Int J Gynecol Cancer 2003, **13,** 791–803

Total mesometrial resection: High resolution nerve-sparing radical hysterectomy based on developmentally defined surgical anatomy

M. HÖCKEL*, L.-C. HORN†, B. HENTSCHEL‡, S. HÖCKEL* & G. NAUMANN§
**Department of Obstetrics and Gynecology, †Institute of Pathology, ‡Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany, and §Department of Gynecology, University of Halle-Wittenberg, Halle, Germany*

Abstract. Höckel M, Horn L-C, Hentschel B, Höckel S, Naumann G. Total mesometrial resection: High resolution nerve-sparing radical hysterectomy based on developmentally defined surgical anatomy. *Int J Gynecol Cancer* 2003;**13:**791–803.

Total mesometrial resection (TMMR) is characterized by: i) the en bloc resection of the uterus, proximal vagina, and mesometrium as a developmentally defined entity; ii) transection of the rectouterine dense subperitoneal connective tissue above the level of the exposed inferior hypogastric plexus; and iii) extended pelvic/periaortic lymph node dissection preserving the superior hypogastric plexus. Since July 1998 we have studied prospectively the outcome in patients treated with TMMR for cervical carcinoma FIGO stages IB, IIA, and selected IIB. By July 2002, 71 patients with cervical cancer stages pT1b1 (*n*=48), pT1b2 (*n*=8), pT2a (*n*=3), pT2b (*n*=12) had undergone TMMR without adjuvant radiation. Fifty-four percent of the patients exhibited histopathologic high risk factors. At a median observation period of 30 months (9–57 months) two patients relapsed locally, two patients developed pelvic and distant recurrences and two patients only distant recurrences. Three patients died from their disease. Grade 1 and 2 complications occurred in 20 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. Based on these preliminary results, we believe TMMR achieves a promising therapeutic index by providing a high probability of locoregional control at minimal short and long-term morbidity.

KEYWORDS: autonomic nerve preservation, cervical carcinoma, human development, radical hysterectomy, surgical anatomy.

Abdominal radical hysterectomy and pelvic lymph node dissection as introduced by Wertheim(1) and Meigs(2) is still regarded as standard in the surgical treatment of carcinoma of the uterine cervix, FIGO stages IA2, IB, and IIA. However, a major shortcoming of these surgical procedures and various modifications are failures within the treatment field(3, 4). As a consequence, postoperative radiation and more recently adjuvant chemoradiation have been recommended for patients with risk factors identified from the histopathologic investigation of surgical specimens to reduce the rate of locoregional relapses(4, 5).

Address correspondence and reprint requests to: Michael Höckel, MD, PhD, Professor and Chairman, Department of Ob/Gyn, Philipp-Rosenthal-Str. 55, 04103 Leipzig, Germany. Email: hoeckelm@medizin.uni-leipzig.de.

However, the resulting long-term morbidity of this multimodality treatment exceeds that for primary radiation, although the oncologic outcome does not appear to be superior[6]. 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 and pain and predisposing for secondary disease are a considerable problem[7–10].

In the surgical treatment of rectal cancer, a significant improvement with respect to postoperative sequelae, locoregional recurrences, and survival was achieved by the introduction of the total mesorectal excision (TME), a high resolution sharp dissection of the rectum and its integrated mesentery based on developmentally defined topographic anatomy[11, 12]. The study of embryologic and fetal development provides a key to understanding the complex topography of the human pelvis and, as a consequence, opens up a new look at its surgical anatomy. Adding these insights to our previous work on radical hysterectomy with autonomic nerve preservation, we developed the total mesometrial resection (TMMR) for the treatment of cervical carcinoma[13–15].

Methods

Surgical procedure

TMMR is performed in up to 21 defined steps, 11 of which are carried out bilaterally:

Step 1. Surgical access is gained through a hypogastric midline incision. Cephalad extension of the laparotomy circumventing the umbilicus at the left side is carried out in obese patients and in cases of periaortic lymph node dissection.

Step 2. After exploring the intraperitoneal pelvis and abdomen, the pelvic and mid-abdominal retroperitoneum is opened by incising the peritoneum at the psoas muscles, paracolic gutters, and along the mesenteric root.

Step 3. The infundibulopelvic ligaments and ureters are exposed. Cecum, duodenum, and sigmoid colon are mobilized. At the base of the mesosigma just caudad to the aortic bifurcation, the superior hypogastric plexus is identified and mobilized (Fig. 1A). With the exception of the rectosigmoid colon, all bowel organs are retracted cephalad.

Step 4. The round ligaments are transected, the anterior and posterior leaves of the broad ligaments are incised. If the adnexae are to be removed with the TMMR specimen, the infundibulopelvic ligaments are ligated and cut, otherwise the adnexae are separated from the uterus. Pararectal spaces are developed with the hypogastric nerves adhering medially to the mesorectum. This maneuver is carried out down to the level where the pelvic splanchnic nerves and the sacral splanchnic nerves join the hypogastric nerves to form the inferior hypogastric plexus but not further dorsally. The ureters are mobilized to the posterior side of the mesometrium which should be completely exposed.

Step 5. Anteriorly, paravesical spaces are developed with the umbilical arteries adhering medially to the bladder, down to the pubococcygeus and iliococcygeus muscles exposing the complete anterior side of the urogenital mesentery (Fig. 1B).

Step 6. The parietal lymph nodes of the anterior pelvic compartments (external iliac and obturator) are removed by completely stripping the external iliac artery and vein and removing the paravisceral pelvic fat pads. The obturator nerve, obturator artery and vein, the arcus tendineus, and proximal sciatic nerve are exposed. The removed lymph nodes are regarded as primary nodes and sent for frozen section investigation. In cases of proven lymph node metastases, perispinous and periaortic lymph node dissection will be added after finishing TMMR (steps 18 and 19).

Step 7. The peritoneum of the vesicouterine pouch is incised and the bladder is separated from the anterior cervix and the proximal vagina by dissection of the loose and dense subperitoneal connective tissue.

Step 8. The umbilical artery together with the superior bladder mesentery is separated from the anterior mesometrium (Fig. 1C).

Step 9. The uterine arteries and veins are ligated at their origins.

Step 10. The peritoneum of the rectouterine pouch is incised and the anterior mesorectum is separated from the posterior vaginal wall down to the midvagina. Laterally, the mesorectum is separated from the dense subperitoneal connective tissue ('uterosacral ligaments') to the level of the inferior hypogastric plexus.

Step 11. The proximal inferior hypogastric plexus is mobilized from the lateral surface of the dense subperitoneal connective tissue which encases the rectum for 1–2 cm enabling the transection of the latter without nerve damage.

Step 12. Immediately above the superior margin of the inferior hypogastric plexus, the dense subperitoneal connective tissue ('rectouterine ligaments', 'uterosacral ligaments') is stepwise transected (Fig. 1D).

Step 13. The operation proceeds in the anterior compartment. Mobilization of the mesometrium

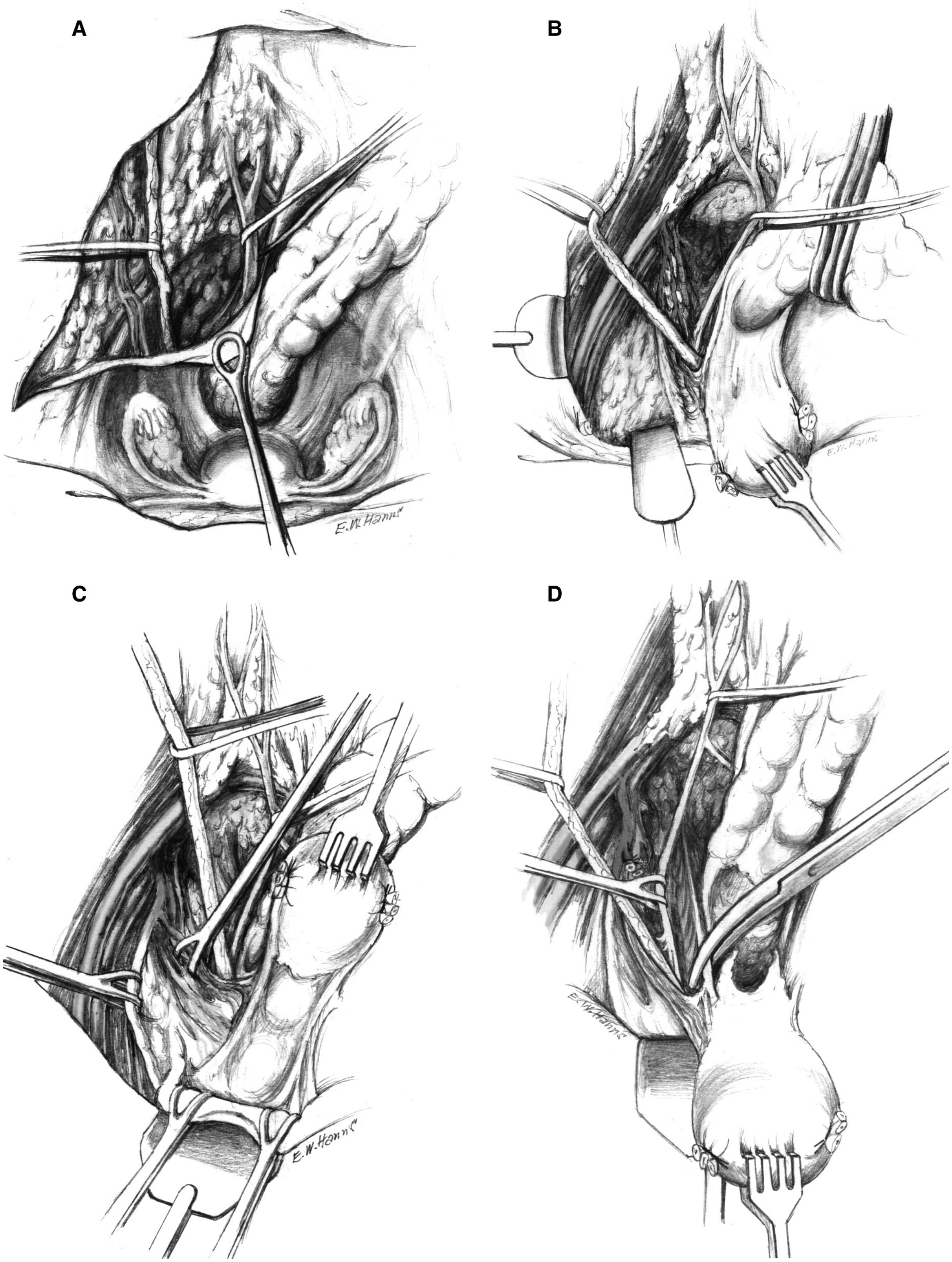

Fig. 1. Surgicoanatomical drawings of specific steps of the TMMR procedure. The complete step by step description is given in the Methods section. The bilateral steps are demonstrated at the right side of the pelvis. A) Exposition of the superior hypogastric plexus; B) complete exposition of the urogenital mesentery (combined bladder mesentery and mesometrium); C) separation of the superior bladder mesentery from the mesometrium; D) transection of the dense subperitoneal connective tissue of the rectouterine pouch above the superior margin of the exposed inferior hypogastric plexus. All drawings were made by E.W. Hanns (Schriesheim, Germany).

from its origin at the site of the already transected uterine artery and vein(s) towards the uterus beyond the superior surface of the ureter.

Step 14. The vesicovaginal venous plexus together with the dense subperitoneal connective tissue above the prevesical segment of the ureter is ligated and divided. After cutting the remaining dorsal attachments the ureter can be completely mobilized laterally.

Step 15. The proximal vagina can now be closed temporarily to avoid tumor contamination before incising the anterior vaginal wall in the midline distal to the clamp and completing the colpotomy. After pelvic lavage the vaginal stump is closed with interrupted intramuscular sutures.

Step 16. Pelvic lymph node dissection is continued in the posterior compartment by removing all lymph nodes and fatty tissue around the internal and common iliac vessels exposing the proximal pelvic obturator nerves and the lumbar rami of the sacral plexus.

Step 17. After mobilization and retraction of the superior hypogastric plexus, the presacral lymph node region is cleared exposing the medial sides of the internal iliac venes and the pelvic splanchnic nerves. The common iliac vessels can now be completely undermined.

Step 18. In case of pelvic lymph node metastases, lymph node dissection is continued cephalad by removing the paracaval, interaortocaval, and paraaortic lymph node chains. The right and left lumbar splanchnic nerves, the main roots of the superior hypogastric nerve plexus are preserved. If the periaortic lymph nodes are tumor-free, dissection is carried out up to the level of the origin of the right ovarian vein, otherwise the dissection proceeds to the left renal vein.

Step 19. In addition to the periaortic lymph node dissection, the perispinous nodes are removed if pelvic lymph node metastases are proven. Liposuction is applied within the inferior urogenital mesentery at the level of the inferior hypogastric plexus medial to the ischial spine to remove fatty tissue and small lymph nodes. Larger lymph nodes are easily visualized after the defatting procedure and can be removed without damaging the nerve and venous plexuses.

Step 20. Generally, the peritoneal surfaces of bladder and rectum are united medially by a running suture. This peritoneal bridge is used for support and revascularization of the denuded mobilized pelvic ureters which are guided through sufficiently wide lateral holes.

Step 21. A suprapubic cystostomy and two easy-flow drains are introduced and the abdominal and pelvic cavity is thoroughly washed. All peritoneal structures are inspected and orthotopically replaced. The laparotomy is closed with a running Smead-Jones suture and skin staples.

Clinical trial

All patients with histologically proven carcinoma of the uterine cervix, FIGO stages IB1, IB2, IIA, referred to our institution for surgical treatment were eligible for the study which had been approved by the Ethics Committee of the University of Leipzig. Patients with FIGO stage IIB cancers underwent an examination under anesthesia to determine whether they were candidates for TMMR as well. Patients were excluded from surgical treatment if the uterus was immobile towards the pelvic side wall or the vesicovaginal septum was felt to be involved with the tumor. Patients were enrolled in the prospective study after exclusion of comorbidity with significant anesthesiologic risk and after giving informed consent. Diagnostic work-up consisted of pelvic magnetic resonance imaging, abdominal CT, chest film and laboratory testing in addition to the clinical investigation. Patients with tumors ≥ 5 cm in diameter were pretreated with two or three cycles of neoadjuvant chemotherapy with 75 mg cisplatin/m^2 to decrease the tumor volume.

Postoperatively, micturition training was initiated at the fifth postoperative day and the suprapubic cystostomy was removed when repeated residual volumes were less than 50 ml. After discharge from the hospital all patients were accrued to a follow-up program in 3-month intervals for the first 2 years postoperatively and in 6-month intervals thereafter. All complications (intra- and postoperative) and sequelae of the treatment were systematically assessed according to the Franco-Italian glossary[16].

All patients undergoing TMMR treatment were asked to participate in a prospective longitudinal investigation of their lower urinary, genital, and intestinal tract functions preoperatively as well as 3 and 12 months after surgical treatment. The patients received standardized questionnaires for self assessment. Clinical investigation consisted of physical pelvic examination, directed neurologic examination, clinical stress test for identifying loss of urine, and measurement of residual urine volume after micturition.

The urodynamic assessment included a water urethrocystometry at a filling rate of 60 ml/min, urethral profilometry at rest, and repeated coughing with bladder filling with 250 ml in the sitting position, and an uroflowmetry with pressure-flow studies. All

Table 1. Histopathologic characterization of 71 TMMR, 71 extended pelvic and 14 periaortic lymph node specimens

Characteristic	Number of patients
Stage	
pT1b1 + ypT1b1	44 + 4
pT1b2 + ypT1b2	4 + 4
pT2a	3
pT2b + ypT2b	11 + 1
pN0 + ypN0	50 + 7
pN1 + ypN1	12 + 2
pM0(LYM) + ypM0(LYM)	6 + 5
pM1(LYM)	3
Resection state	
R0 / R1	70 / 1
Lymphvascular involvement	
L0 / L1 / LX	30 / 40 / 1
V0 / V1 / VX	65 / 5 / 1
Histologic types	
Squamous cell carcinoma	56
Adenocarcinoma	9
Adenosquamous carcinoma	5
Other	1
Invasion depth	
1/3 / 2/3 / 3/3	28 / 13 / 30

studies were performed with microtip transducers for simultaneous measurements of bladder, urethral, and rectal pressures. For the electromyogram, surface electrodes were used. During cystometry, the patient was asked to determine the points of her first desire and strong desire to void and the point at which she felt unable to tolerate any further filling (maximal capacity). At 250 ml bladder filling in the sitting position the microtip transducer was slowly withdrawn through the urethra for continuous recording of vesical and urethral pressure. By subtraction of these pressures, urethral closure pressure was calculated. Functional urethral length, maximal closure pressure at rest, and pressure transmission during coughing were measured. During uroflowmetry with maximally filled bladder, the average and maximal flow rates, voiding time and voiding amount, maximal detrusor pressure at micturition, and detrusor pressure at maximum flow were recorded.

The TMMR specimens and the resected pelvic lymph node-bearing tissues were prepared for histopathologic investigation according to the protocol for the examination of the specimens from patients with carcinoma of the cervix published by the Cancer Committee of the College of American Pathologists[17].

Disease-specific survival and relapse-free survival were analyzed using Kaplan-Meier curves. Changes over time for urodynamic parameters were analyzed with repeated-measures analysis of variance. The type I error for pairwise comparisons was adjusted for multiple comparisons by Bonferroni correction. *P*-values were two-tailed, and *P*-values less than 0.05 were considered significant. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences, Release 10.0.7, SPSS Inc., Cary, NC).

Results

The first TMMR operation was performed in July 1998. By July 2002 71 patients had undergone TMMR without adjuvant radiation and had been followed prospectively. Median age of the patients was 43 years (24–77 years), median body mass index 24 (15–35). FIGO stage distribution was IB1 in 39 patients, IB2 in seven patients, IIA in seven patients and IIB in 18 patients. Nine patients with tumors $\geq$5 cm received two to three cycles of preoperative cisplatinum-based chemotherapy leading to partial responses in all cases. As a consequence of the high surgical resolution the median operating time was 6.5 h (5.0–11.5 h). Median number of intraoperative blood transfusions for the whole group was two units (0–9 units).

The histopathologic results are summarized in Table 1. Mean tumor size was 2.7 cm $\pm$ 1.6 cm. None of the 71 tumors was broken up or fragmented during the course of TMMR. The extended lymph node dissection led to a mean lymph node count of 46 $\pm$ 12 in the pelvis and 12 $\pm$ 8 in the inferior periaortic region. Fourteen patients (20%) had pelvic lymph node metastases (median 2, range 1–18) and three patients (4%) exhibited 2, 20 and 31 periaortic lymph node metastases.

No patient has been lost for follow-up. Median observation time for all patients was 30 months (range: 9–57 months; 95% confidence interval: 24–36 months). Only one out of 53 patients with cervical cancer FIGO stages IB and IIA relapsed at distant sites, no locoregional recurrences appeared in this group. Five further recurrences occurred in the 18 patients with FIGO stage IIB tumors. Two of the 71 patients had a local recurrence. Two patients relapsed with simultaneous locoregional tumors and distant metastases. In two patients only distant metastases were found at the time of relapse. Three patients with recurrences died of their disease, one patient died of intercurrent disease (alcohol-induced liver insufficiency). The Kaplan-Meier curves for relapse-free and disease-specific survival are shown in Figure 2. The 2-year relapse-free and disease-specific

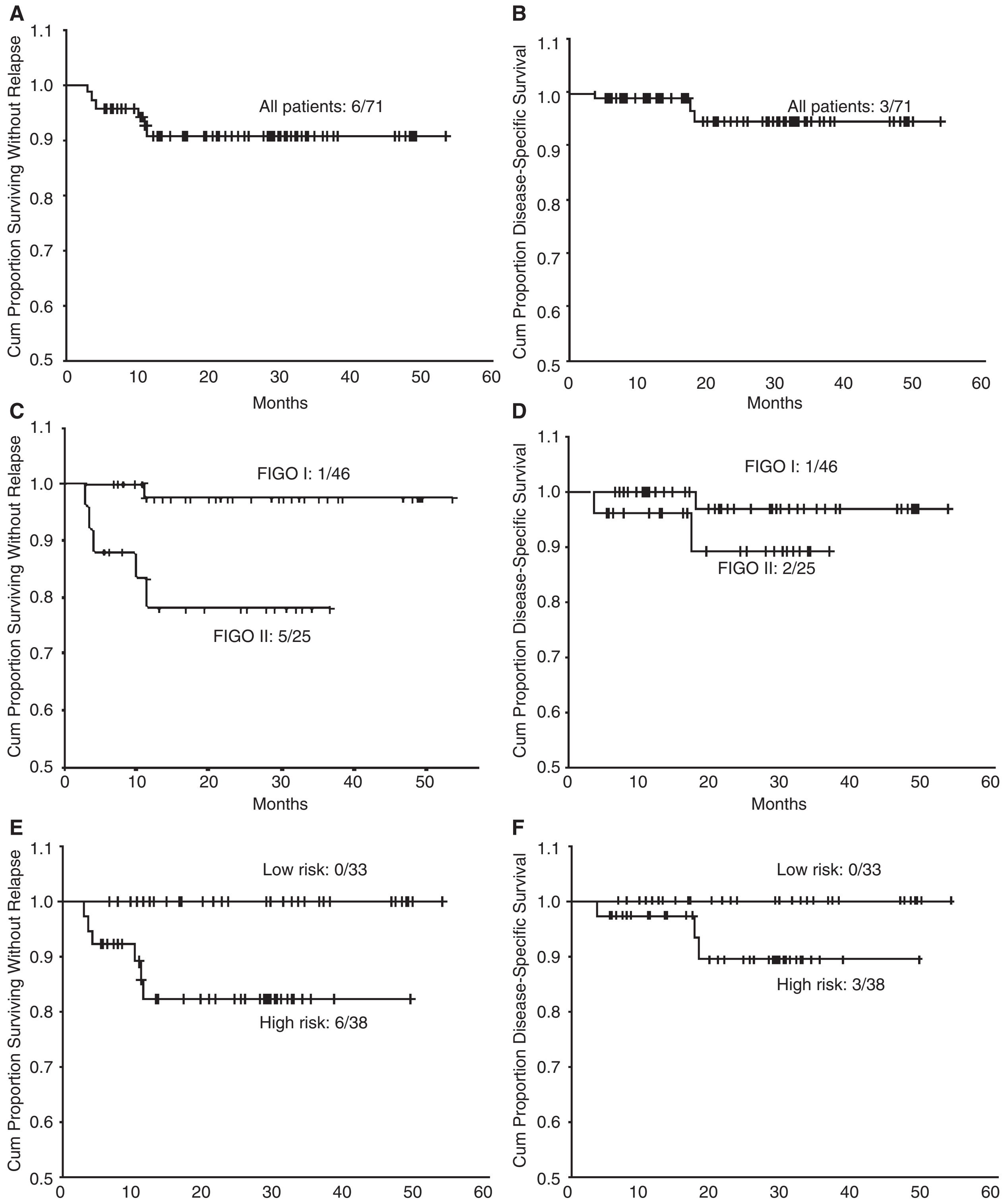

Fig. 2. Kaplan-Meier curves of relapse-free survival (left panels) and disease-specific survival (right panels) of the whole patient cohort (A,B) and of subgroups stratified for FIGO stages (C,D) and histopathologic risk factors (E,F). High-risk factors were pN1, pT2b stages, and combinations of lymphvascular space involvement, cervical stroma invasion, and tumor size according to the GOG#92 trial in pT1bpN0 stages.

survival probabilities are: 91% and 94% for the whole group; 97% and 97% for FIGO stages IB1/IB2; 78% and 89% for FIGO stages IIA/IIB; 82% and 89% for the 38 patients with histopathologic high-risk factors (pN1; pT2b; lymphvascular space involvement, cervical stroma invasion and tumor size according to the GOG#92 trial[4] who did not receive adjuvant radiation).

The complications and sequelae of the TMMR treatment in 71 patients assessed according to the Franco-Italian glossary[16] are compiled in Table 2. TMMR treatment did not lead to any severe (grade 3 and 4) complications/sequelae. The two most severe complications were grade 2 thromboembolism completely resolving with medical treatment which occurred in four patients (6%) and one grade 2 femoral nerve impairment resolving without sequelae after physiotherapy. All other 18 complications/sequelae were grade 1 and concerned 15 patients (21%). Fifty-one patients (72%) had a completely uneventful post-treatment course without sequelae other than infertility and a laparotomy scar.

All 71 patients were investigated with respect to their pelvic visceral functions. Clinical assessment did not reveal a single patient with a severe dysfunction of urethra/bladder, vulva/vagina, or anus/rectum. Forty-seven patients treated with TMMR during the first 3 years (7/98–7/01) were eligible for the prospective longitudinal evaluation of TMMR-related disturbances of the lower urinary, genital, and intestinal functions (Fig. 3). The results of the in-depth evaluation of the lower urinary tract function are demonstrated in Table 3. Statistically significant changes were detected with median residual urine, volume at first desire to void, micturition time, and urethral closure pressure. There were no significant changes after TMMR treatment with respect to all other parameters representing lower urinary tract function. Already preoperatively there have been various deviations from the physiologic function of the lower urinary tract in the patients with cervical cancer. The alterations produced by TMMR treatment are slight based on clinical evaluation and on the perception and estimation of the patients (Fig. 4). Vulvovaginal function as assessed by clinical and questionnaire investigation is summarized in Table 4. More patients perceived reduced vaginal elasticity than reduced vaginal length as sequelae of the surgical treatment. Vaginal lubrication was not altered by TMMR according to the patients' estimation. Although sexual activity of our patient cohort declined 3 months after the operation, the relative number of sexually active patients after 12 months was the same as preoperatively. Six patients were distressed by vulvovaginal dysfunction before TMMR treatment. Based on the questionnaire investigation we could not detect a major impairment of vulvovaginal function by treatment with TMMR (Fig. 4). Anorectal functions evaluated from the patients' questionnaire data are shown in Table 5. Three of 32 cervical cancer patients experienced already preoperatively dysfunctions such as flatus and diarrhea incontinence which distressed them. Treatment with TMMR did not lead to alterations in anorectal functions according to the patients' self estimation (Fig. 4).

Table 2. Total number of complications according to the Franco-Italian glossary by organ system and grade which occurred in 71 patients treated with TMMR

	G1	G2	G3	G4	Total
Gastrointestinal	1				1[a]
Urinary	6				6[b]
Vascular	9	4			13[c]
Cutaneous	1				1[d]
Peripheral nerves	1	1			2[e]
Total	18	5			23

[a]subileus; [b]impaired bladder function, stress incontinence, bladder lesion; [c]lymphcyst, lymphedema, thrombosis or thromboembolism; [d]abdominal wound infection; [e]femoral nerve symptoms.

Discussion

After decades of accepting abdominal radical hysterectomy as standard in the surgical treatment of cervical carcinoma stages IB and IIA, this view has recently been challenged by developments such as combined laparoscopic and vaginal techniques and fertility-preserving procedures[18,19]. However, whereas the common aim of these new procedures has been to improve the therapeutic index by a reduction of specific treatment-related sequelae such as infertility and abdominal scars, no efforts have been made to minimize locoregional recurrences—without additional radiotherapy—by alterations in the surgical concept and techniques.

The first author has developed the total mesometrial resection as high resolution radical hysterectomy with autonomic nerve preservation based on developmentally defined surgical anatomy. TMMR is characterized by en bloc resection of the uterus, proximal vagina and mesometrium, the integral mesentery covered by intact bordering lamellae[20], transection of

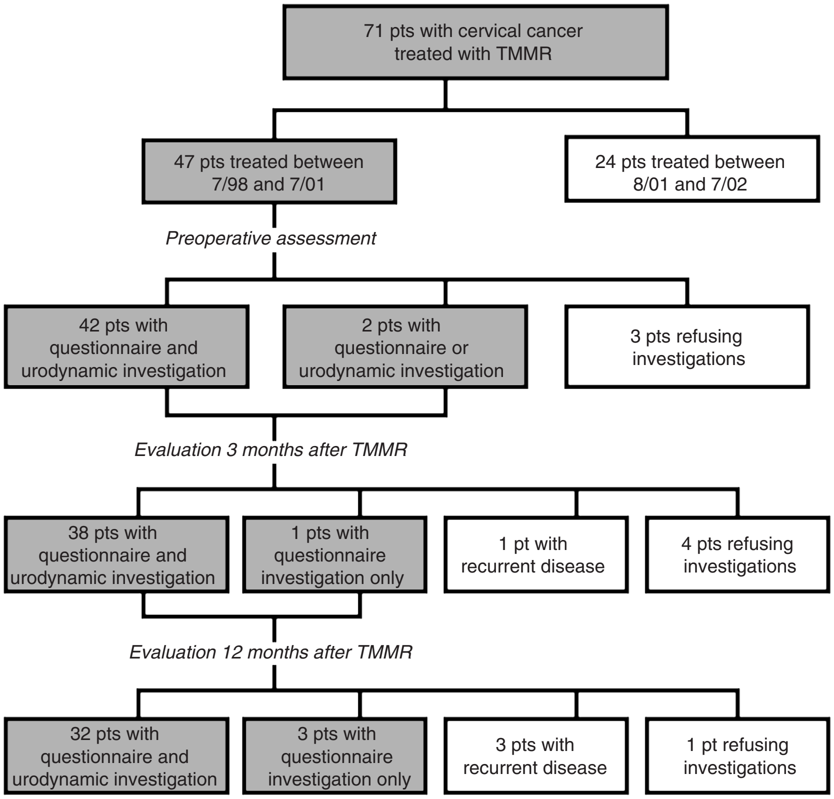

Fig. 3. Flow chart of the patients enrolled in the prospective longitudinal study to assess the influence of TMMR on pelvic visceral functions.

the supporting dense subperitoneal connective tissue[21] directly above the level of the exposed inferior hypogastric plexus, and extended pelvic/periaortic lymph node dissection preserving the superior hypogastric plexus.

TMMR differs from classical radical hysterectomy by consequent sharp separation of the parietal and visceral endopelvic planes instead of blunt dissection; exposition of the complete mesometrium by separation from the bladder mesentery; separate dis-

Table 3. Urethrovesical functions after TMMR

	Preoperative	3 months postoperative	12 months postoperative
Clinical investigation			
Pts with stress incontinence grade I (%)	20	20	28
Median residual urine volume (interquartile range) [ml]	8 (5–19)	15 (10–40)	15 (10–30)
Questionnaire investigation			
Pts with sensory urgency (%)	16	28	28
Pts with nocturia (%)	50	63	52
Pts with reduced bladder filling sensitivity (%)	3	13	13
Pts with bladder emptying by abdominal straining (%)	22	66	53
Pts distressed by urinary dysfunction (%)	6	13	9
Urodynamic investigation (mean ± SD)			
Volume at first desire to void [ml]	267 ± 80	356 ±129	339 ± 100
Volume at maximum capacity [ml]	487 ± 121	543 ± 143	522 ± 125
Compliance at maximum capacity [ml/cm H_2O]	49 ± 20	42 ± 19	45 ± 23
Compliance at first desire to void [ml/cm H_2O]	56 ± 31	59 ± 28	60 ± 27
Max. detrusor pressure at micturition [cm H_2O]	65 ± 22	73 ± 31	72 ± 44
Detrusor pressure at max. flow [cm H_2O]	41 ± 18	48 ± 25	39 ± 22
Maximum flow rate [ml/sec]	20 ± 10	18 ± 11	20 ± 11
Average flow rate [ml/sec]	9 ± 7	7 ± 5	6 ± 5
Micturition time [sec]	51 ± 21	77 ± 41	71 ± 23
Urethral closure pressure [cm H_2O]	69 ± 21	77 ± 32	75 ± 23
Functional urethral length at rest [cm]	32 ± 6	31 ± 7	31 ± 5
Functional urethral length at stress [cm]	29 ± 6	30 ± 9	30 ± 7

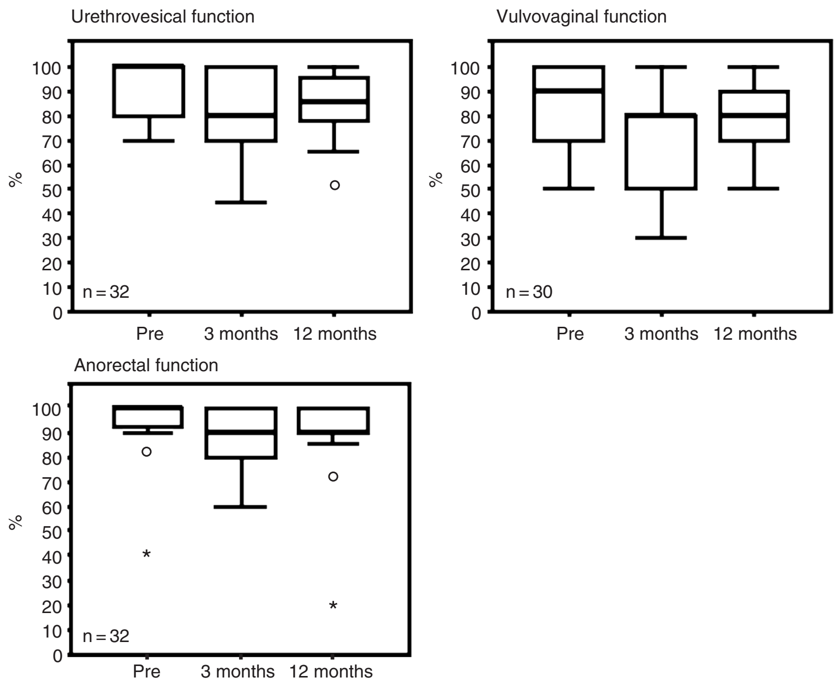

Fig. 4. Box and whisker plots representing the self estimation of overall urethrovesical, vulvovaginal, and anorectal functions of study patients preoperatively, and 3 and 12 months after TMMR treatment. The median of self assessment of preoperative urethrovesical function was 100%, the median of vulvovaginal function at 3 months was 80%, the medians of anorectal function preoperatively and at 12 months were 100%.

section of the mesometrium and the dense subperitoneal connective tissue supporting the uterus and proximal vagina with minimal trauma instead of their composite division as parametrectomy with traumatic clamps (eg, Wertheim clamps); and exposition and mobilization of the superior hypogastric plexus, hypogastric nerves and proximal inferior hypogastric plexus.

The pathomechanism leading to locoregional recurrences of cervical cancer after radical hysterectomy is not exactly known. We have analyzed the relapse pattern of patients seen in our referral center for recurrent cervical cancer with high resolution MRI and surgical exploration(22). In less than 20% of patients, tumor left behind in parietal lymph nodes was the most probable explanation for recurrences. The majority of the pelvic relapses, however, arose at the dissection sites of the radical hysterectomy and appeared to originate from microscopic or occult tumor foci within the endopelvic surgical scars.

Theoretically, the incidence of local scar recurrences can be reduced by a more complete surgical resection of the tissue containing the perifocal tumor foci and by minimizing the wound volume. This was achieved in the surgical treatment of rectal cancer with the total mesorectal excision (TME) pioneered by Heald(11). TME represents a new concept in surgical oncology which is characterized by the removal of the diseased (part of an) organ together with its integral mesentery as a developmentally defined (ontogenetic) entity. Surgery is performed sharply with high resolution and minimal trauma within the cancer field.

With reference to the uterine cervix the ontogenetic entity includes the proximal vagina, corpus, bilateral mesometrium, and dense subperitoneal connective tissue of the rectouterine pouch. The mesometrium

Table 4. Vulvovaginal functions after TMMR

	Preoperative	3 months postoperative	12 months postoperative
Clinical investigation			
Total vaginal length [cm]	9.7 ± 0.7		7.4 ± 1.0
Questionnaire investigation			
Sexually active pts (%)	79	56	81
Pts perceiving insufficient lubrication (%)	6	5	12
Pts perceiving reduced vaginal length (%)	3	14	13
Pts perceiving reduced vaginal elasticity (%)	6	46	31
Pts with dyspareunia (%)	9	0	15
Pts having anorgasmic sex (%)	15	9	15
Pts distressed by vulvovaginal dysfunction (%)	18	27	12

Table 5. Anorectal functions after TMMR

	Preoperative	3 months postoperative	12 months postoperative
Questionnaire investigation			
Pts with flatus incontinence (%)	6	6	6
Pts with diarrhea incontinence (%)	3	0	3 (transient)
Pts with normal stool incontinence (%)	0	0	0
Pts with obstipation(%)	0	3	3
Pts distressed by anorectal dysfunction (%)	9	13	6

originates from the migration of the paramesonephric ducts during the embryologic development from the dorsolateral mesonephros towards the center of the pelvis where they fuse to form the uterus and the proximal vagina[23]. The bilateral structure consists of a larger peritoneal part which forms the broad ligament and a smaller subperitoneal part represented by the uterine artery and vein(s), nerves, lymphatic vessels, lymph nodes, and fibrofatty tissue[20]. Due to a thin bordering lamella the mesometrium can be separated from the superior part of the bladder mesentery. The tissue composition of the mesometrium differs from a true ligamentous structure. The cranial parts of the circular dense subperitoneal connective tissue of the rectouterine pouch correspond to rectouterine and uterosacral ligaments[21]. During conventional radical hysterectomy, the mesometrium is not completely exposed but is clamped together with the dense subperitoneal connective tissue and sometimes even with parts of the mesorectum, bladder mesentery, and obturator lymph node tissue within the perivisceral parietal pelvic adipose tissue[24] (together referred to as parametrium/paracolpium) by use of traumatic instruments (eg, Wertheim clamps) before transection. As a consequence remnants of the mesometrium which may contain tumor cells may be left behind within or close to secondary healing wounds. According to our hypothesis, the interference of these residual occult tumor cells with the microenvironment of the parametrial wounds causes the majority of pelvic recurrences.

According to the TMMR rationale which implies optimal surgery as the only locoregional treatment modality, pelvic lymph node removal must be complete and resection with tumor-free margins (R0) is mandatory. The mean pelvic lymph node count of our TMMR series was 46 which corresponded well to the number of resected pelvic lymph nodes reported by other groups claiming to perform therapeutic lymph node dissection[25, 26]. In only one of 71 patients was an R1 resection status found. In this patient the tumor had also metastasized into at least 49 lymph nodes at the time of the operation.

Due to the median observation period of 30 months, mature oncologic results in terms of relapse-free and disease-specific survival must be awaited. However, the data for 2-year survival probabilities of the patients treated with TMMR as the only locoregional therapy are comparable to the best reported results of radical hysterectomy with (chemo)radiation adjusted for histopathologic prognostic factors such as pT and pN stage, tumor size, depth of cervical cancer, and lymphvascular space involvement, respectively,[4,5]. Mature data are, however, presented for complications and sequelae of the TMMR treatment because their pathogenesis generally does not imply the occurrence of further events at later times. TMMR performed with 71 patients did not lead to grade 3 or 4 complications whereas these are accepted as unavoidable and unpredictable features for primary (chemo)radiotherapy and for radical hysterectomy and adjuvant (chemo)radiation at rates of at least 5–10%[4,6,27,28]. A comparison of the TMMR-related morbidity with that of standard surgical treatment (that is, radical hysterectomy followed by adjuvant radiation in cases of histopathologic high risk factors) is possible as Landoni *et al*.[6] used the same evaluation system of Chassagne *et al*.[16] that we applied. These authors reported 48 grade 2 and 3 complications in 170 patients treated with surgery and adjuvant radiation in cases of high risk factors. The difference to the five grade 2 complications in our cohort of 71 patients is highly significant ($P = 0.00015$).

If the histopathologic criteria established in prospective randomized trials as indication for adjuvant treatment following radical hysterectomy[4,5] are taken into consideration, 38 patients of our cohort should have been treated with postoperative (chemo)radiotherapy. We argue that the advantage of dispensing with adjuvant (chemo)radiation in more than 50% of patients treated surgically for early stage cervical cancer with high risk factors certainly outweighs the disadvantage of applying a more lengthy operation to patients with a lower risk.

Regarding the topographic anatomy of the pelvic autonomic nerve system, it is evident that major parts of that complex structure are at risk of being severed by conventional radical hysterectomy techniques resulting in various pelvic organ dysfunctions (Table 6). Indeed, persistent dysfunction 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[7–10]. Severe handicaps such as grade 2 and 3 stress incontinence, permanent necessity for intermittent self-catheterization, or upper urinary tract disease in cases of lower urinary tract dysfunction after radical hysterectomy have been observed in 10–20% of the patients[29].

TMMR did not result in severe dysfunctions of the lower urinary tract. The main postoperative changes of bladder/urethra function are expressed by an increase of urethral closure pressure and reduced bladder filling sensation. We speculate that some damage of the anterior distal part of the inferior hypogastric plexus may still occur during the mobilization of the distal ureter but various other mechanisms cannot be excluded. However, these changes are slight. 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. Irrespective of the results with TMMR, our prospective longitudinal study confirms the importance of preoperative investigation of patients with cervical cancer in order to evaluate therapy-related effects on pelvic visceral functions as noted by others[30] because a significant number of patients exhibited detectable dysfunctions already before treatment.

Radical hysterectomy techniques with preservation of the autonomic nerve system have a longer tradition in China and Japan (for review see Ref. 13). We had initiated western efforts in developing nerve-sparing radical hysterectomy with the publication of our primordial technique in 1998[13]. Other groups have meanwhile reported first promising results of various ways to combine pelvic autonomic nerve preservation and radical extirpation of the uterus[31,32]. If it is acceptable to combine surgery with adjuvant radiation, pelvic autonomic nerve preservation may also be achieved by reducing the hysterectomy to a type II operation according to the classification of Piver *et al*.[33] without exposing the autonomic nerves. Landoni *et al*. could not detect a survival benefit but observed fewer complications when comparing type II with type III extended hysterectomies followed by postoperative pelvic radiation in the presence of histopathologic risk factors[34].

The combination of neoadjuvant chemotherapy with TMMR is feasible based on the experience with nine patients treated so far. More patients and longer follow-up is necessary to demonstrate the therapeutic efficacy of TMMR combined with preoperative chemotherapy in patients with large volume cervical cancer. Likewise, it is unclear whether neoadjuvant chemotherapy followed by TMMR could improve the results for patients with FIGO stage IIB cervical cancer.

In conclusion, total mesometrial resection, the excision of the uterus and proximal vagina together with its integrated mesentery as an ontogenetic entity supplemented by extended pelvic/periaortic lymph node dissection, differs from the traditional Wertheim-Meigs operation interalia by a much higher surgical resolution, separation of the urogenital mesenteries and support structures, and exposition and preservation of the pelvic autonomic nerve system. Although TMMR is more laborious and time-consuming, the therapeutic index of this surgical treatment without adjuvant radiation for patients with cervical cancer, FIGO stages IB1, IB2, and IIA, is very promising, calling for prospective trials to

Table 6. Potential sites of autonomic nerve damage during conventional radical hysterectomy with pelvic and periaortic lymph node dissection and resulting dysfunction

Part of the autonomic nerve system	Surgical step	Pelvic organ dysfunction
Lumbar splanchnic nerves Superior hypogastric plexus Hypogastric nerves	Periaortic lymph node dissection Presacral lymph node dissection Resection of the rectouterine ligaments	Urinary incontinence Flatus, stool incontinence
Proximal inferior hypogastric plexus	Division of the uterosacral and transverse cervical ligaments	Urinary retention Lack of bladder sensation Impaired sexual response
Distal inferior hypogastric plexus	Transection of the pubocervical ligaments	Obstipation

compare the TMMR approach with conventional treatment.

Acknowledgements

The development of TMMR was supported by a grant from Else-Kröner-Fresenius Foundation, Bad Homburg v.d.H., Germany.

References

1 Wertheim E. The extended abdominal operation for carcinoma uteri (based on 500 operative cases). *Am J Obstet Dis Women Child* 1912;**66:**169–232.
2 Meigs VJ. Radical hysterectomy with bilateral pelvic lymph node dissections. A report of 100 patients operated on five or more years ago. *Am J Obstet Gynecol* 1951;**62:**854–70.
3 Hellebrekers BWJ, Zwinderman AH, Kenter GG *et al.* Surgically-treated early cervical cancer. Prognostic factors and the significance of depth of tumor invasion. *Int J Gynecol Cancer* 1999;**9:**212–9.
4 Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a gynecologic oncology group study. *Gynecol Oncol* 1999;**73:**177–83.
5 Peters WA, Liu PY, Barrett RJ *et al.* Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 2000;**18:**1606–13.
6 Landoni F, Maneo A, Colombo A *et al.* Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet* 1997;**350:**535–40.
7 Low JA, Mauger GM, Carmichael JA. The effect of Wertheim hysterectomy upon bladder and urethral function. *Am J Obstet Gynecol* 1981;**139:**826–34.
8 Sekido N, Kawai K, Akaza H. Lower urinary tract dysfunction as persistent complication of radical hysterectomy. *Int J Urol* 1997;**4:**259–64.
9 Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. *N Engl J Med* 1999;**340:**1383–9.
10 Barnes W, Waggoner S, Delgado G *et al.* Manometric characterization of rectal dysfunction following radical hysterectomy. *Gynecol Oncol* 1991;**42:**116–9.
11 Heald RJ, Husband EM, Ryall RDH. The mesorectum in rectal cancer surgery: the clue to pelvic recurrence? *Br J Surg* 1982;**69:**613–6.
12 Enker WE. Potency, cure, and local control in the operative treatment of rectal cancer. *Arch Surg* 1992;**127:** 1396–402.
13 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:**971–6.
14 Höckel M. Totale mesometriale Resektion: Nervenschonende erweitert radikale abdominale Hysterektomie. *Zentralbl Gynäkol* 2001;**123:**245–9.
15 Höckel M, Naumann G, Hentschel B, Horn L-C, Höckel S. Total mesometrial resection – nerve-sparing extended radical hysterectomy. Surgical techniques and results of a 3-year prospective study. *Gynecol Oncol* 2002;**84:**490 (abstr).
16 Chassagne D, Sismondi P, Horiot JC *et al.* A glossary for reporting complications of treatment in gynecological cancers. *Radiother Oncol* 1993;**26:**195–202.
17 Kurman RJ, Amin MB. Cancer Committee College of American Pathologists. Protocol for the examination of the specimens from patients with carcinomas of the cervix. A basis for checklists. *Arch Pathol Lab Med* 1999; **123:**55–61.
18 Nezhat CR, Burrell MO, Nezhat FR, Benigno BB, Welander CE. Laparoscopic radical hysterectomy with paraaortic and pelvic node dissection. *Am J Obstet Gynecol* 1992;**166:**864–5.
19 Dargent D, Brun JL, Roy M, Rémy I. Pregnancies following radical trachelectomy for invasive cervical cancer. *Gynecol Oncol* 1994;**52:**105 (abstr).
20 Williams PL, Warwick R, Dyson M, Bannister LH. *Gray's Anatomy*, 37th edn. New York: Churchill Livingstone, 1989.
21 Fritsch H. The connective tissue sheath of uterus and vagina in the human female fetus. *Ann Anat* 1992;**174:** 261–6.
22 Höckel M. Pelvic recurrences of cervical cancer. Relapse pattern, prognostic factors and the role of extended radical treatment. *J Pelv Surg* 1999;**5:**255–66.
23 O'Rahilly R & Müller F. *Human Embryology and Teratology*, 3rd edn. New York: John Wiley & Sons, 2001.
24 Fritsch H & Kühnel W. Development and distribution of adipose tissue in the human pelvis. *Early Hum Dev* 1992;**28:**79–88.
25 Girardi F, Pickel H, Winter R. Pelvic and parametrial lymph nodes in the quality control of the surgical treatment of cervical cancer. *Gynecol Oncol* 1993;**50:**330–3.
26 Benedetti-Panici P, Maneschi F, D'Andrea G *et al.* Early cervical carcinoma. The natural history of lymph node involvement redefined on the basis of thorough parametrectomy and giant section study. *Cancer* 2000;**88:** 2267–74.
27 Sinistrero G, Sismondi P, Rumore A, Zola P. Analysis of complications of cervix carcinoma treated by radiotherapy using the Franco-Italian glossary. *Radiother Oncol* 1993;**26:**203–11.
28 Green JA, Kirwan JM, Tierney JF *et al.* Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet* 2001;**358:**781–6.
29 Kadar N, Salbia N, Nelson JH. The frequency, causes and prevention of severe urinary dysfunction after radical hysterectomy. *Br J Obstet Gynaecol* 1983;**90:** 858–63.
30 Lin H-H, Yu H-J, Sheu B-C, Huang S-C. Importance of urodynamic study before radical hysterectomy for cervical cancer. *Gynecol Oncol* 2001;**81:**270–2.
31 Possover M, Stöber S, Plaul K, Schneider A. Identification and preservation of the motoric innervation of the

bladder in radical hysterectomy type III. *Gynecol Oncol* 2000;**79:**154–7.

32 Trimbos JB, Maas CP, Deruiter MC, Peters AAW, Kenter GG. A nerve-sparing radical hysterectomy. Guidelines and feasibility in western patients. *Int J Gynecol Cancer* 2001;**11:**180–6.

33 Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. *Obstet Gynecol* 1974;**44:**265–72.

34 Landoni F, Maneo A, Cormio G *et al.* Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: a prospective randomized study. *Gynecol Oncol* 2001;**80:** 3–12.

Accepted for publication August 1, 2003.