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REVIEW PAPER

Early-stage cervical cancer treatment – what's new?

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Abstract

The gold standard of treatment for patients with early-stage cervical cancer is radical hysterectomy, in agreement with the entire scientific community. During the last decade, growing evidence has supported the minimally invasive approach. Several studies have suggested that the minimally invasive approach could improve surgical and perioperative outcomes. Because of these findings, ESCO/ESTRO/ESP guidelines state that a "minimally invasive approach is favoured" in comparison with open surgery, as a grade B recommendation. Because of the lack of a grade A recommendation, this randomized Laparoscopic Approach to Cervical Cancer trial evaluated open vs. minimally invasive approach in the early stage. It demonstrated an increase in mortality among patients treated with minimally invasive surgery, revolutionizing current thinking on the primary surgical approach to early cervical cancer. The aim of this study is to analyse which is the best treatment for early cervical cancer and which approach is the most effective at the moment. Further studies are needed to state with certainty the appropriateness of the treatments offered to patients with early cervical cancer.

Key words: minimally invasive surgery, gynaecological cancer, laparoscopic approach, cervical cancer, hysterectomy.

Introduction

Cervical cancer is the third most common female cancer worldwide [1], with around 529,800 new cases and 275,100 deaths every year [2]. This represents a major health problem due to its high incidence, especially in developing countries, where it accounts for the majority of gynaecological cancers, and it is still the leading cause of cancer deaths in women [2, 3]. In developed countries, the diffused use of primary and secondary prevention [4] decreased the incidence of cervical cancer enormously [5, 6]

Human papillomavirus (HPV) is the cause of most cervical cancers [7]. In sexually active women, the rate of infection reaches 80%, and except for in rare cases, the immune system is completely able to fight and clear the infection spontaneously [2, 8]. When the infection is persistent, a series of precursor dysplastic lesions of the cervical epithelium develops [5].

Prevention of HPV-related cancers consists of HPV vaccines and early detection through screening programs [9]. All types of vaccines against HPV (bivalent, quadrivalent, and nonavalent vaccines) are very effective in dramatically reducing the incidence of HPV infection and the related lesions [10, 11]. Human papillomavirus vaccination plays a role also in the prevention of recurrent lesions, and it has been shown that the combination of surgical excision and HPV vaccination significantly reduces the risk of recurrent lesions, compared to surgical excision alone [5]. Secondary prevention is done through Pap smear and HPV testing to detect early cervical dysplasia and to eventually treat it, avoiding its progression to cervical cancer [11].

These types of prevention strategies are not applicable for adenocarcinoma of the uterine cervix, which accounts for 15–25% of all cervical cancers; its incidence has increased in the last decades, while the mortality has remained the same [12]. This difference is due to both the difficulty to do a screening program for adenocarcinoma of the cervix and its poor sensitivity to radiotherapy and chemotherapy [13].

There are different therapeutic options to treat cervical cancers, depending on the characteristics of the patient and the cancer itself.

Cancer antigen is treated through radical hysterectomy, either through conventional laparotomy or laparoscopic surgery (minimally invasive surgery) [14, 15]. The latter has been proven to be superior to conventional laparotomy in terms of less intraoperative and postoperative bleeding, lower incidence of lymphocystis, and shorter catheter removal time and hospital stay, while it has equivalent efficacy on complete re-

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moval of lymph nodes [16] and in reducing the levels of circulant biomarkers, such as cancer antigen 125, carcinoembryonic antigen, the soluble form of interleukin 2 receptor (sIL-2R), and tumour necrosis factor α [13, 17].

Cervical dysplasia is treated by conization [18], which is a simple, safe, and effective way to remove the lesion, and it has an excellent prognosis, with negligible effect on fertility. However, this is not true in the case of a recurrent lesion, the management of which is challenging and correlated with some problems such as preterm delivery. Different variables influence the risk of recurrent/persistent lesions, such as age, severity of the lesion, type of HPV, margin status, HPV persistence, and HPV vaccination after surgery. Moreover, positive endocervical margins give a higher risk compared to positive ectocervical margins. However, positive ectocervical margins significantly increase the risk of recurrent/persistent disease. For this reason, it is important to stratify the patients before the treatment, with the help of a nomogram, based on their risk of having recurrent/persistent dysplasia after primary conization [5, 6].

Treatment of early cervical cancer and locally invasive cancer consists of radical hysterectomy or trachelectomy, with pelvic lymphadenectomy, and concurrent chemotherapy and radiotherapy [10, 19]. Treatment options and prognosis vary depending on the International Federation of Gynaecology and Obstetrics (FIGO) stage of the cancer.

There is an ongoing debate on the better surgical method for early cervical cancer: minimally invasive surgery (laparoscopic and robotic surgery) compared to open surgery. Nowadays minimally invasive surgery should be offered only inside a controlled trial [18, 20, 21]. Cervical cancer is complex, and so a combination of chemotherapy and radiotherapy, or immunotherapy is needed. For recurrent/persistent cervical cancer, pembrolizumab combined with chemotherapy and/or bevacizumab is approved as first-line therapy, while tisotumab is approved as second-line therapy [10].

The primary aim of this review of the state of the art is to analyse which is the best treatment for early cervical cancer and which approach is the most effective at the moment.

What we know about early cervical cancer treatment

After diagnosis, patients with cervical cancer should be staged according to the TNM classification (tumour-nodus-metastases) and to the FIGO clinical staging [22, 23]. Understanding the natural history of the disease is a key point in the correct application of staging systems. Based on this principle, it is known that cervical cancer can progressively spread by extension into adjacent areas like the uterus, vagina, parametrial tissue, pelvic floor, bladder, or rectum; it also spreads to regional (pelvic) and para-aortic lymph nodes [24, 25], and eventually distant metastasis may occur by the haematogenous route [26]. Treatment plans and prognosis require accurate staging. Early stages of cervical cancer are classified by FIGO stages as IA1 with lymph-vascular space invasion (LVSI), IA2, IB1, IB2, and IIA1 [23]. Early-stage cervical cancer is most commonly treated through radiotherapy and surgery because both treatments have the same rate of success in oncological outcomes [26, 27]. This result was confirmed by an important randomized clinical trial conducted by Landoni *et al*. in 1997. This trial compared primary surgery with primary radiotherapy in IB-IIA stages and showed that disease-free survival and overall survival for both groups were the same [28, 29]. However, surgery is generally considered the primary method of treatment in early-stage cervical cancer because of quality-of-life issues and ovarian failure [27–31]. As for life quality, even though data are still controversial, it seems that radiotherapy causes more complications and morbidity [32]. Consequently, surgery is considered the best option, especially for young patients who present no comorbidities and for whom preservation of hormonal and sexual functions is relevant. On the contrary, radiotherapy with or without chemotherapy is recommended for elderly patients, for whom the preservation of hormonal and sexual functions are not such priorities in comparison with the risks of radical surgery, or for patients who have comorbidities or low functional status [23].

Radical hysterectomy – which one is best?

In the case of surgery, the standard of care for early cervical cancer is radical hysterectomy [33, 34]. There are several kinds of surgical approach to performing hysterectomy, including abdominal, vaginal, traditional laparoscopic, robot-assisted laparoscopic, single-port laparoscopic/robotic surgery, and vaginal natural orifice transluminal endoscopic surgery [17]. The choice of surgical approach to hysterectomy depends on different elements, but in particular on the clinical indication and the condition of the patient [35–38], on the technical skills of the surgeon, and on the patient's preference [17, 39–42]. A classic landmark surgical procedure of gynaecological oncology for cervical cancer has been represented by abdominal radical hysterectomy (ARH) [43–45]. However, early-stage cervical cancer surgery can be managed by minimally invasive surgery, which, in general, is associated with lower intra-operative morbidity and faster recovery, compared with laparotomy, and permits an accurate nerve-sparing approach [39, 46, 47]. As for radical hysterectomy, data have highlighted its safety and effectiveness in the early stage, because it allows tumour removal and identification of risk factors for personalized adjuvant treatments

[22, 23, 45, 48]. For these reasons, FIGO recommended the utilization of radical hysterectomy for early stages of cervical cancer [46, 47, 49]. In 2017 the National Comprehensive Cancer Network (NCCN) and in 2018 the European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology (ESGO/ESTRO/ESP) recommended the execution of radical hysterectomy via open or minimally invasive surgery [21, 50–53]. Until 2018, the safety and effectiveness also of minimally invasive radical hysterectomy had been highlighted by several retrospective studies [54–58]. Due to this great amount of data, the use of minimally invasive radical hysterectomy was strongly recommended by the whole scientific community [21, 54–58] and, in coherence with this recommendation, the ESGO/ESTRO/ESP guidelines stated that a "minimally invasive approach is favoured (grade B of recommendation)" [22]. In any case, there was no level A of recommendation, so Ramirez *et al*. [56] conducted the Laparoscopic Approach to Cervical Cancer (LACC) trial, designed to test the merit of minimally invasive radical hysterectomy in comparison with the open approach. The aim of the LACC trial was to assess the non-inferiority of a minimally invasive approach in comparison to open surgery. Moreover, it led to a radical change of the surgical treatment of early-stage cervical cancer [56]. The patients included in the LACC trial were patients with stage IA1 (with LVSI), IA2, or IB1 cervical cancer. Their histologic subtype of cervical cancer was squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma. These patients were randomly treated through minimally invasive surgery or open surgery. A total of 319 patients were included in the minimally invasive group, of whom 84.4% and 15.6% had laparoscopic and robotic-assisted surgery, respectively. The primary outcome of the trial was the 4.5-year disease-free survival rate. Ramirez *et al*. observed that patients who underwent minimally invasive surgery experienced worse 4.5-year survival outcomes in comparison with patients who had open radical hysterectomy. In particular, the 4.5-year survival was 86% among women assigned to minimally invasive surgery and 96.5% in those who underwent open surgery. Those patients who had undergone minimally invasive radical hysterectomy proved to be more likely to develop a loco-regional recurrence (HR: 4.26, 95% CI: 1.44–12.60). The 3-year disease-free survival following minimally invasive and open radical hysterectomy was 91.2% and 97.1%, respectively. These data showed that minimally invasive surgery was worse than open surgery [52, 59]. This trial, as is well known, was stopped early by the data and safety monitoring committee after enrolling 631 of a planned 740 patients. Minimally invasive surgery was also associated with inferior overall survival. The results of the LACC trial were confirmed by retrospective analysis using the National Cancer Institute (NCI)'s Surveillance, Epidemiology, and End Results data in the US. It was demonstrated that minimally invasive surgery was associated with an increase in the mortality rate among patients affected by cervical cancer.

Management of early cervical cancer after laparoscopic approach to cervical cancer

When the LACC trial was published, there was a real a shift from the use of minimally invasive to open surgery [58, 60–64]. In fact, the unexpected results of the LACC trial showed that a minimally invasive approach is associated with lower rates of disease-free survival and overall survival than open ARH among women with early-stage cervical cancer [34]. This trial subverted current knowledge and beliefs about minimally invasive surgery. In addition to this, it was demonstrated by 2 secondary analyses of the randomized LACC trial that minimally invasive and open approaches were related to similar morbidity rates and postoperative quality of life (QoL) [62–65]. In the first one, Obermair *et al*. [61] assessed the impact of adverse events (including intraoperative and postoperative events within 6 months of surgery) on patients who received minimally invasive and open radical hysterectomy, while Frumovitz *et al*. [62] evaluated the QoL (at baseline, weeks, and 3 months after surgery) in the LACC population. These studies showed that patients who had undergone minimally invasive surgery and patients who had undergone open surgery experienced a similar risk of treatment-related adverse events. What is more, their QoL (assessed through validated quality-of-life and symptom assessments) was not related to the kind of surgical approach [62]. According to these data, a high risk of recurrence threatens patients with early-stage cervical cancer undergoing minimally invasive surgery [60]. Moreover, minimally invasive surgery, compared with open surgery, is not related to improved perioperative outcomes, such as morbidity rate or QoL [20, 62, 66, 67]. The management of cervical cancer patients was deeply influenced globally by the publication of the results of the LACC. Surgeons were encouraged by SGO to explain the data of the LACC trial to their patients, to advise them properly [68]. Open surgery was suggested as the "standard and recommended approach to radical hysterectomy" by the NCCN [69]. As expected, after the results of the LACC trial were published, there was a dramatic decrease in the number of procedures performed via laparoscopic and robot-assisted surgery. It is not known exactly why the minimally invasive approach is related to worse disease-free and overall survival. There are 3 possible reasons that have been identified by experts:

- lack of radicality,
- surgeon expertise,
- tumour dissemination at the time of colpotomy [70, 71].

The most credible reason seems to be the latter. As previously stated, the LACC trial clearly demonstrated that minimally invasive radical hysterectomy is related to worse survival. Considering this evidence, the minimally invasive approach should be an option only in limited situations, such as in the context of controlled trials. However, improvement of the knowledge on the treatment of early-stage cervical cancer will come from further well-designed retrospective studies. In addition, accumulating evidence suggests that preoperative conization potentially plays a protective role in patients with an IB1 tumour; in particular, patients undergoing preoperative conization (vs. cervical biopsy) were less likely to experience a recurrence [59, 72–77].

Another possible are of research is 3D laparoscopy [78]. In particular, its introduction aims at improving traditional laparoscopic skills without the need for a robotic platform. Data on the applicability of 3D laparoscopy in the setting of gynaecological surgery and gynaecological oncology are poor. The little evidence we have shows that patients undergoing 3D laparoscopy experience a trend toward shorter operative time than patients undergoing conventional laparoscopy, and shorter length of hospital stay [78–81]. Hence, patients' surgical outcomes were better than the surgical outcomes with traditional laparoscopy, but further studies are needed to evaluate the recurrence and complications of this technique.

Conclusions

Results of the LACC trial subverted current knowledge, forcing oncology centres to reflect about the appropriateness of the care offered. Patients should be informed about the conflicting data, underlining that future evidence may change current clinical practice. Patients' chance of survival must not be affected by inadequate surgery, even if technologically more attractive. The target is patients' survival and quality of life, which should always be kept in mind.

Disclosure

The authors report no conflict of interest.

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