Study regarding the prognostic factors and quality of life of patients undergoing radical surgery for cervical cancer

Ph.D. Student: Dr. Mihai Stanca
Ph.D. Supervisor: Prof. Dr. Mihai Emil Căpîlna

SUMMARY

Cervical cancer is one of the malignant diseases which can be prevented by the simplest means of investigation. However, at a worldwide level, every two minutes a woman dies due to cervical cancer which is intertwined with low compliance with screening programs and HPV vaccination, inadequate information, media coverage, ethnicity, conviction, and misinformation. In Europe, Romania is at the forefront in terms of incidence and mortality caused by this disease. Given the above, it is effortless to understand that despite many efforts made to counteract these circumstances, the unfortunate constellation of cervical cancer is a topical issue, which still requires debating. This is all the more necessary in the developing countries of Eastern Europe, which have been subjected to the stigma of the communist regime that prevented the rapid and natural evolution of modern medicine, being indirectly excluded from the large randomized studies conducted in the United States, China, Japan and especially in southern, western and northern Europe who have tried to identify the negative prognostic factors, the quality of life and the most effective therapeutic methods in patients with cervical cancer, therefore the lack of similar studies in this geographical areal. In Eastern European countries, the quality of life of cervical cancer patients may be seen as a "caprice", the difficulties they encounter following radical procedures for cervical cancer being considered a "normal phenomenon". Thus, one of the strengths of this study is its uniqueness in Romania and other Eastern European countries.

For the first time in Romania, this research aims to demonstrate through elements of scientific validation, the prognostic factors with negative implications that have influenced the survival of patients undergoing radical hysterectomy and pelvic exenteration for cervical cancer, also assessing in a rigorous and organized manner their quality of life, using validated questionnaires issued by the European Organization for Cancer Research and Treatment QLQ-C30 and QLQ-CX24, placing Romania alongside those countries that attempt to highlight these issues and find answers. The secondary objective of this thesis was to evaluate the obstetrical and oncological outcomes of pregnant patients undergoing abdominal radical trachelectomy during pregnancy, for the early stages of cervical cancer.

Thus, **study 1** was able to identify a five-year overall survival (OS) of patients undergoing radical hysterectomy (RH) for FIGO 2018 IA2-IIB cervical cancer of 72.4%, contrary to European Society of Oncological Gynecology estimations which approximated an OS in eastern European countries of <55% (Romania was not included in the statistics), while the highest survival rate of 71% was reported in the north European countries.

Currently, this is the first study assessing the OS of these patients in our country. The patients who underwent RH achieved the highest five years survival of 79.9%, followed by those undergoing neoadjuvant radiotherapy + adjuvant RH with 77.6% while patients who received other therapeutic strategies attained a mean survival of 66.4%. This result may be since patients undergoing RH as a single treatment had early stages of cervical cancer (FIGO IA2-IB1), few of which presented negative prognostic factors on the final histopathological examination. Cox multivariate analysis also recognizes clinical-stage FIGO IIB, lymph node metastases, and the histopathologically proved parametrial invasion as self-determining negative prognostic factors, influencing the survival (P <0.05), results that are similar to other studies in the literature [46][50,51,77][180]. The isolated presence of intermediate risk factors (Sedlis standards) had a low impact on the OS and recurrences. In this study, the recurrences were influenced by the clinical-stage FIGO IIB (*P* <0.05). The research reports a satisfactory overall long-term quality of life (QoL) of 64.6 (average) on a 0-100 scale, with good functionality scores. Symptom scales were decent, while lymphedema, peripheral neuropathy, severe menopausal symptoms, and distorted body image perception had the most worrying outcomes. These results are comparable to other similar published studies [140,165–169]. A significant decrease in sexual satisfaction and activity was identified, with unfavorable scores on sexual/vaginal function, sexual anxiety, sexual activity, and sexual pleasure. Although the results are more unfavorable, they are consistent with other published studies [140,159,160,165–169,171,172] that assessed the QoL of patients undergoing the above-mentioned therapies, with similar results.

Study 2 identified a three-year OS of 61% and a five-year OS of 48.7% of patients undergoing pelvic exenteration for FIGO IVA, recurrent or persistent cervical cancer after definitive concomitant radiochemotherapy +/- radical hysterectomy. Similar studies in other geographical regions indicate a five-year survival ranging from 30 to 60% [87,91,95,98,104–107], despite a relatively high perioperative morbidity rate of 5-9%. In our study, the perioperative morbidity was 6%. Patients who managed to obtain R0 resection had a five-year survival of 62.9% compared to those with R1 resection who achieved survival of 33.5% (P <0.05). Survival was also negatively influenced by parametrial invasion, positive resection margins, lymph nodes metastases, sublevatorian exenteration, and early postoperative complications with *P* values <0.05. Although according to the latest guidelines issued by the European Society of Oncological Gynecology in 2018 [193], pelvic exenteration remains the only curative option for patients in FIGO stage IVA with rectovaginal and vesicovaginal fistulas, with good results in patients with pelvic recurrence or persistent cervical cancer following previous treatment, the impaired quality of life and the high-risk of surgical complications still causes concerns. Although pelvic exenteration is a complex surgical procedure that requires a prolonged surgical period and is often linked to a high risk of complications, the benefit of survival justifies its use in daily practice. The QoL of patients following pelvic exenteration has been investigated in a scarcity of studies [109,194,195]. Except for Magrina Dessole et. al [109], the other two studies did not use the validated questionnaires EORTC QoL C-30 and CX-24. The overall QoL of the patients in this study was deeply

affected, with a value of 32.6. The functionality represented by the role, physical, cognitive, emotional, and social scales attained scores of 28.5, 46.4, 37.0, 51.8, and 28.5, respectively. These scores can range from 0 to 100, with a higher score signifying a higher grade of functionality. These results are more unfavorable than those obtained by Magrina Dessole et. al, who reported an overall QoL of 64.6 [109]. The latter study was conducted in Rome, where patients undergoing radical treatments for malignancies can benefit from advanced psycho-emotional counseling and support programs, included in their medical insurance. Consequently, this QoL discrepancy may also occur because the patients with malignancies in our country tend to have depressive disorders linked to the cancer diagnosis, which may be further worsened after the pelvic exenteration in the absence of proper support offered by the family and the healthcare programs. In terms of symptom scales, most of the current study patients experienced insomnia, fatigue, and pain with similar scores compared to the other three studies [109,194,195], but the financial impact caused by the cancer treatment was greater, with a score of 90.2. 61.7% of the patients originate from rural areas, with narrow financial potentials. Also, the financial impact may have influenced certain elements of the functional and symptom scales. Focusing on the sexual life aspects, it is important to note that the average age of the 18 patients who answered the QoL questionnaires in our study was 53 years (36-66 years), with 67% (n = 12) originating from rural environments. Of the 18 patients, 11 (61%) underwent supralevatorian pelvic exenteration and 7 patients (39%) underwent sublevatorian pelvic exenteration, which assumed total resection of the vagina, an unfeasible condition for regular sexual intercourse. However, none of the 18 patients answered any questions regarding their sexual life. It is conceivable that the avoidance of answering these questions is deliberate, as these issues are a taboo subject for many of our country's patients, both for ethnic and religious explanations. In carefully selected cases, vaginoplasty techniques may be provided to maintain decent sexual activity [199,200]. When counseling patients, it is essential to emphasize that the "baseline quality of life" refers to the QoL before the patient undergoes pelvic exenteration.

These two studies acknowledge several limitations. First of all, the limitations lie in their retrospective nature. There is also heterogeneity in treatment received by patients. The studies did not have a control group (eg. healthy participants) or a pre-treatment assessment of the QoL. In addition, the QoL was not analyzed separately according to the treatment regimen received. Therefore, although in some respects the results may be heterogeneous, they are comparable to other prospective control studies [140,159,160,165–169,171,172] [91,98,104–107]. The survival and QoL of patients undergoing radical hysterectomy as well as the survival of patients with pelvic exenteration are similar to other prospective studies [140,159,160,165–169,171,172], but the QoL of the latter group of patients has been profoundly affected compared to other studies [109,194,195]. In both groups of patients, was observed low self-esteem, distorted self-image, anxiety, and marital conflict as a result of sexual dysfunction.

Study 3 aimed to analyze the abdominal radical trachelectomy (ART) performed during pregnancy (ART-DP) for the early stages of cervical cancer in the Obstetrics and Gynecology Clinic I of Târgu Mureș, aiming as well as to bring up-to-date the literature, assessing the obstetrical and oncological outcomes of ART-DP
The recommendations of the Third International Consensus Meeting on Gynecologic Cancers in Pregnancy [121] do not recommend the use of ART-DP for the early stages of cervical cancer approving a less invasive method, giving special importance to the use of neoadjuvant chemotherapy. This decision was based on a small number of published cases (n = 9) reporting a significant loss of blood and a prolonged period of the ART-DP procedure. Currently, together with the 5 cases of the authors, there are 25 ART-DP. Among them, 81% (19 patients) had good obstetric results, giving birth through elective C-section to well-adapted newborns, and only 19% (6 patients) had an unfortunate outcome, miscarrying shortly after the ART-DP procedure. Regarding oncological results, at the time of the study, no disease recurrences were reported during the follow-up period (6–200 months).
This study urges awareness of the fact that ART-DP is an intervention that can be proposed to patients opposed to the idea of neoadjuvant chemotherapy. If the patients have a strong desire to preserve the pregnancy and are not willing to expose the fetus to the risks that may arise due to neoadjuvant chemotherapy, it is worth attempting ART-DP to appropriately selected cases after considering proper information regarding the risks. Also, special attention is recommended to the integrity of the amniotic membrane, which can be compromised by the desire to obtain a good oncological result, leading later to their premature rupture. This study contained the highest number of abdominal radical trachelectomy cases performed during pregnancy for early-stage cervical cancer, including five cases performed by the authors, which were not previously published.

Despite its retrospective nature and the heterogeneity of the studied groups, this thesis includes 482 patients undergoing radical surgery for cervical cancer (430 radical hysterectomies, 47 pelvic exenterations, 5 abdominal radical trachelectomies during pregnancy) followed for a long period, bringing a solid contribution to the current knowledge concerning cervical cancer, providing an image of the survival, prognostic factors and quality of life of patients undergoing radical surgery for cervical cancer in a reference University Center in Romania, providing an overview on the mentioned issues. The favorable survival of patients undergoing radical hysterectomy and pelvic exenteration for cervical cancer has resulted in a modest overall quality of life, with unsatisfactory functional, social, and sexual scores, a high prevalence of cervical cancer-specific symptoms, and negative financial impact, suggesting the importance of adequate psycho-emotional and financial support for these patients following radical procedures. These results provide a basis for future Eastern European prospective randomized trials needed to confirm the results.