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Technical note

High dose three-dimensional conformal boost (3DCB) using an orthogonal diagnostic X-ray set-up for patients with gynecological malignancy: a new application of real-time tumor-tracking system

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Abstract

The feasibility and accuracy of high dose three-dimensional conformal boost (3DCB) using three internal fiducial markers and a two-orthogonal X-ray set-up of the real-time tumor-tracking system on patients with gynecological malignacy were investigated in 10 patients. The standard deviation of the distribution of systematic deviations (Σ) was reduced from 3.8, 4.6, and 4.9 mm in the manual set-up to 2.3, 2.3 and 2.7 mm in the set-up using the internal markers. The average standard deviation of the distribution of random deviations (σ) was reduced from 3.7, 5.0, and 4.5 mm in the manual set-up to 3.3, 3.0, and 4.2 mm in the marker set-up. The appropriate PTV margin was estimated to be 10.2, 12.8, and 12.9 mm in the manual set-up and 6.9, 6.7, and 8.3 mm in the gold marker set-up, respectively, using the formula $2\Sigma+0.7\sigma$. Set-up of the patients with three markers and two fluoroscopy is useful to reduce PTV margin and perform 3DCB.

Keywords: Image-guided radiotherapy; Set-up error; Real-time tracking system; Intra-fractional error; Uterine cervix; Vagina; Carcinoma

1. Introduction

Uterine cervical cancers are curable with radiotherapy with or without chemotherapy in cases in which a sufficient dose can be given to the clinical target volume (CTV), which includes the gross tumor volume (GTV) and surrounding sub-clinical or microscopic tumor extension [2,5,8]. However, it is sometimes quite difficult, even when the operator is highly skilled, to produce a sufficient dose distribution in patients with a narrow vagina or with relapses at the cervical stump by intracavitary radiotherapy (ICR) [3]. A small but definite number of patients are not treatable with standard radiotherapy due to the inability to insert the tandem into the cervical os. Interstitial radiotherapy is often helpful in such cases, but its success rate is strongly dependent on the skill of the operator.

It is anticipated that external radiotherapy will be an alternative to ICR or interstitial radiotherapy for patients who cannot be treated with standard radiotherapy. However, a fundamental shortcoming of external radiotherapy is that detrimental set-up error and internal organ motion may occur. To overcome the shortcoming of external radiotherapy, we have developed a fluoroscopic real-time tumor tracking radiotherapy (RTRT) system [11]. We have previously reported the usefulness of orthogonal X-ray imaging by the RTRT system as a precise set-up procedure for prostate cancer [6,7,10,12]. The purpose of the present study was to investigate the feasibility of set-up using three internal fiducial markers and fluoroscopic measurements for gynecological malignancy. Additionally, uncertainties in usual manual set-up were calculated using the accumulated

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data in the RTRT system. Appropriate margins for planning target volume were estimated using the population-based methods both in manual set-up and in the set-up using RTRT system.

2. Materials and methods

The real-time tumor-tracking system consisted of two or four sets of fluoroscopes equipped with a conventional linear accelerator in a radiotherapy room (Mitsubishi Electronics Co., Ltd, Tokyo), as reported in a previous study [11]. In brief, the fluoroscopes were equipped obliquely to the position of the table to reduce the thickness of the human body passed by the diagnostic X-ray and to improve the visibility of the fiducial markers. Using two sets of fluoroscopic images, it has previously been shown that the 3D coordinates of the three markers can be determined with an accuracy of ± 0.5 mm in static phantoms [11].

If ICR and interstitial radiotherapy were abandoned and the patients agreed to enter this study, three 2 mm-radiopaque gold markers (99.9% Au) were implanted in or near the tumor by a trans-vaginal approach using specially-made equipment (Medikit Co., Ltd, Tokyo). After gold markers were implanted, a CT-scan was performed using 1 mm slice thickness for the level involving the tumor mass and three markers. The coordinates of the CTV and three markers were registered and sent to the website of the RTR system online.

Assuming that the tumor is solid and the 3D relationship between the tumor and the marker does not change significantly, the tumor position can be adjusted to the planned position by translational parallel shift of the treatment couch. After performing the manual set-up of patients on the treatment couch using skin markers and laser localizers in the treatment room by the usual method, two orthogonal fluoroscopic images were taken using the RTRT system. The 3D distance between each marker was calculated using a software in the RTRT system. If the deviation of the 3D distance between each marker was larger than 3.0 mm comparing to the planning CT at the initial treatment day, we assumed that gold marker had migrated from the initial position during the period between CT scan and treatment and thus the fiducial markers were not used for further set-up. If there was less deviation, we assumed that there was no significant migration of the marker and commenced set-up using the three markers. The difference between the coordinates of the center of gravity of the three markers from the planned position relative to the isocenter was calculated and adjusted by moving the treatment couch [7]. After this adjustment, the irradiation was delivered. During the irradiation, fluoroscopic images can be taken at a speed of 2–30 times a second, and one of the markers can be tracked automatically by a real-time pattern recognition algorithm. However, real-time tracking of the marker during the irradiation was not routinely performed for gynecologic malignancy because it was assumed that minimal intra-fractional movement of the target volume would occur in this protocol setting [8]. We took two orthogonal X-ray images while the gantry was moving to the next portal angle and calculated the intra-fractional shift of the center of gravity of the three markers several times during each treatment. If the shift was larger than 3–5 mm, the table position was corrected and the treatment was continued. No external immobilization device was used throughout the planning and treatment.

We call this boost technique as three-dimensional conformal boost (3DCB) in this study. The multi-leaf collimator consisted of 60 leaves of 5 mm width at the isocenter inside of 10×10 cm^2 field and 10 mm width outside of the field, respectively.

As an example of the data analysis, Fig. 1 shows the pooled data of the discrepancy between the planned and actual coordinates of the center of gravity in one patient over four treatment days plotted against the minutes after the manual set-up on the treatment couch. At time zero, the patient is positioned using laser beam localizers to the skin surface so that the discrepancy at time zero is attributed to the set-up error after manual set-up. The couch is adjusted between time 0 and 2 min using gold marker. At 2 min, the position of the marker gradually changed, suggesting intra-fractional organ motion or involuntary movement of the patient. The table position was adjusted again before the start of the next portal irradiation. From 2 to 17 min, the discrepancy was distributed from -2.47 to 3.65 mm and required adjustment of the table position during irradiation several times each day for this patient.

In this study, the inter-fractional set-up error (i.e., external error) both in the manual set-up and in the internal gold marker set-up, and the intra-fractional internal organ motion (i.e., internal error) were analyzed from the coordinates of the center of gravity of three internal gold markers which were stored automatically in the RTRT system in each set-up. Since two orthogonal X-ray images were taken within a period of several minutes, the organ

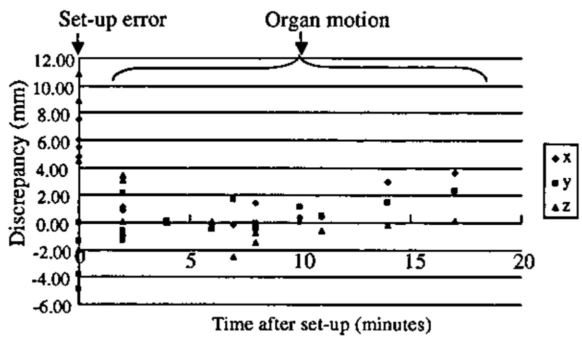

Fig. 1. Discrepancy in mm between the planned and actual positions of the center of gravity of three internal fiducial markers according to the time after manual set-up (time zero) followed by set-up and verification using orthogonal X-ray images. The discrepancy over 2–17 min is consistent with error due to organ motion and patient motion. The data points in four sessions of irradiation were overlapped in this figure.

motion or patient motion over this period can be detected. The rotation angle of the actual coordinates from the planned coordinates around the x-axis (α, degrees), y-axis (β, degrees), and z-axis (γ, degrees) was calculated using the three markers [9,12]. Geometrical uncertainties were evaluated for both systematic and random external and internal errors [15]. The discrepancy of the actual coordinates of the center of gravity from the planned position in the manual set-up was regarded as the external error in the manual set-up. The external error in the gold marker set-up was the deviation of the center of gravity of the three gold markers from its planned position after the gold marker set-up. The intra-fractional motion of the marker during the irradiation was regarded as the internal error during the irradiation.

3. Results

Twelve patients (median age, 60 years; range, 33–78 years) with squamous cell carcinoma at the uterine cervix or stump of the cervix were enrolled after obtaining written consent for participating in the present study. Two patients experienced drop of a marker before CT scan and not treated with the 3DCB. The reason for the drop of the marker was not certain. There was no relationship between the size of the tumor and the drop of the marker. The discrepancy in distances between each marker at the first treatment day from the planning CT was distributed from 0 to 2.8 mm at the median of 0.8 mm in the 10 patients. These discrepancies were judged to be un-correctable and accepted to be used in the gold marker set-up. Thus, 83% (10 out of 12) eligible patients were treated with 3DCB as planned.

The 10 patients were available for the investigation of set-up error and internal organ motion. The external error in manual set-up was estimated from 48 measurements, the external error in gold marker set-up was estimated from 48 measurements, and the intra-fractional error was estimated from 105 measurements in the 10 patients.

The external error in manual set-up was 0.4 ± 3.6, -0.6 ± 4.5, and 0.9 ± 4.6 mm (mean $\pm$ SD) for the x (left-right), y (cranio-caudal), and z (antero-posterior) directions, respectively. The external error in gold marker set-up was 1.0 ± 1.2, 0.3 ± 1.1, and 0.9 ± 1.7 mm for the x, y, and x directions, respectively. The 95% confidence interval of intra-fractional motion of the marker, or internal error during the irradiation, was 1.4–3.4, 1.9–2.5, and 2.4–4.2 mm in the x, y, and z directions, respectively, for the treatment time of 9.4 ± 4.7 min in the 10 patients. The table position required an average of 1.8 corrections (range: 0–6 corrections) in one treatment to correct the dislocation of the center of gravity more than 5 mm.

The standard deviation of the distribution of systematic deviations, total $\Sigma(E+I)$ was 3.8, 4.6, and 4.9 mm in the x, y, and z directions in the manual set-up using the Σ of external error and the Σ of internal error (Table 1). The total

Table 1
Statistical analyses and estimated PTV-margin in manual set-up and marker set-up

		x (mm)	y (mm)	z (mm)
Σ(ext)	Manual	3.6	4.5	4.6
	Marker	2	2	2.1
Σ(int)	Manual	1.2	1.1	1.7
	Marker	1.2	1.1	1.7
Σ(tot)	Manual	3.8	4.6	4.9
	Marker	2.3	2.3	2.7
σ(tot)	Manual	3.7	5.0	4.5
	Marker	3.3	3.0	4.2
σ(ext)	Manual	2.8	4.7	3.1
	Marker	2.2	2.2	2.7
σ(int)	Manual	2.4	2.1	3.2
	Marker	2.4	2.1	3.2
PTV-margin	Manual	10.2	12.8	12.9
	Marker	6.9	6.7	8.3

Sigma (ext): Sigma, Σ, for external error; Sigma (int): Sigma, Σ, for internal error; sigma (ext): sigma, σ, for external error; sigma (int): sigma, σ, for internal error. Sigma (tot): Sigma, Σ, for total error, taken as the systematic error; sigma (tot): sigma, σ, for total error, taken as the random error; PTV-margin: $2\Sigma(\text{tot}) + 0.7\sigma(\text{tot})$; manual: manual set-up; marker: internal gold marker set-up.

$\Sigma(E+I)$ was reduced to 2.3, 2.3, and 2.7 mm in the set-up using the gold markers. The average standard deviation of the distribution of random deviations, total $\sigma(E+I)$ was 3.7, 5.0, and 4.5 mm in the manual set-up using the σ of external error and the σ of internal error. The total $\sigma(E+I)$ was 3.3, 3.0, and 4.2 mm in the gold marker set-up. The appropriate PTV margin was estimated to be 10.2, 12.8, and 12.9 mm in the manual set-up and 6.9, 6.7, and 8.3 mm in the gold marker set-up, respectively, using the equation PTV margin $= 2(\text{total } \Sigma) + 0.7(\text{total } \sigma)$ [13].

The mean rotational error was 0.5, 0.7, and $-2.9°$ for α, β, and γ, respectively. The standard deviation of systematic error of rotation was 7.6, 4.3, and 3.8° for α, β, and γ, respectively. The average random error of rotation was 8.4, 4.3, and 3.0° for α, β, and γ, respectively.

4. Discussion

Stroom et al. have shown that a PTV margin size which ensures at least 95% of the dose (on average) to 99% of the CTV of cervical cancer, appears to be about 1 cm (7 mm for systematic and random error of the pelvic bone and 3 mm for intra-pelvic organ motion and delineation error) [13]. The present study showed that the appropriate PTV margin was 10.2, 12.7, and 12.9 mm in the manual set-up for the x, y, and z directions, and suggested that the estimation of Stroom et al. was reasonable. Stroom et al. have also shown that online set-up corrections using bony landmarks in anterior–posterior portal images during radiotherapy are useful to reduce the PTV margin reduction to about 5 mm [14]. However, Buchali et al. have examined the impact of the filling status of the bladder on the movement of the uterus and concluded that the PTV margin should be 15 mm cranio-caudaly [1]. Kaatee et al. recently investigated organ movement in patients with cervical cancer using fluoroscopic electronic portal imaging and radiopaque markers [4]. They reported that the internal cervical movement was considerably larger than the movement of the pelvic bony structures.

In the present study, the systematic and random external errors decreased significantly using the internal fiducial markers comparing to the manual set-up using skin markers. However, the PTV margin required in the gold marker set-up was larger than we had expected. The residual error in the gold marker set-up was probably due to the distortion of the soft tissue and/or internal organ motion during the period of set-up.

Since we did not use gated irradiation, there was no difference in internal error between the manual set-up and gold marker set-up in this protocol setting. The appropriate PTV margin was suggested to be 6.9, 6.7, and 8.3 mm for the lateral, cranio-caudal, and antero-posterior directions. Since we need to add margins for delineation error, deformation, and rotation error, the appropriate PTV margin must be 2–3 mm larger than these values.

There were several cases with the standard deviation of internal organ motion more than 5 mm. In fact, since the table position was corrected when the shift was more than 3–5 mm, there might have been more dislocation if the table position was not corrected during the irradiation. Thus, the appropriate PTV margins described above may be too small to use in the absence of frequent observations by orthogonal X-ray imaging during the irradiation.

In conclusion, set-up of gynecological malignancy using three markers and RTRT system was useful to reduce the uncertainty due to external and internal error but still requires at least 7–8 mm PTV margin. The fluoroscopic system and three gold markers would be a useful tool to realize individual-based, precise adaptive irradiation for the moving, shrinking, and deforming gynecological malignancy.

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Int J Gynecol Cancer 2005, **15**, 389–397

SURGEON'S CORNER

A systematic nerve-sparing radical hysterectomy technique in invasive cervical cancer for preserving postsurgical bladder function

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Abstract. Sakuragi N, Todo Y, Kudo M, Yamamoto R, Sato T. A systematic nerve-sparing radical hysterectomy technique in invasive cervical cancer for preserving postsurgical bladder function. *Int J Gynecol Cancer* 2005;**15**:389–397.

The objective of this study is to describe a technique for preserving the autonomic nerve systematically, including the hypogastric nerves, pelvic splanchnic nerves, and pelvic plexus and its vesical branches, based on anatomic considerations for the autonomic nerves innervating the urinary bladder, in radical hysterectomies and to assess postsurgical bladder function. A nerve-sparing radical hysterectomy was carried out on 27 consecutive patients with uterine cervical cancer treated between 2000 and 2002. The FIGO stages of the disease consisted of 10 stage Ib1, 6 stage Ib2, 3 stage IIa, and 8 stage IIb. The nerve-sparing procedure was successfully completed in 22 of the 27 patients (81.5%) in the study. At 1 year after the operation, bladder symptoms were significantly improved in the nerve-sparing group compared to the non–nerve-sparing group. Urinary incontinence and abnormal (diminished) bladder sensation were observed in three of the five patients (two patients had both symptoms), for whom the nerve-sparing procedure could not be performed, but none of the 22 patients for whom the nerve-sparing procedure was performed had incontinence, and only two patients had abnormal (increased) bladder sensation ($P = 0.0034$ for incontinence and $P = 0.030$ for abnormal bladder sensation). The patients' survival was not adversely affected by the nerve-sparing procedure. Although it is still preliminary, the surgical technique described in this report is thought to be effective for preserving bladder function, and thus, the quality of life could be improved for patients with cervical cancer who are treated with a radical hysterectomy. For further evaluation of the efficacy of nerve-sparing radical hysterectomy, a prospective randomized trial needs to be performed.

KEYWORDS: autonomic nerve, bladder function, cervical cancer, nerve sparing, quality of life (QOL), radical hysterectomy.

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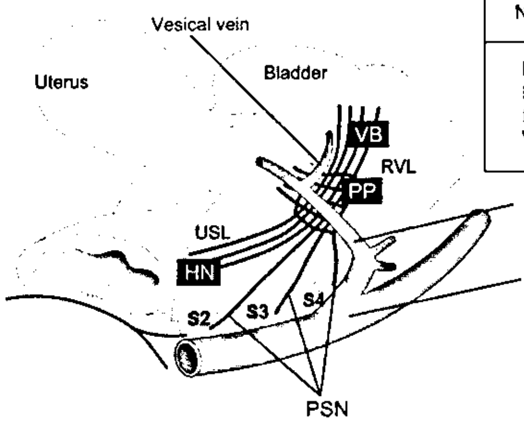
When treating cancer patients, it is important to consider how to minimize deterioration of their quality of life (QOL). Radical hysterectomies are widely performed to treat invasive cervical cancer. Intraoperative and postoperative morbidity includes urinary tract fistula, ileus, thromboembolism, lymphocyst, lymphedema, and bladder dysfunction (neurogenic bladder). Difficulty in urination after the operation impairs the QOL of patients by causing both physical and mental stress. Piver *et al.* described five classes of extended radical hysterectomy[(1)]. Type III (Wertheim–Meigs) operation is the treatment of choice for FIGO stages Ib–IIa cervical cancer in Western countries and for stages Ib–IIb in Japan. The steps of classical radical hysterectomy at which autonomic nerves may be injured are as follows: (1) hypogastric (sympathetic) nerves at resection of the uterosacral ligament at the posterior pelvic wall, (2) pelvic splanchnic (parasympathetic) nerves in dissection of lymph nodes medial to the internal iliac vein and around the deep uterine vein, (3) vesical branches of the pelvic plexus at resection of the vesico-uterine ligament, and (4) pelvic plexus at resection of the uterosacral and rectovaginal ligaments and resection of the vagina (Fig. 1). In order to maintain bladder function, those nerve networks should be preserved intact as much as possible unless these attempts sacrifice the therapeutic role of surgery. Various attempts have been made to preserve urinary function, including recently proposed autonomic nerve–preserving radical hysterectomy techniques[(2–6)]. A detailed anatomic study of the pelvic autonomic nerves was conducted by one of the authors (T.S.) and his colleagues[(7)], providing us with clues on how to develop a theoretical approach for preserving the autonomic nerves when performing a radical hysterectomy. In this preliminary report, we describe a technique for systematic autonomic nerve preservation, which was developed by our institute based on anatomic considerations.

Materials and methods

A total of 27 patients who underwent radical hysterectomies during the period from January 2000 to December 2002 were included in the study. The patients were at the following FIGO stages: 10 at stage Ib1, 6 at stage Ib2, 3 at stage IIa, and 8 at stage IIb. Nineteen of the 27 patients had squamous cell carcinoma, 2 had adenocarcinoma, 5 had adenosquamous carcinoma, and 1 had small-cell carcinoma. A pelvic and para-aortic lymphadenectomy, at least to the level of the inferior mesenteric artery, was carried out in all patients as previously reported[(8)]. The diameter of the tumor and the length of the resected vagina were measured on the extirpated uterus specimen. Postoperative whole-pelvic external radiation therapy (50 Gy) was employed when there was lymph node metastasis or histologically confirmed parametrial invasion. When the tumor had invaded the lymphatic or vascular channels, we treated the patient with cisplatin-based chemotherapy for three to six cycles, unless the patient refused this treatment. The follow-up period ranged from 12 to 48 months (median 29 months).

Statistical analysis

Categorical variables were analyzed using the Chi-square test or Fisher's exact test. The median values of the continuous variables were compared by the Mann–Whitney *U* test. Disease-free survival was calculated



Nerves	Surgical steps that may involve injuries to the nerves
HN	Resection of USL
PSN	Dissection of LN
PP	Resection of RVL and Vagina
VB	Resection of VUL

Figure 1. Autonomic nerves that may be injured in radical hysterectomy. HN, hypogastric nerves; PSN, pelvic splanchnic nerves; PP, pelvic plexus; VB, vesical branches of PP; USL, uterosacral ligament; LN, lymph nodes; RVL, rectovaginal ligament; VUL, vesicouterine ligament.

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according to the Kaplan–Meier method. The statistical significance level was set at $P < 0.05$.

The systematic autonomic nerve preservation technique

Bladder function is controlled by the sympathetic nerves (mainly the hypogastric nerves) and the parasympathetic nerves (pelvic splanchnic nerves). These two nerve fibers intermingle to form the pelvic plexus (Fig. 1). The bladder is innervated by nerve fibers branching from the pelvic plexus (Fig. 2A,B). The following surgical procedure, which was based on anatomic considerations for the autonomic nerves innervating the urinary bladder[7], was used. The pelvic plexus and branches innervating the bladder are the most important nerves to preserve in a nerve-sparing radical hysterectomy, as shown in the autopsy of cadavers (Fig. 2B). Before the hysterectomy, the pelvic lymph nodes were removed. The uterosacral ligaments and rectal pillars (rectovaginal ligament) were then dissected. The first step for preserving the autonomic nerves was to identify and lateralize the hypogastric nerves and the proximal part of the pelvic plexus during the dissection of the uterosacral ligament and rectovaginal ligament. The peritoneum of the cul-de-sac was incised, and the prerectal space was developed, exposing the rectovaginal ligament between the prerectal space and the pararectal space. The hypogastric nerves and pelvic plexus are located laterally, attached to the rectovaginal ligament (Fig. 2A). After lateralizing the hypogastric nerves and the proximal part of the pelvic plexus, the nerve tissue can be preserved by selective resection of the exposed uterosacral and rectovaginal ligaments.

The next step for preserving the autonomic nerves is to identify the pelvic splanchnic nerves fusing to the pelvic plexus. The cardinal ligament lymph nodes were dissected to clearly skeletonize the deep uterine vein, using a suction apparatus. We carefully preserved the pelvic splanchnic nerves arising from the sacral surface. Then, the anterior part of the vesico-uterine ligament was dissected, and the ureteral tunnel was developed. Since the vesical vein drains from the bladder to the deep uterine vein coursing through the posterior part of the vesico-uterine ligament, separation and cutting of the vesical vein is required in order to resect the uterus (Fig. 3). Then, the fatty connective tissue of the posterior part of the vesico-uterine ligament was dissected, without disturbing the main part of the vesical nerve branches of the pelvic plexus, using Kelly forceps introduced from the ventral to dorsal direction (Fig. 4). A small portion of the vesical branches around the ureter may be sacrificed at this step. This enabled identification of the plane between the pelvic plexus and the paracolpium (Fig. 5A,B). Next, the blood vessels of the cardinal ligament were resected at their origin from the internal iliac vein. Careful rubbing of the deep uterine vein in an upward (ventral) direction to its point of attachment to the paracolpium enabled the lower (dorsal) nerve tissue to be spared (Fig. 6). The preserved pelvic splanchnic nerves arise from the sacral surface and fuse to the pelvic plexus parallel to the rectovaginal ligament that composes the medial side of the pararectal space. The space between the pelvic plexus and the paracolpium was developed anteroposteriorly by using Kelly forceps or Metzenbaum scissors (Fig. 7). Using this approach, the pelvic plexus was put to the

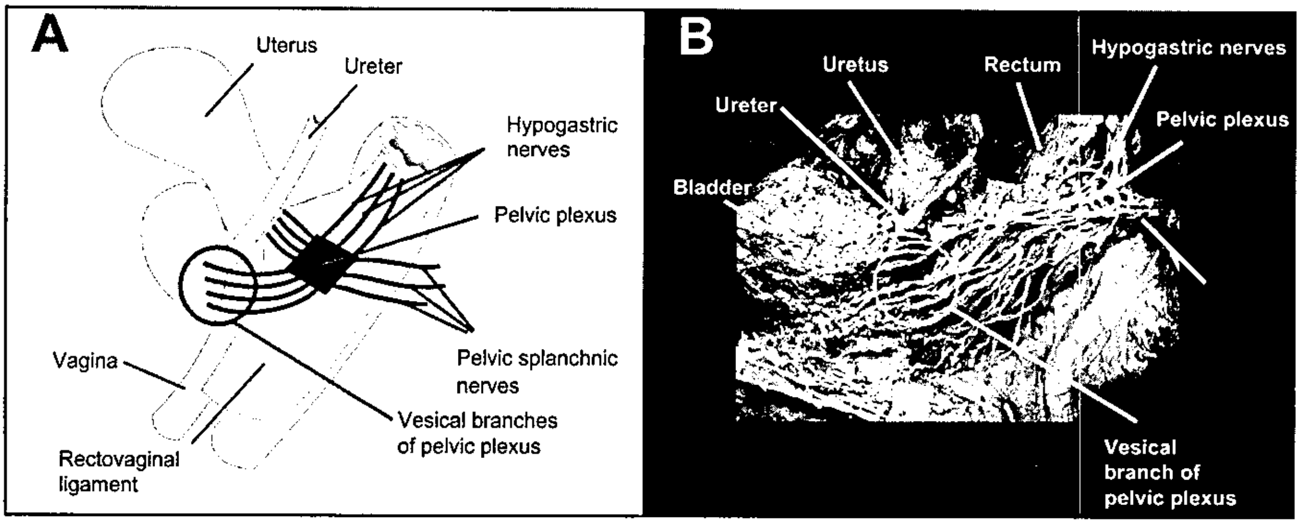

Figure 2. A) Illustration of autonomic nerves that control bladder function and B) anatomic distribution of autonomic nerves in cadavers.

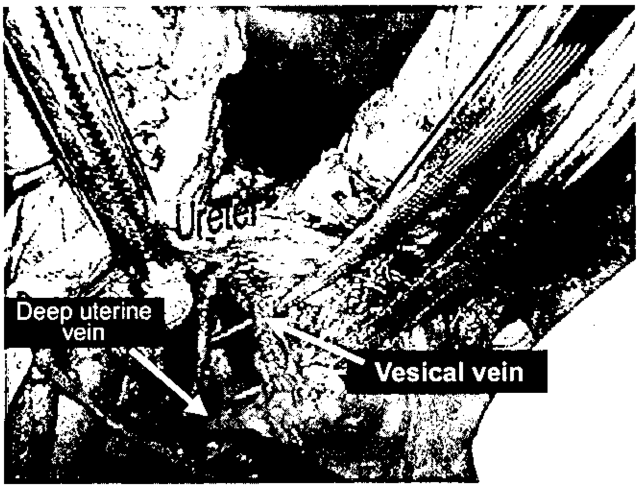

Figure 3. Separation and cutting of the vesical vein in the posterior part of the vesico-uterine ligament. It should be noted that the deep uterine vein had not been cut yet at this step.

side. Then, the uterine branch of the pelvic plexus was cut, which enabled dissection of the paracolpium without involving the pelvic plexus (Fig. 8). Finally, a sufficient length of the vagina was cut by pulling the uterus upward and lateralizing the pelvic plexus. These procedures enabled systematic preservation of the autonomic nerves (Fig. 9).

Results of nerve-sparing radical hysterectomy

The autonomic nerves were completely preserved, at least on one side, in 22 of the 27 patients (group A). For 5 of the 27 patients, the space between the pelvic plexus and the paracolpium could not be developed and therefore the pelvic plexus was not put laterally. The vaginal canal was cut without selective dissection of the uterine branches of the pelvic plexus for these patients (group B). The nerve-sparing procedure in these patients was unsuccessful due to bleeding from the paracolpium and the surgeon's inexperience in performing the procedure. The completion rate of the procedure was 81.5%. The surgical and postsurgical clinicopathologic details on the 27 patients are shown in Table 1. The 22 patients in group A ranged in age from 35 to 60 years (median age 43 years), and the 5 patients in group B ranged in age from 31 to 64 years (median age 46 years). In the group A patients, there were six with stage Ib1, six with stage Ib2, three with stage IIa, and seven with stage IIb cancer. For the stage IIb patients, the nerve-sparing procedure was employed on the uninvaded side only. In the group B patients, there were four with stage Ib1 and one patient with stage IIb. The stage distribution in each group was not significantly different (P = 0.15). The tumor diameter in the group A and B patients ranged from 11 to 70 mm (median 39 mm) and from 12 to 50 mm (median 34 mm), respectively. There was no statistically significant difference between the two groups (P = 0.57). The length of the resected vagina in the patients in each group ranged from 20 to 45 mm (median 30 mm) and from 25 to 45 mm (median 35 mm), respectively, with no significant difference between the two groups (P = 0.30). Therefore, the inability to complete the nerve-sparing procedure does not seem to be related to the patient's age, tumor stage, tumor diameter, or length of the resected vagina.

Figure 4. Dissection of fatty connective tissue (arrowhead) of the posterior part of the vesico-uterine ligament. A portion of the vesical branches of the pelvic plexus, which pass around the ureter, may be sacrificed at this step.

The length of operation time for nerve-sparing and non–nerve-sparing radical hysterectomy ranged from 387 to 791 min (median 515 min) and from 345 to 648 min (median 370 min), respectively. The difference was not statistically significant (P = 0.13) although the length of operation time for the nerve-sparing group was about 2 h longer than that for the non–nerve-sparing group. Our university hospital is a central teaching hospital, and this may partly explain the wide distribution of operation time. Blood loss in nerve-sparing and non–nerve-sparing radical hysterectomy ranged from 640 to 4185 mL (median 1400 mL) and from 450 to 2400 mL (1160 mL), respectively. The difference was not significant (P = 0.62).

Radiation therapy was performed postoperatively in one patient from group A. Radiation therapy combined with chemotherapy was carried out for two patients from group A and none from group B. Chemotherapy was used postoperatively in 15 patients from group A and 3 from group B. None of the

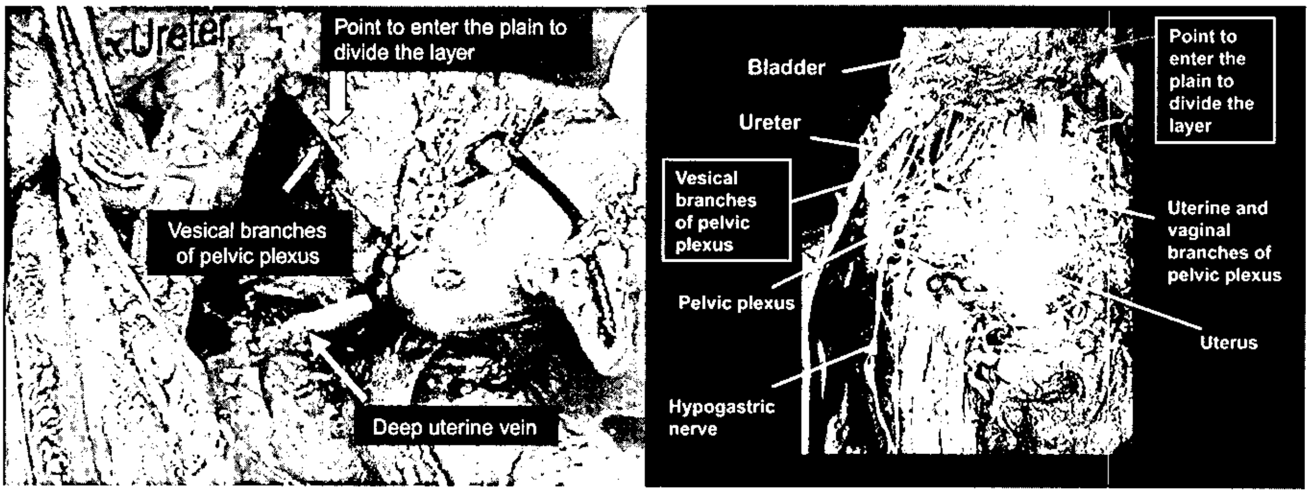

Figure 5. A) Vesical branches of the pelvic plexus after dissection of the vesico-uterine ligament and the point at which the plane must be entered to divide the vesical branches/pelvic plexus and the paracolpium and B) the same point at which the plane must be entered to divide the layers in the cadaver.

patients took cholinergic agents or α1 blocker during the observation period. The duration of disease-free survival in the group A patients ranged from 13 to 48 months and in the group B patients, from 12 to 36 months. One stage IIb patient in group A suffered a recurrence in the pelvis 13 months after the operation but was successfully treated with radiation therapy. The cumulative disease-free survival rate for the group A and group B patients at 24 months was 95.5% and 100%, respectively (Fig. 10).

At 1 year postsurgery, three patients from group B had stress urinary incontinence, but none from group A had urinary incontinence ($P = 0.0034$). In group A, there were 20 patients with normal bladder sensation and two with increased bladder sensation, but none of the patients had a reduced desire to void. In group B, there were three patients (60%) with a reduced desire to void. Abnormal bladder sensation was more frequently observed in the group B patients ($P = 0.030$).

Discussion

Bladder dysfunction, typical of vesicovaginal fistula, ureterovaginal fistula, or urination difficulty in patients who have undergone radical hysterectomy, causes deterioration in the patients' QOL due to physical and mental stress. Many gynecologic oncologists have become knowledgeable about the anatomic

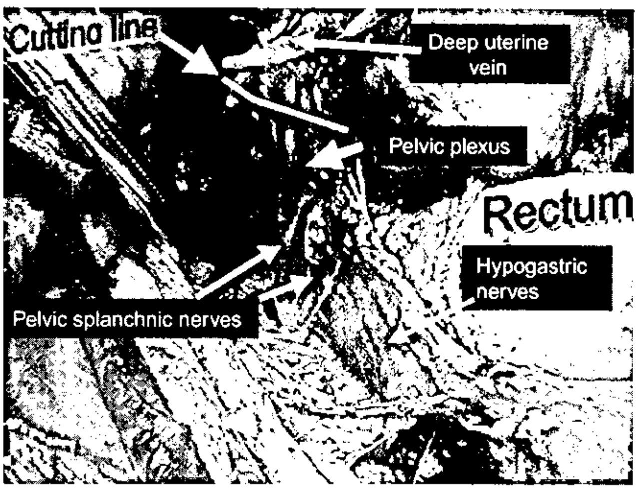

Figure 6. The cutting line between the pelvic plexus and its uterine branch, which is shown after resecting and pulling upward of deep uterine vein.

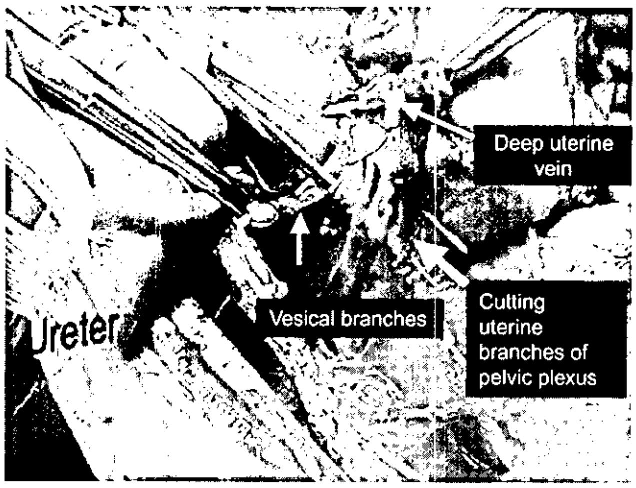

Figure 7. Separation of the pelvic plexus from the rectovaginal ligament.

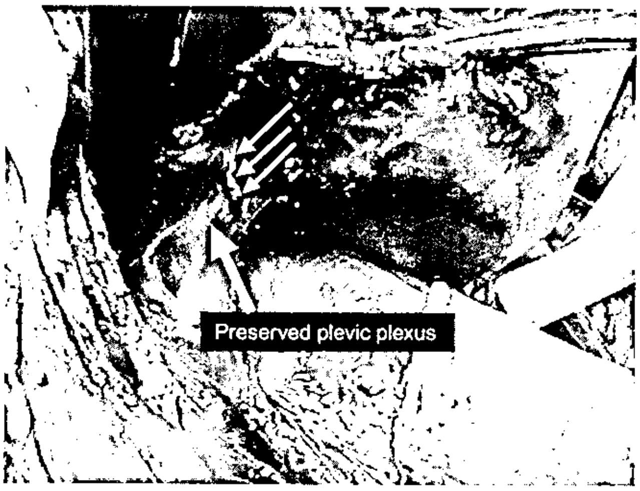

Figure 8. Separated and retracted pelvic plexus after the autonomic nerve preservation.

distribution of the nerves controlling bladder function, and recently, a great deal of interest has been shown in autonomic nerve-sparing surgical techniques[2–6]. It has been known for a long time that the hypogastric nerves, pelvic splanchnic nerves, pelvic plexus, and the distal part of the pelvic plexus (the vesical nerve branch) are important in urination physiology[9,10], and many studies have shown that bladder dysfunction can be reduced by minimizing the extent of the radical hysterectomy[11–13]. However, gynecologic oncologists should balance the cure of disease and QOL, namely, oncologic priorities of removal of disease and all its potential routes of local spread, and bladder function. We have attempted to establish a surgical technique that will preserve the autonomic nerves

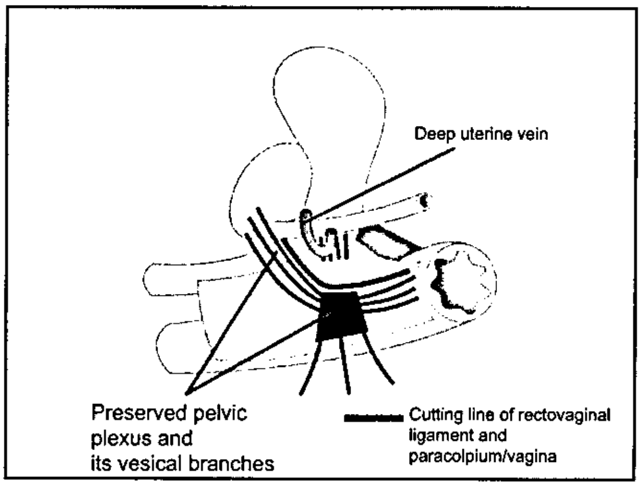

Figure 9. Illustration of systematic autonomic nerve preservation and the cutting line of the rectovaginal ligament, paracolpium, and vagina.

without sacrificing the radicality of the radical hysterectomy procedure.

Piver *et al.* proposed five classes of extended radical hysterectomy[1], and these classes are often used now to discriminate between the types of surgery needed. The surgical technique of Wertheim–Meigs is considered to correspond to type III[14]. In a radical hysterectomy, the uterosacral ligament is resected at the posterior pelvic wall. Hypogastric nerves should be separated from the uterosacral ligaments before cutting the ligament deeply at the posterior pelvic wall in radical hysterectomy to preserve the hypogastric nerves[15]. This technique was also previously described by Sakamoto and Takizawa[16] and is the popular technique employed by many gynecologic oncologists in Japan. The uterosacral ligament may contain lymphatic channels draining caudally to sacral nodes and common iliac nodes. We routinely dissect sacral nodes and common iliac nodes including those of the medial area of common iliac arteries. We previously reported the results of systematic lymphadenectomy for cervical cancer[8]. The incidence of sacral node metastasis was only 1.9%. For the sake of oncologic pertinence in nerve-sparing radical hysterectomy, we have employed systematic lymphadenectomy including sacral nodes, medial part of the common iliac nodes, and para-aortic nodes, and applied a nerve-sparing technique to stage Ib disease and to the uninvaded side of stage II disease.

In a radical hysterectomy, the pelvic plexus is in close proximity to the paracolpium at the depth at which the vagina should be dissected. If separation of the pelvic plexus from the paracolpium is insufficient, the pelvic plexus will be injured when the vagina is amputated. Possover *et al.* recently reported that preservation of the pelvic splanchnic nerves and pelvic plexus, with the middle rectal artery serving as a landmark for identification, is important for preserving bladder function[6]. If the cardinal ligament below the middle rectal artery is dissected, the pelvic splanchnic nerves will be injured. Moreover, if the uterosacral ligaments and rectovaginal ligaments are excised deeply at the posterior wall of the pelvis, the hypogastric nerves and pelvic plexus may also be excised. Therefore, it is not clear, just from hearing that a Piver's type III operation has been performed, whether or not the hypogastric nerves, pelvic splanchnic nerves, and pelvic plexus have been preserved. Thus, accurate evaluation of bladder dysfunction after radical hysterectomy is not possible without detailed information on the surgical procedure used.

The most important step that must be performed in our technique is to separate the pelvic plexus from the

Table 1. Surgical and postsurgical information on the 27 patients with cervical cancer who underwent a radical hysterectomy intended to preserve the autonomic nerves

Case	Age	Stage (histotype)	Diameter of tumor (mm)	Length of RV (mm)	Nerve preservation	LNM	LV	RT	Symptom (1 year after operation)		DFS (months)
									Incontinence	Bladder sensation	
Group A											
1	39	Ib1 (S)	20	40	+	−	+	−	−	Normal	36
2	42	Ib1 (S)	11	30	+	−	−	−	−	Normal	33
3	36	Ib1 (S)	23	20	+	−	−	−	−	Normal	19
4	38	Ib1 (S)	39	40	+	−	+	−	−	Increased	48
5	39	Ib1 (AS)	39	42	+	−	+	−	−	Normal	36
6	57	Ib1 (SM)	18	20	+	−	+	−	−	Normal	15
7	39	Ib2 (S)	45	26	+	−	+	−	−	Normal	39
8	36	Ib2 (S)	45	35	+	+	+	+	−	Increased	37
9	60	Ib2 (S)	70	20	+	−	+	−	−	Normal	20
10	44	Ib2 (S)	50	25	+	−	+	−	−	Normal	19
11	35	Ib2 (AS)	40	25	+	−	−	−	−	Normal	18
12	49	Ib2 (A)	60	35	+	−	−	−	−	Normal	17
13	44	IIa (S)	30	45	+	−	+	−	−	Normal	29
14	35	IIa (S)	25	32	+	+	+	−	−	Normal	18
15	54	IIa (AS)	35	30	+	−	+	−	−	Normal	17
16	44	IIb (S)	55	40	+	−	−	+	−	Normal	46
17	52	IIb (AS)	17	32	+	−	+	−	−	Normal	44
18	38	IIb (S)	25	30	+	+	+	+	−	Normal	41
19	45	IIb (A)	50	30	+	+	+	−	−	Normal	14
20	54	IIb (S)	37	30	+	−	+	−	−	Normal	13[a]
21	42	IIb (S)	20	30	+	−	+	−	−	Normal	31
22	49	IIb (S)	50	25	+	−	+	−	−	Normal	24
Group B											
23	40	Ib1 (S)	35	30	−	−	−	−	+	Reduced	32
24	61	Ib1 (S)	25	40	−	−	+	−	+	Reduced	35
25	64	Ib1 (S)	34	25	−	−	+	−	−	Reduced	36
26	46	Ib1 (S)	12	30	−	−	−	−	−	Normal	12
27	31	IIb (AS)	50	40	−	−	+	−	+	Normal	28

RV, resected vagina; LNM, lymph node metastasis; LV, lymph-vascular space invasion; RT, radiation therapy; DFS, disease-free survival; S, squamous cell carcinoma; AS, adenosquamous carcinoma; SM, small-cell carcinoma; A, adenocarcinoma.

[a]Patient had a recurrence in the pelvis, which was successfully controlled by radiotherapy.

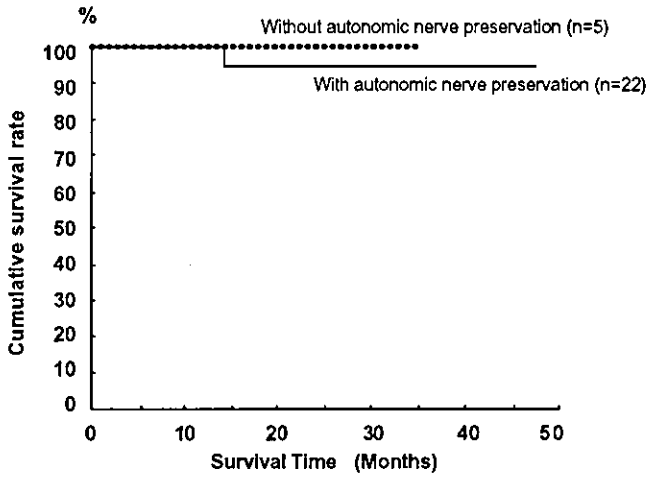

Figure 10. Disease-free survival of patients treated with radical hysterectomy with or without systematic preservation of the autonomic nerves.

paracolpium and to selectively dissect the uterine branch of the pelvic plexus. The sympathetic nerves (hypogastric nerves) and parasympathetic nerves (pelvic splanchnic nerves) fuse to form the pelvic plexus. This important anatomic structure spreads its branches to the bladder. After separating the pelvic plexus from the paracolpium and the rectovaginal ligament (paracervical tissues), we can remove a sufficient length of the vagina, without involving the pelvic plexus. Therefore, we evaluated bladder function by comparing the group in which only the paracolpium was selectively dissected after the uterine branch of the pelvic plexus was cut with the group in which the paracolpium was dissected without dissection of the uterine branches. This study has shown that the bladder function of the group in which only the paracolpium was dissected after dissection of the uterine branches of the pelvic plexus was better preserved than that of the group in which the paracolpium was dissected without dissection of the uterine branches.

We employed our technique for autonomic nerve preservation to the uninvaded side in patients with stage IIb uterine cervical cancer. It has been reported, in experimental animals, that normal urinary function could be maintained when at least one side of the sympathetic nerve was preserved(17). These data suggest that normal urinary function can be maintained by applying the operation with autonomic nerve preservation to the uninvaded side in patients with stage IIb cervical cancer, who have parametrial invasion only on one side.

In conclusion, our technique to preserve the pelvic autonomic nerves, which is based on a detailed anatomic study, is relatively easy to perform and is a feasible technique to employ in the treatment of invasive cervical carcinoma. Our aim of improving the long-term prognosis of bladder function seems to have been achieved because 1 year after the operations, the patients' urinary function is almost normal. A detailed urodynamic study on patients treated with our nerve-sparing radical hysterectomy will be reported in a further paper. The nerve-sparing procedure was thought to give patients better QOL with regard to bladder function, with no additional adverse effects on radical hysterectomy. For further evaluation of the efficacy of nerve-sparing radical hysterectomy, a prospective randomized trial needs to be performed.

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Lymphatic mapping and sentinel node identification as related to the primary sites of lymph node metastasis in early stage ovarian cancer

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Abstract

Objective. We evaluated the primary sites of lymph node (LN) metastasis in patients during the early stage of ovarian cancer.

Methods. Study 1: patients with clinical stage I and II common epithelial ovarian carcinoma (n = 150) underwent systematic retroperitoneal LN dissection of the pelvic and paraaortic areas. The relationship between the incidence and location of LN metastasis and clinical and histological characteristics was examined. Study 2: we studied 11 women with endometrial or fallopian tube tumors. At laparotomy, activated charcoal solution was injected into the unilateral cortex of the ovary. Ten minutes later, the retroperitoneal spaces were opened and charcoal uptake within the pelvic lymph node (PLN) and paraaortic node (PAN) as far as the level of renal vein was examined.

Results. Study 1: The incidence of LN metastasis by stage was 6.5% (8/123) in stage I and 40.7% (11/27) in stage II. Among 19 patients with LN metastasis, 14 had only PAN, 2 had only pelvic LN, and 3 had both PAN and PLN metastases. Metastasis was limited to the ipsilateral side in 12 (63%) patients, but was bilateral in 5 (26%) and contralateral to the neoplastic ovary in 2 (11%). Positive peritoneal cytology was significantly ($P < 0.05$) correlated with lymph node metastasis. Study 2: Lymphatic channels along the ovarian vessels were identified in all injected ovaries. Charcoal was deposited in the LN of all patients. The locations of these nodes included PAN in all patients, common iliac node in three, and external iliac node in one.

Conclusion. PAN is the primary site of LN metastasis in ovarian cancer. Bilateral PAN dissections are necessary to determine the extent of tumors even in stage I ovarian carcinoma.

Keywords: Ovarian cancer; Sentinel node; Lymph node; Metastasis

Introduction

The incidence of positive lymph nodes (LNs) in patients with early (stage I) ovarian cancer is 5.1–15% [1,2]. Thus, over 85% of patients who undergo retroperitoneal lymphadenectomy (RPLND) and who do not benefit from the procedure must endure the associated increase in operative time and blood loss, as well as an increased risk of lymphocyst and lymphedema. In addition, the benefit of RPLND to the survival of patients with early ovarian epithelial cancer confined to the ovary has not been demonstrated. Thus, many gynecological oncologists perform only selective ipsilateral retroperitoneal sampling when disease is grossly confined to one ovary, although the most appropriate and reliable technique for assessing pelvic and paraaortic nodes (PANs) remains uncertain. However, metastasis to retroperitoneal lymph nodes is an important route of ovarian carcinoma spread. To elucidate how ovarian carcinoma spreads to the lymph nodes, we have been dissecting systematic pelvic and paraaortic nodes when the primary tumor could be surgically reduced to below 2 cm in diameter during an initial operative procedure, or at surgery after chemotherapy. Our aim was to reduce the amount of dissection required, so we evaluated the incidence and location of lymph node metastasis in patients with clinical stage I and II ovarian carcinomas to pursue the primary sites of lymph node metastasis during the early stage of the disease. We also designed a pilot study to investigate lymphatic drainage and to identify sentinel nodes.

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Patients and methods

Analysis of lymph node metastasis

Between April 1987 and April 2002, 150 patients (age range, 24–78 years; mean, 51.6 years) with clinical stage I and II epithelial ovarian carcinoma underwent systematic retroperitoneal lymph node dissection in the pelvic and paraaortic area during initial surgery at the Department of Obstetrics and Gynecology, Hokkaido University Hospital and affiliated Hospitals. According to the intra-abdominal status of the tumor and distant metastasis without consideration for lymph node status, 123 patients were in stage I and 27 were in stage II. Histological type, diameter of the primary tumor, peritoneal cytology, and volume of ascites were confirmed. Patients whose tumors were of low-malignant potential were not included. All of the women underwent extended total hysterectomy, bilateral salpingo-oophorectomy, and retroperitoneal lymphadenectomy of the pelvis and paraaorta up to the level of the renal vein. Lymphadenectomy began with resection of the pelvic lymph nodes (PLNs), including common iliac, external iliac, interiliac, obturator, medial deep inguinal, lateral deep inguinal, parametrial (cardinal ligament), and sacral nodes. This was followed by resection of the paraaortic lymph nodes along the aorta and the inferior vena cava including interaortocaval, preaortic, latero aortic, retroaortic, precaval, latero caval, and retrocaval lymph nodes up to the site of renal vein divergence. The incision was made in the midline, beginning at the symphysis pubis, ending at 5–8 cm above the umbilicus, skirting the left side of the umbilicus. It took, on average, 2–3 h to accomplish the retroperitoneal lymphadenectomy. The loose areolar tissue surrounding the vessels was cut and completely removed from the fat tissue containing lymph nodes. The nomenclature of retroperitoneal lymph nodes was based on the definitions in the *General Rules of Clinical Management of Ovarian Tumours*, edited by the Japan Society of Obstetrics and Gynecology [3]. Dissected lymph nodes were submitted for routine hematoxylin and eosin staining. The total number of dissected lymph nodes was counted microscopically by pathologist. All lymph nodes were counted, regardless of the size. The dissected lymph nodes ranged in size from 2 mm to 1.5 cm.

The chi-square test and the Mann–Whitney rank sum test assessed differences in clinical and histological characteristics. Survival curves were obtained using the Kaplan–Meier method. The statistical significance of differences from survival curves was determined using a log-rank test. A P value below 0.05 was considered statistically significant.

Lymphatic mapping

We investigated lymphatic drainage and identified sentinel lymph nodes with the objective of reducing the amount of required dissection.

Eleven women (average age, 58.5 years; range, 49–71 years) with endometrial tumors (n = 10) and with a fallopian tube tumor (n = 1) provided written, informed consent to participate in the study. All of the women underwent extended total hysterectomy, bilateral salpingo-oophorectomy, and RPLND of the pelvis and the paraaorta up to the level of the renal vein as mentioned above. CH40 (1 ml) was composed of 10 mg of carbon particles 20 nm in diameter (Mitsubishi #40 carbon, Mitsubishi Kasei, Japan) and 4 mg of polyvinyl pyrolidone K-30 (Han-i Kagaku, Japan). At laparotomy, CH40 (0.05–0.2 ml) was injected into the unilateral cortex of the ovary using a 23-gauge needle. Pathology of nine samples of endometrial cancer revealed the endometrioid type and another was carcinosarcoma. The fallopian tubal cancer was serous papillary adenocarcinoma. Two of the 11 patients had microscopic metastases in paraaortic nodes according to a pathological review. Ten minutes after injection, the retroperitoneal spaces were opened. Uptake of CH40 within the pelvic and the paraaortic regions up to the level of the renal vein was visually identified and then all lymph nodes were dissected.

Results

Incidence and location of lymph node metastasis

The total mean number of dissected lymph nodes was 64.7 ± 3.1 (mean ± SE) (Table 1). The mean numbers of dissected pelvic and paraaortic lymph nodes were 44.9 ± 2.3 and 18.6 ± 1.7, respectively. The mean number of dissected lymph nodes, tumor size, and volume of ascites did not significantly differ between patients with and without metastatic nodes (Table 1). Positive peritoneal cytology was significantly ($P < 0.05$) correlated with lymph node metastasis.

Table 1
Tumor size, volume of ascites, number of dissected lymph node, peritoneal cytology between patients with and without metastatic nodes

	(n = 150)	LN-negative (n = 131)	LN-positive (n = 19)	
Age (years)	51.6 ± 0.9	51.2 ± 1.0	53.9 ± 2.7	N.S. (P = 0.32)
Tumor size (cm)	13.2 ± 0.5	13.4 ± 0.6	12.4 ± 1.95	N.S. (P = 0.53)
Ascites (ml)	305.7 ± 79.9	313.6 ± 88.8	267.9 ± 161.5	N.S. (P = 0.85)
Number of lymph nodes dissected	64.7 ± 3.1	62.2 ± 3.4	77.5 ± 8.1	N.S. (P = 0.093)
Peritoneal cytology				
Positive	36	28	8	($P < 0.05$)
Negative	114	103	11	

Table 2
Histology and lymph node metastases

Histology	Number of cases	Lymph node metastasis		Positive rate (%)	Stage I (positive LN)	Stage II (positive LN)
		Negative	Positive (PAN only)			
Mucinous[a]	49	47	2 (1)	4.1	48 (2)	1 (0)
Clear cell[b]	46	38	8 (7)	17.4	42 (5)	4 (3)
Serous[c]	35	30	5 (3)	14.3	24 (1)	11 (4)
Endometrioid[d]	15	12	3 (2)	20.0	8 (0)	7 (3)
Undiff[e]	2	2	0 (0)	0	0 (0)	2 (0)
Mixed epi[f]	1	1	0 (0)	0	1 (0)	0 (0)
MMMT[g]	1	1	0 (0)	0	0 (0)	1 (0)
SCC[h]	1	0	1 (1)	100.0	0 (0)	1 (1)
Total	150	131	19 (14)	12.7	123 (8)	27 (11)

[a] Mucinous adenocarcinoma.
[b] Clear cell adenocarcinoma.
[c] Serous adenocarcinoma.
[d] Endometrioid adenocarcinoma.
[e] Undifferentiated carcinoma.
[f] Mixed epithelial tumor.
[g] Malignant mixed mesodermal tumor.
[h] Squamous cell carcinoma.

Table 2 shows histological findings and lymph node metastasis. The incidence of lymph node metastasis was 6.5% (8/123) in stage I and 40.7% (11/27) in stage II. Nineteen of the 150 (12.7%) patients who had clinical stages I and II carcinomas were surgically staged as IIIc based on lymph node status. Table 3 shows the lymph node metastasis of these 19 patients. Fourteen of them had metastasis limited to the paraaortic nodes and two (patients 9 and 11) had metastasis to only the pelvic lymph nodes. Three (patients 7, 14, and 17) had both paraaortic and pelvic lymph node

Table 3
Characteristics of patients with lymph node metastases

Case	(age)	Tumor site	Clinical stage	Histology	Site of metastasis	Number of metastatic/ dissected lymph node
1.	(68)	right	Ia	clear cell	paraaortic/sup[a](rt)	1/71
2.	(31)	right	Ic	clear cell	paraaortic/sup (rt)	2/65
3.	(47)	left	Ic	clear cell	paraaortic/sup (rt, lt) and inf[b] (rt, lt)	4/57
4.	(48)	left	Ic	clear cell	paraaortic/ sup (lt) and inf (rt)	2/71
5.	(68)	left	Ic	clear cell	paraaortic/ sup (lt)	1/93
6.	(65)	left	Ic	mucinous	paraaortic/ sup (lt)	1/65
7.	(68)	left	Ic	mucinous	paraaortic/sup (rt, lt) paraaortic inf (rt, lt) Internal iliac (rt, lt) External iliac (lt)	33/106
8.	(57)	left	Ic	serous	paraaortic/sup (lt) and inf (lt)	2/107
9.	(51)	left	IIb	clear cell	External sacral (lt)	1/67
10.	(52)	right	IIb	clear cell	paraaortic/sup (rt)	2/126
11.	(47)	right	IIb	endometrioid	Internal iliac (rt)	1/63
12.	(56)	right	IIb	SCC	paraaortic/inf (rt)	1/92
13.	(63)	right	IIc	clear cell	paraaortic/sup (rt, lt) and inf (rt, lt)	4/30
14.	(24)	right	IIc	serous	paraaortic/sup (rt, lt) and inf (rt) common iliac (rt) *internal iliac (lt)* obturator (rt, lt)	7/78
15.	(46)	right	IIc	serous	paraaortic/sup (rt)	2/59
16.	(57)	left	IIc	serous	*paraaortic/sup (rt)*	1/70
17.	(62)	left	IIc	serous	*paraaortic/inf (rt)* med sacral	2/133
18.	(45)	right	IIc	endometrioid	paraaortic/sup (rt)	1/70
19.	(56)	left	IIc	endometrioid	paraaortic/inf (lt)	1/14

Bilateral metastasis was underlined in site of metastasis; contralateral metastasis to the neoplastic ovary was expressed in italics.
[a] Paraaortic node superior to inferior mesenteric artery.
[b] Paraaortic node inferior to inferior mesenteric artery, rt: right, lt: left.

metastasis. The clinical stage of the patients with pelvic lymph node metastasis was stage II and the tumor extended to the pelvic peritoneum, suggesting that nodal involvement might have been caused by direct invasion or by the permeation of tumor cells through lymphatic channels opening onto the peritoneal surface. Seventeen patients (89%) had lymph node metastasis on the side ipsilateral to the neoplastic ovary, metastasis in 12 (63%) was limited to the ipsilateral side, and 5 patients (26%) had bilateral metastasis. Two patients (11%) had lymph node metastasis on the side contralateral to the neoplastic ovary (Table 3).

Kaplan–Meier survival curves for overall survival are shown in Fig. 1. The median survival was 7.6 years for patients surgically staged I and II (without lymph node metastasis) and 3.1 years for those at stage IIIc (with lymph node metastasis). The difference in survival between patients with negative and positive lymph nodes was statistically significant ($P < 0.0001$).

Lymphatic mapping

Overall tolerance for the mapping procedure was excellent. None of the patients experienced anaphylaxis during the CH40 injection and no adverse reactions were attributed to the dye injections. CH40 was injected into the left and right ovaries of six and five patients, respectively. In preliminary results, we observed that CH40 was immediately distributed to regional lymph nodes where it remained for several hours. Lymphatic channels along the ovarian vessels were identified from all ovaries injected after the retroperitoneal space was opened. Major and ovarian vessels were exposed through lateral paracolic incisions. CH40 was deposited into the lymphatic channels along the ovarian vessels and the lymph nodes of all patients (Fig. 2). The locations of these nodes included paraaortic sites in all patients (paraaortic nodes from inferior mesenteric artery, IMA) to the renal vein level ($n = 10$; 91%), paraaortic node around IMA ($n = 4$; 36%), paraaortic node below IMA ($n = 4$; 36%), common iliac node ($n = 3$; 26%), and external iliac node ($n = 1$; 9%). CH40 uptake was restricted to the paraaortic node area, especially above the IMA when injected into the left ovary. CH40 staining was bilateral in two of six patients when injected into the left ovary. In contrast, CH40 was uptaken from the paraaortic node to the right external iliac artery when CH40 was injected into the right ovary. CH40 staining was bilateral in three of five patients when injected into the right ovary.

Discussion

If the profile of lymphatic metastasis can be predicted from lymphatic drainage, areas of lymphadenectomy could be selected. Bergman [4] found a high incidence of pelvic lymph node metastasis in 86 autopsies, though he concluded that pelvic lymph node metastasis was the result of the secondary, retrograde spread of cancer cells after paraaortic node metastasis was established. Rose et al. [5] analyzed 428 autopsies and reported that paraaortic nodes were more frequently affected than pelvic lymph nodes. The present study found that 19 of 150 (12.7%) patients who had clinical stages I and II carcinomas were surgically staged as IIIc based on lymph node status. Seventeen of these 19 patients had metastasis to the paraaortic node, but two had metastasis to only the pelvic node. We found that seven of nine solitary lymph node metastases were restricted to the paraaortic node (superior to IMA, five patients; inferior to IMA, two patients). These findings showed that the primary site of lymph node metastasis was the paraaortic node.

We previously reported that the grade of tumor and positive peritoneal cytology are closely related to paraaortic

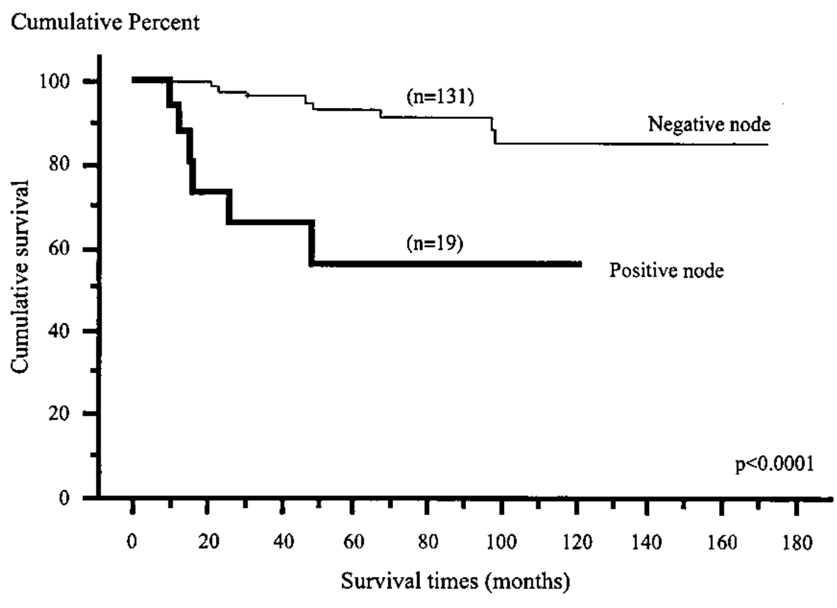

Fig. 1. Kaplan–Meier survival curves for patients with ovarian cancer of early clinical stage by lymph node status.

Fig. 2. CH40 was deposited into the lymph nodes (arrow).

node metastasis of ovarian carcinoma [6]. Petru et al. [7] reported that clinical–morphologic factors such as ascites, adherence, or extracystic excrescences at surgery are not reliable predictors of lymph node status. Stage II has a higher lymphatic metastasis ratio (40.7%) than stage I (6.5%). Histological type did not significantly differ with respect to the status of lymph node metastasis except in mucinous adenocarcinoma, which was associated with a lower incidence of lymph node metastasis (4.1%). This result might be due to the lower incidence of stage II of mucinous adenocarcinoma. Otherwise, this finding supports the studies of DiRe et al. [8] and Lang [9], both of which included many patients with mucinous adenocarcinoma with relatively low rates of metastasis (0–6.7%). When only stage I was considered, the incidence of lymph node metastasis (12%) was higher in clear cell adenocarcinoma compared with other types of tumor (3.7%).

Our data showed that the survival ratio was longer in node-negative, than positive patients at clinical stages I and II ($P <$ 0.0001). However, Onda et al. [10] reported that the 5-year survival rate of stage III patients based only on lymph node positivity was comparable to that of stage I or II patients (84% vs. 96%, $P = 0.107$).

We speculate that the intraoperative identification of sentinel lymph nodes in clinical I stage ovarian cancer will help to reduce the amount of required dissection. Many gynecological oncologists perform only selective ipsilateral retroperitoneal sampling when disease is grossly confined to one ovary. Benedetti-Panici et al. [11] concluded from their review of six patients that ipsilateral lymph node evaluation was adequate for clinical stage IA disease. However, Cass et al. [2] reported in their cohort study of clinical stage I ovarian carcinoma limited to one ovary that bilateral lymph node sampling increased the identification of nodal metastases.

In our study, 17 patients (89%) had lymph node metastasis on the side ipsilateral to the neoplastic ovary. Metastasis in 12 patients (63%) was limited to the ipsilateral side, and 5 patients (25%) had bilateral metastasis. Two patients (11%) had lymph node metastasis on the side contralateral to the neoplastic ovary, and both of them were classified as clinical stage IIc. One had metastasis to the contralateral ovary and the other had invasion of the sigmoid colon. The metastasis might have been caused by direct invasion or by permeation of tumor cells through lymphatic channels opening into the peritoneal surface. These results suggest that bilateral side lymphadenectomy is necessary in stage I, as well as in stage II ovarian cancer.

To elucidate how ovarian carcinoma spreads to the lymph nodes, we designed a pilot study to investigate lymphatic drainage and identified sentinel nodes of the ovary in patients with endometrial and tubal carcinoma.

Intraoperative lymphatic mapping was pioneered and popularized by Morton et al. [12] as a means of evaluating patients with early-stage cutaneous melanoma for potential metastases to regional lymph nodes. Applications involving organs within the abdominal cavity, which have more complex lymphatic drainage patterns, have not been reported. No lymphatic mapping studies have been performed in patients with ovarian cancer.

A dye, isosulfan blue, has been used for lymphatic mapping of cervical or endometrial cancer. It has detected sentinel nodes at a rate of only 60% in cervical cancer [13] and has been deposited into grossly identifiable lymph nodes in 10 of 15 (67%) patients with endometrial cancer [14]. Levenback et al. [15], using radiocolloid as well as blue dye, increased the sentinel node identification rate of cervical cancer to 100%. The activated charcoal solution, CH40, which we used here, was developed by Hagiwara [16], who confirmed that it is immediately distributed to regional lymph nodes where it remains for about 2 days.

We identified the sentinel nodes in all of 11 patients. This might be due to the difference of dye and the nature of the ovary, which is rich in lymphatic channels. In all of these patients, lymphatic channels along the ovarian vessels of the injected site were stained with the black charcoal until the end of ovarian vein. The half-life of blue dye is minutes, whereas that of CH40 is longer. CH40 remains in the regional lymph nodes for 3 days when injected into the wall of the canine stomach [17].

It is important to speculate on how lymphatic mapping will be incorporated into clinical practice. Unlike cervical cancer, our results suggested that the lymphadenectomy region could be selected during early stage ovarian cancer. Anatomically, dominant lymphatic drainage from the ovary shows lymphatic channels along ovarian vessels [18]. Contralateral lymph nodes were stained in 33% (two of six) of patients when CH40 was injected into the left ovary, and 80% (four of five) patients showed the contralateral lymph node staining when injected into right ovary. These results indicate that the bilateral lymph nodes should be dissected in patients with ovarian cancer.

This initial experience with intraoperative mapping to the ovary has raised some technical questions. Do the selected injection sites reflect the true lymphatic drainage of tumor? What is the optimal dye volume for injection? This mapping study was not designed for ovarian cancer. This technique should be further evaluated and tested on more patients with ovarian cancer.

In conclusion, the paraaortic node is the primary site of lymph node metastasis in ovarian cancer. Bilateral paraaortic node dissections are necessary to explore the extent of tumor even in stage I ovarian carcinoma.

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