

New Developments in the Surgical Therapy of Cervical Carcinoma

Michael HÖCKEL, Nadja DORNHÖFER

*University of Leipzig,
Leipzig, Germany*

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Abstract

For almost a century standard surgical treatment of early stage carcinoma of the uterine cervix consisted of abdominal radical hysterectomy. This procedure representing a wide local tumor excision is combined with pelvic and eventually periaortic lymph node dissection to identify resp. treat regional disease. Adjuvant radiation therapy is liberally added in case of histopathological risk factors to improve local control rates. The therapeutic index of the current surgical treatment particularly if combined with radiation appears to be inferior to that of primary radiotherapy.

Several avenues of new conceptual and technical developments are being explored since the 1990s with the goal to improve the therapeutic index including surgical staging, laparoscopically assisted (vaginal) radical hysterectomy, fertility preserving radical trachelectomy, nerve-sparing radical hysterectomy and total mesometrial resection (TMMR), the first literally radical operation for early and intermediate stage cervical carcinoma based on developmentally defined surgical anatomy.

Surgical treatment of locally advanced and recurrent cervical carcinoma has been performed only with central disease as the required operation, pelvic exenteration, is not applicable for tumors fixed to the pelvic wall. The laterally extended endopelvic resection (LEER) allows the extirpation of a subset of visceral pelvic side wall tumors with clear margins and opens up a 50% chance of long-term survival for the affected patients so far regarded without hope for cure.

Keywords: cervical carcinoma, radical hysterectomy, fertility preservation, laparoscopy, pelvic exenteration

Zusammenfassung

Neue Entwicklungen in der operativen Therapie des Zervixkarzinoms

Seit fast einem Jahrhundert gilt die abdominale radikale Hysterektomie als Standard der operativen Therapie des frühen Zervixkarzinoms. Die mit der Resektion des Uterus, der proximalen Vagina und der Parametrien/Parakolprien angestrebte weite lokale Tumorexzision wird durch eine pelvine und eventuell paraaortale Lymphknotendissektion erweitert, um regionäre Metastasen zu identifizieren bzw. zu behandeln. Beim histopathologischen Nachweis von Risikofaktoren wird die Indikation zur adjuvanten Beckenbestrahlung großzügig gestellt. Im Vergleich zur primären Strahlenbehandlung ist der therapeutische Index der operativen Therapie insbesondere in Kombination mit einer Nachbestrahlung deutlich schlechter. Neue Konzepte und Techniken zur Verbesserung des therapeutischen Indexes der operativen Therapie werden seit Mitte der 1990er Jahre verfolgt, wobei in dieser Übersicht die laparoskopisch assistierte (vaginale) radikale Hysterektomie, die fertilitätserhaltende radikale Trachelektomie, nervenschonende radikale Hysterektomietechniken und die totale mesometriale Resektion (TMMR), als die erste im wörtlichen Sinne radikale Operation auf der Grundlage einer entwicklungsbiologisch definierten chirurgischen Anatomie evaluiert werden.

Die bisherigen operativen Behandlungsmöglichkeiten lokal fortgeschrittener und rezidivierender Zervixkarzinome durch Exenteration waren auf zentrale Beckentumore beschränkt, die Fixation des Tumors an der Beckenwand galt als Kontraindikation. Mit der neuen lateral erweiterten endopelvinen Resektion (LEER) ist es möglich, bestimmte Zervixkarzinome mit Beckenwandbeteiligung im Gesunden zu entfernen. Patientinnen in bislang hoffnungsloser Tumorsituation erhalten dadurch eine etwa 50%ige Chance der Heilung.

Özet

Serviks Kanseri Cerrahi Tedavisinde Yeni Gelişmeler

Yaklaşık bir asırdır uterin serviksin erken evre karsinomunun standart cerrahi tedavisi radikal abdominal histerektomidir. Bu prosedür geniş lokal tümör eksizyonu yanında yayılımı anlamak için pelvik ve paraaortik lenf nodu diseksiyonundan oluşmaktadır. Adjuvan radyoterapi liberal olarak lokal hastalığı kontrol etmek için histopatolojik risk faktörü varlığında eklenmek-

Corresponding Author: Michael Höckel, MD, PhD
Professor and Chairman, Department of Ob/Gyn
Philipp-Rosenthal-Str. 55, 04103 Leipzig, Germany
Tel : +341 97 234 00
Fax : +341 97 234 09
E-mail : michael.hoekel@medizin.uni-leipzig.de

tedir. Güncel cerrahi tedavinin terapötik indeksinin özellikle radyasyon ile kombine edildiğinde primer kemoradyoterapiye göre daha kötü olduğu görülmektedir.

1990'ların başından beri terapötik indeksi optimize etmek üzere birçok değişik yaklaşım ve teknik araştırılmaktadır. Bunlar arasında cerrahi evreleme, laparoskopik asiste (vajinal) radikal histerektomi, fertilitte koruyucu radikal trakelektomi, sinir koruyucu radikal histerektomi ve total mezometrial rezeksiyon (TMMR) ve cerrahi anatomi temelli erken ve orta evre serviks karsinomunun radikal operasyonu bulunmaktadır.

Lokal olarak ilerlemiş ve rekürren serviks kanserinin pelvik ekzanterasyondan oluşan cerrahi tedavisi sadece santral hastalıkta uygulanabilmekte, ancak pelvik duvara fikse olan tümörlerde ise uygulanamamaktadır. Laterale uzanan endopelvik rezeksiyon (LEER), visseral pelvik yan duvar tümörlerinin temiz cerrahi sınır ile ekstirpasyonuna izin vermekte ve günümüze kadar kür için ümitsiz olan bu hastalarda uzun dönem sağkalımı %50'ye kadar çıkarmaktadır.

Anahtar sözcükler: serviks kanseri, radikal histerektomi, fertilitte koruyucu cerrahi, laparoskopi, pelvik ekzanterasyon

Introduction

On a global scale carcinoma of the uterine cervix is still a serious health problem with approximately 470.000 new cases and 230.500 deaths per year (1). This neoplasm is less prevalent and its incidence continues to decrease in developed countries due to cancer screening, education about risk factors and probably as a consequence of changes in sexual behaviour (e.g. safer sex techniques, reduced sexual activity due to public stimulation overload).

In Germany and Turkey about 6.700 resp. 1.100 women develop cervical cancer and 3.200 resp. 600 die from it within a year (1). It is suggested that HPV vaccination which proved in recent trials to be successful in preventing the precursor lesions will have a major impact on further reducing cervical cancer numbers in future (2, 3). However, if successful, this effect will need at least 1-2 decades to become epidemiologically apparent.

The current standard in the management of this disease is clinical staging (except microcarcinoma) and stage adjusted treatment with surgery or/and (chemo) radiation (4). A significant draw back of the present treatment practice is the relatively high morbidity from surgical therapy by radical hysterectomy particularly if combined with adjuvant (chemo) radiation. New developments in surgical therapy of cervical carcinoma are mainly based on the application of laparoscopic techniques and focus on surgical staging and the treatment of small volume disease. However, many questions remain unresolved and the superiority of concepts and techniques using laparoscopy compared to open surgery are yet unproven. Moreover, modern laparoscopic surgeons as well as those using standard techniques still rely on historical foundations of surgical anatomy in the female pelvis and of local tumor spread. We have translated insights into female genital tract anatomy and cervical cancer propagation from the perspective of developmental biology into new surgical techniques which appear to improve the therapeutic index in the management of early and intermediate disease (5) and provide local control of advanced and recurrent disease so far not regarded feasible (6,7).

Methodology of search and selection

We searched 3 computerized databases:

- MEDLINE was searched by PubMed from 1990-2005
- POPLINE was searched from inception to 2005
- LILCAS was searched from inception to 2005

The following terms were used to search the databases:

- Trials on laparoscopic staging: *laparoscopic staging* and *cervical cancer*.
- Trials on laparoscopically assisted radical vaginal hysterectomy (LARVH): *LARVH* and *cervical cancer*, *laparoscopic assisted radical vaginal hysterectomy* and *cervical cancer*. Trials comparing results of laparoscopically assisted radical vaginal hysterectomy with the standard abdominal approach were included.
- Trials on radical trachelectomy: *trachelectomy*. Trials reporting on obstetrical and/or oncological outcome were included.
- Trials on nerve-sparing radical hysterectomy: *nerve sparing* and *radical hysterectomy* and *cervical cancer* or *autonomic nerve* and *radical hysterectomy* and *cervical cancer* or *hypogastric plexus* and *radical hysterectomy*.

The reference lists of articles identified by this strategy were searched, and additional relevant publications were selected. Only English-language trials were included.

Staging

After histopathological diagnosis of cervical carcinoma staging of the disease is mandatory to establish a treatment plan. According to the FIGO cervical cancer staging has to be exclusively clinical based on inspection, palpation, cystoscopy, rectoscopy and limited radiographic studies (chest radiograph, skeletal radiograph, barium enema, intravenous pyelogram). The initial FIGO stage should never be changed, additional information from other diagnostic procedures and surgery must not influence the stage but may have therapeutic implications. However, up to now it has not been proven with randomized prospective trials that the additional use of *modern imaging techniques* such as CT, MRI and PET to develop a treatment plan improves the outcome. The results of a recent multicenter trial by the American College of Radiology Imaging Network addressing the relevance of CT and MRI have to be awaited to answer this question (4).

There is an ongoing discussion about the potential benefit of *surgical staging*. The protagonists refer to observational studies that have claimed a place for the resection of bulky pelvic lymph node metastases prior to radiation and argue further that the demonstration of periaortic lymph node metastases would lead to a radiation field extension with a higher probability of locoregional tumor control (8-13).

Laparoscopic surgical staging is recommended for selecting either primary laparoscopically assisted surgical therapy of small volume (< 2 cm) cancers without lymph node metastases or individualized (chemo)radiation for larger and/or nodal positive tumors as main treatment alternatives (14-22). Within the context of this treatment philosophy sentinel lymph node biopsy to substitute for systematic lymph node dissection is currently investigated (23-32). At the time of this writing it is not clear whether this approach using either conventional histopathological investigation or molecular markers to detect metastatic lymph node disease is feasible. Generally, the potential risks of surgical staging cannot be neglected. Transperitoneal approaches may lead to peritoneal adhesions which can significantly increase radiation morbidity. Another concern is the iatrogenic tumor dissemination if the staging surgery is intralesional or tumor bearing anatomical compartments are opened. The only randomized prospective study reported by Lai et al. from Taiwan had to be closed after the interim analysis showed a much inferior outcome of patients whose cervical cancer had been staged surgically as compared to the FIGO criteria (33).

Regarding the high incidence of cervical carcinoma in developing countries with reduced medical resources, the unproven benefits, potential risks and unfavorable results of the Taiwanese trial there is no justification to implement surgical staging in the management of cervical cancer at the present time. Further assessment with optimized surgical staging techniques, i.e. strictly retroperitoneal approaches, no gross tumor debulking is mandatory. The integration of surgical staging into national treatment guidelines as proclaimed by the German Society of Gynecology and Obstetrics appears premature.

Early disease

Standard treatment

The current therapy of carcinoma of the uterine cervix FIGO stage IA1 is conization if the patient desires fertility otherwise vaginal or abdominal total hysterectomy. In case of lymph vascular space involvement pelvic lymph node dissection should be added as this feature is associated with a 8% risk to develop lymph node metastases (34).

Abdominal radical hysterectomy and systematic pelvic lymph node dissection as developed by Wertheim (35) and Meigs (36) is regarded as standard in the surgical treatment of carcinoma of the uterine cervix, FIGO stages IA2, IB, IIA. However, a major short-coming of these surgical procedures and various modifications are failures within the treatment field (37, 38). As a consequence, postoperative radiation and more recently adjuvant chemoradiation are recommended for patients with risk factors identified from the histopathological investigation of the surgical specimens to reduce the rate of locoregional relapses (38, 39). However, the resulting long-term morbidity of this multimodality treatment which is applied in more than 50% of the cases treated initially with surgery exceeds that for primary radiation although the oncologic outcome does not appear to be superior (40). In addition, as current radical

hysterectomy techniques are performed without consideration of the topographic anatomy of the pelvic autonomic nerve system and therefore may lead to damage of these structures postoperative urethrovesical, vulvovaginal and anorectal dysfunctions causing distress, pain and predisposing for secondary disease are a significant problem (41-44).

New developments in the surgical treatment of early cervical carcinoma which will be reviewed here are the *laparoscopically assisted radical (vaginal) hysterectomy* and the *“radical trachelectomy”*. We will then introduce the *total mesometrial resection (TMMR)* by specifying its underlying principles from a developmental approach to surgical anatomy and local tumor spread and reporting results up to now. TMMR will be compared to the treatment standard and other nerve-sparing procedures based on the conventional anatomic view.

Laparoscopically assisted radical (vaginal) hysterectomy

Dargent et al. (45) from France were the first to combine radical vaginal hysterectomy, the Schauta operation, with laparoscopic systematic pelvic lymph node dissection in order to develop a less traumatic surgical treatment alternative to the Wertheim operation for early cervical cancer. Both the Schauta operation as well as the laparoscopic pelvic and periaortic lymph node dissection are standardized procedures which can be performed with a learning curve of at least 20 cases (46, 47). Since 2000 four retrospective studies have been published comparing laparoscopically assisted radical vaginal hysterectomy (LARVH) with standard abdominal radical hysterectomy at a median follow up time of about 3 years (48-51). Table 1 illustrates some of their results in a comprehensive manner. Most importantly, LARVH should be restricted to small volume (< 2 cm) nodal negative cases to achieve oncologic results comparable to the open procedures. Both Querleu et al. (52) and Nam et al. (49) found recurrence rates of 43% if tumor size/volume exceeded 2 cm/4.2 cm³. The studies showed unanimously somewhat longer operation times and a higher intraoperative complication rate but blood loss was reduced and postoperative hospital stay was shorter with LAVHR compared to the Wertheim operation. Other results were inconsistent: whereas Steed et al. (50) observed more Jackson et al. (51) detected less disturbances of the bladder function after LAVRH. Instead of combining laparoscopic lymph node dissection with radical vaginal hysterectomy a solely laparoscopic radical hysterectomy technique has been developed and its feasibility has been proven (53). A study comparing the two approaches is lacking so far. Likewise, no prospective randomized trial has been conducted to date comparing treatment costs and quality of life issues for a properly selected patient cohort with early cervical cancer managed either laparoscopically or with open surgery.

“Radical trachelectomy”

Radical vaginal trachelectomy exploits the LAVRH technique for fertility preservation in young patients with small volume cervical cancer. Uterine cervix, proximal vagina, parametria and paracolpium are resected but the uterine corpus with its

Table 1. Comparison of laparoscopically assisted radical vaginal hysterectomy (LARVH) vs. radical abdominal hysterectomy (RAH)

Procedure	Malur et al., 2000 ⁽⁴⁸⁾		Nam et al., 2004 ⁽⁴⁹⁾		Steed et al., 2004 ⁽⁵⁰⁾		Jackson et al., 2004 ⁽⁵¹⁾	
	LARVH	RAH	LAVRH	RAH	LARVH	RAH	LARVH	RAH
Treatment Period	1994-1999	1991-1994	1997-2002	1996-2003	1996-2003		1996-2003	
Median Follow-up (months)	NR	NR	35	44	17	21	52	49
# of patients	70	70	47	96	71	205	50	50
Histology (%)								
SCC	76	79	77	79	44	54	66	66
Adeno-Ca	23	19	21	17	56	46	34	34
Other	1	2	2	4				
FIGO Stage (%)								
IA1	4	1			20	15		
IA2	19	1			14	6	4	4
IB1	59	73	100	100	64	74	94	94
IB2					1	9	2	2
IIA	4	7						
IIB	13	16						
IIIA	1	0						
IV	0	1						
Mean Tumor Volume (cm ³)	NR	NR	2.8	2.9	NR	NR	NR	NR
Mean Tumor Size (cm)	NR	NR	NR	NR	2.3	2.6	1.6	1.7
pN1 (%)	NR	NR	6	6	7	9	2	2
Intraoperative								
OR Time (min)	292	210	233	239	210	150	180	120
Blood Loss (ml)	NR	NR	NR	NR	300	500	350	875
Complication Rate (%)	11	1	2	1	13	4	8	6
Postoperative								
Hospital Stay (days)	11	23	16	23	1	5	5	8
Adjuvant Treatment (%)								
Chemotherapy	NR	0	17	19	0	0	0	0
Chemo-Radiation	NR	0	4	4	22	21	0	0
Radiation	NR	100	0	2	0	0	7	2
Recurrence (%)	NR	NR	8	2	6	6	4	4
Locoregional	NR	NR	6	NR	NR	NR	2	2
Distant	NR	NR	2	NR	NR	NR	0	0
Both	NR	NR	0	NR	NR	NR	2	2
Disease-free Survival	NR	NR	87 (3y)	99 (3y)	94 (2y)	94 (2y)	NR	NR
Overall Survival (%)	NR	NR	NR	NR	NR	NR	94 (4y)	96 (4y)

NR: not reported, y: years

blood supply from the uterine and ovarian arteries is retained and anastomosed to the middle part of the vagina. Cervical function is substituted by a permanent cerclage. Delivery is achieved by primary cesarian section. Following the pioneering work of Dargent et al. (54, 55) vaginal radical trachelectomy combined with laparoscopic lymph node dissection has been performed in several centers since the 1990's (55-67). More recently an abdominal version modifying the Wertheim procedure has been developed claiming the resection of more parametrial tissue (68-72). Important published results on vaginal and abdominal radical trachelectomy are compiled in table 2. If patients with small nodal

negative tumors are selected surgery related parameters such as operating time, complications, blood loss and postoperative hospital stay correspond to the LAVRH. The question of oncologic safety is not definitively settled. Most studies report only the recurrence rates of the successfully executed cases. However, approximately 10% of planned trachelectomies have to be abandoned. According to Plante et al. (67) the recurrence rate of the abandoned cases has been 30%. In order to correctly estimate the oncological results of the procedures the recurrence rate of all patients treated with the intention to perform radical trachelectomy has to be given.

Another problem arises with the obstetrical outcome. It is remarkable that only 30% of the patients with a strong desire to preserve their fertility despite the diagnosis of cervical cancer try to get pregnant after treatment with radical trachelectomy. Of greater concern is the 25% rate of very premature deliveries related to the overall number of pregnancies leading to viable infants. The treatment of infants born at 24-28 weeks of gestation is extremely expensive and despite major medical progress these children are still at a significant risk to develop cognitive and motoric deficiencies (73). If a very premature baby is born after radical trachelectomy the problematic consequences not only concern the parents but also the child with a potentially impaired future and the society having to provide the financial means from limited resources.

Total mesometrial resection (TMMR), literally radical hysterectomy with autonomic nerve preservation

We have developed a theory claiming that local tumor spread is guided by positional information presented molecularly in the developmentally defined tissue complex or anatomical compartment ("morphogenetic unit") of the tumor origin for a relatively long period during malignant progression. Microscopically occult minimal residual cancer within remnants of the morphogenetic unit left behind after a wide tumor resection recruited, expanded and selected by an ischemic surgical wound could be an important but potentially avoidable cause of local recurrence (74).

A truly radical tumor operation has to remove not only the macroscopical tumor with its microscopic extensions ("wide excision") but should erase a maximum of the occult local tumor load by the extirpation of the complete morphogenetic unit. The morphogenetic unit derived from an embryologic anlage is not only comprised of the adult organ but also of its mesenteries which serve for blood supply, lymphatic drainage, innervation and fixation. The translation of this concept into practice with regard to cervical carcinoma is represented by the total mesometrial resection (TMMR) (5).

TMMR is characterized by the en bloc resection of the uterovaginal morphogenetic unit consisting of the uterus, proximal vagina, subperitoneal mesometrium and mesocolpos. The vascular portion of the mesometrium is completely included into the specimen, the ligamentous part of the mesometrium and the mesocolpos which is a continuum is transected directly above the level of the exposed inferior hypogastric plexus. TMMR includes the extended pelvic/periaortic lymph node dissection preserving the superior hypogastric plexus.

TMMR differs from classical radical hysterectomy by

- consequent sharp separation of the bordering lamellae instead of blunt dissection;
- exposition of the vascular mesometrium by separation from the bladder mesentery;
- separate dissection of the ligamentous mesometrium with minimal trauma instead of their composite division as parametrectomy with traumatic clamps (e.g. Wertheim clamps);

- exposition and mobilisation of the superior hypogastric plexus, hypogastric nerves and proximal inferior hypogastric plexus.

The surgical anatomy of TMMR is derived from the morphogenetic tissue movements of paramesonephroid (Müllerian) ducts, the establishment of the Müllerian mesenchyme and pathways for vascularization, innervation and fixation. It can be clearly outlined in whole pelvic cross sectional specimen and high resolution MRI scans.

As the goal of the operation is the literally radical locoregional tumor erasion adjuvant radiation is not indicated and is completely omitted even in high risk cases. However, large volume tumors with maximum extension of ≥ 5 cm will be treated with neoadjuvant chemotherapy in order to decrease their size and facilitate sharp dissection between the bordering lamellae.

TMMR as single modality locoregional treatment for patients with cervical carcinomas FIGO stages IB, IIA, IIB has been evaluated by a prospective trial at the University of Leipzig since 7/1998. By 7/2002 71 patients with cervical cancer stages pT1b1 (n=48), pT 1b2 (n=8), pT2a (n=3), pT2b (n=12) underwent TMMR without adjuvant radiation. Fifty-four percent of the patients exhibited histopathological high risk factors such as parametrial involvement, lymph node metastases (n=14) and combinations of tumor size, lymphovascular space involvement and stromal invasion depth according to the GOG 92 criteria (38). In only one of 71 patients an R1 resection status was found. In this patient the tumor had also metastasized into at least 49 lymph nodes at the time of the operation. The mean pelvic lymph node count of our TMMR series is 46. At a median observation period of 52 months (30-78 months) two patients relapsed locally, two patients developed pelvic and distant and two patients only distant recurrences. The 5-year relapse-free and disease specific survival probabilities are 90% resp. 93% for the whole cohort, 100% for the low risk subgroup and 82% resp. 87% for the high risk subgroup. Three patients died from their disease. Grade 1 and 2 complications occurred in 15 resp. 5 patients, no patient had grade 3 or 4 complications. No severe long-term impairment of pelvic visceral functions related to autonomic nerve damage was detected. A comparison of the TMMR related morbidity with that of standard surgical treatment (i.e. radical hysterectomy followed by adjuvant radiation in case of histopathological high risk factors) is possible as Landoni et al. (40) used the evaluation system as Chassagne et al. (75) which was also applied by us. These authors reported of 48 grade 2 and 3 complications in 170 patients treated with surgery and adjuvant radiation in case of high risk factors. The difference to the 5 grade 2 complications in our cohort of 71 patients is highly significant ($p = 0.00015$).

Regarding the topographical anatomy of the pelvic autonomic nerve system it is evident that major parts of that complex structure are at risk to be severed by conventional radical hysterectomy techniques resulting in various pelvic organ

Table 2a. Oncological outcome of published studies using vaginal radical trachelectomy (VRT) or abdominal radical trachelectomy (ART)

Author	Plante ⁽⁶⁷⁾	Covens ⁽⁶⁵⁾	Mathevet ⁽⁶⁶⁾	Sheperd ⁽⁶⁰⁾	Burnett ⁽⁶²⁾	Schlaerth ⁽⁶³⁾	Ungar ⁽⁷²⁾	TOTAL
Procedure	VRT	VRT	VRT	VRT	VRT	VRT	ART	
Time Period	1991-2003	1994-2003	1987-2002	1994-2001	1995-2001	1995-1999	1997-2004	
Median Follow-up (months)	60	30	76	23	32	48	32	
# of Patients								
Planned RT (IT)	82	93	108	30	21	12	33	N=379
Abandoned RT	10	0	12	4	2	2	3	9%
Performed RT (ET)	72	93	96	26	19	10	30	91%
Histology (%)								
SCC	58	48	80	70	57	40	NR	62%
Adeno-Ca	38	52	20	27	43	50	NR	36%
Other	4			3		10	NR	2%
FIGO Stage (%)								
IA1	5	42	14					16%
IA2	32	24	15		5	80	33	23%
IB1	60	33	57	100	95	20	50	57%
IB2	0	1	1				17	
IIA	3	0	8					3%
IIB	0	0	5					1%
Tumor Size < 2 cm (%)	89	91	78	97	100	80	NR	87%
pN1 (%)	6	NR	NR	8	NR	0	NR	
Intraoperative								
OR Time (min)	250	180	163	NR	318	NR	NR	202
Blood Loss (ml)	200	300	NR	NR	293	203	NR	257
Postoperative								
Hospital Stay (days)	3	1	NR	NR	3	3	NR	2
Recurrence (%)	4 (3/72)	7 (7/93)	5 (5/96)	0	0	0	0	4%
Locoregional	3	NR	NR					(15/346)
Distant	1	NR	NR					
5y Disease-free Surv.	95	4 (4/93)	NR	NR	NR	NR	NR	

NR: not reported, IT: intention to treat ET: executed treatment

Table 2b. Obstetrical outcome of published studies using vaginal radical trachelectomy (VRT) or abdominal radical trachelectomy (ART)

Author	Roy ⁽⁵⁶⁾	Covens ⁽⁵⁸⁾	Dargent ⁽⁵⁹⁾	Sheperd ⁽⁶⁰⁾	Burnett ⁽⁶²⁾	Schlaerth ⁽⁶³⁾	Bernardini ⁽⁶⁴⁾	Ungar ⁽⁷²⁾	TOTAL
Procedure	VRT	VRT	VRT	VRT	VRT	VRT	VRT	ART	
Time Period	1991-1998	1994-1998	1987-1996	1994-2001	1995-2001	1995-1999	1994-2002	1997-2004	
# of Patients (ET)	30	32	47	26	19	10	80	30	274
Obstetrical Outcome									
# Pt. Attempting Pregnancy	6	13	25	13	3	4	39	5	108
# Pt. Conceiving	6	4	13	8	3	4	18	3	59
# Pregnancies	7	5	20	14	3	4	22	3	78
# Viable Newborns	4	3	10	9	3	2	18b	2	51
# Very Premature Newborn (24-28 weeks)	1 (25)	1 (28)	0	3 (25,26,28)	2 ^a (24)	2 (24,26)	4 ^b (24,26)	0	13 ^c

NR: not reported, ET: executed treatment, ^a twins, ^b 2 sets of twins, ^c including the three sets of twins

dysfunctions. Indeed, persistent dysfunctions of 30-80% for the bladder/urethra, 25-35% for the vagina/vulva and 25-80% for the rectum/anus organ systems have been reported (41-44). Severe handicaps such as grade II and III stress incontinence, permanent necessity for intermittent self-catheterization or upper urinary tract disease in case of lower urinary tract dysfunction after radical hysterectomy have been observed in 10-20% of the patients (76). TMMR did not result in severe dysfunctions of the lower urinary tract. Our study could not detect postoperative disturbances of vulvovaginal and anorectal functions related to autonomic innervation. The resection of the proximal vagina was mainly perceived as reduced vaginal elasticity by the patients who were sexually active after treatment with TMMR, yet the patients were not distressed by that deficit. Based on these results TMMR achieves a promising therapeutic index by providing a high probability of loco-regional control at minimal short and long-term morbidity.

Radical hysterectomy techniques with the preservation of the autonomic nerve system have a long tradition in China and Japan (for review see (77)). Following our first publication of liposuction assisted nerve-sparing extended radical hysterectomy (77) several other groups reported about successful autonomic nerve-sparing radical hysterectomy procedures either with open surgery or laparoscopically (5, 52, 77-89). To date the superiority of nerve-sparing radical hysterectomy has not been proven unequivocally. As long as the surgical anatomy follows the traditional concepts of posterior, lateral and anterior parametria autonomic nerve preservation must be regarded as potential impediment with "oncologic radicality". If it is accepted to combine surgery with adjuvant radiation pelvic autonomic nerve preservation may be achieved by reducing surgical extension of the hysterectomy without exposing the autonomic nerves. With the developmental view on surgical anatomy of the female pelvis which is the basis for TMMR the relevant parts of the autonomic nerve system except the cervicovaginal branches of the inferior hypogastric plexus can be exposed and separated from the uterovaginal morphogenetic unit and spared without compromising the goal of maximum erasion of even the microscopically occult local tumor load.

Advanced and recurrent disease

Standard treatment

Locally advanced carcinoma of the uterine cervix corresponding to the FIGO stages IIB, IIIA,B and IVA is detected at primary diagnosis of cervical cancer in 47% of the patients according to the recent FIGO Annual Report (90). The current treatment standard is chemoradiation, i.e. the combination of percutaneous pelvic radiation, brachytherapy of the cervix and upper vagina and platinum-based systemic chemotherapy (91). Some European authorities regard extended radical hysterectomy usually followed by adjuvant (chemo)radiation as an alternative therapy of FIGO stage IIB cervical carcinoma. However, there is no evidence that tumor control is improved with this treatment but excessive side-effects of extended radical hysterectomy with (and even without) adjuvant radiation are well proven (40).

Pelvic exenteration which has been mainly applied for central pelvic recurrences after primary radiotherapy (see below) is indicated for mobile locally advanced primary disease if radiation therapy is hampered, e.g. by vesicovaginal or rectovaginal fistulas in FIGO stage IVA cancer. However, in the majority of cases with bladder and/or rectal infiltration the tumors also involve the pelvic side wall and are regarded unresectable.

Recurrent carcinoma of the uterine cervix is diagnosed in the pelvis, at distant site(s) or both in the pelvis and at distant site(s). Recurrence rates are 10-20% in FIGO stages IB/IIA cervical cancers and 50-70% in locally advanced cases (FIGO IIB, III, IVA) (4). Tumor persistence or recurrence within the pelvis is the major cause of death in patients suffering from carcinoma of the uterine cervix. Both persistent and locally recurrent pelvic tumors are characterized by an advanced malignant progression and often exhibit an anatomically complex topography rendering a curative treatment very difficult and rarely successful.

With regard to current treatment modalities persistent or locally recurrent tumors are classified as central or pelvic side wall disease. Whereas *central disease* is a relatively homogenous tumor entity derived from the retained cervix and vagina in case of primary radiation or from the vaginal cuff and central scar after surgical therapy, *side wall disease* is more heterogeneous. We have proposed a classification discriminating between *parietal* and *visceral side wall disease*. Parietal disease represents regional lymph node metastases, tumors are mostly located above the level of the obturator nerve. Visceral pelvic side wall disease originates from the parametrium/paracolpium or from the lateral scars of the (radical) hysterectomy and is usually located below the level of the obturator nerve. Visceral side wall disease is the most frequent relapse type irrespective of primary treatment (92). According to the present consensus patients with locally recurrent cervical cancer after surgical therapy should be treated with (chemo-) radiation and central pelvic relapses following (primary or adjuvant) radiation should undergo surgery (93). (Radical) hysterectomy may be adequate for small (< 2 cm) lesions, however, most irradiated patients with central disease will need pelvic exenteration.

Pelvic exenteration inaugurated by Brunschwig in the late 1940s had been designed as an abdominoperineal composite resection of parts of the perineum, urethra and bladder, genital tract, anus and rectum (94). Later, modifications of this mega-operation were anatomically defined with respect to the caudal extension (*suprlevator exenteration*, *translevator exenteration with or without vulvectomy*) and with regard to one pelvic hollow organ to be left in situ (*anterior*, *posterior exenteration*). However, lateral transection through the urogenital mesentery after developing perirectal and perivesical surgical spaces is a common feature of all types of pelvic exenterations. As wide tumor-free margins must be achieved for local control and long-term survival, the indication for pelvic exenteration has to be confined to central pelvic disease. In all cases of tumor involvement of pelvic wall exenteration is abandoned. As a consequence, patients with a pelvic side

wall component of their recurrent tumor in an irradiated pelvis - representing the most common situation of failure - are no longer considered for curative therapy.

Multimodality therapy including surgery for locally advanced primary and recurrent disease

Neoadjuvant cisplatinum-based chemotherapy followed by radical hysterectomy, pelvic with or without paraaortic lymph node dissection and eventually postoperative adjuvant radiation has been compared with primary radiation in squamous cell carcinomas of the uterine cervix FIGO stages IB2, IIA (>4 cm), IIB, III in prospective randomized trials (95, 96).

A survival benefit of the combined surgical treatment modality for FIGO stages IB2 and IIB was observed, whereas an advantage for stage III cervical cancers was not obvious. However, all trials used radiation therapy alone in the standard arm. As concurrent chemoradiation has meanwhile been generally accepted as the new standard therapy for locally advanced cervical cancer due to its proven superior results with respect to disease-free and overall survival, new trials comparing neoadjuvant chemotherapy followed by radical surgery with concurrent chemoradiation are mandatory.

The intraarterial application of cisplatinum-containing neoadjuvant chemotherapy followed by radical hysterectomy, pelvic/paraortic lymph node dissection and eventually adjuvant radiation for locally advanced cervical carcinoma has been tested in several phase II studies (97). The treatment appeared to be feasible and led to promising preliminary results. However, whether it may be superior to systemic neoadjuvant chemotherapy and surgery or to concurrent chemoradiation is not known and cannot be anticipated based on the results reported so far.

Preoperative chemoradiation with cisplatinum-containing regimens up to a total pelvic dose of 45 Gy followed by radical surgery 4–6 weeks later with or without additional intraoperative electron beam radiotherapy for locally advanced primary cancer has been investigated with recent phase I – II trials as well. High local control rates are reported at a 15–20% rate of severe complications (98,99). The studies do not allow conclusions regarding a potential benefit as compared to standard chemoradiation. Current clinical experience indicates that both intraoperative radiation (IORT) and the combined operative and radiation treatment (CORT), i.e. the application of guide tubes for postoperative brachytherapy and protective pelvic wall plasty necessitate complete (R0) tumor resection for local control (99–101). Whether the addition of both forms of site-directed radiation will improve the treatment results with advanced primary and recurrent disease over surgery alone remains to be shown.

Laterally extended endopelvic resection (LEER) for the treatment of visceral pelvic side wall disease

The laterally extended endopelvic resection (LEER) is characterized by the inclusion of the internal iliac vessel system, endopelvic part of the obturator internus muscle,

coccygeus, iliococcygeus and pubococcygeus muscles into the exenteration specimen. Both abdominal and abdominoperineal exenteration as well as total, anterior and posterior exenteration can be laterally extended (6, 7).

The shift of the lateral resection plane to the medial aspects of the lumbosacral plexus, sacrospinous ligament, acetabulum, obturator membrane and ischioanal fossa enables the complete removal of a subset of locally advanced and recurrent cervical carcinomas fixed to the pelvic wall with free margins (R0). The logic of this surgical approach has been confirmed by the histopathological demonstration that recurrent visceral side wall disease as well as advanced primary cervical carcinoma fixed at the pelvic wall usually does not infiltrate the adjacent striated muscle. Inclusion of the pelvic floor and side wall muscles in the surgical specimen therefore provides tumor-free (R0) margins.

Complications, disease-free and overall survival rates and postoperative quality of life scores of patients with visceral side wall disease are comparable to those with central disease treated with standard pelvic exenteration (7). LEER can therefore be offered as novel surgical salvage therapy to a selected subset of patients with locally advanced and recurrent cervical carcinoma involving the pelvic wall including preirradiated patients for whom treatment with long-term survival prospects has been beyond the scope of current therapeutic options. LEER can also be considered for non-irradiated patients in case of bladder and/or rectum infiltration or fistula formation in addition to the side wall involvement.

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