

Analysis of hidden blood loss and its influential factors in myomectomy

Journal of International Medical Research
48(5) 1–11

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DOI: 10.1177/0300060520920417

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Abstract

Objective: This study was performed to quantify hidden blood loss (HBL) and explore its influential factors in myomectomy.

Methods: Two hundred nine patients who underwent myomectomy by laparotomy or laparoscopy from 1 January 2017 to 31 December 2018 were analyzed. Each patient's estimated blood volume and total blood loss (TBL) were calculated by the Nadler formula and Gross formula, respectively. The HBL was calculated by subtracting the visible blood loss (VBL) from the TBL. A multivariate linear stepwise analysis was applied to identify the influential factors of HBL in myomectomy.

Results: The mean perioperative VBL and estimated TBL during myomectomy were 137.81 ± 104.43 and 492.24 ± 225.00 mL, respectively. The mean HBL was 354.39 ± 177.69 mL, which accounted for $71.52\% \pm 15.75\%$ of the TBL and was two to three times higher than the VBL. The duration of surgery, number of removed leiomyomas, and location of removed leiomyomas were independent risk factors for HBL in myomectomy.

Conclusions: HBL accounted for a significant percentage of TBL in myomectomy. A full understanding of the HBL in perioperative blood management may improve patients' postoperative rehabilitation.

Keywords

Hidden blood loss, leiomyoma, myomectomy, influential factors, total blood loss, visible blood loss

Date received: 11 October 2019; accepted: 24 March 2020

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Introduction

Leiomyomas are benign tumors that are derived from the overgrowth of uterine smooth muscle cells.¹ They are the most common gynecological benign neoplasms, with a prevalence ranging from 20% to 40% in women of reproductive age.² Fortunately, many uterine leiomyomas are asymptomatic and require no clinical intervention. Approximately one-third of women with uterine leiomyomas have clinical symptoms such as abnormal uterine bleeding with subsequent anemia; bulk-related symptoms of bowel or bladder dysfunction, pelvic pain, and abdominal distension; infertility; or adverse pregnancy outcomes.³ For women with symptomatic leiomyomas who desire to retain their uterus and fertility, myomectomy should be the gold standard surgical therapy.⁴ The surgical approaches for symptomatic leiomyomas are determined by the location, number, and size of the leiomyomas. Generally, submucosal leiomyomas are resected by hysteroscopy, and intramural and subserosal uterine leiomyomas are removed by laparotomy or laparoscopy.^{1,5}

Sehat et al.⁶ first proposed the conception of hidden blood loss (HBL) in surgical patients in 2000 and demonstrated that HBL accounted for 50% of the total blood loss (TBL) in total knee arthroplasty. Wen et al.⁷ reported that the mean HBL volume in posterior lumbar fusion surgery was 588 mL, which was 39% of the TBL. Another study revealed that the mean HBL was 525 ± 217 mL in hip hemiarthroplasty, accounting for $61.0\% \pm 13.6\%$ of the TBL (859 ± 289 mL).⁸ However, the exact mechanisms of HBL and its risk factors remain incompletely understood. Sehat et al.⁶ proposed that 40% of the HBL was caused by hemolysis and that approximately 60% was attributed to tissue extravasation. In another study, radiolabeled red blood cells were used to illustrate that the HBL was

attributed to shifting of the blood into soft tissue compartments perioperatively.⁹ Additionally, Bao et al.¹⁰ indicated that the free fatty acids in the blood circulation are responsible for the HBL, exerting their function by peroxidation of erythrocytes and hemoglobin (Hb) membrane molecules.

Perioperative hemorrhage is a common complication in myomectomy.^{11,12} Hemorrhage in patients undergoing myomectomy increases the risk of blood transfusion, pyrexia, infection, adhesion formation, and ileus, contributing to delayed postoperative recovery.¹³ Use of vasoconstrictive drugs and tourniquets may effectively limit the perioperative blood loss in myomectomy.^{14,15} However, patients often present with symptoms of anemia and hypovolemia that exceed the severity caused by the perioperative visible blood loss (VBL). This might be attributed to the perioperative HBL. Generally, the TBL in myomectomy is considered to be the sum of the intraoperative and postoperative VBL, but the TBL is underestimated because of HBL.

To the best of our knowledge, no published study has systematically evaluated the HBL and its influential factors in myomectomy. Therefore, we performed the present study to quantify the HBL and explore the risk factors for HBL in patients undergoing myomectomy for treatment of uterine leiomyomas with the purpose of optimizing perioperative blood management and enhancing postoperative recovery.

Patients and methods

Ethical review of clinical research

The research protocol for this retrospective observational study was reviewed and approved by the ethics committee of the Second Affiliated Hospital of Wenzhou Medical University. The need for informed consent from the patients was waived by the ethics committee because of the

retrospective observational nature of the study and the anonymous collection and analysis of the data with no potential harm to the patients.

Patients

We conducted a retrospective cohort study of patients who underwent abdominal or laparoscopic myomectomy from 1 January 2017 to 31 December 2018 at the Second Affiliated Hospital of Wenzhou Medical University to identify the influential factors associated with HBL in myomectomy. The myomectomies were performed by senior gynecologists and their group members, and all senior gynecologists had more than 10 years of clinical experience in myomectomy. All enrolled patients underwent a complete blood cell count examination preoperatively and on postoperative day 3 in our hospital. Anemia was defined as an Hb concentration of <120 g/L according to the World Health Organization criteria.¹⁶

Inclusion and exclusion study criteria

The inclusion criteria were treatment by abdominal or laparoscopic myomectomy, a definitive diagnosis of uterine leiomyoma by postoperative pathologic examination, and administration of general anesthesia during the operation.

The exclusion criteria were hematological diseases, such as coagulation disorders; gastrointestinal hemorrhage; cardiovascular and cerebrovascular diseases, such as hypertension and thromboembolism; severely abnormal liver or renal function; chronic systemic and immune diseases, such as diabetes mellitus and systemic lupus erythematosus; treatment with drugs that are likely to affect perioperative blood coagulation; pregnancy or lactation; and concurrent

endometriosis, adenomyosis, or cervical lesions.

Data collection

The hospital electronic medical records were reviewed to obtain the following demographic and clinical characteristics of the patients: age, height, weight, menstrual cycle and period duration, age at menarche, preoperative albumin concentration, type of surgery (laparoscopy or laparotomy), number of leiomyomas (1, 2–3, or >3) removed intraoperatively, volume of the largest removed leiomyoma, location of the largest removed leiomyoma (intramural or subserosal), Hb concentration and hematocrit (Hct) preoperatively and on postoperative day 3, intraoperative and postoperative VBL, duration of surgery, and length of hospital stay after myomectomy. In patients with multiple leiomyomas, we considered the location of the largest removed leiomyoma as the location of the leiomyoma for analysis. The body mass index (BMI) was calculated as weight divided by height squared.

Calculation methods

Quinn et al.¹⁷ reported that the parallel planimetric method with reference to T2-weighted magnetic resonance images of leiomyomas was a more accurate measurement technique for the leiomyoma volume. However, the patients with leiomyomas in our study did not undergo a preoperative magnetic resonance imaging scan of their leiomyomas. Therefore, the volume of the largest uterine leiomyoma (in cm³) was calculated with the following formula:

$$\text{Volume} = \frac{4\pi}{3} \times \frac{a}{2} \times \frac{b}{2} \times \frac{c}{2} = \frac{\pi \cdot a \cdot b \cdot c}{6}$$

where a, b, and c are the lengths of the three major axes of the leiomyoma, obtained by

measuring the pathologic specimen during the operation in the operating room.^{18,19}

We calculated the patient's estimated blood volume (EBV) using the Nadler equation^{20,21}:

$$\begin{aligned} \text{EBV(L)} = & 0.3561 \times \text{height(m)}^3 \\ & + 0.03308 \times \text{weight(kg)} \\ & + 0.1833 \text{ (for female)} \end{aligned}$$

The TBL during the perioperative period was calculated by the Gross formula, which was widely applied for the estimation of relatively slow and steady blood loss perioperatively²²:

$$\begin{aligned} \text{TBL (L)} = & \text{EBV (L)} \\ & \times \frac{(\text{preoperative Hct} - \text{postoperative Hct})}{\text{average Hct}} \end{aligned}$$

In this formula, the average Hct is the average of the preoperative and postoperative Hct. In patients who have undergone surgery, the body hemodynamics become stable and the body fluid shift obtains homeostasis by the second or third postoperative day.²³ Therefore, the postoperative Hct in the present study was defined as the Hct on the third postoperative day. To minimize the impact of hemodilution on the calculation of blood loss, all patients received no more than 2000 mL of intravenous fluids perioperatively.

Calculation of HBL

The intraoperative VBL corresponded to the total amount of liquid in the suction containers after subtracting the lavage fluid and the weight of the soaked gauze after subtracting the weight of the dry gauze. The intraoperative VBL was calculated and recorded by experienced anesthetists. The pelvic drainage tubes were removed within 48 hours after myomectomy, and the drainage fluid volume was recorded as the postoperative VBL. HBL was then calculated

with the following formula: HBL = TBL – intraoperative VBL – postoperative VBL.²⁴

Statistical analysis

All statistical analyses were performed using SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA). Descriptive statistics are expressed as mean ± standard deviation or as number and percentage. The volume of the largest removed leiomyomas is presented as median (*P*25, *P*75). A multivariate linear regression analysis was conducted to evaluate the potential influential factors of HBL in myomectomy and included three quantitative variables (age, BMI, and duration of surgery) and four qualitative variables (surgery type, location of the largest removed leiomyoma in the uterus, volume of the largest removed leiomyoma, and number of removed leiomyomas). Among the qualitative variables, laparoscopic myomectomy and removed intramural leiomyomas were set as “0”, and each counterpart was set as “1”. The median volume of the largest removed leiomyomas was 95 cm³. Therefore, a largest removed leiomyoma volume of <95 cm³ was set as “0”, and its counterpart was set as “1”. Extraction of a single leiomyoma was set as “0”, extraction of two to three leiomyomas was set as “1”, and extraction of more than three leiomyomas was set as “2”. The multiple linear regression analysis was performed with a stepwise regression process. A *P* value of <0.05 was considered statistically significant.

Results

Patients' baseline characteristics

In total, 209 patients were included in this study. None of the patients received a perioperative blood transfusion. The patients' mean age was 39.11 ± 5.24 years (range, 28–50 years), and their mean BMI was

$22.67 \pm 2.89 \text{ kg/m}^2$ (range, 16.75–32.05 kg/m^2). The patients' demographic characteristics are summarized in Table 1.

Patients' uterine leiomyoma characteristics

The largest removed leiomyoma was intramural in 155 (74.16%) patients and subserosal in 54 (25.84%). The median volume of the largest removed leiomyomas was 95 cm^3 , the P_{25} value was 79.0 cm^3 , and the P_{75} value was 159.5 cm^3 . Additionally, among all removed leiomyomas, the smallest volume was 42 cm^3 and the largest volume was 1641 cm^3 . A total of 83 (39.71%) patients underwent removal of a single leiomyoma, 56 (26.79%) underwent removal of 2 or 3 leiomyomas, and 70 (33.50%) underwent removal of more than 3 leiomyomas. These data are shown in Table 2.

Patients' perioperative clinical characteristics

In total, 105 (50.24%) patients underwent laparotomic myomectomy and 104 (49.76%) underwent laparoscopic myomectomy. All patients' preoperative plasma albumin concentration was normal (mean, $43.37 \pm 2.9 \text{ g/L}$). The mean duration of

myomectomy was 85.17 ± 29.78 minutes. The patients' mean preoperative and postoperative Hb was $124.74 \pm 16.92 \text{ g/L}$ and $108.45 \pm 15.99 \text{ g/L}$, respectively, and the mean Hb loss during myomectomy was $16.28 \pm 8.95 \text{ g/L}$. Preoperative anemia was found in 74 patients and postoperative anemia was detected in 153 patients. The mean length of hospital stay after myomectomy was 4.05 ± 0.97 days. These data are shown in Table 3.

The patients' mean preoperative and postoperative Hct was 0.38 ± 0.04 and 0.33 ± 0.04 , respectively. The mean TBL was $492.24 \pm 225.00 \text{ mL}$, and the mean VBL was $137.81 \pm 104.43 \text{ mL}$. The mean HBL was $354.39 \pm 177.69 \text{ mL}$, which accounted for approximately 71.52% \pm 15.75% of the TBL. The patient's perioperative blood loss data are shown in Table 3.

Multivariate stepwise linear regression analysis of influential factors

The multivariate regression analysis indicated that the duration of surgery (X_1), the number of removed leiomyomas (X_2), and the location of the removed leiomyoma (X_3) were independent risk factors for HBL

Table 1. Patients' demographic characteristics.

| Parameters | Statistics |
|--|------------------|
| Total number of patients | 209 |
| Age, years | 39.11 ± 5.24 |
| Height, m | 1.59 ± 0.05 |
| Weight, kg | 57.36 ± 7.73 |
| Body mass index, kg/m^2 | 22.67 ± 2.89 |
| Duration of complete menstrual cycle, days | 29.07 ± 3.77 |
| Duration of menstrual period, days | 5.83 ± 1.36 |
| Age at menarche, years | 13.99 ± 1.26 |

Data are presented as n or mean \pm standard deviation.

Table 2. Characteristics of leiomyomas.

| Parameters | Statistics |
|--|----------------|
| Location of largest removed leiomyoma in uterus | |
| Intramural | 155 (74.16) |
| Subserosal | 54 (25.84) |
| Volume of largest removed leiomyoma, cm^3 | 95 (79, 159.5) |
| <95 | 104 (49.76) |
| ≥ 95 | 105 (50.24) |
| Number of removed leiomyomas | |
| 1 | 83 (39.71) |
| 2–3 | 56 (26.79) |
| >3 | 70 (33.50) |

Data are presented as n (%) or median (P_{25} , P_{75}).

(\hat{Y}) in myomectomy ($PX_1 = 0.000$, $PX_2 = 0.000$, $PX_3 = 0.044$) (Table 4). The multivariate linear regression equation was $\hat{Y} = 189.708 + 1.552X_1 + 49.166X_2 - 52.646X_3$.

Table 3. Patients' perioperative characteristics.

| Parameters | Statistics |
|--|-----------------|
| Preoperative albumin, g/L | 43.37 ± 2.94 |
| Type of surgery | |
| Laparotomic myomectomy | 105 (50.24) |
| Laparoscopic myomectomy | 104 (49.76) |
| Duration of surgery, minutes | 85.17 ± 29.78 |
| Blood parameters | |
| Preoperative hemoglobin, g/L | 124.74 ± 16.92 |
| Postoperative hemoglobin, g/L | 108.45 ± 15.99 |
| Hemoglobin loss, g/L | 16.28 ± 8.95 |
| Preoperative hematocrit | 0.38 ± 0.04 |
| Postoperative hematocrit | 0.33 ± 0.04 |
| Total blood loss, mL | 492.24 ± 225.00 |
| Visible blood loss, mL | 137.81 ± 104.43 |
| Hidden blood loss, mL | 354.39 ± 177.69 |
| Hidden blood loss as a percentage of total blood loss, % | 71.52 ± 15.75 |
| Length of stay after myomectomy, days | 4.05 ± 0.97 |

Data are presented as mean ± standard deviation or n (%).

Age, BMI, the volume of the largest removed leiomyoma, and the type of surgery were not independent risk factors for HBL in myomectomy.

Discussion

Perioperative HBL in orthopedic surgeries has recently received increasing attention, but limited research of HBL in abdominal or pelvic surgeries has been performed. In a study of laparoscopy-assisted gastrectomy for gastric carcinoma, Zhang et al.²⁵ indicated that the HBL was 322.2 ± 195.9 mL, accounting for nearly 64.3% ± 14.1% of the perioperative TBL. Additionally, they concluded that albumin loss, sex, and hypertension were significantly associated with HBL by a multiple linear regression analysis. In a study of gynecological surgeries, Zhao et al.²⁶ examined HBL in the surgical treatment of stage IA to IIA cervical carcinoma in patients who underwent radical hysterectomy and pelvic lymphadenectomy by laparotomy or laparoscopy. The authors found that the HBL was seriously underestimated and was a significant portion of the TBL. Moreover, a higher HBL was found in laparotomy than in laparoscopy.

Table 4. Multivariate linear regression analysis for influential factors of hidden blood loss in myomectomy.

| Influential factors | Coefficient B | t | P-value |
|---|---------------|--------|---------|
| Constant | 189.708 | 5.296 | 0.000* |
| Duration of surgery (minutes) | 1.552 | 4.024 | 0.000* |
| Number of removed leiomyomas (1, 2–3, or >3) | 49.166 | 3.640 | 0.000* |
| Location of myoma in the uterus (intramural or subserosal) | –52.646 | –2.027 | 0.044* |
| Age (years) | –0.036 | –0.530 | 0.597 |
| Body mass index, (kg/m ²) | –0.063 | –0.981 | 0.328 |
| Volume of largest removed leiomyoma (<95 or ≥95 cm ³) | 0.063 | 0.958 | 0.339 |
| Type of surgery (laparoscopic or laparotomic myomectomy) | 0.050 | 0.649 | 0.517 |

*Statistically significant at $P < 0.05$.

Myomectomy remains the most common treatment of symptomatic leiomyoma,^{27–29} but surgeons usually ignore the possibility of HBL occurring in myomectomy. Placing the patient in the Trendelenburg position during myomectomy can result in underestimation of the VBL because blood can accumulate in the abdominal cavity,³⁰ which increases the perioperative HBL. Our study illustrated that the perioperative VBL (137.81 ± 104.43 mL) was much less than the estimated TBL (492.24 ± 225.00 mL) in patients undergoing myomectomy. Furthermore, the HBL (354.39 ± 177.69 mL) accounted for a substantial proportion of the TBL (71.52% $\pm 15.75\%$) and was up to two to three times higher than the VBL. More importantly, the duration of surgery, number of removed leiomyomas, and location of removed leiomyomas were independent risk factors for HBL in myomectomy. However, age, BMI, volume of the largest removed leiomyoma, and type of surgery were not independent risk factors for HBL in myomectomy.

Our study showed that HBL accounted for a large percentage of TBL, and the mean Hb loss of patients undergoing myomectomy was 16.28 ± 8.95 g/L. Preoperative anemia was found in 74 patients, and postoperative anemia was detected in 153 patients. These results exceeded the severity of anemia caused by perioperative VBL and were probably associated with the HBL. Tian et al.³¹ stated that HBL may contribute to postoperative anemia and a high blood transfusion rate, inducing transfusion-related complications and increasing the incidence of adverse events. Postoperative anemia impairs tissue oxygenation and delays surgical wound healing. Moreover, in the early stage of anemia, the delivery of oxygen to critical organs is compromised and contributes to organ dysfunction.³² HBL generally has a negative impact on patients' outcomes,

contributing to the development of medical complications and prolonging the hospital stay.³³

One study showed that a preoperative plasma albumin concentration of <30 g/L was an independent risk factor for hidden HBL.³⁴ The preoperative plasma albumin concentration of the patients in the present study was normal; therefore, we cannot analyze the influence of the plasma albumin concentration on HBL in myomectomy. The patients' age (mean of 39.11 ± 5.24 years) was not an independent risk factor for HBL in myomectomy. A possible explanation for this finding is that all surgical patients were women of reproductive age, and their age span was small; thus, they had a rather strong compensatory ability perioperatively. Additionally, the patients' BMI had no significant predictive value on the perioperative HBL. A BMI of ≥ 30 kg/m² was defined as obesity.³⁵ A previous study illustrated that obesity may increase the hemorrhage volume, possibly because of the deeper subcutaneous adipose tissues.³⁶ Only three patients in the present study had a BMI of >30 kg/m², and the maximum BMI was 32.05 kg/m². This small sample size may have led to the lack of a significant effect of BMI on HBL. More obese patients should be enrolled in future studies to evaluate the effect of BMI on HBL.

Hsiao et al.³⁷ demonstrated that the maximum myoma diameter was an independent risk factor for blood loss in myomectomy. The present study showed that the size of the removed leiomyoma might not be an effective parameter with which to predict the HBL in myomectomy. Laparoscopic myomectomy is correlated with lower operative blood loss than laparotomic myomectomy as shown in various meta-analyses and reviews.^{4,38,39} However, our study showed that the type of surgery was not an independent risk factor for HBL in myomectomy.

A longer duration of surgery was a risk factor for higher HBL in myomectomy. Consistently, Wen et al.⁷ illustrated that a longer surgical time was correlated with a greater possibility of higher HBL in lumbar fusion surgery. Additionally, Ju and Hart⁴⁰ indicated that the HBL increased as the duration of surgery increased during anterior lumbar interbody fusion. Moreover, a study of the surgical treatment of cervical carcinoma showed that a longer surgical time enhanced the risk of higher HBL.²⁶ Therefore, we hypothesized that a longer duration of surgery may allow the omentum and intestinal space to absorb more blood, resulting in relatively low VBL, which conversely increases the HBL. Furthermore, when the surgery time is longer, the intraoperative blood may coagulate in the anatomical third space and not be drained out, and this blood is usually ignored when evaluating the VBL. Consistent with this, we found that the HBL was higher when the surgery time was longer.

Removal of multiple uterine leiomyomas was an independent risk factor for HBL in myomectomy. When multiple leiomyomas are resected, the contraction ability of the myometrium is attenuated, thus enlarging the potential tissue space and increasing the intraoperative and postoperative blood infiltration. In addition, many more capillaries are opened during enucleation of multiple leiomyomas, which increases the bleeding area of the uterus and blood extravasation. Therefore, removal of multiple uterine leiomyomas is a predictor of higher HBL in myomectomy.

Compared with a subserosal leiomyoma, removal of an intramural uterine leiomyoma has the potential to increase HBL in myomectomy. Subserosal leiomyomas are located outside the uterus, and the shallow defect in the uterus caused by enucleation of the subserosal leiomyoma can be adequately sutured and repaired.⁴¹ In patients with intramural leiomyomas,

however, especially large leiomyomas that have penetrated through the entire myometrium, suturing the deep and total layers of the myometrium may be difficult, resulting in inadequate uterine repair.⁴² This may increase the amount of blood that oozes from the surgical incision, and a hematoma may form, leading to a higher perioperative HBL than in subserosal leiomyoma enucleation. Additionally, more mechanical operations are required when enucleating intramural leiomyomas, thus increasing the mechanical injury of red blood cells and occurrence of hemolysis perioperatively.

In the present study, we quantified the HBL and applied a multivariate linear stepwise analysis to identify independent risk factors for HBL in myomectomy. However, this study still has several limitations. First, we used the patients' preoperative height and weight to calculate the EBV and assumed that the blood volume was constant perioperatively. Additionally, we used the Hct on postoperative day 3 to calculate the TBL and considered that the patients' body fluid shifts had been completed at this time by referring to previous studies. If these conditions were not maintained, minor errors in the blood loss calculation may have occurred. Second, the drainage fluid, which comprised tissue fluid, was calculated as part of the postoperative VBL. This might have led to underestimation of the HBL. Third, no patients in our study underwent a blood transfusion perioperatively. Therefore, we were unable to assess the impact of blood transfusion on the HBL. Finally, no antifibrinolytic or anticoagulant agents were utilized perioperatively, so we were unable to analyze the influence of these drugs on the HBL.

Our study findings indicate that further research is needed. The retrospective sample in our study was small, and a prospective analysis of a large multicenter sample is needed. Recording the volume of all removed leiomyomas during

myomectomy in a prospective study would allow for more precise evaluation of the effect of leiomyoma size on HBL. Importantly, more effort is required to determine the time point at which the bodily hemodynamics become stable post-operatively. Further research is also needed to explore the strategies for reducing the HBL perioperatively.

Conclusion

The HBL accounted for a significant percentage of TBL in myomectomy. Influential factors for higher HBL in this study were the duration of surgery, the number of removed leiomyomas, and the location of the removed leiomyomas during myomectomy. Additionally, the preoperative and postoperative Hct are important reference indexes with which to evaluate the HBL, which is usually neglected during perioperative blood management in clinical practice. Therefore, we should pay close attention to the Hct and have a full understanding of the HBL in perioperative blood management. This will help to establish strategies of appropriate fluid infusion and blood transfusion and improve patients' postoperative rehabilitation.

Abbreviations

EBV: estimated blood volume; TBL: total blood loss; VBL: visible blood loss; HBL: hidden blood loss; Hct: hematocrit; Hb: hemoglobin; BMI: body mass index

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This work was sponsored by the Science and Technology Innovation Team of Wenzhou city-Gynecological Oncology (No. 2017-1-4). The sponsors of the study had no involvement in

the data collection, analysis, or interpretation or the writing of the manuscript.

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