Review Article

Perineural invasion in cervical cancer: pay attention to the indications of nerve-sparing radical hysterectomy

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Abstract: Perineural invasion (PNI) in early-stage cervical cancer, is associated with multiple high-risk factors and represents a poor outcome in the patients. For nerve-sparing radical hysterectomy (NSRH) to become a standard and widely used treatment for cervical cancer, we need to define its oncological safety, and to establish standardized surgical procedures and indications of NSRH. Here, we review the definition and mechanisms, and clinical significance of PNI in cervical cancer, and discuss the indications of NSRH. PNI should be regarded as one of the main pathological features of cervical cancer and a factor affecting prognosis. A deeper understanding of PNI in cervical cancer, hopefully, will provide clear indications of NSRH.

Keywords: Perineural invasion (PNI); nerve-sparing radical hysterectomy (NSRH); indication; cervical cancer; risk factors

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Introduction

In 1898, Ernst Wertheim first introduced the radical abdominal hysterectomy for women with cervical cancer and over time, the procedure was named after him (1). Subsequently, radical hysterectomy and pelvic lymphadenectomy with or without paraaortic nodal sampling is widely used for the treatment of early-stage cervical cancer. However, a conventional radical hysterectomy with extensive parametrial resection can be performed if adequate tumor-free margins are available. Moreover, the procedure was shown to cause damage to the pelvic autonomic nerves leading to difficulties in storage and voiding urine, colorectal disorders, and sexual dysfunction. Additionally, the physical and mental stress was found to impair the quality of life of the patients (2).

In order to avoid long-term adverse effects, nerve-sparing radical hysterectomy (NSRH) was introduced by Japanese surgeons to preserve the pelvic autonomic nerves. A recent meta-analysis demonstrated that NSRH linked to reduced bladder dysfunctions and fewer postoperative complications (3). NSRH is not only a feasible and well-tolerated procedure, but might also improve the quality of life (4). However, there is no standardized technique for NSRH. Recently, it has been found that cervical cancer exhibited a tendency towards neural invasion (5). This neoplastic invasion of nerves is called perineural invasion

(PNI). As PNI is correlated with poor prognosis in cervical cancer, we need to pay attention to strictly control the NSRH indications. It is important to balance the treatment and quality of life of patients, an essential aspect for future developments in surgical techniques for cervical cancer. Further understanding of PNI may open doors to formulate NSRH indication and standardize surgical procedures.

Anatomical bases and definition of PNI

PNI is also called neurotropic carcinomatous spread or perineural spread (6). As the fifth route of cancer spread, which is different from transcoelomic, lymphatic spread, hematogenous spread, and canalicular spread. Nevertheless, PNI is frequently disregarded and is not well understood.

There are three layers of connective tissue covering each nerve, namely the outermost epineurium, the middle perineurium, and the innermost endoneurium (7). The inside part of the nerve is separated from the surrounding tumor by multiple layers of collagen and basement membrane. This anatomical structure serves as a low-resistance plane that provides channels to the tumor cells for spreading along the neural sheaths. Once the tumor cells have invaded the nerve sheath, it may access the growth environment that is beneficial for metastasis. This was the predominant theory for the last 40 years. Through continuous pathological section analysis, it was found that the transfer mode of PNI was continuous, non-jumping, and direct spreading. Thus, tumor cells migrate through a "neural road".

The patterns of invasion of neuron widely varies, including complete and incomplete encirclement, concentric lamination, and tangential contact (8). A more common exist in PNI is tumor cells free inside of the nerve sheath but tumor-nerve contact within the perineurium (9). The current pathological diagnostic criteria of PNI is "tumor in close proximity to nerve and involving at least 33% of its circumference or tumor cells within any of the 3 layers of the nerve sheath" (9). In fact, there is no agreement regarding the interpretation of PNI among pathologists who conduct microscopic examination of tissue specimens (10). Thus, the conventional H & E stained section and immunohistochemical examination of biomarkers of autonomic nerves and cancer cells will be necessary. Furthermore, it is necessary to establish a risk model exploring the relationship between nerve-tumor distance and nerve diameter with clinical outcomes (11). These examinations will definitely form the basis of radical hysterectomy in the era of precision surgery.

Mechanisms of PNI

In the mid-1800s, researches in the field of head and neck cancers first reported PNI. They showed that these tumors exhibited a predilection for growth along nerves leading their way to the intracranial fossa. However, at the time, the molecular mechanism of certain carcinomas predilection for PNI was largely unknown. Traditionally, tumor propagation occurs along the perineural space, which has a low resistance depending on the connective tissue covering the peripheral nerve (12). Nevertheless, recent studies including animal models and human tissues have demonstrated that cancer cells have an innate nature to migrate along axons in a mechanism named neural tracking, thereby challenging the conventional knowledge. To migrate along the nerves, the cancer cells need the support of multiple growth factors and chemokines secreted by various types of cell in the perineural niche (13). New evidences suggest a complex interaction between nerves and tumor cells invading the nerves; signal transduction through neurotrophic growth factors such as neurotropin, granulocyte colony-stimulating factor (G-CSF), and cytokines has been observed (14-16). Neurotrophins and their receptors are being investigated as viable therapeutic targets (17-20). Moreover, researchers have focused on the genetic mechanism of PNI including gene defect and the role of tumor suppressor gene (*p73*) (21).

Sympathetic nervous system regulates the tumor microenvironment. The cervix and uterus are innervated by the autonomic nervous system (ANS) (22). Activation of the sympathetic division of the ANS in particular modulates gene expression that promotes metastasis of solid tumors (23). A tumor is able to induce neoneurogenesis; high levels of nerve growth factor and axon guidance molecules have been observed in the presence of a tumor (24). High levels of norepinephrine released by the sympathetic nerves contribute to tumor development and metastasis, indicating a mutually beneficial relationship between tumor cells and neurons (25). Recent research demonstrates that Schwann cells have a unique and specific affinity for tumor, and aid in tumor dissociation, migration, and invasion (26-28). Neural cell adhesion molecule 1 (NCAM1) is an important molecular mediator of Schwann cell directed PNI (25,29). During PNI, there is communication between nerves and cancer cells. The new findings have demonstrated that cancer invasion is promoted by prostaglandin E2. Following the feedback mechanism,

which Galanin (GAL) released by cancer cells induces neuritogenesis, facilitating PNI (30). Nerves and cancer cells are like two "waltz" dancers going to each other, and eventually lead to tumor cells invading and spreading. The tumor cells can use splanchnic nerves as conduits and spread from the end organ to the lumbosacral plexus (31). Epidemiological studies and preclinical trials suggested that the nervous system plays an important role in tumorigenesis, and that denervation might reduce or slow down tumor progression and PNI (32-34).

PNI in cervical cancer and clinical significance

PNI has been shown to be an important pathological feature of cervical cancer and along with cancer of other organs, including head and neck, pancreas, colon, rectum, prostate, biliary tract, and stomach (35-39). PNI is related to morbidity and play a key role in the poor outcome and overall survival of the patients.

The treatment of early-stage cervical cancer includes radical hysterectomy and pelvic lymph node dissection, followed by neoadjuvant chemotherapy (NACT) if necessary. This can achieve 5-year survival rates of approximately 85% (40-42). Additional adjuvant treatment is considered based on the risk factors of recurrence. Well-known high-risk factors such as lymph node metastasis, parametrial invasion and resection margin involvement could increase the recurrence rate ≤40% in postoperative cervical cancer (43,44). Intermediate-risk factors include tumor size, depth of stromal invasion, and lymphovascular space invasion (LVSI) (45,46). However, so far, numerous large-scale studies in terms of morphologic parameters do not recognize PNI (47-52), and the histopathologic description of parametria has usually ignored the existence of PNI.

Table 1 summarizes the studies of PNI in early-stage cervical cancer, including its incidence, coexistence with other pathological and clinical features, as well as its prognostic value. In previous studies, PNI was observed in 7.0–35.1% patients with early-stage cervical cancer (53-60). Unfortunately, some patients in these studies received NACT before the operations, and the rate of PNI in operated samples was thought to significantly decrease. Future research should focus on standardizing the definition, reporting methods as well as histopathology of relevant nerve-specific antigens.

PNI was significantly associated with multiple high risk and intermediate-risk factors for recurrence (*Table 1*), especially, larger tumors (≥4 cm), depths of invasion (≥15 mm), and LVSI, which play a crucial part in deciding the adjuvant therapy. A previous study has shown that more than half of the patients with PNI (75.0–92.3%) also had evidence of LVSI, compared with 7.7–39.9% of those who had no PNI. Memarzadeh *et al.* (53) suggested the spread of malignancy from primary cervical tumor to parametrium in the form of LVSI or parametrial PNI with subsequent involvement of the lymphatic channels with tumor cells. Larger tumor (≥4 cm) as well as deeper invasion (≥15 mm) were more common in PNI-positive than in PNI-negative tumors. Moreover, some studies reported that PNI was associated with other risk factors as well (*Table 1*). It seemed to imply that PNI was associated with more aggressive diseases. In previous studies conducted by Elsahwi *et al.* (57) and Cho *et al.* (58), 70–90% cervical cancer patients with PNI were recommended for adjuvant radiotherapy, which is significantly higher than that for patients without PNI. In cervical cancer, PNI was not an isolated event. Particularly, PNI was significantly associated with LVSI and larger tumors (≥4 cm). From the existing literature reports, there must be some high-risk factors for recurrence when PNI presents in cervical cancer. But, not vice versa, the existence of high-risk factors are not equal to PNI. There is no relevant report on the rate of occurrence PNI present independent of the presence of cancer. Multicenter, randomized, prospective trials are needed to further confirm these observations.

The clinical significance of PNI as a potential prognostic factor for cervical cancer has not been well studied. Memarzadeh *et al.* (53) and Horn *et al.* (56) demonstrated that the presence of PNI proved to be an independent predicting factor of poor outcome in patients with cervical cancer. Skręt-Magierło *et al.* (60) found that patients with PNI had shorter disease-free and overall survival; however, PNI was not identified as an independent risk factor. Contrary to these studies, others demonstrated that PNI did not increase the risk for recurrence or death. Five of eight studies shown in *Table 1* did not consider PNI as a risk factor. However, these differences were not surprising because the subjects and surgical procedures widely varied in these studies. Recently, a meta-analysis, including three studies and 571 patients, demonstrated that PNI is closely related to the risk factors for recurrence and is an ominous morphologic prognostic factor in cervical cancer (61). Unfortunately, the sample number was too small and two of these three studies did not provide a direct hazard ratio.

PNI may be a new intermediate-risk factor for patients

Table 1 The data from studies dealing with PNI in cervical cancer

Reference	N	Stage	Region of PNI assessment	Incidence of PNI (%)	Correlations of PNI with	PNI with poorer outcome
Memarzadeh *et al.* 2003 (53)	93	IA2IIA	Parametrium	7.5	LVSI	Yes
Ozan *et al.* 2009 (54)	36	IB1IB2	No reported	33	Vaginal/uterine invasion	No
					LVSI	
					Depth of invasion	
Tavares *et al.* 2009 (55)	301	III	Cervix	27	No reported	No
Horn *et al.* 2010 (56)	194[†]	IBIIB	Cervix	35.1	Depth of invasion	Yes
					Tumor stage	
					Lymph node involvement	
Elsahwi *et al.* 2011 (57)	192	III	Cervix	12.5	Tumor size ≥4 cm	No
					LVSI	
					Parametrial invasion	
Cho *et al.* 2013 (58)	185	IA2IIA2	Cervix	7	LVSI	No
					Parametrial invasion	
Zhu *et al.* 2014 (59)	50[‡]	IB1IIB	Parametrium	9	Stage	No
					Depth of invasion	
					Tumor size ≥4 cm	
Skręt-Magierło *et al.* 2016 (60)	210	IA2IIA	Cervix	8.6	LVSI	Yes
					Parametrial invasion	
					Depth of invasion	
					Tumor size ≥4 cm	

[†], patients received neoadjuvant therapy, incomplete tumor resection and with other than squamous cell histologic type were excluded from the study; [‡], patients accompanied by high-risk factors for recurrence were considered for the study. PNI, perineural invasion; N, number of patients; LVSI, lymphovascular space invasion.

with cervical cancer, which is helpful to determine the strategy for providing adjuvant treatment to the patient. Adjuvant therapy would improve overall survival and disease-free survival. At this point, the use of PNI as an independent predictor for prognosis is limited. Further studies are required for estimating the prognostic value of PNI in cervical cancer.

Indication of NSRH

Currently, NSRH is an important topic in clinical research. Studies demonstrate the cure rates for cervical cancer are equivalent to those of the conventional technique, which can also decrease vesical, rectal, and to a lesser degree, sexual dysfunction. However, for this surgical procedure, the postoperative recurrence rate is still unclear, and it lacks a standardized research methodology. Recently, three meta-analyses on NSRH criticized that there was no standardized technique for NSRH and controversies still exist about its safety in patients with cancer (3,62,63). In the presence of PNI, NSRH may preserve not only the nerve but also the cancer cells invading the nerves. Therefore, it must be very strict to NSRH indications and pay attention to PNI, which is particularly important. Perineural spread increases the difficulties of completely removing the tumor with safe margins at the time of diagnosis. Therefore, optimal resection in such cases is rare (64,65).

PNI was correlated with the well-known risk factors. Furthermore, PNI may be present in the parametrium in early-stage cervical cancer, so NSRH may retain the risk of

recurrence (or residual tumor). High-risk factors including PNI should be excluded by preoperative examinations to ascertain the eligibility criteria for performing of NSRH. At present, PNI is diagnosed by pain symptoms, magnetic resonance imaging (MRI), and examination of intraoperative frozen sections. In 60% of the patients with malignant tumor of the pelvis have been shown to experience a neuropathic pain. The infiltration of the perineal nerves results in lumbosacral plexopathies and complete destruction of the nerve, which may be a reason for the pelvic pain (66). Because the early symptoms of cervical cancer are mild, it is easy to misdiagnose and often ignore the underlying PNI.

It has been reported that PNI may be detected by preoperative imaging studies using computed tomography (CT) or MRI and histologic evaluation (67,68). PNI evaluation by 3.0 high-field MRI may map the exact location of the tumor and improve critical surgical and treatment planning (69). Gil *et al.* (70) reported that PNI of the tumor cells transfected with NV1066, could be detected using stereo microscope or positron-emission tomography (PET) imaging. However, these findings were observed in oral squamous cell carcinoma, cutaneous squamous cell carcinoma, pancreatic cancer, prostate carcinoma, and adenoid cystic carcinoma, but data on cervical cancer are scarce or even nonexistent. Although still controversial, the information in literature regarding other types of cancer should be used as a reference for preoperative diagnosis of PNI in cervical cancer. Recently, Howe *et al.* reported that perineural spread in a case of cervical cancer to the sciatic nerve or a place 15 cm away could be detected by MRI (5). Thus, preoperative imaging is valuable for the detection of PNI, and could be used as a diagnostic method of PNI.

Previous studies have shown that when patients had a tumor sized <2 cm, there was no lymphovascular invasion, and the depth of invasion was limited. The risk of parametrial involvement is nearly 1% (62,71). We can use these favorable preoperative features to select patients who would receive maximum benefit from NSRH; subsequent postoperative radiation can also be avoided. During NSRH, the lower hypogastric plexus, vesical plexus, and rectal branches are saved, but the uterine branches are dissected. Skręt-Magierło *et al.* demonstrated that examination of an intraoperative frozen section of small slices of the uterine branches may be performed in the presence of high-risk factors including tumor size of ≥40 mm, depth of invasion of ≥15 mm, and/or pelvic or paraaortic lymph nodes identified using CT scans (60). Based on intraoperative frozen section examination, the procedure of nerve sparing can continue if the sample is free from invasion. This approach is difficult to clear the status of nerve trunk, so it seems to be great risk. There are still some issues that need to be addressed in the intraoperative frozen section examination, for example: where should be examined? How many sites should be examined? How can the diagnostic accuracy be guaranteed in case of such intraoperative exam with frozen samples? Simultaneous identification of HPV 16 E6 and S100 by double immunofluorescence may be helpful to detect PNI in cervical cancer (72,73).

NSRH can be subdivided into unilateral nerve-sparing radical hysterectomies (UNSRH) and bilateral nerve-sparing radical hysterectomies (BNSRH) (74). The therapeutic effect of BNSRH is better than UNSRH. Therefore, patients with International Federation of Gynecology and Obstetrics (FIGO) stage IA2 and IB1 (<2 cm) cervical cancer could undergo BNSRH; however, to ensure the efficacy, UNSRH is needed for FIGO stage IIA1 (<2 cm and small lesion in the vagina vault) patients. The patients with FIGO stage IB2 and IIA2 who underwent NACT are not suitable for performing NSRH, since NACT may mask the occurrence of PNI. In addition, patients with the lowest possibility of postoperative radiotherapy may gain maximum benefit from NSRH in terms of quality of life.

Conclusions

There is no doubt that PNI should be regarded as one of the main factors affecting NSRH indications for cervical cancer. The aim to study PNI in cervical cancer is to develop clear indications of NSRH, and not to deny this surgical technique. The advantages of NSRH can be reflected more perfectly. It is important to ensure the survival of patients as well as, to improve the quality of life. Further multi-center and large prospective trials are needed to define the recommendations and guidelines for conducting NSRH.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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