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Review Article

Surgery for cervical cancer: consensus & controversies

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Surgery plays an important role in the management of early-stage cervical cancer. Type III radical hysterectomy with bilateral pelvic lymph node dissection using open route is the standard surgical procedure. There is level I evidence against the use of laparoscopic/robotic approach for radical hysterectomy for cervical cancer. Emerging data support the use of sentinel lymph node biopsy and nerve sparing radical hysterectomy in carefully selected patients with early-stage disease. In locally advanced cervical cancer patients, the use of neoadjuvant chemotherapy (NACT) followed by radical surgery yields inferior disease-free survival compared to definitive concurrent chemoradiation therapy. Therefore, definitive concurrent chemoradiation is the standard treatment for locally advanced disease. Fertility preserving surgery is feasible in highly selected young patients. Role of less-radical surgical procedures in patients' with low-stage disease with good prognostic factors is under evaluation.

Key words Early-stage cervical cancer - fertility preservation - minimal invasive surgery - neoadjuvant chemotherapy - ovarian preservation - radical surgery

Cervical cancer continues to be a major health challenge globally. Although there has been a gradual decline in the incidence of cervical cancer in India, it still ranks the second most common cancer amongst Indian women[1]. Due to lack of organized screening programmes in the country, majority of patients with cervical cancer present with advanced disease and are treated with radical radiotherapy with or without concurrent chemotherapy. For patients presenting with early-stage disease, radical surgery is the preferred treatment. Conventionally, type III open radical hysterectomy with bilateral pelvic lymph node dissection has been the standard surgical procedure for operable cervical cancer. This surgical approach leads to an excellent survival, but at the cost of treatment related short and long-term complications[2]. In order to reduce surgery-related complications without compromising disease-free and overall survivals (OS), a variety of modifications in the standard surgical approach have been tried. A critical evaluation of important nuances in cervical cancer surgery is presented in this review.

Role of minimal invasive surgery in cervical cancer

Until recently, minimally invasive surgery (MIS), both laparoscopic and robotic approaches, has been widely used by gynaecologic oncologists for cervical cancer surgery and was referred by many international scientific bodies as the standard of care[3]. However, these recommendations were based on small observational studies and their meta-analyses showed

less intra-operative blood loss, fewer post-operative complications and faster recovery with equivalent survivals using MIS compared with open surgery in patients with early cervical cancer[4-6]. In 2015, Wang *et al*[4] presented a systematic review of 12 non-randomized studies comparing laparoscopic radical hysterectomy (754 patients) with open radical hysterectomy (785 patients) and found no significant difference in the five-year OS between the two approaches. Cao *et al*[5] in a meta-analysis of 22 studies involving 2292 patients concluded that laparoscopic approach was safe and had lower operative complications than open route. In a multicentre, retrospective study, Sert *et al*[6] compared robot-assisted radical hysterectomy with historical cohort of patients who underwent open surgery and found no significant differences in survival between the two groups and better perioperative outcomes with robotic surgery.

In 2018, results of Laparoscopic Approach to Cervical Cancer (LACC) trial were reported[7]. The LACC was the first phase III randomized control trial (RCT) that compared minimally invasive (laparoscopic or robotic) radical hysterectomy with open radical hysterectomy in women with early-stage cervical cancer. The study was designed to test non-inferiority of MIS compared with open route, and the primary end point was disease-free survival (DFS) at 4.5 yr. The quality standard of surgery was evaluated by an expert committee before a surgeon was allowed to participate in the trial. In the MIS group, majority of women were treated by conventional laparoscopy (84%), whereas 16 per cent women underwent robot-assisted surgery. The original sample size was 740 patients. However, the trial was stopped prematurely by data and safety monitoring committee (DSMC) in November 2017 after an interim analysis revealed a significantly lower DFS and OS in MIS group. At the time of termination, 631 (85%) patients were enrolled into the study. The rate of DFS at 4.5 yr was significantly inferior with MIS compared with open route; 86.0 per cent versus 96.5 per cent [hazard ratio (HR), 3.74; 95% confidence interval (CI), 1.63-8.58]. The study also showed a worse OS with MIS compared to open surgery; three-year OS 93.8 per cent versus 99.0 per cent (HR, 6.00; 95% CI, 1.77-20.30), respectively. MIS radical hysterectomy was associated with higher rates of all-cause mortality (HR, 6.00; 95% CI, 1.77-20.3), disease-specific mortality (HR, 6.56; 95% CI, 1.48-29.0), and loco-regional recurrence (HR, 4.26; 95% CI, 1.44-12.6) compared to open surgery[7].

The LACC trial also refuted previously held belief that MIS approach was associated with fewer perioperative complications and better quality of life compared with open route in patients undergoing radical hysterectomy[8,9]. There was no significant difference in rates of intra-operative complications, serious adverse events or long-term morbidities between the two arms[8]. In addition, no differences in mean FACT-Cx (Functional Assessment of Cancer Therapy – Cervix) total scores were identified between the MIS and open groups at six weeks or three months after surgery[9].

Along with LACC trial, a cohort study was conducted on National Cancer Database which included 2461 women who had undergone either a MIS or open radical hysterectomy for Stage IA2 to IB1 cervical cancer from 2010 to 2013[10]. Results of this retrospective study revealed that, at a median follow up of 45 months, the four-year mortality was significantly higher in women who underwent surgery using minimally invasive route compared to those who underwent open surgery; 9.1 per cent among women who underwent MIS and 5.3 per cent among those who underwent open surgery (HR, 1.65; 95% CI, 1.22 to 2.22; P=0.002). The widespread use of minimally invasive route for cervical cancer surgery in the United States coincided with a 0.8 per cent (95% CI, 0.3-1.4) per year decline in the four-year relative survival rate after 2006[10].

Since the publication of LACC trial, many observational studies comparing survival outcomes of MIS and open radical hysterectomy have been conducted by researchers. A recently published systematic review and meta-analysis of 15 such studies involving 9499 patients that compared survival outcomes after MIS (laparoscopic or robot-assisted) and open radical hysterectomy in patients with early-stage cervical cancer concluded that MIS radical hysterectomy was associated with an increased risk of recurrence and death compared with open surgery[11]. The pooled hazard of recurrence or death was 71 per cent higher (HR, 1.71; 95% CI, 1.36-2.15; P<0.001) and the hazard of death was 56 per cent higher (HR, 1.56; 95% CI, 1.16-2.11; P=0.004) with MIS compared with open surgery[11]. In contrast a large, retrospective, multi-institutional study from Germany by Köhler *et al*[12] revealed overall and recurrence-free survivals with vaginally assisted laparoscopic radical hysterectomy that were comparable to the open surgery arm of the LACC trial. However, patients included in this study had more favourable features (*i.e.,* smaller

tumours, less frequent lymph node involvement and less need for adjuvant therapy) compared to LACC trial population. Therefore, comparison of this study with LACC trial is not appropriate.

In view of level I evidence against the use of MIS in cervical cancer, many international guidelines including National Comprehensive Cancer Network (NCCN) and European Society of Gynecologic Oncology (ESGO) revised their previous recommendations and now state that the standard approach for radical hysterectomy is open abdominal surgery[13,14]. In September 2019, the Society for Gynecologic Oncology (SGO) released an update declaring 'the preponderance of the contemporary published literature suggests poorer survival outcomes for women undergoing radical hysterectomy for cervical cancer with minimally invasive compared with open radical hysterectomy'[15].

Many hypotheses have been postulated to explain poor survival with MIS in cervical cancer. These include the use of intrauterine manipulator, CO_2 gas for pneumo-insufflation and intracorporeal colpotomy, leading to tumour spillage in the peritoneal cavity during MIS[12]. An additional consideration may be the quality of surgery and extent of surgical resection in MIS compared with open radical hysterectomy. Currently, ongoing robot-assisted approach to cervical cancer trial is expected to address some of these issues[16]. However, until more data on oncological safety of MIS are available, open route continues to be the standard of care in patients with early cervical cancer.

Sentinel lymph node biopsy (SLNB) in cervical cancer

Lymph node metastasis is the single most important prognostic factor in patients with clinically early-stage cervical cancer. Lymph node status is also crucial for planning adjuvant treatment. Therefore, pelvic lymph node dissection (PLND) is an essential component of radical surgery for cervical cancer. The incidence of lymph node involvement in clinically early cervical cancer is estimated to be only 10-20 per cent[17]. Though PLND helps to identify lymph node metastasis, the procedure may be associated with intra- and post-operative complications. PLND-related intra-operative complications include neurovascular and ureteral injuries, increased blood loss and blood transfusion and increased surgical time. In the post-operative period, there is potential risk of infection, venous thrombo-embolism, lymphoedema and lymphocyst formation[18]. In order to reduce complications associated with PLND without compromising the detection of lymph node metastasis, sentinel lymph node biopsy (SLNB) has been extensively studied in patients with early cervical cancer with encouraging results. SLNB may serve as a relatively simple and effective method to know lymph node status in these patients. Sentinel lymph node technique may also increase identification of nodal metastasis due to the detection of lymph nodes at unusual locations and by identification of micro-metastases and isolated tumour cells[19,20].

The AGO Study Group conducted a large, prospective, multicentre study across Germany and Austria on SLN detection using either radio-labelled technetium, patent blue or both[21]. They found SLN detection rate of 88.6 per cent and the overall sensitivity of 77.4 per cent. Although the overall sensitivity of SLNB was low, but it was higher in tumours ≤20 mm (90.9%), with bilateral detection (87.2%), or when the combination of technetium and patent blue was used. Salvo *et al*[19] conducted a retrospective analysis of 188 patients with early cervical cancer who underwent SLN mapping using blue dye, technetium-99m sulphur colloid (Tc-99), and/or indocyanine green (ICG) followed by complete pelvic lymphadenectomy and showed a sensitivity of 96.4 per cent and negative predictive value (NPV) of 99.3 per cent. The false-negative rate was 3.6 per cent. In 2011, results of SENTICOL study were published, wherein 139 cervical cancer patients with Stage IA1–IB1 tumours underwent SLN biopsy followed by complete pelvic lymphadenectomy[20]. The authors reported a high sensitivity of 92 per cent and a NPV of 98 per cent of SLNB technique.

Use of ICG dye in place of methylene blue has improved overall and bilateral sentinel lymph nodes detection rates[22]. SLNB has been included in the NCCN guidelines for stage IB1 disease (<2 cm tumour)[23]. Adherence to the SLN mapping algorithm is important. A side-specific complete nodal dissection must be done in case of failure of SLN detection and all suspicious or grossly enlarged nodes must be removed regardless of SLN mapping. Adequate and quality pathological evaluation along with ultra-staging of sentinel lymph node is a prerequisite for SLNB because any undetected metastasis may adversely affect patient's prognosis.

Neoadjuvant chemotherapy (NACT) prior to surgery

Theoretically neoadjuvant chemotherapy (NACT) prior to surgery in locally advanced cervical cancer has

the potential to improve local control by increasing operability rates and offer a better systemic control by taking care of micro-metastasis. Earlier studies showed improvement in DFS and OS with NACT-surgery compared to radiation alone in patients with locally advanced cervical cancer[24,25]. However, these studies were conducted in pre-concurrent chemoradiation era and therefore their control arm was sub-optimal as per the current standard. The results of two well conducted RCTs that compared NACT-surgery with concurrent chemoradiation have been reported. The Indian study was a single-centre, phase III, randomized trial which recruited 633 patients with squamous cervical cancer (SCC) in stages IB2, IIA and IIB (FIGO 2009). Patients were randomized between three cycles of NACT (paclitaxel + carboplatin; three weekly) followed by radical hysterectomy (experimental arm) versus standard concurrent chemoradiation (control arm)[26]. The study revealed a poorer DFS in NACT-surgery group compared with chemoradiation group; five-year DFS 69.3 per cent versus 76.7 per cent (HR, 1.38; 95% CI, 1.02-1.87; *P*=0.038). The overall survival was similar between the two arms; five-year OS 75.4 and 74.7 per cent, respectively. In NACT arm, radical surgery was feasible in 72.15 per cent of patients and 32.2 per cent of patients required adjuvant treatment (radiation or chemoradiation) after surgery. Therefore, a considerable fraction of patients in NACT-surgery arm required multimodality treatment. The study concluded that chemoradiation was superior to NACT-surgery in locally advanced cervical cancers. The second trial by EORTC group was a multicentre, multinational phase III RCT which included 620 patients with stages IB2, IIA and IIB (FIGO 2014) cervical cancer[27]. There was no difference in OS (72 *vs.* 76%, *P*=0.332) between the two arms. Results on the quality of life and long-term toxicity are yet to be reported. A meta-analysis of the above studies also showed superiority of concurrent chemoradiation over NACT-surgery for DFS and severe acute toxicity and no difference in OS in patients with locally advanced cervical cancer[28]. In view of level I evidence, NACT surgery cannot be recommended in patients with locally advanced cervical cancer and concurrent chemoradiation remains the standard of care.

Nerve sparing radical hysterectomy (NSRH)

Intra-operative injury to autonomic nerve during a radical hysterectomy is the cause for postoperative pelvic dysfunction including bladder, sexual and colorectal dysfunctions. Due to their close proximity to cardinal, uterosacral and vesicouterine ligaments, pelvic autonomic nerves are at risk of injury during a conventional radical surgery for cervical cancer. Damage may occur to the hypogastric nerve (sympathetic nerve), the pelvic splanchnic nerve (parasympathetic nerve), and the vesical branch of the pelvic plexus (both sympathetic and parasympathetic nerves) at various steps in a radical hysterectomy. The concept of nerve-sparing hysterectomy was described and popularized by Japanese gynaecologists who took great efforts to modify the classical radical hysterectomy so as to preserve pelvic autonomic nerves while maintaining the oncological outcome (the so-called Tokyo method)[29]. Data from various observational studies have demonstrated that NSRH minimizes surgery-related pelvic dysfunction, with similar oncological outcomes as conventional radical hysterectomy. A meta-analysis by Lee *et al*[30] including 1796 patients from 23 studies revealed a lower incidence of urinary, colorectal, sexual dysfunction and similar DFS and OS with NSRH compared with conventional radical hysterectomy. A retrospective cohort study on 406 patients from China demonstrated that NSRH for cervical cancer patients had better urinary outcomes than conventional radical hysterectomy without compromising survival[31]. Although NSRH has shown a positive impact on the quality of life of the patients, the technique has not been standardized and oncological safety has not been proven in randomized studies[32,33]. Therefore, further studies are required to establish the role of NSRH.

Fertility sparing surgery

The standard surgery for cervical cancer leads to permanent loss of fertility. The innovative concept of radical trachelectomy for fertility preservation in a young patient with early-cervical cancer was conceived and popularized by Dargent *et al*[34] in the early 70s. Since then, the procedure has undergone several modifications. Dargent procedure involved the resection of the cervix, the upper part of the vagina and the medial part of the parametria through a vaginal approach while preserving the uterine corpus combined with laparoscopic PLND. With the introduction of abdominal trachelectomy using either MIS or an open route, the vaginal procedure has become less common.

Both oncological and fertility outcomes should be kept in mind while considering fertility sparing treatment and a detailed pre-operative counselling must be done. The proper selection of patients for fertility-

sparing surgery is important. Pre-treatment fertility potential, cervical tumour size and location, histological subtype, depth of stromal invasion, lymph vascular space invasion (LVSI) and nodal status are important factors in deciding for fertility-sparing surgery[35]. Aggressive histologic types such as neuroendocrine carcinoma and clear cell carcinoma are not suitable for fertility-sparing surgery[36]. The presence of lymph nodal metastasis is an absolute contraindication for trachelectomy.

Fertility-preserving surgical procedure can be further tailored based on the disease stage. In women with stage 1A1 disease without LVSI, radical cone with negative margins can be done as the risk of lymph node metastasis is <1 per cent in these patients[37]. In women with FIGO stage IA2 or stage 1A1 with LVSI, the risk of pelvic lymph node metastasis is around 5-8 per cent[38]. Therefore, radical trachelectomy with PLND is recommended, although some centres also utilize radical cone or simple trachelectomy along with PLND. For women with stage 1B1 disease, radical trachelectomy (abdominal or vaginal) combined with pelvic lymphadenectomy is the procedure of choice. Currently, three studies are ongoing to evaluate the role of cone biopsy or simple trachelectomy compared to radical trachelectomy in women undergoing fertility-preserving surgeries[39-41].

An abdominal radical trachelectomy (ART) allows a more extensive paracervical and paravaginal dissection compared with vaginal approach. Einstein *et al*[42] showed a 50 per cent wider parametrial resection in ART compared with vaginal radical trachelectomy. However, ART is also associated with increased risk of adhesions and increased frequency of ligation of uterine artery which may potentially impair subsequent fertility. A few cases of uterine necrosis, septic complications and higher rates of premature delivery have also been reported[43]. Stage 1B2 tumours (>2 cm) are associated with a higher rate of lymph node metastasis and local recurrence and conventionally not considered for fertility-preserving surgery. NACT preceding fertility-sparing surgery has been introduced as a treatment option to preserve fertility in cervical cancer patients with tumours more than 2 cm. However, only limited data are available on oncological outcomes and safety of such procedures[44]. NACT reduces the tumour volume and the risk of microscopic disease thus increases feasibility of fertility-sparing surgery. A combination of paclitaxel and cisplatin doublet is used commonly. Cervical cancer treated with neoadjuvant chemotherapy followed by fertility sparing surgery (CoNteSSa) and Neoadjuvant chemotherapy and conservative surgery in cervical cancer to preserve fertility (NeoCon-F) are two combined prospective phase II studies evaluating the feasibility of NACT in such cases[45]. These studies aim to examine the safety and efficacy of NACT and fertility-preserving surgery by simple trachelectomy/conization in women with node negative FIGO 2018 stage IB2 cervical cancer.

Intrauterine infection and premature rupture of membranes are two most important antepartum complications after radical trachelectomy. Obstetric outcome is better with a less radical approach. A recent meta-analysis by Nezhat *et al*[46] found mean clinical pregnancy rate after vaginal radical trachelectomy at 67.5 per cent and mean live birth rate at 67.9 per cent. A low cancer recurrence rate at 3.2 per cent at a median follow up of 39.7 months was also noted.

Ovarian preservation

The median age for cervical cancer is mid 40s; therefore, preservation of ovarian function is an important quality of life consideration in these patients. The incidence of ovarian metastasis is low in early-stage cervical cancer and therefore, ovarian preservation is safe in carefully selected patients. Risk factors for ovarian metastasis in early-stage cervical cancer include histopathological subtype, LVSI[45]; age, FIGO stage, depth of stromal involvement[47,48] and parametrial invasion[49]. Ovarian preservation is controversial in adenocarcinoma due to a higher risk of ovarian metastasis compared with squamous carcinoma[50]. However, Cheng *et al*[49] in a meta-analysis of cervical adenocarcinoma did not find any significant difference in survival with or without ovarian preservation. Striking a balance between oncological safety and benefits of ovarian preservation is crucial in a young patient with early cervical cancer and must be discussed with the patient before treatment. Preserved ovaries may be left *in situ* or transposed outside pelvis in case adjuvant radiation is anticipated.

Less- or non-radical surgery

Parametrectomy is responsible for the majority of complications related to radical hysterectomy for cervical cancer. In patients with low-risk disease, *i.e.,* tumour size ≤2 cm, superficial stromal involvement, absence of LVSI and negative lymph nodes, the risk of parametrial involvement is <1 per cent[49-52]. Considering the rarity of parametrial involvement in patients with low-risk cervical cancer, many researchers have

questioned the need for removal of parametrial tissue and extensive dissection of adjacent vital structures in the pelvis and have proposed non-radical procedures such as a simple hysterectomy or conization. Landoni *et al*[53] in a small prospective randomized trial of 125 patients compared class I (extrafascial hysterectomy) to class III (radical hysterectomy) hysterectomy in patients with stages IBI and IIA cervical cancer with ≤4 cm tumour diameter. This study showed no significant difference in adjuvant treatment, recurrence and overall survival rates between the two arms but a higher surgical morbidity after Class III radical hysterectomy (84 vs. 45%). Reade *et al*[54] analyzed 341 patients with early-stage cervical cancer who were treated with either simple hysterectomy or simple trachelectomy and showed crude recurrence rate 6.3 per cent and disease-related mortality rate 1.5 per cent, comparable outcomes were achieved by radical procedures.

These and other small studies raised the possibility that non-radical surgical procedures may be considered in carefully selected low-risk cervical cancer patients. The criteria for low-risk are not well defined but generally include stage IB 1 (tumour size ≤2 cm), without deep stromal invasion, no LVSI and negative pelvic lymph nodes[51,52]. A preoperative magnetic resonance imaging is useful to determine tumour size, depth of cervical stromal invasion and parametrial and vaginal spread.

Currently, one randomized trial (the SHAPE trial: NCT01658930) and two prospective cohort studies (GOG278: NCT01649089 and ConCerv: NCT01048853) are ongoing to assess oncologic safety, treatment-related morbidity, quality of life and cost-effectiveness of non-radical surgery for low-risk early-stage cervical cancer[39-41]. The SHAPE (simple hysterectomy and pelvic node dissection in early cervix cancer) trial is a phase III randomized trial comparing simple hysterectomy and pelvic LND to radical hysterectomy and pelvic LND (or cone biopsy to radical trachelectomy) in women with stage IA2–IB1cervical cancer with favourable features (squamous or adenocarcinoma or adenosquamous histology, tumour size ≤2 cm, stromal invasion <50 per cent and negative lymph nodes on imaging[39]. The primary end point of the study is pelvic relapse-free survival in two groups. Treatment-related morbidity, quality of life and cost-effectiveness will also be evaluated. The GOG 278 is a prospective study evaluating the impact of non-radical surgery (extrafascial hysterectomy or cervical conization and pelvic LND) on bladder, bowel and sexual function and the incidence and severity of lymphoedema after non-radical surgery. The study includes women with stage IA2–IB1 disease and favourable pathologic characteristics (squamous cell carcinoma of any grade or grade 1-2 adenocarcinoma, tumour size ≤2 cm, stromal invasion <10 mm and no LVSI)[40]. The MD Anderson Cancer Center, USA is conducting a prospective, international, multicentre cohort study ConCerv (NCT01048853) with the aim to assess the oncologic safety and feasibility of simple hysterectomy or cone biopsy for early-stage (IA2–IB1 <2 cm) low-risk (negative LVSI, negative margins on cone specimen) cervical cancer[41].

Until results of these ongoing studies become available, non-radical surgery cannot be considered a standard procedure and should not be practiced outside a clinical trial setting.

Conclusion

Surgery plays an important role in the management of early-stage cervical cancer. A careful selection of patients is the key to successful outcomes. Conventional type III open radical hysterectomy with bilateral pelvic lymph node dissection continues to be the standard procedure. Recent evidence is compelling against the use of minimally invasive route and open route is recommended for radical hysterectomy. There is emerging evidence in favour of SLNB, but each centre must standardize the procedure before implementing it in routine practice. Fertility preservation is possible in highly selected patients. Ovaries can be preserved in a young patient undergoing radical hysterectomy. The role of less-radical surgery in patients with early-cervical cancer with good prognostic features is still investigational and must not be offered outside a trial.

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