

Radical hysterectomy and its importance in the concept of cervical cancer treatment

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ABSTRACT

The role and place of a radical hysterectomy in the concept of cervical cancer treatment, despite over one hundred years of its traditional use, still excites controversy.

To fully understand the value of the surgical treatment, it is worth analysing and understanding the evolutionary path of the radical hysterectomy and the changes that have occurred in this method over the years. This knowledge will allow for a better understanding as to why the choice of therapy between surgery and radiochemotherapy in the early and locally advanced stages of cervical cancer still raise doubts.

Both the introduced changes in the scope of surgery and the use of multi-module treatment - surgery with subsequent radiation therapy did not significantly improve the results of cancer treatment, but significantly increased the prevalence of side effects and therapy complications.

As cervical cancer most often affects relatively young women, the number of potential years of life after treatment is high. Over 30% of women in Poland with cervical cancer are in the 45–49 years-old age group. From the perspective of these data, obtaining a high therapeutic index, which is defined as the ratio of the number of healed patients to complications and side effects of treatment significantly reducing the quality of life, is very important in the therapy process.

Regardless of the classical radical surgery, which has evolved over many years, a new concept of radical hysterectomy based on tissue morphogenesis, called total mesometrial resection (TMMR) with therapeutic Lymph Node Dissection (tLND) with no adjuvant radiotherapy, has recently been proposed.

Based on the ontogenetic research and the study of cancerous tumour development, the concept of TMMR was first introduced by M. Höckel in 2001. In the research conducted by the author, encouraging results of the treatment of stages IB1, IB2, IIA1 and IIA2, and selected cases of stage IIB [according to 2009 International Federation of Gynecology and Obstetrics (FIGO)] cervical cancer were obtained.

Key words: cervical cancer, radical hysterectomy, total mesometrial resection

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INTRODUCTION

Surgical treatment of cervical cancer in accordance with the recommendations of the National Comprehensive Cancer Network (NCCN) and other leading scientific societies in the field of gynaecologic oncology covers the stage of disease progression from IA to IIA according to the classification of the International Federation of Gynaecology and Obstetrics (FIGO 2018). In the updated FIGO 2018 classification, stage IB has been divided into three groups according to tumour size: < 2cm; 2–4 cm; > 4 cm. In stage IA, the horizontal diameter is no longer used, only the depth of invasion is measured. No changes were made in stage II, except for the possibility of using imaging diagnostics

techniques and/or pathological assessment to assess the size and extent of the tumour. [1–3].

The standard type of surgery performed in the treatment of stage IB-IIA cervical cancer according to FIGO 2018 is a radical hysterectomy with pelvic lymphadenectomy.

The concept of a radical hysterectomy was created at the turn of the 19th and 20th centuries.

In over 100 years of surgical development, the introduced modifications have allowed significant progress in reducing side effects, but both these modifications and classification changes have not had a positive effect on improving the oncological outcomes that are not satisfac-

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tory in early and particularly locally advanced stages of cervical cancer.

The first systematised work describing in detail the method based on 500 surgery cases was published in 1912 by E. Wertheim [4]. At the very start of the author's work they pointed out that in order to achieve good results in the treatment of cervical cancer, the development of an appropriate surgical technique is of great importance.

Over the years, the technique of radical hysterectomy has undergone further modifications.

An important element of this development was the introduction of a systematic lymphadenectomy to the surgery protocol proposed and conducted by J.W. Meigs [5].

In Meigs' original surgery, the intraoperative exclusion criterion was the assessment of lymph nodes of the aortic bifurcation region (by palpation or histopathological examination in cases of macroscopically unsuspected nodes). In the absence of metastases, a full surgery including pelvic lymph nodes was performed in this region. In the former years, only enlarged-suspected pelvic lymph nodes were removed [4]. The Wertheim-Meigs radical surgery has become the standard treatment since the 1950s and the next half century.

Further modifications to a radical hysterectomy were intended to demarcate and possibly reduce its radical nature in cases of less advanced disease. These concepts were aimed at reducing possible complications associated with surgery and introduced so-called tailoring.

Piver et al. [6], published a paper in which they introduced five classes of extended hysterectomy depending on the extent of a parametrial resection.

The classification of Piver et al., has been used for many subsequent years. However, a prospective study conducted by Landoni et al., demonstrated that there were no differences in the oncological outcomes between class II and III according to Piver, but only an increase in the percentage and severity of side effects when using class III (the extent of class III surgery according to Piver corresponded to the Wertheim-Meigs operation) [7].

At the same time, over the years, a significant progress has been made in tissue preparation techniques and a deeper understanding of pelvic anatomy for radical surgery. A new approach to anatomy, considering the topography of vasculature and innervation of the pelvic organs, has been described [8].

Consequently, a new technique of radical surgery was introduced, saving the vegetative innervation, which has a significant impact on the functions of the large intestine, urinary bladder and vagina. The exact description and information of the importance of this technique can be found in a Japanese work by S. Fujii from 2007 [9].

S. Fujii originated from the school of Okabayashi H. in Kyoto, Japan, who, as early as the 1920s, was one of the

world's pioneers of radical hysterectomy in that part of the world and drew attention to the possibility and need to save innervation [10].

The classification of Piver et al., did not include the principles of saving vegetative innervation proposed mainly by Japanese surgeons and adopted in European surgery [8, 9, 11–13]. In addition, other types of treatment, including the ultra-radical hysterectomy and fertility-saving surgery developed by French surgeons that were also not included in the Piver classification, were introduced [14–17].

Finally, the Piver classification only concerned open surgery and did not include the development of laparoscopic techniques and vaginal surgery. In this situation, the Piver classification ceased to be valid and was replaced by a new one introduced by Querleu and Morrow, which has been used as the most common one until now [18].

All the mentioned modifications of radical surgery were mainly associated with the concept of tailoring its radical nature and reducing universally understood side effects, but did not improve oncological effectiveness, which is still not satisfactory.

The Wertheim-Meigs radical surgery with its modifications is based on the so-called utero-centric model of anatomy described more empirically than in accordance with the biological process of human embryonic development. In the oncological aspect, it is based on the theory of accidental non-directed and uncontrolled development of a cancerous tumour. As a result of these assumptions, radical surgery should remove the organ/tumour along with a wide margin of surrounding tissues to achieve oncological effectiveness.

To a certain extent, contrary to the concept described above, another method of surgical treatment of cervical cancer was proposed by M. Höckel [19] in 2001 under the name of total mesometrial resection (TMMR).

The interesting and at the same time distinctive aspect in TMMR is an innovative approach to the anatomy of the pelvic organs and a fresh look at the resulting local and regional tumour development [20–22].

The TMMR idea is based on 3 concepts:

1. Description of embryologically defined pelvic anatomy.
2. Research on the development of a cancerous tumour that does not spread accidentally and during an initial phase of progression, only occupies tissues belonging to the embryological compartment in which it arose.
3. Development of a surgery that aims at the resection of the embryological compartment, from which a given organ, in this case the cervix, arose as a potential area at risk of the recurrence of the disease, taking into account the microscopic and molecular non-detectable aspects before and during surgery [23].

An essential and equally important element of this surgery is therapeutic lymph node dissection (tLND) [24].

Lymph nodes are one of the most important risk factors for a regional recurrence. From the perspective of the compartmental concept, all lymphatic tissue within the Mullerian compartment should be removed.

As a result of the analyses of embryological development carried out by the author of the method, the autonomic nervous system does not belong to the compartment from which the uterus originates, and therefore TMMR surgery is a nerve sparing surgery. According to the concept of this method all tissues belonging to the Mullerian compartment, which has its clear and described boundaries, should be removed. However, there is no need for extensive removal of tissues that do not belong to the compartment, although they may be in the vicinity of the cancerous tumour [25].

In the analysis of their research work, the author suggests the possibility of improving oncological outcomes based on the tissues potentially exposed to tumour development are completely removed. In a single-centre prospective study conducted by the author on a group of over 500 patients, encouragingly good results were obtained for patients treated with TMMR with tLND suffering from stage IB-IIA cancer according to FIGO 2009 (In the TMMR study, it was impossible to retrospectively adapt the current 2018 FIGO staging due to differences in diagnostic methods).

This study demonstrates that TMMR with tLND without adjuvant radiotherapy in stages IB1, IB2, IIA1 and IIA2 provides results comparable to those obtained by traditional surgery with postoperative radio/radiochemotherapy. The results for stage IIB treated with the TMMR or EMMR (extended mesometrial resection) method correspond to the oncological outcomes achieved using the latest radiotherapy techniques. An exceptionally low percentage of side effects was also observed: 21% of second grade and 3% of third grade ones according to Franco-Italian glossary. In a retrospective single-centre trial, complete or extended mesometrial resection with therapeutic nodectomy based on cervical cancer ontogenesis has good therapeutic outcomes. However, the results need to be ultimately confirmed in prospective multicentre studies [26].

It should be noted that according to the TMMR concept described above, patients do not require adjuvant radiation therapy and none of these patients received such treatment. It is assumed that surgical treatment applies to patients in whom the disease has not exceeded the compartment (up to FIGO 2009 stage IIB), which, when removed completely, leaves no room for adjuvant irradiation [26–28].

Of course, this management applies only to patients involved in the TMMR study, as it does not meet the current standards of adjuvant treatment.

According to the current standard, in the case of postoperative presence of unfavourable risk factors (positive resection margins, involvement of the parametrium, size

of the primary tumour >3cm, involvement of the vascular spaces of the cervix, low histological differentiation, positive lymph nodes, exceeding the nodal capsule, invasion of the uterine muscle, histological type — glandular or anaplastic cancer, deep cervical stromal infiltration, uterine muscle infiltration, incomplete histopathological report), patients in stage I (FIGO 2018 staging) undergo adjuvant radio/radiochemotherapy and those in clinical stage IIB are treated with radiochemotherapy [31].

In the TMMR study, adjuvant chemotherapy was given only to patients with two or more metastatic lymph nodes in the postoperative specimen [26].

Similar studies were performed for the treatment of colorectal cancer in terms of oncological outcomes with the introduction of total mesorectal excision (TME). As a result of the application of TME, the 5-year survival rate increased from 45–50% to 75%, the number of local recurrences decreased from 30% to 5–8%, and the percentage of sphincter-sparing surgery increased by 20%. Thanks to TME it was possible to withdraw from adjuvant treatment in cases of colorectal cancers of stage T3N0M0 [29].

SUMMARY

The concept of treatment using the TMMR method seems interesting and inspiring, however, the question is whether it will be possible to introduce it more widely, because it is a type of surgery constituting a major challenge to a surgeon.

In over 100 years of surgery development, the introduced modifications have allowed significant progress in reducing side effects, but both these modifications and classification changes have not had a positive effect on improving oncological outcomes that are not satisfactory in early and particularly locally advanced stages of cervical cancer.

Assuming that the method of TMMR with tLND proves efficient in multi-centre studies (the study No. NCT01819077 is currently underway), it is the only one that proposes to improve oncological outcomes and, interestingly, despite its radical nature, it results in improved outcomes in terms of side effects, considering that it is a nerve sparing surgery and patients are not subjected to multi-module treatment.

An important problem in the traditional approach to a radical hysterectomy is that up to 50% of patients are qualified for adjuvant radio/radiochemotherapy, which does not improve the oncological effectiveness as compared to the methods used separately, and significantly increases the number of side effects [30].

If no improvement in terms of the oncological outcomes for independent surgery is achieved, it seems very reasonable to limit surgical treatment to very early lesions (up to stage IB1 according to FIGO 2018 without suspected pelvic lymph node metastases in pre- and intraoperative tests).

This is in line with current recommendations of leading scientific societies and is highly understandable, because the excessively frequent qualification of patients for multi-module treatment seems the least beneficial.

In this context, classification and sparing techniques of the classical radical hysterectomy are of lesser importance. The case would be simple and patients with large tumours or suspected lymph node metastases should qualify for radiochemotherapy, however the results of such treatment are not satisfactory, and at the same time it also often concerns relatively young women to whom late complications of radiation therapy pose a serious threat.

A detailed description of the surgery protocol for TMMR with tLND, its subsequent modifications and treatment outcomes for individual stages of cervical cancer is not included here, because it is available and has been already reported by the author, while the present study is focused on the general concept of surgical oncology treatment of cervical cancer [24].

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