The value of sentinel lymphadenectomy in radical operative treatment of cervical cancer

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Abstract

Background/Aim. Therapy of the early stages of cervical carcinoma is surgical or radiation therapy, and for advanced stages chemoradiotherapy. Pelvic and paraaortic lymphadenectomy in early stages offers the most important prognostic factor for survival. To evaluate the method and possible influence on surgical staging and therapy of the disease, we performed sentinel node (SN) identification and excision during open radical hysterectomy and lymphadenectomy in stage Ib-IIa cervical carcinoma. Methods. Fifty patients initially diagnosed with invasive squamous-cell cervical cancer stage Ib-IIa were included in the study. Only blue dye was used for sentinel node mapping. During the surgery sentinel nodes were identified and sent to histopathology separately from the other lymph nodes. After lymphadenectomy, radical hysterectomy was performed. Results. The mean age of our fifty patients was 49.10 years (SD = 5.92), and the mean number of extracted lymph nodes per patient was 25.78 (SD = 5.58). The number of sentinel nodes identified per patient was between 0 and 5, mean 2.60 (SD = 1.54). There were no inframammary paraaortic sentinel nodes found among the patients. The dominant tumor grades were 1 and 2, 40% and 50% respectively, and 37 out of 50 patients (74%) had tumor diameter less than 2 cm. In four patients (8%) SN were not identified. In the rest of 46 patients the presence of SN was bilateral (19 patients, 38%) or unilateral (27 patients, 54%). Positive SN were found in 17 patients (34%), and negative in 29 patients (58%). Out of the whole group of patients (50), 21 of them (42%) had positive lymph nodes (LN). In the crosstab statistics, no differences were noticed in the group without SN found, in comparison with tumor grade and diameter. Finally, our test showed sensitivity of 85% (SE = 8%), specificity: 100%, positive predictive value of 100%, negative predictive value of 89.6% (SE = 5.6%), and effectiveness of 93% (SE = 3.6%) regarding sentinel lymphadenectomy. Conclusion. This method of sentinel lymph node identification is simple, but not reliable enough to support further laparoscopic SN excision in order to make the final decision about the treatment of cervical cancer.

Key words: uterine cervical neoplasms; neoplasm metastasis; sentinel lymph node biopsy; hysterectomy; prognosis.

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Introduction

The global incidence of almost 400,000 cases and the annual death rate of nearly half the previous estimate qualifies cervical cancer as one of the greatest XXI century problems. Whereas preinvasive disease makes no problem after diagnosis, invasive cervical cancer still remains an issue of debate on therapeutic approach, particularly in the early stages. So far, a management plan depends not only on the anatomical extent of the disease, but also on age and general health of a patient. “The staging of cancer of the cervix is a clinical appraisal, preferably confirmed in a patient under anesthesia; it cannot be changed later if findings at operation or subsequent treatment reveal further advancement of the disease.” With the aim to achieve utmost accuracy in determining clinical staging, we occasionally use, apart from physical examination, radiography, colposcopy, cystoscopy, proctosigmoidoscopy, intravenous pyelogram (IVP) and barium enema. Lymphography, computerized tomography, magnetic resonance imaging, arteriography, venography, laparoscopy and hysteroscopy are not recommended for staging, as they have not been standardized. It is usual for early stages to be treated by surgery or radiation therapy, and for advanced stages to be treated by chemotherapy. Pelvic and paraaortic lymphadenectomy in early stages offers the most important prognostic factor for survival. Whether it should influence the decision about radical surgery or radiotherapy and in which cases, remains to be discussed. One question, however, seems to be answered: brachytherapy is much more effective with the uterus in situ. Also, there are some authors who support the opinion on therapeutic benefit in dissection of positive, enlarged lymph nodes, so that doses of radiotherapy can be successful in eradication of metastatic disease. High morbidity in patients who undergo radical surgery followed by radiotherapy makes many surgeons avoid surgery in case of lymph node involvement in order to improve life quality and retain good results.

Therefore, the assessment of lymph node (LN) status seems to be important for the decision regarding the treatment plan. Whether sentinel nodes (SN) represent the LN status of the region is still questionable.

Sentinel node mapping is performed using blue dye and/or Technetium (99Tc). After Malur and Levenback et al., the accuracy of the combined method is between 90 and 100%, compared to 50–70% when using blue dye and 99Tc separately. Recently, Marchiole et al. reported the false-negative rate of 12.5% which lowers a negative predictive value down to 87.5%, as the most important issue.

The aim of this prospective study was to evaluate SN mapping using blue dye, as the representative of the LN status. This would potentially lead to a better judgement in deciding whether to perform radical hysterectomy in patients with cervical cancer at an early stage, all on the basis of minimally invasive surgery (endoscopy).

Methods

The number of radical hysterectomies performed in our clinic slightly varies, it is about 140 annually for the past five years. This number represents a failure of prevention programs, as well as the concentration of cases in a couple of centers in our country.

Every patient with invasive cervical cancer has to be examined by a board of physicians, and after their considering the case, the decision on therapeutic approach is made. That is a general rule. After that, patients are referred for surgery stay in our clinic, and the others are sent into the regional oncology centers for radio- and chemotherapy.

Our study group consisted of 50 patients, randomly selected among those with invasive squamous cell cervical cancer, clinically staged as FIGO stage Ib-IIa and referred for radical hysterectomy. The research lasted from March 2003 to December 2004.

For SN identification we chose only blue dye for two reasons: firstly, the easy-performing method offers chances to be widely accepted; secondly, and more importantly, the use of 99Tc as a standard procedure is still not feasible in our clinic.

Thirty minutes prior to operation we injected 3 mL of blue dye in each side of cervix (clock position 3 and 9). During the course of the procedure we identified SN, excised them and sent them to histopathology separately from the others. After that we performed paraaortic lymphadenectomy up to the inferior mesenteric artery, bilateral pelvic lymphadenectomy, and finally, radical class III hysterectomy.

All relevant data underwent statistical analysis. We used descriptive statistics, frequency tables, logistic regression, Student t test, crosstabs and χ2 test.

Results

Our study lasted 22 months, and all the radical hysterectomies were performed by the authors of this paper.

The mean age of our patients was 49.10 years (SD = 5.92) in the 38–67 age group. Twenty patients (40%) had grade I tumor, 25 (50%) had grade II tumor, the remaining 5 patients (10%) had grade III tumor.

A tumor smaller than 2 cm in diameter was found in 37 patients (74%). We found 11 (22%) cases with tumors between 2 and 4 cm in diameter, and 2 cases (4%) with tumors larger than 4 cm in diameter. The correlation between nodal metastases and the tumor size fits relevant data.

The mean number of extracted lymph nodes per patient was 25.78 (SD = 5.58), ranging from 15 to 39.

The number of SN identified per patient varied between 0 and 5, with the mean value of 2.60 (SD = 1.54).

There were no inframesenteric paraaortic SN found in the group of patients, yet in four patients (8%) nodes of that location were positive.

In four patients (8%) SN were not identified and in all the statistics they were treated as missing.

In the rest 46 patients the presence of SN was bilateral (19 patients, 38%) or unilateral (27 patients, 54%). The positive SN were found in 17 patients (34%) and negative in 29 patients (58%). Out of the whole group of patients (n = 50), 21 of them (42%) had positive LN.

Crosstab statistics showed no difference between “no SN found” group and the rest of the patients, regarding tumor grade and diameter.

In five cases (10%) we noticed complete staining of the posterior leaf of the broad ligament.

Our test showed sensitivity of 85% (SE = 7.98%), specificity of 100% (SE = 0%), positive predictive value of 100% (SE = 0%), negative predictive value of 89.6% (SE = 5.6%) and effectiveness of 93% (SE = 3.6%).

**Discussion**

Clinical staging of cervical cancer has, so far, been mandatory in defining the extent of the disease, and radical hysterectomy, with pelvic and paraaortic lymphadenectomy, is the mainstay of therapy for the early stages (IB-IIa). Although confident enough to discover parametrial infiltration, clinical examination is not reliable in discovering the nodal metastatic disease.

Additional diagnostic tools that we use in an attempt to check up lymph node status are not, unfortunately, accurate enough. That is the reason why we often exceed limits of an adequate therapy in terms of an overtreatment or undertreatment. In our attempt to tailor the treatment to the measure of the disease, we turn to surgical staging in order to obtain relevant data. On the other hand, surgical staging would be potentially beneficial only if we could individualize treatment and perform it less radically in some cases (nerve sparing surgery, preservation of fertility, better clinical outcome, etc).

Metastases in LN are the predictors of bad prognosis in the early stages of cervical cancer. They put the patient into the high-risk group for adjuvant oncological therapy, which is almost inevitable. That is the reason we all want to know about the LN status before radical surgery, if possible before systemic lymphadenectomy, as well.

The matter of debate is the question of wheather SN could represent LN status with acceptable probability or not. If yes, the next question is about the method of sentinel mapping, which should be as simple and efficient as it could be. Finally, the answer is yet to come if there is any real benefit of sentinel biopsy.

The central point of our work is the evaluation of our method of SN mapping by the use of blue dye only.

As it has previously been said, the combination of blue dye injection and 99mTc lymphography significantly improves the accuracy of SN detection according to numerous authors, but the data are still inconsistent. However, it is not applied in our clinic as a routine procedure and, probably, neither it is in many other clinics. Besides, someone will find lymphography not so convenient for the patient. On the other hand, injection of blue dye is a simple and convenient procedure, short-lasting and performed while a patient is already under general anesthesia for the surgery.

We choose to inject the contrast in clock positions 3 and 9 of the cervix rather than to inject it in the tumor itself, in order to prevent additional metastatic spread and achieve bilateral mapping. We found the volume of 3 ml to each side optimal regarding cervical compliance and staining potential in several testings before starting the study. We choose a 30-minute period of time because it enables at least pelvic SN staining, during which we usually do the necessary preparations of the operative field.

The mean age of 49 years reveals a typical group of patients.

We choose the most common histopathological type, squamous-cell carcinoma, supposing that merging with other types (ie adenocarcinoma) may potentially influence the results.

The distribution of tumor sizes and histological tumor grades is listed in the results. The percentage of lymph node involvement according to the tumor size fits the other relevant data.

An average number of lymph nodes in pelvis is about 50 and changes during a lifetime. Our lymphadenectomy of 25–26 LN per patient seems to represent the European standard.

The mean number of 2.6 SN per patient (range from 0–5) would be close to our intentions. Unfortunately, in four patients (8%) we could not find SN at all. In the subsequent statistics they were treated as missing, but that fact affected sensitivity (drop to 85%) and effectiveness (drop to 93%). Furthermore, we could not find any inframesenteric paraaortic SN in the whole group of patients. It is worth repeating that we have performed inframesenteric paraaortic lymphadenectomy for Benedetti-Panici reasons, and because this region is laparoscopically easily accessible. However, our finding is not in correlation with other data showing about 9% paraaortic SN found in stage Ib1, marking this location as the first place of metastatic spread in about 9% in stage Ib1. Perhaps, we would have found some SN performing complete paraaortic lymphadenectomy, but then, the question of sentinel mapping would arise again. Also, the time distance from dye injection to SN excision (30–35 min) could have been rather short for LN staining. Still, we have 8% inframesenteric paraaortic LN positive in stages Ib-IIa, all of them with positive pelvic SN, therefore, not influencing the statistics.

The percentage of lymph node involvement according to the stage of disease (42%) in our material is significantly higher than in other reports (about 30%). Reevaluation of histopathological materials showed no understaging.

In the group of patients (n = 4; 8%) without SN found, there was no difference regarding the tumor grade and diameter when compared to the rest of the patients (n = 46; 92%).

In five cases, besides SN being found, a complete staining of the posterior leaves of the broad ligaments occurred. That finding could be in correlation with the recent

results showing parametrial extension in 7% of Ib stage patients and 34% of IIb stage patients. 

Our method for SN mapping is simple, fast and comfortable both for the patient and the doctor, yet having comparable values. The shortcomings are less efficiency and lower negative predictive value than in the more sophisticated, combined 99mTc + blue dye lymphography. Having in mind that even the combined method has not yet convinced gynecologic oncologists in its superiority and necessity, we think that there is some space for this procedure in selected cases. Perhaps, a part of the problem regarding the extended field radiation could be solved by performing excision of all inframesenteric paraaortic lymph nodes as the first step. After that, pelvic SN mapping could be useful in some cases.

Conclusion

This method of sentinel lymph node identification is simple, but not reliable enough to support further laparoscopic SN excision in order to make the final decision about the treatment of cervical cancer.

R E F E R E N C E S


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