TABLE III. Risk Factors for Poor Survival After Hepatectomy Evaluated by a Multivariate Analysis Using Cox Proportional Hazard Model

Clinical variables	Odds ratio	95% C.I.	*P*-value
Bilobar metastasis	5.598	1.918–16.339	0.002
Tumor size ≥ 4 cm	3.295	1.413–7.687	0.006

C.I., confidence interval.

Tokyo, that the number of tumors in LMGC was an important factor influence the prognosis [2]. Considering the present results with this previous report, the number and distribution of tumors in LMGC might be significant prognostic factors.

Regarding the difference between synchronous and metachronous metastases, several authors have reported significantly better survival in patients with metachronous metastasis than in those with synchronous disease [13,16]. Neither the results of the present study nor the previous reports from the two cancer centers suggested that the timing of hepatectomy as a factor influencing the survival. We believe that synchronous metastasis is not a contraindication for hepatectomy, provided extrahepatic disease is absent.

Metachronous hepatectomy necessitates the dissection of adhesions between the pancreas, liver, and residual stomach to prepare for Pringle's maneuver. Especially, the upper part of the pancreas adheres to the inferior part of left liver following lymphadenectomy during gastrectomy for the primary tumor. Dissection of such severe adhesion is sometimes technically demanding for surgeons in comparison with hepatectomy for colorectal metastasis, in which minimal dissection of the upper abdominal organs is required. Therefore, hepatectomy should be performed with careful attention paid to the prevention of pancreatic leakage and injury to the bile duct and other adjacent organs.

We also encountered some patients who developed rapidly growing multiple hepatic metastases or peritoneal dissemination while waiting for surgery, who were then excluded. In order to exclude these cases with progressive disease, careful preoperative evaluation of hepatic/extrahepatic metastasis by repeated imaging studies will also be important.

In conclusion, we reviewed the outcomes of highly selected 37 patients who underwent hepatectomy for LMGC. Patients with unilobar LMGC, and/or metastatic tumors measuring < 4 cm in diameter, may be good candidates for a hepatectomy. Synchronous metastasis is not a contraindication for hepatectomy.

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Treatment Strategy for Locally Recurrent Rectal Cancer

Yoshihiro Moriya

Colorectal Surgery Division, National Cancer Center Hospital, Tokyo, Japan

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Review Article

Treatment Strategy for Locally Recurrent Rectal Cancer

Yoshihiro Moriya

Colorectal Surgery Division, National Cancer Center Hospital, Tokyo, Japan

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Despite radical surgery, up to 33% of patients with rectal cancer will develop locoregional relapse. The management of these patients is particularly challenging. Surgery is the mainstay of treatment for those with a mobile recurrence. However, the majority of patients develop recurrence involving the pelvic wall. In these patients, multimodality therapy including radical surgery and intraoperative radiotherapy have been reported with 5-year survival of up to 31% and local control rates of 50–71%. The most important factor for obtaining long-term local control and survival is R0 resection. Extended surgery such as abdomino-sacral resection has not been popular because of 5-year survival rates of 16–31%, and significant postoperative morbidity. Re-recurrence following surgery occurs locally and in the lung, and remains a significant problem. In surgical treatment for local recurrence, surgeon-related factors are crucial. A staging system using degree of fixation and other prognostic factors should be developed so that appropriate treatment modalities are applied to each case.

Key words: locally recurrent rectal cancer – multimodality therapy – extended surgery

INTRODUCTION

In patients who undergo radical surgery for rectal cancer, 4–33% develop locoregional relapse. Without treatment, these patients with locally recurrent rectal cancer (LRRC) have a median survival of ~8 months. If no treatment is given, they suffer from severe symptoms, especially pain, and their quality of life (QOL) becomes extremely poor (1–4). Nearly half of LRRCs are located in the pelvis without distant metastasis. The best treatment for LRRC in this setting is a complete resection of the recurrent tumor.

There are a number of different options for treating LRRC. There options are influenced by the nature of the LRRCs, which may present as a mobile recurrence or a huge mass occupying the pelvis.

In non-fixed recurrent tumors, complete resection can be achieved with limited surgery such as abdomino-perineal resection and the outcomes are relatively favorable.

When an LRRC grows within the narrow pelvis, it can easily invade the pelvic wall, appearing in the form of fixed recurrent tumor (FRT). If FRT involves only anterior structures, total pelvic exenteration achieves adequate margins. However, the majority of patients with LRRC present with dorsal and/or dorsolateral involvement of the pelvis. These patients present a particular challenge. Extensive surgery such as abdomino-sacral resection may be required. However, inappropriate surgical intervention in these patients may cause an iatrogenic cancer spread, leading to impaired QOL.

CONVENTIONAL TREATMENT

In patients with LRRC who are unsuitable for surgical intervention, chemoradation is the main therapeutic option available. The effect of radiotherapy depends on the tumor size and the total radiation dose given. A dose of 45 Gy provides good palliation of pain in 50–80% of patients (5), with low risk of toxicity to the small intestine. However, an anti-tumor effect that may achieve complete response or survival benefit cannot be expected at this dose. Another approach is to administer a dose of 50 Gy to the same radiation field used for the treatment of the primary rectal cancer. The radiation field is then reduced to include only the site of tumor recurrence and a total dose of 60–70 Gy is delivered to this site. However, external beam radiotherapy (EBRT) alone has not been shown to achieve significant survival benefit.

For this reason, the combination of radiotherapy and chemotherapy is usually employed. The rationale for combined therapy includes (i) enhancement of cytotoxicity

For reprints and all correspondence: Yoshihiro Moriya, Colorectal Surgery Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: ymoriya@ncc.go.jp

using an antitumor agent and radiation, (ii) use of chemotherapy, which provides treatment of distant metastasis in addition to the local control of the tumor provided by radiotherapy and (iii) the potential to reduce the dosage of agents and therefore their toxicity by combining different treatment modalities without reducing the overall efficacy (6,7).

EBRT used alone or in combination with chemotherapy provides temporary symptomatic improvement in most patients. Median survival time is 14 months and time of local control is 5 months. Five-year survival rate in these patients is usually <5% (8).

Preoperative chemoradiation is used for primary rectal cancer to downstage the tumor and improve resectability. The same approach has also been used for LRRC. Rodel et al. (9) administered chemoradiotherapy preoperatively in 35 patients with LLRC using 5-FU (1000 mg/m^2/day). They reported that they achieved margin-free resections in 17 cases (61%). Other chemotherapy agents such as CPT-11 and Oxaliplatin are expected to play an important role in the management of these patients in the future (10).

MULTIMODALITY TREATMENT

Reports from some western centers suggest that improved local control and survival can be achieved in selected patients by the use of preoperative chemoradiotherapy, radical surgery and intraoperative radiotherapy (IORT) (11–22). This approach recognizes that satisfactory antitumor effect cannot be achieved by chemoradiation alone. The addition of IORT means that the maximum radiation dose possible can be delivered to the recurrent tumor. This has the potential to allow less extensive surgery to be undertaken.

One of the benefits of IORT is that it produces up to three times the biological effect produced by fractionated EBRT. In addition, IORT has the advantage of delivering radiation accurately to the tumor bed while displacing adjacent normal structures from the irradiation field. The use of IORT allows a reduction of the EBRT dose and so reduces toxicity of this modality. Mayo Clinic researchers reported a 3-year survival rate of 39% and a 5-year survival rate of 20% in 123 patients with LRRC who were treated with IORT and surgery (14). Mannaerts et al. (16,18) in the Netherlands used a preoperative radiotherapy dose of 50.4 Gy (30 Gy in patients who had received ratiotherapy) before surgery, during which they carried out IORT. The dose of IORT was determined by the R status of the resection. Patients who had undergone R0 resection (microscopically negative margins) were treated with a dose of 10 Gy, R1 resections (microscopically positive margins) with a dose of 15 Gy and R2 cases (macroscopically positive margins) with a dose of 17.5 Gy. Overall 3-year survival rate reached 58%. However, patients who had undergone R2 resection showed a worse prognosis in this series. Wiig et al. (19) reported a 5-year survival rate of 60% in patients given preoperative irradiation who had R0 resection. This does raise the question as to whether IORT is really necessary in cases with previous R0 resection, particularly as not all R0 cases in this series received IORT. It can be argued that a true R0 resection leaves no cancer cells to be eradicated by IORT. In clinical practice, however, because it is not always easy to differentiate fibrosis from recurrent cancer, some patients who undergo R0 resection may have residual disease and may benefit from IORT (20,21).

Abuchaibe et al. (12) and Bussieres et al. (15) have reported on patients with R2 resection given IORT but no postoperative EBRT. This strategy resulted in a poor outcome and suggests that additional EBRT is important in achieving local control. Irradiation of patients who have received radiotherapy previously has generally been avoided because of the fear of severe late radiation toxicity. Mohiuddin et al. (2,23) reported on 103 cases who received reirradiation and showed acceptable late toxicity (17% with chronic severe diarrhea, 15% with small bowel obstruction and 4% with fistula).

Despite the use of multimodality therapy, 5-year survival rates of patients with LRRC remain 22–31% and local control rates 50–71% (Table 1). IORT cannot be expected to compensate for R2 resection (13) and is itself associated with potential complications. The commonest side effects are ureteric stenosis and peripheral neuropathy. In a series of 123 cases at the Mayo Clinic (14), partial ureteric stenosis as a complication occurred in 6% of patients with 10% requiring insertion of ureteric stents. Peripheral neuropathy was observed in 16–34% of the patients.

Table 1. Outcome after multimodality therapy

Author	Year	No. of cases	Resection (%)	Surgery	5-YSR (%)	Re-local recurrence (%
Willet et al. (11)	1991	30			27	38
Magrini et al. (32)	1996	16	100	Extended	48 (2Y)	36
Bussieres et al. (15)	1996	73	57	Mixed	31	29
Valentini et al. (17)	1999	47	45	Limited	22	31
Wiig et al. (19)	2000	107	41	Limited	30	50
Mannaerts et al. (18)	2001	33	64	Mixed	60 (3Y)	27
Hahnloser et al. (21)	2003	304	100	Limited	25	

5-YSR: 5-year survival.

Brachytherapy uses gamma rays or beta rays emitted by the encapsulated sealed radioactive source to carry out interstitial irradiation. More recently, concerns about the surgeon's exposure to radiation and patient isolation have seen the increased use of high-dose-rate remote afterloading system (24,25). Goes et al. (24) reported the use of afterloading tubes inserted intraoperatively after tumor reduction surgery to deliver brachytherapy in 30 previously irradiated patients. In these patients with LRRC, local control was achieved in 18 cases (64%) with a median follow-up period of 36 months. The advantage of brachytherapy is that it minimizes the amount of radiation to which surrounding tissues are exposed, and hence it is a useful method for previously irradiated patients. However, accurate placement of the afterloading tubes can be difficult because the recurrent lesion is surrounded by scar tissue and is deep within the pelvis. Alternative methods for placing the tubes accurately include CT-guided percutaneous insertion, but this is associated with the risk of small bowel injury and fistula formation if the tube damages a part of the small intestine lying within the pelvis. Consequently, brachytherapy has not yet become a standard therapy for LRRC.

COMBINED RESECTION

To achieve long-term local control and survival benefit in patients with LRRC, it is clear that it is necessary to achieve an R0 resection. This is a particular challenge when patients have FRTs with dorsal and/or dorsolateral involvement.

In 1981 Wanebo introduced the technique of abdominosacral resection, which was adopted by other surgeons (26–39). Extended surgery for FRT has not become popular because of reported 5-year survival rates of 16–31% (Table 2). Bozzetti et al.(34) indicated limitations of surgical treatment, and Wiggers et al. (33) showed a critical attitude toward extended surgery. In 1999, Wanebo et al. (36) reviewed the outcome of extended surgery in 53 patients. The operative mortality was 8%, the mean blood loss was more than 8000 ml and the mean operative time was ~20 h. All the patients had been irradiated previously. The overall 5-year survival rate was 31%, and the disease-free 5-year survival rate was 23%. High amputation of the sacrum was performed in 32 cases (60%) for pelvic recurrences extending to the sacral promontory or sciatic notch. In all cases, the internal iliac vessels were preserved and lymph node dissection in the pelvis was performed. Lateral node metastasis was observed only in one case (1.8%), which is a surprisingly low rate. It remains unclear as to whether this was due to the influence of radiation or due to the method used for searching the metastasis. One can hardly assert that extended surgery is acceptable in terms of both surgical invasiveness and oncological outcomes, and consequently this therapy has been positioned as a formidable and demanding treatment.

In 2004, we reported the treatment outcome of total pelvic exenteration with distal sacrectomy (TPES) in 57 patients with FRT (39). The operative mortality was 3.5%, and the median blood loss and operative time were 2500 ml and 682 min, respectively. These results are different from those reported by Wanebo et al. (36). We have analyzed factors that may be responsible for this difference. Our patients with primary rectal cancer undergo total mesorectal excision or a more extended surgery, whereas in the US less extensive surgery was generally performed. All Wanebo's patients received preoperative radiotherapy resulting in pelvic fibrosis. However, in our patients postoperative scarring after extensive primary resection leads to more technical difficulties in the resection of the recurrent disease. In addition, half of our patients received preoperative radiotherapy. Our conclusion is that overall the difference in results is not related to the extent of the initial surgery the patient had undergone or to whether radiation was given preoperatively. The major difference between the two series is the extent of the sacral resection. In contrast to Wanebo, we limited the level of the sacral amputation to the inferior margin of the second sacral vertebra or below in order to preserve the second sacral nerves. High sacral amputation is associated with more severe morbidity including mobility difficulties and a significantly impaired QOL. After less extensive sacral amputation, patients achieved an acceptable QOL except for living with double stomas and temporary pain owing to the resection of sacral nerves (39,40). For our patients, we achieved survival rate of 61% at 3 years and 46% at 5 years. Despite these improved results compared with the Wanebo's series, local re-recurrence and lung metastasis occur in more than 90% of the patients.

Measures to prevent further local recurrence and metastatic disease remain a challenge in the management of these patients. We conclude that surgical treatment including pelvic

Table 2. Outcome after combined resection

Author	Year	No. of cases	TPE	PW	RT	5-YSR (%)	Re-local recurrence (%)
Hafner et al. (28)	1991	21	11		1	20	38
Maetani et al. (35)	1998	59	39	43	26	25	61
Wanebo et al. (36)	1999	53	27	53		31	49
Yamada et al. (38)	2001	60	30	23		16	
Moriya (39)	2004	57	57	57	23	36	25

TPE, total pelvic exenteration; RT, radiotherapy; PW, resection of pelvic wall; 5-YSR: 5-year survival.

wall resection and IORT is the optimum method for improving local control rates in patients with LRRC. New antitumor agents such as CPT-11, UFT, Capecitabine and Oxaliplatin have shown efficacy in the treatment of rectal cancer and will play an increasing role in patients with metastatic disease.

PROGNOSTIC FACTORS

The factors that predict the success of the surgery for LRRC remain controversial. Several parameters such as the type of initial surgery, tumor size, presence of severe symptoms and the serum CEA level before re-resection have been assessed as potential prognostic indicators (41). Willet and Wanebo found improved resectability in patients having initial low anterior resection compared with initial APR (11,31). In contrast, we found no difference in either resectability or survival in patients who developed FRT (39). Among other factors, negative CEA and R0 resection were associated with better prognosis. Shoup et al. (42) reported that vascular invasion and R1/R2 resection are factors for poor prognosis. Both reports emphasize that the most important prognostic factor is whether R0 resection was achieved or not.

It has already been shown that in surgical treatment for primary rectal cancer, surgeon-related factors as well as biological factors are crucial. Surgical margin status and complications are exclusively determined by the surgeon's technical skills (43). Complicated surgery such as TPES or abdomino-sacral resection should be undertaken only in specialized centers that have particular expertise with such complex surgery.

STAGING SYSTEM

There is no established method of staging for patients with LRRC. Suzuki et al. (44,45) have assessed the degree of tumor fixation to surrounding structures according to surgical and pathological findings, and proposed their own staging method. Valentini et al. (17) also reported a similar staging system based on CT scan. They mentioned that degree of fixation is an independent prognostic factor. Wanebo et al. (36) have proposed a new staging system for stages TR1-2–TR-5, which are determined by the extent of invasion.

It is very important that a staging system is developed for these complex patients so order that the appropriate therapy is undertaken.

CONCLUSION

The management of patients with LRRC presents a formidable challenge. Potentially, there are a large number of therapeutic options available. Surgery remains the optimum treatment of local recurrence, if this can be achieved with acceptable QOL. The role of chemotherapy and radiotherapy remains to be clarified. IORT has the potential to improve local disease control in patients in whom an R0 or R1 resection can be achieved.

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SURGICAL ENDOSCOPY
and Other Interventional Techniques

Reduction of prolonged postoperative hospital stay after laparoscopic surgery for colorectal carcinoma

S. Yamamoto, S. Fujita, T. Akasu, K. Uehara, Y. Moriya

Division of Colorectal Surgery, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan

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Abstract
Background: In evaluating the quality of laparoscopic surgery (LS) for colorectal carcinoma, many previous reports have used median or range values to assess the length of postoperative hospital stay and to show the complication and conversion rates separately. However, with this method, it is impossible to assess the proportion of patients who required prolonged postoperative hospital stay because of perioperative morbidities. This study investigated the proportion of patients who benefited from LS as minimally invasive surgery by assessing the percentage of patients who required prolonged postoperative hospital stay because of major perioperative morbidities.
Methods: A review of 202 patients who underwent LS for colorectal carcinoma at the authors' hospital between January 2002 and December 2004 was performed. Short-term outcomes were compared among the patients who underwent LS in 2002, 2003, and 2004.
Results: No significant differences were observed in baseline characteristics among the groups, and all the procedures in this study were completed laparoscopically. There were no significant differences in the operative times and intraoperative blood losses among the groups. Most of the patients resumed liquid intake on postoperative day 1 and solid food on day 3. However, there was a significant difference in the rate of postoperative prolonged hospital stays by year of surgery. In 2004, 97.3% of the patients (72/74) undergoing LS could be discharged to home within 8 days postoperatively. Major complications occurred at a low rate of 1.4% (1/74) in 2004. Regarding the reasons for prolonged postoperative hospital stay, inappropriate judgment of the physician in charge, based primarily on requests from patients without medical necessity, disappeared in 2004.
Conclusions: When LS is performed properly by specialists who have accumulated sufficient experience in both LS and conventional open surgery for colorectal carcinoma, up to 97% of patients undergoing LS can benefit from minimally invasive surgery.

Key words: Colorectal carcinoma — Complication — Laparoscopic surgery — Postoperative hospital stay — Short-term outcome

In many randomized and nonrandomized studies comparing laparoscopic surgery (LS) and conventional open surgery for colorectal carcinoma, several advantages of LS have been reported, including reduction of postoperative pain, shortened duration of postoperative ileus, shortened hospital stay, and favorable effects on cytokine and hormonal responses. Consequently, LS is now termed "minimally invasive surgery" [1, 10, 15–17].

At our institution, much consideration has been given to the technical and oncologic safety of LS. Since our first LS for colorectal carcinoma in 1993, approximately 400 LS for colorectal malignancies have been performed at our institution. Most of our early experience was confined to early (Tis or T1) colorectal cancer located at the cecum, ascending colon, sigmoid colon, or rectosigmoid because of technical problems and concerns regarding port-site and peritoneal recurrences. In June 2001, we unified our surgical and postoperative management procedures and expanded our indications for LS to include advanced colorectal cancers (i.e., T2 lesions and beyond) located anywhere in the colon or rectum. As a consequence, the complication rate and mean length of hospitalization have been reduced at our institution [23, 24].

If LS is truly minimally invasive surgery, it should reflect a shortened postoperative hospital stay. With regard to assessment of the quality of LS for colorectal carcinoma, many previous reports have used median or range values to assess the length of postoperative hospital stay and to show the complication and conversion rates separately. However, with this approach, it is

Correspondence to: S. Yamamoto

impossible to assess the proportion of patients who required prolonged postoperative hospital stay because of perioperative morbidities. Moreover, the effect of major complications on the length of postoperative hospitalization is unknown.

In the current study, short-term outcomes were compared among selected patients who underwent LS for colorectal carcinoma at our hospital in 2002, 2003, and 2004. We investigated the proportion of patients who benefited from LS as minimally invasive surgery by assessing the percentage of patients who required prolonged postoperative hospital stay because of perioperative major morbidities. Moreover, the results of our efforts to reduce postoperative hospitalization also were examined.

Patients and methods

Patients

Between January 2002 and December 2004, we performed 202 continuous LS for selected patients with colorectal carcinoma. Because the safety of LS for cancer patients remains to be established, our candidates for radical LS were patients with a preoperative diagnosis of T1 or T2. Additionally, our LS cases also included patients with a preoperative diagnosis of T3 who wished to undergo LS, as well as those with colon or upper rectal carcinoma for which palliative resection was considered necessary. Contraindications for LS included tumors larger than 6 cm, a history of extensive adhesions, severe obesity (body mass index > 32 kg/m^2), intestinal obstruction, and refusal of a patient to undergo LS.

All patients were evaluated before surgery by clinical investigation including barium enema, total colonoscopy, chest x-ray, abdominal ultrasonography, and computed tomography. For patients with rectal malignancy, a primary rectal carcinoma was defined according to its distance from the anal verge, as determined by colonoscopy. The tumors were grouped according to their location in the lower rectum (0–7 cm), the middle rectum (7.1–12 cm), and the upper rectum (12.1–17 cm). We defined conversion to open surgery as any incision larger than 7cm, except for cases in which the incision was enlarged because of a large specimen that could not be removed through a 7-cm incision.

Laparoscopic technique

The techniques for LS have been thoroughly described previously [23–25]. For right-sided lesions, the right colon was mobilized initially, and the vascular pedicles were divided at their origin, together with the draining lymph nodes intracorporeally. For patients with a preoperative diagnosis of T2–T3 lesions, a laparoscopic no-touch isolation technique was performed. With this technique, mobilization of the right colon was performed after early proximal ligation of the tumor-feeding vessels and resection of the mesentery intracorporeally. The bowel loop was delivered under a wound protector through a small incision, and division of the marginal vessels and anastomosis was performed extracorporeally.

For transverse colon lesions, mobilization of hepatic, splenic, or both flexures was performed according to the tumor location. Proximal ligation of the right, left, or both branches of the middle colic vessels at their origins was performed intracorporeally or extracorporeally. The bowel loop was delivered, and anastomosis was performed in the same way.

Descending colon and proximal sigmoid colon lesions for which extracorporeal anastomosis was considered possible were managed by initial mobilization of the left colon. After mobilization of the splenic flexure, intracorporeal ligation of the tumor-feeding vessels (left colic artery, sigmoid arteries, inferior mesenteric vessels) at their origins was performed. The bowel loop was delivered through a small incision under a wound protector, and division of the mesenterium was performed extracorporeally, followed by extracorporeal anastomosis.

For distal sigmoid colon and rectal lesions, mobilization of left colon and splenic flexure, if necessary, was followed by intracorporeal high ligation of the inferior mesenteric vessels, then by mobilization of the rectum. For higher lesions, mesorectal tissue down to 5 cm below the tumor was excised routinely. Middle and lower rectal tumors were treated by total mesorectal excision. Before rectal transection, laparoscopic rectal clamping immediately above the anticipated point of rectal transection was performed using a bowel-clamping device introduced through the 12-mm mid lower port. Rectal washout was routinely performed using 1,000 ml of 5% povidone–iodine solution. Rectal transection then was performed by the multiple firing technique using Endo GIA Universal staples (Auto Suture; U.S. Surgical Corp., Norwalk, CT, USA) introduced through the 12-mm right midabdominal port. A 4- to 5-cm incision then was made over the mid lower port site, and the bowel was exteriorized under wound protection.

After the anvil head of the circular stapler had been inserted into the end of the proximal colon, the proximal colon was internalized and the incision closed. Intracorporeal anastomosis under laparoscopic view was performed by the double-stapling technique using a circular stapler (ECS 29 or 33mm; Ethicon Endo-Surgery Inc, Cincinnati, OH, USA). For patients with lesions located within 2 cm of the dentate line, laparoscopic intersphincteric rectal resection and hand-sewn coloanal anastomosis (ISR-CAA) were performed [21]. For patients undergoing abdominoperineal resection (APR), laparoscopic procedures were followed by perineal dissection in the standard fashion and end colostomy creation using the left lower abdominal port site.

Study parameters

The parameters analyzed included gender, age, body mass index, prior abdominal surgery, operative time, intraoperative blood loss, conversion rate, days to resumption of diet, duration of postoperative hospital stay, and both intraoperative and postoperative complications within 30 days of surgery. Pathologic staging was performed according to Dukes' stage. In the current study, major complication was defined as morbidity that required the patient to stay in the hospital 9 or more postoperative days. Prolonged postoperative hospital stay was defined as 9 or more days of postoperative hospitalization, regardless of the underlying reasons, because patients are supposed to be discharged by the postoperative day 8 when there is no major complication after LS at our institution. With regard to the operative and postoperative results, patients with colon and rectal carcinoma were evaluated separately, considering the technical difficulties of the laparoscopic procedure.

Statistical analysis

Statistical analysis was performed using one-way analysis of variance (ANOVA) and chi-square testing as appropriate. A p value less than 0.05 was considered significant.

Results

The demographics for the patients in this study are summarized in Table 1. There were no significant differences in baseline characteristics among the groups. However, the proportion of the patients with Dukes' B, C, and D stages scheduled for LS is increasing, although the difference is not yet significant ($p = 0.093$). With regard to simultaneously performed surgical techniques, one patient underwent resection of a benign submandibular gland tumor in 2002, and three patients underwent laparoscopic cholecystectomy in 2003. In 2004, three patients underwent combined surgery as follows: laparoscopic enucleation of an 8-cm hysteromyoma, partial resection of the lingua for carcinoma, and hemilateral neck lymph node dissection for

Table 1. Patient characteristics[a]

	2002 (n = 59)	2003 (n = 69)	2004 (n = 74)	p Value
No. of patients	59	69	74	
Sex ratio (male:female)	35:24	39:30	37:37	0.533
Age (years)	58.5 (30–83)	60.2 (38–88)	61.1 (34–79)	0.360
Body mass index (kg/m^2)	22.9 (14.9–32.4)	23.1 (17.3–30.5)	23.1 (16.3–31.5)	0.872
Prior abdominal surgery: n (%)	15 (25.4)	16 (23.2)	16 (21.6)	0.875
Dukes' stage (n)				
A	45	52	46	
B	2	2	9	
C	8	11	18	
D	4	4	2	
A:B + C + D	45:14	52:17	46:29	0.093
Location (n)				
Cecum	3	10	5	
Ascending colon	4	13	15	
Transverse colon	6	9	7	
Descending colon	6	5	7	
Sigmoid colon	23	20	27	
Rectosigmoid/upper rectum	10	7	4	
Middle rectum	3	3	4	
Lower rectum	4	2	6	
Colon:rectum	42:12	57:12	60:14	0.238
Laparoscopic colorectal procedures (n)				
Ileocecal resection	5	7	7	
Right hemicolectomy	5	18	14	
Transverse colectomy	4	4	4	
Left hemicolectomy	0	1	1	
Descending colectomy	5	4	6	
Sigmoid colectomy	20	17	24	
Partial resection	3	6	5	
Anterior resection with DST	16	10	12	
Anterior resection with ISR-CAA	1	2	1	
Abdominoperineal resection	0	0	1	
Transverse-coloplasty pouch	0	2	2	
Covering ileostomy	4	2	5	

DST, double-stapling technique; ISR-CAA, intersphincteric rectal resection and handsewn coloanal Anastomosis
[a] Values are mean (range)

metachronous lymph node recurrence from lingual carcinoma. Data on these combined surgical techniques all were included in the analyses of colorectal carcinoma surgeries.

Our operative results are shown in Table 2. All the procedures in this study were completed laparoscopically. There were no significant differences in operative time or intraoperative blood loss among the groups. The postoperative courses are shown in Table 3. Most of the patients started liquid intake on postoperative day 1 and solid food on day 3. However, there was a significant difference in the rates of prolonged postoperative hospital stay by year of surgery. All the patients were discharged to home.

The postoperative complications are listed in Table 4. There were no perioperative mortalities. No significant differences in complication rates over the years were observed, although a major complication, anastomotic leakage, occurred for one patient in 2004 and was successfully treated conservatively. None of the patients in the current series required reoperation.

The reasons for prolonged postoperative hospital stays are listed in Table 5. Inappropriate judgment of the physician in charge, based primarily on requests from patients without medical necessity, disappeared in 2004. By the end of the study period, two patients had experienced recurrence (hepatic metastases). At this writing, in 2005, 49 patients have undergone LS, and all have been discharged to home without major complication.

Table 2. Operative results[a]

	2002 (n = 59)	2003 (n = 69)	2004 (n = 74)	p Value
Lap colectomy				
Operative time (min)	201 (115–345)	200 (117–348)	214 (140–495)	0.219
Intraoperative blood loss (ml)	30 (6–219)	30 (10–248)	38 (7–256)	0.157
Conversion (n)	0	0	0	
Lap-AR + APR				
Operative time (min)	244 (190–392)	263 (200–472)	283 (215–430)	0.570
Intraoperative blood loss (ml)	54 (10–265)	63 (11–250)	84 (14–477)	0.661
Conversion (n)	0	0	0	

Lap, laparoscopic; AR, anterior resection; APR, abdominoperineal resection
[a] Values are medians (range)

Table 3. Postoperative results

	2002 (n = 59) n (%)	2003 (n = 69) n (%)	2004 (n = 74) n (%)	p Value
Lap colectomy				
Liquid intake range (days)				
1 POD	38 (90.4)	54 (94.7)	59 (98.3)	
2 POD	2 (4.8)	3 (5.3)	0 (0)	
3 ≤ POD	2 (4.8)	0 (0)	1 (1.7)	
Solid food (days)				
2 POD	0 (0)	0 (0)	0 (0)	
3 POD	31 (73.8)	51 (89.5)	56 (93.3)	
4 ≤ POD	11 (26.2)	6 (10.5)	4 (6.7)	
Hospital stay (days)				
7 POD	5 (11.9)	19 (33.3)	28 (46.7)	
8 POD	17 (40.5)	28 (49.1)	31 (51.7)	
9 ≤ POD	20 (47.6)	10 (17.5)	1 (1.7)	
Range	7–20	7–15	7–21	
Lap-AR + APR				
Liquid intake range (days)				
1 POD	16 (94.1)	10 (83.3)	13 (92.9)	
2 POD	1 (5.9)	1 (8.3)	0 (0)	
3 ≤ POD	0 (0)	1 (8.3)	1 (7.1)	
Solid food (days)				
2 POD	3 (17.6)	1 (8.3)	3 (21.4)	
3 POD	6 (35.3)	9 (75.0)	9 (64.3)	
4 ≤ POD	8 (47.1)	2 (16.7)	2 (14.3)	
Hospital stay (days)				
7 POD	2 (11.8)	4 (33.3)	5 (35.7)	
8 POD	3 (17.6)	6 (50.0)	8 (57.1)	
9 ≤ POD	12 (70.6)	2 (16.7)	1 (7.1)	
Range	7–12	7–17	7–23	
Total (Lap-colectomy + AR + APR)				
Hospital stay (days)				
7–8 POD	27 (45.8)	57 (82.6)	72 (97.3)	<0.0001
9 ≤ POD	32 (54.2)	12 (17.4)	2 (2.7)	

Lap, laparoscopic; POD, postoperative days; AR, anterior resection; APR, abdominoperineal resection

Discussion

To date, the quality of LS for colorectal carcinoma has been assessed by the median or range of the postoperative hospital stay, the complication rate, and the conversion rate. However, with only these values, it is impossible to assess accurately the degree of the effect that each complication has on the length of postoperative hospitalization for patients overall. This means that the rate of patients undergoing LS who have benefited from minimally invasive surgery has not been properly evaluated. If the greatest advantage of LS is minimal invasiveness, LS must ultimately be linked to shortened postoperative hospitalization. However, no reports have focused on the rate of reduction in the length of postoperative hospital stay after LS. In our hospital, patients are supposed to be discharged after LS until postoperative day 8. As experience with LS cases accumulated, surgical and postoperative management procedures became unified. The timing for the start of solid food intake became earlier in 2004 than in 2002, and this may have contributed to the significantly shortened period of postoperative hospitalization in 2004. Furthermore, major complications that required prolonged postoperative hospital stay were reduced. As a result, in 2004, 97.3% (72/74) of our patients undergoing LS could be discharged to home within 8 days postoperatively. Major complications occurred at a low rate of 1.4% (1/74) in 2004. Needless to say, this low rate contributed greatly to the current results.

The current report deals with the length of postoperative hospital stay. Recent reports from randomized controlled trials (RCTs) and single institutions investigating a number of cases in western countries indicate that the median or mean length of hospital stay after LS for colorectal carcinoma ranges from 5 to 9 days [1, 2, 6, 7, 9, 14, 16]. The appearance of this range may be attributable to social factors such as differences in medical fees, medical insurances, and medical systems among countries rather than differences in the quality of surgery. According to former studies from Japan, Japanese patients tend to stay in the hospital longer than patients in western countries [20]. The reasons for this tendency include the following facts. From the perspective of patients in Japan, public health insurance covers 70% of the total medical cost for every patient, with the patients paying only 30% of the cost. Socially disadvantaged people do not have to bear their medical expense no matter how many days they are hospitalized. Furthermore, for a patient undergoing surgery, the cost of surgery accounts for the greater part of the total medical cost. Hence, if the duration of hospital stay is lengthened by 1 day, the patient pays only several tens of dollars in additional cost. Furthermore, many Japanese patients have private health insurance, which pays the patient a specified amount of money per day of hospitalization. Under some types of insurance contract, the longer the patient stays in hospital, the more the insurance dividend will be, thereby yielding greater "earn-

Table 4. Morbidities and mortality[a]

	2002 (n = 59)	2003 (n = 69)	2004 (n = 74)	p Value
Lap colectomy				
Mortality	0	0	0	
Morbidity				
Wound sepsis	3 (1)	2	6	
Bowel obstruction	2 (1)	3 (1)	1	
Urinary tract infection	2 (2)	1	0	
Pneumonia	0	1 (1)	0	
Pneumothorax	0	1 (1)	0	
Pulmonay embolism	0	1 (1)	0	
Enterocolitis	0	1	0	
Total	7 (4)	10 (4)	7 (0)	
Reoperation	0	0	0	
Readmissions	1	3	0	
Lap-AR + APR				
Mortality	0	0	0	
Morbidity				
Wound sepsis	0	2	1	
Bowel obstruction	0	1 (1)	0	
Anastomotic leakage	0	0	1 (1)	
Abscess	0	1 (1)	0	
Pneumonia	0	0	1	
Neurogenic bladder	1 (1)	0	0	
Total	1 (1)	4 (2)	3 (1)	
Reoperation	0	0	0	
Readmissions	0	0	0	
Total complication: n (%)	8 (13.5)	14 (20.3)	10 (13.5)	0.4595
Major complication: n (%)	5 (8.5)	6 (8.7)	1 (1.4)	0.111

Lap, laparoscopic; AR, anterior resection; APR, abdominoperineal resection

[a] No. of major complications in parentheses

Table 5. Reasons for prolonged postoperative hospital stay

	2002 (n = 32)	2003 (n = 12)	2004 (n = 2)
Major complication	5	6	1
Others			
Treatment for comorbid disease	3	1	1
Ileostomy management	4	0	0
Inappropriate judgment of the physician in charge	20	5	0

ings." Under these circumstances, patients do not need to be discharged from the hospital quickly.

In contrast, at our institution, if there is no major complication after LS, the patient is supposed to be discharged by postoperative day 8, but no patients wished to leave hospital earlier than postoperative day 6. Furthermore, the results of the current study in terms of postoperative stay after LS for colorectal carcinoma are some of the shortest reported in Japan. Obviously, this situation in Japan is wasting medical funds. It goes without saying that the situation must be improved. From the results of the current study, we consider that the appropriate duration of postoperative hospital stay after LS is 5 to 7 days. Early discharge within 5 days might be possible for some patients. However, it is necessary to confirm the safety of early discharge, especially for patients with rectal carcinoma who have undergone anterior resection, because for some patients, fatal complications accompanied by anastomotic leakage might occur approximately 7 days after surgery.

With regard to the oncologic outcome of LS for colorectal carcinoma, recently reported RCTs have demonstrated that LS is comparable with open surgery or superior to it [6, 12, 14]. The results of some other RCTs to be published in the near future also are attracting attention. However, in Japan, RCTs for gastrointestinal malignancies have not been widely accepted in the past because of concerns about consequences if one form of treatment is shown to be inferior to the other. For this reason, a prospective multicenter trial with patients undergoing laparoscopic colectomy for advanced carcinoma has not been performed. However, fertile ground for RCTs comparing surgical techniques has finally begun to develop among both patients and surgeons in Japan. Consequently, a multicenter RCT comparing LS and open surgery outcomes for advanced colorectal cancer was begun in 2004 [11]. The distinctive features of this trial are that all the participating institutions have sufficient experience not only in open surgery, but also in LS, and that D3 lymphadenectomy is being required as a rule for all patients because this has been regarded as the standard surgical procedure for advanced colorectal carcinoma in both LS and open surgery. The results of this Japanese study will be published later than those of similar studies in western countries, but this study is receiving attention as an RCT performed by surgeons with sufficient accumulated experience in LS and specializing in colorectal carcinoma surgery using LS.

The issue in the expansion of the indications for LS for colorectal carcinoma is whether it can be performed for patients with middle or lower rectal carcinoma. The technical difficulty of surgery is high in such cases. If the rate of conversion to open surgery increases, the short-term outcomes of LS will be shifted to the outcomes of open surgery, thus making it difficult to detect differences between the two surgeries [9, 22]. In addition, if the complication rate increases, it could lead to prolonged postoperative hospitalization, thereby canceling the advantages of LS. The most important issue is whether LS can yield a treatment outcome comparable with that of open surgery in cases of advanced rectal cancer. The most difficult complication to manage is anastomotic leakage. In cases of middle and lower rectal carcinoma, the occurrence of anastomotic leakage requires not only prolonged hospitalization, but also a temporary or permanent stoma in some patients, thereby resulting in an unavoidable deterioration in quality of life. Moreover, anastomotic leakage may cause fatal peritonitis, or may promote intrapelvic recurrence in some cases [4]. However, with regard to the technical issue, as shown by the results of this study and recently published papers, when surgeons with sufficient experience in LS for rectal carcinoma are in charge of the procedure, it can be performed successfully as minimally invasive surgery in cases of middle and lower rectal carcinoma [2, 3, 5, 8, 13, 18, 19, 24].

In the previous report from our institution, short-term outcomes were compared between patients with

colon carcinoma and those with rectal carcinoma, all of whom underwent LS. The complication rates and postoperative courses between the two approaches were similar [23]. Needless to say, in cases of middle and lower rectal carcinoma as well, further investigations in multicenter RCTs are needed regarding short- and long-term outcomes.

One distinctive feature of LS for rectal carcinoma at our institution is that only one patient underwent APR. The background factor behind this is that whether we select open surgery or LS, we usually perform ISR-CAA in T1–T2 cases of lower rectal carcinoma, and also in many T3 cases if the patient expresses a request. Recently, favorable oncologic and functional outcomes of ISR-CAA have been reported, and the number of patients undergoing ISR-CAA using LS is expected to increase in the coming years [18, 21]. Only one patient who underwent laparoscopic APR in 2004 was preoperatively judged to be a candidate for ISR-CAA by LS. However, that patient's choice was APR.

The mean operative time in the current study was slightly longer than that reported in previous studies. This may be partially because of gradual increases in the proportion of patients with relatively advanced stages of disease who underwent LS. Other reasons might be that trainee doctors perform part or all of the surgical procedure under the guidance of staff doctors in many cases, and that we have been unable to establish a laparoscopic team. However, it is evident that the quality of our operations has not been lowered, as demonstrated by the results of this study.

In conclusion, the surgical outcome for LS at our institution demonstrated that when LS is performed properly by specialists who have accumulated sufficient experience in both LS and open surgery for colorectal carcinoma, up to 97% of patients undergoing LS can benefit from minimally invasive surgery. To expand the use of minimally invasive surgery for advanced colorectal carcinoma, it goes without saying that while making efforts to acquire high-level technical skills, it is also necessary to confirm the oncologic safety of LS.

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Allelic Status of Chromosomes 17p, 18q, 22p, 3p and their Clinical Usefulness in Colorectal Cancer

SHIN FUJITA[1], HIDEO BABA[2,3], SEIICHIRO YAMAMOTO[1], TAKAYUKI AKASU[1], YOSHIHIRO MORIYA[1] and KOKICHI SUGNO[2,4]

[1]Department of Surgery and [2]Clinical Laboratory Division, National Cancer Center Hospital, Tokyo; [3]Department of Surgery, Saitama Municipal Hospital, Saitama; [4]Oncogene Research Unit/Cancer Prevention Unit, Tochigi Cancer Center Research Institute, Tochigi, Japan

Abstract. *Background: To determine whether the allelic status of chromosomes is clinically useful in colorectal cancer, the allelic losses at chromosomes 17p, 18q, 22q and 3p and their relationships with the clinicopathological features in colorectal cancer (CRC) patients, who had undergone curative surgery without adjuvant chemotherapy, were examined. Materials and Methods: The allelic status at 17p, 18q, 22q and 3p was analyzed by PCR-SSCP (polymerase chain reaction single-strand conformation polymorphism) in 139 CRC from patients who had undergone curative surgery between October 1994 and June 1996. The relationships between these allelic losses and the clinicopathological features were investigated. Results: The lymph node status was significantly associated with the allelic status of 17p, 18q and 22q. The tumor site and tumor differentiation were significantly associated with the allelic status of 18q. When patients with more than two allelic losses were defined as the high allelic loss group and those with no, or only one allelic loss were defined as the low allelic loss group, it was found that the lymph node involvement was significantly higher in the high than in the low allelic loss group. Only three out of 25 patients in the low allelic loss group had lymph node metastasis, and 15 patients in this group without lymphatic invasion had no lymph node metastasis. There was no relationship between the allelic status and survival at any stage. Conclusion: The allelic status was significantly associated with lymph node metastasis. A combination of allelic status and lymphatic invasion assessment can predict the lymph node status before radical surgery.*

Correspondence to: Shin Fujita, Department of Surgery, National Cancer Center Hospital, 1-1 Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, Japan. Tel: 81-3-3542-2511, ext. 7089, Fax: 81-3-3542-3815, e-mail: sfujita@ncc.go.jp

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There have been many reports on the relationships between the clinicopathological features of colorectal cancer (CRC) patients and the allelic status of chromosomes 1p (1, 2), 2p (3), 3p (4), 4p (5), 5q (6), 8p (7, 8), 17p (1, 8, 9) and 18q (8-15), or a combination of different allelic statuses (8, 16). Several reports have shown that the prognosis for patients with allelic losses is worse than for those without allelic losses. However, there have been conflicting results for chromosomes 5q (6), 17p (15, 17-19) and 18q (1, 17, 19, 20) and for combinations of chromosomal alterations (21). Therefore, these genetic alterations of allelic status are not clinically used for CRC.

To determine whether the allelic status is, in fact, clinically useful in CRC, four chromosomes were studied: 17p, 18q, 22q and 3p. Chromosomes 17p and 18q have tumor suppressor genes, p53 and DCC, respectively, and their allelic status has been suggested, in many reports, to be associated with clinicopathological features (1, 8, 10-15). The allelic loss of 22q is relatively frequent in CRC (22-24), but there have been no reports of a relationship between the clinical background and the allelic status of 22q. The allelic status of 3p was reported to be associated with survival prognosis (4), and preferential allelic loss of 3p was observed in metastatic tumors in comparison with primary CRC (25). The status of these four chromosomes in 139 cancers, obtained from CRC patients who had undergone curative surgery without adjuvant chemotherapy, was analyzed. Then, the relationship between the allelic status and clinicopathological features was examined.

Materials and Methods

Patients and tissues. A total of 139 CRC, from patients who had undergone curative surgery without adjuvant chemotherapy at the National Cancer Hospital, Tokyo, Japan, between October 1994 and June 1996, were examined. The primary tumors had been obtained immediately after surgery and stored frozen in liquid nitrogen until DNA extraction. All surviving patients had been followed for more than 5 years, initially at 3-month intervals for

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2 years and at 6-month intervals thereafter. Adjuvant chemotherapy had not been given.

Blunt-end SSCP analysis of allelic status. The allelic status was determined by blunt-end SSCP (single-strand conformation polymorphism) analysis (26, 27). Briefly, three intragenic polymorphic markers (intron 1, exon 4 and intron 7) of the *p53* gene, and two 17p13 markers (D17S695, D17S919), a 17p11 marker (D17S969), two 18q21 markers (D18S51, D18S499), a 22q12 marker (D22S685) and a 3p23 marker (D3S2396) were analyzed by blunt-end SSCP. For the amplification of these polymorphic markers, the primers shown in Table I were used. The forward and reverse primers were synthesized and labelled with indodicarbocyanine (Cy5) amidite reagent, a fluorescent dye (Pharmacia, Uppsala, Sweden), using an Oligo 1000 DNA synthesizer (Beckman, Fullerton, CA, USA). In PCR, the first denaturation step was done at 95°C for 5 min. PCR amplification was performed for 30 to 40 cycles under the following conditions: denaturation at 95°C for 30 to 60 sec, annealing at 50 to 67°C for 30 to 60 sec and extension at 72°C for 30 to 60 sec. For the blunting reaction, 0.5 units of Klenow fragment (TAKARA BIO, Shiga, Japan) was added to 5 μL of the PCR product and incubated at 37°C for 30 min. One microliter of the reaction mixture was mixed with 10 μL of the loading buffer and denatured at 80°C for 5 min. One microliter of the aliquot was electrophoresed on 15% polyacrylamide gel at 20°C to 24°C for 10 h at 20 W using an ALFred DNA sequencer (Pharmacia). The data were analyzed using the Fragment Manager (Pharmacia) software package. In the analysis of a normal heterozygote, the ratio of the peak heights of the signal from each allele was constant, with a variation of within 5% (27). Therefore, an allelic loss was defined as when one of the peak heights for a tumor sample was decreased by more than 10% of that of the corresponding normal tissue. Supposing the A1 allele is lost in a heterozygote carrying the A1 and A2 alleles, T is the peak height of the signal from the tumor samples, and N is the peak height of the signal from the normal control. Then, the percent peak height (%) is given as:

$$(N_{A1}/N_{A2} - T_{A1}/T_{A2}) \times 100 / (N_{A1}/N_{A2})$$ (26).

If at least one of the markers of the same chromosome showed an allelic loss, the chromosome was defined as having an allelic loss.

Statistical analysis. Statistical analysis was carried out by the Chi-squared test. The survival rates were calculated by the Kaplan-Meier method and survival curves were compared by the log-rank test. Cox's proportional hazard model was used for multivariate analysis. The level of statistical significance was set at <0.05.

Table I. *Primers used for PCR-SSCP analysis.*

Forward	Reverse
17p11-13	
D17S695	
5'CTGGGCAACAAG AGCAAAATTC3'	5'TTTGTTGTTGTTCAT TGACTTCAGTCT3'
D17S919	
5'AGGCACAGAGT GAGACTTG3'	5'GCTTAATTTTCACGA GGTTCAG3'
p53 intron 1	
5'TCTTAGCTCGCG GTTGTTTC3'	5'ACTGGCGCTGTGT GTAAATG3'
p53 exon 4	
5'AGCTCCCAGAAT GCGAGAG3'	5'CTGGGAAGGGACA GAAGATG3'
p53 intron7	
5'AGGTCAGGAGCC ACTTGCC3'	5' GTGATGAGAGGTG GATGGGT3'
D17S969	
5'ATCTAATCTGTCA TTCATCTATCCA3'	5'AACTGCAGTGCTG CATCATA3'
18q21	
D18S51	
5'GAGCCATGTTCA TGCCACTG3'	5'CAAACCCGACTAC CAGCAAC3'
D18S499	
5'CTGCACAACATA GTGAGACCTG3'	5'AGATTACCCAGAA ATGAGATCAGC3'
22q12	
D22S685	
5'TTCTTAGTGGGGA AGGGATC3'	5'TGAGTTTGATGTTT TTGATAGACA3'
3p23	
D3S2396	
5'ACCTCTTACTTGT GTTCTTGGG3'	5'TGACCAAGCC AGTATTGGAT3'

Results

Allelic status and clinicopathological backgrounds. The allelic status of 17p was informative in all the patients, the allelic status of 18q was informative in 136 patients (98%), that of 22q was informative in 122 patients (88%) and that of 3p was informative in 106 patients (76%). Representative electropherogram profiles from the SSCP analyses are shown in Figure 1. The clinicopathological backgrounds of the informative cases are shown in Table II. The lymph node status was significantly associated with the allelic status of 17p, 18q and 22q ($p<0.01$, <0.01 and 0.01, respectively). The tumor site and tumor differentiation were significantly associated with the allelic status of 18q ($p<0.01$ and 0.03, respectively). To examine the relationships between the number of allelic losses and the clinicopathological backgrounds, the examined patients were classified into high and low allelic loss groups. The high allelic loss group contained patients with more than two allelic losses. The low allelic loss group contained patients with no, or only one allelic loss. Patients with more than two non-informative alleles or with one allelic loss and one non-informative allele were excluded, because these patients' allelic status could not be classified into either group. In this way

Table II. *Clinicopathological backgrounds for informative cases.*

Chromosomes	17p		18q		22q		3p	
	Loss	Retained	Loss	Retained	Loss	Retained	Loss	Retained
Gender								
Male	68	16	68	15	41	31	28	37
Female	38	17	41	12	27	23	15	26
p	0.11		0.51		0.75		0.51	
Age								
<60	40	11	43	8	23	20	16	23
60≤	66	22	66	19	45	34	27	40
p	0.65		0.35		0.71		0.94	
Tumor site								
Colon	63	25	63	23	42	38	30	39
Rectum	43	8	46	4	26	16	13	24
p	0.09		< 0.01		0.32		0.40	
Tumor differentiation								
Well	46	20	47	18	38	24	19	26
Moderate	60	13	62	9	30	30	24	37
p	0.08		0.03		0.21		0.77	
Lymphatic invasion								
Negative	47	19	50	14	30	31	17	31
Positive	59	14	59	13	38	23	26	32
p	0.18		0.58		0.14		0.33	
Venous invasion								
Negative	56	22	57	19	39	32	24	33
Positive	50	11	52	8	29	22	19	30
p	0.16		0.09		0.83		0.73	
Depth of invasion (pT)								
pT1, pT2	18	10	23	5	11	13	9	14
pT3, pT4	88	23	86	22	57	41	34	49
p	0.10		0.77		0.28		0.87	
Lymph node status (pN)								
Negative	49	25	49	22	31	37	22	34
Positive	57	8	60	5	37	17	21	29
p	<0.01		<0.01		0.01		0.77	

seven patients were excluded. The clinicopathological backgrounds of patients in the high and low allelic loss groups are shown in Table III. The lymph node status was significantly associated with high and low allelic status ($p<0.01$). In the low allelic loss group, only three CRC patients out of 25 (12%) patients had lymph node metastases, while 15 patients without lymphatic invasion had no lymph node metastasis.

Allelic status and disease-free survival. The disease-free survival rates are shown in Table IV. In stages I and II, the high allelic loss group showed slightly worse survival than the low allelic loss group. In stage III, patients with allelic loss at 18q showed worse survival than those without allelic loss at 18q, and the high allelic loss group also showed worse survival than the low allelic loss group (Figure 2). Patients with allelic loss at 3p and those with allelic loss at 22q showed better survival than those without these allelic losses. However, these differences were not significant. In multivariate analysis, only the lymph node status was selected as a significant prognostic factor.

Discussion

Many reports have shown relationships between the clinicopathological background or prognosis of CRC patients and their allelic status (1-16). However, these allelic status relationships are not used clinically because the results have not been fully validated. Of the four chromosomes examined here, allelic loss at chromosome 18q has been suggested to have a strong association with poor prognosis for CRC patients in many reports (8-15). However, some reports, including our study, did not show a significant association between the allelic status of 18q and prognosis (1, 17, 19, 20). Barratt *et al.* suggested that there was an interaction between the allelic status and response to adjuvant therapy (19). Their results showed that only patients without allelic loss gained survival benefits from adjuvant therapy, while those with allelic loss did not. This explains the conflicting results of the association between allelic status and prognosis, because many studies into allelic status included patients who either did or did not receive

A

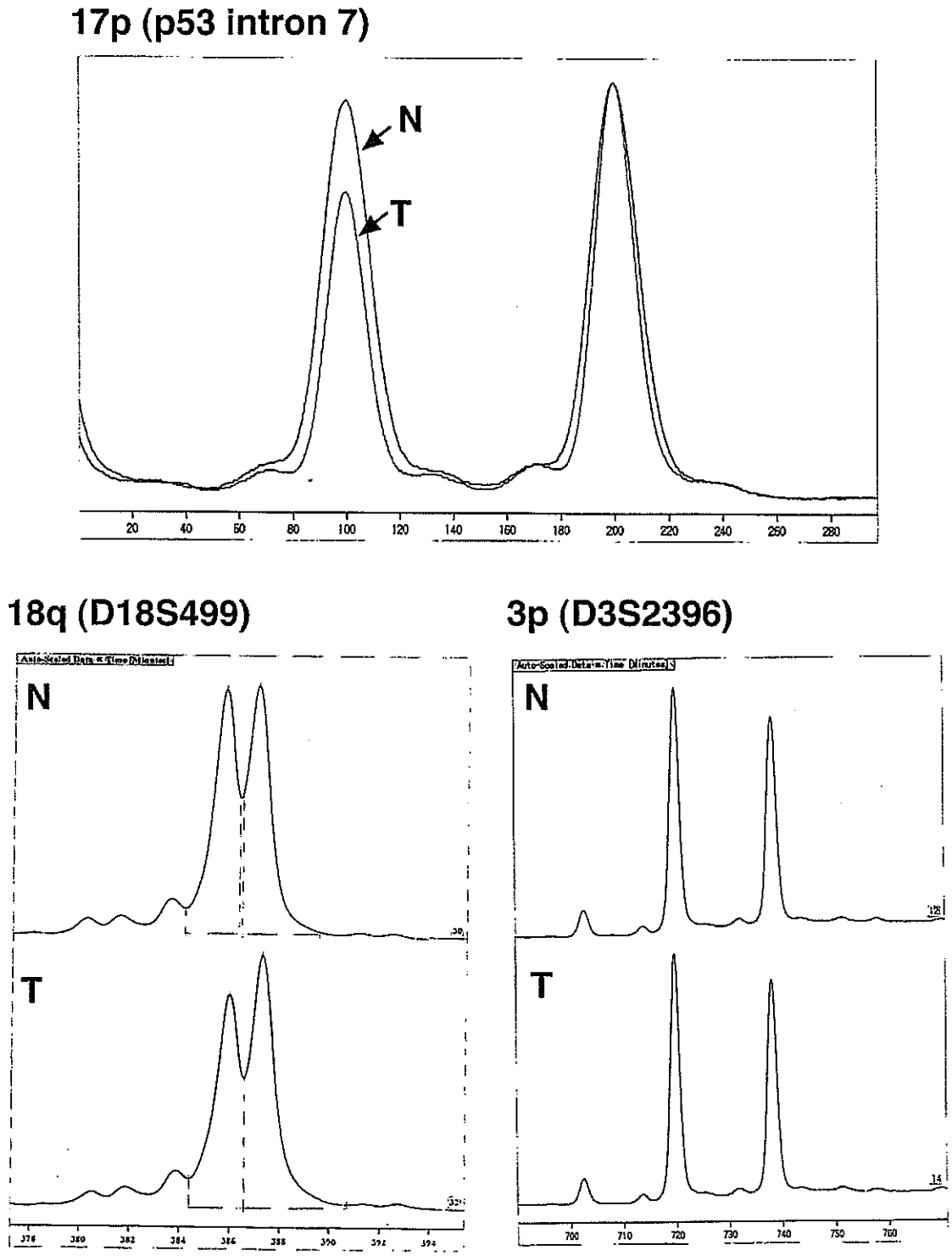

Figure 1. *Electropherogram profiles in SSCP analysis. A: Percent peak height of tumor tissue profile was 23%, 14% and 1% at p53 intron 7, D18S499 and D3S2396, respectively. As defined in Materials and Methods, this patient had allelic loss of 17p and 18q, while the allele of 3p was retained. The allele of 22q was not informative (data not shown). B: Percent peak height of the tumor tissue profile was 43%, 36%, 18% and 22% at D17S969, D18S499 D22S685 and D3S2396, respectively. All the alleles examined were lost in this patient.*

B

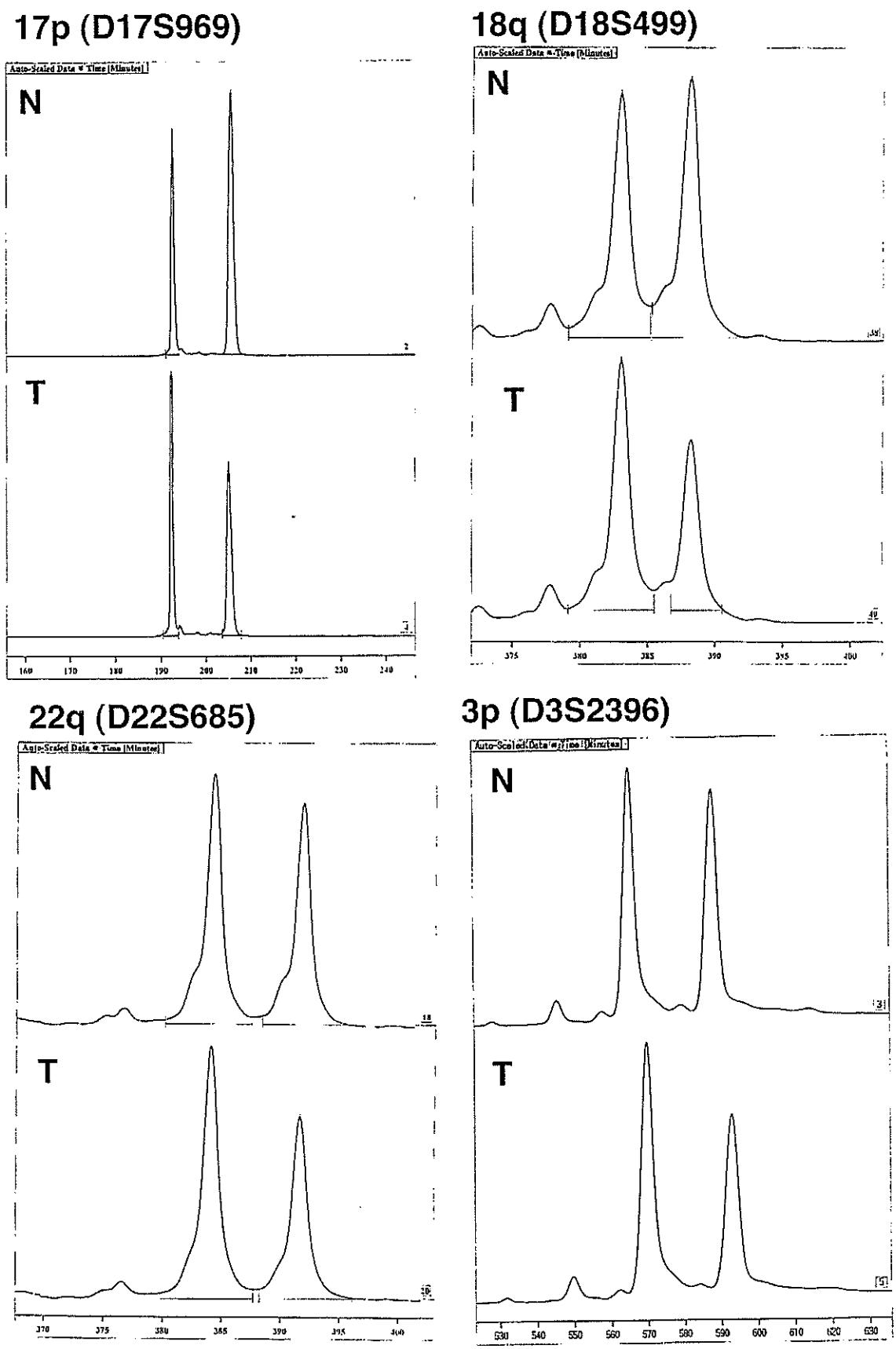

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Table III. *Clinicopathological backgrounds of low and high allelic loss groups.*

Allelic loss	Low (n=25)	High (n=107)	*p*
Gender			
Male	12	68	
Female	13	39	0.29
Age			
<60	8	40	
60≤	17	67	0.61
Tumor site			
Colon	19	63	
Rectum	6	44	0.11
Tumor differentiation			
Well	15	47	
Moderate	10	60	0.15
Lymphatic invasion			
Negative	15	49	
Positive	10	58	0.20
Venous invasion			
Negative	17	57	
Positive	8	50	0.18
Depth of invasion (pT)			
pT1, pT2	7	19	
pT3, pT4	18	88	0.25
Lymph node status (pN)			
Negative	22	47	
Positive	3	60	<0.01

Table IV. *Disease-free survival according to allelic status.*

		5-year disease-free survival rate			
		Stage I, II	*p*	Stage III	*p*
17p	Loss	80% (n=49)		56% (n=57)	
	Retained	80% (n=25)	0.96	63% (n=8)	0.80
18q	Loss	81% (n=49)		54% (n=60)	
	Retained	85% (n=22)	0.62	71% (n=5)	0.34
22q	Loss	83% (n=31)		68% (n=37)	
	Retained	83% (n=37)	0.79	47% (n=17)	0.19
3p	Loss	82% (n=22)		67% (n=21)	
	Retained	81% (n=34)	0.79	45% (n=29)	0.36
High and low allelic loss status					
	High	77% (n=47)		59% (n=60)	
	Low	86% (n=22)	0.30	67% (n=3)	0.83

adjuvant therapy. Another explanation for the conflicting data is non-specific allelic loss. Because chromosomal losses and gains are driven by chromosomal instability that persists throughout the lifetime of the tumor cells (28), some of the allelic losses may not affect the malignant potential of cancer cells, and these non-specific alterations may decrease the prognostic importance of the allelic losses, *i.e.*, these non-specific alterations may obscure the effects of allelic loss.

We showed that the allelic status was significantly related to the lymph node status. If the lymph node status could be predicted before radical surgery, it would be useful for clinical decision making. Taking the high-risk factor for lymph node metastasis, lymphatic invasion (29, 30), into account, patients without allelic loss and without lymphatic invasion had a very low incidence of lymph node metastasis. Among 14 patients without allelic loss at 18q or lymphatic invasion, only one patient (7%) had lymph node metastasis. Among 19 patients without allelic loss at 17p or lymphatic invasion, only one patient (5%) had lymph node metastasis. Fifteen patients in the low allelic loss group without lymphatic invasion had no lymph node metastasis. However, the presence of lymphatic invasion cannot be determined before resection, only after. These results suggested that the combination of allelic loss status and lymphatic invasion status can predict lymph node metastasis before radical surgery. This is particularly useful information, especially for T2 or more so for rectal cancer because, *e.g.*, in the absence of these risk factors, such tumors can be treated by local excision, by endoscopic resection or transanal resection. Therefore, further examination of the relationship between allelic status and lymph node status is warranted in future studies.

The DNA of tumor tissues is inevitably not homogeneous because of stromal cell contamination or the genetic heterogeneity of tumor cell populations, which have also been proposed to cause a wide range of allelic losses. In conventional RFLP (restriction fragment length polymorphism) or PCR-based RFLP analysis, to detect allelic loss the proportion of tumor cells in the sample must exceed at least 50% of the total cells, and a large amount of DNA is required. Clinical samples are often contaminated with normal cells, and the tumor cellularity is sometimes less than 50%. In such cases, conventional techniques cannot detect allelic loss and the allelic status is considered to be retained. This suggests that conventional techniques cannot be used to detect clear associations between allelic loss and prognosis. Here, blunt-end SSCP analysis, which can detect allelic losses when the tumor cellularity of the sample is around 10% and requires only a small amount of DNA, was used. These advantages enabled the detection of allelic losses using small amounts of DNA obtained from biopsy specimens, surgical materials and formalin-fixed, paraffin-embedded sections. The method is clinically very useful, because surgical materials and biopsy samples of cancer are usually contaminated with many normal cells.

It was found that the number of allelic losses was not associated with the prognosis of CRC. However, Choi *et al.* showed that the number of allelic losses was associated with prognosis, this factor still being significant in multivariate analysis (8). Because they had examined eight chromosomes (3p, 4p, 5q, 8p, 9p, 13q, 17p and 18q), this conflicting result might be explained by the difference in the chromosomes examined. If the level of chromosomal loss is an important

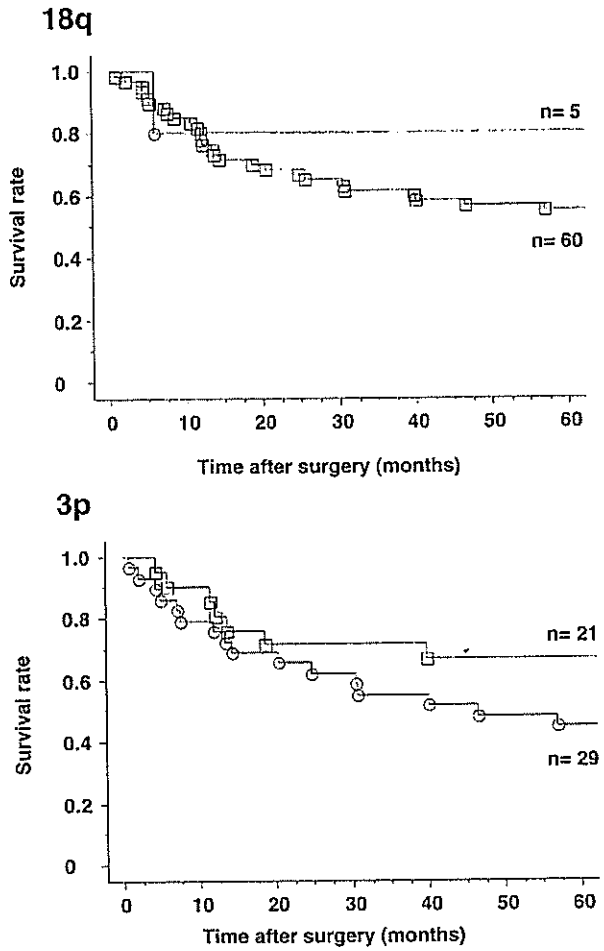

Figure 2. *Disease-free survival curves in stage III CRC. Patients with allelic loss at 18q showed worse survival than those without allelic loss at 18q, and patients with allelic loss at 3p showed better survival than those without this allelic loss. These differences were not significant.* □: *Lost,* ○: *Retained.*

prognostic factor, then it is of importance to determine which chromosomes are important for prognosis and how many chromosomes are to be examined. On the other hand, Rooney *et al.* obtained contrary results using comparative genomic hybridization (21). In their study, Dukes' C patients with more than two genomic aberrations had a better survival rate than did patients with fewer regions. Rooney *et al.* also showed that single genomic instabilities were not correlated with survival.

The allelic loss of chromosome 17p is a very common event in CRC. Although the allelic status of chromosome 17p is correlated with some clinicopathological backgrounds, only a small number of reports have suggested the prognostic importance of this allelic loss (1, 8), while other reports, including this study, showed no correlation between prognosis and allelic loss (15, 17-19). For p53, intragenic polymorphic markers were used. Even where the intragenic markers were informative, there was no correlation between prognosis and allelic loss of p53 (data not shown).

The allelic loss of chromosome 22q is relatively frequent in CRC (22, 23, 25, 31). However, there is no report of a tumor suppressor gene on 22q. Although Iino *et al.* have shown that allelic loss of chromosome 22q was correlated with lymph node metastasis (31), there have been no reports of a relationship between the allelic loss of chromosome 22q and prognosis. No relationship was found between the allelic loss of 22q and the clinicopathological background or prognosis, meaning that it probably is not a prognostic factor in CRC patients.

The allelic loss of chromosome 3p is also relatively frequent in CRC, and detailed deletion mapping studies have suggested the existence of tumor suppressor genes on this chromosome, although non have been reported. Iniesta *et al.* showed that allelic loss of 3p was significantly associated with worse prognosis in CRC patients (4). Although theirs was the first report to demonstrate the prognostic significance of the allelic loss of 3p, our study revealed no relationship between the clinicopathological background and allelic status. Choi *et al.* suggested that allelic loss of 3p was correlated with cancer-related death (8). Blaker *et al.* (25) showed preferential loss of chromosome 3p in CRC. However, no additional studies have supported this result, and we were unable to show a relationship between the clinicopathological background or prognosis and allelic loss of 3p.

In summary, although allelic status was not associated with prognosis in CRC patients without adjuvant chemotherapy, it was significantly associated with lymph node metastasis, and a combination of the allelic status and lymphatic invasion status can be used to predict the lymph node status before radical surgery. When allelic loss and lymphatic invasion are not detected after local excision, additional lymph node resection is not required.

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