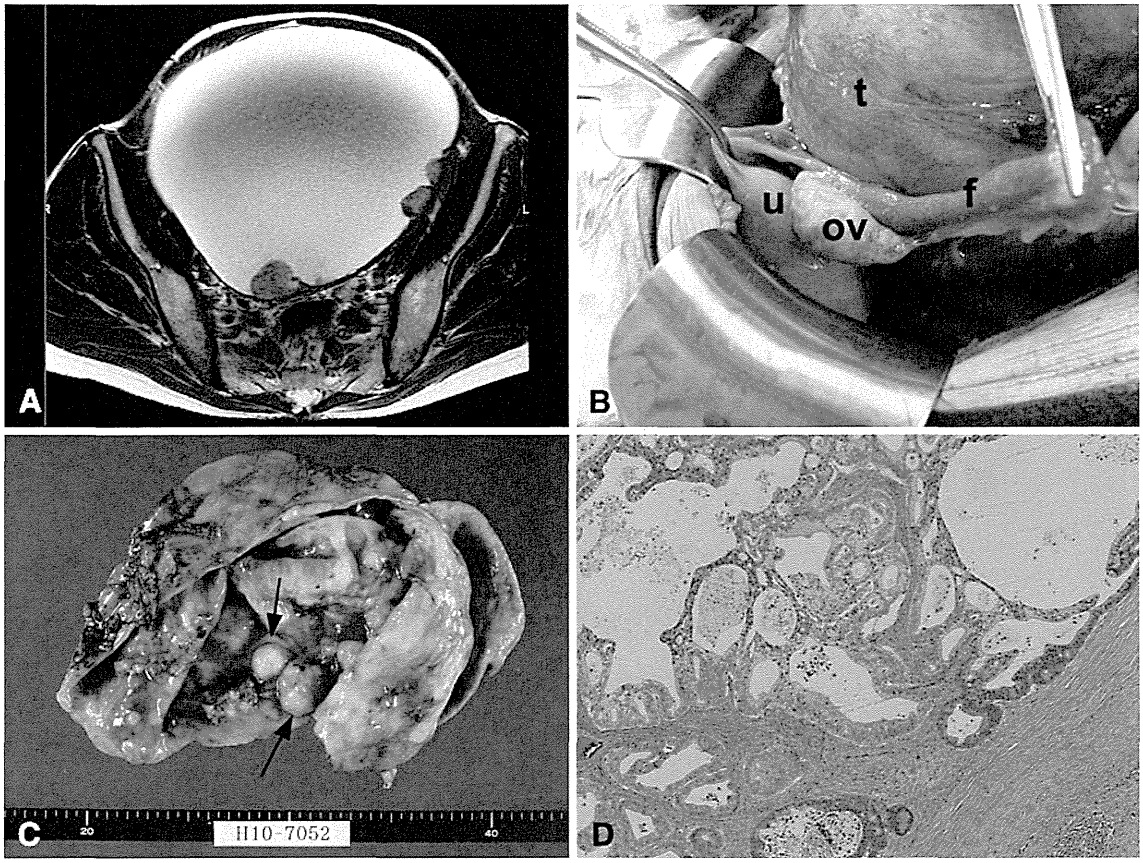

Fig. 1 **a** Magnetic resonance image of the cystic tumor with mural nodules. **b** Intraoperative photo showing the association of the tumor (*t*), uterus (*u*), ovary (*ov*), and fallopian tube (*f*). **c** Gross appearance of the formalin-fixed tumor. *Arrows* mural nodules. **d** Microphotograph of the tumor with hematoxylin and eosin staining showing mucinous cystadenocarcinoma (×40)

any adverse events. She has been given no further treatment, and at the current time, 6 months after surgery, she has no evidence of the disease.

Pathologic findings

On gross examination, there was no direct connection of the cyst to the right ovary. The cyst was 25 cm in diameter and contained mucin, with solid nodules in the cyst wall (Fig. 1c).

A total of 17 tissue sections were prepared for diagnosis. Microscopic examination revealed that the cyst was lined by papillae composed of atypical mucinous cells which also exhibited stromal invasion (Fig. 1d). In the mucinous cystadenocarcinoma cells, the cytokeratin CK7 was positive and CK20 was negative for staining. In the mural nodules, the stromal cells were spindle-shaped and varied in size, and their nuclei were pleomorphic (Fig. 2a, b). The stromal cells in the mural nodule were immunoreactive for vimentin, but negative for both cytokeratins (Fig. 2c) and for epithelial membrane antigen (EMA). These stromal cells also showed strong immunoreactivity for Ki-67, indicating high proliferation (Fig. 2d). These results on the mural nodules provided sufficient evidence for the diagnosis of a sarcoma. Immunohistochemical staining for estrogen and progesterone receptors was negative in the stromal region of the cyst and its nodules, leading to the conclusion that the tumor did not originate from ectopic ovarian tissue [1–3].

Computed tomography (CT), magnetic resonance imaging, and positron emission tomography/CT were used preoperatively to exclude the diagnosis of metastatic tumor. However, the suspected origin of the cyst was not detected in the respective images. Surgery did not locate any other tumor mass in the abdominal cavity. In addition, results from immunohistochemistry of CK7 (+) and CK20 (−) indicated that this retroperitoneal tumor did not originate from the large intestine. We therefore concluded that this case involved a PRMC.

Based on these findings, we diagnosed the lesion as a PRMC with mural nodules (true sarcoma). No metastases were observed in the resected pelvic and para-aortic lymph nodes.

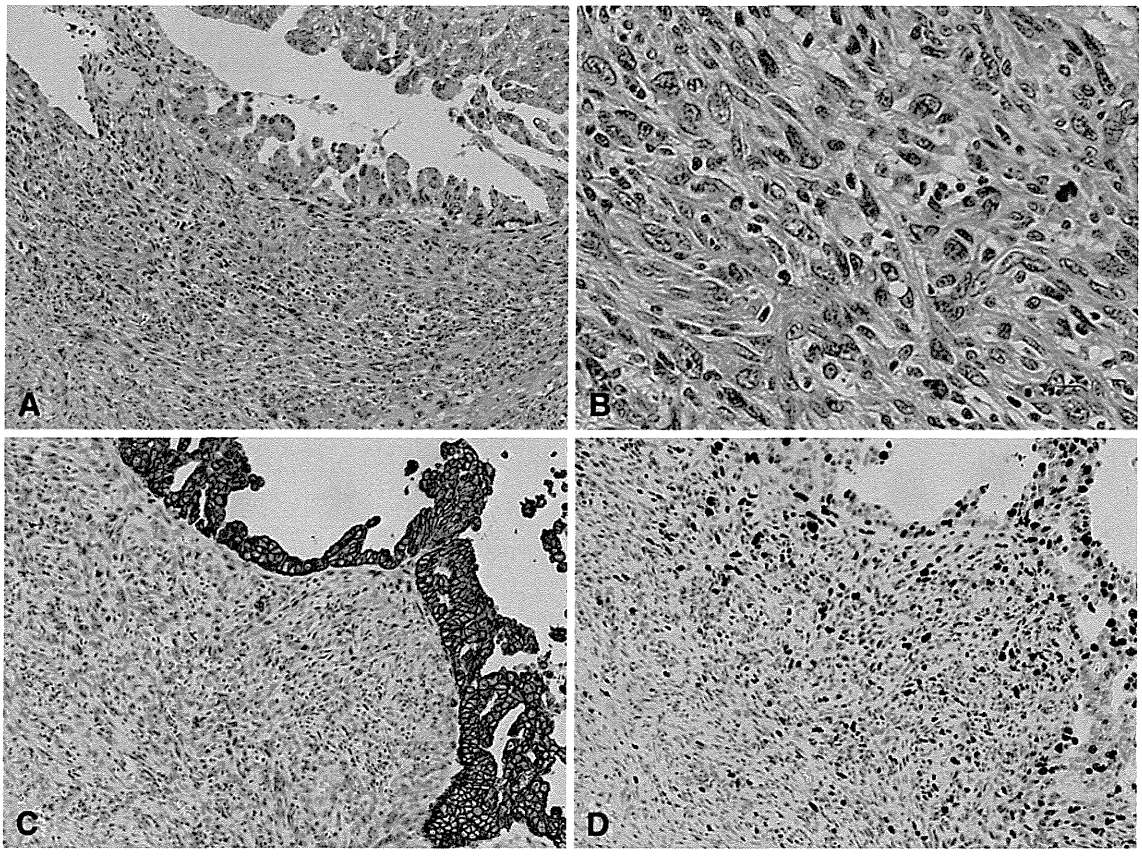

Fig. 2 **a** H&E staining of the mural nodule (×40). **b** Higher magnification of the nodule; the stromal cells can be seen to be spindle shaped and to vary in size. The nuclei are pleomorphic (×400). **c** Cytokeratin staining in the stroma of the nodule was negative (×40). **d** Ki-67 was strongly immunoreactive in the stroma of the nodule (×40)

Discussion

The mucinous tumor is a common histological type of gynecological neoplasm that occurs especially in the ovaries. However, a PRMT is quite rare, with the first PRMT described in 1965 [4]. We performed a literature search and identified only 90 published cases of PRMT [5–8]. Of these, 49 cases were malignant, i.e., involved a PRMC [6, 7].

As shown in Table 1, in the cases reported to date, PRMC with nodules occurred in relatively young patients (mean age 41.4 years); in comparison, the mean age of patients with PRMC without nodules was 44.6 years. Thus, there was no significant difference between patients with PRMC with nodules and those with PRMC without nodules in terms of age, although both occurred at a younger age than ovarian mucinous adenocarcinoma.

The pathogenesis of PRMC is of interest. Although the exact origin of PRMC remains unclear, four main theories have been put forward regarding its pathogenesis: (1) ectopic ovarian tissue origin, (2) retroperitoneal primary monodermal teratoma originating from displaced germ cells, (3) intestinal duplication, also known as enterogenous genesis [9–11], and (4) tumors that arise from invagination of the peritoneal mesothelial layer that undergoes mucinous metaplasia with cyst formation [12, 13].

Patients with PRMC generally have a good prognosis after complete removal of the [14, 15]. Among the 49 reported cases of PRMC, only five patients died of their disease. Of these five patients, four had mural nodules and an aggressive clinical course. To date, 11 of the 49 PRMC cases, including our case, involved one or more mural nodules [6, 16–21] (Table 1). As Mikami et al. [19] have described, the presence of mural nodules in PRMC may predict a worse prognosis. In their case, the patient died of her disease at 18 months postoperatively. There are also other reports of two patients with mural nodules who died of their disease at 4 and 6 months postoperatively, respectively [16, 18]. In contrast, in one case of a patient with mural nodules, there was no evidence of recurrence at 18 months postoperatively [20]. Thus, PRMC with mural

Table 1 Summary of reports of primary retroperitoneal mucinous cystadenocarcinomas (PRMC) with mural nodules

Case	Age of patient (years)	Pathological diagnosis	Tumor size	Treatment	Status (months)	Reference
1	48	PRMC with poorly differentiated adenocarcinoma	550 g	Tumor excision	DOD (6)	Roth and Ehrlich [16]
2	37	PRMC with sarcoma-like anaplastic carcinoma	18 cm	Tumor excision, TAH, BSO + chemo	NED (18)	Sondergaard and Kaspersen [17]
3	44	PRMC with sarcoma	12.5 cm	Tumor excision	DOD (4)	Gotoh et al. [18]
4	38	PRMC with mural nodule (anaplastic sarcomatoid tumor)	18 cm	Tumor excision + chemo	DOD (18)	Mikami et al. [19]
5	68	PRMC with osteoid-forming sarcoma-like mural nodule	17 cm	Tumor excision, TAH, BSO	NA	Fan et al. [20]
6	32	PRMC with sarcoma-like mural nodule	10 cm	Tumor excision + chemo	NED (42)	Lee et al. [21]
7	40	PRMC with nodules	15 cm	Tumor excision + chemo	NED (58)	Roma and Malpica [6]
8	43	PRMC with nodules	10 cm	Tumor excision + chemo	DOD (5)	Roma and Malpica [6]
9	35	PRMC with nodules	NA	Tumor excision + chemo	NED (91)	Roma and Malpica [6]
10	31	PRMC with nodules	18 cm	Tumor excision + chemo	AWD (26)	Roma and Malpica [6]
11	40	PRMC with mural nodule (sarcoma)	25 cm	Tumor excision, PLN, PAN	NED (6)	This case

AWD Alive with disease, *BSO* bilateral salpingo-oophorectomy, *DOD* died of disease, *NA* not available, *NED* no evidence of disease, *PAN* para-aortic lymphadnectomy, *PLN* pelvic lymphadnectomy, *TAH* total abdominal hysterectomy

nodule(s) may have an aggressive prognosis. Therefore, it appears that all mural nodules warrant careful histological assessment and careful postoperative follow-up.

According to a report by Baergen and Rutgers [22], the diagnostic criteria for a mural nodule includes its association with an epithelial ovarian tumor, its localization inside a cystic tumor surrounded by an epithelial component, and a minimal or no mixing between the epithelial component and the nodule. Histologically, mural nodules are classified as: (1) reactive lesions (sarcoma-like nodule) and (2) tumors (carcinoma, sarcoma and mixed carcinoma/sarcoma).

Some authors have noted that even though the ovaries and the uterus appear to be normal, the removal of both, in addition to an excision of the retroperitoneal tumor, should be performed to improve the prognosis after surgery. Currently, in part because of the rarity of the lesion, there is no clear evidence showing the benefit of adjuvant chemotherapy to PRMC patients, as has been suggested previously. There is a report of adjuvant chemotherapy in six patients, with only limited success [19].

For cases of PRMC, both precise macroscopic and microscopic studies are crucial. In addition, therapeutic experience with this rare tumor should be accumulated and shared among clinicians in order to gain a better understanding of this disease and to improve treatment regimens.

Conflict of interest The authors declare that there is no conflict of interest.

References

1. Kehagias DT, Karvounis EE, Fotopoulos A et al (1999) Retroperitoneal mucinous cystadenoma. Eur J Obstet Gynecol Reprod Biol 82:213–215
2. Subramony C, Habibpour S, Hashimoto LA (2001) Retroperitoneal mucinous cystadenoma. Arch Pathol Lab Med 125:691–694
3. Erdemoglu E, Aydogdu T, Tokyol C (2003) Primary retro peritoneal mucinous cystadenoma. Acta Obstet Gynecol Scand 82:486–487
4. Douglas GW, Kastin AJ, Huntington RW Jr (1965) Carcinoma arising in a retroperitoneal Muellerian cyst, with widespread metastasis during pregnancy. Am J Obstet Gynecol 91:210–216
5. Benkirane A, Mikou A, Jahid A et al (2009) Primary retroperitoneal mucinous cystadenoma with borderline malignancy in a male patient: a case report. Cases J 2:9098
6. Roma AA, Malpica A (2009) Primary retroperitoneal mucinous tumors: a clinicopathologic study of 18 cases. Am J Surg Pathol 33:526–533
7. Tjalma WA, Vaneerdeweg W (2008) Primary retroperitoneal mucinous cystadenocarcinomas are a distinct entity. Int J Gynecol Cancer 18:184–188
8. Rifki Jai S, Bouffetal R, Chehab F et al (2009) Primary retroperitoneal mucinous cystadenoma. Arch Gynecol Obstet 280:479–483
9. Chen JS, Lee WJ, Chang YJ et al (1998) Laparoscopic resection of a primary retroperitoneal mucinous cystadenoma: report of a case. Surg Today 28:343–345
10. Matsubara M, Shiozawa T, Tachibana R et al (2005) Primary retroperitoneal mucinous cystadenoma of borderline malignancy: a case report and review of the literature. Int J Gynecol Pathol 24:218–223
11. Orvis GD, Behringer RR (2007) Cellular mechanisms of Mullerian duct formation in the mouse. Dev Biol 306:493–504

12. Guioli S, Sekido R, Lovell-Badge R (2007) The origin of the Mullerian duct in chick and mouse. Dev Biol 302:389–398
13. Yang DM, Jung DH, Kim H et al (2004) Retroperitoneal cystic masses: CT, clinical, and pathologic findings and literature review. Radiographics 24:1353–1365
14. Suzuki S, Mishina T, Ishizuka D et al (2001) Mucinous cystadenocarcinoma of the retroperitoneum: report of a case. Surg Today 31:747–750
15. Law KS, Chang TM, Tung JN (2006) Fertility-sparing treatment of a primary retroperitoneal mucinous cystadenocarcinoma. BJOG 113:612–614
16. Roth LM, Ehrlich CE (1977) Mucinous cystadenocarcinoma of the retroperitoneum. Obstet Gynecol 49:486–488
17. Sondergaard G, Kaspersen P (1991) Ovarian and extraovarian mucinous tumors with solid mural nodules. Int J Gynecol Pathol 10:145–155
18. Gotoh K, Konaga E, Arata A et al (1992) A case of primary retroperitoneal mucinous cystadenocarcinoma. Acta Med Okayama 46:49–52
19. Mikami M, Tei C, Takehara K et al (2003) Retroperitoneal primary mucinous adenocarcinoma with a mural nodule of anaplastic tumor: a case report and literature review. Int J Gynecol Pathol 22:205–208
20. Fan YS, Thomas TM, Ip PP et al (2006) Osteoid-forming sarcoma-like mural nodule in a retroperitoneal mucinous cystadenocarcinoma. Histopathology 49:201–204
21. Lee SA, Bae SH, Ryoo HM et al (2007) Primary retroperitoneal mucinous cystadenocarcinoma: a case report and review of the literature. Korean J Intern Med 22:287–291
22. Baergen RN, Rutgers JL (1994) Mural nodules in common epithelial tumors of the ovary. Int J Gynecol Pathol 13:62–72

Arch Gynecol Obstet (2012) 285:1427–1432
DOI 10.1007/s00404-011-2147-8

GYNECOLOGIC ONCOLOGY

Prediction, based on resection margins, of long-term outcome of cervical intraepithelial neoplasia 3 treated by Shimodaira-Taniguchi conization

Yukari Miyoshi · Takashi Miyatake · Yutaka Ueda · Akiko Morimoto · Takuhei Yokoyama · Shinya Matsuzaki · Toshihiro Kimura · Kiyoshi Yoshino · Masami Fujita · Hiroshi Ohashi · Eiichi Morii · Takayuki Enomoto · Tadashi Kimura

Received: 4 May 2011 / Accepted: 11 November 2011 / Published online: 23 November 2011

Abstract
Purpose The aim of the present study was to analyze the long-term outcome of cervical intraepithelial neoplasia 3 (CIN 3) after treatment with the Shimodaira-Taniguchi conization procedure, based on the status of the resection margins.
Methods In the Osaka University Hospital, conization using the Shimodaira-Taniguchi procedure has been routinely performed for CIN 3. Medical records of patients during the period from 2001 to 2008, whose post-conization diagnosis was CIN 3, were retrospectively analyzed for outcome versus margin status.
Results During the median follow-up period of 565 days (range 34–3,013), CIN disease was again detected in 14 of 243 patients; it was found in 7 patients among 198 margin-negative cases, and in 7 patients among 45 margin-positive cases. There was a significant difference in the reappearance rate demonstrated between the cases with positive and negative margins ($p = 0.0018$). Among the patients whose first follow-up post-conization cytology was normal, recurrence-free probability was significantly higher in margin-negative cases than in margin-positive ones (hazard ratio, 5.19; 95% CI, 1.175–22.994; $p = 0.0041$).
Conclusion For the first time, we demonstrate that after treatment of CIN 3 lesions by Shimodaira-Taniguchi conization the status of the resection margin was a significant predictor for long-term outcome.

Keywords CIN 3 · Shimodaira-Taniguchi conization · Resection margin status · Outcome · Predictor

Abbreviations

AIS	Adenocarcinoma in situ
CIN	Cervical intraepithelial neoplasia
SCC	Squamous cell carcinoma
HSIL	High-grade squamous intraepithelial lesion
HPV	Human papillomavirus
LEEP	Loop electrosurgical excision procedure
LSIL	Low-grade squamous intraepithelial lesion
NILM	Negative for intraepithelial lesion or malignancy

Introduction

Cervical intraepithelial neoplasia (CIN), a non-invasive neoplastic lesion widely regarded as a precursor of squamous cell carcinoma (SCC) of the uterine cervix, has its highest incidence during women's reproductive years. Hysterectomy or radiation therapy is required to treat cases of invasive cervical SCC; however, conization, a fertility-conserving surgery, is often effectively substituted to treat the less dangerous CIN.

Y. Miyoshi and T. Miyatake contributed equally to this work.

Y. Miyoshi · Y. Ueda (✉) · A. Morimoto · T. Yokoyama · S. Matsuzaki · T. Kimura · K. Yoshino · M. Fujita · T. Enomoto · T. Kimura
Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan
e-mail: ZVF03563@nifty.ne.jp

T. Miyatake
Department of Gynecology, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1179-3, Higashinari-ku-Nakamichi, Osaka 537-8511, Japan

H. Ohashi · E. Morii
Department of Pathology, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan

Conization refers to a biopsy of the cervix in which a cone-shaped sample of tissue is removed from the uterine cervix, either for diagnostic reasons, or for therapeutic purposes to remove pre-cancerous cells. A recent study showed that conization and lymphadenectomy may be a potential treatment for small IB1 cervical cancer patients desiring conservative management [1]. Although fertility preserving, the procedure is not without risk; side effects of the treatment may include cervical stenosis and may increase the risk of incompetent cervix.

Our medical indications for performing conization are CIN 3, which includes carcinoma in situ (CIS), and severe dysplasia. According to a review of previous studies, CIN 3 is significantly more likely to persist, or to progress to SCC, than is a CIN 1 lesion; progression from CIN 3 to SCC occurs more than 15% of the time, whereas CIN 1 progresses to SCC only 1% of the time [2].

The standard conization device has evolved from the cold knife to the more conservative, and now widely accepted, 'loop electrosurgical excision procedure' (LEEP) device [3]. There is one study which showed that cold knife conization was less favorable in terms of the appearance of further CIN 3 and cancer risk [4]. However, there is yet another paper from the same period with a different finding; it suggests that conization modalities have a similar efficacy with respect to eliminating CIN and reducing further cancer risk [5]. However, LEEP is also not without its known drawbacks; the cervical tissue is removed as several divided specimens and is accompanied with thermal damage to the resected specimens, making pathological evaluation of the CIN lesions and their margin status difficult.

The Shimodaira-Taniguchi conization procedure was introduced in 1992; it addresses the disadvantages of LEEP by using a high-frequency current and a triangular probe with a 0.25-mm linear excision electrode to extract the tissue as a single informative specimen, without incurring accompanying thermal trauma [3, 6]. Matsumura et al. [3] have recently demonstrated the high utility and reliability of the Shimodaira-Taniguchi conization procedure. However, in comparison to our current study (which looks only at CIN 3 outcomes), their study included many cases of both more advanced microinvasive SCCs, and less advanced CIN 1, CIN 2, and adenocarcinoma in situ (AIS) lesions. In addition, the median follow-up period was not reported in their analysis. The long-term cumulative persistence/recurrence rate, the most important outcome measure of conservative treatment for any pre-malignant lesions, was demonstrated in their report; however, the rate was not compared by the status of their resection margin data, which has been demonstrated elsewhere to be of significant value for the prediction of the outcome of conization procedures for CIN 3 [7, 8]. In our present study, the long-term outcome of CIN 3 treated by Shimodaira-Taniguchi conization in our facility was re-analyzed by the status of their resection margins. The cutting probes for the Shimodaira-Taniguchi conization procedure are illustrated in Fig. 1.

Materials and methods

In the Department of Obstetrics and Gynecology of the Osaka University Hospital in Osaka, Japan, conization using the Shimodaira-Taniguchi procedure was routinely performed for CIN 3, and, in some rare cases, for more advanced microinvasive squamous cell carcinoma of the uterine cervix. Resected cervical tissue by conization was carefully divided into 12 specimens and the pathological diagnosis was made by pathologists in the Department of Pathology of the Osaka University Hospital.

During the 8-year period from 2001 to 2008, a post-conization diagnosis of CIN 3 was made in 243 patients. Medical records, including pathology reports of these patients, were retrospectively analyzed. Patients were routinely followed by cervical cytology conducted every 1–3 months in the first year after conization, every 6 months in the second year, and then annually thereafter. Patients who were consistently 'negative for intraepithelial lesion or malignancy' (NILM) were followed in this manner. However, whenever a case displayed a positive cytological test, a colposcopic observation was performed to biopsy the suspicious lesions for CIN.

For any case that presented with an abnormal cytology anytime within the first 3 months after conization, in which a CIN lesion was confirmed at that time by biopsy under colposcope, the lesion was regarded as a 'persistence' of the earlier CIN, regardless of whether the initial conization

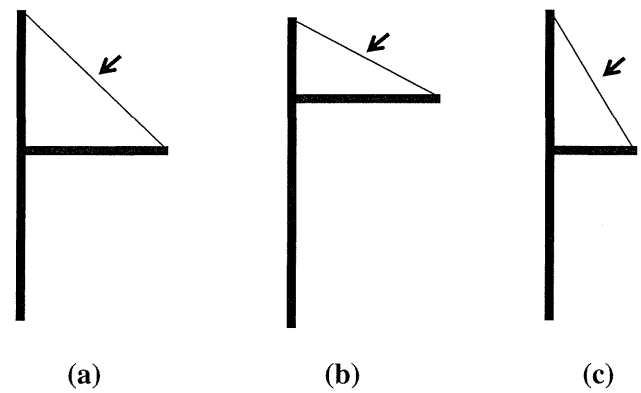

Fig. 1 The cutting probes for the Shimodaira-Taniguchi conization procedure. **a** A triangular probe which has the same base length and height. **b** A triangular probe which has shorter height than base length. **c** A triangular probe which has longer height than base length. *Arrow* excision electrode

pathology report had noted a negative or positive resection margin. For any case in which the first cytology report within the first 3 months after conization was negative, and for which (only at some later time point outside of 3 months) a CIN lesion was later detected by biopsy under colposcope, the case was regarded as a 'recurrence' of CIN. The time to diagnosis of persistent/recurrent disease was calculated from the date of the conization procedure to the day on which the colposcopic biopsy was taken for the CIN diagnosis.

Statistical analysis

MedCalc (MedCalc Software, Mariakerke, Belgium) was used for the statistical analysis. Recurrence-free probability (survival) curves were constructed using the Kaplan–Meier method and evaluated for statistical significance by the log-rank test. Association of the rate of persistence/recurrence of CIN lesions and the status of resection margins was analyzed by Fisher's exact test. Results were considered to be significant when the p value was <0.05.

Results

Clinical characteristics of patients whose post-conization diagnosis was CIN 3

During the study period, a post-conization diagnosis of CIN 3 was made in 243 patients (Table 1). Among them, 132 patients (54%) were pathologically diagnosed as having carcinoma in situ (CIS) and the other 111 patients (46%) were cases of severe dysplasia. The median age of these patients was 37 (21–74) years. A positive resection margin was detected in 45/243 cases (19%); the remaining 198 patients (81%) had a promising negative margin. All the patients were followed after conization by periodic cervical cytology. During the median follow-up period of 565 days (34–3,013), a persistent or recurrent CIN disease was subsequently detected in 14 patients (5.8%); 7 patients had been diagnosed as margin positive and the other 7 had been margin negative (Table 2). The median time to diagnosis of the persistent/recurrent CIN lesions was 316 days (64–2,465). None of these characteristics of the post-conization diagnosis was different between those with CIS versus those with severe dysplasia (data not shown).

Table 1 Clinical characteristics of patients whose post-conization diagnosis was CIN 3

Clinical characteristics	
Total number (cases)	243
Age (years)	21–74 (median 37)
Post-conization diagnosis (cases)	
CIS	132 (54%)
Severe dysplasia	111 (46%)
Status of resection margin (cases)	
Negative	198 (81%)
Positive	45 (19%)

Persistent/recurrent cases after conization

The persistent/recurrent cases are shown in Table 3. Among the 198 patients whose resection margin had been negative, persistence/recurrence was detected in 7 patients: cases 1, 2, 3, 4, 6, 7, and 8 (3.5%) (Tables 2, 3). Pathological diagnosis of the persistent/recurrent lesion was CIN 1 in three cases (cases 2, 6, 7), CIN 2 in one case (case 3), and CIN 3 in three cases (cases 1, 4, 8). Among these margin-negative cases, the first cytology exhibited normal appearance (NILM) and the CIN lesions were detected beyond the initial 3 months of observation (after 299–2,465 days from conization) in three cases (cases 6, 7, 8). These cases were regarded to be recurrences.

In the other four margin-negative cases (cases 1, 2, 3, 4), a low-grade squamous intraepithelial lesion (LSIL) or a high-grade squamous intraepithelial lesion (HSIL) was detected by the first cytology after conization (within the first 3 months), and CIN 1, CIN 2, or CIN 3 was pathologically diagnosed by colposcopic biopsy. These cases were regarded as persistent lesions.

Among the 45 patients whose resection margin had been positive, persistence/recurrence was detected in 7 patients (cases 5, 9, 10, 11, 12, 13, 14) (16%) (Tables 2, 3). The rate of persistence/recurrence was significantly higher in margin-positive cases than in margin-negative ones (3.5 vs. 16%; $p = 0.0018$ by Fisher's exact test) (Table 2). In a

Table 2 Follow-up data of patients whose post-conization diagnosis was CIN 3

Follow-up data		p value
Observation period after conization (days)	34–3,013 (median 565)	–
Persistent/recurrent disease after conization (cases)	14 (5.8%)	0.0018*
Negative margin	7 (3.5%)	
Positive margin	7 (16%)	
Time to diagnosis of persistence/recurrence after conization (days)	64–2,465 (median 316)	–

Time to diagnosis of persistent/recurrent disease was calculated from the date of conization to the day on which CIN was diagnosed by colposcopic biopsy

* The difference in the rates of persistence/recurrence between margin-negative and margin-positive cases was statistically significant ($p = 0.0018$ by Fisher's exact test)

Table 3 Persistent/recurrent cases after conization

Case	Age (years)	Margin status	First cytology after conization	Time to diagnosis of persistence/recurrence (days)	Persistent/recurrent disease diagnosis	Treatment for the persistent/recurrent disease
Persistence						
1	23	−	HSIL	64	CIN 3 (polyp)	Polypectomy
2	57	−	LSIL	93	CIN 1	Observation
3	28	−	LSIL	131	CIN 2	Laser vaporization
4	31	−	HSIL	175	CIN 3	Laser vaporization
5	70	+	HSIL	82	CIN 3	Hysterectomy
Recurrence						
6	37	−	NILM	299	CIN 1	Observation
7	50	−	NILM	821	CIN 1	Observation
8	37	−	NILM	2,465	CIN 3	Re-conization
9	47	+	NILM	252	CIN 2	Re-conization
10	43	+	NILM	333	CIN 3	Unknown[a]
11	36	+	NILM	740	CIN 1	Observation
12	57	+	NILM	1,047	CIN 3	Re-conization
13	34	+	NILM	1,272	CIN 1	Observation
14	35	+	NILM	1,825	CIN 3	Re-conization

Among the cases in which CIN lesion was detected after conization, margin-positive cases with an abnormal first cytology (within 3 months after conization) were regarded as cases of persistence of CIN. Cases of negative first cytology were regarded as recurrence of CIN. Time to diagnosis of persistent/recurrent disease was calculated from the date of conization to the day on which CIN was diagnosed by colposcopic biopsy

NILM negative for intraepithelial lesion or malignancy, *LSIL* low-grade squamous intraepithelial lesion, *HSIL* high-grade squamous intraepithelial lesion

−, Negative resection margin; +, Positive resection margin

[a] The treatment and final outcome for one recurrent CIN 3 case (case 10) was unknown, because the patient moved to another hospital after the diagnosis of recurrence

single case of CIN 3 whose resection margin had been positive (case 5), the result of the first cytological test of the uterine cervix performed in the second month after conization was HSIL (high-grade squamous intraepithelial lesion). The pathological result of a colposcopic biopsy performed 1 month later, in the third month, indicated the lesion was CIN 3; the patient elected to undergo a prophylactic hysterectomy at that time. This case was regarded to be persistent.

In the other six margin-positive patients, the results of the first cytological test were negative (NILM). CIN lesions were first detected after 252–1,825 days from conization. These cases were regarded to be recurrent and not persistent ones.

Long-term outcome of the CIN 3 cases

The long-term outcome of CIN cases treated by Shimodaira-Taniguchi conization was analyzed for persistence/recurrence-free probability, which was found to be significantly higher in margin-negative cases than in margin-positive ones ($p = 0.007$ by log-rank test). The five cases of persistent CIN 3 were set aside from further analysis. Only the nine recurrent cases, whose initial treatment had been successful by the Shimodaira-Taniguchi procedure, as characterized by being negative upon the first cytology follow-up within the first 3 months after conization, and margin-positive cases, which were negative at the first cytology follow-up, were retained. Recurrence-free probability in these cases was significantly higher in the margin-negative cases than in the margin-positive ones (hazard ratio 5.19; 95% CI, 1.175–22.994; $p = 0.0041$ by log-rank test) (Fig. 2).

Discussion

Currently, conization is the standard option for treatment of CIN 3, a precursor of SCC of the uterine cervix. LEEP has largely replaced the cold knife procedure because it overcomes several of the former's drawbacks (including significant blood loss, longer operation times, and a higher rate of post-operative hemorrhage). Both cold knife conization and LEEP have a similar margin-positive rate [9]. Although a high margin cure rate is achieved by LEEP

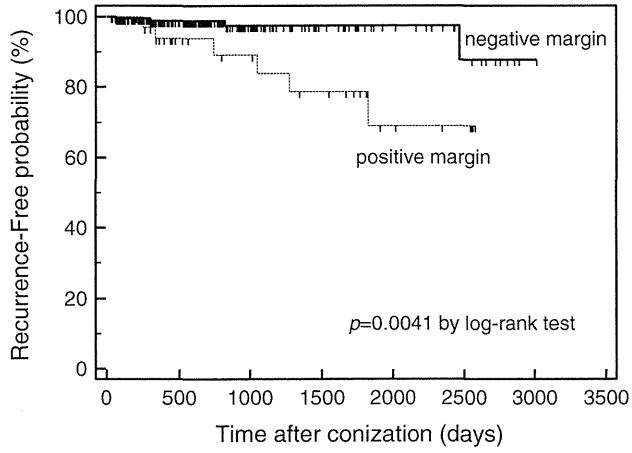

Fig. 2 Long-term outcome of the recurrent cases after conization for CIN 3 by resection margin. Recurrence-free probability was significantly higher in margin-negative cases than in margin-positive ones (hazard ratio 5.19; 95% CI, 1.175–22.994; $p = 0.0041$ by log-rank test)

conization, significant thermal damage is usually observed in the resected tissues [3]. The cervical tissue is also resected into several separated specimens during the LEEP, resulting in later difficulties in determining the critical margin status of the specimens, and the corresponding cervical location of any remaining lesions detected at the margin.

The Shimodaira-Taniguchi conization procedure addresses the disadvantages of LEEP by using a high-frequency current and a triangular probe with a 0.25-mm linear excision electrode to extract the cone of tissue as a single informative specimen, and does so without incurring any undue thermal trauma [3]. Matsumura et al. have demonstrated the benefits of the procedure: the number of the excised specimens was only one per patient in 79% of the case they studied (358 of 455 cases); the mean operation time was 11 min; and the average blood loss was only 9.9 ml.

Matsumura et al. found that persistent disease was observed in 2 (0.7%) of 268 CIN patients soon after the procedure, and, after 6–20 months post-conization, recurrence was detected in only slightly higher numbers (3/268; 1.1%). They also found recurrences within 16–30 months in 4.8% (3/62) of the more advanced microinvasive SCC cases treated with the Shimodaira-Taniguchi conization procedure. Among these six recurrent cases, four cases had been margin positive and the other two were margin negative.

There is one published study which did not find any significant value for using resection margin status in the prediction of long-term outcome of CIN 2 and CIN 3 after conization; that study was done using a CO_2 laser or cold knife [10]. However, others have found that the resection margin of CIN lesions produced by LEEP, cold knife, or laser was demonstrated to be able to aid in predicting the subsequent recurrence of CIN 3 [7, 8]. According to Chen et al., the persistence/recurrence rate of margin-positive cases, 33% (47/141 cases), was significantly higher than that of the margin-negative cases, 2% (21/972 cases) ($p < 0.0001$ by Fisher's exact test).

In our present study, the long-term outcome of CIN 3 cases treated by the Shimodaira-Taniguchi conization procedure was retrospectively analyzed relative to the status of their resection margins. The margin-positive rate for all CIN 3 cases was 19% (45 of 243 cases), and the rate for persistence/recurrence was 5.8% (14 of 243 cases). Our 19% margin-positive rate was lower than the 39% found in the previous study [3], and our 5.8% persistence/recurrence rate was higher than their 1.8%. Although the outcome results in our study were not different between the cases of CIS versus severe dysplasia (defined by the post-conization diagnosis), a previous study had shown that the persistent/recurrent rate was higher in CIS cases than in severe dysplasia cases ($p = 0.007$). The reasons for these discrepancies are currently unclear.

We found, as might be expected, that the probability of being persistence/recurrence-free was significantly higher in the margin-negative cases than in margin-positive ones ($p = 0.007$ by log-rank test), and this result was quite consistent with that of a previous study [7]. When we looked only at CIN cases which had passed their first test for being cured (those that had a normal cervical cytology at some point during the initial 3-month follow-up, regardless of whether they were judged margin negative or margin positive), we again found that the recurrence-free probability was significantly lower in margin-positive cases than in margin-negative cases (hazard ratio 5.19; 95% CI, 1.175–22.994; $p = 0.0041$ by log-rank test). Moreover, these recurrences occurred relatively long after the initial conization (252–1,825 days; median: 894 days).

The late arising lesions, those that were not detected at 'first cytology', possibly indicate very slow growth of a very small number of dysplastic or predisposed cells, which were not detectable by a normal pathological investigation. HPV may be more likely, for some unknown reason, to persist and/or cause progression in the cervix of margin-positive cases, perhaps because of the specific microenvironment of the positive margin; however high-risk type of HPV infections associated with CIN was previously demonstrated to clear gradually after successful conization in most patients showing clear resection margins [11]. The discrepancy of finding persistence of the CIN lesions after receiving a margin-negative status was, in part we feel, due to the presence of minute CIN lesions which had not been detected at the time of conization, or 'skip lesions' that were not detected at the surgical margins even by dividing the specimens of resected cervical tissue into 12 pieces for individual examination.

In our present study, we have re-evaluated the long-term outcome of CIN lesions after treatment with the Shimodaira-Taniguchi conization procedure routinely used in our facility to see if we could gain insight into predicting recurrence of the lesions. A recent study showed unexpected tumor progression after conization for CIS [12]. We found that the positive/negative status of the resection margin was a significant predictor for long-term outcome. Specifically, it was demonstrated that recurrence occurred at a significantly higher rate in margin-positive cases than in margin-negative cases whose post-conization cytology was normal. Further study is still needed to clarify the mechanism of the relatively late recurrences noted in margin-positive cases after Shimodaira-Taniguchi conization.

Acknowledgments We would like to thank Dr. G.S. Buzard for his constructive critique and editing of our manuscript.

Conflict of interest The authors state that there are no conflicts of interest. The authors also declare (1) that the article has not been published elsewhere; (2) it is not being considered for publication elsewhere; and (3) that it has been submitted with the full knowledge and approval of the institution or organization given as the affiliation of the authors.

References

1. Maneo A, Sideri M, Scambia G, Boveri S, Dell'anna T, Villa M, Parma G, Fagotti A, Fanfani F, Landoni F (2011) Simple conization and lymphadenectomy for the conservative treatment of stage IB1 cervical cancer. An Italian experience. Gynecol Oncol. (Epub ahead of print)
2. DiSaia PJ, Creasman WT (2002) Clinical gynecologic oncology, 6th edn. Mosby, St. Louis, pp 1–33
3. Matsumura M, Ota T, Takeshima N, Takizawa K (2010) Shimodaira-Taniguchi conization method: its utility and reliability. Int J Gynecol Cancer 20:1025–1030
4. Kalliala I, Nieminen P, Dyba T, Pukkala E, Anttila A (2007) Cancer free survival after CIN treatment: comparisons of treatment methods and histology. Gynecol Oncol 105:228–233
5. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D, 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference (2007) 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. Am J Obstet Gynecol 197:346–355
6. Taniguchi S (1992) Treatment of CIN by high frequency electric radical conization. Sanfujinka Tiryo 6:889–897 (in Japanese)
7. Bertelsen B, Tande T, Sandvei R, Hartveit F (1999) Laser conization of cervical intraepithelial neoplasia grade 3: free resection margins indicative of lesion-free survival. Acta Obstet Gynecol Scand 78:54–59
8. Chen Y, Lu H, Wan X, Lv W, Xie X (2009) Factors associated with margin-positives in patients with cervical intraepithelial neoplasia grade 3 and postconization management. Int J Gynaecol Obstet 107:107–110
9. Jakus S, Edmonds P, Dunton C, King SA (2000) Margin status and excision of cervical intraepithelial neoplasia: a review. Obstet Gynecol Surv 55:520–527
10. Ørbo A, Arnesen T, Arnes M, Straume B (2004) Resection margins in conization as prognostic marker for relapse in high-grade dysplasia of the uterine cervix in northern Norway: a retrospective long-term follow-up material. Gynecol Oncol 93:479–483
11. Kim YT, Lee JM, Hur SY, Cho CH, Kim YT, Kim SC, Kang SB (2010) Clearance of human papillomavirus infection after successful conization in patients with cervical intraepithelial neoplasia. Int J Cancer 126:1903–1909
12. Omatsu K, Takeshima N, Matoda M, Nomura H, Umayahara K, Sugiyama Y, Utsugi K, Tanaka H, Akiyama F, Takizawa K (2011) Unexpected tumor progression after conization for carcinoma in situ of the uterine cervix. J Obstet Gynaecol Res. doi: 10.1111/j.1447-0756.2011.01632.x (Epub ahead of print)

THE JOURNAL OF
Obstetrics and Gynaecology Research

The official Journal of Asia and Oceania Federation of Obstetrics and Gynaecology
Japan Society of Obstetrics and Gynecology

doi:10.1111/j.1447-0756.2012.01849.x J. Obstet. Gynaecol. Res. Vol. 38, No. 9: 1194–1200, September 2012

Total laparoscopic hysterectomy in 1253 patients using an early ureteral identification technique

Eiji Kobayashi, Toko Nagase, Kazuko Fujiwara, Tomonori Hada, Yoshiaki Ota, Yoshihiro Takaki, Hiroyuki Kanao and Masaaki Andou

Department of Obstetrics and Gynecology, Kurashiki Medical Center, Kurashiki, Japan

Abstract

Aim: The aim of this study was to determine the incidence of perioperative complications and evaluate risk factors for the major complications of total laparoscopic hysterectomy (TLH) using an early ureteral identification technique. We describe the technique we standardized and used for TLH, without exclusion criteria.

Material and Methods: A retrospective study was carried out at Kurashiki Medical Center, Japan, based on 1253 TLH procedures performed from January 2005 to March 2009. We reviewed records to identify the major perioperative complications, including bladder, ureteral, and intestinal injuries, and incidences of reoperation. Risk factors for major complications were analyzed using multivariate logistic regression models.

Results: A total of 24 patients encountered major complications (1.91%). Complications included 10 intraoperative urologic injuries, five cases of postoperative hydronephrosis, five cases of vaginal dehiscence, one bowel injury, one postoperative hemorrhage, one bowel obstruction, and one ureterovaginal fistula. All 11 cases of intraoperative visceral injury were recognized during the surgery and repaired during the same laparoscopic surgical procedure. Of the risk factors analyzed, a history of abdominal surgery was the only one associated with the occurrence of major complications, with an odds ratio of 2.48 (95% confidence interval 1.23–6.49).

Conclusion: While complications are inevitable, even in the hands of the most skilled surgeon, they can be minimized without conversion to laparotomy by a sufficiently developed suturing technique and a precise knowledge of pelvic anatomy. The presented data indicate that our method allows for safe TLH and minimization of ureteral injury, without the use of stringent exclusion criteria.

Key words: complication, no exclusion criteria, total laparoscopic hysterectomy, ureteral identification, ureterolysis.

Introduction

The first laparoscopic hysterectomy was reported by Reich *et al.* in 1989.[1] This procedure is currently indicated as an alternative to conventional laparotomy in cases where vaginal approach is difficult because of an immobile uterus or poor vaginal accessibility.[2] Its value has been questioned by those who cite a high complication rate and suggest that the procedure has a steep learning curve.[3,4] Proponents of the procedure, however, have gained sufficient experience that this is currently their preferred technique for hysterectomy.[5,6] A meta-analysis of 27 randomized trials indicated that the advantages of laparoscopic gynecologic surgery over abdominal include: decreased pain, fewer surgical site infections, shorter hospital stay, quicker return to activity, and a lower incidence of postoperative adhesions.[7] Although the complications of TLH have been described several times, many of these studies were limited to TLH for specific indications.

Received: June 3 2011.
Accepted: December 18 2011.
Reprint request to: Dr Eiji Kobayashi, Department of Obstetrics and Gynecology, Kurashiki Medical Center, 250 Bakuro-cho, Kurashiki, Okayama 710-8522, Japan. Email: ekobayashi@gyne.med.osaka-u.ac.jp

The aim of this study was to determine the incidence of perioperative complications and the risk factors for major complications when the standardized technique is applied in the absence of any patient exclusion criteria on the basis of substantial experience.

Methods

A retrospective analysis of all patients who underwent total laparoscopic hysterectomy (the American Association of Gynecologic Laparoscopists [AAGL] Classification IVe)[8] at Kurashiki Medical Center from 1 January 2005 to 1 April 2009 was conducted. Subjects undergoing concomitant lymph node dissection for malignant disease and rectal resection for intestinal endometriosis were not included in this study. All patients provided written informed consent before inclusion of their data in the study.

Complications were classified as major (reoperation and bladder, ureteral, and intestinal injuries) and minor (all other complications). Intraoperative and postoperative complications were included. All patients were reviewed 4 weeks after surgery, and underwent ultrasonography to exclude postoperative silent hydronephrosis on postoperative day 3, and 4 weeks after the surgery.

All laparoscopic hysterectomies were performed by the same team, consisting of two experienced surgeons (M.A., H.K.), both of whom had considerable experience with advanced laparoscopic procedures. Notably, patients with endometriosis, pelvic inflammatory disorders, previous abdominal or pelvic surgery, obesity, or very large uteri were not excluded. No upper limit for uterine size was set. Operating time was defined as the duration from incision to wound closure.

This study was approved by the Institutional Review Board at the Kurashiki Medical Center.

Statistical analysis

Complication rates were calculated and the means of the two populations with and without complications were compared using the *t*-test for continuous variables, and the χ^2-test for categorical variables. Variables with a *P*-value of <0.05 by univariate analysis and those that had been previously reported as risk factors for operative complications were further analyzed using multivariate analysis. All the analyses were performed with STATA software (Version 11.1). Statistically significant differences were defined as those with a *P*-value of <0.05. Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

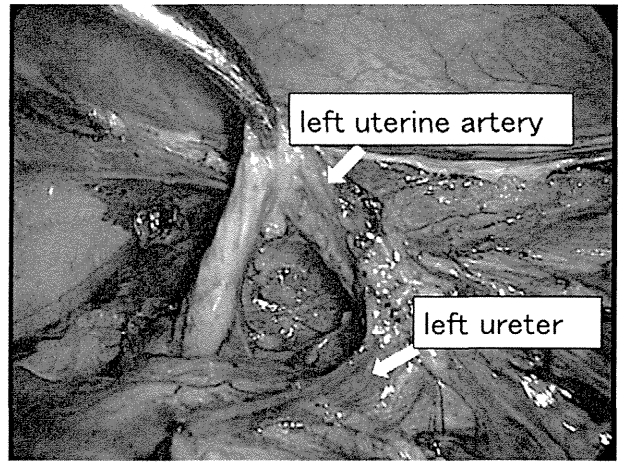

Figure 1 Early identification and isolation of the ureter and uterine artery. Arrow indicates left ureter and uterine artery.

Techniques

All laparoscopic procedures were performed under general anesthesia in the dorsal lithotomy position. A transvaginally inserted uterine manipulator was used to help maneuver the uterus during the surgery. We used the following eight-step laparoscopic technique (please refer to the supplementary video). (i) A 12-mm port is inserted through a transumbilical incision for placement of the operative laparoscope. Three ancillary ports are positioned, one in each lower quadrant and one suprapubic. We routinely used the suction irrigator probe with a built-in integrated monopolar electrode (ENDOPATH Probe Plus II). (ii) The uterovesical peritoneum is opened from the cervix to the round ligament. In order to prevent ureteral injury, the course of the ureter is usually exposed until the entrance of the ureteral tunnel at the beginning of the surgery (Fig. 1), before dissecting the upper uterine pedicles. If it is difficult to identify the ureter due to cervical myoma or some another reason, the upper uterine pedicles are dissected first. After identifying and isolating the ureter and uterine artery, which is adherent to the retroperitoneum, the uterine artery is ligated at its origin three times with 2-0 Vicryl to reduce the blood flow into the uterus. The uterine artery is then cut between the inner sides of the ligatures. If this approach proves unfruitful, we proceed to locate the umbilical ligament in the retroperitoneal space near the abdominal wall. After exposing the umbilical ligament, we search for the uterine artery caudally along it. (iii) If the adnexa are preserved, the round ligament, utero-ovarian

Journal of Obstetrics and Gynaecology Research © 2012 Japan Society of Obstetrics and Gynecology

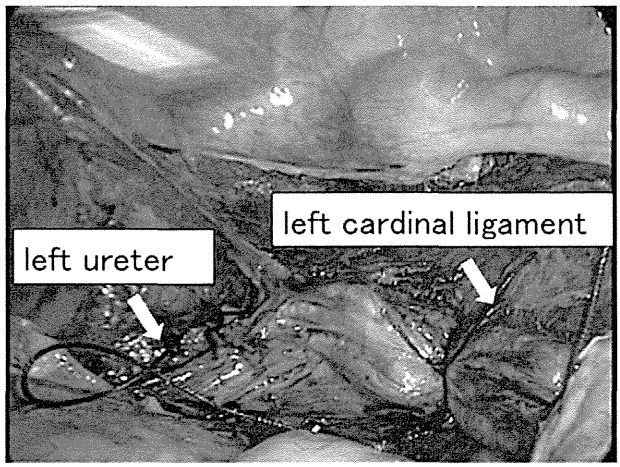

Figure 2 Suturing the cardinal ligament.

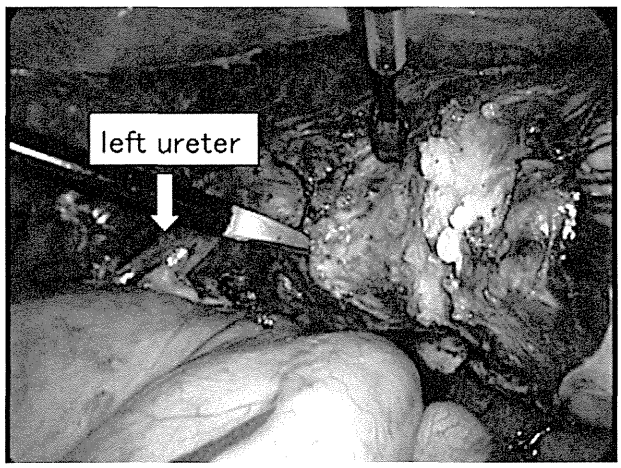

Figure 3 Desiccation and cutting of the cardinal ligament.

ligament, and fallopian tube are desiccated and cut, and the posterior leaf of the broad ligament is opened toward the uterosacral ligament to expose the cardinal ligament. (iv) The cardinal ligament is ligated twice above the ureter with 2-0 Vicryl (Fig. 2). This ligation serves two purposes: to reduce the blood flow from vagina and ovarian vein and to act as a landmark that is separate from the ureter and thus enables better anatomical orientation. It is then desiccated and cut between the ligatures (Fig. 3). (v) The uterine manipulator is removed, and a vaginal fornix delineator inserted (Vagi Pipe). When the outline of the vaginal fornix is visible, the circumference of the vaginal wall is cut until the cervix is separated. The vagina is cut using an integrated monopolar electrode (pure cutting current, 40–60 Watts). Bleeding from the vaginal cuff is treated by monopolar (coagulation, 40 Watts) or a bipolar electrosurgical knife (35 Watts). (vi) Vaginal retrieval of the uterus: If the uterus is very large, transvaginal morcellation is performed. In case the uterus is too large to perform transvaginal morcellation, the specimen is morcellated via the median port site using a long scalpel, before vaginal retrieval. (vii) After the uterus is delivered, the vaginal vault is closed laparoscopically by intracorporeal suturing with 0-Vicryl. To be precise, both sides of the vaginal cuff are sutured with Z-plasty and continuous sutures are used on the inside. (viii) The trocar insertion site is closed.

Table 1 Characteristics of all the patients (n = 1253)

Characteristics	n (%) or Mean (standard deviation)
Mean body mass index (kg/m^2)	23.0 ± 3.35
Mean age	46.3 ± 6.64
Nulliparous	187 (15.0)
No vaginal delivery	242 (19.3)
Parity (median)	2 (0–5)
History of abdominal surgery	316 (27.0)
History of cesarean	91 (7.0)

Results

Data from 1253 patients were included in the study. During this period, 92 total abdominal hysterectomies (TAH) and 336 cases of vaginal hysterectomies were performed. Patient characteristics are detailed in Table 1. The mean body mass index (BMI) was 23.0 kg/m^2 and the mean age was 46.3 years. A total of 187 (15%) women were nulliparous and 242 (19.3%) women did not have vaginal birth. Median parity was 2 (0–5). A total 316 patients (27%) had at least one previous abdominal operation documented in their medical history (including laparoscopic gynecologic surgery and appendectomy, but excluding laparoscopic cholecystectomy); 91 (7%) patients had a history of cesarean section.

The indications for TLH were leiomyoma and adenomyosis (79.8%), ovarian tumor (10.1%), cervical neoplasia (4.0%), endometrial neoplasia (3.7%), and uterine prolapse (0.7%). The mean operating time was 88 min (37–364 min). The mean blood loss was 181 mL (0–2140 mL). The mean uterine weight was 416 g (40–2970 g) with 28% of the uteri weighing over 500 g, and 5% weighing over 1000 g. Conversion to laparotomy occurred in one patient, owing to obesity, which

hindered maintenance of the surgical field and the presence of adenomyosis and pelvic endometriosis rendered the uterus completely immobile. Transfusion was necessary in one patient. Overall, 24 severe perioperative complications are summarized in Table 2, accounting for 1.91% of total operations. There were 11 urologic injuries, six to the bladder, four to the ureter, and one ureterovaginal fistula. There were five incidences of vaginal dehiscence, one bowel injury, one bowel obstruction, and one case of postoperative hemorrhage. There were five cases of postoperative hydronephrosis that necessitated reoperation. All 11 cases (six vesical, four ureteric, one to the bowel) of visceral injury were recognized intraoperatively and repaired laparoscopically during the same surgical procedure. Each ureteral injury was at a different site, with one at the infundibulopelvic ligament, one at the cardinal ligament, one at the utero-ovarian ligament, and one near the vesicoureteral junction. The first case was managed by end-to-end anastomosis and the other three were managed by ureteroneocystostomy.[9] The reason we selected ureteroneocystostomy in these cases, was that the severity of the widespread thermal damage prevented the generation of adequate tension by end-to-end anastomosis.

The ureterovaginal fistula occurred on postoperative day 12, and was treated conservatively by inserting a ureteral stent. The five cases of vaginal dehiscence occurred on postoperative days 18, 40, 47, 96, and 103. All cases were repaired transvaginally with no sequelae. Postoperative hydronephrosis necessitating reoperation was repaired by ureteroneocystostomy in three cases (two of these laparoscopic), and perirureteral adhesiolysis in two cases (one laparoscopic). One bowel injury occurred during the adhesiolysis procedure. The patient had previously undergone two surgical procedures and we recognized cauterization-induced injury. We dissected the damaged small intestine and performed laparoscopic functional end-to-end anastomosis.

Preoperative patient parameters and the occurrence of major complications are reported in Table 3. There was no association between the incidence of complications and age, BMI, parity, previous vaginal birth, previous cesarean section, or uterine weight. However, a statistically significant association was found between the incidence of major complications and a history of abdominal surgery, which was confirmed by multivariate analysis in Table 4.

Table 2 Postoperative severe complications ($n = 24$)

Complication	No. patients
Bladder injury	6
Vaginal dehiscence	5
Postoperative hydronephrosis	5
Ureteral injury	4
Bowel injury	1
Postoperative hemorrhage	1
Bowel obstruction	1
Vesicoureteral fistula	1

Discussion

Although hysterectomy is a common gynecologic operation, the level of expertise required for laparos-

Table 3 Characteristics of the participants by complications after laparoscopic hysterectomy

Characteristics	Patients without major complications ($n = 1229$) n (%) or Mean (SD)	Patients with major complications ($n = 24$) n (%) or Mean (SD)	P-value
Age	46.4 (6.67)	45.1 (5.01)	NS
Body mass index (kg/m^2)	23.0 (3.35)	22.0 (3.62)	NS
Weight (g)			
<500	868 (70.6)	15 (62.5)	NS
≧500	361 (29.4)	9 (37.5)	NS
Parity	1048 (85.3)	18 (75.0)	NS
Non-parity	181 (14.7)	6 (25.0)	NS
Vaginal delivery	996 (81.0)	17 (70.8)	NS
Non-vaginal	233 (19.0)	7 (29.2)	NS
Prior cesarean	88 (7.2)	3 (12.5)	NS
No prior cesarean	1141 (92.8)	21 (87.5)	NS
Prior abdominal surgery	305 (24.8)	11 (45.8)	0.019*
No prior abdominal surgery	924 (75.2)	13 (54.2)	NS

NS, not statistically significant; SD, standard deviation.

Table 4 Multivariate logistic regression of the complications of laparoscopic hysterectomy

Variables	OR	(95%CI)
Age	0.98	(0.91–1.05)
Body mass index (kg/m^2)	0.89	(0.78–1.03)
Weight (g)		
<500	1.00	
≧500	1.58	(0.67–3.70)
Previous vaginal delivery	0.86	(0.33–2.22)
Prior abdominal surgery	2.66	(1.14–6.22)

CI, confidence interval; OR, odds ratio.

copy suggests that most hysterectomies are still performed by laparotomy. However, technical advances and consumer demand have led to a steadily increasing rate of laparoscopic hysterectomy in recent years. In Japan, 11.2% of hysterectomies in 2004 and 16.5% in 2008 were performed by laparoscopy.[10,11]

Laparoscopic hysterectomy requires greater surgical expertise and takes longer to master compared to abdominal or vaginal hysterectomies. Laparoscopic hysterectomy has also been associated with a longer operating time and a higher incidence of operative complications than either abdominal or vaginal hysterectomy.[12,13] In our institute, the major complication rates in benign cases during TAH and vaginal hysterectomy were 0% and 1.2%, respectively. Laparoscopy does not allow a 3-D perception, and the inevitable blind spot in the laparoscopic view limits visualization of beyond or lateral to the target organ. This lack of depth perception may cause misjudgments in estimating in the direction and position of the forceps, and the surgeon is obliged to watch carefully for visceral injury. To prevent operative complications during TLH, it is critical to recognize the situations that pose a high risk for complications. There have been several reports of factors associated with laparoscopic complications, with each study reporting different results. Bonnila *et al.* and Ficaventto reported an association between uterine weight and operative complications, with a uterine weight over 500 g being associated with more complications.[14,15] O'Hanlan *et al.* reported association between a lower BMI and operative complications.[16] In contrast, Chopin *et al.* reported that perioperative complications do not increase in cases with obesity, provided that operating technique is meticulous.[17] Pillet *et al.* reported that previous cesarean section or laparotomy led to a higher incidence of bladder injury.[18] In our study, multivariate analysis revealed previous abdominal surgery as a risk factor for major complications. We did not find any other patient variables that affected the outcome. Although we do not consider that previous abdominal surgery is one of the exclusion criteria, it will depend on the surgeon's skill whether to convert to laparotomy or not in the presence of severe intraperitoneal adhesion due to previous abdominal surgery.

The most common major complication in our study was urinary tract injury. Johnson *et al.* reported a significant increase in ureteral injuries in laparoscopies compared with laparotomy (OR, 2.61; 95%CI, 1.22–5.60).[19] Our study demonstrated an intraoperative urinary tract injury incidence of 0.31%, which is comparable to that previously reported in abdominal (0.03–2.0%) and vaginal (0.02–0.5%) hysterectomy.[20–22] Indeed, in our institute, intraoperative urinary tract injury rates during TAH and vaginal hysterectomy were 3.3% and 0%, respectively. However, the two procedures cannot be directly compared because each has different indications. The indications for TAH were ovarian malignancy or suspicion of ovarian malignancy (61.9%), leiomyoma (18.5%), uterine malignancy (16.3%) and others (3.3%). The indications for vaginal hysterectomy were prolapse (54.5%), leiomyoma and adenomyosis (30.3%), uterine malignancy and cervical intraepithelial neoplasia (15.1%) and others (0.4%). We believe that certain modifications of the technique, that we implemented, contributed to the low rate. Although most authors do not expose the ureter routinely,[16–19] we routinely expose the course of ureter and dissect the ureter from the uterine artery early in the course of surgery, which allows us two advantages. First, early exposure of the ureter enables us to manage any unexpected hemorrhage near the ureter or uterine artery more precisely and safely, minimizing the risk of ureteral injury. Second, routine exposure of the ureter gives us the opportunity to become more closely acquainted with periureteric anatomy. Using this as a routine method would be especially useful in advanced surgery, especially in gynecologic oncology and severe endometriosis. Routine ureteral dissection is often not practiced because of the increased risk of intraoperative bleeding and devascularization of the ureter,[23] which could in turn cause ischemia and necrosis of the ureter at a later stage. While we allow that the exposure of the ureter may be unnecessary in the uncomplicated case, we believe that early ureteral exposure was an important contributor to the low incidence of urinary complications that we achieved, and that the previously reported risk of ureteral complications associated with

ureteral dissection could be a result of inadequate surgical technique without recognition of the avascular retroperitoneal space, namely Latzko's and Okabayashi's pararectal space. Another concern about routine ureteral dissection is retroperitoneal fibrosis. We cannot deny the possibility of retroperitoneal fibrosis after routine ureteral dissection. We experienced postoperative hydronephrosis which necessitated adhesiolysis in two cases (0.15%). Even if these two cases were due to retroperitoneal fibrosis, the incidence is minimal. We consider that if we did not expose the ureter the chance of ureteral injury would be higher.

Even with the best efforts to minimize complications, as TLH is extended to a wider range of indications, their chances increase. Thus, knowledge and evaluation of strategies for their management is also critical. Among our cases, 11 sustained intraoperative visceral injury. All of these (six vesical, four ureteric, one to the bowel) were repaired laparoscopically without any sequelae. These results, obtained by experts in centers with considerable experience, may not represent the general situation. We believe laparoscopic repair is feasible if the surgeon has an adequate suturing technique and precise knowledge of pelvic anatomy.

To the best of our knowledge, the current study is the largest reported series of TLH using a routine early ureteral identification technique that is not restricted to certain indications.

Our data showed that complications in laparoscopic hysterectomy can be minimized with training, experience, and meticulous technique, even when extended to patients who possess risk factors that have been reported to be associated with complications.

In conclusion, we describe a TLH technique that, when diligently applied by an experienced surgeon, results in a lower complication rate than previously reported. We therefore believe that practicing laparoscopic skills, which lead to experience with laparoscopic suturing techniques as well as a better understanding of surgical anatomy, should be encouraged.

Disclosure

There is no conflict of interest.

References

1. Reich H, Decaprio J, McGlynn F. Laparoscopic hysterectomy. *J Gynecol Surg* 1989; **5**: 213–216.
2. Chapron C, Dubuisson JB, Ansquer Y, Gregorakis SS, Morice P, Zerbib M. Bladder injuries during total laparoscopic hysterectomy: Diagnosis, management, and prevention. *J Gynecol Surg* 1995; **11**: 95–98.
3. Richardson RE, Bournas N, Magos AL. Is laparoscopic hysterectomy a waste of time? *Lancet* 1995; **345**: 36–41.
4. Garry R, Hercz P. Initial experience with laparoscopic-assisted Doderlein hysterectomy. *Br J Obstet Gynaecol* 1995; **102**: 307–310.
5. O'Shea RT, Gordon SJ, Seman EI, Verco CJ. Total laparoscopic tube hysterectomy: A safer option? *Gynecol Endosc* 2000; **9**: 285–291.
6. O'Shea RT, Cook JR, Seman EI. Total laparoscopic hysterectomy: A new option for removal of the large myomatous uterus. *Aust N Z J Obstet Gynaecol* 2002; **42**: 282–284.
7. Johnson N, Barlow D, Lethaby A, Tavender E, Curr E, Garry R. Surgical approach to hysterectomy for benign gynaecological disease. *Cochrane Database Syst Rev* 2005; (1): CD003677.
8. Munro MG, Parker WH. A classification system for laparoscopic hysterectomy. *Obstet Gynecol* 1993; **82**: 624–629.
9. Andou M, Yoshioka T, Ikuma K. Laparoscopic ureteroneocystostomy. *Obstet Gynecol* 2003; **102** (5 Part 2):1183–1185.
10. Shiota M, Hoshiai H, Hiramatsu Y *et al.* Investigation of the rate of laparoscopic surgery. *Gynecol Obstet Surg* 2005; **16**: 114–118. (In Japanese.)
11. Shiota M, Hiramatsu Y, Mitsuhashi N *et al.* Investigation of the rate of laparoscopic surgery. *Gynecol Obstet Surg* 2010; **21**: 127–131. (In Japanese.)
12. Garry R, Fountain J, Mason S *et al.* The eVALuate study: Two parallel randomised trials, one comparing laparoscopic with abdominal hysterectomy, the other comparing laparoscopic with vaginal hysterectomy. *BMJ* 2004; **328**: 129–136. Epub 2004 Jan 7. Erratum in: *BMJ* 2004; 328: 494.
13. Johnson N, Barlow D, Lethaby A, Tavender E, Curr L, Garry R. Methods of hysterectomy: Systematic review and meta-analysis of randomised controlled trials. *BMJ* 2005; **330**: 1478–1486.
14. Bonilla DJ, Mains L, Whitaker R, Crawford B, Finan M, Magnus MJ. Uterine weight as a predictor of morbidity after a benign abdominal and total laparoscopic hysterectomy. *Reprod Med* 2007; **52**: 490–498.
15. Fiaccavento A, Landi S, Barbieri F *et al.* Total laparoscopic hysterectomy in cases of very large uteri: A retrospective comparative study. *J Minim Invasive Gynecol* 2007; **14**: 559–563.
16. O'Hanlan KA, Dibble SL, Garnier AC, Reuland ML. Total laparoscopic hysterectomy: Technique and complications of 830 cases. *JSLS* 2007; **11**: 45–53.
17. Chopin N, Malaret JM, Lafay-Pillet MC, Fotso A, Foulot H, Chapron C. Total laparoscopic hysterectomy for benign uterine pathologies: Obesity does not increase the risk of complications. *Hum Reprod* 2009; **24**: 3057–3062.
18. Lafay Pillet MC, Leonard F, Chopin N *et al.* Incidence and risk factors of bladder injuries during laparoscopic hysterectomy indicated for benign uterine pathologies: A 14.5 years experience in a continuous series of 1501 procedures. *Hum Reprod* 2009; **24**: 842–849.

19. Wattiez A, Soriano D, Cohen SB *et al.* The learning curve of total laparoscopic hysterectomy: Comparative analysis of 1647 cases. *J Am Assoc Gynecol Laparosc* 2002; **9**: 339–345.
20. Goodno JA Jr, Powers TW, Harris VD. Ureteral injury in gynecologic surgery: A ten-year review in a community hospital. *Am J Obstet Gynecol* 1995; **172**: 1817–1820.
21. Harkki-Siren P, Sjoberg J, Tiitinen A. Urinary tract injuries after hysterectomy. *Obstet Gynecol* 1998; **92**: 113–118.
22. Stanhope CR, Wilson TO, Utz WJ, Smith LH, O'Brien PC. Suture entrapment and secondary ureteral obstruction. *Am J Obstet Gynecol* 1991; **164**: 1513–1519.
23. Gilmour DT, Baskett TF. Disability and litigation from urinary tract injuries at benign gynecologic surgery in Canada. *Obstet Gynecol* 2005; **105**: 109–114.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Video S1 Total laparoscopic hysterectomy with early ureteral identification technique.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

Prognostic significance of elongator protein 3 expression in endometrioid adenocarcinoma

YI WANG[1], JUN-ICHIRO IKEDA[1], NUR RAHADIANI[1], SUHANA MAMAT[1,3], YUTAKA UEDA[2], TIAN TIAN[1], TAKAYUKI ENOMOTO[2], TADASHI KIMURA[2], KATSUYUKI AOZASA[1] and EIICHI MORII[1]

Departments of [1]Pathology and Obstetrics and [2]Gynecology, Osaka University Graduate School of Medicine, Suita 565-0871, Japan; [3]Department of Basic Health Science, Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, 25200 Kuantan, Pahang, Malaysia

Received March 1, 2011; Accepted July 27, 2011

DOI: 10.3892/ol.2011.428

Abstract. Elongator protein 3 (ELP3), the catalytic subunit of the elongator complex of RNA polymerase II, is involved in various functions, including transcriptional elongation, chromatin modification and cytoskeletal regulation. In this study, ELP3 expression was immunohistochemically examined in normal uterus tissue and uterine endometrioid adenocarcinoma tissue. ELP3 was abundantly expressed in both the proliferative and secretory phases of the endometrial cycle. However, ELP3 expression levels varied among cases of endometrioid adenocarcinoma. In patients with endometrioid adenocarcinoma, a low ELP3 expression was correlated to a high T-factor (p=0.036), tumor stage (p=0.001), lymph node metastasis (p<0.001), resistance to chemotherapy (p=0.045), recurrence (p=0.004) and poor prognosis (p=0.003). Univariate and multivariate analyses revealed that a low ELP3 expression was an independent factor for poor prognosis. In conclusion, this is the first study to examine the clinical implications of ELP3 expression in cancer.

Introduction

Elongator protein 3 (ELP3), the catalytic subunit of the elongator complex of RNA polymerase II, is involved in transcriptional elongation (1,2). Besides transcriptional elongation, ELP3 possesses various functions, including chromatin modification by acetylation of histones (2) and demethylation of paternal DNA in zygotes (3). ELP3 is required for cell cycle progression in the presence of DNA-damaging agents in yeast (4). However, the opposite effect was reported in humans; ELP3 overexpression causes cell cycle arrest in a human embryonic kidney cell line (5). ELP3 also acetylates actin or tubulin in the microtubules of neurons (6-9). ELP3 mutation results in the degeneration of motor neurons in humans, suggesting a role for ELP3 in the migration and differentiation of neurons (10). Although a number of functions of ELP3 are known, the role of ELP3 in cancers and its clinical implications have yet to be studied.

Endometrioid adenocarcinoma is the most common invasive malignancy of the female genital system (11,12). Despite advances in the methods of detection and treatment, the prognosis of patients with endometrioid adenocarcinoma remains unfavorable. We examined the clinical implications of the expression of a number of markers, including CDCP1 and ALDH1, in endometrioid adenocarcinoma. ELP3 expression has not been studied in endometrial tissue of the uterus. In the present study, ELP3 expression was immunohistochemically examined in normal endometrium and clinical samples with endometrioid adenocarcinoma, and its clinical implications were evaluated.

Materials and methods

Patients and methods. One hundred patients who underwent surgery for endometrioid adenocarcinoma at Osaka University Hospital, Japan, during the period between January 1998 and January 2007 were examined. Clinicopathological findings of the patients are shown in Table I. Patient ages ranged from 22 to 75 years (median 54.7). Resected specimens were macroscopically examined to determine the location and size of the tumors. Normal endometrial tissue (6 cases in the proliferative and 4 in the secretory phase), collected from patients with functional bleeding, was included as a control. Histological specimens were fixed in 10% formalin and paraffin-embedded. Paraffin-embedded specimens were stored in a dark room in the Department of Pathology of Osaka University Hospital at room temperature, sectioned at 4-μm at the time of staining, and stained with H&E and an immunoperoxidase procedure. The histological stage was determined according to the International Federation of Obstetricians and Gynecologists (FIGO) staging system (15). The patients were followed up with laboratory examinations, including routine peripheral blood cell counts at 1- to 6-month intervals, X-ray, computed tomographic scan and pelvic examination at 6- to

Correspondence to: Dr Eiichi Morii, Department of Pathology, Graduate School of Medicine, Osaka University, Yamada-oka 2-2, Suita, Osaka 565-0871, Japan
E-mail: morii@patho.med.osaka-u.ac.jp

Key words: elongator protein 3, endometrioid adenocarcinoma, prognosis