

Minimally invasive surgery in radical hysterectomy for cervical cancer

Chyi-Long Lee¹, Kuan-Gen Huang¹, Peng-Teng Chua^{1,2}

¹Department of Obstetrics & Gynaecology, Division of Gynaecological Endoscopy & Minimally Invasive Therapy, Chang Gung Memorial Hospital, Chang Gung University, 33305, Linkou, Taiwan

²Mahkota Medical Centre, 75000, Malacca, Malaysia

Introduction

Since the inception and practice of Minimally Invasive Gynecology (MIG) for Cervical Cancer began in 1992/1993, significant strides have been made in the forms of improved patient outcomes, technological expertise and quality of life. After the publication of the LACC Trial, many societies & organizations throughout the world have changed their stance from the previous support of MIG to an open approach. Recently the SUCCOR study comparing Minimally Invasive versus Open Approach in 1B1 Cervical Cancer pointed out that Disease-Free survival, relapse rate and death seemed to be higher in the Minimally Invasive group and findings were consistent with the LACC trial [1]. There are many centers worldwide performing minimally invasive radical hysterectomy that continue to perform Minimally Invasive Surgery for Early Stage Cervical Cancer. In this article the doctrine of “The Poisonous Tree” will be explored as well as discussion on a review of various outcomes of patients operated by Laparoscopic Radical Hysterectomy in a tertiary hospital, by experienced surgeons and standardization in radicality, for Cervical Carcinoma Stage 1A1-1B1 from January 2009 to May 2014.

The metaphor: fruit of the poisonous tree

The well-known legal metaphor from the textbook “Understanding Criminal Procedure” by Dressler & Joshua states: “Fruit of the poisonous tree” to describe evidence that is obtained illegally. The logic behind this states that assuming the source (the “tree”) of the evidence or evidence itself is contaminated or not pure, then everything or anything gained from the “tree” (the “fruit”) is contaminated as well.

Hence the tainted fruit cannot be used as evidence. This is similar to findings from the LACC trial which had originated from obvious study bias and methodology flaws, cannot be accepted as truth or evidence in the practice of Minimally Invasive Gynecology [2, 3].

Minimally Invasive approach to Cervical Cancer which was associated with reduced surgical morbidity and good oncologic outcome had been an accepted treatment for the past two decades until publication of findings from

a prospective, randomized controlled trial comparing survival of Cervical Cancer patients who underwent Open Approach and Minimally Invasive Surgery (LACC study). Among important findings from the said study include: Outcomes were compared between MIS and Open Radical Hysterectomy in a 1 : 1 ratio, pointing that the 4.5-year disease free survival rate & overall survival rate for Minimally Invasive Surgery (MIS) was inferior compared to Open Radical Hysterectomy, as well as higher rates of loco-regional recurrence. Survival rate for MIS vs. Open approach was reported to be 86% vs. 96.5%. Such findings have resulted in a constant debate regarding feasibility and the role of Minimal Invasive Surgery in Cervical Cancer till today.

Real-world impact so far

Despite many centres worldwide performing Minimally Invasive Surgery for Endometrial, Cervical, Ovarian Cancer with proven track record and excellent outcomes, a large number of societies and organisations around the world has adopted a policy of not favouring MIS in cervical cancer. For example, the European Society of Gynaecological Oncology 2019 guideline in an updated statement, states that MIS approach is no longer valid and should be removed and replaced by ‘open approach is the gold standard’. This was mainly out of fear and concerns that Minimally Invasive Surgery (MIS) was associated with poorer disease-free survival and overall survival based on the LACC trial [2]. This is in contrast to many other centres who have compared their data to those of the LACC trial and findings were inconsistent [4-8]. Particularly, studies have found that with appropriate patient selection, Laparoscopic Radical Hysterectomy is safe for the management of Early Stage Cervical Cancer with small tumors that are 2 cm or less in size [9]. The debate continues however, as seen in the SUCCOR study whereby the international European cohort showed a higher relapse and risk of death in the MIG group. The authors also found the use of uterine manipulator to be associated with poorer outcomes in patients, though agreeable with its technical advantage in performing Radical Hysterectomy [1].

The “three-men talking” idiom

This is an illustration of the idiom: “Three Men Talking Makes A Tiger” (Repeated Rumor Becomes A Fact): When one person points out there is a tiger in the city, many would not believe or take it seriously. When a second or third person points out the same however, it becomes a truth that is not questioned and the entire city starts to panic. Although the LACC study is fraught with irregularities in patient selection and bias, it was published in an influential journal. The acceptance of the study results by one society quickly and gradually amplified into more and more societies adopting a negative stance against MIS in Radical Hysterectomy. There is now a trend of regressing back to 120 years ago when open surgery was the norm for Cervical Cancer. It is clear that the evidence put forth by the influential journal was from a questionable research, hence should not be accepted like the metaphor “Fruit From The Poisonous Tree”, at the same time repeated reinforcement of negative views on Minimally Invasive Surgery by the “Three-Men” For Cervical Cancer has resulted in a false wide-spread belief that MIS in Cervical Cancer yields poor outcome. Rigorous and repetitive critical appraisal of the baseline methodology is crucial before publication of any study and result. This is especially true when in the LACC Trial, standardization of surgical technique and surgeon appraisal was deemed to be inadequate. Hence the “Fruit” from such study should not be easily accepted by the MIS community.

How do we, as a responsible surgical community respond to this false-affirmed bias towards MIS in Cervical Cancer? The Asia Pacific Association For Gynecological Endoscopy & Minimally Invasive Therapy released a 12-point statement and amongst the points, was a crucial fact stating that surgeon performance and technique of surgery should be standardized before any conclusions can be drawn [10]. The Surgeon Skill cannot be simply compared to a drug, as individual skills are highly variable and cannot be evaluated in a manner similar to drugs [11].

A tertiary hospital experience on minimally invasive radical hysterectomy

Because of such debate regarding MIS in Cervical Cancer, in 2012, a team in Chang Gung Memorial Hospital, Taiwan, performed a surgical outcome analysis of 139 patients who were operated and findings showed that despite being in the early stages of learning curve for Laparoscopic Radical Hysterectomy, the disease-free survival (DFS) was 91.01% and overall survival (OS) was 92.78% [12]. A follow-up detailed analysis of patients who underwent Laparoscopic Radical Hysterectomy from Year 2009–2014 was carried out to ascertain the safety and efficiency of Minimally Invasive Therapy in Radical Hysterectomy [13]. Fifty-three patients with stage 1A1 to 1B1 Cervical Cancer (based on 2009 FIGO Staging) underwent Laparoscopic Radical Hysterectomy from January 2009 to May 2014. Class II-III Piver-Rutledge Radical Hysterectomy was performed Laparoscopically with standardized

approach adopted by qualified surgeons.

Standardized surgical technique

The Main focus of technique includes: Uterine artery ligation and transection at its origin, complete mobilisation of ureter from pubo-vesicle ligament to entry point of the bladder base. Care was taken to preserve its lateral part as well as the superior vesicle artery. The uterosacral ligaments were transected at the junction 2/3rd and 1/3rd between uterine and sacral attachments. Medial portion of the cardinal ligaments were removed at least at the mid-point keeping as close as possible to the lateral pelvic sidewall. Standardised Radical Pelvic Lymphadenectomy was also performed whereby bilateral pelvic lymph nodes were dissected and removed; starting from approximately 2-3 cm caudal to the common iliac bifurcation down to the level of Obturator nodes in the vicinity of the Obturator fossa. This involved removing nodes from the Internal and External Iliac Chain, as well as pelvic sidewall nodes.

The outcome of standardization & surgical technique

53 patients were followed up for a mean of 96.7 months. The longest follow-up in this review was 127 months. The 5 year-survival rate was 100% for all patients with no recurrence or death. Two patients received post-operative pelvic radiation concurrent with chemotherapy (Cisplatin) due to greater than 1/3 cervical stromal invasion. One patient had stage 1B1 Squamous Cell Carcinoma with 70% cervical stromal invasion, while the other patient had stage 1B1 Adenocarcinoma with 85% cervical stromal invasion. The final histopathology results for both patients were negative for lymphovascular space invasion, nodal and parametrial metastases. (Table 1 & 2) With adequate Parametrium and Paracolpium regional resection, the entire uterine and cervical specimen with associated Parametrium and Paracolpium resemble a triangular structure (Figure 1) with a “Triangular Hand-Fan” appearance (Figure 2).

How the “poisonous tree” bears “poisonous fruit”

A study on the Quality of life in patients with Cervical Cancer after Open vs. Minimally Invasive Radical Hysterectomy looked at secondary outcome of a multicentre, randomised, open-label, phase 3, non-inferiority trial [14]. The authors found significant differences in physical component scores of the SF12 at 6 weeks after surgery favours the MIS group with absolute difference of 2%. Despite clear advantages of MIS seen in this study with regards to quality of life (QOL), the article has instead stressed and proposed Open Radical Hysterectomy for Early Stage Cervical Cancer. This study was aimed at QOL assessment but surprisingly, the final conclusion seemed to provide support for the LACC trial which had a different aim of comparing outcomes. Ever since the LACC study has established a baseline alleging MIS is inferior to open approach, subsequent studies and results will invariably follow the lines of discouraging minimally invasive approach. Hence this is an example of the “poisonous tree bearing poisonous fruit”.

Table 1. — Patient demographic data, Pre-operative FIGO 2009 Cervical Cancer Staging, Final Histology results after surgery.

Parameters	Mean (SD)
BMI (kg/m ²)	24.5 (3.2)
Weight (kg)	60.0 (9.2)
Height (cm)	156.1 (5.5)
Age (Years)	49.7 (10.4)
Stage (No. of patients)	
1A1	23
1A2	3
1B1	27
Histology (No. of patients)	
Squamous Cell Carcinoma	41
Adenocarcinoma Carcinoma	11
Adenosquamous Carcinoma	1
Adjuvant Therapy (No. of patients) (> 50% stromal invasion)	2
Lymph node positivity for malignancy (Histopathology)	0
Parametrium positivity for malignancy (Histopathology)	0
Surgical margin positivity for malignancy (Histopathology)	0

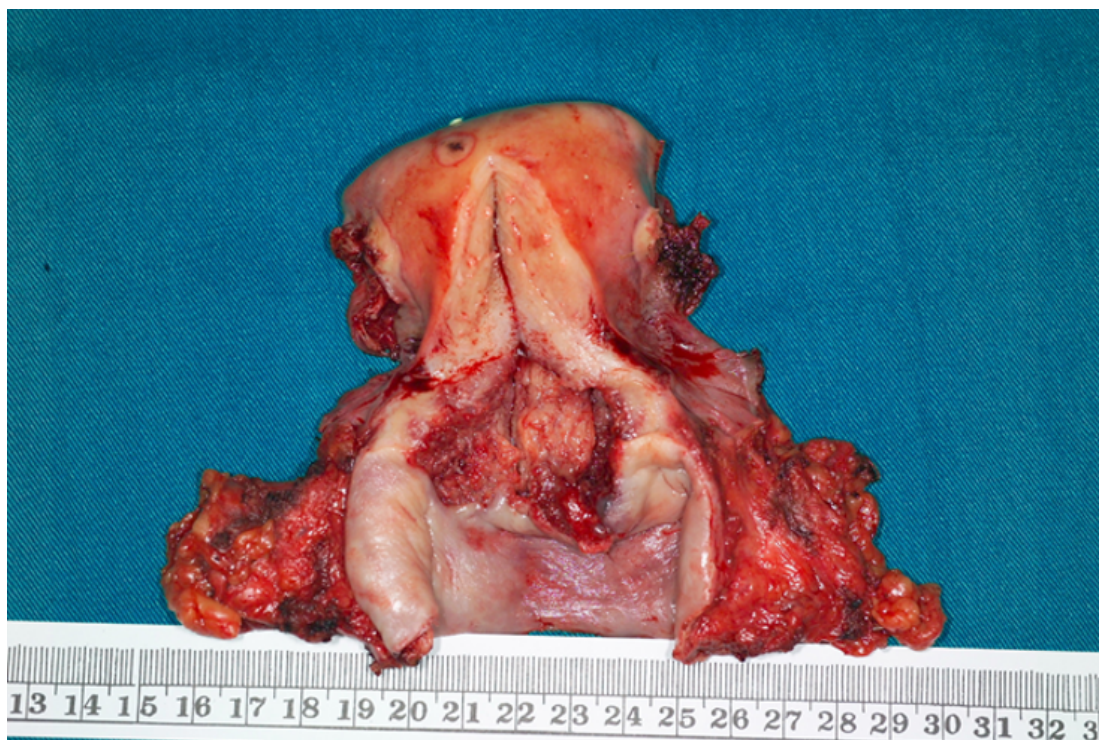


Figure 1. — Adequate Parametrium and Paracolpium regional resection shown in final specimen: Note the lateral margins of specimen which are indicative of good regional surgical margin obtained. Specimen should resemble a “triangular” structure.

Minimally invasive surgery in other disciplines

Minimally Invasive approach for General & Colorectal surgery bear similarities to Gynecology in the field of operation. A randomized trial assessing short term Quality of Life Outcomes following Laparoscopic Assisted Colectomy Versus Open Colectomy For Colon Cancer concluded that MIS in early Colonic Cancer, as in Gynecologic LAP2

Trial for Endometrial Cancer, provides a better QOL short term, but longer term QOL will require more research [15, 16]. Biere *et al.* in a multicentre, open label, randomized controlled trial comparing MIS versus Open Esophagectomy also found better short term QOL for MIS [17]. Toritani *et al.* in a randomized controlled trial evaluated Laparoscopic versus Open Surgery in Transverse and Descending Colon Cancer patients, and not surprisingly found bet-



Figure 2. — After adequate Parametrium and Paracolpium regional resection, the entire uterine and cervical specimen with associated Parametrium and Paracolpium resemble a “Triangular Hand-Fan” structure.

Table 2. — *Surgical outcome data, Post-operative follow up data.*

Parameter	Mean (SD)
Surgical Outcomes:	
Length of Operation (Minutes)	189.0 (63.4)
Estimated Blood Loss (mL)	257.61 (217.1)
Hospital Stay (Day)	2.8 (5.1)
Total Lymph Nodes (N)	18.3 (8.9)
Bladder Training needed (Day)	2.4 (3.7)
Complication (N)	1
Follow-Up (Month)	96.7 (17.6)*
Recurrence (N)	0
Death (N)	0
5-Year Survival (%)	100

*Follow up period: Longest at 127 months. Mean 96.7 months

ter short and mid-term QOL favouring MIS. Hence there are similarities between the practice of MIS in Gynecology and General/Colorectal Cancer. The only difference however, is while MIS is not discouraged in General/Colorectal Surgery, the same cannot be said regarding MIS in Cervical Cancer. This produced more doubts and debate regarding the discouraging approach towards MIS in carefully selected Early Stage Cervical Cancer patients.

Various other studies have proven similarly good out-

comes for Minimally Invasive Radical Hysterectomy such as Diver *et al.* in a retrospective cohort study on 383 women, concluding that Minimally Invasive Radical Hysterectomy does not compromise patient outcomes [18]. Gil-Moreno *et al.* in a prospective controlled study after 17 years of experience in Radical Hysterectomy, concluded that MIS appear to reduce morbidity without affecting Oncologic Outcomes [19].

Does the use of uterine manipulator increase loco-regional recurrence?

The postulated theory of uterine manipulator use resulting in increased locoregional recurrence is in doubt [2]. The uterine manipulator commonly used in Laparoscopic Radical Hysterectomy in our center is a blunt-tip atraumatic insert with blunt colpotomy cup (The Donnez Manipulator). Due to its blunt tip and cup, it is unlikely to spread tumour cells into the peritoneum. A “Tumour-Free” concept is practiced and the hysterectomy specimen is retrieved vaginally with endo-bag protection, followed by generous lavage of the peritoneal cavity with Normal Saline or Ringer’s Lactate, thereby reducing potential peritoneal contamination with tumour cells. The lavage is done in a gravity-dependant manner though vaginal expulsion. It was concluded in our review there were no cases of loco-regional recurrence in any of the patients because of this, and any increased loco-regional recurrence reported in other studies is likely due to inadequate radicality of surgery

with lack of adherence to the “Tumour-Free” Concept. The findings of the SUCCOR trial highlighted a negative impact of uterine manipulator on potential tumour spread and seeding with 2.76 times higher relapse rate [1]. It has to be pointed out, however, that in the SUCCOR study there is no uniform agreement on the type of uterine manipulator and there is a lack of information on the “Tumour-Free” concept that was practiced by our group of surgeons. While the suggested practice of vaginal protection is promising and should be considered in Minimally Invasive Surgery for Cervical Cancer, the use of uterine manipulator should be further researched with an aim to establish a standardised technique and type being used. The “Tumour-Free” concept should be part and parcel of uterine manipulator technique in Minimally Invasive Radical Hysterectomy for Cervical Cancer.

How to achieve 5-year survival rate of 100 percent

Standardization of surgical procedure and experience of the surgeon have proven to be important. Literature has shown that patient outcomes improved only after a surgeon has crossed the learning curve of at least 50 cases of such procedure [20]. The “Tumour-Free” concept with timely administration of adjuvant therapy is vital as well. In animal studies, loco-regional metastasis or tumour growth were related to the number of intraperitoneal cell load; if fewer than 200,000 cells were present, there was no difference in rate of tumour cell wound implantation between laparoscopic or open surgical approach. Hence adequate Parametrium and Paracolpium resection coupled with good lavage and protection of operative field from contamination will reduce the risks of loco-regional recurrence. At the same time, the use of MIS will allow patients to undergo adjuvant therapy faster after primary surgery. This is likely a benefiting factor to further reduce risks of recurrence and improve survival. In our tertiary centre, the adjuvant chemotherapy is initiated latest by 2 weeks after primary MIS for Cervical Cancer if the indication arises [21]. Plante *et al.* presented a series of 50 cases whereby patients underwent a Simple Vaginal Trachelectomy/Conization with Laparoscopic Sentinel Lymph Node mapping ± complete pelvic node dissection. As per FIGO 2009 classification, patients had stage IA1-1B1 disease. There was only one local recurrence and the 5-year progression-free survival and overall survival was 97.9% and 97.6% respectively [22]. An earlier analysis of 16 patients has shown that with careful selection of low-risk small volume Cervical Cancer of < 2 cm in size, a less invasive Vaginal Trachelectomy instead of Radical Hysterectomy yielded negative surgical margins in all cases. Among these, 81% of patients had no residual dysplasia in trachelectomy specimens [23]. Future directions of applying Minimally Invasive surgery in Cervical Cancer should focus on careful case selection, standardized surgical technique and a “Tumour -Free” Concept.

Conclusions

Similar to the practice of MIS in the field of General & Colo-Rectal Surgery, progress is a constant and probably is the only thing that remains constant. With the danger of regressing back to the practice of open surgery for Gynecologic Cancers more than 120 years ago, it is with anticipation and hope that the upcoming MITOR trial (Minimally Invasive Therapy Versus Open Radical Hysterectomy) involving multiple centres and expert surgeons in a large scale, will provide answers and concrete evidence to support Minimally Invasive Surgery in Cervical Cancer.

Ethics approval and consent to participate

All subjects provided informed consent for inclusion before participation in the study. This study was conducted in accordance with the Declaration of Helsinki & protocol was approved by Chang Gung Medical Foundation Institutional Review Board (IRB No: 201900626B0C601).

Acknowledgments

The authors would like to thank Cindy WENG, for language editing of this manuscript.

Conflict of Interest

The authors report no conflict of interest with regards to this article.

Submitted: September 29, 2020

Accepted: November 02, 2020

Published: December 15, 2020

References

- [1] Chiva L., Zanagnolo V., Querleu D., Martin-Calvo N., Arevalo-Serrano J., Capilna M.E., *et al.*: “SUCCOR study: an international European cohort observational study comparing minimally invasive surgery versus open abdominal radical hysterectomy in patients with stage IB1 cervical cancer”. *Int. J. Gynecol. Cancer*, 2020, 30, 1269-1277.
- [2] Ramirez P.T., Frumovitz M., Pareja R., Lopez A., Vieira M., Ribeiro R., *et al.*: “Minimally invasive versus abdominal radical hysterectomy for cervical cancer”. *N. Engl. J. Med.*, 2018, 379, 1895-1904.
- [3] Guo S.: “Keep the pressure on for more transparency of clinical trials on endometriosis”. *Gynecol. Minim. Invasive Ther.*, 2013, 2, 73-74.
- [4] Brandt B., Sioulas V., Basaran D., Kuhn T., LaVigne K., Gardner G.J., *et al.*: “Minimally invasive surgery versus laparotomy for radical hysterectomy in the management of early-stage cervical cancer: Survival outcomes”. *Gynecol. Oncol.*, 2020, 156, 591-597.
- [5] Vergote I., Magrina J.F., Zanagnolo V., Magtibay P.M., Butler K., Gil-Moreno A., *et al.*: “The LACC trial and minimally invasive surgery in cervical cancer”. *J. Minim. Invasive Gynecol.*, 2020, 27, 462-463.
- [6] Uppal S., Gehrig P.A., Peng K., Bixel K.L., Matsuo K., Vetter M.H., *et al.*: “Recurrence rates in patients with cervical cancer treated with abdominal versus minimally invasive radical hysterectomy: A multi-institutional retrospective review study”. *J. Clin. Oncol.*, 2020, 38, 1030-1040.
- [7] Zhao Y., Hang B., Xiong G.W., Zhang X.W.: “Laparoscopic radical hysterectomy in early stage cervical cancer: A systematic review and meta-analysis”. *J. Laparoendosc. Adv. Surg. Tech.*, 2017, 27, 1132-1144.

- [8] Zhang S., Ding T., Cui Z., Lv Y., Jiang R.: "Efficacy of robotic radical hysterectomy for cervical cancer compared with that of open and laparoscopic surgery". *Med (Baltimore)*, 2019, 98, e14171.
- [9] Lim T.K., Lin K.M., Wong W., Aggarwal I., Yam P.L.: "Surgical and oncological outcome of total laparoscopic radical hysterectomy versus radical abdominal hysterectomy in early cervical cancer in Singapore". *Gynecol. Minim. Invasive Ther.*, 2019, 8, 53-58.
- [10] Lee C., Huang K., Nam J., Lim P., Shun F.W., Lee K., *et al.*: "The statement of the Asia-Pacific Association for Gynecologic Endoscopy and Minimally Invasive Therapy for LACC study". *Gynecol. Minim. Invasive Ther.*, 2019, 8, 91-93.
- [11] Lee C.: "Minimally invasive therapy for cancer: It is time to take actions for training system in minimally invasive therapy after lacc report". *Gynecol. Minim. Invasive Ther.*, 2019, 8, 1-3.
- [12] Lee C., Wu K., Huang K., Lee P., Yen C.: "Long-term survival outcomes of laparoscopically assisted radical hysterectomy in treating early-stage cervical cancer". *Am. J. Obstet. Gynecol.*, 2010, 203, 165.e1-165.e7.
- [13] Chua P.T., Lee C.L., Huang K.G.: "100% 5-year survival rate in laparoscopic radical hysterectomy for early-stage cervical cancer is an achievable task". *Gynecol. Minim. Invasive Ther.*, 2020, 9, 53.
- [14] Frumovitz M., Obermair A., Coleman R.L., Pareja R., Lopez A., Ribero R., *et al.*: "Quality of life in patients with cervical cancer after open versus minimally invasive radical hysterectomy (LACC): a secondary outcome of a multicentre, randomised, open-label, phase 3, non-inferiority trial". *Lancet Oncol.*, 2020, 21, 851-860.
- [15] Weeks J.C., Nelson H., Gelber S., Sargent D., Schroeder G.: "Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: A randomized trial". *JAMA*, 2002, 287, 321-328.
- [16] Walker J.L., Piedmonte M.R., Spirtos N.M., Eisenkop S.M., Schlaerth J.B., Mannel R.S., *et al.*: "Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic oncology group study LAP2". *J. Clin. Oncol.*, 2009, 27, 5331-5336.
- [17] Biere S.S.A.Y., Cuesta M.A., van der Peet D.L.: "Minimally invasive versus open esophagectomy for cancer: A systematic review and meta-analysis". *Minerva Chir.*, 2009, 64, 121-133.
- [18] Diver E., Hinchcliff E., Gockley A., Melamed A., Contrino L., Feldman S., *et al.*: "Minimally invasive radical hysterectomy for cervical cancer is associated with reduced morbidity and similar survival outcomes compared with laparotomy". *J. Minim. Invasive Gynecol.*, 2017, 24, 402-406.
- [19] Gil-Moreno A., Carbonell-Socias M., Salicrú S., Centeno-Mediavilla C., Franco-Camps S., Colas E., *et al.*: "Radical hysterectomy: efficacy and safety in the dawn of minimally invasive techniques". *J. Minim. Invasive Gynecol.*, 2019, 26, 492-500.
- [20] Chong G.O., Park N.Y., Hong D.G., Cho Y.L., Park I.S., Lee Y.S.: "Learning curve of laparoscopic radical hysterectomy with pelvic and/or para-aortic lymphadenectomy in the early and locally advanced cervical cancer". *Int. J. Gynecol. Cancer*, 2009, 19, 1459-1464.
- [21] Lee C., Kay N.: "Inhibition of ovarian cancer growth and implantation by paclitaxel after laparoscopic surgery in a mouse model". *Am. J. Obstet. Gynecol.*, 2006, 195, 1278-1281.
- [22] Plante M., Renaud M.C., Sebastianelli A., Gregoire J.: "Simple vaginal trachelectomy in women with early-stage low-risk cervical cancer who wish to preserve fertility: the new standard of care?". *Int. J. Gynecol. Cancer*, 2020, 30, 981-986.
- [23] Plante M., Gregoire J., Renaud M., Sebastianelli A., Grondin K., Noel P., *et al.*: "Simple vaginal trachelectomy in early-stage low-risk cervical cancer: a pilot study of 16 cases and review of the literature". *Int. J. Gynecol. Cancer*, 2013, 23, 916-922.

Corresponding Author:

PENG-TENG CHUA, M.B.B.S, M.O.G, F.A.C.S
 Mahkota Medical Centre, Department of Obstetrics &
 Gynaecology, No.3, Mahkota Melaka, Jalan Merdeka,
 75000, Melaka, Malaysia
 e-mail: drchuapt@yahoo.com