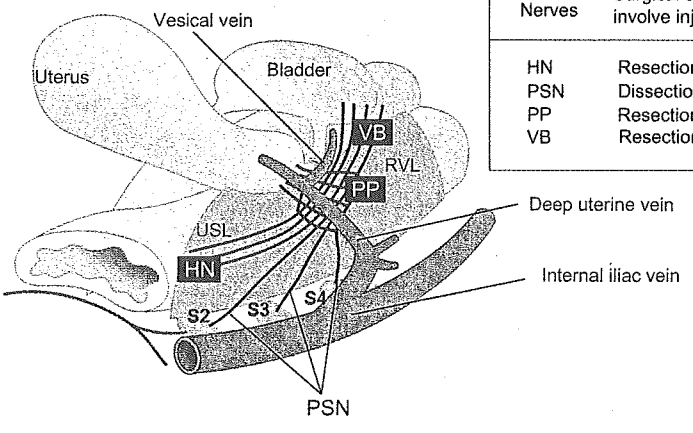
When treating cancer patients, it is important to consider how to minimize deterioration of their quality of life (QOL). Radical hysterectomies are widely performed to treat invasive cervical cancer. Intraoperative and postoperative morbidity includes urinary tract fistula, ileus, thromboembolism, lymphocyst, 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.

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

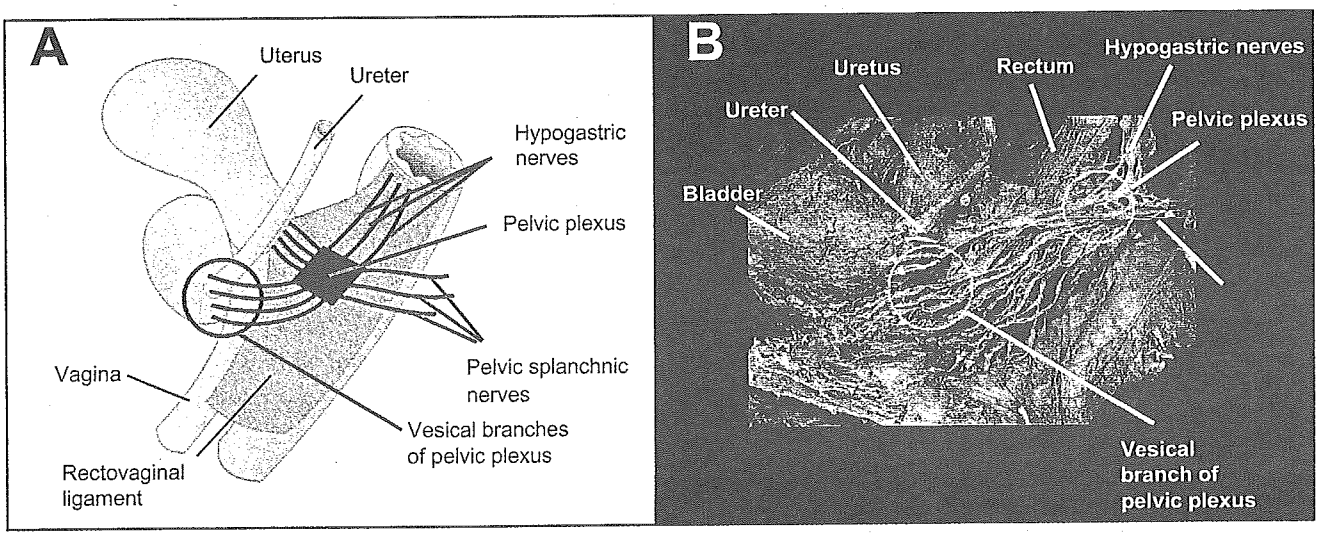



**Figure 2.** A) Illustration of autonomic nerves that control bladder function and B) anatomic distribution of autonomic nerves in cadavers.

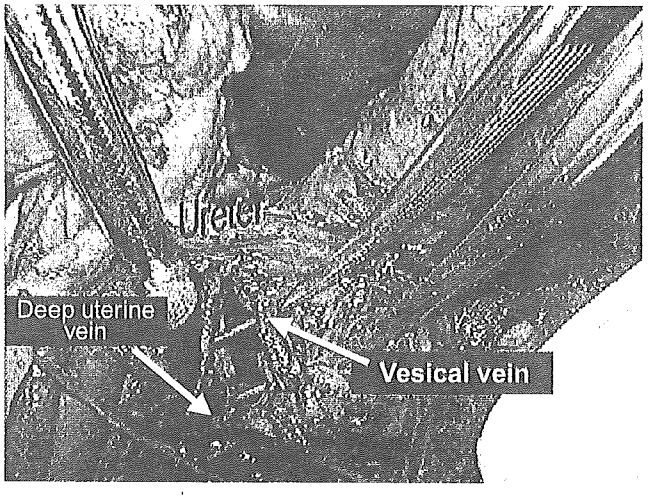



**Figure 3.** Separation and cutting of the vesical vein in the posterior part of the vesico-uterine ligament. It should be noted that the deep uterine vein had not been cut yet at this step.

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.

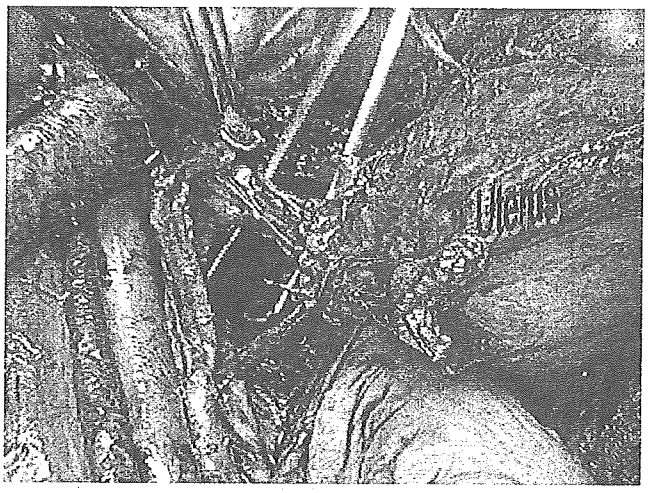


**Figure 4.** Dissection of fatty connective tissue (arrowhead) of the posterior part of the vesico-uterine ligament. A portion of the vesical branches of the pelvic plexus, which pass around the ureter, may be sacrificed at this step.

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

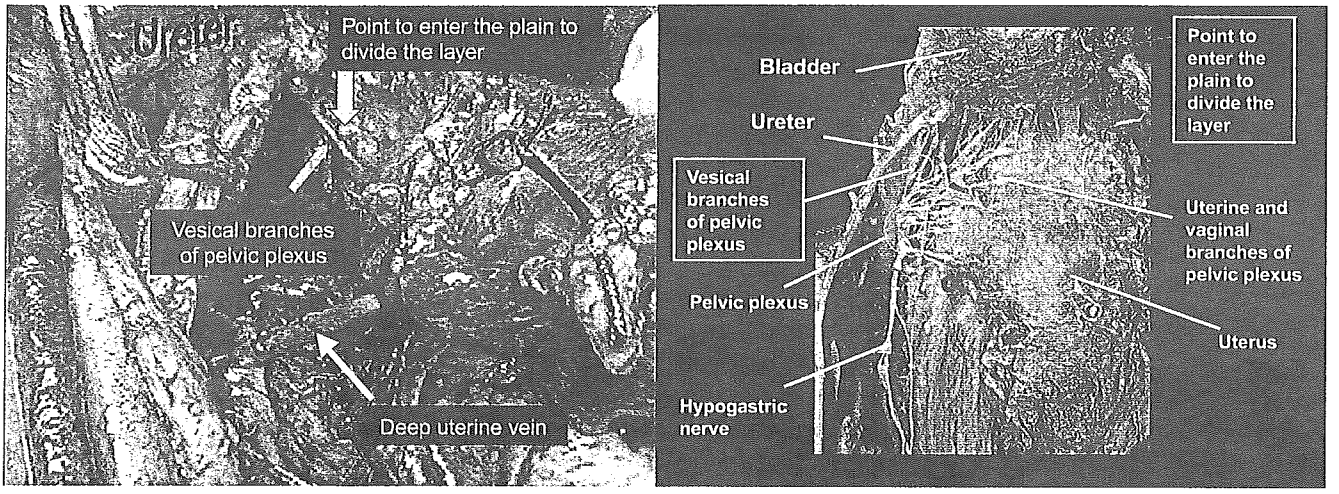



**Figure 5.** A) Vesical branches of the pelvic plexus after dissection of the vesico-uterine ligament and the point at which the plane must be entered to divide the vesical branches/pelvic plexus and the paracolpium and B) the same point at which the plane must be entered to divide the layers in the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

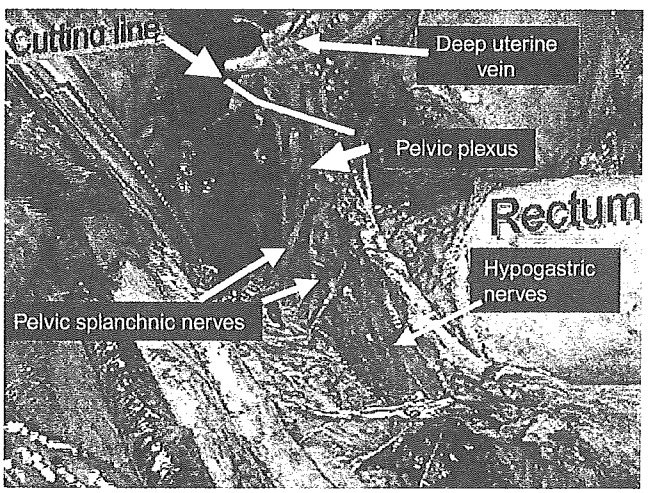



**Figure 6.** The cutting line between the pelvic plexus and its uterine branch, which is shown after resecting and pulling upward of deep uterine vein.

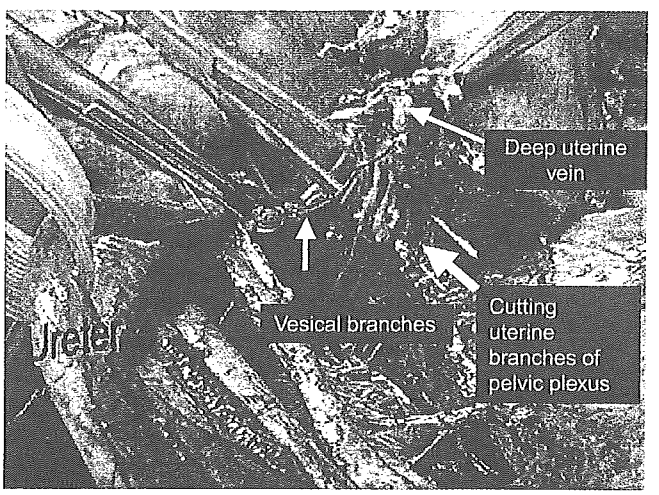



**Figure 7.** Separation of the pelvic plexus from the rectovaginal ligament.

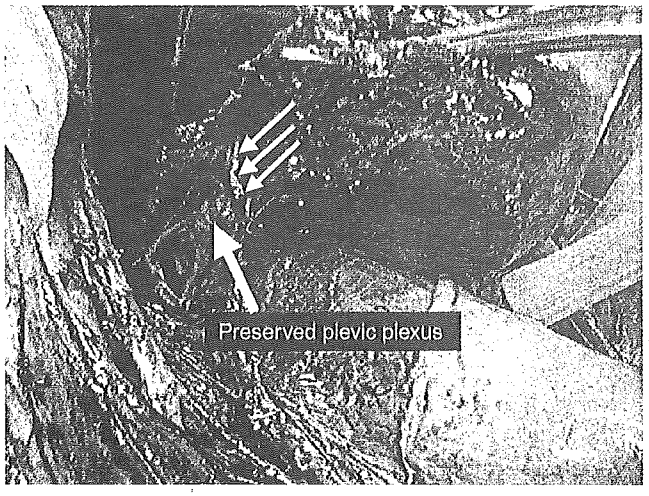



**Figure 8.** Separated and retracted pelvic plexus after the autonomic nerve preservation.

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 without sacrificing the radicality of the radical hysterectomy procedure.

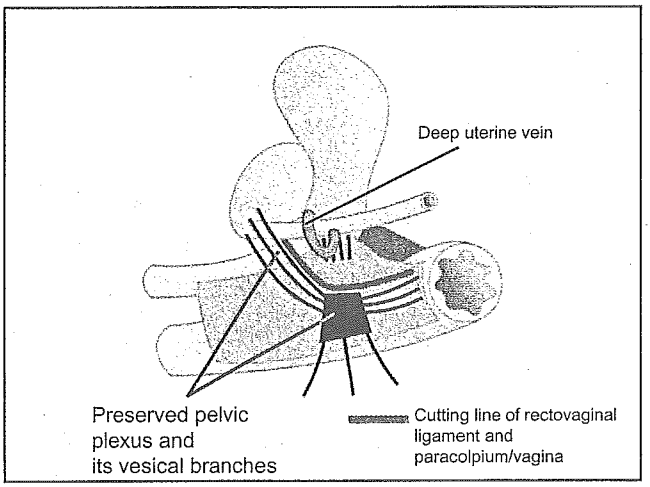



**Figure 9.** Illustration of systematic autonomic nerve preservation and the cutting line of the rectovaginal ligament, paracolpium, and vagina.

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.



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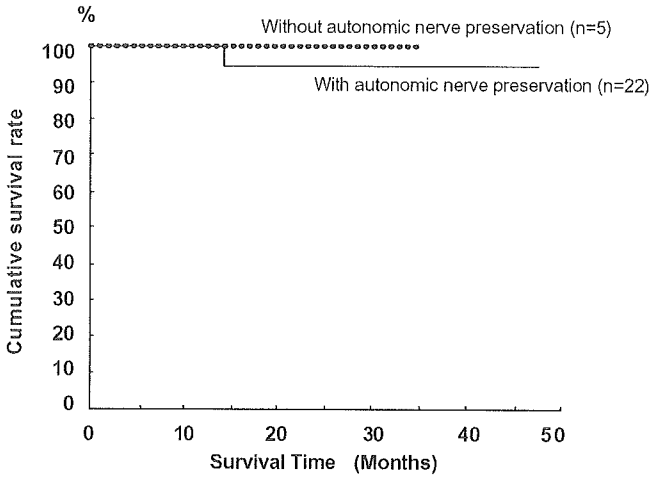


**Figure 10.** Disease-free survival of patients treated with radical hysterectomy with or without systematic preservation of the autonomic nerves.

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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# Adjuvant oral 5-fluorouracil for cervical cancer: Japanese Gynecologic Oncology Group report

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**Abstract.** Japanese women with low-stage cervical cancer receiving radical hysterectomy and radiotherapy have a good 5-year survival rate. However, women with risk factors such as nodal metastasis may benefit from adjuvant chemotherapy, which was studied in women having surgery alone or surgery plus radiotherapy. Patients having surgery alone (S) (n=623) or surgery and radiotherapy (SR) (n=919) were randomly assigned to receive or not receive oral 5-fluorouracil (5-FU) for 1 year. The effect of various factors on survival was studied by multivariate analysis. Patients who received S obtained no benefit from 5-FU, whereas 5-FU-treated SR patients had significantly better 5-year survival than those not receiving chemotherapy (P=0.043). The SR patients without nodal metastases had a better survival rate if they received 5-FU (P<0.001), whereas those with nodal metastases did not. Oral 5-FU after radical hysterectomy with radiotherapy appears useful for patients with low-stage cervical cancer who have some risk factors but not for those with pelvic lymph node metastases.

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*Key words:* cervical cancer, adjuvant chemotherapy, 5-FU

## Introduction

Although the prevalence of invasive cervical cancer among Japanese women has been gradually decreasing, new cases still are diagnosed in approximately 7000 women annually, and 60% of these women have progressive disease (1). In Japan, the treatment of choice for patients with FIGO stage Ib or stage II cancers is radical hysterectomy, whereas this disease is commonly treated with radiotherapy alone in Europe and North America. In Japan, patients with stage Ib or stage II cancers who are judged to be at low risk for recurrence do not receive additional treatment. Patients with pT1b or pT2a tumors and negative pelvic lymph nodes have 5-year survival rates of 82.5 and 78.5%, respectively (2). Patients with risk factors such as pelvic lymph node metastasis, deep stromal invasion, lymphovascular space invasion, positive parametria, and positive margins have a poor prognosis (3), so surgery generally is followed by pelvic radiotherapy (45-50 Gy). However, in patients with nodal metastases, the 5-year survival rate is low (pT1, 61.8%; pT2, 53.5%) (2). To improve the prognosis for these patients, ongoing studies are aggressively addressing the utility of adjuvant chemotherapy.

The Japanese Gynecologic Oncology Group (JGOG; Head, Kiichiro Noda) investigates the usefulness of chemotherapy in gynecologic malignancies. The Committee on Cervical Cancer has been conducting multicenter randomized controlled studies since 1981. In four trials, we investigated the usefulness of oral 5-fluorouracil (5-FU) as adjuvant chemotherapy after surgery or surgery plus radiotherapy. The JGOG1001 and JGOG1002 trials (4) were performed from October 1981 through September 1988, and the JGOG1008 and JGOG1009 trials (5) were performed from November 1983 through October 1990. In these trials, the control groups did not receive

Table I. Characteristics of 1542 patients with cervical cancer receiving radical hysterectomy alone or with radiotherapy, with or without oral 5-FU adjuvant chemotherapy.

| Characteristic | Surgery (S) | | Surgery + radiotherapy (SR) | |
|---|---|---|---|---|
| | 5-FU | Control | 5-FU | Control |
| Total patients entered | 366 | 370 | 582 | 580 |
| No. of ineligible patients | | | | |
| Age | 0 | 4 | 1 | 1 |
| Stage violation | 4 | 1 | 19 | 12 |
| Operation/radiation violation[a] | 9 | 13 | 14 | 17 |
| Others | 46 | 36 | 86 | 93 |
| Eligible for evaluation | 307 | 316 | 462 | 457 |
| Age (mean ± SD) | 50.6±10.3 | 49.9±10.2 | 52.6±10.5 | 52.8±10.5 |
| FIGO stage (%) | | | | |
| Ib | 230 (74.9) | 245 (77.5) | 175 (37.9) | 183 (40.0) |
| IIa | 19 (6.2) | 16 (5.1) | 51 (11.0) | 42 (9.2) |
| IIb | 58 (18.9) | 55 (17.4) | 236 (51.1) | 232 (50.8) |
| Histology (%) | | | | |
| Squamous | 249 (81.1) | 278 (88.0) | 405 (87.7) | 417 (91.2) |
| Others | 58 (18.9) | 38 (12.0) | 57 (12.3) | 40 (8.8) |
| Pelvic lymph node metastasis (%) | | | | |
| Negative | 298 (97.1) | 310 (98.1) | 309 (66.9) | 326 (71.3) |
| Positive | 9 (2.9) | 6 (1.9) | 153 (33.1) | 131 (28.7) |
| Preoperative complications (%) | 40 (13.0) | 39 (12.3) | 70 (15.2) | 58 (12.7) |
| Postoperative complications (%) | 23 (7.5) | 44 (13.9) | 89 (19.3) | 96 (21.0) |
| Immunotherapy (%) | 44 (14.3) | 23 (7.3) | 121 (26.2) | 113 (24.7) |

[a]Non-curative operation; intracavitary irradiation only.

adjuvant chemotherapy. Because none of the individual studies yielded meaningful statistical results, we combined the data for multivariate analysis to determine the usefulness of adjuvant oral 5-FU.

## Patients and methods

*Patients.* All four studies enrolled patients with stage Ib or stage II cervical cancer. In JGOG1001 and JGOG1008, patients received radical hysterectomy alone (the S group), whereas in JGOG1002 and JGOG1009, they also received radiotherapy 1.8-2.0 Gy/day, 5 days per week, for a focal total dose of 40.0-50.0 Gy (the SR group). The eligibility criteria for all studies were: a) no previous chemotherapy; b) age <75 years; c) adequate hepatic, renal, and hematopoietic function; d) a WHO performance score of 0 to 3; e) no active second cancer; f) no history of serious cardiac, hepatic, renal, or pulmonary disease; and g) no other serious complications. All patients gave their informed consent according to institutional regulations.

In each of the studies, patients were randomly assigned to receive or not receive oral 5-FU at a dose of 200-300 mg daily for 1 year. Chemotherapy was started 4 weeks after surgery in the S group and as soon as possible after radiotherapy in the SR group. The median total dose of oral 5-FU was 73.0 g in the S group and 68.6 g in the SR group. Some patients received immunotherapy consisting of PSK [protein-bound polysaccharide (ß-D-glucan) extracted from mycelia of *Coriolus versicolor* strain CM-101 of the Basidiomycetes] or OK-432 (group A *Streptococcus pyogenes* type 3 Su strain inactivated with penicillin G), which are biological response modifiers (BRMs).

We reviewed the initial, enrollment, and the follow-up reports at the JGOG central office. The data were checked for accuracy by each of the 13 members of the committee.

*Statistical methods.* Time to death, measured from the date of surgery, was the primary endpoint. Follow-up continued for 5 years postoperatively or until the patient's death. The median follow-up was 5.4 years in the S group and 5.1 and 5.3 years,

respectively, in the SR groups (the JGOG1002 and JGOG1009 studies).

Statistical analyses were performed using the PHREG procedure of the statistical analysis system (SAS; Cary, NC, USA). The Cox proportional hazards model was used to adjust for patient characteristics. The selected prognostic factors differed in the S group and the SR group, and the risk of recurrence also differed greatly in the two groups. Therefore, we selected a multivariate analysis method that allowed us to consider prognostic factors separately by treatment group (S and SR). In analyzing the S group, we selected prognostic factors from the control groups and used a Cox proportional hazards model stratified by study (JGOG1001 vs. JGOG1008). In the same way, for SR analysis, we selected prognostic factors from the control groups and used a Cox proportional hazards model stratified by study (JGOG1002 vs. JGOG1009). Control group characteristics were selected using variable reduction methods by Cox regression procedures based on age, clinical stage, tumor histology, incidence of metastasis to the pelvic lymph nodes, incidence of preoperative or post-operative complications, and use or non-use of immunotherapy. The clinical effects were evaluated by risk ratios (as defined by the Cox model hazards ratio) and 95% confidence intervals. Survival curves were calculated and compared with the log-rank test. P-values were calculated with Wilcoxon rank-sum test or the $\chi^2$ test as appropriate, with values <0.05 considered statistically significant. The Cox regression model was also used to estimate the 5-year survival rates for both groups.

Table I shows a breakdown of ineligible patients excluded from the analysis. The category of 'others' includes a history of treatment with or current receipt of anticancer drugs other than 5-FU. In all, 1542 patients were analyzed: 623 in the S group and 919 in the SR group (Table I). No significant differences in patient characteristics were observed between the control and the 5-FU group except in the use of immunotherapy in the S group.

## Results

*Efficacy of oral 5-FU after surgery.* An analysis of prognostic factors by the variable reduction method in the control group resulted in the finding of clinical stage as the only adjustment characteristic, so this factor was adjusted for skewing. The number of patients and the adjusted 5-year survival rate were 307 and 95.8%, respectively, for the 5-FU group and 316 and 94.9%, respectively, for the control group. The relative risk of death from all causes was 0.826 (95% CI 0.421-1.596; P=0.575), which indicated no significant difference in prognosis in the two groups.

*Efficacy of oral 5-FU after surgery plus radiotherapy.* An analysis of prognostic factors by the variable reduction method in the control group selected metastasis to the pelvic lymph nodes, clinical stage, tumor histology, and preoperative complications as adjustment characteristics (Table II), so these factors were adjusted for skewing. The number of patients and the adjusted 5-year survival rate were 462 and 83.4%, respectively, for the 5-FU group and 457 and 78.2%, respectively, for the control group. The adjusted 5-year survival curve and rates are shown in Fig. 1. The relative risk of death was 0.744 (95% CI 0.558-0.991; P=0.043), indicating that the prognosis was significantly better in patients who received 5-FU.

Table II. Relative risk associated with prognostic factors among 919 cervical cancer patients in SR group.

| Factor | n | Relative risk (5-FU vs. control) | 95% CI | P-value[a] |
|---|---|---|---|---|
| FIGO stage | | | | |
| Ib | 358 | 0.522 | 0.300-0.910 | 0.022 |
| IIa | 93 | 0.509 | 0.149-1.742 | 0.282 |
| IIb | 468 | 0.890 | 0.627-1.264 | 0.514 |
| Histology | | | | |
| Squamous | 822 | 0.743 | 0.543-1.015 | 0.062 |
| Others | 97 | 0.750 | 0.361-1.561 | 0.442 |
| Pelvic lymph node metastasis | | | | |
| Negative | 635 | 0.423 | 0.273-0.656 | <0.001 |
| Positive | 284 | 1.247 | 0.831-1.871 | 0.286 |
| Preoperative complications | | | | |
| Absent | 791 | 0.808 | 0.586-1.113 | 0.191 |
| Present | 128 | 0.538 | 0.283-1.021 | 0.058 |

[a]Log-rank test.

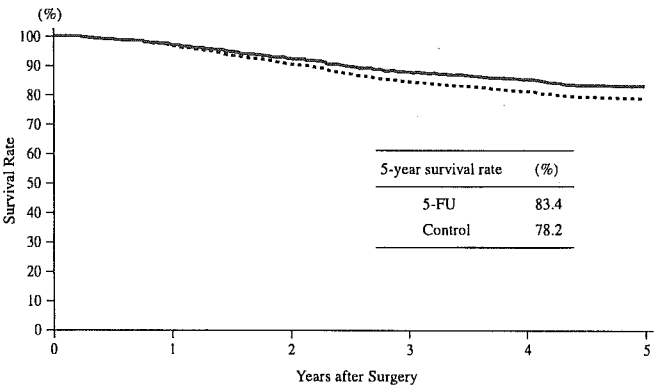


Figure 1. Adjusted survival curves for patients with stage Ib or stage II cervical cancer (SR group) with (n=462) or without (n=457) oral 5-FU adjuvant chemotherapy (relative risk 0.744, 95% CI 0.558-0.991; P=0.043, log-rank test).

The selected prognostic factors were studied to determine whether they caused differences in the efficacy of oral 5-FU. Only metastases to the pelvic lymph nodes influenced the effect of oral 5-FU. Therefore, patient data were categorized by the incidence of nodal metastasis, and the effect of oral 5-FU was re-examined for this factor. Among the SR patients

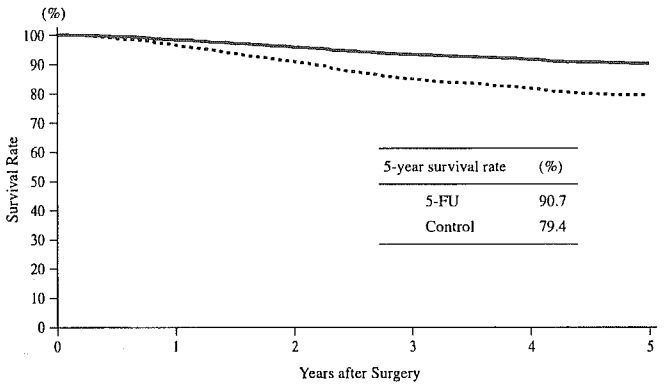


Figure 2. Adjusted survival curves for patients with stage Ib or stage II cervical cancer (SR group) without pelvic lymph node metastasis with (n=309) or without (n=326) oral 5-FU adjuvant chemotherapy (relative risk 0.423, 95% CI 0.273-0.656; P<0.001, log-rank test).

without nodal metastases, the adjusted 5-year survival rate was 90.7% in the 5-FU group (n=309) and 79.4% in control group (n=326) (Fig. 2, Table III), indicating a significantly better prognosis with adjuvant chemotherapy (relative risk 0.423, 95% CI 0.273-0.656; P<0.001). No significant difference was observed in the 5-year survival rate of the SR patients with nodal metastases who did (n=153) and did not (n=131) receive 5-FU (Table III).

*Adverse drug reactions.* An analysis of grade 2 or greater adverse drug reactions, assessed in accordance with the Japan Society for Cancer Therapy: Criteria for the Evaluation of the Clinical Effects of Solid Cancer Chemotherapy (which are essentially the same as the WHO criteria except for minor revisions made for Japanese patients), showed that leukopenia (<3000/mm$^3$) developed significantly more often in patients given 5-FU than in the controls, with leukopenia being more common in patients who had received radiotherapy (S group, 11.5% vs. 5.1%; P=0.021; SR group, 28.1% vs. 20.0%; P=0.037). At least 10% of the patients in both groups experienced loss of appetite and nausea or vomiting. Additionally, at least 10% of patients in the SR group experienced general malaise and stomatitis. However, all of these symptoms were mild, and no serious complications were noted.

## Discussion

5-Fluorouracil is commonly a primary drug for the treatment, not only of gastrointestinal cancer, but also of other tumors, including cervical cancer. The drug transitions through 5-fluorouridine triphosphate (FUTP) and is taken up by RNA (6), where it causes abnormal splicing (7,8). This action is thought to be cell-cycle non-specific (9). However, much remains unknown with regard to the precise mechanism of antitumor activity. The activity of thymidylate synthase (TS), the rate-limiting enzyme of the synthesis of the DNA structural constituent thymidine monophosphate (dTMP), is inhibited by the 5-FU metabolite 5-fluorodeoxyuridine monophosphate (FdUMP) (10). The extent of TS gene expression correlates closely with antitumor effects and prognosis (11,12). Thus, the antitumor effects of 5-FU are presumed to be more closely associated with inhibition of DNA synthesis than with inhibition of RNA function. This action appears to be both time-dependent and cell-cycle specific (9). Long-term administration of 5-FU is thus reasonable to maintain the drug's antitumor and recurrence-preventing effects.

There are several reports on the utility of oral 5-FU in patients with colorectal cancer (13,14). However, studies of oral 5-FU as adjuvant chemotherapy in cervical cancer are still in the pilot stage. Although a univariate analysis performed separately on the four JGOG studies did not reveal significant benefit from adjuvant oral 5-FU, multivariate analyses did show a significant survival advantage in patients in the SR group.

Our findings indicate that oral 5-FU adjuvant chemotherapy produced no significant improvement in the prognosis in the S group, which consisted of patients judged to be at low risk for recurrence. A significant difference was not observed because of the high survival rate of the entire group and because the number of patients was too small to provide reliable conclusions.

Generally, the indication for postoperative radiotherapy in patients with stage Ib or stage II tumors are factors such as pelvic nodal metastases; deep tumor invasion; lymphovascular space invasion; parametrial involvement; and positive surgical margins. In this study, the incidence of metastasis to the pelvic lymph nodes was 2.4% for the S group and 30.9% for the SR group. Despite radiotherapy, the prognosis in the SR group was less favorable than that of the S group. However, subsequent adjuvant oral 5-FU significantly improved the prognosis.

Table III. Five-year survival rates for cervical cancer patients of SR group according to status of pelvic lymph nodes.

| Nodal metastasis | 5-FU (%) n | Control (%) n | Relative risk 5-FU vs. control (95% CI) | P-value[a] |
|---|---|---|---|---|
| Negative | 90.7 (309) | 79.4 (326) | 0.423 (0.273-0.656) | <0.001 |
| Positive | 65.9 (153) | 71.4 (131) | 1.247 (0.831-1.871) | 0.286 |
| Overall | 83.4 (462) | 78.2 (457) | 0.744 (0.558-0.991) | 0.043 |

[a]Log-rank test.

When these data were classified according to the presence or absence of metastases to the pelvic lymph nodes, benefit was noted only in the patients without metastases, with a relative risk of 0.423 ($P<0.001$). This benefit can be clearly noted in the 'medium-risk group', who are considered to require post-operative radiotherapy because of deep stromal invasion, lymphovascular space invasion, positive parametria, or positive margins without nodal metastasis.

The oral 5-FU was well tolerated, and all adverse drug reactions were mild. No correlation of leukopenia with dose was observed, and compliance rates were 101.4% and 95.3% in the S and SR groups, respectively. The fact that 78% of patients were able to take at least 80% of the specified dose further indicates the tolerability and usefulness of this drug.

Oral 5-FU adjuvant chemotherapy did benefit patients with many risk factors but was not useful in the treatment of patients with lymph node metastases after surgery and radiotherapy. We look forward to further research and the development of new anticancer agents for patients in this high-risk group (15-20).

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