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ORIGINAL ARTICLE – COLORECTAL CANCER

Male Urinary and Sexual Functions After Mesorectal Excision Alone or in Combination with Extended Lateral Pelvic Lymph Node Dissection for Rectal Cancer

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ABSTRACT

Background. Mesorectal excision reduced the incidence of genitourinary dysfunction compared with conventional surgery. In Japan, extended lateral pelvic lymph node dissection (ELD) is added to mesorectal excision when lateral pelvic node metastasis is suspected. The aim of this study was to evaluate male genitourinary function after mesorectal excision or mesorectal excision plus ELD for rectal cancer.

Methods. According to the degree of pelvic-plexus preservation (PPP) and ELD, patients were grouped into PG1, mesorectal excision alone (bilateral PPP without ELD) ($n = 27$); PG2, bilateral PPP with ELD ($n = 12$); PG3, unilateral PPP with ELD ($n = 26$); and PG4, no PPP with ELD ($n = 4$). The assessment included measurements of the time interval to residual urine becoming <50 mL, interviews assessing sexual function, and nocturnal penile tumescence measurements.

Results. Proportions of patients with residual urine becoming <50 mL within 14 days after surgery were 96% in PG1, 73% in PG2, 23% in PG3, and 0% in PG4 ($P < .001$). Proportions of patients answering the ability to maintain sexual intercourse at 1 year were 95% in PG1, 56% in PG2, 45% in PG3, and 0% in PG4 ($P < .001$). Proportions of patients having nocturnal penile rigidity of >65% at 1 year were 95% in PG1, 33% in PG2, 50% in PG3, and 0% in PG4 ($P < .001$).

Conclusions. Patients undergoing mesorectal excision alone can expect excellent genitourinary function, but functional results after mesorectal excision plus ELD are far worse. Degrees of dysfunction depend on the extents of both autonomic nerve resection and ELD.

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Urinary and sexual dysfunctions are well-recognized complications after rectal cancer surgery.[1–3] Damage to the lumbar splanchnic nerves, superior hypogastric plexus, or hypogastric nerves results in ejaculatory dysfunction, whereas injury to the pelvic splanchnic nerves or pelvic plexuses causes urinary and erectile complications. These nerves are located just outside the mesorectal fascia, which envelops the rectum and mesorectum.

Blunt and blind dissection in conventional rectal cancer surgery frequently results in damage to these nerves with resulting reported rates for urinary and sexual dysfunction of 10% to 30% and 40% to 60%, respectively.[4–7] In contrast, mesorectal excision, a new world standard, removes the mesorectal fascia, including the mesorectum, completely and preserves the pelvic autonomic nerves by precise and sharp dissection under direct vision.[8,9] Introduction of mesorectal excision has been reported to reduce the incidences of urinary and sexual problems to 0% to 12% and 10% to 35%, respectively.[10–15]

In Japan, mesorectal excision is also standard for stage I to III rectal cancer above, and stage I rectal cancer below, the peritoneal reflexion. For stage II to III rectal cancer below the peritoneal reflexion, however, extended lateral pelvic lymph node dissection (ELD) with pelvic autonomic nerve preservation (PANP) is usually added.[2,16] Because the incidence of lateral pelvic lymph node metastasis is estimated to be 6.5% to 9.4% for T1–4 tumors and approximately 16% in T3 tumors, ELD is performed for patients having clinically positive lateral pelvic lymph nodes or those at high risk of such metastases.[2,16,17] In addition, if the autonomic nerves are directly invaded or threatened by the tumor, they are resected partially or completely. Clearly, precise understanding of functional results under such circumstances would be of major benefit for appropriate preoperative explanation and treatment choice for patients.

There have been several cross-sectional studies of Japanese-style surgery, but few longitudinal studies with objective evaluation of urinary and sexual functions. The purpose of this study was a longitudinal and objective evaluation of male urinary and sexual functions after mesorectal excision or mesorectal excision plus ELD for rectal cancer.

PATIENTS AND METHODS

Between March 1992 and January 2000, a total of 69 men with rectal cancer underwent radical surgery at the National Cancer Center Hospital, Tokyo. All patients were <70 years old, reported normal urination and erection within 3 months before operation, agreed to be examined with the RigiScan instrument (Timm Medical Technologies, Eden Prairie, MN), and gave informed consent for examination, treatment, and use of their data for analysis.[18,19] Approval by the institutional review board was not required for this observational study. Data on patient characteristics, treatment, pathology, and urinary and male sexual function were collected prospectively, and they were analyzed retrospectively. The median age of the 69 patients was 54 (range, 33–67) years. The median distance between the tumor and the anal verge was 5 (range 0–12) cm.

Treatment

All of the patients underwent mesorectal excision or mesorectal excision plus ELD with or without complete or partial PANP in each procedure, which was performed by each author. Type of surgery, extent of lymph node dissection, extent of PANP, and combined resection of neighboring organs were determined by each surgeon according to preoperative and intraoperative findings on tumor location, transmural invasion depth, and lymph node involvement, as outlined above and described previously.[2,16,17] Lymph node dissection and PANP were classified as detailed below.

Classification of Extent of Lymph Node Dissection

Abdominopelvic lymph node dissection consists of upward dissection and lateral pelvic lymph node dissection (LD).[16] Extent of LD is classified as follows: LD1, mesorectal excision alone; LD2, LD1 plus dissection of the internal iliac lymph node; LD3, LD1 plus complete resection of the internal iliac and obturator lymph nodes; and LD4, LD3 plus combined resection of the internal iliac artery and vein. ELD is LD3 or LD4.[16] Upward dissection, right LD, and left LD were classified and recorded separately.

Classification of PANP

Preservation or resection of the pelvic plexuses and hypogastric nerves were recorded separately for each patient on each side. Partial preservation of the pelvic plexus was defined as preservation of only the lower half. If a nerve (or plexus) is preserved but the pathway from the nerve (or plexus) to a target organ is completely disrupted, the nerve (or plexus) is regarded as being resected. Resection or complete disruption of the superior hypogastric plexus are regarded as being equal to no preservation of the bilateral hypogastric nerves.

Combinations of pelvic plexus preservation and LD were classified as follows: PG1, mesorectal excision alone (bilateral pelvic plexus preservation with bilateral LD1); PG2, bilateral pelvic plexus preservation with ipsilateral or bilateral ELD; PG3, contralateral pelvic plexus preservation with ipsilateral or bilateral ELD; and PG4, no preservation of the pelvic plexuses.

Combinations of hypogastric nerve preservation and LD were classified as follows: HG1, mesorectal excision alone (bilateral hypogastric nerve preservation with bilateral LD1); HG2, bilateral hypogastric nerve preservation with ipsilateral or bilateral ELD; HG3, contralateral hypogastric nerve preservation with ipsilateral or bilateral ELD; HG4, no preservation of the hypogastric nerves.

Evaluation of Urinary Function

To assess urinary function objectively, the interval between the date of surgery and the date of residual urine becoming <50 mL was measured without any medication. A Foley catheter was put in place immediately before surgery. Intermittent clamping of the catheter was started on the fifth postoperative day, and the catheter was removed when the patient felt urinary sensation. Residual urine measurement was then started and performed at least twice. When two successive measurements showed <50 mL, further measurements were canceled and the date of residual urine becoming <50 mL was recorded. If residual urine did not become <50 mL during the hospital stay, patients were instructed to do self-catheterization and record data for residual urine. Data sheets were then collected on an outpatient basis.

Evaluation of Male Sexual Function

To evaluate male sexual function objectively, nocturnal penile tumescence was measured before and 12 months after surgery with a RigiScan instrument.[18,19] Patients measured nocturnal penile tumescence during two successive nights by themselves.[18,19] Tumescence and rigidity were measured at the tip of the penis (5 mm proximal from the glans penis) and at the base of the penis (5 mm distal from the root of the penis). The highest rigidity value that was maintained for >5 minutes at the tip was considered as representative.[18] When rigidity recovered to the preoperative value at optional 6-month measurement, further measurements were canceled and the last rigidity represented the value at 1 year.

To assess male sexual function subjectively, patients were interviewed with a standardized questionnaire about male sexual function without any medication before and 12 months after surgery. Table 1 summarizes classification of grades of subjective erectile function. Grades of subjective ejaculatory function are classified as follows: grade 4, normal ejaculation; grade 3, ejaculation of decreased semen; grade 2, no ejaculation, with orgasm; grade 1, no ejaculation, without orgasm. The most favorable functional status within 3 months was regarded as representative. When the functional status recovered to the preoperative level at optional 6-month interview, further interviews were canceled and the last status was taken to represent the function at 1 year.

Statistical Analysis

Mann-Whitney *U*-tests were used to compare quantitative variables, and χ^2 tests were used to compare proportions. Kruskal-Wallis tests were used to analyze variance. The significance of pairwise correlation was evaluated with the Spearman's correlation coefficient. All statistical analyses were performed by SPSS for Windows, version 11.0 J (SPSS-Japan Inc., Tokyo, Japan). All P values were two sided, and a P value of <.05 was considered to be statistically significant.

RESULTS

Treatment Results and Pathology

Forty-four patients underwent a low anterior resection, and 25 underwent an abdominoperineal resection. Rates of sphincter preservation did not differ among surgeons (23 of 33 vs. 10 of 20 vs. 11 of 16, $P = .37$). Twenty-nine patients had a mesorectal excision alone, 15 one with unilateral ELD, and 25 one with bilateral ELD. Combined resection of the liver was performed for three patients, the bladder and prostate for one, the liver and seminal vesicles for one, the prostate and neurovascular bundle for one, and the internal iliac vessels for one. Combinations of pelvic plexus preservation and LD were PG1 in 27 patients, PG2 in 12, PG3 in 26, and PG4 in 4 (Table 2). Combinations of hypogastric nerve preservation and LD included HG1 in 21 patients, HG2 in 6, HG3 in 17, and HG4 in 25. Adjuvant radiotherapy was provided to one patient with a low anterior resection in the PG2 and HG3 group because of lateral pelvic lymph node metastasis.

Sixty-seven patients had adenocarcinomas, and two carcinoid tumors. Histopathologic International Union Against Cancer tumor, node, metastasis system stages were stage 0 in 1 patient, stage I in 22, stage II in 14, stage III in 26, and stage IV in 6. Eight patients had lateral pelvic lymph node metastasis, and six had distant metastases (liver, four patients; para-aortic lymph node metastasis, two patients). Sixty-eight patients had R0 and one R1 resections. At 1 year after surgery, 61 patients were free of disease, 7 were alive with disease, and 1 was dead of disease.

Pelvic Nerve Function

Patient characteristics in each grade of combinations of pelvic-plexus preservation and LD (PG group) are summarized in Table 2. Age ($P = .40$), pathological stage ($P = .077$), incidence of postoperative pelvic sepsis ($P = .52$), disease status at 1 year ($P = .14$), and distribution of operator (data not shown, $P = .75$) did not differ among the PG groups.

TABLE 1 Classification of subjective erectile function

Grade	Maintaining intercourse ≥ 5 min	Maintaining intercourse < 5 min	Intercourse possible	Erection possible
5	Yes	Yes	Yes, easy	Yes
4	No	Yes	Yes, easy	Yes
3	No	No	Yes, difficult	Yes
2	No	No	No	Yes
1	No	No	No	No

TABLE 2 Patient characteristics in each group

Characteristic	Group			
	PG1	PG2	PG3	PG4
Pelvic plexus preservation	Bilateral	Bilateral	Unilateral	No
Extended lateral dissection	No	Unilateral/bilateral	Unilateral/bilateral	Bilateral
No. of patients	27	12	26	4
Age (y)				
Median	57	53	53	57
Range	33–67	43–66	38–65	52–62
Distance of the tumor from the anal verge (cm)				
Median	8	5	5	4
Range	1.5–12	2.5–10	0–10	3–8
Sphincter preservation				
Yes	26	5	12	1
No	1	7	14	3
Pathological UICC TNM stage				
0	1	0	0	0
I	13	4	5	0
II	4	3	5	2
III	8	3	13	2
IV	1	2	3	0
Postoperative pelvic sepsis				
No	24	11	20	3
Yes	3	1	6	1
Disease status at 1 y				
No evidence of disease	26	11	20	4
Alive with disease	1	1	5	0
Dead of disease	0	0	1	0

PG1 mesorectal excision alone (bilateral pelvic plexus preservation without extended lateral pelvic lymph node dissection [ELD]), *PG2* bilateral pelvic plexus preservation with ipsilateral or bilateral ELD, *PG3* contralateral pelvic plexus preservation with ipsilateral or bilateral ELD, *PG4* no preservation of the pelvic plexuses, *UICC* International Union Against Cancer, *TNM* tumor, node, metastasis system

Although distance of the tumor from the anal verge and rate of sphincter preservation did not differ among PG2, PG3, and PG4 groups, patients in the PG1 group had significantly longer distance ($P = .005$) and more frequent sphincter preservation ($P < .001$) than their counterparts in the other PG groups.

Urinary Function At the initial interview, none of the 69 patients had urinary dysfunction. Postoperative days for residual urine becoming <50 mL could be evaluated in 67 patients, and results are summarized in Table 3. With the other two patients, those days could not be evaluated because of severe postoperative complications. Proportions of patients with residual urine becoming <50 mL within 14 days after surgery were 96% in PG1, 73% in PG2, 23% in PG3, and 0% in PG4, with the variation being significant ($P < .001$). Median postoperative days for residual urine becoming <50 mL were 6.5 (range, 5–18) in PG1, 12 (range, 5–83) in PG2, 27.5 (range, 7–324) in PG3, and 217 (range, 81–256) in PG4. There were significant differences between PG1 and PG2 ($P = .004$), between PG2 and PG3 ($P = .004$), and between PG3 and PG4 ($P = .004$).

Subjective Erectile Function At the initial interview, three patients reported an inability for erection, and they rejected further evaluation of sexual function but agreed to be assessed for urinary function. Of the other 66 patients who reported an ability for intercourse, 55 patients had grade 5 subjective erectile function, 8 patients had grade 4, and 3 patients had grade 3 (Table 4). The last three patients were excluded from further analyses of erectile functions. Preoperative erectile function did not differ among each PG group ($P = .86$).

Subjective erectile function at 1 year was evaluated in 55 patients; the results are shown in Table 4. Proportions of patients reporting an ability to maintain intercourse at 1 year were 95% in PG1, 56% in PG2, 45% in PG3, and

TABLE 3 Postoperative days for residual urine becoming <50 mL according to pelvic plexus preservation and extended lateral pelvic lymph node dissection

Characteristic	Group			
	PG1	PG2	PG3	PG4
Pelvic plexus preservation	Bilateral	Bilateral	Unilateral	No
Extended lateral dissection	No	Unilateral/bilateral	Unilateral/bilateral	Bilateral
No. of patients	27	12	26	4
Postoperative days				
≤7	16	2	1	0
8–14	9	6	5	0
15–21	1	1	5	0
22–30	0	1	3	0
31–60	0	0	6	0
>60	0	1	6	4
Not available	1	1	0	0

PG1 mesorectal excision alone (bilateral pelvic plexus preservation without extended lateral pelvic lymph node dissection [ELD]), *PG2* bilateral pelvic plexus preservation with ipsilateral or bilateral ELD, *PG3* contralateral pelvic plexus preservation with ipsilateral or bilateral ELD, *PG4* no preservation of the pelvic plexuses

TABLE 4 Subjective erectile function at 1 year according to pelvic-plexus preservation and extended lateral pelvic lymph node dissection

Characteristic	Group			
	PG1	PG2	PG3	PG4
Pelvic plexus preservation	Bilateral	Bilateral	Unilateral	No
Extended lateral dissection	No	Unilateral/bilateral	Unilateral/bilateral	Bilateral
No. of patients	23	12	24	4
Erection grade before surgery				
Grade 5	20	10	22	3
Grade 4	3	2	2	1
Erection grade at 1 year				
Grade 5	16	2	4	0
Grade 4	5	3	6	0
Grade 3	0	0	2	0
Grade 2	1	2	3	0
Grade 1	0	2	5	4
Not available	1	3	4	0

PG1 mesorectal excision alone (bilateral pelvic plexus preservation without extended lateral pelvic lymph node dissection [ELD]), *PG2* bilateral pelvic plexus preservation with ipsilateral or bilateral ELD, *PG3* contralateral pelvic plexus preservation with ipsilateral or bilateral ELD, *PG4* no preservation of the pelvic plexuses

0% in PG4, with the variation being significant ($P < .001$). There were significant differences between PG1 and PG2 ($P = .002$) and between PG3 and PG4 ($P = .023$), but not between PG2 and PG3 ($P = .91$).

Nocturnal Penile Rigidity Nocturnal penile rigidity before surgery was evaluated in 63 patients. Median tip penile rigidities before surgery were 77% (range, 56%–99%) in PG1 ($n = 23$), 75% (range, 43%–87%) in PG2 ($n = 12$), 75% (range, 40%–95%) in PG3 ($n = 24$), and 76% (range, 58%–77%) in PG4 ($n = 4$). Preoperative nocturnal penile rigidity did not differ among the PG groups ($P = .64$).

Nocturnal penile rigidity at 1 year was evaluated in 44 patients, and the data are shown in Fig. 1. Proportions of patients having nocturnal tip penile rigidity of >65% at 1 year were 95% in PG1 ($n = 19$), 33% in PG2 ($n = 9$), 50% in PG3 ($n = 14$), and 0% in PG4 ($n = 2$), with the variation being significant ($P < .001$). Median tip penile rigidities were 83% (range 57%–100%) in PG1, 54% (0%–84%) in PG2, 60% (0%–87%) in PG3, and 11% (1%–20%)

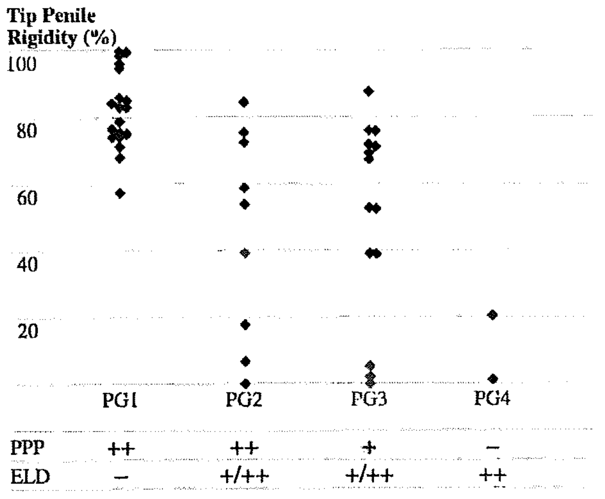

FIG. 1 Nocturnal tip penile rigidity 1 year after surgery according to the degrees of pelvic-plexus preservation (PPP) and extended lateral pelvic lymph node dissection (ELD). ++, bilateral; +, unilateral; –, none. PG1, mesorectal excision alone (bilateral PPP without ELD); PG2, bilateral PPP with ipsilateral or bilateral ELD; PG3, contralateral PPP with ipsilateral or bilateral ELD; PG4, no PPP

in PG4. There was a significant difference between PG1 and PG2 ($P = .001$), but not between PG2 and PG3 ($P = .89$) and between PG3 and PG4 ($P = .15$). There was a significant correlation between subjective erectile function grades and the nocturnal tip penile rigidity 1 year after surgery (Spearman's correlation coefficient = .73, $P < .001$)

Hypogastric Nerve Function

Although patient characteristics in each hypogastric nerve function group (HG group) are not shown, age ($P = .44$), incidence of postoperative pelvic sepsis ($P = .84$), disease status at 1 year ($P = .34$), and distribution of operator ($P = .53$) did not differ among the HG groups. Neither distance of the tumor from the anal verge nor rate of sphincter preservation differed among HG2, HG3, and HG4 groups; however, patients in the HG1 group had significantly longer distance ($P = .003$) and more frequent sphincter preservation ($P = .004$) than their counterparts in the other HG groups. In addition, patients in the HG2 group had a significantly higher stage than those in the HG3 group ($P = .022$).

Subjective Ejaculatory Function Of the 65 patients who reported an ability for ejaculation at the initial interview, 48 had grade 4 ejaculatory function, and 17 had grade 3 (Table 5). Preoperative ejaculatory function did not differ among the HG groups ($P = .34$).

Subjective ejaculatory function at 1 year could be evaluated in 56 patients, and the results are shown in Table 5. Proportions of patients reporting an ability to have normal ejaculation at 1 year were 56% in HG1, 20% in HG2, 14% in HG3, and 0% in HG4, with the variation being significant ($P = .001$). There was a significant difference between HG3 and HG4 ($P < .001$), but not between HG1 and HG2 ($P = .32$) and between HG2 and HG3 ($P = .10$).

TABLE 5 Subjective ejaculatory function at 1 year according to hypogastric-nerve preservation and extended lateral pelvic lymph node dissection

Characteristic	Group			
	HG1	HG2	HG3	HG4
Hypogastric nerve preservation	Bilateral	Bilateral	Unilateral	No
Extended lateral dissection	No	Unilateral/bilateral	Unilateral/bilateral	Bilateral
No. of patients	18	6	16	25
Ejaculation grade before surgery				
Grade 4	11	5	12	20
Grade 3	7	1	4	5
Ejaculation grade at 1 year				
Grade 4	10	1	2	0
Grade 3	8	4	5	0
Grade 2	0	0	7	14
Grade 1	0	0	0	5
Not available	0	1	2	6

HG1 mesorectal excision alone (bilateral hypogastric nerve preservation without extended lateral pelvic lymph node dissection [ELD]), *HG2* bilateral hypogastric nerve preservation with ipsilateral or bilateral ELD, *HG3* contralateral hypogastric nerve preservation with ipsilateral or bilateral ELD, *HG4* no preservation of the hypogastric nerves

DISCUSSION

This study clearly demonstrated that >90% of male patients who had normal urinary and sexual functions preoperatively and who underwent mesorectal excision with complete PANP and without ELD had a normal urination within 14 days and an ability to maintain intercourse and to ejaculate at 1 year. The results were obtained both subjectively and objectively in a prospective longitudinal fashion. In accordance with previous cross-sectional or longitudinal studies that used interview or self-administered questionnaire, functional benefit of mesorectal excision over any other radical operation was confirmed.[2,10–15,20–23]

Moreover, we found that degrees of urinary and sexual dysfunction greatly depended not only on the extent of autonomic nerve resection, but also on the extent of LD. When the unilateral pelvic plexus or hypogastric nerve was removed, the rates for patients with normal functions almost halved. Furthermore, complete resection of the pelvic plexuses or hypogastric nerves resulted in complete destruction of these functions. Similar observations were reported in previous cross-sectional or longitudinal studies that used interviews or self-administered questionnaires.[2,12,20,21]

In this investigation, the addition of ELD influenced urinary and sexual functions adversely, independently of the extent of PANP. Several cross-sectional studies that used self-administered questionnaire reported similar observations, but one revealed no influence of ELD on functions.[12,22–24] Although exact mechanisms of dysfunction caused by ELD despite PANP are not clear, mechanical injury to nerve fibers during lymph node dissection and/or ischemic injury due to devascularization by dissection may play a role. The influence of ELD seems smaller and more unpredictable than that of autonomic nerve resection. This is probably because the extent of LD varies case by case. The more extensive lymph node metastasis looks, the more aggressively an operator should resect.

On the other hand, the influence of ELD seems more limited on ejaculatory function than on erectile function. This may be because the distance between the pelvic splanchnic nerves and the internal iliac vessels, along which the lymph nodes are located, is smaller than that between the hypogastric nerve and these vessels. The shorter the distance, the higher the probability of injury to the nerve during dissection along the vessels.

This study had a number of limitations. First, patients in the PG1 group had higher-lying tumors and more frequent sphincter preservation than patients in other PG groups, although age, stage, pelvic sepsis, disease status at 1 year, and preoperative urinary and erectile functions were comparable. This bias is inevitable because autonomic nerve resection and ELD are indicated only in low-lying tumors. The previously reported high incidence of male sexual dysfunction with abdominoperineal resection was caused by damage to the neurovascular bundle during dissection of the lower rectum rather than sphincter resection itself.[10] Indeed, our PG1 patients with tumors located within 5 cm who underwent cautious dissection of the neurovascular bundle retained excellent functions. A similar argument is applicable to the bias with hypogastric nerve function. Second, the use of a validated self-administered questionnaire is preferable to a nonvalidated questionnaire or interview to avoid unreliability or influence of attending physisian.[25] Because there were no validated questionnaires at the beginning of this study, we used both interview and nocturnal penile tumescence measurement, the latter being an objective index to assess erectile function, which is essential for differentiating psychogenic and organic erectile dysfunctions.[18,19] Third, because this study included only one patient who received adjuvant radiotherapy, who belonged to the PG2 and HG3 group and who had mild urinary dysfunction and severe erectile and ejaculatory dysfunction, effects of radiotherapy on genitourinary function could not be evaluated. Finally, the present findings on functional influence of ELD may not be applicable outside of Japan. However, in the context of clinically suspected lateral pelvic node metastasis, an attempt to perform ELD can be generally recommended.[9] Where this is the case, the present findings should facilitate appropriate preoperative explanation and treatment choice for patients.

To prevent unnecessary injury to the pelvic autonomic nerves, we should avoid both inadvertent and intentional damage. The former is caused by inability to identify the nerves during surgery, either as a result of a lack of knowledge of anatomy or simple failure in identification. If an appropriate anatomical plane—the "holy plane"—is entered with correct knowledge, the nerves can be easily identified as whitish and firm fibers.

Intentional damage results from either excessive nerve resection or ELD caused by overestimation of direct invasion and metastasis. Accuracy of evaluation of pelvic anatomy and tumor extent has now been improved by high-resolution magnetic resonance imaging.[26] This proved to be sufficiently accurate for predicting the involvement of the mesorectal fascia adjacent to the pelvic autonomic nerves with an accuracy of 88% in a large prospective study.[27] Thus, it can be recommended to reduce overestimation of nerve invasion. Excessive ELD is caused by either overestimation of lateral pelvic lymph node metastasis or prophylactic ELD for patients who are at risk but who do not have clinical metastasis. Although ELD for clinical metastasis is allowed in Western countries, prophylactic ELD is widely practiced only in Japan.[2,9,12,16,17,20–23] Because the incidence of such metastasis is approximately 16% even in T3 tumors, accurate diagnosis should reduce unnecessary ELD.[17] Koh et al. reported that there were four distinct uptake patterns of ultrasmall particles of iron oxide on T2*-weighted magnetic resonance imaging in mesorectal lymph nodes.[28] Furthermore, these patterns were associated with metastasis. Such application of new technology advances may also be beneficial for diagnosis of lateral pelvic lymph node metastasis.

In conclusion, patients undergoing mesorectal excision alone reported preservation of excellent sexual and urinary function. The functional results after mesorectal excision plus ELD, however, were worse than those after mesorectal excision alone. Degrees of sexual and urinary dysfunction depend on the degrees of both autonomic nerve resection and LD. Therefore, unnecessary resection of the pelvic autonomic nerves and ELD should be avoided if oncologic safety is not compromised.

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Differences in rectal cancer surgery: east versus west


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In this issue of *The Lancet Oncology*, Georgiou and colleagues[1] report the results of their meta-analysis of observational studies comparing extended lymphadenectomy (EL) for rectal cancer with non-EL. After analysing 20 studies published over the past 25 years, the authors concluded that the efficacy of EL was insufficient to recommend it instead of conventional surgery.

Although this paper is important, its role in clinical decision making for rectal cancer is unclear for a number of reasons. During the past 25 years, imaging modalities and surgical techniques have made remarkable progress. In EL, nerve-sparing surgery with lateral nodal dissection (LND) was developed, while in non-EL, total mesorectal excision has become the standard. In surgery, techniques of LND can vary from "node picking" to "en-bloc dissection". Even without accounting for time effect or bias, interpreting the results of Georgiou and colleagues is problematic.

Also problematic are the author's failure to take lateral nodal metastases (LNM) into account. The definition of low rectum is slightly different between Japan and the west. LNM are found only in cancers of the low rectum, below the peritoneal reflection. It is well-known that the deeper the invasion and the lower the tumour, the higher the risk of LNM.[2] Heald once described LNM as "a Japanese mystery": LNM are not considered of surgical importance in the west. However, progress in MRI has been made, and the preoperative evaluation of LNM has become more reliable. Whether or not the sterilisation of LNM by pre-operative radiotherapy or chemoradiotherapy (pre-[C]RT) is possible is also an important point. There are no reports on the efficacy of pre-(C)RT for the treatment of LNM, but some researchers claim that the sterilisation of LNM can be achieved.[3]

Overtreatment, which is seen in both Japanese and western populations, also needs to be addressed. LND in patients without extra-mesenteric metastasis is overtreatment. However, in Japanese hospitals, LND was done in almost all cancers of the low rectum of T2 stage or higher until 1985. Although this wide application of LND clarified the frequency and sites of LNM, LND caused dysfunction. Because of this, Japanese surgeons investigated pelvic autonomic nerve anatomy, and developed nerve-sparing surgery with LND.[4,5] A randomised trial of nerve-sparing surgery with LND versus total mesorectal excision has been started in Japan to measure the effectiveness of LND for occult LNM. For high-risk patients, such as those with obvious LNM or c-stage IIIb disease, a randomised trial of pre-CRT with extended surgery versus pre-CRT with total mesorectal excision should be done in Japan.

Overtreatment is also a problem in the west. In particular, many cases of rectal cancer that can be locally controlled by surgery alone are actually treated with pre-(C)RT. As a result, the incidence of dysfunction rises, with accompanying costs. For the treatment of rectal cancer, the role of surgery is central. In reports about neoadjuvant radiotherapy in the west, patients with T1 and T2 tumours were also included in the Swedish and Dutch trials, whereas in a German trial, the patient population was restricted to only those with T3 or T4 and N-positive disease, indicating an improvement in patient selection over time. Since the incidence of local recurrence in tumours above the peritoneal reflection is low, the clinical significance of pre-(C)RT for this population is disputed. However, in the west, tumours up to 15 cm from the anal verge are treated with pre-(C)RT. If pre-(C)RT is expected to result in downsizing of the tumour, overtreatment could be avoided by setting size criteria, in addition to T stage, in treatment protocols. Radiation increases occlusion, induces changes in hyaline in the blood and lymph vessels, and affects fibrosis over time, and brings about organ dysfunction. Owing to fibrosis, surgery for local recurrence after pre-(C)RT becomes very difficult, and radiation carcinogenesis can also develop.[6] For patients whose life expectancy is long, the adverse effects of pre-(C)RT should be taken into account. Therefore, since we now know more about the risk factors for local recurrence, and imaging modalities have been improved, high-risk tumours can be selected accurately. The east and the west should join hands and define research criteria for surgery and neoadjuvant treatment to prevent over-treatment and dysfunction, and to improve future oncological results.

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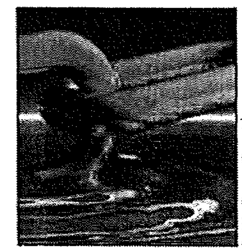
Treatment of gastric cancer in Asia: the missing link



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Conventional chemotherapy for gastric cancer is known to improve overall survival, quality of life (QOL), and the length of time a patient is free of symptoms compared with best supportive care,[1] but outcomes for advanced gastric cancer are still extremely poor. Although various combinations of platinum compounds and fluoropyrimidine derivatives improve patient outcomes, no accepted global standard exists for the treatment of gastric cancer. Additionally, there are marked geographical differences in the prevalence of types of gastric cancer, with intestinal-type distal gastric cancer related to *Helicobacter pylori* predominant in Asia, compared with the predominance of proximal and diffuse types of gastric cancer in Europe and North America. There are also marked regional differences in how gastric cancer is treated.

One common trend in chemotherapy is the replacement of intravenous infusion with oral administration, thus improving patient QOL and decreasing the length of time spent in hospital. In this issue of *The Lancet Oncology*, Boku and colleagues[2] show that S-1, an oral fluoropyrimidine derivative, is as effective as continuous infusion of fluorouracil for the treatment of advanced gastric cancer. S-1 contains tegafur (a prodrug of fluorouracil), 5-chloro-2,4-dihydropyrimidine (a reversible inhibitor of dihydropyrimidine dehydrogenase), and potassium oxonate. In phase 2 trials, S-1 showed good results in Japanese patients. It has recently been suggested that S-1 should be given in adjuvant settings to Asian patients with locally advanced gastric cancer after D2 dissection.[3] The SPIRITS trial[4] comparing S-1 plus cisplatin with S-1 alone, which started 2 years after the study by Boku and colleagues, showed that the combination of S-1 plus cisplatin seems to be more effective than S-1 monotherapy (p=0·04 for overall survival). Thus the study by Boku and colleagues is a missing link: together, the study by Boku and colleagues and the SPIRITS trial indicate that the combination of cisplatin plus S-1 should replace cisplatin plus fluorouracil as the first-line treatment of choice for Japanese patients with advanced gastric cancer. However, S-1 shows a different toxicity profile in patients in Europe and the USA, including severe diarrhoea and frequent neutropenia, and is therefore not always as effective as has been seen in Japan because of low dose intensity. Although the efficacy of S-1 plus cisplatin was similar to fluorouracil plus cisplatin in the FLAGS study,[5] oral administration of capecitabine, another fluoropyrimidine derivative, is recommended for western patients because of its efficacy and lower toxicity. Cisplatin plus capecitabine is non-inferior to fluorouracil plus cisplatin in advanced gastric cancer,[6] and capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin in first-line triplet therapy with epirubicin for oesophagogastric cancer,[7] suggesting cisplatin plus capecitabine or capecitabine plus oxaliplatin plus epirubicin as a standard therapy for advanced gastric cancer or oesophagogastric cancer. Therefore, there are several different standards for the treatment of advanced gastric cancer throughout the world.

A combination regimen with platinum compounds, fluorouracil derivatives, and/or taxanes is usually more effective than monotherapy.[1] Boku and colleagues also examined whether the doublet of irinotecan plus cisplatin was more effective than fluorouracil, but noted that it was not (p=0·055). This may be partly due to the design of the three-group comparison, and relatively low statistical power. Nevertheless, triple therapy is hopefully more effective than monotherapy or doublet therapy. Several phase 2 studies have indicated that docetaxel plus cisplatin and fluorouracil is promising, despite its high toxicity.[1] However, targeted agents with more favourable toxicity profiles, such as trastuzumab, combined with cytotoxic agents might substantially improve survival and reduce toxic side-effects, as was seen in the ToGA

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ORIGINAL ARTICLE

Risk factors of lateral pelvic lymph node metastasis in advanced rectal cancer

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Abstract

Background To clarify the risk factors of lateral pelvic lymph node (LPLN) metastasis of rectal cancer, we examined associations between LPLN status and clinicopathological factors including LPLN status diagnosed by computed tomography (CT).

Methods We reviewed a total of 210 patients with advanced rectal cancer, of which the lower margin was located at or below the peritoneal reflection, who underwent preoperative CT with 5-mm-thick sections and lateral pelvic lymph node dissection at the National Cancer Center Hospital between February 1998 and March 2006.

Results Forty-seven patients (22.4%) had LPLN metastasis. Multivariate analysis showed that LPLN status diagnosed by CT, pathological regional lymph node status, tumor location, and tumor differentiation were significant risk factors for LPLN metastasis. Among 45 patients with well-differentiated adenocarcinoma who were LPLN-negative and in whom CT had found no regional lymph node metastasis, none had LPLN metastasis. On the other hand, among 13 patients with moderate or less differentiated lower rectal adenocarcinoma who were LPLN-positive and in whom CT had revealed regional lymph node metastasis, 12 (92.3%) had LPLN metastasis.

Conclusions LPLN status diagnosed by CT, pathological regional LN status, tumor location, and tumor differentiation are significant risk factors for LPLN metastasis. Using these factors, patients can be classified as having a low or high risk of LPLN metastasis.

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Introduction

Lateral pelvic lymph node dissection (LPLD) is widely performed for advanced lower rectal cancer in Japan, and the incidence of lateral pelvic lymph node (LPLN) metastasis has been demonstrated to be 15–30% [1–3]. In spite of the relatively high incidence of LPLN metastasis, most surgeons, except for those in Japan, do not perform LPLD, and instead adjuvant chemoradiotherapy and total mesorectal excision (TME) have become the standard therapy for rectal cancer. In order to clarify the indications for, and the possible benefits of, LPLD, a retrospective multicenter study was conducted in Japan, and this demonstrated that LPLD was effective for local control, and might be indicated for patients with T3–T4 lower rectal cancer [3]. The 5-year survival rate of patients with LPLN metastasis is about 40% [1–3], which is comparable with that of patients with resectable liver or lung metastasis. From this viewpoint, LPLN metastasis should be classified as distant metastasis, and resected if at all possible. Kim et al. demonstrated that LPLN metastasis is a major cause of local recurrence in patients who receive preoperative chemoradiotherapy without LPLD [4]. This indicates that LPLD should not be neglected even in the era of neoadjuvant therapy for rectal cancer. Therefore, accurate preoperative diagnosis of pelvic lateral node metastasis is important. Although Yano et al. showed that conventional CT accurately predicted LPLN status [5], validation studies are necessary. In this study, therefore, we examined the association between clinicopathological factors, including CT diagnosis of lymph nodes and LPLN status, and selected high-risk factors for LPLN metastasis, enabling classification of patients according to LPLN metastasis risk.

Patients and methods

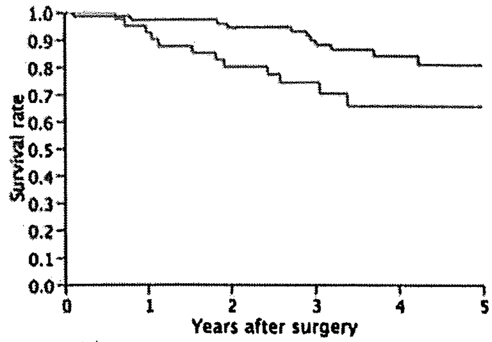
Patients

We reviewed a total of 210 patients with advanced rectal cancer, of which the lower margin was located at or below the peritoneal reflection, who underwent preoperative computed tomography (CT) with 5-mm-thick sections and lateral pelvic lymph node dissection (LPLD) at the National Cancer Center Hospital between February 1998 and March 2006. All the patients underwent TME or tumor-specific mesorectal excision. Pelvic autonomic nerves were preserved completely or partially in 187 patients (89%). The patients were followed up at 3-monthly intervals for 2 years, and at 6-monthly intervals thereafter. Tumor markers were examined at every patient visit. CT of the liver and lung or abdominal ultrasonography with chest X-ray was performed at least every 6 months. Colonoscopy was performed twice within 5 years after surgery. Median follow-up time was 3.8 years. Six patients received preoperative or postoperative radiotherapy. Pathological stage III patients were given adjuvant chemotherapy.

Diagnosis

All the patients underwent preoperative CT with 5-mm-thick sections using intravenous contrast media, and lymph nodes more than 5 mm in diameter were considered positive (Fig. 1). A radiologist interpreted the CT images preoperatively, and one author (SF) interpreted the images postoperatively. The author finally determined the lymph node status. Lymph nodes were classified according to their location. Lymph nodes in the lateral pelvic area outside the pelvic plexus and hypogastric nerves along the internal ileac, external ileac, common ileac vessels, and in the obturator space were considered LPLN. Patients with LPLN metastasis were classified as stage III in this study. Lymph nodes in the area lying along the inferior mesenteric vessels were considered regional lymph nodes. Tumor size and annularity were determined preoperatively by colonoscopy, barium enema, or virtual colonoscopy. Depth of invasion (T) and tumor location were determined preoperatively by CT or magnetic resonance imaging (MRI), and tumor location was finally confirmed during surgery. All the cancers were biopsied and a pathological diagnosis obtained before surgery.

Fig. 1 Representative lateral pelvic lymph node swelling detected by CT. Left lateral pelvic lymph node swelling is seen (*arrowhead*). The lymph node diameter is 10 mm. This patient underwent lateral pelvic lymph node dissection and metastasis was found by pathological examination 201 × 285 mm



No. at risk
Without LPLN metastasis (Blue line)
70 68 66 55 36 15
With LPLN metastasis (Red line)
40 38 32 21 11 7

Fig. 2 Survival curves for patients with stage III rectal cancer with and without LPLN metastasis. 201×285 mm

Statistical analysis

Statistical analysis was carried out by the chi-squared test. Survival rates were calculated by the Kaplan–Meier method, and survival curves were compared by the log-rank test. A logistic regression model was used for multivariate analysis. Data differences between groups were considered statistically significant at $P<0.05$.

Results

Incidence of LPLN metastasis and prognosis

Among the 210 patients, 47 (22.4%) had LPLN metastasis. The survival curves for stage III patients are shown in

Fig. 2. The survival rate of stage III patients with LPLN metastasis was significantly poorer than that of stage III patients without LPLN metastasis (P=0.014). Although the follow-up period was insufficient, the estimated 5-year survival rate for the patients with LPLN metastasis was 54%. The incidence of local recurrence in stage III patients with LPLN metastasis was 22.5% (9/40) and that in stage III patients without LPLN metastasis was 10.0% (7/70). Although the incidence of local recurrence in stage III patients with LPLN metastasis was higher than that in stage III patients without LPLN metastasis, the difference was not statistically significant (P=0.074).

Table 1 Incidence of LPLN metastasis and preoperative clinicopathological factors

	LPLN metastasis positive (n=47)	LPLN metastasis negative (n=163)	P
Age (years)			0.749
<60	25	91	
≥60	22	72	
Sex			0.336
Male	30	116	
Female	17	47	
CEA (ng/ml)			0.072
≤5	25	110	
>5	22	53	
Tumor location			0.018
Ra	3	35	
Rb	44	128	
Clinical T			0.616
T1, 2	4	14	
T3	31	118	
T4	12	31	
Regional LN status			0.014
Negative	13	78	
Positive	34	85	
LPLN status			<0.001
Negative	18	147	
Positive	29	16	
Tumor size (cm)			0.673
≤5	22	82	
>5	25	81	
Annularity			0.197
≤2/3	23	97	
>2/3	24	66	
Tumor differentiation			<0.001
Well	14	92	
Moderate	26	66	
Poor, mucinous	7	5	

Ra tumor center located above the peritoneal reflection; *Rb* tumor center located below the peritoneal reflection

Table 2 Incidence of LPLN metastasis and postoperative clinicopathological factors

	LPLN metastasis positive (n=47)	LPLN metastasis negative (n=163)	P
Pathological T			0.058
T1, 2	4	38	
T3	40	111	
T4	3	14	
Pathological regional LN status			<0.001
Negative	7	84	
Positive	40	79	
Lymphatic invasion			<0.001
Negative	17	116	
Positive	30	47	
Venous invasion			0.002
Negative	11	80	
Positive	36	83	
Perineural invasion			0.001
Negative	27	131	
Positive	20	31	
Tumor budding			0.073
Negative	15	76	
Positive	32	87	

Associations of LPLN metastasis with clinicopathological factors

Associations of LPLN metastasis with preoperative clinicopathological factors are shown in Table 1. LPLN status and regional lymph node status diagnosed by CT, tumor location, and tumor differentiation were significantly associated with LPLN metastasis. Associations of LPLN metastasis with postoperative clinicopathological factors are shown in Table 2. Pathological regional lymph node status, lymphatic invasion, venous invasion, and perineural invasion were significantly associated with LPLN metastasis. Multivariate analysis showed that LPLN status diagnosed by CT, pathological regional lymph node status, tumor location, and tumor differentiation were significant risk factors for LPLN metastasis (Table 3).

Incidence of LPLN metastasis according to risk factors

In order to identify patients at low risk and high risk for LPLN metastasis preoperatively, patients were classified into four groups according to the significant risk factors of LPLN metastasis. Although pathological regional lymph node status was a significant risk factor for LPLN metastasis, regional lymph node status diagnosed by CT

Table 3 Multivariate analysis of clinicopathological factors associated with LPLN metastasis

	Odds ratio (95% C.I.)	*P*
LPLN status (positive/negative)	28.00 (9.19–102.46)	<0.001
Pathological regional lymph node status (positive/negative)	7.21 (2.19–28.08)	0.002
Tumor location (Rb/Ra)	12.56 (2.35–107.87)	0.009
Tumor differentiation (moderate, others/well)	4.05 (1.47–12.23)	0.009

C.I. confidence interval

was used for the classification, because pathological lymph node status was not clarified preoperatively. Tumors located at Ra (tumor center located above the peritoneal reflection) and tumors located at Rb (tumor center located below the peritoneal reflection) were analyzed separately, and other risk factors were used for the classification. Group I was the group with no risk factors. Group II was the group with negative LPLN status diagnosed by CT but with at least one of the other two risk factors. Group III was the group with positive LPLN status diagnosed by CT but without at least one of the other two risk factors. Group IV was the group with all of the risk factors. Incidences of LPLN metastasis according to this classification are shown in Table 4. Irrespective of tumor location, no patients (0/45) had LPLN metastasis in group I. On the other hand, in group IV, 50.0% (2/4) of the patients with Ra tumors and 92.3% (12/13) of the patients with Rb tumors had LPLN metastasis. When pathological regional lymph node status was used for this classification instead of regional lymph node status diagnosed by CT, 75 patients were classified into group I or group II without pathological lymph node metastasis, and these patients also had no LPLN metastasis.

Discussion

The incidence of LPLN metastasis in patients with advanced lower rectal cancer is 15–30% [1–3]. Although the prognosis of patients with LPLN metastasis is poor, the 5-year survival rate is 40%, being comparable to that of patients with resectable liver or lung metastasis. Sugihara et al. estimated that LPLD would improve the 5-year survival rate of patients with T3–T4 lower rectal cancer by 8% [3]. Therefore, LPLD for patients with LPLN metastasis should be considered. Because accurate diagnosis of LPLN metastasis is difficult, LPLD is routinely performed in Japan for stage II or III rectal cancer located at or below the peritoneal reflection. However, it is still unproved whether LPLD is necessary for patients without LPLN metastasis. In order to acquire level 1 evidence, we are currently performing a clinical trial to compare TME alone with TME plus LPLD for rectal cancer patients without LPLN metastasis (JCOG0212) (ClinicalTrials.gov Identifier NCT00190541). Because accurate preoperative diagnosis of LPLN metastasis is important for treatment of lower rectal cancer, we selected four high-risk factors for LPLN metastasis and were able to estimate the incidence of LPLN metastasis using a combination of these factors. Patients without LN metastasis diagnosed by CT and with well-differentiated adenocarcinoma have no LPLN metastasis, and would not require LPLD. On the other hand, more than 80% of patients with LPLN metastasis diagnosed by CT and with moderate or less differentiated adenocarcinoma have LPLN metastasis, and should undergo LPLD. Therefore, our classification is thought to be useful for determining the indications for LPLD.

Late adverse effects of LPLD are sexual and urinary dysfunction [6]. Recently, TME plus LPLD with autonomic nerve preservation has been performed in Japan, and the incidences of sexual and urinary dysfunction following this treatment have been comparable to those after TME [7–9]. Because the oncological outcome of TME plus LPLD with autonomic nerve preservation is also comparable to that without autonomic nerve preservation [10], the former has become the standard therapy for rectal cancer in Japan. However, when patients have LPLN metastasis or if the tumor has invaded the autonomic nerves, nerve preservation is not possible. Therefore, the autonomic nerves were not preserved in 11% of the patients in this series.

Sex, tumor location, depth of invasion, mesorectal LN status, tumor differentiation, and tumor size are reported to be factors associated with LPLN metastasis [3, 11]. Although our findings were comparable, these previous reports did not take into account LPLN status diagnosed by

Table 4 Incidence of LPLN metastasis according to risk factors

	Incidence of LPLN metastasis
Ra (*n*=38)	
Group I (*n*=7)	0.0% (0/7)
Group II (*n*=27)	3.7% (1/27)
Group III (*n*=0)	–
Group IV (*n*=4)	50.0% (2/4)
Rb (*n*=172)	
Group I (*n*=38)	0.0% (0/38)
Group II (*n*=93)	18.3% (17/93)
Group III (*n*=28)	53.6% (15/28)
Group IV (*n*=13)	92.3% (12/13)

CT. As demonstrated in the present study, LPLN status diagnosed by CT was the most important risk factor associated with LPLN status. Therefore, accurate diagnostic imaging is important. In this study, the sensitivity, specificity, and accuracy of LPLN status diagnosis using CT were 62%, 90%, and 84%, respectively. Arii et al. demonstrated that the accuracy of LPLN status diagnosis using MRI was 83%, whereas that using CT was 77% [12]. Matsuoka et al. reported that MRI diagnosis of LPLN status had 67% sensitivity, 83% specificity, and 78% accuracy [13]. These results were comparable to ours. On the other hand, Yano et al. showed that CT diagnosis of LPLN status had 95% sensitivity, 94% specificity, and 95% accuracy [5]. However, because the number of patients they examined was small (n=39) and patients who did not undergo LPLD were excluded, the results were not directly comparable with other studies. Quadros et al. reported the preliminary results of LPLN detection using lymphoscintigraphy and blue dye [14]. However, the sensitivity and specificity were 17% and 79%, respectively. Tada et al. demonstrated the effectiveness of ultrasonographic examination for determining LPLN status, the sensitivity, specificity, and accuracy being 75%, 94%, and 93%, respectively [15]. Although this result was excellent, there were some problems and limitations; for example, obturator space lymph nodes were sometimes overlooked, and the use of ultrasonography in obese patients was difficult.

A meta-analysis of mesenteric lymph node diagnosis has indicated that the sensitivity and specificity of CT, MRI, and endoscopic ultrasonography are compatible [16]. Matsuoka et al. also demonstrated that multidetector-row CT was as equally effective as MRI for local staging of rectal cancer [17]. We preliminarily examined the capacity of MRI for diagnosis of lymph node status, and found that its sensitivity was higher and its specificity lower than that of CT, with roughly comparable accuracy. The use of new criteria for lymph node status instead of size [18], or a new MRI contrast agent [19], has been reported to yield better sensitivity and specificity for MRI diagnosis of mesenteric lymph nodes. However, further examinations will be necessary to establish an optimal approach for diagnosis of lymph node status using imaging modalities.

If patients with LPLN metastasis do not undergo LPLD, they would suffer LPLN or local recurrence. Kim et al. showed that adjuvant preoperative radiotherapy without LPLD was unable to control LPLN metastasis and local recurrence [4]: lateral pelvic recurrence was observed in 2.3%, 12.5%, and 68.8% of patients with LPLN measuring <5, 5–10, and$\geq$10 mm, respectively, determined by MRI. On the other hand, Quadros et al. showed that patients who received preoperative adjuvant chemoradiotherapy did not develop LPLN metastasis [14]. A small randomized study that compared adjuvant radiotherapy with LPLD also suggested that LPLD was unnecessary for patients who underwent preoperative radiotherapy [20]. Syk et al. demonstrated that LPLN metastasis was not a major cause of local recurrence of rectal cancer [21]. A comparative study demonstrated that the local recurrence rate in Korean patients who received adjuvant chemoradiotherapy without LPLD was lower than that in Japanese patients who underwent LPLD alone [22]. Moreover, the local recurrence rate in patients with LPLN metastasis has been reported to be 25.6% [3]. In our study, the local recurrence rate in patients with LPLN metastasis was 22.5%, which was significantly higher than that in patients without LPLN metastasis. These facts suggest that LPLD alone is not sufficient for local control in patients with LPLN metastasis. Therefore, a combination of adjuvant radiotherapy with LPLD is thought to be important for treatment of advanced rectal cancer, and a randomized study is required to determine whether LPLD is necessary for patients with LPLN metastasis receiving preoperative chemoradiotherapy.

In conclusion, LPLN status diagnosed by CT, pathological regional LN status, tumor location, and tumor differentiation are significant risk factors for LPLN metastasis. Using these factors, patients can be classified as having a low or a high risk of LPLN metastasis. This classification suggests that LPLD should be considered in patients with advanced lower rectal cancer.

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Abdominal Sacral Resection for Posterior Pelvic Recurrence of Rectal Carcinoma: Analyses of Prognostic Factors and Recurrence Patterns

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Background: Local recurrence of rectal cancer presents challenging problems. Although abdominal sacral resection (ASR) provides pain control, survival prolongation, and possibly cure, reported morbidity and mortality are still high, and survival is still low. Thus, appropriate patient selection and adjuvant therapy based on prognostic factors and recurrence patterns are necessary. The purpose of this study was to evaluate the results of ASR for posterior pelvic recurrence of rectal carcinoma and to analyze prognostic factors and recurrence patterns.

Methods: Forty-four patients underwent ASR for curative intent in 40 and palliative intent in 4 cases. All but one could be followed up completely. Multivariate analyses of factors influencing survival and positive surgical margins were conducted.

Results: Morbidity and mortality were 61% and 2%, respectively. Overall 5-year survival was 34%. The Cox regression model revealed a positive resection margin (hazard ratio, 10 [95% confidence interval, 3.8–28]), a local disease-free interval of < 12 months (4.2 [1.8–9.8]), and pain radiating to the buttock or further (4.2 [1.6–11]) to be independently associated with poor survival. The logistic regression model showed that macroscopic multiple expanding or diffuse infiltrating growths were independently associated with a positive margin (7.5 [1.4–40]). Of the patients with recurrence, 56% had failures confined locally or to the lung.

Conclusions: ASR is beneficial to selected patients in terms of survival. To select patients, evaluation of the resection margin, the local disease-free interval, pain extent, and macroscopic growth pattern is important. To improve survival, adjuvant treatment should be aimed at local and lung recurrences.

Key Words: Therapy—Surgery—Rectal cancer—Local recurrence—Recurrence—Prognostic factor.

Posterior pelvic recurrence[1–3] (PPR) of rectal carcinoma, which involves the sacrum and/or sacral nerves, presents challenging clinical problems. It may cause sacral nerve pain, perineal ulcers, fistula formation, bleeding, bowel and/or urinary tract obstruction, sepsis, and, finally, death.[3] These conditions are difficult to treat, and chemotherapy provides only minimal benefits at present.[4–6] Radiotherapy may give pain relief, but its effectiveness is limited and temporary.[4,7–9] Conventional abdominoperineal resection or local excision is only palliative.[10,11]

In 1981, Wanebo and Marcove[11] reported the advantage of the abdominal sacral resection (ASR), which was first described by Brunschwig and Barber[12] in 1969, for PPR of rectal carcinoma. Although published data on this operation are still limited and

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there have been few long-term follow-up studies, this aggressive operation provides pain control, prolongation of survival, and possibly cure.[13–22] However, reported morbidity and mortality are significantly high,[13–22] and survival is still low.[13–22] Therefore, appropriate selection of patients, especially with reference to the probable prognosis, is necessary. In addition, adjuvant therapy based on recurrence patterns may be required. The purpose of this study was to evaluate the results of ASR for PPR of rectal carcinoma and to analyze prognostic factors and recurrence patterns.

PATIENTS AND METHODS

Between March 1983 and May 2000, 44 patients with PPR of rectal carcinoma that involved the sacrum on computed tomography (CT) were considered candidates for ASR and admitted to the National Cancer Center Hospital, Tokyo. There were 35 men and 9 women, with a median age of 55 years (range, 32–73 years). Of these, 40 patients underwent initial operation at other hospitals. Selection criteria for curative-intent ASR were as follows: (1) medical fitness for ASR; (2) no signs of disseminated disease on preoperative imaging; (3) tumors involving the sacrum but not the first sacral bone and the bony lateral walls; and (4) tumors anatomically confined within the pelvis, with or without resectable solitary liver metastasis. The imaging studies routinely performed before resection were abdominal and pelvic CT, abdominal ultrasonography, and chest roentgenogram until 1989; pelvic magnetic resonance imaging and chest CT were added thereafter.

Of the 44 patients for whom ASR was attempted, 40 received curative-intent ASR, and 4 received palliative-intent ASR because of 1 or 2 lung metastases in 3 and 3 liver metastases in 1. Of the 40 who received curative-intent ASR, 33 patients underwent macroscopic curative ASR, 2 with solitary liver metastasis underwent macroscopic curative ASR with complete resection of liver metastasis, 1 with 4 peritoneal metastases adjacent to the main tumor underwent macroscopic curative ASR with complete resection of peritoneal metastases, and the remaining 4 underwent palliative ASR because of macroscopic residual local tumor in 3 and residual lymph node metastases in 1. Of the four who received palliative-intent ASR, three with lung metastases underwent palliative ASR leaving only residual lung metastases in two and both residual lung and local tumors in one, and one with three liver metastases underwent macroscopic curative ASR with complete resection of liver metastases. Conseuently, 37 underwent macroscopic curative resection, and 7 underwent macroscopic palliative resection. Of them, 27 patients received no radiation, 13 received preoperative adjuvant radiation of 30 to 73 Gy (median, 44 Gy), and 4 received 44 to 50 Gy (median, 50 Gy) as previous treatment.

Data for these patients were collected and entered prospectively into the database of the Colorectal Surgery Division. They included the following: (1) patient demographics; (2) treatment and pathology of the primary rectal cancer; (3) presentation of PPR; (4) treatment and pathology of recurrent tumor; (5) operative details; (6) hospital course, including complications; and (7) outcome. Of these, 15 variables were selected for prognostic factor analysis (Table 1) by consideration of their potential relationship to survival after ASR, as indicated by previous studies.[13–15,17–19,22] The local disease–free interval (LDFI) was defined as the interval between the initial curative operation and the occurrence of symptoms or detection of asymptomatic PPR by CT.

Surgical Procedure

Our surgical procedure was basically similar to that originally described by Wanebo and Marcove[11] and Wanebo et al.;[13] however, it was slightly modified.[23] Our sacral resection was performed immediately after the abdominal phase as a one-stage procedure instead of a two-stage procedure.[13] The presence of liver metastasis did not preclude continuation of the procedure if it was solitary and if the disease-free interval was sufficiently long. Solitary liver metastasis was resected simultaneously. We did not make full-thickness fascial myocutaneous flaps for sacroperineal wound closure but sutured the wound simply because there were no patients with large exposed tumors at the perineum.

After the patient was placed in a supine position with flexed and abducted thighs, dissection was started at the aortic bifurcation, and the common and external iliac vessels were dissected. The internal iliac vessels were divided at their root or beyond the superior gluteal artery. Adipose tissue, lymphatics, and the nodes surrounding these vessels, including obturator nodes, were removed completely, and the muscular pelvic side walls and the sacral nerve roots were exposed. The upper limit of the tumor was identified, and the anterior surface of the sacrum was dissected down to the planned level of sacral transection. When the tumor adhered or invaded into

TABLE 1. *Univariate Predictors of Adverse Outcome*

Variable	No. of Patients	Overall survival (%)			*P*
		1-yr	3-yr	5-yr	
Overall	44	90	47	34	
Gender					
Female	9	87	45	45	.41
Male	35	91	48	32	
Age					
< 60 years	30	96	55	40	.10
≥ 60 years	14	92	31	23	
Primary cancer stage					
I, II	2, 13	93	64	48	.046 (I, II, III vs. IV)
III	22	90	39	31	
IV	7	85	28	14	
Initial surgery					
Local excision, anterior resection	1, 20	90	51	36	.83
Abdominoperineal resection	23	90	44	34	
Initial lymphadenectomy					
Conventional	33	93	55	41	.25
Extended	11	81	27	18	
Local-disease-free interval (months)					
≤ 12	17	75	20	20	.0042
> 12	27	96	62	43	
Preoperative CEA level (ng/ml)					
≤ 10	23	91	70	49	.025
> 10	21	90	25	20	
Extent of preoperative pain					
None, perineum	15, 17	93	55	43	.0006 (none, perineum vs. buttock, more)
Buttock	7	85	35	0	
Thigh, leg	3, 2	50	0	0	
Tumor extent					
Solitary pelvic tumor	24	95	55	40	.17 (solitary tumor vs. others)
Pelvic metastasis	12	75	43	29	
Distant metastasis	8	85	28	28	
Largest tumor diameter (cm)					
≤ 5	26	92	50	40	.086
> 5	18	88	40	24	
Sacral involvement					
Adhesion	27	84	56	37	.85
Periosteum, marrow	11, 6	94	32	32	
Resection margin					
Microscopic negative	24	95	81	62	< .0001 (microscopic negative vs. others)
Microscopic positive	13	91	16	8	
Gross positive, residual	7	71	0	0	
Pathological grade					
Well, moderate	4, 29	90	40	35	.49 (poor, signet vs. others)
Mucinous, adenosquamous	6, 1	85	57	42	
Poor, signet-ring cell	3, 1	75	75	0	
Macroscopic growth pattern					
Solitary expanding	15	92	70	70	.0027 (solitary vs. others)
Multiple expanding	5	80	40	20	
Diffuse infiltrating	24	87	34	13	
Preoperative radiation					
Yes	13	91	55	46	.55
No	31	90	44	29	

CEA, carcinoembryonic antigen.

urogenital organs, the remaining rectum, pelvic nerves or muscles, and involved organs were all resected en bloc to avoid incomplete resection and cancer cell spillage. To facilitate resection and hemostasis and to shorten operating time, a combined abdominal and perineal approach was used.

After dissection of the lateral, cephalad, anterior, and caudal aspects of the tumor with surrounding organs to be resected was accomplished, the patient was placed in a prone position with flexed and abducted thighs. A posterior sacral incision including the perineal lesion was made, and the sacrum and gluteal muscles were exposed. The gluteal muscles, sacrotuberous ligament, sacrospinous ligaments, and pyriformis muscles were divided as far from the tumor as possible. After the level of abdominal dissection and the extent of the tumor were confirmed by hand in the pelvic cavity, a laminectomy proximal to the planned level of sacral transection was performed to preserve the noninvolved sacral nerve roots and ligate the dura. The sacrum was transected by an osteotome, and en-bloc resection of the tumor with the sacrum and the surrounding organs was accomplished. The gluteal muscles and skin were closed primarily. Again, the patient was placed in a supine position with flexed and abducted thighs. A colostomy and an ileal conduit were made.

Extent of Resection

Levels of sacral transection included S2 in 6 patients, S2–3 in 19, S3 in 5, S3–4 in 11, S4 in 1, and S4–5 in 2. Thirty-nine patients underwent total pelvic exenteration, one underwent posterior pelvic exenteration, and four underwent abdominoperineal resection. En-bloc resection of entire pelvic lymph nodes with the bilateral internal iliac arteries and veins was performed for all patients. Resected organs included the rectum in 20 cases, the urinary bladder in 39, the uterus and vagina in 8, the external genitalia in 2, the obturator internis muscle in 12, the gluteus maximus muscle in 5, and the small intestine in 7. Urinary diversions were an ileal conduit in 37 patients and a ureterocutaneostomy in 2. Three patients underwent complete resection of one, one, and three synchronous liver metastases. In addition, one patient underwent complete resection of four peritoneal metastases.

Follow-Up

One patient returned to Indonesia and was lost to follow-up. The other 43 were followed up completely, with a median follow-up time for live patients of 4.7 years (range, 1.2–15.8 years). They were examined with abdominal and pelvic CT, chest roentgenogram or CT, and carcinoembryonic antigen (CEA) measurement every 4 months for 0 to 1 years, every 6 months for 2 to 4 years, and annually for 5 to 10 years.

Statistical Analysis

Survival, disease-free survival, and local disease-free survival distributions were estimated by using the Kaplan-Meier product-limit method. Univariate comparisons of survival were made by using the log-rank test, and multivariate analysis was performed by using the Cox regression model with the forward stepwise method (likelihood ratio). All variables were dichotomized for analysis. Differences in proportions were analyzed by Fisher's exact test and by multivariate analysis with the logistic regression model and the forward stepwise method (likelihood ratio). All statistical analyses were performed with SPSS for Windows, version 10.0J (SPSS-Japan Inc., Tokyo, Japan). All P values were two sided, and a P value of $<.05$ was considered to be statistically significant.

RESULTS

Pathologic Findings

Histological diagnoses of the PPR cases are listed in Table 1. The bone marrow or periosteum of the sacrum was histologically involved in 17 patients. The remaining 27 had no sacral invasion, but dense fibrotic tissues adhered extensively to the sacrum, and cancer cells were found within them. Of 13 patients with pelvic lymph node involvement, 12 had intrapelvic metastases alone, and 1 had both intrapelvic and extrapelvic metastases. Eight patients had distant metastasis, including liver metastasis in three, lung metastasis in three, peritoneal metastasis in one, and distant lymph node metastasis in one.

Resection margins were microscopically negative in 24 patients, microscopically positive in 13, macroscopically positive in 3, and grossly residual in 4 (lung, n = 2; lung and local, n = 1; lymph node, n = 1; Table 1). The sites of macroscopic positive margins included cut ends of the sacrum and/or presacral connective tissue in two, cut ends of the sacral nerves and the external iliac artery in one, and the lateral pelvic sidewall in one. The major artery was involved only in one patient with prior extended lateral pelvic lymph node dissection. The sites of microscopic positive margins included the cut end of the sacrum in two, the cut end of the presacral connective tissue in three, the cut ends of the sacrospinous ligament and sacrotuberous ligament in one, the cut ends of the sacrospinous ligament and obturator internis muscle in one, the cut end of the obturator lymph node in one, and the cut ends of the sacral nerves in one.

Macroscopic growth patterns were based on macroscopic views of sections of resected specimens and were classified as solitary expanding growth, multiple expanding growth, and diffuse infiltrating growth (Fig. 1; Table 1). Expanding growth featured smooth