

Modulation of radicality in the surgery of early cervical cancer

Motto: "The Wertheim operation is a surgical nonsense and there is no reason for it to exist, since it is incomplete without an iliopelvic lymphadenectomy."

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Abstract

Initial stages of I-IIA cervical cancer benefit from an exclusive surgical treatment where radical hysterectomy is considered the standard method regardless of the approach or technique used. Although mortality is insignificant, perioperative morbidity is marked by complications due to the tendency to resect as much parametrial tissue as possible and due to the lymphadenectomy itself. Evacuation disorders of the bladder and rectum or a compromised sexual function are only a part of the complications overshadowing the high survival rate of the surgical treatment. Research in the last decade has concentrated on reconsidering the limits of radicality for hysterectomy and on reducing the invasiveness in the sense of a less aggressive surgery aiming at anatomical and functional conservation.

Keywords: cervical cancer, radical hysterectomy, lymphadenectomy

1. Parametrial dissemination in early cervical cancer

1.1. Parametrial. Surgical anatomy

The extension of the tumor from the level of the cervix may run along the vascular, lymphatic or nervous structures existing in the structure of the parametrium.

Parametrial (cardinal ligaments, Mackenrodt ligaments, lateral cervical ligament or transversal cervical ligament) are structures deriving from the endopelvic fascia making the anatomic connection between the uterus and the pelvic walls and are defined as a lateral extension of the subserous uterine connective tissue situated at the base of large ligaments⁽¹⁾.

Parametrial contain a supraureteral segment, *pars vasculosa*, which contains blood-lymphatic vessels, parametrial lymph nodes, an infraureteral segment, *pars nervosa*, which contains fibrous connective tissue and nervous structures which are components of the inferior hypogastric plexus⁽²⁾. The limit between the two parametrial territories is marked by the deep uterine vein. The parametrial supraureteral segment is composed of three distinct divisions⁽³⁾. The most important division is the lateral supraureteral parametrium (*pars vasculosa*, or mesometrium described by Hoeckel), composed by uterine origin and cervico-vaginal vessels, fatty cells and lymphatic tissue. Previously the lateral parametrium is delineated by the vesico-uterine ligament covering the ureter up to its entry into the bladder. The posterior parametrium is constituted from a sheet

cellular-fibrous tissue situated between the pararectal and the rectovaginal space, which are continued with the parietal pelvic fascia. On its cranial side it forms the uterosacral ligament which inserts itself on the *torus uterinus* and on the caudal side the sacrogenital slide which anchor the superior vagina.

The conclusions of the studies performed by intraoperative laparoscopic dissection on cadavers or by MRI support the idea that under the level of the ureter there is no parametrial tissue, a fact which radically changes the point of view concerning the limits of lateral parameter resection and the various classes of radical hysterectomy (HR)⁽²⁾.

1.2. The Hoeckel Theory

Hoeckel has demonstrated the common embryological mullerian origin of an assembly composed of the fallopian tubes, the uterus, the proximal and medial vagina, together with the adjacent peritoneal, subperitoneal structures which consists the mezometrium and which are different histologically as well as embryologically from the subureteral parameter and paravaginal tissues.

The mezometrium forms a morphogenetic specific unit which defines its own extracellular matrix in the course of ontogenetic evolution. In the early stages of cervical cancer the tumor extension is limited to the mezometrium, because the tumor cells can only develop in the specific internal environment to this area. Tumor invasion outside this territory takes place in advanced stages of the disease histologically and clinically defined.

Hoeckel demonstrates by clinical and anatomic studies, that the resection of the uterus along with the mesometrial structures may replace the extensive parametrial excision with a direct benefit in the conservation of the extra-divided vascular and nervous structures in other territories, with a different embryologic origin.

The conclusion of this research is the establishing of a RH technique called total mesometrial resection, which has been applied in practice, proving today its efficiency^(2,4).

1.3. Maintaining the pelvic innervation in RH

RH in which exceed the parametrial ureteral limit (class III-Piver, class C-Querleu) is entailed by neurological complications due to the interception of the autonomous innervation of the pelvis. Yabuki⁽⁵⁾ in 1991 communicates for the first time the results obtained after using its own RH technique, maintaining the enervation of the bladder, rectum and vagina⁽³⁾.

Hypogastric nerves are the main source of sympathetic enervation of the pelvis, deriving from the superior hypogastric plexus. They can be identified starting with the presacral region under the bifurcation of the aorta, on each side, then in the cellular fatty tissue on the lateral sides of the uterosacral ligaments up to the vicinity of the previously parametrial, where they form the dorsocranial part of the inferior hypogastric plexus. During dissection they can be isolated by the lateral detachment of the mesoureter from the fibrous uterosacral slides. The space created posterior delineates the mesometrial territory (Hoeckel) and allows for the cutting of the uterosacral ligaments without the interception of the hypogastric nerves⁽⁵⁾.

The inferior hypogastric plexus is situated in the lateral and dorsal part of the cardinal ligaments and it is a conglomeration of nervous fibres and lymph nodes from where branches spread to the bladder, uterus and rectus. The hypogastric inferior plexus is found in the deep part of the paracervix (*pars nervosa*). The sympathetic component is due to the hypogastric nerves and the parasympathetic component to the splanchnic pelvic nerves with the origin in the medullar roots S2-S4. Outgoing branches of the hypogastric inferior plexus are constitute of three separate plexuses: vagino-rectal plexus situated medially under the intersection of the uterus with the uterine artery, the vesical plexus which sends out lateral bladder branches and medial trigonal branches and rectal plexus composed by the inferior branches of the inferior hypogastric plexus. The preservation of the inferior hypogastric plexus is performed by limiting the parametrial resection at the level of the ureter, at the back and the origin of the uterine laterally artery, described by Hoeckel.

1.4. The parametrial dissemination type in early cervical cancer

Early stages of cervical cancer are defined by consensus as IA2 - IIA stages where there is no clinical parametrial extension. The parametrial tumor invasion it is correlates in all cases with the metastasis in the pelvic

lymph nodes⁽⁶⁾ unlike lymph node metastasis which can exist in the absence of parametrial invasion.

The parametrial invasion of a clinical appreciation is not in line with the histological stage, so in Ist stage the parametrial invasion is present in 18% of cases, and in IInd stage in only 34% of cases. Parametrial tumor invasion can be discontinuous, in over 60% of cases, by presence of some isolated islets of tumour cells in a seemingly unaffected parameter, a fact which explains recurrences in Ist stage⁽⁶⁾.

In Ib1 stage the risk of parameter invasion is reduced when tumors are smaller than 2 cm, regardless of the histology and the degree of differentiation^(7,8,9).

Pelvic lymphatic metastasis as well as para-aortic can be present in 0-31% and 0-22%, respectively of the forms of early cervical cancer⁽¹⁰⁾.

In 30% of cases, pelvic lymph nodes can be affected without being a parametrial invasion, the survival rate being 71%, in contrast with the concomitant parametrial and lymph node invasion, where the survival rate decreases to 41%⁽¹¹⁾.

2. Lymph node dissemination in early cervical cancer. The role of the sentinel lymph node (SLN)

Pelvic lymphadenectomy (PL) and para-aortic lymphadenectomy (PAL) are complementary to RH techniques for uterine cancer entailed by the risk of vascular and urologic nervous lesions, intestinal and infectious of certain specific complications such as lymphatic cysts in 20% of the cases and chronic oedema of pelvic members which can appear in 15% of cases. The limitation of the radically lymphadenectomy is in line with the general tendency in the treatment of uterine cancer by reducing the risk of these complications⁽¹²⁾.

The introduction of the SLN concept in early cervical cancer was a major step in modern oncologic surgery. The SLN concept is based on the hypothesis by which the drainage of the lymphatic basin coming from the level of the cervix is sequential and the first affected lymph node functions as a filter in the road of tumor cell diffusion. The possibility of lymphatic metastasis to produce skipping this lymph node is extremely rare. Levenback⁽¹³⁾ has demonstrated for cervical cancer, that in case the SLN has not been invaded, the chance of the other pelvic lymph nodes to be unaffected is over 95%⁽¹⁴⁾.

The most frequent positions of the SLN were identified in 43% of the external iliac group, in 26% of the obturator, in 21% of the parameter and 7% of the common iliac groups, in 1% of the presacral and in 1% of the paraaortic⁽¹⁵⁾.

The SLN can be identified unilaterally or bilaterally. The predictive negative value of close to 100% makes it possible that in early stages of cervical cancer, lymphadenectomy to be limited to only the SLN⁽¹⁶⁾. However, the possibility of existence of micro-metastasis at this level, undetected during the extemporaneous examination, will limit the applicability of the methods to the

centres which can perform at the same time molecular PCR analysis, immunohistochemical analysis (IHC) or the cytokeratine 19 detection complementary to the standard eosin hematoxylin staining⁽¹⁷⁾.

The risk of discovering micro-metastasis in cases when the SLN was negative at standard staining can be of up to 42,8% for PCR and of 20% for IHC⁽¹⁸⁾. In this situation a systematic PL even in the presence of a negative SLN remains the alternative insuring oncologic security in early cases of cervical cancer. The significance of a positive SLN in Ib1 stage consists in the possibility that tumor cells have spread outside the regional lymphatic basin, situation in which systematic PL is associated with an PAL during the same operation. For Ib2 or IIa stage PAL has a value of surgical staging and justification of an adjuvant chemoradiation therapy. The therapeutic role of PAL per se is arguable.

3. Modulation of Radically Hysterectomy

RH is practiced in the majority of cases by open abdomen approach, according to various techniques and variants. In relationship with the alternatives of laparoscopic abdominal or transvaginal approach, the open abdominal route is most invasive, prone to specific postoperative complications and with the longest hospitalisation time. In contrast vaginal RH reopens the perspective of a minimally invasive surgery by natural route, initiated by Pawlik and then Schauta, where the sequence of the operative steps is anatomical^(19,20).

Nowadays, vaginal RH combined with laparoscopic PL offers a minimally invasive variant which has

indications for cases of obesity or high pathological load.

The most common method of surgical treatment of cervical cancer is RH according to the Wertheim-Meigs technique, by which the uterus tumor is excised along with the superior vagina, parametrial tissues and pelvic or paraaortal lymph nodes.

The preoperative estimate of the RH extension, whatever the approach way can be performed by imaging, sonography, magnetic resonance or positron emission, it's focus on the degree of stromal and lymph node invasion corroborated with the histological type obtained through biopsy. The intention is to plan a limited intervention from the radically point of view, according to the parameter or lymph node invasion. In this sense various classes of hysterectomy have been defined, in agreement with the anatomo-clinical stage of the disease. The oldest classification dating from 1974 is that of Piver-Rutledge-Smith defining five classes of hysterectomy and referring strictly to the Wertheim-Meigs⁽¹⁷⁾ type of hysterectomy. Practice has shown that there are some doubts in differentiating IInd from IIIrd and IVth from Vth classes, and the classification in itself cannot apply to vaginal or laparoscopic RH.

At present there are two classifications accepted, which can be used for all types of approach to RH (table 1 and 2).

For vaginal RH, Massi has defined a classification into three classes which has proven to be in full line with the limited parametrial resection techniques and the preservation of the pelvic enervation (table 3).

Table 1 Classification of the European Organization for Research and Treatment of Cancer-Gynecological Cancer Group (EORTC-GCG) of hysterectomy classes (after Verleye et al.)⁽¹⁸⁾

Type I	Simple hysterectomy
Type II	Modified RH <ul style="list-style-type: none"> ■ Ureter dissected up to the entry to the bladder ■ Proximal resection of uterosacral ligaments ■ Resection of the medial part of parametria ■ Resection of 1-2 cm of the vagina
Type III	RH <ul style="list-style-type: none"> ■ Resection of as much as possible of the uterosacral ligaments ■ Complete resection of parametria ■ Resection of the upper third of the vagina
Type IV	Extended RH <ul style="list-style-type: none"> ■ Like type II but with the resection of ¾ of the vagina and the paracolpos
Type V	Partial exenteration <ul style="list-style-type: none"> ■ Terminal uterus with a segment of the bladder or the rectum in block with the uterus and the parametria
Type II-V	<ul style="list-style-type: none"> ■ PL is added from the half of the common iliac artery up to the femoral ring, including ■ Bilateral aneectomy is not part of the RH <i>per se</i>

Table 2 Classification of RH (after Querleu)⁽¹⁹⁾

Extension of the resection		Ureter	Remarks
A - minimal resection of the paracervix	The paracervix is cut medially to the ureter, but laterally to the cervix; the bladder-uterus and uterosacral ligaments are not cut at a distance from the uterus; the superior vagina is minimally resected	Palpation or direct visualisation without release	
B - resection of the paracervix at the level of the ureter	The paracervix is cut at the level of the ureteral tunnel; partial resection of the bladder-uterus ligaments and uterosacral ligaments; nervous paracervix will not be resected under the level of the deep uterine vein; resection of the vagina at maximum 10 mm from the cervix or tumour	Opening the ureter channel and lateral reclining	The limit between the paracervical lymph nodes and the iliac lymph nodes is the obturator nerve; the dissection of both groups is equivalent with what we have established for type C1
B1	As described before		
B2	As described before with lymphadenectomy		
C - cutting the paracervix at the junction with the internal iliac vascular system	Uterosacral ligaments are resected at the level of the rectum, bladder - uterus ligaments at the level of the bladder; the resection of 15-20 mm of the vagina removed from the cervix or the tumour with the respective paracolops	Completely mobilised	
C1	With the conservation of autonomous innervation		
C2	Without the conservation of autonomous innervation		
D - lateral extended resection	Resection of the paracervix at the level of the pelvic wall, along with the branches of the anterior hypogastric trunk and the evidence of the root of the sciatic nerve	Completely mobilised	
D1	Resection of the paracervix at the level of the pelvic wall, together with the hypogastric vessels and the according fascial and muscular structures		
D2			

Table 3 Classification of vaginal RH (after Massi)⁽²⁰⁾

Class	Schuchard incision	Ureter dissection	Parametrial resection + LUS	Resection of vagina	Indication	Laparoscopic lymphadenectomy
I	superficial	no	no	1-2 cm	Cerv. T. IA2	no
II	deep	incomplete	1/3 medial	1-2 cm	Cerv. t. IB1	yes
III	deep	complete	At pelvic insertion	1/2	Cerv.t. 1B2	yes

Preoperative, there are two situations according with the different degrees of hysterectomy extension:

■ Tumors with stromal invasion under half of the thickness of the cervical wall or under 10 mm, without lympho-vascular invasion, where the parametrial and lymph node invasion is rare (Kinney)^(6,7). This type be-

nefits from limited RH of A or B type (Querleu) or Ist-IInd classes (Massi);

■ Tumors where stromal invasion is larger than two thirds of the thickness of the cervical wall or invading the pericervical fascia or miometer, where parametrial invasion or lymph node invasion is frequent and which

Table 4 Indications for various RH types

FIGO stage	Querleu	EORTC	Hoeckel	Dargent	Massi	PL	PAL
IA2	A,B	I	-	RT**, SLN	I	Yes	
IB1	B2	II	TMMR*	RT**, SLN	II***	Yes	SLN+
IB2	B2,C1	II	TMMR*	-	II***	Yes	SLN+
IIA	C1	II, III	TMMR*	-	II***	Yes	SLN+

*TMMR - total mesometrial resection, **RT - radical trachelectomy, SLN - sentinel lymph, node, PL - pelvic lymphadenectomy, PAL - paraortic lymphadenectomy, *** - vaginal RH with laparoscopic PL

Table 5 Quality indicators for HR⁽¹⁸⁾

Structure	Number of RH per surgeon per year Number of RH per institution per year	≥10 ≥20
Results	5 year survival rate for stages I-IIa Pelvic recurrence percentage after RH Percentage of short term complications after RH <ul style="list-style-type: none"> ■ Post operative mortality ■ Post operative haemorrhage ■ Lesions of the urinary tract ■ Intestinal occlusions ■ Deep vein thrombosis Percentage of long term complications after RH <ul style="list-style-type: none"> ■ Symptomatic lymphocyst ■ Ureteral stenosis ■ Incision herniae ■ Surgically treated fistulas (of the bladder, ureter, recto-vaginal) Percentage of positive margins per resected element	≥80% ≤15% ≤1% ≤1% ≤1% ≤3% ≤5% ≤3% ≤3% ≤3% ≤3% ≤5%
Processing	Percentage of cases where >11 pelvic lymph nodes have been extracted Percentage of cases where the lymph nodes from the external iliac group, internal and obturator group are analysed separately under the microscope. Percentage of cases without peritonisation and retroperitoneal drain Percentage of cases where post-op administration of antibiotics was needed Percentage of cases where a normal diet was instituted from the first day	≥90% ≥95% ≥95% ≥95% ≥90%

benefits as primary treatment of radiotherapy followed by RH of C or D type, or IInd - IIIrd Massi classes.

Intraoperative assessment of the lymph node invasion and resection margins, by extemporaneous histological analysis, adds an additional safety in establishing a type of limited paracervical resection, to allow for the conservation of vascular and nervous structures of the adjacent organs. Recent studies have shown that in cases of cervical cancer of IB stage without a lympho-vascular invasion and without an invasion of pelvic lymph nodes, parametrial invasion can be excluded (table 4)⁽²¹⁾.

If a RH of A or B type was initially performed with systematic lymphadenectomy and where the postoperative

histopathological examination has identified a number of up to 2-4 invaded lymph nodes, the subsequent evolution was favourable without a necessity for adjuvant treatment by telerradiation or chemotherapy⁽²²⁾.

The idea of radical trachelectomy (RT) was taken over by Dargent from Aburel who at the beginning of the 50s had imagined the technique of subfundal hysterectomy by abdominal route⁽²³⁾.

The introduction of the SLN concept as integrated part of vaginal, laparoscopically assisted RH or RT techniques, has allowed the elaboration of a strategy by which the preoperative pelvic radiation is meaningful only materialized with lymph node invasion proven by intraoperative histological examination.

Quality indicators for RH

The quality of the surgical act performed by RH is the main factor insuring local control of tumor growth and of a positive influence on the survival rate. RH techniques used at present have numerous variants resulting from the practice of every centre or surgeon, sometimes with dogmatic elements maintained and perpetuated by oral transmission. For this reason the necessity has appeared to provide a comparison and control element over RH.

The evaluation of RH quality is performed by statistical analysis of three layers concerning structure, results and processing the data from postoperative evolutions⁽²³⁾. Based on an analysis of the data from literature, EORTC-GCG has elaborated a set of criteria for the appreciation of RH quality in early cervical cancer⁽¹⁷⁾.

It is appreciated that in an institution where the number of RHs performed in one year is fewer than 20 and where a surgeon practices under 10 such interventions in one year, resulting and processed quality indicators do not reflect reality.

In evaluating results the following aspects are considered: survival at 5 years for stadialised I-IIA cases, pelvic recurrence percentage and percentage of distance and perioperator complications (table 5).

Processing data include efficiency indicators in connection with the surgical act per se, such as the number of extracted pelvic lymph nodes, the number of cases where peritonization and retroperitoneal

drain was not performed, but also data from postoperative care technique.

Conclusions

For early stages of cervical cancer, the lateral limitation of the parametrial resection at the level of the supraureteral pediculum from the origin of the uterine artery is sufficient. The previously limit of parametrial resection is the subureteral pediculum with maintenance of vascularisation and enervation of urinary bladder. The posterior limit is the resection of the sacral-genital slide in the cranial half, medial, without mesoureter. In this way the autonomous enervation of the bladder, rectum and vagina are maintained without being oncologically compromised (EORTC modified RH, B type- Querleau, IInd Massi type).

Systemic PL is necessary in all early stages of cervical cancer including micro invasive carcinoma. Positive SLN supports the indication for PAL, along with PL. PL can be limited only with a negative SLN at standard staining, if it stays negative also for IHC or PCR examination, to exclude micrometastasis. Positive paraaortic lymph nodes recommend left scalene lymph node biopsy as indicator of extra-abdominal metastasis and for the institution of chemotherapy.

Vaginal RH associated with laparoscopic PL and total laparoscopic RH represents the optimal solution for the majority of early cervical cancers. ■

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