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Surgery after Chemoradiation Therapy in Persistent/ Recurrent locally advanced cervical cancer. Is Exenteration Always Necessary?

Albert Reyes Claret[1]* and Ángel Martín Jiménez[2]

Department of Obstetrics and Gynecology, Son Llàtzer Hospital, Spain

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***Corresponding author**: Albert Reyes Claret, Obstetrics and Gynecology, Hospital Son Llàtzer, Spain, Tel: +0034679575814; Email: reyesclaret.albert@gmail.com

Abstract

In cases of persistent or recurrent disease in locally advanced cervical cancer after chemoradiation therapy, surgery will be the last chance for survival, with pelvic exenteration representing the most used option. However, in cases of small central recurrences (<2 centimetres) limited to the cervix or vagina may be candidates for a less radical approach, specifically laparoscopic radical hysterectomy. This intervention has received little attention in the literature. The current article comprehensively outlines the rationale behind the management of these cases and discusses the existing literature. Indications for this approach must ensure that neighbouring organs such as the rectum or the bladder are not affected in the preoperative studies. The intention is to offer a less mutilating surgery than exenteration in cases of small persistent or recurrent disease.

Keywords: Cervical cancer; Chemoradiation therapy; Radical hysterectomy; Laparoscopy

Mini Review

Since 1999 chemoradiation therapy (CRT) has represented the standard treatment for locally advanced cervical cancer (LACC) [1,2]. However, about 30-50% of patients diagnosed with LACC will recur and ultimately die because of the disease [3]. Complete response after concurrent CRT and stage, are the two most important prognostic factors. The rate of residual disease after primary treatment increases in relation to the FIGO stage, and range between 35-61% [4-7]. It's accepted that surgery is the only curative treatment for patients with recurrent or persistent pelvic cancer after CRT.

Although exenteration is the common surgical approach in post-radiation patients with isolated pelvic relapse, radical hysterectomy may be an option in carefully selected patients with small central recurrences (< 2 cm) limited to the cervix or upper vagina [8]. (NCCN Guidelines Version 1. 2018 Cervical Cancer). This treatment option has barely been published in literature [9-11]. In a series of 50 patients at Memorial Sloan-Kattering Center [10] that were operated on by laparotomy (radical hysterectomy PIVER II, III), a 5-year survival rate of 90% was found in lesions smaller than 2cm, versus 64% for bigger lesions. The high initial rates of serious postoperative complications (20-40%) with 26% of postoperative fistula [9], took to the practical abolishment of this technique. Most recent papers about completion surgery after CRT in LACC by laparotomy have had better results [5,12,13]. Perhaps, these improved results are due to the fact that surgeons tend to perform hysterectomy soon after CRT to avoid development of radiation-induced fibrosis. However, the role of this adjuvant surgery performed a few weeks after primary chemoradiation treatment (4-8 weeks) remain controversial [12-13] and the benefit to overall or disease free survival has never been demonstrated [14].

Ferrandina et al. [15] reported in a 362 consecutive LACC (FIGO stage IB2-IVA) patients submitted to laparotomic radical hysterectomy after CRT (interval to radical surgery around 6 weeks) a 25.7% postoperative complication rate. Classe et al. [16] showed that uretero vaginal fistulas occurred in 3.5%, whereas Toubul et al. [5] found a urinary fistula rate of 7.3% and 2 deaths linked to surgery. The literature describes radicality of the hysterectomy, residual disease and pelvic lymph node involvement as major risk factors for the occurrence of complications [5,17,18]. The effect of CRT on pelvic tissues had been proven to increase the difficulties of surgical dissection, due to an inflammation process, vascular fibrosis and firm adhesions. This effect promotes the loss of anatomical planes and determines an increased risk of morbidity.

Firm pelvic tissue fibrosis is documented in almost 50% of cases [19] and often involves the visico-uterine ligament and paracervix tissue. Due to these difficulties, a laparoscopic

approach is generally not used to perform radical hysterectomy after CRT. In our knowledge, there are only 6 articles employing minimally invasive approach to perform a radical hysterectomy [6,19-23]. All of them, except a case reported by Zygouris [22] and our previous study [23], were performed as part of adjuvant surgery a few weeks after completion CRT treatment. The two major studies published up to now with a minimally invasive approach by laparoscopy, are a prospective phase II study by Gallota [19] and a retrospective cohort study by Colombo [6].

In Gallota's study, with 58 patients submitted to a laparoscopic radical hysterectomy at 6-8 weeks after CRT, the feasibility rate was 94.8% with no intraoperative complications and a postoperative rate of Grade II-III complications of 14.5%. In Colombo's study with 46 patients with IB2, IIA and IIB cervical cancer submitted to laparoscopic radical hysterectomy at 4-6 weeks after CRT were compared with a cohort of 56 patients operated by laparotomy. The feasibility rate was 85% in the laparoscopic group, with a conversion to laparotomy rate of 15%. The intraoperative complications rate was 10.9%, whereas postoperative complications rate was 23.9% for grade II and 4.3% for grade IV.

Clear margins were obtained in 91.3% of cases. Compared with the laparotomy group, the laparoscopic group showed significant reduction of morbidity, with fewer urinary complications, blood loss and hospital stay. In our previous study [23] about five suspected persistent disease cases; the surgery was performed at least 4 months after CRT therapy was finished. Our complication rate was higher than above mentioned studies performed by laparoscopy. Feasibility rate was 100%. All cases underwent type C1 radical hysterectomy. The median operating time was 214 (140-360) min. Only one intraoperative complication was registered (ureteral injury). Three postoperative complications were found, two of them were grade II. However, one grade IV complication was documented: a patient with a vesicovaginal fistula who died due to long-term postoperative complications (urinary sepsis) at 1 year and 5 months after surgery. Histopathological study reported tumour-free specimens in four patients with complete response after CRT, and one patient had 1mm residual tumour. Clear surgical margins were obtained in all cases. With mean follow-up of 20.8 months (range 8-58) secondary recurrence after radical hysterectomy was not documented.

This higher rate of complications, compared to the other series, is justified by further delayed surgery and the progressive effect of radiation therapy over the time. Toxicities that develop later than 3 months after the completion of radiation are termed late or chronic effects. The late effects of radiation are due to the damage at the capillary level where endothelial cell proliferation results in a lower diffusion of oxygen into the tissues, resulting in fibrosis. There is less resistance to infection, trauma or functional stress due to this change in vasculature and circulation [24].

Tissue fibrosis is related with major intraoperative complications and high morbidity rates particularly in the presence of preoperative brachytherapy. On the other hand, the extent of surgery is related with high rate of morbidity especially urinary complications [5]. Radical hysterectomy could be more logical in patients with residual disease to guarantee free margins, and complete parametrical excision improves the percentage of complete resection. However this radicality entails more complications. On the other hand, laparoscopic approach could also be a way to decrease the morbidity of the surgery, especially in blood loss, wound infections and hospital stay, without a higher rate of positive margins [6]. Although radiotherapy inevitably affects the autonomous innervations of the bladder, and radiation fibrosis involves the vesicouterine ligament, with the magnified vision of laparoscopy, the nerve-sparing surgery is possible, with more accuracy and safety [23].

Based on literature, radical hysterectomy after CRT therapy in small central recurrent or persistent disease is feasible with an acceptable rate of complications and oncological results. However, the main problem is how to determine certainly the presence of residual disease after CRT. Currently, there is no accurate method of detecting residual or recurrent disease after CRT, which makes it difficult to determine population of women who needs salvage surgery. Physical examination is the most often used method for diagnosis with sensitivity and specificity rates of 51 and 62% respectively [25]. Histological confirmation prior to surgery is difficult to achieve.

It is well known that radiation-induced morphologic changes continue also after finishing CRT with a risk of false positive findings in biopsies or cytology. Sensitivity of vaginal cytology is poor, probably due to radiation-induced dysmorphia. Imaging techniques have been included to improve the diagnosis of residual/persistent disease. The magnetic resonance image (MRI) is the standard imaging technique used. However, its accuracy in predicting response after CRT still is under debate because of the high risk of false positive results. Studies show sensitivities of 80%, specificities of 55% and positive and negative predictive values of 50 and 83%, respectively [26]. In the other hand, over the last few years, there has been an increase in the use of positron emission tomography/computed tomography (PET/TC) to detect residual or recurrent disease. Meta-analysis showed that the sensitivity and specificity of PET-CT for local regional recurrence were 0.82 (95 % CI: 0.72–0.90) and 0.98 % (95 % CI: 0.96–0.99), respectively [27]. So, the use of PET-CT in local regional recurrent/persistent cervical cancer is not currently supported by published literature [28].

Conclusion

Indications for this approach, needs a positive preoperative biopsy and ensure that neighbouring organs such as the rectum or the bladder are not affected in the preoperative studies. The intention is to offer a less mutilating surgery than exenteration in cases of small persistent or recurrent central disease. Although radical hysterectomy is a valid option to avoid an exenteration in carefully selected cases, a multicentre prospectively study is needed.

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