

Smaller but Better? The Effort to Shrink Surgical Scale for Selected Early Stage Cervical Cancer

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Cervical Cancer (CC) is the third most common gynecologic malignancy in United States. In 2012, new discovery and death cases are estimated to be 12,170 and 4,220 [1]. The probability of developing invasive CC in population statistics from 2006 to 2008 is 0.68% (1 in 147) life-long, and 0.15% (1 in 680) from birth to 39 years old [2]. CC is caused by the long term, repeated infection of high-risk group Human Papillomatous Virus in the transitional zone of uterine cervix. Because the sexual exposure starts younger now, approximate 60% CC is diagnosed younger than 50 years of age [1]. Early Stage Cervical Cancer (ESCC) is defined as the cancer only restricted in the uterine cervix. According to recent official stage system of Federation of International Gynecology and Obstetrics (FIGO), 2009, ESCC includes from stage IA1 to IB2. Fortunately, based on recent effective screening system and easily notable self-warning symptoms, near 42-49% CC cases are found to be ESCC [1]. Epithelial histology, including squamous cell carcinoma, adenocarcinoma and adenosquamous cell carcinoma, is covered over 95% of CC and its tumor behavior looks better than other rare histology [3].

Surgical excision plays a major role in treating ESCC. The surgical scale depends on the disease stage, risk factors, surgeons' experience and patients' desire. If the childbearing is no longer considered, uterus with cervix is recommended to be removed. Simple extrafascial hysterectomy is accepted for FIGO stage IA1 CC without Lymphatic Vascular Space Invasion (LVSI). From FIGO stage IA1 with LVSI to IB2, the standard recommendation is radical hysterectomy and complete Bilateral Pelvic Lymph Nodes Dissection (BPLND) [4], in order to remove uterus, para-cervical tissue, partial upper vagina and lymphatic tissue. If childbearing is still strongly desired, to preserve uterine corpus in ESCC is reasonable because the invasion of upper uterine part is rare in such cases. Today, the choice and indication of fertility-preserving surgery in ESCC been increasing, not only because of the increase of ESCC in reproductive age female, but also the childbearing age is delayed in our society. Decreasing the co-morbidity and keeping the quality of life in surgery for ESCC are the important focus. The trend and evidence of fertility sparing surgery of ESCC will be discussed according to its disease stage.

FIGO Stage IA1 ESCC without LVSI

According to the guideline of National Comprehensive Cancer Network (NCCN) [4], the standard acceptable fertility sparing procedure is just cervical cone excision to obtain negative surgical margin. This kind of ESCC is treated the same as high grade pre-cancer, intra-epithelial neoplastic lesion.

FIGO Stage IA1 with LVSI, Stage IA2 and "Selected Small Tumor Volume" Stage IB1 ESCC

LVSI is an important histological factor for predicting the risks of recurrence and metastases in ESCC after reviewing of literatures. The relationship of LVSI, parametrial invasion and pelvic lymph node metastasis has been established after histopathological studies. Increase of primary tumor size is usually correlated with deeper cervical stromal invasion, which also increase the risk of parametrial spread. For

preserving fertility, pelvic lymph nodes and paracervical tissue are suggested to be removed. NCCN guideline traditionally recommends modified (type II) Radical Trachelectomy (RT) with BPLND for LVSI positive stage IA1 ESCC. Class-III RT with BPLND is recommended for all ESCC cases with stage IA2 or "selected small tumor volume" stage IB1 regardless of LVSI.

Because of the heterogeneity of stage FIGO IB1, the "small tumor volume" needs to be defined clearly. Recent most acceptable criteria are: Age \leq 45 years old, favorable epithelial histology, gross visible tumor \leq 2 cm, tumor limited to the cervix which is confirmed by image study, no corpus or uterine cavity invasion, no evidence of pelvic lymph node metastasis and/or other distant metastases [5]. For preserving the ability of childbearing, these cases chosen for RT should desire their future fertility without known documentation of infertility [6].

RT is to remove entire exo-cervix, majority of endo-cervix, some upper vagina and parametrium via vaginal, abdominal and minimal invasive (laparoscopic or robotic) approach. Dargent et al. described their first series of vaginal approach in 1994 [7]. After couple decades, the recurrent and death rate of RT in selected ESCC is approximate 5% and 3%, which is comparative to traditional radical hysterectomy [3]. However, for the purpose of fertility sparing, this procedure still seems imperfect in clinical practice. Major possible complications are classified into 3 parts:

Surgical related complications: RT has the same surgical complication as radical hysterectomy. Damage to bladder, ureters, rectum, and autonomic nerve intra-operatively are all possible although they are rare. Urinary retention, constipation or ileus is frequent during post-operative period [8].

Menstrual or sexual related complications: Menstrual problems are most frequently encountered after surgery. Dysmenorrhea, metrorrhagia and amenorrhea are easily complained. Problems with cerclage sutures include excessive vaginal discharge, isthmic stenosis, and occasional deep dyspareunia [9]. Obstetrical complications: This is the most criticized part of RT. Infertility, high possibility of second trimester miscarriage (double than normal population), premature rupture of membranes and premature delivery (near 30%) are all reported, probably originated from the ascending infections because of absence of cervix [10].

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Alternative Smaller Scale Surgery for FIGO Stage IA1 with LVSI, Stage IA2 and “Specific Selected Small Tumor Volume” Stage IB1 ESCC

After accumulating experience from many trials and literatures gradually, to shrink the surgical scale has been proposed in many kinds of cancers. Smaller scale decreases the surgery related complications but not the therapeutic effect. For example, surgical scale of breast and vulvar cancer is smaller than it used to be. However, more strict selective criteria is reasonable in decision making of choosing smaller scale surgery, in order not to compromise patients' disease free period and survivorship.

RT can preserve the fertility, but it is not good enough in maintenance of fertile and obstetrical outcome clinically. Lack of real cervical stroma and para-cervical tissue probably the underlying problem. Parametrial invasion is estimated to be only 0.6% if primary tumor ≤ 20 mm, cervical stromal invasion ≤ 10 mm and absence of pelvic lymph nodes metastases in ESCC [11]. The surgical role of trachelectomy with parametrectomy for such early stage cases is questionable now. Surprising, some pioneers try to introduce large cone excision (cold knife, laser or loop) for specific small tumor volume stage IB1 candidates after pathologic negative pelvic lymph nodes confirmed by laparoscopic BPLND [12,13]. FIGO stage IA1 and IA2 can also fit these selective criteria because they are only microscopic tumors in ESCC.

Their selective criteria for specific stage IB1 cases include: gross tumor size ≤ 15 -20 mm, depth of stromal invasion ≤ 10 mm [12], or tumor volume ≤ 500 mm³ (length² \times depth \times 1/2) [13], with pathologic negative pelvic lymph nodes. Other requirements are the same as RT. In the preliminary retrospective data compared with RT, they showed comparative prognosis, survivorship, but markedly decreased post-operative co-morbidities with excellent obstetrical outcome [7,8]. Now, large scale, ongoing prospective trials have been carried out for confirming this inspiring result [14].

FIGO Stage IB1 ESCC which Cannot Fit the Criteria of RT or Experimental Cone Excision

This kind of stage IB1 is not suitable for fertility preserving surgical procedure because of high failure rate of local control. The possibility of LVSI, microscopic parametrial invasion and pelvic lymph nodes metastases are still higher [15]. Radiation therapy seems not avoidable in this group if any of major risk factor presents. For such cases with strong desire of child-bearing, there are two possible solutions in this group: the first one is to try laparoscopic BPLND for excluding nodal disease in this group, then start Neoadjuvant Chemotherapy (NACT) before RT in node-negative group. Case series has been published [16] but the experience and evidence are not sufficient. Large scale prospective trial may be necessary in the future. The second choice is the transposition of both ovaries out of pelvic region in nodal positive group if pelvic radiation therapy is not avoidable. This procedure is effective to prevent ovarian damage [17], make them possible to process artificial reproductive procedure later.

Stage IB2 ESCC

Some experts exclude this stage from ESCC. According to recent

NCCN guideline, no fertility preserving procedure is recommended. Laparoscopic BPLND follow by NACT then RT for nodal negative cases or ovarian transposition for nodal positive cases are their possible choices like bulky IB1 ESCC mentioned above [16,17].

In conclusion, many experts did their much effort to preserve the reproductive ability in ESCC. Shrinking surgical scale to preserve more and more residual cervical stroma, reducing primary tumor volume by NACT and laparoscopic BPLND for excluding nodal and parametrial metastases before conservative procedure all make childbearing possible. But some management still needs time and strong enough evidence to support the safety and acceptance in the future.

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