Introduction

Because of the effective use of screening, an increasing number of women are being diagnosed with cervical cancer in an early stage of the disease. Individualization of treatment to reduce therapy-associated early and late morbidity is the most current trend in cervical cancer surgery [1,2]. Radical hysterectomy and pelvic lymphadenectomy in different modifications are the standard surgical treatment for patients with stage IA2 and IB1 cervical cancer [3–6]. Extensive lymphadenectomy and parametrectomy are the main cause of postoperative complications [6–11]. However, the majority of patients with early stage disease do not present lymph node metastases and parametrial involvement is rare. Quite a large number of retrospective studies show that the incidence of parametrial involvement is very low in the subgroup of patients with a tumor less than 2 cm in diameter, less than 10 mm of invasion and negative lymph nodes [12–16]. Stegeman et al., who performed a review of the literature, found that only 0.6% (5 of 799) of the patients with low-risk pathologic characteristics had parametrial involvement [16]. Research over the past 8 years on sentinel lymph nodes (SLNs) has greatly expanded our knowledge on lymphatic propagation of early stage cervical cancer [17–24]. Our prospective study demonstrates that, if the SLNs are negative, the risk of tumor involvement of the parametria is minimal in cervical cancer less than 2 cm in diameter and infiltrating less than one half of the cervical stroma [25].

The purpose of this pilot study was to evaluate the feasibility and safety of a less radical surgery; namely laparoscopic lymphadenectomy followed by a simple vaginal hysterectomy in SLN negative early cervical cancer patients. Treatment-associated morbidity and oncological outcome were also evaluated.
Patients and methods

From December 2000 to September 2007, 60 female patients (3 patients — IA1, 11 patients — IA2 and 46 patients — IB1) were enrolled in the prospective study. The patients were selected based on favorable cervical tumors (IA1 with lymph–vascular space invasion (LVSI) and IA2 and IB1 with tumor size less than 20 mm in diameter and infiltration of less than half of the cervical stroma). Mean age was 44.6 years (range 33–64 years). MRI and ultrasound volumetry were performed after biopsy (wide excision, large loop excision of the transformation zone or needle cone) to identify residual disease. On bases of these examinations when the tumor was more than 20 mm in the biggest diameter or stromal invasion was more than half of stroma, all women were excluded from the study and underwent radical hysterectomy. A second reading of the histopathology was done in all cases if the biopsy was performed out of our hospital. Protocol of the study was approved by the local institutional ethical committee in our hospital (Fig. 1) and informed consent was signed by all patients.

All 60 patients underwent laparoscopic SLN identification. The most important aspect of SLN mapping is timing, the isotope injection technique and the blue dye into the cervix. We used radiocolloid 20 MBq 99mTc-labeled Sentiscint colloidal albumin measuring 100–600 nm in diameter (MEDI–RADIOPHARMA LTD, Hungary), diluted in 2 ml of saline solution and 2 ml of Patent blue (BLEU PATENTÉ V 2.5% – Guerbet, France) diluted in 2 ml of saline solution. In the operating room, after the introduction to general anesthesia, 99mTc was very slowly injected peritumorally into the tumor bed (5–8 s to each quadrant); 10 to 15 min later laparoscopic visualization of the small pelvis was performed. As in the case of 99mTc, Patent blue is then applied using the vaginal approach under direct visualization. Direct visualization of the pelvis allows the surgeon to observe the individual blue-colored lymphatic channels. The retroperitoneum was open for 5 min after the injection of Patent blue, which means 15 to 20 min after the injection of the radioisotope. We used a short protocol of 99mTc administration and did not employ preoperative lymphoscintigraphy. Upon identification of the individual blue-dyed lymphatic channels and blue-colored nodes, we performed radioactivity detection with a laparoscopic gamma probe (Neoprobe, Johnson and Johnson, USA). SLNs were extirpated separately. Identification of SLNs in the medial part of the lateral parametrium (between the cervical fascia and obliterated umbilical artery) is possible in vivo only by blue dye because radioactivity is very high near the cervix [20]. In case of detection of blue node in the parametrium of the patients radioactivity was measured out of the body. The blue lymphatic channel from the medial part of lateral parametrium was removed separately and sent for histopathological evaluation. Having sent the sentinel nodes from frozen section analysis, we performed a complete laparoscopic pelvic lymph node dissection. If the frozen section was...
positive, laparoscopy was abandoned and we continued with laparotomy and radical hysterectomy as well as lower paraaortic lymphadenectomy. If the frozen section was negative, patients were treated with a simple vaginal hysterectomy. Laparoscopically assisted vaginal hysterectomy or total laparoscopic hysterectomy would be other option to vaginal hysterectomy. All patients underwent US of abdomen and kidneys before they were discharged from the hospital and 6 weeks after surgery.

Elaboration of the sentinel node (ultramicrostaging) and other lymph nodes that were removed was done by standard protocol [20]. Nodes larger than 8 mm were divided into two halves, parallel to the long axis of the node. Both halves were frozen in one block. Nodes less than 8 mm were frozen in one piece. Nodes were cut at intervals 40 μm by 4 μm section cut and were stained with Harris hematoxylin. After the frozen section the lymph node slices were fixed in a buffered 4% formaldehyde, pH 7.2. The tissue was embedded in a paraffin wax by standard serial sectioning techniques. Each level was stained for hematoxylin and eosin (HE). Every third slide was immunostained with an anti-cytokeratin antibody — large spectrum, cytokeratines mixture CK 5, 6, 8, 17, 19 (Immunotech, France). All other surgically removed lymph nodes were examined histopathologically using routine hematoxylin and eosin (HE) staining.

Results

In the protocol there were 3 patients with stage IA1 (100% with LVSI), 11 IA2 patients (36.4% with LVSI) and 46 IB1 patients (26.1% with LVSI). Of the 60 cases, 83.3% (50 cases) were of squamous cell histology and 16.7% (10 cases) adenocarcinoma. The preoperative diagnosis was established by a loop electrosurgical excision procedure (LEEP) or cervical conisation in 45 patients (75%) and cervical biopsy in 15 patients (25%).

We detected SLNs in all of the patients. The detection rate (DR) per patient was 100% and the specific side detection rate (SSDR) 94.2%. The average number of sentinel nodes per side was 1.4 (range 1–4). Positive SLNs were detected in 5 patients (8.3%) Table 1. All node-positive patients were only with SLN positive. No false negative SLNs were noted in any of the 60 patients. Three frozen sections were positive, and in these cases a Wertheim radical hysterectomy with low parametrial involvement in SLN negative patients. When the SLNs are positive, risk of parametrial involvement is about 28%[25]. Involve-ment of isolated parametral SLNs without the incidence of other pelvic lymph nodes is very rare (about 1%) in early cervical cancer [4,12,20,25]. In our view, identification of SLNs and blue lymphatic channels and eventually blue lymph nodes in paracervical tissue should be a part of less radical surgery in early cervical cancer.

Discussion

Complete resection of the parametria by radical hysterectomy was considered a standard operative procedure in invasive stage la2 and Ib1 cervical cancer during the 1970s and 1980s [28–30]. In the 1990s, the concept of modified radical hysterectomy was accepted [3–5], which reduced the radicality of resection of the parametria. The primary aim of this procedure was to reduce long-term morbidity, which is associated with the radical resection of the parametria, where potential injury to the innervation of the rectum and bladder can occur. Extension and utility of the resection of the paracervical tissue (parametrium) in radical hysterectomies in women with early stage cervical cancer have been discussed extensively in the literature over the past 15 years [2–5,9,12–16]. Numerous studies have confirmed a correlation between size of the tumor or infiltration of the cervical stroma and positive lymph nodes with involvement of the parametra [3,4,9,12–16]. When we performed a detailed analysis of the data, risk of parametral involvement is lower than 1% in cervical cancer la2 and Ib1 when the tumor size is less than 20 mm in diameter and invasion is less than 10 mm and the pelvic lymph nodes are negative [4,12,15]. When we excluded from this prognostically favorable group patients with LVSI, the parametrium involvement is very rare. In this pilot study we do not consider LVSI as an exclusion criterion for either less radical surgery or fertility sparing surgery, because intraoperative sentinel lymph nodes evaluation is in our institution accurate except micrometastases [26–27].

The most important prognostic factor in our opinion is patients with positive SLNs. We did not register any recurrences in our group of patients after less radical surgery with negative SLNs, including patients with LVSI. Our prospective study, which was the first of its kind that had evaluated risk of parametral involvement independent of the involvement of the SLNs, confirmed the minimal risk of parametral involvement in SLN negative patients. When the SLNs are positive, risk of parametral involvement is about 28% [25]. Involvement of isolated parametral SLNs without the incidence of other pelvic lymph nodes is very rare (about 1%) in early cervical cancer [4,12,20,25]. In our view, identification of SLNs and blue lymphatic channels and eventually blue lymph nodes in paracervical tissue should be a part of less radical surgery in early cervical cancer. Measuring of radioactivity of blue parametrical lymph nodes has to be done out of the operation field after extirpation. Identification of SLNs is an important component of our management and reduces the risk of less radical surgery. The pivotal element of successful SLN detection
in early cervical cancer is good timing in the administration of radiocolloid and blue dye, the right technique with respect to peritumoral injection of radioactive colloids, experience with the method and good cooperation with a histopathologist [20,27,28]. When all these conditions are met, we obtain a 95% detection rate of SLN, with more than 99% sensitivity [20,22].

Morbidty of radical surgery is not only dependent on the reduction of resecting the parametria but also on good pelvic lymphadenectomy (more than 25 lymph nodes), even laparoscopic-related morbidity. Another benefit of SLN detection is a reduction in radicality of lymphadenectomy in patients with peroperative negative SLN [28,30]. In patients who underwent surgery at the end of the study radicality of lymphadenectomy was reduced in all cases with a negative frozen section of the SLNs. In these patients there were fewer lymphocysts and almost no clinical lymphedema of the legs.

Using frozen sections of SLNs is still controversial issue. We routinely perform FS of SLNs in cervical cancers, where a metastasis larger than 2 mm was always diagnosed with FS in our group of more than 300 cervical cancers. Only micrometastases less than 2 mm can be diagnosed as late as during the serial sectioning of SLNs. There is a question regarding what is considered clinical significance of micrometastases from removed SLNs. Metastatic disease was never diagnosed in other pelvic nodes in cases of false negative FS of SLNs. Furthermore, in this group of patients who underwent less radical surgery only micrometastases less than 2 mm were not identified by FS.

Radical hysterectomy type III when the frozen section of SLN was positive is controversial. If we diagnose positive SLN by frozen section, it is not micrometastatic disease. There is a risk for involvement of other nodes and risk for parametrial involvement is about 28% [25]. Debunking in these cases has sense by our opinion. In cases when only SLN is positive and other upper nodes are negative, we used for adjuvant treatment only small radiation field on the pelvis.

In select early cervical cancer the combination of lymphatic mapping and SLN is a procedure that makes it possible to perform less radical surgeries of the parametria and to reduce the radicality of lymphadenectomy in patients with peroperative negative SLNs [28,30]. In patients who underwent surgery at the end of the study radicality of lymphadenectomy was reduced in all cases with a negative frozen section of the SLNs. In these patients there were fewer lymphocysts and almost no clinical lymphedema of the legs.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

Acknowledgment
This work is supported by grant IGA MZCR NS9914-4.

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