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**UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
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DOMENIUL MEDICINĂ**

Minimally Invasive Surgical Treatment of Locally Advanced Cervical

THESIS ABSTRACT

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Introduction

Cervical cancer is a national health problem; even now in the year 2024, when many of the world's nations have advanced screening programs, Romania is still considered a developing country in this respect and the need to know the appropriate treatment methods becomes all the more important, as this disease is still diagnosed in its advanced stages.

The theme of the paper is not chosen by chance and complements the continuing concern for the right treatment options by a team of physicians who were among the first to use minimally invasive surgery in the treatment of gynecologic malignancies. It is important to keep in mind that over time, the role of surgical treatment in the cure of this disease has gradually diminished with the evolution of oncologic therapies and prevention has become a key point. Methods of approach have also changed.

When talking about cervical cancer, things are divided into "before 2018" and "after 2018". What exactly has changed and why? What are the new diagnostic standards and what do they entail? More importantly, what implications do these changes have for the treatment of locally advanced cervical cancer? And of course, in parallel with these discussions about the indications for surgery in the treatment of locally advanced cervical cancer, what is the role of laparoscopy and robotic surgery? What would be the advantages and disadvantages of using these approaches? And last but not least, what are the prospects? Because, as one can well intuit, minimally invasive surgery will keep its important place in oncology.

In an attempt to answer the above questions, the current study retrospectively follows the outcome and survival of patients diagnosed with locally advanced cervical cancer who underwent minimally invasive surgery in one of the treatment stages. The study of postoperative complications is not the subject of the present study and has been dealt with in a separate article, which is part of a separate PhD thesis. By analyzing information related to patients' age, comorbidities, stage of disease, type of resection and postoperative outcome, the study aims to identify significant prognostic factors and correlations that could influence overall survival .

Hypothesis and objectives

As mentioned in the introduction of the thesis, the treatment of locally advanced cervical cancer has undergone changes over time that have placed surgery in a position that is not always favorable. Many of the studies that have been published lately describe curative-intent CRT as the first option in the treatment of staged IB3- IVA patients. However, all these articles emphasize that CRT has a success rate of only 65-70% and that these limitations have led to the treatment of each patient by a multidisciplinary team, the therapeutic regimen itself being individually tailored according to the outcome of this first stage. (1,2) Also, in current practice, many patients present fistulous lesions following irradiation methods, sometimes with significant impairment of quality of life or even intestinal transit disorders, up to intestinal occlusion, lesions that have as only solution - surgery. (3-5)

In order to achieve the overall objectives of this thesis, already published studies will be presented first, followed by a new study presenting results not yet reported in an original article.

The first study- an unsystematized literature review- provides context for surgical treatment in locally advanced cervical cancer. Although the study was published in 2019, it looks exclusively at the period before Ramirez's article that ended the momentum that minimally invasive cervical cancer surgery had gained. Moreover, surgical interventions in general were finding it increasingly difficult to make sense in the context of oncologic therapies that most recommended as first-line treatment. The study thus clarifies, or rather shows that the opinion is still divided and that surgery is far from having disappeared from the treatment of this malignant pathology.

Subsequently, studies 2 and 3 refer to pelvic exenteration, a surgical intervention that is still topical in the treatment of stage IVA cervical cancer but also in recurrences or disease continuations that may occur after oncologic treatment with curative intent. It should be noted that in advanced stages of disease, cervical cancer behaves like other locally advanced or relapsed pelvic malignancies, all of which are included in the category of 'advanced pelvic disease'. The two studies also support the idea of a minimally invasive approach as a feasible

alternative to open surgery, and sometimes even a necessary one. Pelvic exenteration remains a firm indication for stage IVa disease, and the possibility of performing it in a laparoscopic or robotic manner has multiple advantages, without sacrificing oncologic outcomes.

Finally, the last study of the thesis presents the experience of the surgical team led by Prof. Dr. C. Vasilescu regarding the evolution of 89 patients with locally advanced cervical cancer who were operated on by a minimally invasive approach - namely robotic surgery - between 2008-2018, i.e. before the publication of Ramirez's article, which changed the general attitude towards this type of approach.

In this way, the thesis aims to cover the indications for surgery in all stages of locally advanced cervical cancer disease, emphasizing once again the usefulness of the minimally invasive approach, which has indisputable advantages for these fragile patients, who often during the course of the disease are abandoned due to progression patterns that do not allow the administration of additional oncologic therapies. (6-8) The analysis of postoperative complications is not the subject of our study and the information regarding these aspects was contained in a separate article, which was subsequently included in a different PhD thesis. (9) The present study analyzes the survival of these patients in relation to different parameters, attempting to develop some models of evolution, which allow to classify them in certain risk categories.

Mind the Gap Between Scientific Literature Recommendations and Effective Implementation. Is There Still a Role for Surgery in the Treatment of Locally Advanced Cervical Carcinoma?

It all stems from a poor screening system and a rather high detection rate of cervical cancer in the already advanced stages. (10) Often the patient presents because of clinical warning signs, but there is a high chance that the malignant lesion has already passed FIGO stage I. Biopsies, complementary imaging and oncologic planning also lengthen the time to initiation of radio-chemotherapy. External radiotherapy is carried out concurrently with chemotherapy sessions and together they involve a serial, uninterrupted treatment phase over a defined time period. Results depend largely on patient compliance and associated pathology. Both situations predispose to failure to achieve the maximum desired effect. Furthermore, the brachytherapy stage involves the use of intra-vaginally mounted devices and here again, in addition to patient non-compliance, there are a number of issues related to individual local anatomy and the patient's ability to complete the treatment in the context of irradiation of adjacent organs.

Moreover, access to radiotherapy still remains low in Romania. Despite investments in radiotherapy, there is currently about 1 linear accelerator per 1 million inhabitants, compared to an EU average of 5.5. It must also be said that geographical access to radiotherapy facilities is inadequate. They are concentrated in oncology institutes, large cities and university centers. Another major problem is accessibility to brachytherapy, which is absolutely necessary for curative treatment. Thus, radiotherapy in Romania can often be considered suboptimal.

A special mention should be made here for staged IIIB-IVA patients, who have at the time of diagnosis either urinary excretion disorders or bladder invasion (3). In order to administer sensitizing chemotherapy, it is necessary to resolve the associated renal failure syndrome by ureteral stenting or by performing nephrostomy or cystostomy. Otherwise, treatment is incomplete and as a result, the chances of the patient developing further disease increase. Also, where stage IVA involves invasion of the rectum, CRT sessions may lead to the development of occlusive syndromes, requiring an ostomy to be performed beforehand.

It should be noted that, both in our experience and in data published in the international literature, up to 30-40% of patients operated on for locally advanced cervical cancer following CRT are diagnosed with residual tumor tissue on pathological examination of the hysterectomy specimen. There is an opinion that, paradoxically, in about 60% of these women the progression is not to recurrence. (1,11) In this context, there is, however, a fraction that does present with local recurrence, or rather a continuation of disease.

Thus there are operating teams, which propose "salvage" hysterectomy if there is imaging data showing residual tumor after definitive CRT. Performing surgery not only allows assessment of the pathologic response to CRT, but also allows better local control. A special note should be made here for stage IVA cervical cancer (either bladder and/or rectal involvement). (11)

It has to be said that there is a dynamic and continuous process in surgical practice, including technical innovations in the instruments used (laparoscopy, robotics, NOTES), as well as new concepts and perspectives applied to surgery (morphogenetic field surgery). (6,12,13) However, following Ramirez's publication, oncologic outcomes poorer than those of classical surgery, placed this type of approach in inferiority and as a result, the surgical world gradually abandoned it. (14)

But recently, seriated studies and even trials have re-analyzed the pre-existing data and come up with new study groups to re-establish minimally invasive methods, especially robotic ones, which have slightly better results than laparoscopy. (15,16)

Robotic or laparoscopic pelvic exenteration for gynecological malignancies: feasible options to open surgery

Laparoscopic pelvic exenteration was first described in 2003 by Pomel et al (17), followed by robotic-assisted procedures and fully robotic interventions, which have been systematically performed to prove the benefits of the technique.(18) In the light of the 2018 LACC study, MIS was associated with worse oncologic outcomes and faced significant negative feedback; in contrast, the robotic approach is suggested to have the same oncologic benefits, while surgery-related morbidity at 90 days is not influenced. (19,20) As the indications for pelvic exenteration have expanded, surgery has been shown to be safe and effective (with a 5-year survival rate of 40%). (20-22)

In terms of the difficulties encountered, urinary reconstruction is one of the reasons why laparoscopy is more difficult, which makes the robotic approach preferred. The 3D stereoscopic view provides a better visualization, and the articulated robotic instruments, together with the harmonic scalpel, reduce tremor and can achieve better control of the dissection of the vessels in the pelvic side walls. (23) However, robotic interventions are expensive procedures. The duration of surgery is influenced by the preparative and endocare steps, favoring laparoscopy, but Bizzarri et al. reported just the opposite, describing a significantly shorter operative time for the robotic approach. The success of this surgery is highly dependent on the operating team, the number of patients treated and the learning curve. Several studies have shown that minimally invasive pelvic exenteration is a feasible procedure. (22,24,25)

By the end of 2018, 163 minimally invasive pelvic exenterations were reported, 155 of which were for gynecologic malignancies. (24) With the advent of the LACC study, minimally invasive surgery in the gynecologic sphere has been put at a turning point. Evidently, as the vast majority of practitioners quickly gave up these habits, but it seems that pelvic exenteration was the only one that continued its course.

According to the literature, the cervix is the most common primary site (85.8%) of gynecologic malignancies approached by MIS pelvic exenteration and the most commonly

performed is anterior pelvic exenteration. Laparoscopy has an 80% weight of robotic surgery. (24)

It must be said that the evolution is encumbered by an important percentage, even in its minimally invasive variant. The early postoperative complications are mostly infectious in nature, while the late ones are related to urinary pathology, common in urinary shunts and the occurrence of digestive fistulae. Their development is directly influenced by intra-operative incidents, the duration of surgery and the type of shunts performed. (7)

Continent reconstruction is reserved only for young patients and may be associated as a complication with fistula development and consequent septic shock. Widely used techniques, such as Bricker and Wallace incontinent reconstruction, are preferred to reduce the frequency of postoperative problems. (24)

In terms of oncologic outcomes, disease-free survival is estimated to be approximately 11 months. Several studies have reported OS rates at 2 and 5 years of 40.7% and 27.0% respectively. (18,24)

Pelvic Exenteration - Open to minimally invasive procedure in the treatment of advanced pelvic disease

In the light of surgical and anesthetic advances, pelvic exenteration has over time become safer, and mortality and morbidity rates are now lower than before. (26,27) On the other hand, oncologic treatment gaining ground has placed surgery in an unfavorable position, especially this type of extended procedure. Therefore, the main condition for pelvic exenteration to be performed is to achieve curative status- R0 resection, palliative surgery has been shown not to improve overall quality of life and to have poor outcomes in terms of survival rates. (27)

Although the subject of this thesis concerns surgery for locally advanced cervical cancer, disease continuations or recurrences in the gynecological sphere- whether with a central or lateral starting point, all fall into the same pattern of evolution."Advanced pelvic disease" is a term that encompasses all these forms of presentation and as a result, the discussion of pelvic exenteration as a form of treatment is applicable to all these cancers.(27,28) Thus, it becomes a useful treatment tool, all the more so as there are, of course, also cases where local complications - recto-vaginal or vesico-vaginal fistulas, tumor necrosis or bleeding that cannot be controlled with CRT treatment - can occur following oncological treatments, which are life-threatening.(29)

Moreover, over the years, experienced centers have reported a trend toward treating recurrent rather than advanced primary cancers. Again, as the procedure has become even more standardized and oncologically effective, surgeons have been able to offer this solution for more complex cases.(30)

The resection technique now includes options for anterior invasion - pubic bone resection, for posterior invasion - sacrectomy, and for lateral invasion - the possibility of performing vascular, neural or muscle resection of the lateral pelvic wall. With Hockel's theory, these patients gained an extra chance of survival, because the limits of pelvic exenteration were pushed to the maximum and even laterally developed tumors, sometimes so-called "wall-fixed", found their resolution.(6,8)

On the other hand, the share of gynecological malignancies treated by pelvic exenteration has decreased over the years in favor of malignancies of the gastrointestinal tract, due to better screening policies applied in particular for cervical cancer. An improvement in survival has also been observed in relation to a change in histologic types from squamous cell carcinoma to adenocarcinoma, with patients with ADK known to have better survival chances than those with SCC. (27,31)

When it comes to the type of exenteration performed, the open procedure is much more practiced than the minimally invasive approach. (27) Also, laparoscopy is preferred to the robotic approach, with 82.8% of publications in the literature describing it as the first choice. TP exenteration is generally the most commonly practiced type, especially when OP is involved, while AP is usually associated with MI surgery (80% of cases). (24,27)

R0 resection is the most important decision factor in choosing whether to perform pelvic exenteration. Palliative surgery is now reserved only for hemorrhagic tumors or life-threatening fistulas and, to compensate for higher morbidity and mortality rates, the minimally invasive approach is recommended. (27,32,33)

Studies show that perioperative morbidity varies between 20% and 80%, with a median of 53.6%. As other publications conclude, late urologic complications are the most common. (27) Another important predictor of OS is the outcome of lymph node involvement, all the more so as studies have also examined its importance in relation to gynecologic malignancies in particular. (28)

Major immediate post-operative events have a negative effect on OS, with complications such as cardiac events and sepsis usually leading to in-hospital mortality. Other publications show the same results regarding CD 3-4 complications and recommend thorough patient selection and preparation beforehand, avoiding cases with unfavorable cardiopulmonary performance or nutritional status.(27,34,35)

Stages IB3- III cervical cancer- robotic surgery indications and overall survival analysis

When we talk about radical hysterectomy, we think of the surgical treatment of early cervical cancer, when fertility preservation is not the goal. Basically according to the Piver-Rutledge-Smith classification, we are talking about a radical resection in class II-V. (36) However, in the light of the information gathered over the years on the pattern of disease progression, which predominantly shows a lateral extension, it was necessary to replace this classification with that of Querlou-Morrow.(37) And when we talk about robotic radical hysterectomy, we are talking about a standard of care until 2018, the year of the Ramirez study. (14) Following this phase III trial, which included patients with early-stage disease (IA1- with LVSI+, IA2 and IB1)- MI-performed interventions were found to be less effective in terms of oncologic outcomes compared to open surgery. However, there were also some weaknesses of this trial.(16)

Melamed et al. observed in their study published in the same year that with the implementation of large-scale MI surgery the death rate also increased by 0.8% per year and further concluded that the 4-year mortality of patients in this subgroup was 9.1% compared to 5.3% reported for open surgery. (15) Nitecki confirmed with his meta-analysis that recurrence risk and mortality are higher for the MI approach. (38) All of these authors have pushed the view that the standard of care remains open surgery, and the NCCN has in turn taken up this view, publishing it in its treatment guideline. (39)

At the opposite pole, voices have emerged arguing that there are nuances to this issue. The LACC study was closely followed by two other large studies - CIRCOL and MEMORY. (40,41)

However, radical hysterectomy, together with pelvic lymph node dissection, can also be used as a therapeutic step in the treatment regimen of locally advanced cervical cancer for stage IB3-III (historical IB2- III) disease. It is true that the role of surgery has been minimized with the advancement of oncologic therapies, but in selected cases, surgery is still indicated.

According to the guidelines, in staged IIA1 patients, surgery may be considered as the first stage of treatment. Moreover, numerous studies have observed that as tumor stage increases, the effectiveness of curative intent CRT decreases, so that patients with stage III disease

experience a lower percentage of complete response to cancer therapies, and the chances of relapse or continuation of disease are much higher. (29,42)

A study published in 2016 retrospectively analyzed, in a literature review of surgery after CRT, complete response to CRT and persistence of malignant foci on resection sites. Finally, associated morbidities were noted. Response to CRT has improved over the years reaching from 30-40% in 2005-2006 to over 70% in 2014. Also, the number of patients confirmed by anatomic-pathologic result to have residual malignant lesions on the resection piece decreased from 37% to 17% in the related periods. Basically, improved oncologic schemes resulted in higher overall survival. The reported morbidities for surgery to complement these therapies were also acceptable, ranging from 13 to 38%.(42)

Moreover, the very fact that the quality of the pelvic tissues is indeed impaired following CRT treatment, leading to the formation of areas of fibrosis and automatically increasing the difficulty of a good local resection, is also a further reason for choosing the minimally invasive approach. As a result, the patients included in study IV of this thesis are cases in which, for the diagnosis of cervical cancer stages IB2 (now IB3)-III, a radical hysterectomy was performed after neoadjuvant CRT by robotic approach.

One of the most important aspects to take into account in the outcome of these patients after first-line curative CRT is the stage of disease. The response to oncologic treatment is also different depending on the stage of the disease and automatically so are the chances of recurrence or continuation of the disease. If for stage IB3 (IB2) the percentage is 10%, for IIA2 and IIB it varies between 17% and 23%, for stage III the percentage is extremely high, around 42%. This aspect should therefore also be taken into account when analyzing the therapeutic decision, and the indication to perform surgery in addition to oncologic therapies should be more nuanced.

The most recent study published in May 2024 - a meta-analysis of robotic radical hysterectomy, although with FIGO-staged patients no more than stage IIB as inclusion criteria, is a good model to demonstrate the safety and feasibility of the method. We note that compared to laparoscopy, the duration of surgery is shorter, blood loss is about the same, but with reduced transfusion requirements and hospitalization days are also fewer. In terms of the number of lymph nodes harvested during the surgical procedure, RRH is again superior to LRH.

Postoperative morbidity, number of recurrences, mortality and DFS are equivalent between the two methods.(43)

The factors that influence the survival of these RRH patients are age, associated pathology, BMI, cancer histology and clinical stage of disease. Closely related to the latter are all the other parameters that derive from it: namely days of hospitalization, occurrence of postoperative complications- immediate or distant and very importantly- the presence of residual tissue on the resection piece (44-46).

Conclusions and personal contributions

Surgical treatment of locally advanced cervical cancer is under continuous debate and although the first intention in the therapeutic regimen of these patients is CCRT, surgery still occupies an important position.

First of all, surgery still retains a central place when, for various reasons, oncologic treatment is suboptimal. Each individual step contributes to achieving the most complete response and as a result, starting with the patient's overall health, continuing with the hospital setting in which CRT is performed and ending with the variability of individual response to these therapies; all are responsible for the patient's subsequent course.

Further, we consider that statistically, only about 65-70% of patients are statistically cured following this first-line treatment. An important component will progress to recurrence or continuation of disease, either locally - central or with lateral extension, or distally - metastases, either with a starting point at the vaginal transection or by lymphatic or blood dissemination. As a result, to ensure superior local control and limit recurrence, surgical treatment is once again useful in addition to other oncologic therapies.

Last but not least, because the treatment of CRT with curative intent is much different today, even compared to the period of study of this thesis, very often complications arise that are eminently surgically resolved.

A special mention will be made here, related to stage IVA disease, which, although it implies the initiation of treatment with the same sequence of CRT, has a particular surgical solution. Whether we are talking about lateral extended resection, based on the principles of Hockel's theory, or pelvic exenteration, we are considering a radical method, which although sometimes mutilating, has as its primary aim to perform a R0 resection.

On the other hand, a parallel discussion remains open about the type of approach of these surgeries. Certainly, open surgery is the first solution considered, especially after 2018, when experience with early stages of the disease has shown that oncologic outcomes are inferior to the minimally invasive approach. Again, here are a few points to note, in terms of relating these

findings to locally advanced cervical cancer. First, we are talking about different therapeutic sequences - surgery in locally advanced cervical cancer follows CRT. On the one hand the first step towards curative intent has been made but on the other hand it is true that the quality of local tissue is compromised. Thus, laparoscopy and especially robotic laparoscopy are able to perform a more thorough dissection, at least similar from an oncologic point of view, but with greater gentleness on these already damaged tissues. Second, operative parameters are improved- blood loss, transfusion requirements, days of hospitalization and ultimately associated procedural morbidity is equal or even reduced. Moreover, the use of the robotic approach additionally brings increased operator comfort and superior visualization, managing to nullify many of the shortcomings of laparoscopy.

Concerning the issues of possible contamination of the peritoneal cavity, according to the vaginal cuff theory, there are multiple options to prevent the spread of malignant cells during tumor manipulation and resection piece. Standardization of this stage takes out recurrences due to these previously overlooked procedural flaws.

We thus consider minimally invasive surgical treatment as an extremely important element in the management of patients with locally advanced cervical cancer, without, however, obviously omitting the stage preceding oncologic therapies of curative intent. Particularly in countries where screening and vaccination programs are still deficient, surgery will maintain a secure place. Discussions are still open on the establishment of negative prognostic factors that could lead to a better classification of patients at risk and, as a result, the establishment of clearer working protocols.

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1. Blidaru A, Bordea C, Burcoş T, **Duduş L**, Eniu D, Ioanid N, et al. Mind the Gap Between Scientific Literature Recommendations and Effective Implementation. Is There Still a Role for Surgery in the Treatment of Locally Advanced Cervical Carcinoma? Chirurgia (Bucur). 2019;114(1):18.; Chirurgia (2019) 114: 18-28; No. 1, January - February

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2. **Duduş L**, Minciuna C, Tudor S, Lacatus M, Stefan B, Vasilescu C. Robotic or laparoscopic pelvic exenteration for gynecological malignancies: feasible options to open surgery. J Gynecol Oncol. 2023 Oct 19;35.; J Gynecol Oncol. 2024 Mar;35(2):e12; pISSN 2005-0380-eISSN 2005-0399; **2023 Impact Factor= 3,4**

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