Conservative treatment in cervical cancer

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Abstract

Cervical cancer (CC) is increasingly being diagnosed in women of reproductive age, and fertility-sparing treatment has become an essential part of the therapeutic strategy for early stage CC (FIGO stage IA1-IB1). Conization is currently considered a safe and feasible treatment for stage IA1 CC without lymphovascular space invasion (LVSI). After the first report proposing vaginal radical trachelectomy (VRT) for the treatment of stage IB1 cervical tumors, several studies have evaluated vaginal, abdominal, and minimally-invasive approaches. Recent decades have been characterized by increased conservative treatment of more advanced tumors; in addition, several series assessing the oncological and obstetric outcomes of less radical surgery have been published. This review provides and overview of current evidence-based knowledge about the conservative management of CC, focusing on new perspectives and controversial issues.

Key words: cervical cancer, conization, fertility, trachelectomy

Introduction

Due to the widespread institution of screening programs, an estimated 40% of women with cervical cancer (CC) will receive their first diagnosis while they are of child-bearing age [1]. Standard treatment for patients with early stage CC (from stage IA1 to IB1) is radical hysterectomy with pelvic lymphadenectomy (PLND), However, fertility-sparing surgery (FSS) has become an essential part of the treatment strategy and dedicated sections have been included in international guidelines [2-4].

Rationale for conservative surgery in cervical cancer

CC spreads locally into the vagina, parametria and lymph nodes (LN). The risk of pelvic LN involvement increases with disease stage and ranges from 5–7% in stage IA2, up to 16% in stage IB1 <2 cm, and >30% in locally advanced neoplasia, but is not an issue for stage IA1 without lymphovascular space invasion (LVSI) where the risk of LN involvement is estimated to be <1%. In these cases, cone biopsy might represent the definitive treatment, provided that endocervical margins are negative. In all other patients, the feasibility of conservative management mainly depends on the absence of LN metastases and parametrial invasion. However, there is strong association between pelvic nodal involvement and parametrial status [5-7]. In fact, parametrial involvement was only found in 0.4% of women with negative LN, no LVSI and tumor size <2 cm [8, 9] and it has been reported that parametrial disease is associated with tumor size >2 cm, depth of invasion >10 mm and LN involvement [10]. These data suggest that a less radical approach could be considered for selected patients.

Patient selection and counselling

Conservative treatment of CC patients needs to take a "personalized" approach and each situation has to be considered unique. A multidisciplinary team potentially including a gynecologic surgeon, an oncologist, an expert in reproductive medicine, a gynecologic pathologist and a psychologist should be involved in the management of each case. Before undergoing fertility-sparing treatment, all pathological specimens should be reviewed to examine the histological subtype, grade, depth of invasion, LVSI and margin status [11]. After that, thorough patient counseling with discussion of all potential is-

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sues relating to both oncologic and obstetric outcomes is mandatory; patients should be informed about international guidelines and the current standard of care. An inadequate approach to these patients could influence their attempts to get pregnant and nullify all the efforts made to conservatively manage the disease.

Fertility-sparing surgery in CC

Lymph node assessment

Assessing LN status is mandatory before considering FSS. Pelvic lymph node dissection (PLND) is associated with several morbidities and it is important to note that the risk of LN metastases in stage IB1 tumors <2 cm is <6%. As a result, several authors have suggested the use of sentinel lymph node (SLN) mapping to reduce the rate of unnecessary LN dissection. A recently published meta-analysis reported the accuracy of SLN in this setting to be around 89% [12]. The large prospective SENTICOL trial has evaluated the use of pre-operative lymphoscintigraphy and intraoperative SLN mapping in women with stage IA1 to IB1 CC [13]. Sensitivity of SLN biopsy for detection of LN metastases was 92%, with a negative predictive value (NPV) of 98.2%, and these values were higher for tumors <2 cm. Based on these findings, it was been suggested that this procedure be performed in selected women; in international guidelines, SLN mapping is considered feasible but still experimental [14].

Surgical approach, oncological and fertility outcomes

In the presence of negative LN status, use of several conservative surgical techniques has been reported, and the chosen approach mainly depends on the risk of parametrial invasion for each stage and on surgery-associated morbidity. Given that the risk of LN involvement for stage IA1-2 tumors with no LVSI is <1%, cone biopsy is recommended when endocervical margins are negative [3]. One debated issue is whether the cold knife conization (CKC) or loop electrosurgical excision procedure (LEEP) technique are preferred to guarantee adequate and negative margins. National Comprehensive Cancer Network (NCCN) guidelines list CKC as the preferred method; LEEP is also acceptable despite the remote possibility of thermal artifact. Regarding obstetric outcomes, the largest report on conization documented 21 pregnancies in 36 patients, and four miscarriages (three in the first trimester and one in the second trimester) [15]. However, a lack of consensus about the preferred technique remains given that the reported incidence of pregnancy-related morbidities with CKC or LEEP is inconsistent [16].

Considering stage IB1 tumors, radical trachelectomy (RT) with PLND could be considered an option for patients who want to preserve their fertility. Use of vaginal radical trachelectomy (VRT) was first proposed in 1994; since then, several studies of this approach have been published [17, 18]. Concerning oncological outcome, the reported recurrence rate was 5%, with a higher risk for tumors >2 cm. In 1997, the technique of abdominal radical trachelectomy (ART) was described, with a more radical parametrial resection even in cases with altered anatomy cited as an advantage. In a 2009 study, the average parametrial length obtained abdominally was significantly wider than that obtained vaginally [18]. This supports the idea that ART should be reserved for larger tumors, in particular in IB1 tumors >2 cm, because the risk of parametrial invasion is very low in smaller tumors with no LVSI [19-21]. More recently, minimally invasive surgery (MIS) has been widely applied, and laparoscopic and robot-assisted RT have been introduced, ensuring less blood loss and shorter hospital stay. A review comparing MIS with open RT has been recently published [22]. No oncological outcome data were available, but the ART group had a more favorable obstetric outcome (pregnancy rate 51% *vs* 28%). While promising, data regarding robotics are scarce, and obstetric and oncological outcomes need to be monitored further.

Based on available literature, RT requires the removal of the parametria and this might lead to increased morbidity and worse obstetric outcomes. A recent review pooled the results from several studies, including patients with low-risk CC after VRT and ART [20]. In the VRT group, a pregnancy rate of 27.3% was reported, with miscarriage rates of 16% in the first trimester and 7% in the second trimester, and 22% of infants delivered before 36 weeks' gestation; 46% of infants were born at term. After ART, the pregnancy rate was 18.1%, with a similar rate of third trimester deliveries. In this population, the shortened cervix and reduced amount of intracervical mucus facilitate the development of infection (chorioamnionitis), increasing the risk of premature labor. Moreover, cervical stenosis has been reported with an average incidence of 10.5% [23]. In such cases, another very important point has to be considered: for patients with IB1 tumors, negative LN and tumor size <2 cm, the risk of parametrial involvement varies between 0.4-0.6% [15, 24]. Therefore, these data clearly support a more conservative approach in this patient group, who would be safely cured with simple hysterectomy, simple trachelectomy or even conization. Actually, for this particular subset of patients, outcomes after more conservative surgery are comparable to those of radical procedures [25]. A recent

review pooled the oncological and obstetrical outcomes of 260 patients with low-risk disease (FIGO IA1 with LVSI, FIGO IA2, IB1) treated with less radical surgery. After a median follow-up of 47 months, 2 patients relapsed and 1 had died of their disease [11]. The largest report on conization associated with PLND included 36 women; after a median follow-up of 66 months, only 1 patient experienced recurrence and 21 pregnancies were registered, with three fetal losses in the first trimester and one in the second trimester [15].

Several series have described oncological and fertility outcomes of patients with bulky tumors of the cervix (FIGO IB1 >2 cm up to IIA1). For these patients, neo-adjuvant chemotherapy (NACT) followed by FSS is a conservative option. A recent review summarizes the evidence from all available studies [26]. It is important to note that this procedure is currently only offered in selected centers and is therefore still considered experimental. Furthermore, patient selection in this setting is even more important and a strong desire to retain fertility and appropriate counselling are mandatory. The most commonly used neoadjuvant regimen is a combination of paclitaxel and cisplatin with ifosfamide or epirubicin (TIP/TEP). Among 149 patients treated at two centers managing higher-risk patients, only five disease recurrences have been reported; two patients died of their disease [26]. However, accurate determination of oncological outcomes was limited by patient heterogeneity [26]. Regarding pregnancy rates, a better outcome was observed for less radical procedures compared with RT. The best candidates for FSS seem to be those with only microscopic disease after NACT; patients with LN involvement should be excluded. Currently, there is not yet any definitive consensus on the optimal surgical approach for these patients (ART, VRT, simple trachelectomy). Further studies are needed in this setting. A note of caution is that NACT might affect ovarian reserve because cisplatin is moderately gonadotoxic and ifosfamide is a highly gonadotoxic alkylating agent. Fertility preservation techniques should be considered before starting such treatments.

Cervical cancer in pregnancy

A total of 1-3% of women with CC are diagnosed during pregnancy or in the postpartum period. In this context, treatment is still experimental and should therefore only be offered in specialized centers and to selected patients. Each case should be assessed individually. When the CC diagnosis occurs before 22 to 25 weeks' gestation, diagnostic conization is better performed between 12 and 20 weeks, and LN status could be assessed laparoscopically.

Conization is considered a safe treatment, but RT is not recommended for stage IA2 and IB1 tumors <2 cm because 32% of pregnancies among 19 reported cases in the literature resulted in an abortion. Less radical surgery is possible, even if data in this specific setting are lacking. For patients with stage IB1 >2 cm or higher, NACT could be considered but oncological safety still needs to be assessed. For diagnosis after 22-25 weeks' gestation, LN status cannot be evaluated. In early-stage disease, delay of treatment until fetal maturity or disease progression is advisable. In these cases, or if higher stage disease is present, NACT until fetal maturity is the only option to retain pregnancy [27, 28].

Follow-up after treatment

As suggested in the 2016 NCCN guidelines, recommended surveillance should be based on a patient's risk of recurrence and personal preferences [14]. In most centers, follow-up, including clinical, colposcopic and cytologic examination, is scheduled every 3-4 months for the first two years, then every 6 months until the fifth year after surgery and annually thereafter [19, 29]. A high rate of false positive smears have been detected among these patients, with atypical cells found in 58-60% [30]. Some centers perform magnetic resonance imaging at 6, 12 and 18 months after surgery, even if interpretation of the findings could be misleading due to altered anatomy.

Future perspectives, debated issues, ongoing trials

Three ongoing trials are prospectively assessing the role of conservative surgery in low-risk, early-stage CC. The ConCerv multicenter trial (NCT01048853) is evaluating safety and feasibility of simple hysterectomy and PLND with SLN in patients with IA2-IB1 <2 cm, no LVSI CC. The second study is the SHAPE randomized trial (NCT01658930), coordinated by the Gynecologic Cancer InterGroup (GCIG), in which patients with stage IA2-IB1 <2 cm CC (with or without LVSI and with <10 mm stromal invasion) are randomized to receive radical hysterectomy + PLND (control arm) or simple hysterectomy + PLND (experimental arm). The aim is to assess the safety and morbidity of simple hysterectomy to standard treatment. The third ongoing trial (GOG 278 [NCT01649089]) is evaluating physical function and quality of life before and after extrafascial hysterectomy or cone biopsy with pelvic lymphadenectomy for stage IA1 (LVSI+) and IA2-IB1 (≤2 cm) CC.

For patients who need radical hysterectomy due to locally advanced CC, ovarian transposition allows preservation of ovarian function (both endocrinologically and for

possible future embryo transfer) before delivery of gonadocidal doses of radiation therapy. Uterine transplantation is another option, and has been shown to be feasible in a group of seven patients, one of whom had undergone radical hysterectomy for CC [31]. One live birth has been recorded in one patient who underwent uterine transplant due to Rokitansky syndrome [32]. However, several concerns exist because all patients studied to date have received immunosuppressive therapy which might increase the risk of relapse in a CC patient. Moreover, radiation therapy could affect the uterine vasculature, potentially impairing embryo implantation. Uterine transplantation requires further investigation before it becomes a realistic option for patients who cannot undergo FSS for CC.

Conclusions

Current literature demonstrates that conservative treatment appears to be the ideal option for women with early-stage CC and is likely to replace radical hysterectomy as the standard of care for these patients. In international guidelines, RT is already considered a standard FSS for patients with IB1 <2 cm tumors; however, the high postoperative morbidity rate has led clinicians to evaluate a less radical approach. For tumors >2 cm, NACT followed by FSS could be carefully considered. Ongoing prospective trials will provide further evidence for the safety and feasibility of FSS in patients with early stage CC.

Acknowledgments

Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

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