nomic nerves in the pelvis.[10] At the beginning of the 1980s, having reflected upon the previous results, researchers began to vigorously conduct basic and clinical studies to investigate the running patterns and functions of the intrapelvic autonomic nerves; and, consequently, autonomic nerve-preserving surgery with lateral node dissection came into existence.[11–13] The combination of TME with autonomic nerve identification, which was subsequently proposed by Heald and Enker, reflects the findings of research on the pelvic autonomic nerves conducted in Japan.[14]

The gross anatomy of the autonomic nerves in the pelvis has been almost totally elucidated. When TME is accurately performed, urinary and sexual dysfunctions, theoretically, do not occur. However, even with accurate anatomical knowledge, there are differences among individuals in the running patterns of the nerves and the volumes of nerve fibers in each region of the pelvis; and if a factor such as obesity or narrow pelvis is added, intraoperative nerve identification will be difficult, possibly causing nerve injury. If the cancer directly invades the autonomic nerves, combined resection of these nerves must be performed.

Urinary function (UF)

The sympathetic nerves inhibit contraction of the detrusor muscle and promote constriction of the bladder neck, ensuring urinary continence. But there are still many questions concerning UF; for example, to what extent the sympathetic nerves such as the superior hypogastric nerve plexus (SHNP) and hypogastric nerves (HN) are actually responsible for normal urination is still unknown. On the other hand, the parasympathetic nerves innervate the detrusor muscle and are therefore necessary for urinary voiding. Currently, the rate of urinary dysfunction after surgery for rectal cancer ranges from 30% to 70%. Many factors other than nerve preservation play a role in minor incontinence of bladder function.[15,16] Loss of sympathetic innervation, which may be the result of damage to the hypogastric nerves, may result in urgency and stress incontinence in females. The fact that major incontinence as a result of precise autonomic nerve-preserving techniques was not reported indicates that substantial urinary morbidity was avoided.[17,18] Posterior tilting of the bladder after an abdominoperineal resection (APR) or inflammatory change in the paravesical tissues may also cause difficulty in bladder empting.[19] However, urinary dysfunction after bilateral resection of the inferior hypogastric nerve plexus (IHNP) is devastating. A surprisingly large proportion of patients suffer various urinary tract problems due to extended lymphadenectomy. The extent of resection should be decided by the extent of the cancer, and routine excision of the IHNP should not be performed.[10]

Sexual function (SF)

Results of studies of male SF after conventional rectal cancer surgery show impotence rates ranging from 20% to 46%, while 20%–60% of potent patients are unable to ejaculate.[17,20] These sexual dysfunctions are, of course, due to intraoperative nerve injury. Therefore, preservation of the pelvic autonomic nerves such as the HP and IHNP seems to adequately lower the incidence of sexual morbidity. Havenga,[18] and Enker[21] reported that the use of autonomic nerve-preserving pelvic sidewall dissections enabled preservation of potency and ejaculation in 86.7% and 87.9%, respectively, of male rectal cancer patients. The reports by Maas et al.[17,22] and others[11] about Dutch patients with rectal cancer, although the number of patients was small, are also worth paying attention to. In a pilot study, several types of autonomic nerve-preserving techniques were performed according to the extent of rectal cancer. Of 17 patients in whom the bilateral IHNPs were preserved, 16 (94%) maintained erectile ability. With preservation of the SHNP, ejaculation was maintained in 90% of the patients. These two results practically proved that when precise autonomic nerve preservation is done, nearly 90% of male sexual function can be preserved. This means that in the treatment of rectal cancer, surgeon-related factors are extremely important, not only in achieving local control but also in preserving function.[23]

In all rectal cancer patients whose SHNP was sacrified for an oncological reason, the operation was associated with ejaculation dysfunction. But when the IHNPs are preserved, impotence does not occur. In other words, ejaculation dysfunction results from the sacrifice of the SHNP, and impotence results from the sacrifice of the IHNP. Another important finding is that a 2-year follow-up with questionnaires showed that both urinary and sexual functions were preserved unchanged compared with findings in the first postoperative questionnaire.

In Western countries, clinical trials investigating the role of preoperative radiotherapy (PRT) for stage T3 or more rectal cancer were conducted and a significant effect of PRT in preventing local recurrence was reported.[5,6] Consequently, PRT became a standard treatment for rectal cancer in Western countries. However, is this treatment strategy correct, as expected? The advantages and disadvantages of radiotherapy should be discussed not only in terms of local control but also in terms of dysfunction. The nature of radiation damage to tissues and organs is the manifestation of damage to lymphatic and blood vessels: tissues within the radiation field become fibrotic, blood flow becomes impaired, and the functions of organs exposed to radiotherapy deteriorate over time. These are all well-known basic facts about radiation biology. There were reports that erectile deficiency occurred in as many as 62% of patients undergoing radiotherapy for prostate cancer.[24,25] Thus far, there have been only a small number of reports regarding its negative effects; however, the number of such reports has recently begun to increase. Heriot et al.[26] reported that radiotherapy had an adverse effect on the ability to have and mantain an erection, to attain orgasm, and to be sexually active in comparison with patients undergoing surgery alone (7.4%, 12.6%, 16.2%, and 13.7% reductions, respectively, 8 months after surgery; $P < 0.05$). In addition, in a report by Marijnen et al.,[27] the realities of sexual dysfunc-

tion due to preoperative short-term high-dose radiotherapy in the Dutch trial are described as follows. At 24 months, 76% of male patients without PRT and 67% of patients with PRT who were previously active were still sexually active. For female patients, these figures were 90% and 72%, respectively. A negative influence of PRT was observed in males for ejaculation disorders, with a further deterioration over time, which can be explained by the fact that the seminal vesicles have been irradiated and may stop function. Irradiated men show a decrease in erectile function for up to 2 years, suggesting late radiation damage to the small vessels. As noted above, urinary and sexual dysfunctions due to PRT were reported to occur at a high frequency, but the realities of dysfunctions, that last for 2 years or longer remain unclear. Furthermore, no clinical trial has yet been conducted to investigate differences in the dysfunctions between short-term high-dose (25 Gy in five fractions over 5–7 days) and conventional (50.4 Gy) radiation therapy protocols. Therefore, the creation of a protocol that enables analysis of long-term functional outcome will be essential for future clinical trials.

Laparoscopic rectal surgery (LRS) is applied in the treatment of rectal cancer, but there have been only a few reports on functional outcomes due to LRS. The report from the conventional versus daparoscopic-Assisted Surgery In Calorectal Cancer (CLASICC) trial shows that LRS did not adversely affect bladder function, but there was a trend towards worse male sexual function. This may be explained by the higher rate of TME in the LRS group.[28] LRS, in which the running patterns of nerves in each region can easily be identified compared with open surgery, needs to be further investigated in terms of functional outcomes in the treatment of rectal cancer.

The physiologic function of autonomic nerves in females is considered as follows: the sympathetic nerves are responsible for emissions and the rhythmic contraction of the genital ducts and organs during orgasm. The parasympathetic nerves are responsible for increased blood flow to the vagina and vulva, causing vaginal lubrication and swelling of the labia and clitoris. Hendren et al.[29] observed that specific sexual problems in women were loss of libido (41%), loss of arousal (29%), loss of lubrication (56%), lack of orgasm (35%), and dyspareunia (46%), and they speculated that deterioration of SF after an APR in women were due to colostomy and radiation-induced scarring. However, in women, information on SF before and after surgery is not easily obtained, and there are more unknown aspects than in men.

Defecation function (DF)

Transanal hand-sewn anastomosis and intersphincteric resection (ISR) have also begun to be employed for rectal cancer within 5 cm of the anal verge, which was conventionally considered as an indication for APR, thereby expanding the indications for sphincter-preserving surgery (SPS).[30,31] Ueno et al.[32] investigated intramural distal spread using pathologic specimens obtained during APR, and reported that three factors: tumor budding in the invasive front, involvement of three-quarters or more of the circumference, and type 3 gross appearance were correlated with the frequency of intramural distal spread; hence, if none of these factors was present, the 1-cm rule of distal clearance can be applied. This finding provided a pathologic basis for expanding the indications for ISR.[32]

A study has investigated the use of magnetic resonance imaging (MRI) to visualize the presence or absence of tumor invasion of the internal and external anal sphincters and the levator ani muscle, for the purpose of obtaining a basis for confirming the indications for ISR.[33] ISR involves contradictory factors including: (1) compromising the radicality of cancer surgery; (2) deteriorating DF after operation; and (3) intraoperative implantation. At the same time, it is necessary to know that the degree of technical difficulty of ISR depends on the patient's body shape. Large males with well-developed muscles and obese patients with a narrow pelvis require a deep transanal approach, which involves a high degree of technical difficulty.

Normal DF is achieved by the neurological coordination between reservoir and sphincteric functions (defecation reflex). SPS, particularly transanal anastomosis and ISR, inevitably involves the deterioration of reservoir function and loss of defecation reflex. Bittorf et al.[34] reported that J-pouch reconstruction enabled the improvement of DF. However, in order to determine whether the creation of a colonic pouch or straight coloanal anastomosis is an effective reconstruction technique for improving DF in Japanese patients, it is necessary to conduct an investigation specifically designed for Japanese patients, because the properties of the stool differ according to eating habits.

In two randomized studies, postoperative DF was investigated in groups who had received preoperative short-term high-dose radiotherapy. Dahlberg et al.[35] reported that the number of defecation was significantly increased in the irradiated group. Incontinence for loose stools, urgency, and emptying difficulties were also more frequent in that group, compared with the surgery-alone group. On the other hand, Marijnen et al.[36] reported that there was no significant difference in DF between their two groups (PRT- arm and PRT + arm) at 24 months after surgery.

Gervaz et al.[37] investigated the impact of adjuvant chemoradiotherapy on DF in patients undergoing J-pouch reconstruction. In their study, incontinence to gas, liquid stool, and solid stool were significantly more frequent in the irradiated group. Moreover, irradiated patients reported more frequent pouch-related problems, such as clustering and sensations of incomplete evacuation. Regression analysis demonstrated that radiation-induced sphincter-dysfunction was progressive over time.

After a comprehensive evaluation of DF using a validated instrument, Temple et al.[38] concluded that patients treated with adjuvant radiotherapy, coloanal anastomoses, or handsewn anastomoses had significantly worse function.

As we have seen, DF in irradiated patients is significantly impaired, similarly to SF. The probable reasons for the

impairment include fibrosis of the anal sphincteric muscles or anal canal epithelium and lowered compliance of the intrapelvic organs. Therefore, long-term observations are required to investigate to what extent irradiation has a negative impact on DF.

There are differences in radiation sensitivity among organs, but radiation damage extends widely over the intrapelvic organs; hence, one should understand, from a comprehensive viewpoint, that urinary, sexual, and defecation dysfunctions reflect neurogenic, vasculogenic, and musculogenic damage. It can possibly be said that now is the time to strictly limit the indications for preoperative radiotherapy for rectal cancer to patients at high risk of local recurrence.

Is sentinel lymph node (SLNS) navigation surgery (SLNNS) effective for rectal cancer?

SLNs are the lymph nodes most likely to harbor metastasis from a primary lesion, and SLNNS is a concept based on the assumption that such lymph nodes exist. During this procedure, SLNs are marked, using a dye and/or radioactive material for identification, and are subsequently excised to examine for the presence or absence of metastasis. If the SLNs identified are found without metastasis, then the lymph node dissection is not performed; if the SLNs contain metastasis, the lymph node dissection is performed. In other words, the sentinel node examination is an intraoperative test to confirm that limited surgery or function-preserving surgery is beneficial. For breast cancer and malignant melanoma, this test is effective, because SLNs are located at sites far from the primary lesion. Conversely, the colon and the rectum, particularly the rectum, are organs rich in lymphatics, and their lymphatic pathways start just below the tumor. For this reason, the marker is injected near the tumor site, which then overlaps with the injected site, thus making it difficult to differentiate SLNs from the background, and reducing the effectiveness of the procedure. There have been attempts to investigate SLN biopsy for digestive tract cancer, but with sensitivity ranging from 70% to 100% and false-negative rates of 0 to 40%, SLN biopsy loses importance as a method for selecting patients for lymph node dissection. It can be said that the significance of SLNs rather relies on the efficient retrieval of lymph nodes. In Western countries, SLNNS has been applied to colorectal cancer, with the view that the expansion of patient selection for adjuvant therapy by upgrading stage I/II to stage III can benefit patients.[39,40]

Are there true scales for quality of life (QOL) evaluation?

It is difficult to evaluate QOL after rectal cancer surgery. In many articles, analyses show that if there is no tumor invasion into the anal sphincter muscles, SPS should be selected.[41] But in the Dutch trial, an analysis using health-related QOL showed no difference in QOL between APR and SPS.[36] To decide whether or not to perform SPS, discussion with the patient and consideration of the patient's personal situation are required. A report from Norway shows that, with a better body image and fewer male sexual problems, patients had a more favorable QOL after SPS compared with that after APR; however, there was no difference in overall QOL.[42] Even after total pelvic exenteration, even the patients with double stomas reported having a good QOL. This may be attributable to the adaptation or response shift seen particularly in individuals who have overcome cancer, a disease that threatens the patient's life.[43,44] Thus, the question arises as to whether there really are evaluation methods that can objectively produce an overall QOL score. Even with the use of the randomized controlled clinical trial, a methodology with a high level of evidence, it is difficult to evaluate QOL studies. Is there a difference in the basic evaluation scale between the logic of the medical professional and the logic of patients? If there is, medical professionals may be still at a stage where information about QOL should be humbly learned from patients.

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Diseases of the Colon & Rectum

Intersphincteric Resection in Patients with Very Low Rectal Cancer: A Review of the Japanese Experience

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PURPOSE: This study was designed to evaluate the feasibility and oncologic and functional outcomes of intersphincteric resection for very low rectal cancer. METHODS: A feasibility study was performed using 213 specimens from abdominoperineal resections of rectal cancer. Oncologic and functional outcomes were investigated in 228 patients with rectal cancer located <5 cm from the anal verge who underwent intersphincteric resection at seven institutions in Japan between 1995 and 2004. RESULTS: Curative operations were accomplished by intersphincteric resection in 86 percent of patients who underwent abdominoperineal resection. Complete microscopic curative surgery was achieved by intersphincteric resection in 225 of 228 patients. Morbidity was 24 percent, and mortality was 0.4 percent. During the median observation time of 41 months, rate of local recurrence was 5.8 percent at three years, and five-year overall and disease-free survival rates were 91.9 percent and 83.2 percent, respectively. In 181 patients who received stoma closure, 68 percent displayed good continence, and only 7 percent showed worsened continence at 24 months after stoma closure. Patients with total intersphincteric resection displayed significantly worse continence than patients with partial or subtotal resection. CONCLUSIONS: Curability with intersphincteric resection was verified histologically, and acceptable oncologic and functional outcomes were obtained by using these procedures in patients with very low rectal cancer. However, information on potential functional adverse effects after intersphincteric resection should be provided to patients preoperatively. [Key words: Very low rectal cancer; Intersphincteric resection; Abdominoperineal resection; Coloanal anastomosis; Anal function]

Local control and survival for patients with rectal cancer have been improving with the development of surgical techniques and combined adjuvant therapies.[1,2] The advent of mechanical low-stapling and double-stapling techniques and sutured coloanal anastomosis has facilitated easier anastomosis at the distal rectum. These methods have increased the frequency of sphincter salvage. Nevertheless, permanent colostomy is still performed in approximately 20 percent of patients with low rectal cancer. Abdomi-

Sponsored by a Grant-in-Aid (14-10) for Cancer Research from the Ministry of Health, Welfare and Labor of Japan.

Reprints are not available.

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Dis Colon Rectum 2006; 49: S13–S22
DOI: 10.1007/s10350-006-0598-y

noperineal resection (APR) is a standard surgery for low rectal cancers located <5 cm from the anal verge or <2 cm from the dentate line (DL). These cancers may be associated with lymph node metastasis along the levator ani muscle or in the fatty tissue of the ischiorectal fossa,[3] and also may have the potential for microscopic involvement of the rectal wall below the tumor.[4] APR has been established as a standard procedure in patients with lower rectal cancer. Patients undergoing APR can experience some problems with quality of life, because permanent colostomy results in psychologic and social limitations.[5,6]

In recent years, intersphincteric resection (ISR) with coloanal anastomosis has been proposed to avoid permanent colostomy for rectal cancers located <5 cm from the anal verge, although these tumors are not generally considered for sphincter-saving procedures.[7–13] Several studies have reported that local control and functional results after ISR are satisfactory.[7,10–14] Experiences with ISR, including partial external sphincteric resection (PESR), also have been reported in recent studies[12,15]; however, data remain scarce. The rationale for ISR in patients with very low rectal cancer is described in this review article by using data from Japanese experiences and Western reports, and our theoretic background is provided based on the histologic evidence.

PATIENTS AND METHODS

Pathologic and Theoretic Background

The pathologic study was performed by a surgical pathologist (KS) at Kurume University. In this pathologic study of 213 surgical specimens from APR for lower rectal cancer or anal canal cancer excluding anal cancer, the external sphincter muscle, puborectalis muscle, and fatty tissue of ischiorectal fossa were investigated for direct invasion and skip metastasis. The entire tumor mass was sectioned at 5-mm intervals, including oral and anal parts up to 5 cm from the tumor. The same surgical pathologist (KS) made all final pathologic diagnoses.[15,16]

Patient Population

A total of 228 consecutive patients (168 males) who underwent ISR between 1995 and 2004 were identified from the hospital databases, and medical charts were retrospectively reviewed. These 228 patients received ISR at seven institutions in Japan that participated in the "Studies on preservation of anal function for very low rectal cancer patients," sponsored by Grant-in-Aid 14-10 for Cancer Research from the Ministry of Health, Welfare and Labor of Japan. Median age was 58 (range, 27–77) years. All 228 patients displayed adenocarcinoma located <5 cm from the anal verge.

The anal verge was defined as the terminal part of the surgical and anatomic anal canal. The intersphincteric groove (ISG) exists between the terminal part of the internal sphincter (IS) and the subcutaneous part of the external sphincter (ES). Exact level of the lower edge of the tumor from the anal verge was assessed and measured by digital examination and endoscopy. All tumors found infiltrating the rectal wall on digital examination, computed tomography (CT), magnetic resonance imaging (MRI), or endorectal ultrasonography (US) were eliminated from consideration for local excision. Patients were classified according to International Union Against Cancer (UICC) standards[17] after preoperative diagnosis using CT, MRI, US, colonoscopy, chest radiography, and biopsy.

An exception to selection of ISR was made if malignant infiltration of other organs or of the striated muscles of the pelvic floor (such as levator ani muscle or external sphincter) was suspected, if tumors displayed low differentiation on histopathology, or if preoperative anal function demonstrated marked insufficiency. Patients with synchronous metastases also were excluded from ISR. These patients were treated by using conventional APR. In the present study, ISR was performed mainly in very low rectal cancer patients with T3, T2, or T1 (massive invasion of the submucosa) disease lying <5 cm from the anal verge. All resected specimens were examined to determine macroscopic and microscopic surgical margins (distal and radial). Postoperative mortality and morbidity, local control, and survival also were investigated.

Surgical Technique and Classification

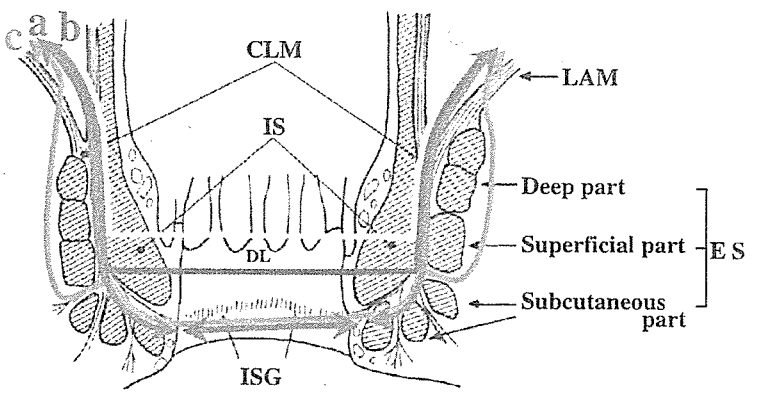
ISR was performed according to the methods previously reported by Schiessel *et al.*[7] and others.[10,12,15] The surgical technique included both abdominal and perianal approaches. Abdominal dissection was performed first. Total mesorectal excision (TME) with lateral node dissection was undertaken. During the abdominal approach, the autonomic nerve system was preserved to the fullest

extent possible, using Japanese methods previously described.[18–22] The rectum was mobilized carefully as low as possible to the pelvic floor to facilitate the perianal approach. The IS was then exposed and circumferentially divided from the puborectalis muscle and ES. During these procedures, the tumor was evaluated through gentle palpation by the surgeon. If tumor had invaded beyond the rectum into the puborectalis muscle or ES at the anorectal junction or anal canal, the puborectalis muscle was resected and fatty tissue of the ischiorectal fossa was visualized. ISR plus PESR was performed in those patients.

After the abdominal approach, perianal resection was performed. Circumferential incision of the mucosa and IS was initiated 1 to 2 cm distal to the tumor. The anal orifice was closed by pursestring suture to avoid spread of tumor cells during perianal operation.[12] Once the intersphincteric space was entered, careful dissection continued upward between the smooth and striated sphincters under constant guidance by the abdominal surgeon.

Total ISR involved complete excision of the IS for tumors spreading to or beyond the DL. The distal cut-end line was at the ISG. Total ISR was unnecessary in patients with tumor located ≥2 cm from the DL. Those patients underwent subtotal ISR. The distal cut-end line was between the DL and ISG, and the DL was included in the resected specimen. In patients with tumor located from >2 to 3 cm from the DL, the distal cut-end line was just on or above the DL. This procedure, partial ISR, sometimes includes conventional coloanal anastomosis procedures. When patients displayed tumor invading the ES, ISR plus PESR was performed. At least the subcutaneous part of the ES was preserved in these patients. ISR was classified into four types: total ISR; subtotal ISR; partial ISR; and ISR + PESR (Fig. 1).

After specimen removal and generous irrigation of the pelvic cavity, the sigmoid colon was pulled down and coloanal anastomosis with or without colonic pouch was made according to the method described by Parks.[23] Anastomoses were performed by using perianal manual suturing in all patients.



Type of ISR	Anastomotic line	Sacrificed sphincter
Partial	Just on DL or within 1cm oral side from DL	Partial IS
Subtotal	Between DL and ISG	Almost all of IS
Total	Just on ISG	Total IS without or with partial ES

Figure 1. Resecting lines in intersphincteric resection (ISR) are illustrated. PESR=partial external sphincteric resection.

Finally, a diverting stoma using terminal ileum or transverse colon was established. This stoma was closed at three to six months postoperatively.

Adjuvant Therapy

Preoperative radiochemotherapy was performed in 57 patients with T3 tumors who agreed to preoperative adjuvant therapy at the National Cancer Center Hospital East (NCCHE), National Defense Medical College, or Chiba University. Other patients underwent surgery alone, because preoperative radiochemotherapy for resectable rectal cancer is not standard in Japan. The 44 patients from the NCCHE received 45 Gy during a five-week period, followed by operation two weeks later. In addition, continuous infusion of 5-flurouracil (250 mg/m^2/day) was administered to these patients during radiotherapy to increase radiotherapeutic efficacy. Although revaluation using CT, MRI, US, and colonoscopy was performed in these patients after completion of preoperative radiochemotherapy, all patients underwent ISR. Most patients with Stage III tumor (pTNM pathologic classification) received postoperative chemotherapy with 5-fluorouracil and folinic acid, or tegaful uracil, or others for six months or more.

Follow-Up and Functional Assessment

Follow-up examinations were performed every three months for two years postoperatively, and subsequently every six months. Examinations included clinical, laboratory (including tumor markers, such as carcinoembryonic antigen and carbohydrate antigen 19-9), and radiologic (abdominal and pelvic CT and chest radiography) investigations.

Functional outcomes also were assessed at the same time by using our functional questionnaire. This functional questionnaire asked about stool frequency (number of bowel movements per 24 hours), feces and flatus discrimination, urgency (ability to defer stool evacuation for >15 minutes), fragmentation (≥2 evacuations in 1 hour), soiling during the day and night, use of pads, use of medications, and alimentary restriction. Incontinence was assessed by using the continence scores of both the Jorge and Wexner,[24] and classification by Kirwan *et al.*[25]

Median follow-up was 41 (range, 10–84) months. No patients were lost to follow-up, and 57 percent of patients were observed for ≥36 months.

Statistical Analysis

Overall survival (OS) and disease-free survival (DFS) were calculated by using Kaplan-Meier methods. Duration to final follow-up evaluation, treatment failure, or death was measured from the date of rectal resection. Assessment of local recurrence was evaluated by using a cumulative local disease-free survival curve. Assessment of recurrence and survival was performed in patients with microscopically curative surgery.

RESULTS

Pathologic Validity

Pathologic study of the 213 surgical specimens from APR for lower rectal cancer or anal canal cancer (excluding anal cancer) revealed neither direct invasion nor skip metastasis in subcutaneous external sphincter muscle or fatty tissue of the ischiorecal fossa; however, spread of cancer to the deep and superficial ES muscles or puborectalis muscle was observed in 14 percent. Curative operation was thus accomplished by using ISR in 86 percent of patients undergoing APR. When tumor invasion exceeds the IS at the surgical anal canal, safe surgical margins can be obtained using ISR with combined resection of the deep and superficial ESs. Complete radical surgery can theoretically be accomplished even if subcutaneous ES muscle is not resected.

Population

The study was comprised of 228 patients with very low rectal cancer (including surgical anal canal cancer) who underwent ISR between 1995 to October 2004. Tumor characteristics and surgical procedures are shown in Table 1. Median lower edge of the tumor was 3.4 (range, 2–5) cm from the anal verge. Tumor staging was T3 tumor (n = 103), T2 tumor (n = 78), or T1 (n = 46). Surgical procedure was subtotal ISR in 124 patients, total ISR with or without PESR in 69 patients with tumor located ≤ 2 cm from the anal verge, and partial ISR in 35 patients. These procedures were decided according to tumor localization. All patients underwent coloanal anastomosis by manual suturing. Anastomosis involved a colonic J-pouch (n = 51), coloplasty (n = 25), side-to-end anastomosis (n = 5), or straight anastomosis (n = 147).

Table 1.
Patients Undergoing ISR

	(n = 228)
Age (yr)	58 (27–77)
Male/female ratio	168/60
Tumor	
Distance from anal verge (cm)	3.4 (2–5)
Clinical stage	
T1	46
T2	78
T3	103
T4	1
Procedure	
Partial ISR	35
Subtotal ISR	124
Total ISR (with or without PESR)	69
Morbidity rate	24 percent (55/228)
Mortality rate	0.4 percent (1/228)

ISR = intersphincteric resection; PESR = partial external sphincteric resection.

Data are medians with ranges in parentheses or numbers of patients.

Fifty-seven patients received preoperative radiochemotherapy.

Morbidity and Mortality

Postoperative complications occurred in 55 patients (24 percent), including anastomotic leakage (n = 23), pelvic infection and abscess (n = 10), anastomotic stenosis (n = 7), colonic ischemia and necrosis (n = 4), anovaginal fistula (n = 3), postoperative bleeding (n = 3), mucosal prolapse (n = 3), and postoperative ileus (n = 2). In 9 of these 55 patients (4 percent), additional surgery, such as APR or Hartmann's operation, was required because of postoperative massive hemorrhage, colon necrosis, or anastomotic insufficiency. Surgery-related death occurred in one patient (0.4 percent) who experienced a breakdown of colonic J-pouch and died of sepsis. No differences in morbidity were identified between the radiochemotherapy and surgery-alone groups.

Pathologic Findings

Radical resection of the tumor was achieved in all 228 patients. Surgery was judged as microscopically curative in 225 patients (98.7 percent) who displayed adequate cancer-free margins (distal and radial). Unclear surgical margins were noted in three patients with Type 3 tumor, because microscopic vessel involvements were observed very near to the surgical margins. These three patients were excluded from assessments for recurrence and survival, although none of these patients received additional surgery, such as APR, because obvious positive margins were not identified. Follow-up was performed as usual.

Recurrences

During the median observation time of 41 months, 30 of 225 patients developed recurrence. These recurrences comprised lung metastasis (n = 11), liver metastasis (n = 11), local recurrence including regional lymph node metastasis (n = 8), inguinal lymph node metastasis (n = 4), bone metastasis

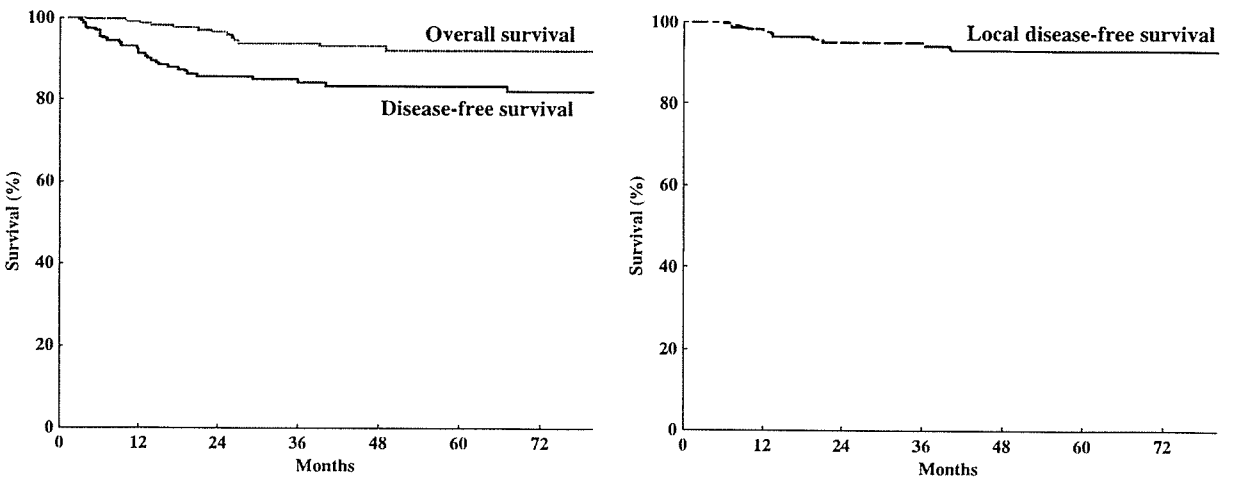


Figure 2. Overall survival was 91.9 percent and disease-free survival was 83.2 percent at five years. Acceptable local control also was obtained.

Table 2.
Functional Results After Stoma Closure

	(n = 181)			
	3 Months	6 Months	12 Months	24 Months
Continence				
Wexner score (n = 110)	17 ± 1.7	11.2 ± 4	8.4 ± 4.5	7.8 ± 4.2[a]
Kirwan classification				
I Perfect	17	19	36	36
II Incontinence of flatus	11	12	16	32
III Occasional minor soiling	45	51	36	25
IV Frequent major soiling	19	16	12	7
V Incontinent (required colostomy)	8	2	0	0

ISR = intersphincteric resection.
Data are means ± standard deviations or percentages.
[a] Partial ISR (mean, 6); subtotal ISR (mean, 7.8); total ISR with or without partial external sphincteric resection (mean, 11.1).

(n = 1), and abdominal wall metastasis (n = 1). In seven of eight patients with local recurrence, recurrence occurred in lateral nodes[18–22] located between the pelvic plexus and lateral pelvic wall, or in the tissue surrounding the external iliac artery. Local recurrence in one patient occurred in the prostate with multiple lung metastases. Patients with liver or lung metastasis alone received curative partial hepatic or lung resection (n = 9). Patients with regional or inguinal lymph node metastasis also received lymphadenectomy (n = 4). Cumulative local recurrence rate was 5.8 percent at three years and 6.7 percent at five years (Fig. 2). No patients displayed anastomotic recurrence. No differences in recurrence rate or site were noted between preoperative radiochemotherapy and surgery-alone groups, although median observation time was shorter in the preoperative radiochemotherapy group (26 months) compared with the surgery-alone group.

Survival

A total of 18 patients died, with 16 deaths from distant metastasis. OS was 91.9 percent at five years, and DFS was 83.2 percent at five years (Fig. 2). No significant differences in OS or DFS were identified between preoperative radiochemotherapy and surgery-alone groups at three years (DFS: 75.1 *vs.* 85.8 percent).

Functional Outcome

Of 219 patients excluding patients with additional surgery, such as APR or Hartmann's operation, 181 received diverting stoma closure at a median of five (range, 3–24) months postoperatively. Stoma closure is planned for 30 patients. Conversely, no plan for stoma closure was made in eight patients because of anal dysfunction (n = 3), early-phase recurrence (n = 3), or anovaginal fistula (n = 2). Continence status is shown in Table 2. Although only 30 percent of patients displayed good continence (Kirwan's Grade 1–11) at six months after stoma closure, 68 percent of patients showed good continence at 24 months after stoma closure. Worsened continence was observed in only 7 percent of patients.

Wexner score was investigated sufficiently in 110 patients, with scores of 11.2 ± 4 at six months after stoma closure, 8.4 ± 4.5 at 12 months, and 7.8 ± 4.2 at 24 months. Anal function improved monthly until 24 months after stoma closure. However, day or night soilings were sometimes observed at 24 months after stoma closure in patients with total ISR. Mean Wexner score at 24 months after stoma closure was 6 in the partial ISR group, 7.8 in the subtotal ISR group, and 11.1 in the group that underwent total ISR with or without PESR. Although no significant differences in Wexner score were apparent between partial and subtotal ISR groups, patients who underwent total ISR with or without PESR exhibited significantly worse continence than those with partial or subtotal ISR (Wexner score, 11.1 *vs.* 6 and 7.8, respectively; $P < 0.05$).

DISCUSSION

The general consensus is that most rectal cancers <5 cm from the anal verge or <2 cm from the dentate line are treated by using APR. In recent years,

however, the need for a margin of ≥2 cm margin has been challenged, and a distal margin of 1 to 2 cm is now considered sufficient in most instances. Sphincter-saving operations, such as ultralow and conventional coloanal anastomosis for cancer of the lower third of the rectum, have been reported by specialized teams, with local recurrence rates of 4 to 13 percent.[26–31] Although ultralow and coloanal anastomosis have been associated with some controversial functional results, patients without permanent stoma have been widely accepted as displaying better quality of life. However, most tumors in these studies have been located ≥5 cm from the anal verge. In more recent years, ISR with coloanal anastomosis has been reported for rectal cancer located <5 cm from the anal verge by a few specialized teams.[7–13] However, some fears of oncologic results and poor anal functions have been noted, as patients display reduced surgical margins compared with APR and the internal sphincter is removed.

This study was designed to investigate the pathologic evidence and oncologic and functional results of ISR. In the present series, tumors were located ≤5 cm from the anal verge. All these patients would have required APR if treated using standard procedures. According to pathologic examination using resected specimens from APR in this study, curative operation can be accomplished by ISR in almost all patients undergoing APR. In fact, 225 of 228 patients (98 percent) who underwent ISR were considered to display histologically curative results. These results demonstrate the pathologic appropriateness of ISR and the possibility of preserving anal function during the surgical treatment of very low rectal cancers.

Rullier *et al.*[13] reported 92 rectal carcinomas at 3 cm from the anal verge, finding that the distal resection margin was 2 cm and negative in 98 percent of cases. They also reported that median circumferential margin was 5 (range, 0–15) mm and positive (≤1 mm) in ten cases (11 percent). These results show that radical tumor resection can be achieved by ISR procedures in almost all patients with very low rectal cancer.

Morbidity in our study was relatively high, with 55 of 228 patients (24 percent) experiencing complications, although the rate of serious complications was low. Our findings do not differ from those of other reports. Rullier *et al.*[13] reported similar results, with a morbidity rate of 27 percent, whereas Schiessel *et al.*[7] described a rate of 18.4 percent (7/38 patients). Unfortunately, one procedure-related death occurred in the present study. Morbidity rate was particularly high in the first half of our study, although no changes in surgical technique were enacted during this period. Careful treatment and skillfulness in this procedure are needed for these patients if surgery-related complications are to be kept at a minimum.

Although an increase in local recurrence was feared in ISR because of reduced surgical margins compared with APR, cumulative five-year local recurrence rate was 6.7 percent in this series. All local recurrences in this study were outside the normal TME planes. These recurrences would not have been prevented using standard APR and seemed to result from inadequate lateral node dissection. Rullier *et al.*[13] reported that 1 of 58 patients (2 percent) developed local recurrence during a median observation of 40 months. Schiessel *et al.*[7] reported that 4 of 38 patients (10.5 percent) exhibited local recurrence during a median follow-up of three years. Local control in this study does not differ substantially from rates in these other reports. These results demonstrate that acceptable local control can be obtained by using ISR procedures. However, two of three patients with unclear surgical margins in this study developed local recurrence with distant metastases during a median observation of 28 months. Achievement of complete microscopic resection seems important for local control. The five-year overall survival rate in our series was 91.9 percent, whereas the five-year disease-free survival rate was 83.2 percent. Rullier *et al.*[13] reported similar results, with an 81 percent five-year survival rate. Conversely, data for APR patients who underwent surgery in our seven institutions during the same time period showed that APR patients displayed tumors with the same background compared with patients who received ISR, with a median five-year DFS of 65.1 (range, 63.6–70) percent, and median five-year local recurrence rate was 10 (range, 3–19) percent. These data led us to consider the oncologic results of ISR obtained in this study as acceptable. The limit for ISR procedures seems to be circumferential clearance, rather than distal.

Some fears were held for functional outcomes after ISR procedures, because loss of the rectum and IS may induce anal dysfunctions, such as stool frequency, urgency, fragmentation, soiling, and fecal incontinence.[14,32] Approximately 30 to 60 percent of low colorectal or coloanal anastomoses induce functional disturbances collectively termed anterior resection

syndrome.[33–37] Most authors believe preservation of the whole anal sphincter and mucosa is crucial for maintenance of good continence. APR thus represents a standard surgery when distance between the lower edge of the tumor and the anal ring is <2 cm.[38] However, in this study, 93 percent of patients showed good or relatively good continence (Kirwan's Grade 1–111) at 24 months after stoma closure. Mean Wexner score was 7.8 at 24 months after stoma closure. Bretagnol *et al.*[14] and others have reported similar results.[7,10–12] However, seven patients displayed worsened continence. In addition, three patients could not undergo closure of the diverting stoma because of anal dysfunction. Furthermore, patients who underwent total ISR with or without PESR displayed significantly worsened continence compared with partial and subtotal ISR groups in our experience. Information on the potential functional adverse effects after total ISR should be provided to patients preoperatively.

Fecal incontinence after ISR is primarily caused by anal-sphincter insufficiency. Physiologic studies have shown that removal of the internal anal sphincter is associated with a significant decrease in resting pressure.[7,10,12] Anal sphincter insufficiency also may be caused by injury of the external anal sphincter during ISR. Furthermore, neorectal insufficiency may facilitate fecal incontinence, as demonstrated by randomized studies comparing straight and J-pouch coloanal anastomoses.[14,39,40] Anal functions in ISR procedures need to be investigated to compare straight, J-pouch, and transverse coloplasty coloanal anastomoses. More careful intraoperative management, additional surgery, such as colonic pouch, biofeedback treatment, and careful patient selection may facilitate improved outcomes in terms of anal function.

CONCLUSIONS

Curability with ISR procedures was verified histologically in patients with very low rectal cancer. Acceptable oncologic and functional results were obtained by using ISR procedures in patients with very low rectal cancer <5 cm from the anal verge. These procedures can be recommended for APR candidate patients; however, information on potential functional adverse effects after ISR should be provided to patients preoperatively.

ACKNOWLEDGMENTS

Patients with intersphincteric resection studied in this series were registered from the following institutions: Department of Surgical Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Department of Surgery, National Cancer Center Hospital, Tokyo, Japan; Department of Surgery, Faculty of Medicine, Kurume University, Kurume, Japan; Department of Surgery, Fujita Health University, Toyoake, Japan; Department of Surgery 1, National Defense Medical College, Tokorozawa, Japan; Department of Gastroenterological Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan; Department of Gastroenterological Surgery, Aichi Cancer Center, Nagoya, Japan.

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Diseases of the Colon & Rectum

The Risk of Multiple Primary Malignancies with Colorectal Carcinoma

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PURPOSE: With advances in diagnostic techniques and treatment modalities, the number of patients identified with colorectal carcinoma who develop multiple primary malignancy during long-term follow-up has been increasing. We investigated multiple primary malignancies occurring in a large number of colorectal carcinoma patients who had undergone surgery in the 1980s at our institution. METHODS: A total of 1,304 Japanese patients with colorectal carcinoma treated between January 1980 and December 1989 were prospectively followed to investigate the situations in which multiple primary malignancies occurred. To determine whether the incidence of multiple primary malignancies in this series was higher than expected, we calculated the expected numbers of carcinoma occurrences and evaluated these findings by exact binomial test. RESULTS: The median follow-up period was 95 months. The incidence of multiple primary malignancy was 18.7 percent (143/765) among males and 14.7 percent (79/539) among females. The most common site of multiple primary malignancy among males was the stomach, followed by the lung, prostate, larynx, liver, esophagus, and urinary bladder. The most common site among females was the uterus, followed by the stomach, breast, and liver. The sites that showed a higher incidence of multiple primary malignancy than the expected value were: the prostate, larynx, urinary bladder, oral cavity/pharynx and thyroid among males, and the uterus and oral cavity/pharynx among females. CONCLUSIONS: Fifteen to 20 percent of Japanese colorectal carcinoma patients experienced multiple primary malignancies. Postoperative long-term screening methods should be established considering the actual occurrence numbers and risk rate of multiple primary malignancies in addition to metachronous colorectal carcinoma. [Key words: Colorectal carcinoma; Multiple primary malignancy; Follow-up; Expected numbers of carcinoma occurrences]

The incidence rates of each organ carcinoma vary with the times, racial or ethnical groups, and countries. In terms of age-adjusted incidence rates in Japan, a recent report showed that the most common carcinoma among males is gastric carcinoma, followed by colorectal carcinoma and lung carcinoma; and the most common carcinoma among females is colorectal carcinoma, followed by breast carcinoma and gastric carcinoma.[1] Among those carcinomas, the incidence of colorectal carcinoma is rising among both males and females. With advances in diagnostic techniques and treatment modalities, the outcomes of colorectal carcinoma treatment have improved, whereas the number of patients who develop multiple primary malignancy during long-term follow-up has simultaneously increased. However, with regard to the incidence of concurrent colorectal carcinoma and multiple primary malignancy in Japanese patients, many previous reports have merely indicated the number of concurrences, and few reports have described the incidence of the concurrences in relation to patient age and follow-up period.[2–5]

Taking patient age and follow-up period into consideration, we investigated the situations in which multiple primary malignancies occurred during long-term follow-up of a large number of colorectal carcinoma patients who had received treatment in the 1980s at our institution. This paper reports the findings of the investigation.

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Dis Colon Rectum 2006; 49: S30–S36
DOI: 10.1007/s10350-006-0600-8

PATIENTS AND METHODS

A total of 1,304 Japanese patients underwent colorectal carcinoma surgery at our institution between January 1980 and December 1989, and patient information and follow-up data were prospectively collected and added to the department database. In terms of follow-up, we routinely conducted periodic check-ups for the recurrence of colorectal carcinoma until the fifth postoperative year. No routine examinations were performed for multiple primary malignancies. Multiple primary malignancies were confirmed only when patients with multiple primary malignancies were diagnosed or treated at our institution, or documentation from other hospitals was obtained. The follow-up periods was defined as the interval between the date of surgery for colorectal carcinoma and the date at which information regarding the occurrence or absence of multiple primary malignancies was confirmed. We defined metachronous and synchronous carcinomas according to the criteria used by Warren and Gates[6]; synchronous carcinoma was defined as tumors detected after an interval of less than one year, and metachronous carcinoma was defined as tumors detected after an interval of one year or longer. Fifteen patients with familial adenomatous polyposis were excluded, but six patients with hereditary nonpolyposis colorectal carcinoma (HNPCC) were included in this study.

Statistical Analysis

To determine whether the incidence of multiple primary malignancies in this series was higher than the average incidence in Japan, we calculated the expected numbers of carcinoma occurrences by gender and tumor site for each of the following three periods: 1) from the date of birth to the date of surgery, 2) from the date of surgery to the final date of confirmation of survival, and 3) from the date of birth to the final date of confirmation; then we compared those expected numbers with the observed numbers.

The expected numbers of carcinoma incidences were computed by summing the cumulative risk of developing carcinoma for each patient during the period; those numbers were calculated based on the age-specific and gender-specific carcinoma incidence rates in Japan.[1,7] For example, the cumulative risk of stomach cancer from the date of surgery (1985) to the final date of confirmation of survival (1995) for a female patient aged 60 years at surgery was obtained by the sum of the incidence rates of stomach cancer for females aged 60 years in 1985, that for females aged 61 years in 1986, . . . , and that for females aged 70 years in 1995. In the case of a period of less than one year, the probability was obtained by multiplying the incidence rate by the number of days per 365.25. The methods of estimating cancer incidence in Japan and their limitations have been explained in previous reports, and corrections were applied to minimize any possible bias.[7–9] The cancer incidence rates after 2000 and before 1974 were assumed to be equal to those of 1999 and 1975, respectively, because data before 1974 and after 2000 have not been published. The two-tail P value was calculated exactly based on binomial distribution (exact binomial test).

Clinicopathologic parameters, such as gender, age, location of tumor, Dukes stage, and presence or absence of adjuvant treatment were compared by using Student's t-test or the chi-squared test where appropriate. $P < 0.05$ was considered significant.

RESULTS

Patient Characteristics

The follow-up periods for all patients ranged from 1 to 269 (median, 95) months. The mortality rate for male patients was 51.9 percent (397/765), and that for female patients was 41.7 percent (225/539). The patient demographics are summarized in Table 1. The incidence of multiple primary malignancy was 18.7 percent (143/765) among males and 14.7 percent (79/539) among females, showing no difference between the two groups ($P = 0.0614$). A comparison between patients with only colorectal carcinoma (O) and patients with multiple primary malignancies (M) demonstrated that the mean age at the onset of colorectal carcinoma was significantly higher in the M group among both males and females ($P < 0.0001$, $P = 0.0008$, respectively). With regard to the locations of colorectal carcinoma, the proportion of M was significantly higher among male colon carcinoma patients ($P = 0.0002$), but there was no difference among females ($P = 0.6277$). Patients with a more advanced Dukes stage had a significantly lower proportion of M in both males and females ($P < 0.0001$, $P = 0.0049$, respectively). With regard to adjuvant treatment, 37 patients underwent adjuvant radiotherapy and no patients developed subsequent

Table 1.
Characteristics of the Patients

Variable	Male (n = 765)		Female (n = 539)	
	Only Colorectal Carcinoma (n = 622)	Multiple Primary Malignancies (n = 143)	Only Colorectal Carcinoma (n = 460)	Multiple Primary Malignancies (n = 79)
Mean age at surgery for colorectal carcinoma (yr)	58.9[a]	65[a]	58.4[b]	63.2[b]
Synchronous		67.5		67.5
Metachronous–colorectal carcinoma preceding				
Age at colorectal carcinoma (yr)		61.2		59.4
Age at multiple primary malignancies (yr)		69.6		67.1
Metachronous–multiple primary malignancies preceding				
Age at multiple primary malignancies (yr)		58.1		53.5
Age at colorectal carcinoma (yr)		67.4		64.6
Location[g]				
Colon	272[c]	87[c]	229[d]	37[d]
Rectum	348[c]	55[c]	229[d]	42[d]
Dukes stage				
A	105[e]	41[e]	86[f]	17[f]
B	177[e]	49[e]	110[f]	31[f]
C	194[e]	33[e]	142[f]	22[f]
D	146[e]	20[e]	122[f]	9[f]

[a] $P < 0.0001$;
[b] $P = 0.0008$;
[c] $P = 0.0002$;
[d] $P = 0.6276$;
[e] $P < 0.0001$;
[f] $P = 0.0049$.
[g] Five patients with synchronous or metachronous carcinoma of the colon and rectum were excluded from the analysis.

Table 2.
Observed and Expected Number of Multiple Primary Malignancies in Males (n = 143)

Site	Total No. of Malignancies			Multiple Primary Malignancies Preceding and Synchronous			Colorectal Carcinoma Preceding		
	Obs	Exp	*P* Value	Obs	Exp	*P* Value	Obs	Exp	*P* Value
Stomach	59	54.7	0.5277	37	33.4	0.8596	22	20.9	0.7395
Lung	25	22.9	0.5957	13	10.2	0.0063	12	12.3	1
Prostate	12	5.5	0.0144	1	1.7	<0.001	11	3.6	0.0013
Larynx	11	2.1	<0.001	8	1.2	0.0066	3	1	0.0735
Liver	10	14	0.3441	3	6.9	0.2435	7	7	1
Esophagus	10	6.1	0.1468	5	3.2	0.0156	5	2.9	0.2198
Urinary bladder	10	4.9	0.0361	7	2.3	0.0283	3	2.6	0.7475
Oral cavity/pharynx	7	2.9	0.0274	4	1.6	0.0217	3	1.3	0.1412
Malignant lymphoma	5	3.7	0.4248	3	2.1	0.4786	2	1.5	0.6642
Kidney	4	2.8	0.372	2	1.3	0.0428	2	1.5	0.6643
Skin	4	1.7	0.093	4	0.9	0.5772	0	0.8	1
Pancreas	3	5.8	0.3958	1	2.9	0.7657	2	2.8	1
Thyroid	3	0.6	0.025	3	0.3	0.2849	0	0.3	1
Other	6			1			5		
Total	169			92			77		

Obs = observed; exp = expected.

Table 3.
Observed and Expected Number of Multiple Primary Malignancies in Females (n = 79)

Site	Total No. of Malignancies			Multiple Primary Malignancies Preceding and Synchronous			Colorectal Carcinoma Preceding		
	Obs	Exp	*P* Value	Obs	Exp	*P* Value	Obs	Exp	*P* Value
Uterus	26	8.1	<0.001	19	6.3	0.3079	7	1.8	0.0026
Stomach	18	17.1	0.8053	7	10.9	0.4458	11	6.1	0.061
Breast	14	9.4	0.1342	12	6.2	0.5413	2	3.1	0.7761
Liver	4	3.1	0.5618	0	1.4	0.0589	4	1.6	0.0845
Biliary tract	3	3.0	0.7744	1	1.3	0.1521	2	1.6	0.6755
Oral cavity/pharynx	3	0.7	0.0398	1	0.4	0.0617	2	0.3	0.0456
Malignant lymphoma	3	1.4	0.161	1	0.7	0.1713	2	0.6	0.1287
Skin	3	0.9	0.0628	1	0.4	0.0619	2	0.5	0.0842
Thyroid	3	1.4	0.1638	2	0.8	0.0434	1	0.6	0.4602
Lung	2	4.6	0.3431	1	2.1	0.7298	1	2.4	0.7397
Other	11			9			2		
Total	90			54			36		

Obs = observed; exp = expected.

malignancies. On the other hand, subsequent malignancies developed in 36 of 516 patients (7 percent) who received adjuvant chemotherapy and in 85 of 788 patients (10.8 percent) who did not receive adjuvant chemotherapy ($P = 0.0263$).

Multiple Primary Malignancies

The most common site of multiple primary malignancy among males was the stomach, followed by the lung, prostate, larynx, liver, esophagus, and urinary bladder (Table 2). In detail, the most common site of multiple primary malignancy in male colon carcinoma patients was the stomach (45 percent, 40/88) followed by the lung (14 percent, 12/88), whereas the incidences of stomach (35 percent, 19/55) and lung (23.4 percent, 13/55) carcinoma differed in male rectal carcinoma patients. The most common site among females was the uterus, followed by the stomach, breast, and liver (Table 3).

The sites that showed a higher incidence of multiple primary malignancy than the expected value were the prostate, larynx, urinary bladder, oral cavity/pharynx, and thyroid among males, and the uterus and oral cavity/pharynx among females. In particular, sites showing a significantly higher rate of malignancy than the expected value after colorectal carcinoma surgery were the prostate among males, and the uterus and oral cavity/pharynx among females.

With regard to uterine carcinoma, 14 cases had cervical carcinoma (12 cases of squamous-cell carcinoma and 2 cases of adenocarcinoma), 10 cases had corpus carcinoma (9 cases of adenocarcinoma and 1 case of adenosquamous carcinoma), and the details were unknown in 2 cases. The mean age at the onset of carcinoma was 55.3 (range, 33–76) years in cervical carcinoma cases, and 59.4 (range, 35–82) years in corpus carcinoma cases.

DISCUSSION

In Japan, the incidence of colorectal carcinoma has shown a tendency to increase in recent years, and as the treatment outcomes for each organ carcinoma have improved, it is not unusual to see patients with multiple malignancies involving the colorectum and other organs.[1,2] In the current series of Japanese colorectal carcinoma patients, multiple primary malignancy occurred in 18.7 percent of males, among whom the most common site was the stomach, and in 14.7 percent of females, among whom the most common site was the uterus. The organs in which multiple primary malignancies occurred in colorectal carcinoma patients at a higher incidence than the expected values were the prostate, larynx, urinary bladder, oral cavity/pharynx, and thyroid among males, and the uterus and oral cavity/pharynx among females, which were not necessarily correlated with the numbers of carcinoma occurrences. In previous studies, the reported incidence of other organ carcinomas among colorectal carcinoma patients in Japan ranged from 3 to 8.7 percent, but all of those studies used shorter follow-up periods than our study.[2–5] Our long-term follow-up demonstrated that 15 to 20 percent of Japanese colorectal carcinoma patients experience multiple primary malignancies.

In the results indicated above, there are some noteworthy observations. First, for gastric carcinoma, its incidence in Japan ranks high among both males and females, and also in our study, the occurrence of gastric carcinoma ranked high among both males and females,[1,10,11] but the number was almost the same as the expected value. Hence, it is conceivable that the high occurrence of gastric carcinoma in Japanese colorectal carcinoma patients is merely a reflection of the high incidence of gastric carcinoma in Japan. However, uterine carcinoma was the most common carcinoma among female patients, showing a significantly higher rate than the expected value. With regard to the occurrence of uterine carcinoma among Japanese females, a comparison between data from 1975 and data from 1998 shows that the age-standardized incidence of invasive cervical carcinoma decreased by approximately one-half from 13.4 to 7.2 per 100,000 females; conversely, the corpus carcinoma incidence increased from 1.4 to 4.5 per 100,000 females,[12] and in 1998, the ratio of invasive cervical carcinoma to corpus carcinoma was 1.6:1. In this study, these two carcinomas occurred to ratio of 14:10, and the inclusion of HNPCC cases did not result in a particularly high proportion of corpus carcinoma occurrence. The incidence of uterine carcinoma in Japanese females with colorectal carcinoma needs further investigation in the light of the increasing tendency of patients with corpus carcinoma.

An interesting point in this study is that, in male patients, the incidence of malignancies such as larynx, urinary bladder, and oral cavity/pharynx carcinomas, was significantly higher than the expected value. One of the background factors contributing to such a higher rate may be cigarette smoking. In Japan, adult males have a smoking rate of approximately 50 percent, compared with 20 to 30 percent in Western countries.[13] Recently it has been reported that smoking also is associated with colorectal polyp and colorectal carcinoma.[14–16] To determine whether colorectal carcinoma is a cigarette-associated malignancy and whether cigarette-associated malignancies are likely to occur frequently in colorectal carcinoma patients, it is necessary to conduct further study analyzing a large number of patients followed for a long period.

Regarding the occurrence of other organ carcinomas in colorectal carcinoma patients, the role of genetic factors that contribute to diseases, such as HNPCC, also should be investigated. The reported frequency of HNPCC accounts for up to 5 percent in Western countries, whereas in Japan the frequency ranges from 0.15 to 0.2 percent, which is a greatly low incidence.[17–20] This low rate will possibly rise in future long-term investigations, because the surveillance of patients with HNPCC has just begun in Japan.[19] The incidence of multiple primary malignancy has been reported to be high in patients with HNPCC.[18,21] In this study, we found ten cases of corpus carcinoma; however, as described above, the inclusion of HNPCC cases did not result in a particularly high proportion of corpus carcinoma. Similarly, we also found carcinoma of the renal pelvis in only one case among males, and carcinoma of the small intestine and ureter in only one case among females. It has been pointed out that gastric carcinoma also may occur frequently in patients with HNPCC, but as indicated above, it could be speculated that the high occurrence of gastric carcinoma in Japanese colorectal carcinoma patients is merely the result of the high gastric carcinoma incidence in Japan.[3,19]

In this study, patients with a more advanced Dukes stage had a significantly lower proportion of multiple primary malignancies in both males and females (Table 1). This can be explained by patients with a more advanced Dukes stage having a lower survival rate, resulting in shorter term follow-up and a lower proportion of multiple primary malignancies. However, patients with multiple primary malignancies demonstrated that the mean age at the onset of colorectal carcinoma was significantly high in both males and females compared with that in patients with single colorectal carcinoma. Although patients with single colorectal carcinoma are candidates for subsequent multiple primary malignancies with colorectal carcinoma, the reason for this result needs further investigation. Regarding the proportion of multiple primary malignancies, the proportion rate was significantly higher among male colon carcinoma patients than male rectal carcinoma patients. One possible reason for this is that HNPCC patients were included in this study. Obviously, the rates of colon carcinoma and multiple primary malignancies are elevated in HNPCC patients; however, there was no difference among females, although HNPCC patients also were included. The reason for the difference in incidence between male colon and rectal carcinoma patients needs further investigation.

Obviously, this study has some limitations. With regard to the effects of cigarette smoking, the patients in our series were not interviewed in detail

about their smoking history and we, therefore, could not accurately investigate the contribution of smoking to carcinogenesis in patients with colorectal carcinoma or in patients who developed multiple primary malignancy. In addition, no investigation into carcinoma occurrence in family members was performed during the long-term follow-up period, and hence we also could not obtain data regarding situations in which HNPCC and other hereditary colorectal carcinomas occurred. Moreover, the influence of adjuvant treatment on subsequent malignancies needs further investigation. In this study, no patient developed subsequent malignancies after radiotherapy. One possible reason for this is that patients who received radiotherapy were in a relatively advanced stage, and that only 9 of 37 patients who received radiotherapy survived for more than five years from the surgery for colorectal carcinoma. These points need to be improved in further studies.

CONCLUSIONS

This study was able to obtain some interesting findings on the incidence of other organ carcinomas in Japanese colorectal carcinoma patients. By conducting long-term follow-ups, we found that 15 to 20 percent of these patients in Japan develop multiple primary malignancies. This frequency is projected to rise in future studies with long-term follow-up. For colorectal carcinoma patients, postoperative long-term screening methods should be established, considering the actual occurrence numbers and the risk rate of multiple primary malignancies in addition to metachronous colorectal carcinoma.

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