

Preservation of fertility in cervical cancer: a new look

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The first virtue of knowledge is the ability to face what is not evident.

Jacques Lacan



The development of surgical procedures for the preservation of fertility in cervical cancer in the last two decades has allowed that a significant proportion of patients can not only be cured of their disease but maintain their reproductive potential. In June 2016, Enrica Bentivegna et al¹ published in *Lancet Oncology* the article *Oncological outcomes after fertility-sparing surgery for cervical cancer: a systematic review*, an interesting revision of the oncological safety of fertility sparing procedures. In the article, they make a thorough tour between the different techniques available for the moment: the radical vaginal trachelectomy or Dargent operation, the simple trachelectomy or cone biopsy, laparoscopic or assisted by robot abdominal trachelectomy and neoadjuvant chemotherapy with sparing surgery.

In a review of the literature in French and English published between January 1987 and February 2016, they insisted on the analysis of factors such as tumor size, Histologic Type, lymphovascular invasion (LVI) and histologic type. They also assessed the influence of margins in morbi-mortality and fertility preservation performance. One of the aspects of greatest interest was the analysis of the pattern of relapse and the importance of the stromal invasion, to date two of the less studied aspects. Their analysis results were reported separately according to the type of procedure.

One of the most innovative contributions of this review was the data presented with the use of neoadjuvant chemotherapy and fertility preservation procedures. One hundred fourteen cases were collected and grouped into 17 series. Eighty-six patients (75%) had stage IB1 disease while the remaining 28 patients had more advanced disease (25 stage IB2 and 3 stage IIA1). In patients with stage IB1, 66% (52 patients) had tumors between 2 and 4 cm. Thirteen patients were excluded for lymph node involvement, progression of the disease or positive margins. In total 99 patients were subjected to neoadjuvant chemotherapy and uterine preservation.

Almost all patients received platinum-based schemes through intra-arterial exclusively (femoral or uterine) or in combination with intravenous therapy. In some patients, it was decided to perform a lymphadenectomy prior to neoadjuvant therapy in order to establish the nodal status.

Forty-two patients were subjected to radical trachelectomy, while 51 patients underwent a simple trachelectomy, cold or laser conization. By the time of the publication two patients were awaiting his surgery. Forty five patients presented a complete histopathologic response or presence of pre-invasive disease, seven had a response greater than 50% and tumor persistence equal to or greater than 3mm was recorded in 31 patients. Nineteen patients required some type of adjuvant therapy and 15 were submitted to a hysterectomy for bulky residual disease, positive margins or progression of disease. Six patients (6%) relapsed, of whom 2 died. These six recurrences were distributed as follows: two patients with disease IB2 and post- neoadjuvant chemotherapy residual disease, three in patients with stage IB1 with tumors between 2 and 4 cm and a patient with stage IB1 disease less than 2 cm.

There were 54 pregnancies, noting a better trend in patients who underwent surgical procedures that did not include a parametrectomy. In this series does not communicate the number of live and preterm births.

While this review is the best documented published so far its results do not allow to obtain an immediate clinical applicability, if best delineate the criteria to include patients with bulky tumors in a treatment that preserves their fertility. It is well known that about one-third of patients with stage IB2 will have pelvic or para-aortic lymph node metastasis for the diagnosis. In which the concurrent chemo-radiation therapy would be unavoidable. To a lesser extent tumors stage IB1 with diameters between 2 and 4 cm, especially with deep invasion of the stroma, will present an increased risk of pelvic lymph node metastasis than lesions less than 2 cm. It is for this reason that this subgroup of patients with stage IB1 greater than 2 cm is prudent to recommend a procedure that allow establishing with certainty the nodal status before ordering neoadjuvant chemotherapy supplemented with any surgical procedure that preserves the uterus. Methods that are emerging are either the extraperitoneal iliac dissection pelvic or laparoscopic sentinel lymph node biopsy.

As for the estimation of tumor volume, magnetic resonance imaging remains the method of choice, not only to evaluate the diameter and the stromal invasion but the ability to predict best the sufficiency margin in the uterine isthmus. The histological type continues to be one of the limiting factors in the selection of patients, keeping as the main contraindication Neuroendocrine tumors. In adenosquamous or the *glassy cell* tumors, the indication of a fertility preserving procedure must be done in a very cautious way. In the establishment of the LVI, especially in stage IB1 less than 2 cm, the authors pose the need for staging conization in order to consistently determine the LVI in patients candidates for a sparing procedure, since a punch biopsy is not sufficient to assess this aspect.

Recommendations proposed by the authors for the stages IB1 less than 2 cm without LVI are a cone with sufficient margin or a simple trachelectomy, with very similar rates of disease control

procedures. Is to point out that most likely in a few years, with the publication of data from SHAPE², ConCerv³ and GOG 278⁴ studies, the parametrectomy will not be necessary in patients with tumors less than 2 cm.

In patients with disease IB1 with LVI the vaginal trachelectomy with laparoscopic lymphadenectomy or Dargent operation is the best indication. The realization of a radical abdominal trachelectomy emerges as an excellent alternative in care teams without experience in vaginal radical surgery.

As for IB1 stages between 2-4 cm, given the best profile of lateral margins, the conventional abdominal trachelectomy, laparoscopic or robot-assisted, is the most accepted indication at the present time. It should be noted that a rate of recurrence has been reported discreetly greater in patients treated by laparoscopy. Similarly, reported that Dargent operation has a rate of recurrence in this subgroup of 17% which completely limits its role. The use of neoadjuvant chemotherapy in this subgroup of patients, followed by a sparing procedure looks an attractive option, however in comparison with the abdominal radical trachelectomy, the profile of tolerance is best for this last option. The rates of recurrence and pregnancies of the abdominal radical trachelectomy and neoadjuvant chemotherapy plus surgery were 7% vs 6% and 49% vs 69%, respectively. These aspects can be better cleared with the publication of studies NCT02624531 and NCT02323841.

Finally, for stage IB2, a stage that is still considered potentially lethal, the authors consider that with existing data evaluated in his review, try a preserving fertility, any procedure be, is infeasible.

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