

REVIEW

COMPARTMENT-BASED RADICAL RESECTION: TOTAL MESOMETRIAL RESECTION BY MICHAEL HÖCKEL. A NOVEL APPROACH TO THE RADICAL TREATMENT OF EARLY-STAGE CERVICAL CANCER PATIENTS

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SUMMARY

Aim: During the last 12 years a new theory regarding the radical treatment of cervical cancer has been embraced by onco-gynecologists aiming at improving surgical outcomes, decreasing the complications rates and the need for adjuvant radiotherapy.

Rationale: This new theory named ontogenetic compartment theory has been proposed by Michael Höckel and is based on the fact that tumor growth is restricted to certain compartments which have their origin in the same primordium during the ontogenesis. Höckel's principles of radicality specifically refer to the radical resection of tumor-bearing compartment with metrically-intact borders. A complete resection of this compartment has the advantage of avoiding removal of adjacent tissues with other embryonic origin, whereas an incomplete removal of the compartment is associated with a high risk of tumor recurrence and poor local control. Total mesometrial resection (TMMR) is the surgical technique developed in the school of Radical Pelvic Surgery from Leipzig, Germany basing on the same principle of ontogenetic compartment-based resection. A complete radical compartment resection provides a good local control, a low rate of postoperative complications and the avoidance of adjuvant radiotherapy.

Conclusion: Analyzing the scientific evidence about TMMR in terms of morbidity, mortality, survival rates, and local control, TMMR may represent the future in the treatment of early-stage cervical cancer patients.

Abbreviations: TMMR = total mesometrial resection; FIGO = International Federation of Obstetrics and Gynecology; LN = lymph node; VS = Piver-Rutledge-Smith; OS = overall survival

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

RÉSUMÉ

Réséction radicale du compartiment antogénétique: résection totale du mésomètre d'après Michael Höckel. Une nouvelle approche du traitement radicale des patients avec cancer cervical en stade incipient

Objectif: Au cours des 12 dernières années, une nouvelle théorie concernant le traitement radical du cancer du col a été adopté par les onco-gynécologues visant à améliorer les résultats chirurgicaux, en diminuant les taux de complications et la nécessité d'une radiothérapie adjuvante.

Justification: Cette nouvelle théorie appelée théorie du compartiment ontogénétique a été proposée par Michael Höckel et est basée sur le fait que la croissance de la tumeur est limitée à certains compartiments qui ont leur origine dans la même ébauche lors de l'ontogenèse. Les principes de Höckel de radicalité se réfèrent spécifiquement à la résection radicale du compartiment portant la tumeur avec des frontières métriques intactes. Une résection complète de ce compartiment a l'avantage d'éviter l'élimination des tissus adjacents avec une autre origine embryonnaire, alors que l'élimination incomplète du compartiment est associée à un risque élevé de récurrence de la tumeur et un contrôle local faible. La résection totale du mésomètre (TMMR) est la technique chirurgicale développée par l'école de chirurgie radicale pelvienne de Leipzig, Allemagne se basant sur le même principe de base de la résection ontogénétique compartimentale. Une résection radicale compartimentale offre un bon contrôle local, un taux de complications postopératoires bas et l'évitement de la radiothérapie adjuvante.

Conclusion: en analysant la preuve scientifique sur TMMR en termes de morbidité, de mortalité, taux de survie, et le contrôle local, la TMMR peut représenter l'avenir dans le traitement des patients atteints de cancer du col utérin dans un stade précoce.

Mots clés: cancer du col utérin, hystérectomie radicale, résection totale du mésomètre

INTRODUCTION

Although improvements in the screening and prevention programs (Papanicolaou Test, vaccination against HPV) have led to a significant decrease in the incidence of cervical cancer, almost 490 000 women are still annually diagnosed with this disease which puts carcinoma of the uterine cervix on the second place among the most common cancers in women. Moreover, as more women are diagnosed with cervical cancer at a young age (mean age 40 years), the number of deaths is relative high-almost 270 000 deaths annually with a mean loss of 26 years per patient dying of cervical cancer[1,2].

The classical surgical radical treatment for cervical cancer stages IB-IIA according to the International Federation of Obstetrics and Gynecology (FIGO) consists of radical abdominal hysterectomy developed by Wertheim who has presented his surgical principles regarding radicalness in cervical cancer at the International Congress of Surgery and Gynecology in Rome in 1902. He stated that the radical abdominal hysterectomy should imply excision of the uterus and the surrounding connective tissue, bilateral adnexectomy, excision of the superior part of the vagina and the removal of only the palpable (possible metastatic) lymph nodes (LNs) [3]. Since then, the technique has been continuously developed in terms of radicalness with the introduction of para-cervical tissue dissection, dissection of the vesico-ligament, pelvic and para-aortic LN dissection as well as the vaginal, laparoscopic or robotic approaches [4,5]. However, all these variants of the radical hysterectomy techniques respect the same doctrine which involves: radical organ resection with microscopically metrically-defined negative margins (R0). "Almost" negative resection or positive margins (histopathological defined) as well as the presence of other pathologic risk factors require postoperative irradiation [6].

Although achievement of a R0 resection after radical hysterectomy represents the goal of the surgical radical treatment of cervical cancer, the rate of local recurrence is still high- between 5% and 50% which means that the established surgical principles are not strong enough to control the appearance of local or distant metastases [7]. Furthermore, studies have demonstrated that the combined treatment with surgery followed by radiation does not provide satisfactory results in terms of morbidity and survival rates: the 5-year overall survival rate is 80% while the complication rate achieves almost 30% [8].

The above presented results suggest that the current concept about the surgical radical treatment of cervical cancer- utero-centric anatomy and ligament focused- is inconsistent and no more valid. The fact that almost 50% of women with cervical cancer FIGO stages IB-IIA are submitted to adjuvant radiotherapy after surgery suggest that surgery is not as radical as it should be.[9].

In the same way, it has been demonstrated that extension of para-cervical radicality and extended LN dissection are not associated with better overall survival outcomes in cervical cancer FIGO stage IB-IIA. Moreover, by taking into consideration the Piver-Rutledge-Smith classification,

which divides the radical hysterectomy technique into 5 classes, depending on the extent of dissection, it has been demonstrated that there are no advantages in terms of pelvic tumor control, morbidity and mortality rates when an extended resection is performed (for e.g Type II vs Type III radical hysterectomy according to the PVS classification)[8].

Assuming that all the above presented unsatisfactory surgical outcomes (the often need of radiotherapy, high morbidity and recurrence rate, poor local tumor control) cannot all be owed to inadequate performance of the surgical procedure or diagnostic methods, Höckel and Fritsch [10] from Leipzig School of Radical Pelvic Surgery, Germany, followed the embryonic evolution of the female reproductive tract from the embryo development to fetal differentiation and further maturation in the adult focusing on the embryological different compartments. They have identified the area of resection and named it the distal Müllerian morphogenetic unit. Basing on the same principles of nerve-sparing extended radical hysterectomy, Höckel developed the TMMR which implies the resection of the Müllerian morphogenetic unit[11].

Höckel's theory states that the cervical tumors develop themselves within a certain permissive embryological compartment and remain confined to this compartment during their natural course of evolution. The borders of the compartments can normally inhibit the tumor extent beyond the compartment, if the invasion into adjacent organs of different embryonic origin; it means that phenotypical changes into the tumor cells have occurred during the malignant growth and invasion. If residual malignant cells remain within the compartment after radical resection, then the risk of local recurrences is high.

Description of the Müllerian Compartment

For a good understanding of the spread of cervical cancer, the knowledge of the embryologic development of the female genital tract is mandatory. Three processes are necessary for the development of the ovaries, fallopian tubes, corpus and cervix uteri, vagina and the vulva. Excepting the vagina which has its origin in the endodermal urogenital sinus or the Wolffian ducts (mesonephric ducts), the rest of the adult female genital tract has its origin in the Müllerian ducts (paramesonephroid ducts). During the 6 weeks, the two Müllerian ducts appear in the mesenchyme of the urogenital ridges in male and female human embryos as an invagination of the coelomic epithelium lateral to the Wolffian ducts. In males, the Müllerian ducts regress during an embryologic healthy development. In the female genital tracts, the development process continues in the 7th week and implies epithelialization, stroma formation, vascularization, and innervation. This results into three Müllerian subunits as follows [12]:

- the proximal subunit which includes the fallopian tubes without the fimbria and their mesosalpinx;
- the intermediate subunit which includes the corpus uteri and the bilateral peritoneal mesometrium (road ligament);
- the distal subunit which includes the cervix, the

proximal two-thirds of the vagina and the associated neurovascular structures;

The utero-vaginal (Müllerian) compartment described by HÖckel is the final part of the differentiation process and it includes the uterine blood vessels (uterine artery and uterine vein) and the utero-vaginal branches of the autonomic nerves [13].

The subperitoneal part of the Müllerian is a separate sub-unit consisting of arterial capillaries and venous connections to the bladder and rectum compartments. The subperitoneal mesometrium can be subdivided into [14]:

- the vascular mesometrium which includes: uterine and vaginal blood vessels and LNs; it is crossed by the ureters;
- the ligamentous mesometrium which includes: posterior broad ligaments, uterosacral ligaments, the recto-uterine and rectovaginal ligaments, the rectovaginal septum and the plexus hypogastricus inferior;

With regard to the pelvic therapeutic lymphadenectomy, the LNs have also been deduced from ontogenetic lymphatic compartments and are classified into two groups [15]:

- The primary lymphatic basins including the external iliac LNs, paravisceral (anterior internal iliac, supra-obturator and infraobturator, presciatic) LNs and mesometrial LNs;
- The secondary lymphatic basin including the common iliac LNs, superior gluteal LNs, and presacral LNs (posterior internal iliac, aortic, and caval bifurcation LNs).

Principles and benefits of Total Mesometrial Resection

TMMR is a modified radical technique, distinct from the conventional radical hysterectomy and supposes a complete resection of the utero-vaginal (Müllerian) compartment with preservation of its distal part in order to assure a functional vaginal vault [10].

If the extirpation occurs intact borders, the pelvic autonomic nerves and bladder vessels which are part of the adjacent compartment are preserved even if they are closely located to the malignant cervical tumor as it has been shown that the tumor grows, invades and destroys the Müllerian compartment differentiated from the para-mesonephric-mesonephric complex connected to the deep urogenital sinus but does not extend into the adjacent compartments as long as phenotypical changes in the structure of the tumor cell do not occur [16]. Invasion is most frequently into the bladder because of the common embryological origin of the Müllerian unit and the lower urinary tract. The mesonephric and paramesonephric tissues originate in the intermediate mesoderm, and the mesonephric system is involved in the development process of both the urinary and genital tract [12].

As regards to the benefits from TMMR in terms of recurrence-free and overall survival (OS) rate, morbidity rate, local pelvic control and the percentage of women who required adjuvant radiotherapy, the team of HÖckel has presented the results from a prospective analysis from 2009 [17] on 212 women with cervical cancer FIGO stages IB-IIB who were treated with TMMR. At a median follow-up of 41 months,

the reported OS and recurrence-free survival rates were 96% and 94% respectively, while the morbidity rate was only of 9% (second grade treatment related morbidity). The pelvic local tumor control rate was almost 98% and no women has been submitted to radiotherapy although 63% of them presented histopathological risk factors. Taking into account the above presented results and other scientific evidence on the advantages of TMMR, it seems that an embryologically based resection without performing adjuvant radiation can increase the OS by 15–20%. Furthermore, postoperative anorectal and bladder dysfunction are rare as the TMMR does not involve the resection of the autonomous nerve because they are not part of the Müllerian unit [18].

As regards the therapeutic pelvic lymphadenectomy, TMMR involves the dissection of the presacral, gluteal, and presciatic LNs which have led to a reported 5-year OS of 91% [12], in comparison with other studies that have reported OS rates ranging between 68%–78% [19].

Other benefits of the TMMR technique refer to [16,20,21]:

- precise identification of the anatomy of the permissive compartment;
- an accurate and anatomically-based dissection;
- good local pelvic tumor control although the resection occurs very close to the border with the adjacent compartments;
- by avoiding the adjuvant radiotherapy the treatment-related morbidity rate is low;
- if the tumor is attached to the pelvic wall, an en bloc removal of the pelvic floor and side wall muscles (laterally extended endopelvic resection) also provides an excellent local tumor control and suggests that the tumor adhesion at the pelvic wall may still be resected as these adhesions are fibrotic adherence of the tumor which is still part of the Müllerian compartment;

Why TMMR and not radical conventional hysterectomy?

In comparison to conventional radical hysterectomy, TMMR involves a precise and anatomically-based resection and a sharp separation of bordering lamellae. Both techniques suppose the excision of the uterus and vagina. However, as it is not part of the morphogenetic unit, TMMR does not resect the anterior and lateral paracervical tissue compared to radical hysterectomy which involves the extirpation of these tissues. Taking into consideration the embryological notions, the paracervical tissue corresponds is part of the uterovaginal and bladder mesentery mixed with parietal LNs. Separation from the rectum is often bluntly performed while adjacent hypogastric nerves and the inferior hypogastric plexus are disregarded. Although inadequate, the common radical hysterectomy resects the paracervical tissue, thus increasing treatment-related morbidity. On the other hand, TMMR implies the resection of the perirectal tissue, a resection which does not represent a step in the performance of radical hysterectomy. In the same way, with the intend of being as most radical as

possible, radical hysterectomy unnecessarily sacrifices adjacent tissues (e.g. bladder vessels) to the uterovaginal compartment.

Pelvic recurrences result from residual tumor cells within the Müllerian compartment as demonstrated by the pelvic Magnetic Resonance Imaging (MRI) usually performed after conventional radical hysterectomy. The high rate of postoperative complications and the poor pelvic tumor control are a consequence of the unnecessary resection of the paracervical tissue and of the performance of adjuvant radiotherapy [21].

CONCLUSIONS

The novel concept of embryologically-based radical resection of a malignant solid tumor respecting the borders of the morphogenetic unit is currently a standardized technique with excellent surgical outcomes. Firstly, the radical resection of the Müllerian compartment provides a very good local tumor control and a low rate of treatment-related complications as it avoids the performance of postoperative radiotherapy. However, a metrically defined tumor-free resection margins is mandatory. Secondly, in contrast to the conventional radical hysterectomy, adjacent organs, as part of compartment with different embryological origin, are not removed even if they are located closely to the tumor border.

It is now clear that TMMR has the ability to improve the therapeutic index of the radical surgical treatment of early-stage cervical cancer. However, the implementation of TMMR in the standard protocol treatment of cervical cancer requires multi-institutional controlled trials in order to validate the results obtained by Höckel and his collaborators. Last but not least, a deep understanding of the principles of this concept, as well as the technical ability (and financial resources) to perform this advanced oncogynecologic surgery are mandatory.

REFERENCES

- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69-90.
- GLOBOCAN Cancer Fact Sheets: Cervical Cancer. globocan.iarc.fr/factsheet.asp. Accessed December 31, 2013.
- Dornhöfer N, Höckel M. New developments in the surgical therapy of cervical carcinoma. *Ann. NY. Acad. Sci.* 2008; 1138, 233-252.
- Cibula D, Abu-Rustum NR, Benedetti-Panici P, et al. New classification system of radical hysterectomy: emphasis on a three-dimensional anatomic template for parametrial resection. *Gynecol Oncol.* 2011; doi: 10.1016/j.ygyno.2011.04.029.
- Webb MJ. Radical hysterectomy. *BaillieresClinObstetGynaecol.* 1997 Mar;11(1):149-66L. Verleye I, Vergote NR, Ottevanger PB. Quality assurance for radical hysterectomy for cervical cancer: the view of the European Organization for Research and Treatment of Cancer—Gynecological Cancer Group (EORTC-GCG). *Ann Oncol.* 2009;doi: 10.1093/annonc/mdp196.
- Viswanathan AN, Lee H., Hanson E., Berkowitz RS., Crum CP. Influence of margin status and radiation on recurrence after radical hysterectomy in stage IB cervical cancer. *Int. J. Rad. Oncol. Biol. Phys.* 2007;65:1501-1507.
- Höckel M, Dornhöfer N. The hydra phenomenon of cancer: why tumors recur locally after microscopically complete surgical resection. *Cancer Res.* 2005;65(8):2997-3002.
- Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib–IIa cervical cancer. *Lancet.* 1997;350(9077):535-40.
- Jain P, Hunter RD, Livsey JE et al. Pattern of failure and long-term morbidity in patients undergoing postoperative radiotherapy for cervical cancer. *Int. J. Gynecol. Cancer* 2006; 16:1839-1845.
- Höckel M, Horn LC, Fritsch H. Association between the mesenchymal compartment of uterovaginal organogenesis and local tumour spread in stage IB–IIB cervical carcinoma: a prospective study. *Lancet Oncol.* 2005;6(10):751-6.
- Höckel M, Konerding MA, Heussel CP. Liposuction-assisted nerve-sparing extended radical hysterectomy: oncologic rationale, surgical anatomy, and feasibility study. *Am J Obstet Gynecol.* 1998;178(5):971-6.
- Palaksha MA, Shivarudraiah G. Embryologically Based Resection of Cervical Cancers: A New Concept of Surgical Radicality. *The Journal of Obstetrics and Gynecology of India (January–February 2012)* 62(1):5-14 . DOI 10.1007/s13224-012-0162-8
- Höckel M, Kahn T, Eienkel J, Manthey N, Braumann U-D, Hildebrandt G, Leo C, Hentschel B, Vaupel P, Horn L-C: Local spread of cervical cancer revisited: a clinical and pathological pattern analysis. *GynecolOncol* 2010,117:401-408.
- Höckel M: Do we need a new classification for radical hysterectomy? Insights in surgical anatomy and local tumor spread from human embryology. *GynecolOncol* 2007, 1:106-112.
- Höckel M, Horn L-C, Tetsch E, Eienkel J: Pattern analysis of regional spread and therapeutic lymph node dissection in cervical cancer based on ontogenetic anatomy. *GynecolOncol* 2012, 125:168-174.
- Höckel M. Ultra-radical compartmentalized surgery in gynaecological oncology. *Eur J SurgOncol.* 2006;32(8):859-65.
- Höckel M, Horn LC, Manthey N, et al. Resection of the embryologically defined uterovaginal (Müllerian) compartment and pelvic control in patients with cervical cancer: a prospective analysis. *Lancet Oncol.* 2009;10(7):683-92.
- Lai CH, Hong JH, Hsueh S, et al. Preoperative prognostic variables and the impact of postoperative adjuvant therapy on the outcomes of Stage IB or II cervical carcinoma patients with or without pelvic lymph node metastases: an analysis of 891 cases. *Cancer.* 1999;85(7):1537-46.
- Kim SM, Choi HS, Byun JS. Overall 5-year survival rate and prognostic factors in patients with stage IB and IIA cervical cancer treated by radical hysterectomy and pelvic lymph node dissection. *Int J Gynecol Cancer.* 2000;10(4):305-12.
- Höckel M. Laterally extended endopelvic resection (LEER)—principles and practice. *GynecolOncol.* 2008;111(2 Suppl): S13-7.
- M. Höckel, “Do we need a new classification for radical hysterectomy? Insights in surgical anatomy and local tumor spread from human embryology,” *Gynecologic Oncology*, vol. 107, supplement 1, pp. S106–S112, 2007.