

In the CRT group, surgery was performed within 2 to 3 weeks after completion of preoperative CRT, and the investigated histological changes occurred during this period. Anal function improved with the postoperative course in some cases, suggesting that nerves and tissue including muscle can regenerate and result in improved anal function. However, an investigation of anal function after ISR in patients who underwent surgery at our hospital suggested that functional recovery cannot be expected in cases with unfavorable function at 6 to 12 months after surgery.<sup>13</sup> Because CRT-induced early-phase tissue degeneration is associated with anal function at 12 months after surgery (as found in this study), tissue degeneration early after CRT may have a long-term effect on anal function.

Various factors may exert an influence on anal function, and this makes it difficult to predict postoperative anal function before surgery. However, the results of this study showed a significant correlation between the degeneration score defined in the study and the Wexner score in the Spearman analysis. Furthermore, there was no significant relationship between each histological finding and Wexner score, and no significant association between each item for evaluation of neural degeneration and Wexner score in multivariate regression. These results suggest that tissue degeneration should be evaluated by examining various items, rather than based on only a single item, because neural degeneration associated with anal dysfunction may be reflected by several critical items. A further study is needed to identify these important items.

Postoperative maintenance of anal function is important after ISR and further research is necessary to develop a compensatory treatment for maintenance of function (for example, reconstruction of functional muscles) for CRT cases with functional failure. Simultaneous management of therapeutic benefit and anal function is required following ISR, and we intend to examine approaches to maintenance of the therapeutic benefit of preoperative CRT in a future study. For example, preoperative chemotherapy alone may be appropriate based on the improvement of colorectal cancer observed with this approach.

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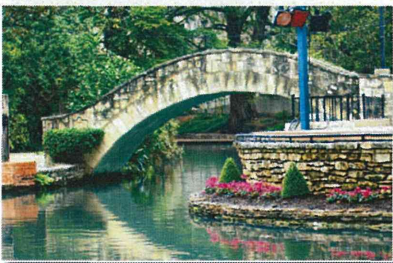
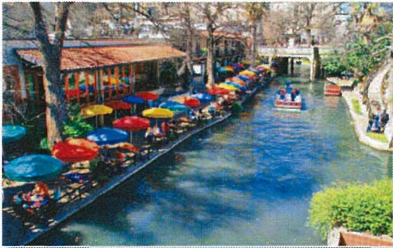
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# The indications for a diverting stoma in low anterior resection for rectal cancer: a prospective multicentre study of 222 patients from Japanese cancer centers

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## Abstract

**Aim** The aim of the study was to determine the present state of diverting stoma construction in Japanese cancer centres and to investigate the relationship between symptomatic leakage and diverting stoma after low anterior resection for rectal cancer.

**Method** Two hundred and twenty-two consecutive patients undergoing low anterior resection for rectal cancer located within 10 cm from the anal verge were investigated in a prospective, multicenter study.

**Results** The overall leakage rate was 9.0% (20/222). Of 31 cases with an anastomosis within 2.0 cm from the anal verge, 22 (71%) had a diverting stoma. Of cases anastomosed within 5.0 cm, the absence of a diverting stoma and tumour size were significantly related to an increased rate of leakage [leakage in 13 (12.7%) of 102 cases without a diverting stoma; in three (3.8%) of 80 cases with a diverting stoma]. Among anastomoses within

2.0 cm from the anal verge, leakage occurred in four (44.4%) of nine cases without and in none (0%) of 22 cases with a diverting stoma.

**Conclusion** We recommend a diverting stoma for an anastomosis within 5.0 cm of the anal verge and strongly recommend it for a very low anastomosis within 2.0 cm.

**Keywords** Rectal cancer, low anterior resection, anastomotic leakage, diverting stoma, defunctioning stoma

### What is new in this paper

Recently, a DS construction is recommended for a low anastomosis in LAR, but the definition of a low anastomosis is not clear. In the present study, we focused on the relationship between the anastomotic level and leakage.

## Introduction

With advances in surgical procedures and adjuvant treatment, sphincter-preserving surgery has become the standard operation for most patients with rectal cancer. Anastomotic leakage is, however, still an important complication. A temporary diverting stoma (DS), which is often constructed in many cases of low anterior resection (LAR), aims to divert the faecal stream.

However, it remains unproven whether this in itself can prevent clinical leakage. Recent randomized control studies [1–4] and meta-analyses [5,6] have shown that a DS does reduce the incidence of symptomatic leakage in LAR for rectal cancer, but the evidence is still limited and the definition of a low anastomosis is not clear.

The aim of this prospective study was to determine the present state of DS construction in Japanese cancer centres and to investigate the relationship between symptomatic anastomotic leakage and DS. This is the first prospective, multicenter, large-scale study from Japanese colorectal cancer centres.

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## Method

### Patients

The design was a prospective, multicenter study. Data were collected from nine participating cancer centres involved in the 'Studies on the standardization for diagnosis, treatment, and follow up of colorectal cancer patients', sponsored by Grant-in-Aid 21-2 for Cancer Research from the Ministry of Health, Welfare and Labour of Japan. The study was approved by the local ethics committee of each hospital and informed consent was obtained.

From January 2008 to May 2009, 222 consecutive patients with primary rectal cancer underwent LAR. This was performed for patients with rectal cancer in which the lower edge of the tumour was within 10 cm from the anal verge and all anastomoses were carried out using circular staplers. Patients having a sutured colo-anal anastomosis were excluded. Cases having laparoscopic anterior resection, subtotal colectomy, total proctocolectomy, abdominoperineal resection, Hartmann's procedure or pull-through procedures were also excluded. No patient received neoadjuvant radiotherapy or chemoradiotherapy. The decision to construct a DS and the choice of ileostomy/colostomy were made by the individual surgeon in each case. When a DS was constructed, each surgeon reported the primary reason for the decision.

### Anastomotic leakage

Anastomotic leakage was defined by the emission of gas, pus or faeces from the drain or wound or the vagina or the discharge of pus *per anum*. All clinically suspicious leakages were confirmed by one or more of the following techniques: contrast enema radiography, computed tomography scan and endoscopy. When there was no abnormal communication of the intraluminal and extraluminal compartments due to a dehiscence of intestinal wall integrity, the patient was said to have a pelvic abscess and not anastomotic leakage.

### Analysis of variables

Variables recorded included age, sex, body mass index (BMI), neoadjuvant therapy, bowel obstruction, tumor location, UICC-TNM stage, level of IMA ligation, mobilization of splenic flexure, lateral lymph node dissection, types of reconstruction (including straight, colonic J-pouch, transverse coloplasty, or other), completeness of doughnuts, intra-operative blood loss, operating time, DS construction, synchronous resections of other organs (hepatectomy for simultaneous liver metastasis or extended surgery to adherent organs, or addi-

tional cancer resection for synchronous cancers), tumour size, the distal resection margin of the specimen, level of the anastomosis from the anal verge, and use of a pelvic or intraluminal drain.

Bowel obstruction was defined as stenosis preventing the passage of a fibroscope. The level of the lower border of the tumour from the anal verge was measured just before the operation under general anesthesia and the lithotomic position using an anoscope. Clinical stage was classified preoperatively according to the UICC-TNM classification (6th edition) [8]. Tumour size and distal resection margin were measured on the specimen before fixation with formalin. The level of anastomosis from the anal verge was measured by digital examination just after completing the reconstruction, with the patient in the lithotomy position.

### Statistical analysis

In the univariate analysis the  $\chi^2$  and the Mann-Whitney *U*-test were used. After univariate analysis, variables with a *P* value  $\leq 0.1$  were selected for multivariate analysis. A multivariate analysis was performed using a binary logistic regression model. This was performed using IBM SPSS Statistics software version 18 (SPSS Inc., an IBM company, Chicago, Illinois, USA). All *P* values  $< 0.05$  were considered statistically significant.

## Results

### Patient characteristics

From January 2008 to May 2009, 222 consecutive patients with primary rectal cancer who underwent LAR were included in this prospective, multicentre study. They included 144 (65%) males. The mean age was  $62.2 \pm 10.1$  years, the mean body mass index (BMI) was  $22.5 \pm 3.4$  kg/m<sup>2</sup>, the average distance of the tumour from the anal verge was  $6.7 \pm 1.8$  cm and the average level of the anastomosis was  $4.0 \pm 1.5$  cm. Neoadjuvant chemotherapy was performed in five patients only. Neoadjuvant radiotherapy or chemoradiotherapy was not performed in this series. All anastomoses were performed using the circular stapling instrument by the double staple technique in 221 patients. Most patients (202) had a straight anastomosis and 20 underwent a side-to-end anastomosis. No colonic J pouch or transverse coloplasty was constructed. Twenty-one synchronous resections included nine extended resections for direct invasion of adjacent organs; eight hepatectomies for liver metastasis, three resections of double primary cancers and one adrenalectomy for adrenal metastasis were carried out. There was no mortality.



### Diverting stoma

In the initial LAR, 80 (36.0%) of the 222 patients received a diverting stoma (DS). Ileostomy was chosen in 70 (87.5%) patients and a transverse colostomy in 10 (12.5%).

The primary reasons stated by the surgeons for the decision to construct a DS included low level of anastomosis (41 cases) and low tumour location (16 cases). Other reasons are listed in Table 1.

Clinical factors associated with DS construction included neoadjuvant chemotherapy, low tumour location, low anastomotic level, long operating time, massive intra-operative bleeding, mobilization of splenic flexure, and incompleteness of doughnuts. As shown in Table 2, no DS construction was performed in patients whose anastomosis was more than 5.1 cm from the anal verge.

**Table 1** Primary reason for diverting stoma construction ( $n = 80$ ).

	No.	Rate (%)
Anastomotic level was too low	41	51.3
Tumour location was too low	16	20.0
Synchronous resections of other organs	4	5.0
History of diabetes or previous steroid abuse	4	5.0
Tumour size was too large	2	2.5
Incomplete anastomotic ring	1	1.3
Incomplete bowel preparation	1	1.3
Operating time was too long	1	1.3
Poor blood supply to anastomotic site	1	1.3
Intra-operative leakage test was positive	1	1.3
History of previous angina pectoris	1	1.3
Multiple firings during rectal division	1	1.3
Injury to vaginal wall	1	1.3
Others	5	6.3

**Table 2** Relationship between the anastomotic level and diverting stoma construction rate.

Anastomotic level from AV (cm)	DS rate (%)	Leakage rate	
		Without DS	With DS
1.0–2.0	71.0	4/9 (44.4%)	0/22 (0%)
2.1–3.0	41.5	3/31 (9.7%)	1/22 (4.5%)
3.1–4.0	52.6	3/27 (11.1%)	2/30 (6.7%)
4.1–5.0	14.6	3/36 (8.3%)	0/6 (0%)
5.1–6.0	0	3/24 (12.5%)	0/0 (0%)
6.1–7.0	0	0/10 (0%)	0/0 (0%)
7.1+	0	1/5 (25.0%)	0/0 (0%)

AV, anal verge; DS, diverting stoma.

**Table 3** Multivariate analysis of leakage risk factors.

	P-value	Odds ratio (95% CI)
Intra-operative bleeding (ml)	0.12	1.0 (1.00–1.00)
Tumour size (cm)	0.02	1.3 (10.5–1.62)
Diverting stoma	0.04	4.2 (1.04–16.6)

Most of the patients (22 of 31; 71.0%) whose anastomosis was within 2.0 cm from the anal verge received DS. Of the patients whose anastomosis was within 2.1–5.0 cm from the anal verge, 38.4% (58 of 151) received a DS (Table 2).

### Anastomotic leakage

The overall rate of anastomotic leakage was 9.0% (20 of 222). This was 12.0% (17 of 142) in patients without a DS compared with 3.8% (3 of 80) of cases with a DS ( $P < 0.05$ ). Every pelvic abscess was accompanied by anastomotic dehiscence.

Clinical variables were analysed to investigate the risk factors for anastomotic leakage. Patients whose anastomosis was above 5.1 cm were excluded. Among patients whose anastomosis was within 5.0 cm, the absence of a DS and tumour size were significantly related to an increased leakage rate ( $P < 0.05$ ) on univariate analysis. In this subgroup, 13 (12.7%) of 102 cases without DS had leakage, whereas three (3.8%) of 80 cases with DS had leakage. On multivariate analysis, the absence of a DS had a significantly high leakage rate (Table 3). Furthermore, among cases with an anastomosis, within 2.0 cm from the anal verge, four (44.4%) of nine cases without DS had leakage, whereas none (0%) of 22 cases with DS had leakage. ( $P < 0.05$ ) (Table 2).

Three (3.8%) of 80 patients who underwent LAR with DS experienced leakage. All were treated conservatively. Of the 17 (12%) patients who had leakage without a DS, 14 needed urgent surgery and only three were treated conservatively. The need for reoperation was significantly increased in patients without DS compared with those with DS ( $P = 0.018$ ).

### Discussion

This prospective study has confirmed that the indication for DS construction in Japanese cancer centres is limited to patients having an anastomosis within 5.0 cm from the anal verge. In patients with an anastomosis at this level, DS was significantly associated with a reduced rate of clinically relevant anastomotic leakage. Our data further identified that DS construction for patients with

an anastomosis within 2.0 cm from the anal verge had a marked association with reduced leakage. This is the first prospective, multicentre study regarding DS construction in rectal cancer surgery from Japanese cancer centres.

Symptomatic anastomotic leakage has been reported to occur in 5–20% of cases [9–17]. When it occurs, the associated risk of postoperative mortality is increased to between 6% and 22% [17]. Theoretically, DS is constructed to divert the faecal stream to protect the healing anastomosis. However, it is unproven whether diverting the faecal stream in itself directly prevents anastomotic dehiscence.

Several retrospective or nonrandomized prospective studies have shown that the absence of a DS is a risk factor for leakage after LAR [12,16,18,19], but others have disputed this [20,21]. Four randomized control studies have investigated the association between DS and leakage [1–4]. Matthiessen *et al.* [3] reported the results following intra-operative randomization of patients undergoing LAR for rectal cancer within 15 cm from the anal verge and anastomosed within 7 cm. Leakage occurred in 10.3% (12 of 116) of patients with a defunctioning stoma compared with 28.8% (33 of 118) of patients without a stoma. They concluded that a defunctioning stoma significantly decreased the rate of symptomatic leakage and therefore recommended it in cases of LAR. In a trial by Chude *et al.* [1], 256 patients were randomized into two arms. Anastomotic leakage developed in 2.2% (3 of 136) of patients with a defunctioning stoma and in 10.0% (12 of 120) of patients without ( $P < 0.05$ ). Thus, they also recommended a DS in surgery for low rectal cancer. Two meta-analyses were reported recently [5,6]. Both concluded that a DS reduces the rate of clinically relevant anastomotic leakage.

Despite these studies there is less information on the effect of DS related to a detailed analysis of the level of the anastomosis. In the present study, therefore, we focused on the relationship between the anastomotic level and leakage. Matthiessen *et al.* [3] recommended that a DS was indicated for patients whose anastomosis was within 7 cm. In the light of the present study, this would appear to be too broad a generalization. When the level is divided in distances of 1 cm from the anal verge, as in the present study, it is clear that the risk increases steadily the lower the anastomosis is performed. It is also noteworthy in our study that no patient with an anastomosis above 5 cm received a stoma and in these patients the incidence of leakage was 10.3%, which is the same as that reported by Matthiessen *et al.* in defunctioned patients. This raises the question of whether a stoma is necessary for an anastomosis above 5 cm, which is well below the level of anastomosis of many patients who would have undergone

a stoma on the advice of Matthiessen *et al.* It seems that the definition of 'low anastomosis' for Japanese surgeons was more selective.

In the study by Chude *et al.* [1], their inclusion criterion consisted of rectal cancer located 5 cm above the anal verge but the level of the anastomosis ranged from 5 to 6 cm from the anal verge, which when allowing for an adequate distal clearance [22] would put the level of the tumour at a level well above 5 cm. Furthermore, some tumours within 5 cm of the anal verge may need an intersphincteric dissection, especially in some males with a narrow pelvis [23]. Thus not all of such patients would be able to have a standard low anterior resection.

There are many other reported risk factors for leakage, such as male sex [10,12,14,17], previous radiation therapy [10,14], poor bowel preparation [9], blood transfusion [9] and low anastomotic level. Interestingly, in our study, DS tended to be constructed in patients in whom there was considerable anticipated risk to the anastomosis. Despite this selection bias in our nonrandomized study, although paradoxical, the leakage rate was lower in patients with DS compared with patients without. This may prove that DS is preventative for anastomotic leakage.

The indication for DS in the present study was applied to selected patients with a low anastomosis and was more limited than in the controlled trials. There may be an explanation based on differences in the patient populations between Japan and western countries. First, preoperative radiation therapy is considered to be a risk factor by some authors [10,14]. Although randomized multicentre trials have shown that it does not increase postoperative morbidity [24,25], Peeters *et al.* [16] retrospectively analysed risk factors from the database of the Dutch Colorectal Cancer Group [24], and reported that a defunctioning stoma was constructed more often in patients who had received radiation, and that the absence of a DS was significantly associated with a higher leakage rate. In Japan, particularly in our study group, preoperative therapy (including chemoradiotherapy) for resectable rectal cancer was not standard [7,26], whereas it was so in western countries. This may be one reason for the limited number of DSs.

Secondly, our low mortality rate may have influenced the limited indication for DS. In the present series, there was no mortality, even in cases of leakage without DS. This reflects our low leakage rate in cases without DS (12%; 17 of 142), which is comparable to that reported by Matthiessen *et al.* [3] in cases with DS (10.3%; 12 of 116). Chude *et al.* [1] reported two deaths in their patients who did not receive a DS.

Ulrich *et al.* [27] also conducted a randomized controlled trial of patients undergoing low anterior



resection. The symptomatic anastomotic leakage rate in the groups with and without a DS were 5.5% and 37.5% ( $P = 0.02$ ) and the study was terminated prematurely as a result.

There are four main limitations of the present study. First, the clinically unapparent leakages might have been missed in either group because no systematic assessment of the anastomosis for clinically stable patients was performed. Second, the study was not randomized. Certainly, a randomized clinical trial is the best methodology to determine this evidence. But Matthiessen *et al.* [3] stated that the proportion of eligible patients in their randomized study was less than one-third (28.5%) of all patients who would have been eligible owing to intra-operative adverse events and patient refusal to participate. Consent is one of the main difficulties of a randomized clinical trial. Third, the level of the tumour was measured by anoscopy, but the level of the anastomosis in the present study was measured by digital examination performed by the operating surgeon. Fourthly, we did not investigate operating surgeon as a risk factor for leakage.

In conclusion, the indication of DS construction in our group was limited to anastomoses below 5 cm from the anal verge, lower than that recommended in a recent randomized study. Leakage was less in patients with DS compared with patients without and this was related to the distance of the anastomosis from the anal verge. We therefore recommend DS construction where the anastomosis is within 5.0 cm of the anal verge and strongly recommend it for a very low anastomosis within 2.0 cm.

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## Male sexual dysfunction after rectal cancer surgery

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### Abstract

**Purpose** The aims of the study were to determine the extent of male sexual dysfunction after surgical treatment of rectal cancer and to examine the outcome of postoperative treatment with sildenafil.

**Methods** A prospective study was performed in patients who underwent attempted curative total mesorectal excision (TME) for low rectal cancers. Sexual function scores were determined by questionnaire preoperatively and at 3 and 12 months postoperatively. Outcomes were examined in patients who were sexually active preoperatively.

**Results** From 2000 to 2007, 207 patients underwent TME at our institution, of whom 49 (24%) were sexually active preoperatively. Erectile dysfunction and ejaculatory problems were present in 80% and 82%, respectively of the 49 patients at 3 months postoperatively, and in 76% and 67%, respectively at 12 months. Lateral lymph node dissection was a strong risk factor for postoperative sexual dysfunction. The impotency rate was 37% and 47% of patients were unable to ejaculate. Sildenafil was administered to 16 patients who requested the drug during follow-up, and sexual dysfunction was improved in 11 of these patients (69%).

**Conclusion** Sexual dysfunction occurs frequently after rectal cancer treatment and is mainly caused by surgical damage in lateral lymph node dissection. Sildenafil may be effective for the treatment of sexual dysfunction.

**Keywords** Male sexual dysfunction · Rectal cancer · Sildenafil · Total mesorectal excision

### Introduction

The past two decades have witnessed substantial improvement in survival from rectal cancer due to earlier diagnosis, improved efficacy and delivery of radiotherapy and advances in surgical techniques such as total mesorectal excision (TME) [1, 2]. The degree of autonomic nerve preservation in surgery for rectal cancer is an important factor associated with postoperative sexual and urinary functions. Sexual dysfunction occurs due to intraoperative nerve injury, and preservation of pelvic autonomic nerves such as the pelvic plexus and superior hypogastric plexus seems to lower the incidence of sexual morbidity. In particular, damage to the cavernous nerves of the penis distributed in the nerve-vascular bundle is directly associated with postoperative sexual dysfunction.

The incidence of erectile dysfunction after surgery for rectal cancer has been reported to be 20–70% [3–7], and ejaculation dysfunction occurs in 20–60% of cases with erectile ability [3–5, 8]. A high rate of sexual function can be maintained by autonomic nerve preservation [9, 10], but the incidence of dysfunction has varied among reports. Surgeon-related factors are also important in treatment of rectal cancer, both for achieving local control and for preserving function [11]. Sexual dysfunction is an important postoperative issue, but the relationship between differences in surgical procedures and the incidence of postoperative sexual dysfunction has not been examined. Moreover, reduced function and functional impotence have not been investigated separately, and the severity of dysfunction has not been evaluated in previous studies of sexual function after surgery for rectal cancer.

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At our hospital, we perform a prospective questionnaire-based survey of functions (defecation, urination and sexual function) after surgery for rectal cancer. In this study, we investigated the items concerning sexual function in this survey. Data on sexual function were obtained, patients who were sexually active before surgery were identified and postoperative sexual function was investigated in these patients. Oral sildenafil was administered to patients in whom sexual dysfunction occurred after surgery and the outcome was also investigated.

## Methods

### Prospective questionnaire-based study of sexual function

The subjects were 207 patients who underwent TME for rectal cancer at our hospital between 2000 and 2007. The treatment was given with curative intent in all cases. Hospital records were analyzed to obtain details of the surgical procedures related to the degree of nerve preservation in all patients. Questionnaires on anal, sexual and urinary functions were completed by patients who gave informed consent, and the answers were accumulated prospectively. Sexual function scores were determined preoperatively and at 3 and 12 months postoperatively based on the questionnaires, and the preoperative level of sexual activity was analyzed.

Among patients who completed the questionnaire on sexual function, those who provided answers to items concerning ejaculation and erection before and after surgery were regarded as eligible for the study. Those without sexual function before surgery were excluded. Sexual function outcome was assessed using questions related to pre- and postoperative libido, erection, stiffness for penetration, ejaculation and orgasm, as measured by the International Index of Erectile Function (IIEF) scale [12–15]. Patients with active sexual function preoperatively were selected based on an answer of one or two to both of the following questions on the IIEF questionnaire. What is your condition of erection? [1. Normal erection 2. Slightly reduced 3. Almost no erection 4. No erection 5. Not indicated]. What is your condition of ejaculation? [1. Normal ejaculation 2. Slightly reduced 3. Almost no ejaculation 4. No ejaculation 5. Not indicated 6. Retrograde ejaculation]. The results of questionnaires given at 3 months and 1 year after surgery were analyzed for the patients who met this criterion.

Postoperative urinary function was also investigated. Residual urine was measured after removal of a urethral catheter after surgery. A residual urine volume of  $\geq 100$  mL was regarded as residual urine-positive, and early urinary dysfunction was defined as three consecutive residual

urine-positive measurements. Long-term urinary dysfunction was defined based on the results of a questionnaire given on urinary dysfunction at 6 months after surgery. Urinary dysfunction was defined as a reduction in urinary function compared to the preoperative condition.

### Surgical treatment

TME was performed up to the level of exposing the levator ani muscle. The application of TME was used as a criterion for selection of low rectal cancer cases. Patients in whom TME was performed using a detailed Operation Record Form were initially selected. When the pelvic autonomic nerves were injured during surgery or partial/combined resection was performed, the patients were included with a description of the procedure. However, cases of combined resection of multiple organs and total resection of the pelvic autonomic nerves were excluded. Lateral lymph node dissection was performed in patients with suspected lateral metastasis and those with lower rectal cancer of clinical stage II or III receiving standard therapy. Anastomosis methods such as the double stapling technique and colo-anal anastomosis were disregarded on the condition that TME was performed, and abdominoperineal resection (APR) cases, which were colostomized, were also included. The anastomosis method and the presence or absence of a pouch was described in the Operation Record Form. Use of temporary colostomy was determined by the attending physicians.

### Postoperative adjuvant chemotherapy

Postoperative chemotherapy was initiated for cases of pathological stage III diagnosed histopathologically in which lymph node metastasis was positive, after confirming that the patient met the criteria for adjuvant chemotherapy. The time and duration of this therapy were not examined in the study.

### Treatment of sexual dysfunction

Oral sildenafil was administered to patients who developed sexual dysfunction during outpatient follow-up and requested treatment. An informed consent was obtained concerning the potential adverse effects of the drug. The patients received 25 mg of sildenafil and 5 mg of vardenafil, or 50 mg of sildenafil and 10 mg of vardenafil. Sexual function was surveyed by questionnaire after initiation of oral treatment and the outcome was investigated.

### Protection of privacy

The study design was approved by the ethics committee of our institution and all patients provided informed consent



prior to participation in the study. The privacy of the patients was strictly protected. Patients were identified with a registration number, initials, birth date and a medical history number. Physicians (investigators) participating in the study followed the study protocol to ensure that the safety and human rights of the patients were protected. The study was performed within the ethical standards of the 1964 Declaration of Helsinki.

#### Statistical analysis

A Student's *t* test and a Fisher's exact test were used to examine differences in erection, ejaculation and urinary dysfunction between the groups of patients with and without sexual dysfunction. All statistical analyses were performed using SPSS for Windows, v.13.0 J (SPSS-Japan Inc., Tokyo, Japan). A *p* value <0.05 was considered to be significant.

## Results

#### Patient background

Of the 207 patients who underwent TME between 2000 and 2007, 149 (72%) answered the questions concerning sexual function, and preoperative sexual function was identified in 49 cases (24%). The median age of the 49 patients was 58 years old, and 28 were ≤60 years old. The tumour size was ≤5 cm in 21 patients. One patient had undergone preoperative chemoradiotherapy. The clinical tumour stage was T3 in 40 cases (Table 1). The surgical procedures were very low anterior resection in 19 cases (39%), low anterior resection in 12 (25%), APR in 1 (2%) and intersphincteric

resection (ISR) in 17 (35%). A stoma was prepared during surgery in 21 patients (43%). No stoma was closed within 3 months after the surgery. The stoma was closed in 13 patients by 12 months after surgery but remained open in eight patients (16%).

Bilateral lateral lymph node dissection was performed in 32 cases (65%). Of 35 patients who underwent lateral lymph node dissection, lateral lymph node metastasis was observed in four (11%) and lymph node metastasis, including that to regional lymph nodes (i.e. pathological stage III), was observed in 17 (35%).

Unilateral resection of the hypogastric nerves was performed in four (8%) and partial resection of the pelvic plexus in six (12%). Laparoscopic surgery was performed in two cases (Table 2).

Erectile dysfunction and ejaculatory problems occurred in 80% and 82%, respectively of the 49 patients at 3 months after the operation and in 76% and 67%, respectively at 12 months. Impotence was present in 37% and failure to ejaculate occurred in 47%.

#### Sexual dysfunction

A preoperative IIEF score of ≤21, which suggests erectile dysfunction, was not found in any patient. Sexual dysfunction after surgery was compared with the preoperative status, with the following results. Erectile and ejaculation functions were reduced in 39 (80%) and 40 (82%) patients, respectively at 3 months after surgery, and in 37 (76%) and 34 (67%), respectively at 12 months, including 18 patients (37%) with no erection and 23 (47%) who were unable to ejaculate. There were no significant differences in the incidences of erectile or ejaculation dysfunction by age, surgical procedure, tumour factors, the presence or absence of a stoma, preservation of the hypogastric nerve, or preservation of the pelvic plexus or splanchnic nerves at 3 or 12 months based on the questionnaire. However, these incidences were significantly higher at 12 months in cases treated with lateral lymph node dissection ( $p \leq 0.01$ ), although no significant differences were noted at 3 months (Tables 3). Therefore, lateral node dissection appeared to be the main risk factor for postoperative sexual dysfunction. Erectile and ejaculation functions improved from 3 to 12 months after surgery in two (5%) and six (18%) cases, respectively. The autonomic hypogastric nerve, pelvic plexus and splanchnic nerve were totally preserved in all of these cases. Each of these items was analyzed in cases with no erection or ejaculation, but no significant differences were found (Table 4).

#### Urinary dysfunction

Early urinary dysfunction occurred in 18 cases (37%) and long-term dysfunction at 6 months postoperatively was

**Table 1** Patient characteristics ( $n=49$ )

Procedure	Number of cases
Age (years)	
Median	58
Range	36–76
<60	28
>60	21
Tumour size (cm)	
Median	6.0
<5	21
>5	28
Clinical tumour stage	
T1	1
T2	8
T3	40
Preoperative radiotherapy	1

**Table 2** Treatment characteristics ( $n=49$ )

Procedure	Number of cases
Type of resection	
LAR (low anterior resection)	12
vLAR (very low anterior resection)	19
ISR (intersphincteric resection)	17
APR (abdominoperineal resection)	1
Laparoscopy	2
Stoma	21
Lateral lymph node dissection	35
Hypogastric nerves	
Total preservation	45
Unilateral resection	4
Pelvic plexus	
Total preservation	43
Partial resection	6

noted in two cases (4%). Lateral lymph node dissection was significantly associated with the incidence of early urinary dysfunction ( $p \leq 0.01$ ) (Table 4).

#### Treatment of postoperative sexual dysfunction

Sildenafil tablets were administered to 16 patients (mean age 54.7 years old) who requested treatment during follow-up. These cases included eight (50%) that underwent lateral lymph node dissection and two (13%) that received partial resection of the pelvic splanchnic nerves. Sexual function was improved in 11 (69%) of the 16 cases based on a questionnaire after initiation of oral drug treatment, but no functional improvement was achieved in the two cases with partial resection of the pelvic splanchnic nerves (Table 5). Anal function was additionally improved in one case after ISR.

#### Discussion

Investigation of surgery-associated sexual dysfunction alone is difficult after surgery for rectal cancer because of the influences of postoperative mental factors and surgery-associated reduction of function. From a QOL perspective, the significance of preservation of sexual function is low if the patient's satisfaction with this function is low. The IIEF [12–15] is a questionnaire on sexual function that is completed by patients without intervention by a third party and provides a comprehensive evaluation of sexual function. Therefore, our hospital uses the IIEF as a postoperative functional questionnaire. In this study, two items concerning erection and ejaculation were selected from the

IIEF items to identify patients with active sexual function before surgery.

Patient satisfaction with sexual function is of most importance and some patients are satisfied even though they are unable to become erected or to ejaculate. However, from the viewpoint of function-preserving surgery, the ability to obtain an erection and to ejaculate is important with regard to surgical accuracy. Therefore, both functional and psychological approaches are necessary to assess sexual function after surgery, but accurate evaluation of these issues is difficult and has not previously been described in detail. Thus, we selected patients with active preoperative sexual function and investigated their postoperative function. Satisfaction was evaluated by questionnaire and functional preservation was investigated by examining impotence. It is difficult to obtain information on sexual function from all patients because the survey may markedly intrude on patient privacy. Therefore, we performed a prospective postoperative functional survey after surgery for rectal cancer, extracted cases in which sexual function could be evaluated from the results and selected cases with active preoperative sexual function. There have been very few reports in which the status of sexual function has been examined after surgery for rectal cancer.

The incidence of sexual dysfunction was slightly higher than those in previous reports [3–5], which may have been due to inclusion of only TME cases, a preoperative T factor of T3 in many cases, and treatment with lateral lymph node dissection as the standard treatment in Japan. ISR was also applied in many cases. Since preoperative chemoradiotherapy has been shown to have a negative influence on anal function after ISR [16, 17], our hospital generally does not perform preoperative chemoradiotherapy (CRT). This is one reason for the high frequency of T3 cases. Preoperative CRT was performed in only one case, and therefore the influence of CRT on sexual function could not be evaluated.

Reportedly, the presence of a stoma after surgery is associated with postoperative sexual dysfunction. This effect may also be dependent on mental issues. We found no significant difference in postoperative sexual function between patients with or without a stoma, but this may have been due to the investigation being limited to erection and ejaculation, since we attached greater importance to function. An association between postoperative complications and sexual dysfunction has been suggested. Anastomotic leakage and intrapelvic abscess occurred in three patients (incidence, 6%) and sexual dysfunction occurred after surgery in one of these patients. However, it was difficult to investigate the correlation between complications and dysfunction because of the small number of complications.



**Table 3** Male sexual function after TME (n=49)

Item	After surgery	Erection Disorder (%)		Ejaculation Disorder (%)	
		3 months	12 months	3 months	12 months
Age (years)	□ 60 (n=28)	82	73	89	82
	□ 60 (n=21)	76	71	71	82
Tumour size (cm)	□ 5 cm (n=21)	76	76	81	67
	□ 5 cm (n=28)	82	75	82	71
Type of resection	LAR (n=12)	75	67	83	75
	vLAR (n=19)	84	89	74	63
	ISR (n=17)	76	65	88	75
	APR (n=1)	100	100	100	0
Tumour stage	T1 (n=1)	100	100	100	100
	T2 (n=8)	87	62	75	75
	T3 (n=40)	77	77	82	67
Stoma	Yes(n=21)	81	75	81	62
	No(n=28)	79	76	82	71
Lateral lymph node dissection	Yes (n=35)	83	86	86	80
	No (n=14)	71	50	71	43
Hypogastric nerve damage	Total preservation (n=45)	80	76	80	67
	Unilateral resection (n=4)	75	75	100	100
	Pelvic plexus damage preservation (n=43)	80	74	80	65
Pelvic plexus damage	Partial resection (n=6)	83	83	100	100

\* $p \leq 0.01$ 

Lateral lymph node dissection is an important factor involved in sexual and urinary dysfunctions [8, 18, 19] and

was the only surgical factor that influenced postoperative sexual function in our patients. This shows the high

**Table 4** Male sexual impotence and male urinary function after TME

Item		No erection (%)	Unable to ejaculate (%)	Early urinary dysfunction (%)
Age (years)	<60	39	50	42
	>60	33	42	28
Tumour size (cm)	<5	29	43	33
	>5	43	50	39
Type of resection	LAR	42	42	42
	vLAR	26	42	42
	ISR	47	59	23
	APR	0	0	0
Tumour stage	T1	100	100	0
	T2	25	38	13
	T3	38	48	43
Lateral lymph node dissection	Yes	43	51	45
	No	21	36	14
Hypogastric nerve damage	Total preservation	36	44	33
	Unilateral resection	50	75	75
Pelvic plexus damage	Total preservation	37	44	32
	Partial resection	33	67	66

LAR low anterior resection, vLAR very low anterior resection, APR abdominoperineal resection

accuracy of questionnaire surveys on sexual function for patients after surgery. In addition, we selected cases with active sexual function before surgery to perform an analysis of two functional items (erection and ejaculation) among those of the IIEF. Using this approach, we obtained information that reflected the marginal effect of surgery on postoperative function. Neuropathy associated with the lateral pelvic nerve plexus has been reported to be caused by lateral lymph node dissection, and injury of the cavernous nerves of the penis on the peripheral side of

the nerve-vascular bundle via the medial approach in TME may be strongly associated with sexual dysfunction. Of our patients who underwent lateral lymph node dissection, lateral lymph node metastasis was observed in 11%. It was difficult to evaluate the efficacy of lateral lymph node dissection because of the target patient group and the small number of cases. This is currently under investigation in a comparative clinical study of mesorectal excision with lateral lymph node dissection versus the same procedure without lateral lymph node dissection for lower rectal cancer of clinical stages II and III (JCOG0212).

An improved understanding of the pelvic anatomy has permitted the establishment of anus-preserving surgical procedures such as resection of the internal sphincter muscle of the anus. In the dissection of Denonvilliers' fascia, an association between preservation of this membrane and the cavernous nerves of the penis has been reported [20]. The microanatomy of the membrane has been visualized by magnification with development of laparoscopy, which may facilitate more accurate autonomic nerve-preserving surgery. However, only two patients underwent laparoscopic surgery in this study.

In a retrospective analysis of a randomized trial comparing open versus laparoscopic rectal cancer resection, seven (47%) of 15 sexually active men in the laparoscopic group reported impotence or impaired ejaculation, compared with only 1 (5%) of 22 patients who underwent open surgery ( $p=0.01$ ) [12]. The authors concluded that autonomic nerve preservation is more difficult to achieve with a laparoscopic approach, particularly for patients with low

**Table 5** Effect of sildenafil ( $n=16$ )

Item		Number
Age (median)		54.7
Lateral lymph node dissection (%)		8 (50)
Autonomic nerve partial resection (%)		2 (13)
Tumour size	<5 cm	8
	>5 cm	8
Type of resection	LAR	5
	vLAR	4
	ISR	7
	APR	0
Effect of sildenafil (%)	Yes	11 (69)
	No	5 (31)
Side effect (%)	Yes	0 (0)
	No	16(100)

LAR low anterior resection, vLAR very low anterior resection, APR abdominoperineal resection

rectal cancers or bulky tumours, probably because of insufficient tension on the planes that need to be dissected. However, this is based on a small sample size and laparoscopy for distal rectal resection was partially performed through a small suprapubic incision for completion of rectal dissection and division of the rectum. There is general agreement that entire TME dissection, vascular control and distal division of the rectum all are essential parts of laparoscopic TME and should be completed by laparoscopy. Therefore, the technique described by Quah et al. [12] may not represent optimal laparoscopic TME. Jayne et al. [13] assessed the bladder and sexual function of patients who had undergone laparoscopic or open rectal resection as part of the CLASSIC randomized controlled trial, and concluded that laparoscopic rectal resection did not adversely affect bladder function, but noted a trend toward worse male sexual function.

Many devices for surgical dissection that are less damaging to nerve tissue have also been developed, and the utility of laparoscopy as function-preserving surgery requires investigation with use of these devices. The degree of pelvic autonomic nerve preservation in surgery is commonly based on the subjective evaluation of surgeons, and an objective evaluation of preservation of the functional autonomic nerve has rarely been reported. We are currently evaluating preservation of the cavernous nerves of the penis during surgery electrophysiologically in a new clinical study. We are also planning to perform a more accurate and objective evaluation of the association between nerve preservation and postoperative function. Laparoscopic surgery was performed in only two patients in the current study. However, we suggest that magnification in laparoscopic surgery may facilitate autonomic nerve-preserving surgery, which is more reliable than laparotomy. Evaluation of this issue requires accumulation of cases treated with autonomic nerve-preserving surgery.

The efficacy of sildenafil (Viagra®) for sexual dysfunction after surgery for rectal cancer has been reported [21, 22], and we observed improvement of sexual function in 70% of cases treated with sildenafil. We also found no adverse effects, similarly to previous studies with a low incidence of adverse effects, and this suggests that this drug may be actively administered in cases with sexual dysfunction. Sildenafil has also been reported to improve anal function [23, 24], and we also observed an improvement of anal function in one case. Although the effect of sildenafil on anal function after ISR was examined in only a small number of cases, we believe that the results warrant further investigation of this effect in a randomized controlled trial.

Overall, we conclude that sexual dysfunction occurs frequently after rectal cancer treatment. This effect is mainly caused by surgical damage in lateral lymph node dissection. Our results also suggest that sildenafil is effective for treatment of postoperative sexual dysfunction after surgery.

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**Conflicts of interest** The authors declare that they have no conflicts of interest.

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# Cyclin D1 predicts the prognosis of advanced serous ovarian cancer

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**Abstract.** We previously reported that cyclin E (*CCNE1*) amplification is strongly associated with resistance to treatment in serous ovarian cancer by high-resolution oligonucleotide copy number analysis. Dysregulation of cell cycle control has been implicated as the key event in human oncogenesis, and aberrant expression of G1-S phase-related genes in particular has been reported in epithelial ovarian cancer (EOC). Nevertheless, there are conflicting results concerning the prognostic values of these abnormalities in EOC. This study focused on advanced serous EOC cases and investigated the association between the expression of G1-S phase-regulatory proteins and clinicopathological parameters. The utility of these proteins as prognostic factors was assessed, and whether these targets reflect chemoresistance of advanced serous EOC was investigated. A total of 66 patients treated by primary surgery were evaluated in this study. Immunohistochemical analysis for cyclin D1, pRb, p16, p53, p27<sup>Kip1</sup>, p21<sup>Waf1/Cip1</sup> and cyclin E was performed on formalin-fixed tissue sections collected from primary surgical specimens. The correlations between the expression of these proteins and the clinicopathological parameters, including progression-free survival (PFS), overall survival (OS) and chemosensitivity, were examined. Upon univariate analysis, overexpression of cyclin D1 was positively correlated with reduced PFS ( $p=0.00062$ ) and OS ( $p=0.00037$ ). Reduced expression of p27<sup>Kip1</sup> was associated with shorter OS ( $p=0.064$ ). Upon multivariate analysis, overexpression of cyclin D1 ( $p=0.0019$ ), reduced expression of p27<sup>Kip1</sup> ( $p=0.042$ ) and residual tumor volume ( $p=0.0092$ ) were identified as independent predictors of OS. Overexpression of cyclin D1 ( $p=0.011$ ) as well as residual tumor volume ( $p=0.006$ ) were significantly associated with first-line chemosensitivity. In advanced serous EOC, overexpression of cyclin D1 contributed largely to poor prognosis, and this may

have been in part mediated by chemoresistance. Cyclin D1 is a possible target for overcoming the refractory nature of advanced serous EOC.

## Introduction

Ovarian cancer is the most lethal gynecological malignancy in developed countries and is the 9th most common cancer in Japanese females. An estimated 8,304 new cases and 4,467 mortalities occurred in 2005 (Center for Cancer Control and Information Services, National Cancer Center, Japan). Although ovarian cancer patients respond to cytoreductive surgery and combination chemotherapy satisfactorily, advanced cases exhibit a high level of recurrence, and the overall survival (OS) rate has not significantly changed for decades. However, clinical trials have been undertaken to improve prognosis. Since there are different clinical behavior patterns for certain histopathological subgroups, separate trials have been developed for clear cell (1) and mucinous carcinomas (2). The alteration of dose/schedule and the use of intraperitoneal therapy have been shown to be superior in at least one trial (3,4).

A number of clinicopathological factors, including the volume of residual tumor after primary surgery, FIGO stage and tumor grade, are reported to be the key prognostic factors (5,6). Cytoreduction to a non-macroscopic residual tumor is the ultimate goal, and it improves prognosis (7-9). However, in order to improve the prognosis of advanced epithelial ovarian cancer (EOC) cases, other predictive biomarkers should also be elucidated.

We previously described that cyclin E (*CCNE1*) amplification was strongly associated with resistance to treatment in serous ovarian cancer by high-resolution oligonucleotide copy number analysis (10). Therefore, the amplification status of cyclin E has potential for therapeutic exploitation, whereby patients exhibiting cyclin E amplification may benefit from novel, cyclin-related targeted treatments. Dysregulation of cell cycle control has been implicated as the key event in human oncogenesis, and aberrant expression of G1-S phase-related genes in particular has been reported in a number of human cancers, including EOC (5,11). Aberrant expression of the p16-cyclin D1-CDK4/6-pRb and p21-p27-cyclin E-CDK2 pathways have been reported to correlate with prognosis (5,11-14).

Barbieri *et al* reported in their series of 70 EOC cases that overexpression of cyclin D1 was associated with a shorter

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OS. In particular, among patients with stage III/IV tumors and residual disease greater than 2 cm, cyclin D1 expression significantly influenced clinical outcome (5). Bali *et al* reported on 134 serous ovarian cancers for which molecular markers predicted reduced OS in univariate analysis, which included overexpression of cyclin D1 and p53, and reduced expression of p27<sup>Kip1</sup> and p21<sup>Waf1/Cip1</sup> (11). In contrast, it was reported that low nuclear p27 expression was associated with improved 3-year OS and progression-free survival (PFS) in 150 advanced stage (FIGO stages II, III and IV) EOC patients (12). Kommoss *et al* carried out immunohistochemical analysis of p16<sup>INK4a</sup> and pRb expression levels and found that they correlated with survival in a series of 300 patients with FIGO stage II-IV ovarian carcinoma. They reported that p16<sup>INK4a</sup>-negative tumors had a significantly worse prognosis in both univariate and multivariate analyses. High expression levels of pRb were associated with an incremental deterioration of prognosis, which was also the case in the subgroup of optimally debulked patients (15). Meanwhile, Khouja *et al*, using immunohistochemistry, evaluated 171 primary stage III ovarian carcinoma tumors for expression of Ki-67, p16, p14 and p57. High expression of p16 was correlated with poor differentiation and survival in univariate analysis. However, in multivariate analysis, p16 expression was not significantly associated with shorter survival (13). Some of the results are contradictory, probably due to the variety of histotypes and stages of EOC as well as disease heterogeneity, different research methodologies or the sample sizes of the studies. As serous ovarian cancer is the most common histological type of EOC and the prognosis of advanced cases remains poor, we limited our analysis to the serous histotype and advanced cases to eliminate such bias.

We focused on advanced serous EOC (stage III/IV) cases in particular and investigated the association between the expression of G1-S phase-regulatory proteins and the clinicopathological parameters. We aimed to identify the utility of these proteins as prognostic factors and to evaluate whether these targets reflect chemoresistance of advanced serous EOC.

## Patients and methods

**Patients and tumor specimens.** The Jikei University School of Medicine Ethics Review Committee approved the study protocol, and informed consent was obtained from the patients. The tumor specimens were surgically obtained from a group of 66 patients with advanced primary ovarian serous adenocarcinoma who were treated at the Department of Obstetrics and Gynecology, The Jikei University School of Medicine, and Jikei University Kashiwa Hospital. The tumors were staged in accordance with the International Federation of Gynecology and Obstetrics (FIGO) system (1988). The clinical and pathological characteristics of the patient cohort are shown in Table I. The age at diagnosis, volume of postoperative residual disease, FIGO stage, presence of intraoperative ascites and patient outcome were obtained retrospectively from patient records as shown. The median follow-up time for the cohort was 15.5 months (range 3-72). The 66 patients received first-line platinum-based chemotherapy. Among them, 62 cases received taxane simultaneously as T-C chemotherapy following primary surgery (93.9%).

Table I. Clinical and pathological characteristics of the serous epithelial ovarian cancer patient cohort (n=66).

Clinicopathological parameters	No. of patients (%)
Age	
≤65 years	55 (83.3)
>65 years	11 (16.7)
FIGO stage	
III	52 (78.8)
IV	14 (21.2)
Residual disease	
≤2 cm	28 (42.4)
>2 cm	38 (57.6)
Ascites	
≤500 ml	25 (37.9)
>500 ml	41 (62.1)
Disease progression	
No	9 (13.6)
Yes	57 (86.4)

**Immunohistochemistry.** Immunostaining was performed on buffered formalin-fixed, paraffin-embedded tissue sections. The sections were deparaffinized, and standard immunohistochemical techniques were performed using Ventana XT system (BenchMark<sup>®</sup> XT; Ventana Medical Systems, Inc., Tuscon, AZ, USA) in accordance with the manufacturer's instructions. Antigen epitopes were retrieved using Ventana Benchmark CC1 standard program. The primary antibodies used in this study were: anti-cyclin D1 (rabbit monoclonal clone SP4; Ventana Medical Systems, Inc.), anti-pRb (mouse monoclonal clone 13A10; Novocastra Laboratories Ltd., UK; 1:100), anti-p16 (mouse monoclonal clone 16P04; Ventana Medical Systems, Inc.), anti-p53 (mouse monoclonal clone DO-7; Ventana Medical Systems, Inc.), anti-p21<sup>Waf1</sup> (mouse monoclonal clone EA10; Calbiochem, Darmstadt, Germany; 1:50), anti-p27<sup>Kip1</sup> (mouse monoclonal clone SX53G8; Dako, Glostrup, Denmark; 1:20) and anti-cyclin E (mouse monoclonal clone HE12; Medical and Biological Laboratories Co., Ltd., Japan; 1:500). Antibodies from Ventana Medical Systems, Inc. were pre-diluted. The antibodies were incubated at 37°C for 32 min (60 min for p21, Rb and cyclin E). The slides were counterstained with hematoxylin and mounted for microscopic examination. Positive and negative controls were tested in parallel for each staining.

**Immunostaining evaluation.** At least 500 tumor cells were evaluated for immunostaining, and the percentage of stained cells was calculated. The evaluation of immunostaining was conducted in a blinded manner by two independent screeners, without knowledge of the clinical and pathological characteristics of the cases. Standardization of scoring was achieved by comparison of scores between screeners, and discrepancies were resolved by consensus. The percentage of positive nuclear immunostaining in cells of the tumor sections was calculated. Scores are expressed as a percentage of positive nuclear