Minimization of curative surgery for treatment of early cervical cancer: a review

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Abstract

Surgery is effective and useful for curative treatment of patients with early invasive cervical cancer, yet minimization of surgical procedures provides many additional advantages for patients. Because the mean age of patients diagnosed with cervical precancer and invasive cancer has been decreasing, the need for minimization of surgery to reduce disruption of fertility is increasing. Trachelectomy is an innovative procedure for young patients with invasive cancer. Minimally invasive procedures are increasingly implemented in the treatment of patients with early cervical cancer, such as laparoscopic/robotic surgery and sentinel lymph node navigation. The use of modified radical hysterectomy may not only be curative but also minimally invasive for Stage IA2–IB1 patients with a tumor size <2 cm in diameter. Here, we have summarized and discussed the minimally invasive procedures for the treatment of patients with early cervical cancer.

Key words: cervical cancer, minimally invasive surgery, trachelectomy, laparoscopic surgery, sentinel lymph node, fertility-sparing, modified radical hysterectomy

Introduction

Minimization or simplification of treatment strategies may be favorable for any cancer patient who undergoes curative treatment, particularly surgical therapy. Surgical therapy is one of the most common strategies for treatment of cervical cancer, and minimally invasive surgery should be considered for early-stage patients with invasive cancer. Therefore, in recent years, advancement in surgical procedures for treatment of patients with early-stage cervical cancer have been directed by several objectives, including improving post-operative quality of life, and being fertility-sparing, minimally invasive and nerve-sparing. This has culminated in the development of new surgical procedures, such as trachelectomy, sentinel lymph node mapping and laparoscopic or robotic surgery, which are summarized in this review.

Recently, gynecologic oncologists have been able to utilize laparoscopic surgery not only for hysterectomy and trachelectomy, but also for lymphadenectomy; others have accomplished robot-assisted
surgery (1,2). Navigation utilizing sentinel lymph nodes has also used been shown to minimize lymphadenectomy for treatment of patients with invasive cervical cancer. Indications for modified radical hysterectomy (RH), not radical, for Stage IA2–IB1 patients to reduce the incidence of post-operative adverse events are also discussed.

In this review, we have summarized and discussed minimized surgical procedures for non-bulk cervical cancer (Stages I A1, I A2, I B1 and IIA1): minimally invasive laparoscopic and robotic surgeries, sentinel lymph node navigation for minimization of lymphadenectomy, trachelectomy for fertility-sparing surgery and indications for modified RH for early cervical cancer.

**Laparoscopic approach for cervical cancer**

Laparoscopic radical hysterectomy (LRH) was initially introduced in the early 1990s (3); however, there have been few prospective studies. A randomized Phase 2 trial with only 15 Stage IB cervical cancer patients who underwent either laparoscopically assisted radical vaginal hysterectomy (LARVH) or open abdominal radical hysterectomy (ARH) reported that duration of bladder catheterization (median 4 days versus 21 days) and hospital stay (median 5 days versus 7 days) were significantly reduced in patients who underwent LARVH than those who underwent ARH (4). Median blood loss was also reduced in LARVH (400 versus 1000 ml). However, the radicality was significantly lower in LARVH, with resected vaginal cuff (mean 1.26 versus 2.16 cm), resected cardinal ligament length (mean 1.30 versus 2.79 cm) and resected uterosacral ligament length (mean 1.47 versus 4.68 cm) significantly reduced in LARVH (4). This trial did not provide information about prognosis, and the authors had noted that the trial lacked statistical power due to the small number of women in each group and the low number of observed events (5). Currently, a randomized Phase 3 trial of LRH (or robotic) versus ARH is ongoing (6).

On the other hand, multiple retrospective studies have compared the use of LRH and ARH. One report matched patients with Stage IA2 to IIA cervical cancer with risk factors for recurrence, and compared 263 patients who underwent LRH with 263 patients who underwent ARH (7). The prognosis between these two groups were not significantly different; the LRH and ARH groups had 5-year recurrence-free survival rates of 92.8 and 94.4%, respectively (P = 0.499). However, blood loss (379.6 versus 541.1 ml, P < 0.001), post-operative hospital stay (12.5 versus 20.3 days, P < 0.001), and post-operative complication rate (9.2 versus 21%, P < 0.001) were lower in the LRH group than the ARH group (7). Of note, risk factors of either recurrence or death, even when limited to patients with bulky tumors by LRH (14–16). One retrospective analysis was performed with 303 patients with Stage IB2 and IIA2 cervical cancer (LRH group (n = 115) and ARH group (n = 188)) (14). In this study, there was no significant difference between the 5-year progression free survival (78% in the LRH group and 77% in the ARH group) and 5-year overall survival (83% in both groups); however the LRH group had reduced blood loss, post-operative hospital stay, and time to recovery for normal bowel movements (14). Other studies have also suggested the non-inferiority of LRH compared with ARH in the treatment of bulky cervical cancers (15,16). However, these retrospective studies may have had selection bias for the decision of surgical procedure (8). Therefore, further study is required to clarify indications for LRH, particularly in patients with bulky tumors, and prospective studies are warranted for demonstrating the safety of LRH for treatment of bulky tumors.

Laparoscopic radical trachelectomy (LRT) remains a challenging procedure to perform, and little is known about the outcome of patients who underwent LRT. In one study, 79 patients (IA2, n = 2; IB1, n = 72; IB2, n = 2; IIA1, n = 1) underwent LRT, 9 of whom (11%) showed recurrence with a median follow-up of 44 months (17). Six of the nine patients with recurrence had tumors >2 cm, and the authors reported that tumor size >2 cm and a depth of stromal invasion >50% were risk factors for recurrence with LRT (17). An analysis of LRT in Japan was published in 2013 (18), and reported that among 56 patients with I A2–IB1 cervical cancer, LRT were performed in 53 patients, and recurrence was observed in only one patient (1.8%) (18). The obstetric outcomes both in this study as well as another reported that pregnancy rates after LRT was 52–56%, and preterm birth was more frequently observed (48–60%) among the pregnant patients (18,19). Thus, further study is required to verify the use of LRT as a safe and effective fertility-sparing surgery, with focus on both recurrence rate and obstetric outcome. The high preterm birth frequency in these studies suggests that technical improvement may be necessary to improve the overall outcome of LRT.

**Navigation by sentinel lymph node**

Although lymph node metastasis is relatively rare in patients with early-stage cervical cancer, it is major prognostic factor. Systemic pelvic lymphadenectomy is normally performed with hysterectomy or trachelectomy in the surgical treatment of early-stage cervical cancer, despite that the majority of patients are usually free of lymph node metastasis. Systemic pelvic lymphadenectomy may have intraoperative complications, such as longer operation time and more blood loss, and post-operative complications, such as lymphoedema, lymph-o-cyst and bowel obstruction. To avoid these, sentinel lymph node mapping is a utilized as a useful screening method for detection of lymph node metastasis without the need for extended lymphadenectomy (20). In the NCCN Guidelines Version 2.2015, sentinel lymph node mapping is listed in Category 2B as recommended for surgical management of Stages I A1, I A2, I B1 and IIA1 cervical cancer.

Sentinel lymph nodes are the first lymph nodes to receive drainage from the tumor; when cancer cells begin their spread through the lymphatic system, the cells are initially trapped in the sentinel lymph nodes. The high preterm birth frequency in these studies suggests that technical improvement may be necessary to improve the overall outcome of LRT.
at the start of operation, allowing sentinel lymph nodes visualization during operation. In addition to the aforementioned conventional tracers, the use of near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) has merged as a complementary method for detection of sentinel lymph nodes. In this method, an NIR fluorescence probe (fluorophore) is injected at the start of the operation, and sentinel lymph nodes are visualized with a special imaging system which is able to both excite the fluorophore in vivo or ex vivo and to detect the emitted fluorescence, displaying the signal on a screen. Because the tissue penetration of NIR fluorescence is higher than that of vital dyes, NIR fluorescence enables surgeons to detect sentinel lymph nodes hidden under soft tissue, such as adipose or muscular tissues. Moreover, NIR does not disturb the surgical field because fluorescence is not visible to the naked eye.

The lymphatic flow from the uterine cervix normally drains into the obturator, external iliac, internal iliac or inter-iliac nodes, with 94% of sentinel lymph nodes detected in these areas (25). However, it has also been reported that sentinel lymph nodes may be found in other areas such as the common iliac (6.6%), para-aortic (2.0%), pre-sacral region (1.3%) and inguinal chain (0.07%). Therefore, sentinel lymph node mapping is very useful for detection of sentinel lymph nodes in these unusual areas which are not always dissected or evaluated.

A meta-analysis including 67 studies reported that the pooled detection rate of sentinel lymph nodes was 90.9, 80.9 and 92.3% by radioisotope, vital stains and combination of the two types of tracers, respectively, and the pooled sensitivity of sentinel lymph node detection was 92.0, 86.3 and 91.3%, respectively (26). NIR fluorescence had a pooled detection rate and sensitivity of 76.5 and 90.9%, respectively. Some of the studies included in this meta-analysis are shown in Table 1. Evaluation of the NIR fluorescence system has been reported in only a small number of cases, and a large randomized multicenter trial comparing NIR fluorescence with vital stains has been reported that sentinel lymph nodes may be found in other areas which are not always dissected or evaluated.

In summary, use of established protocols of sentinel lymph node mapping under intraoperative pathological testing with the aforementioned precautions may be a useful screening method to identify metastatic lymph nodes. However, the recommendation level of sentinel lymph node mapping by the NCCN Guidelines Version 2.2015 only falls under category 2B; furthermore sentinel lymph node mapping is not mentioned in the Japanese Cervical Cancer Treatment Guidelines of 2011. Therefore, further study is required for the potential routine use of sentinel lymph node mapping for the avoidance of unnecessary intensive lymphadenectomy in the treatment of early-stage cervical cancer.

### Table 1. Clinical studies on sentinel lymph node mapping in cervical cancer using conventional methods (vital stains, Tc or both) and near-infrared (NIR) fluorescence imaging

<table>
<thead>
<tr>
<th>Method</th>
<th>Study</th>
<th>Year</th>
<th>Stage</th>
<th>n</th>
<th>Detection rate</th>
<th>Optimal mapping rate</th>
<th>Sens</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stains and/or Tc</td>
<td>Haupsy</td>
<td>2007</td>
<td>IA1-BA</td>
<td>39</td>
<td>97.4%</td>
<td>28</td>
<td>73.7%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Altgassen</td>
<td>2008</td>
<td>IA1-IVB</td>
<td>507</td>
<td>99.4%</td>
<td>213</td>
<td>42.3%</td>
<td>77.4%</td>
</tr>
<tr>
<td></td>
<td>Gibula</td>
<td>2009</td>
<td>IB1-IBA</td>
<td>44</td>
<td>77.3%</td>
<td>26</td>
<td>76.5%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Comier</td>
<td>2011</td>
<td>IA1-IBA</td>
<td>122</td>
<td>93.4%</td>
<td>91</td>
<td>79.8%</td>
<td>87.5%</td>
</tr>
<tr>
<td></td>
<td>Lecru</td>
<td>2011</td>
<td>IA1-IB1</td>
<td>139</td>
<td>97.8%</td>
<td>104</td>
<td>76.5%</td>
<td>92.0%</td>
</tr>
<tr>
<td></td>
<td>Devaja</td>
<td>2012</td>
<td>IA1-IBA</td>
<td>86</td>
<td>97.7%</td>
<td>63</td>
<td>75.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Gibula</td>
<td>2012</td>
<td>IA-IBB</td>
<td>645*</td>
<td>NA</td>
<td>463</td>
<td>71.8%</td>
<td>91.0%</td>
</tr>
<tr>
<td></td>
<td>Slama</td>
<td>2013</td>
<td>IA2-IBB</td>
<td>225*</td>
<td>NA</td>
<td>175</td>
<td>77.8%</td>
<td>56.0%</td>
</tr>
<tr>
<td>NIR fluorescence</td>
<td>Furukawa</td>
<td>2010</td>
<td>NA</td>
<td>12</td>
<td>83.3%</td>
<td>10</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Crane</td>
<td>2011</td>
<td>IA2-IBA</td>
<td>10</td>
<td>60.0%</td>
<td>3</td>
<td>50.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Van der Vorst</td>
<td>2011</td>
<td>IB1-IB2</td>
<td>9</td>
<td>100.0%</td>
<td>8</td>
<td>88.9%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Schaafsma</td>
<td>2012</td>
<td>IB1</td>
<td>18</td>
<td>77.8%</td>
<td>11</td>
<td>78.6%</td>
<td>50.0%</td>
</tr>
</tbody>
</table>

*Patients with a sentinel lymph node detected on at least one pelvic side were included in these studies.
cancer in Japan over the past 20 years; however, incidence among women in the 20–39 years age group has gradually increased (30), possibly due to comparatively reduced screening in young women. Recently, radical trachelectomy (RT) has been performed for early-stage invasive cervical cancers, with demonstration of good survival ranging between 95 and 98% in cases without evidence of pelvic lymph nodes metastasis (31). Therefore, loss of fertility has become the primary concern for these women of childbearing age. RT is a modification of the traditional RH, which includes the section of the uterine arteries, removal of the paracervical tissue and vaginal cuff, preservation of the ovarian ligaments and reanastomosis of the uterine corpus and upper vagina with formation of a neo cervix. RT is a fertility-preserving technique initially described by Daniel Dargent in 1994 (32) for use in the treatment of FIGO Stage IA2–IIA cervical cancer. Interestingly, the concept of preserving the uterine corpus and the adnexa during RH, named ‘subfundic RH’, had already been described by Aburel et al. in 1932 (33); however, no follow-up data have been reported for this technique. To date, two types of RT, consisting of vaginal and abdominal approaches, are widely recognized around the world. In Japan, the abdominal approach is performed preferentially according to a survey conducted by the Japan Society of Obstetrics and Gynecology (34). In this section, we summarize the current status of both approaches and their clinical implication as fertility-sparing surgeries for cervical cancer.

Radical vaginal trachelectomy

Radical vaginal trachelectomy (RVT) is performed both laparoscopically and transvaginally, and Dargent’s method was initially developed using laparoscopic lymphadenectomy (32). Dargent had originally described that laparoscopic assessment was preliminary performed for pathologic confirmation of negative metastasis, which was then followed by trachelectomy. Because the entire width of the parametrial resection of the broad ligament in RVT corresponds to a Piver Class II RH (35), the radicality of RVT may not be comparable to traditional RH. However, RVT is now a widely accepted approach in patients with a lesion ≤2 cm in diameter, impairing oncogenic safety and preserving fertility (36,37).

Abdominal radical trachelectomy

As an alternative to the vaginal approach, Smith et al. (38) introduced the abdominal radical trachelectomy (ART). The size of the parametrial specimen obtained with the abdominal approach is >50% larger than that obtained with the vaginal approach (39). Therefore, the radicality of ART may correspond to that of a traditional Piver Class III RH. While RVT is restricted to patients with a tumor size of ≤2 cm in diameter, this limitation may not be applicable to ART (40,41). Thus, ART is a technically feasible fertility-sparing option for patients with larger tumors who are excluded from RVT, as long as patients are given informed consent of the risks and benefits of the procedure. Therefore, development of clinical eligibility criteria is required for ART for proper patient selection.

Complications and outcomes of both types of radical trachelectomy

Intraoperative complication rates, including the median duration of operation time, estimated blood loss and length of hospital stay for ART appear to be similar to those of RH (40). In contrast, these rates for RVT have been reported to be lower because the procedure is less extensive (42,43). Neither type of radical trachelectomy appear to have an increased recurrence rate compared with RH (44); however, Plante et al. (37) demonstrated that patients with a tumor size >2 cm who underwent RVT had a significantly higher risk of recurrence. In addition, lymph-vascular involvement or deep stromal invasion was suggested to be risk factors for recurrence after use of either approach (45). Pre-operative determination of the exact tumor size and lymph node status is an important measure for the selection of appropriate treatment for patients, and recently, several imaging modalities, such as ultrasonography, MRI and PET have been used for the evaluation of tumor size. Furthermore, intraoperative and post-operative assessment of the resected cervix is important for evaluation of the endocervical margin. However, it should be noted that the recurrence rate after radical trachelectomy has not yet been verified (46).

The extent and completeness of surgery affects the future fertility and obstetric outcomes of patients following RT. The fertility of women who undergo the abdominal approach compared with the vaginal approach is controversial (47,48). While favorable fertility and obstetric outcomes after RVT have been well documented despite the difference in surgical radicality compared with ART (49), poor obstetrical outcome has also been well reported in patients who underwent either RVT or ART (50–53). In Japan, a retrospective study at a single institution reported a pregnancy rate of 36% after ART, and a higher preterm birth rate between 32 and 36 weeks of gestation (64.7% of all pregnancies) (53). In addition, another retrospective study in Japan reported that all pregnancies after ART were achieved by assisted reproductive technology with in vitro fertilization and embryo transfer (54). Thus, with appropriate patient selection, RT may be a promising fertility-sparing procedure for women with early-stage cervical cancer. However, the need for counseling of risk of recurrence, infertility issues and obstetric risks before and after the surgery remains an issue to be addressed.

Modified radical hysterectomy for early invasive cancer

Over the past six decades, patients with early cervical cancer (Stages IB–IIA) have been treated with RH, due to the possibility of pelvic lymph node metastases and pathological parametrial involvement. However, RH leads to bladder dysfunction because the pelvic splanchic nerve is injured from the surgery (55). Therefore, it is important to identify patients with early invasive cancer whose lesions are amenable to a less-radical surgery. It has been demonstrated that elderly age, depth of invasion, tumor diameter, lymph-vascular space invasion and pelvic lymph node metastases are associated with parametrial involvement in Stage I cervical carcinoma (56,57). In particular, several studies have shown that the frequency of pathological parametrial involvement in Stage IB1 cervical cancer with a tumor size ≤2 cm was very low. Sartoli et al. investigated 263 patients who underwent ARH for treatment of early primary cervical cancer (215 with Stage IB and 48 with Stage IIA). Of patients with a tumor diameter ≤2 cm, the incidence of parametrial node metastases was 0%, while positive parametral nodes were found in 8.4% of patients with lesions ≥2 cm (P = 0.038) (58). Kinney et al. (59) reported that none of the 83 Stage IB cervical cancer patients with a tumor diameter ≤2 cm had parametrial lymph node metastasis. In an investigation of 842 patients with Stage IA–IB1 cervical cancer, Covens et al. (56) showed that the incidence of parametrial involvement in those with a tumor size of ≤2 cm, negative pelvic lymph nodes and depth of invasion ≤10 mm was 0.6%. The results of these studies suggest removal of the parametrium in surgery may not be necessary in Stage IB1 cervical cancer.
patients with tumors ≤2 cm. In these patients, it may be worth considering less-radical surgery in conjunction with pelvic lymphadenectomy.

Modified radical hysterectomy (MRH) is a surgical technique enabling preservation of the pelvic splanchnic nerves compared with RH. The MRH surgical procedure entails the cutting of the anterior layer, not the posterior, of the vesicouterine ligament of the uterus, mobilizing the ureter laterally, and removing the part of the parametrium and vaginal wall away from the uterine cervix. There have been several reports on the use of MRH for early-stage cervical cancer; however, the only randomized study of radical vs. MRH for Stage IB–IIA cervical cancer showed no significant differences in recurrence rate (26% RH vs. 24% MRH) or overall five-year survival (77% RH vs. 81% MRH), but significant differences in urologic morbidity (28% RH vs. 13% MRH) (60). Michalas et al. (61) performed a retrospective analysis with 435 Stage I–IIA cervical cancer patients (86.7% with Stage IB) treated by MRH and reported the five-year overall survival rate was 88.7%, concluding that MRH may be effectively utilized for treatment of early-stage cervical carcinomas ≤2 cm or smaller, with optimal surgical margins. Yang et al. (62) compared 39 Stage IB1 uterine cervical cancer patients having a tumor diameter ≤2 cm who underwent MRH, with 102 Stage IB1 cervical cancer patients who underwent RH, and showed the 3-year recurrence-free survival of patients who underwent MRH was 100%. The time to voiding smoothly of the MRH group was significantly shorter than that of the RH group (P < 0.001). Thus, the results of these studies indicate that MRH may be a superior procedure in the treatment of early cervical carcinoma.

The Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (JCOG) retrospectively analyzed the surgeries and pathologic findings of patients with Stage IB1 cervical cancer (JCOG0806-A), and reported that the five-year overall survival was 95.8%, and that pathological parametrial involvement was observed in only 1.9% patients with a tumor diameter ≤2 cm who underwent RH. On the other hand, five-year overall survival was 97.0% in patients with a lesion size ≤2 cm who underwent MRH (63). In 2013, the JCOG initiated a multi-institutional non-randomized confirmatory study to evaluate the efficacy of MRH in FIGO Stage IB1 uterine cervical cancer patients with a tumor diameter ≤2 cm (JCOG1101). A total of 240 patients will be recruited from 37 institutions over a period of 3 years. The primary endpoint is 5-year overall survival, with a non-inferiority margin set at 5% within the expected 5-year overall survival of RH, and a threshold of 90.8% (63).

In summary, MRH may not only be curative but also a minimally invasive surgical procedure for Stage IB1 cervical cancer patients with a tumor not exceeding 2 cm in diameter. However, further investigation is required to determine the prognosis of Stage IB1 cervical cancer patients treated with MRH. The results of the JCOG1101 trial may provide useful information for the appropriate management of such patients.

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Conflict of interest statement
None declared.

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