Stage II/III cancer of the rectosigmoid junction: An independent tumor type?

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Abstract. The 5-year relapse-free survival rate (5Y-RFS) and 5-year overall survival rate (5Y-OS) were investigated in 766 patients with stage II/III colorectal cancer (CRC). The Stage II group included 283 patients with colon cancer (CC), 40 patients with rectosigmoid junction cancer (RSC), and 74 patients with rectal cancer (RC), while the Stage III group comprised 226 patients with CC, 52 patients with RSC, and 91 patients with RC. Stage III patients with RC were further divided into 68 patients with Ra cancer (Ra, rectum/above the peritoneal reflection) and 23 patients with Rb cancer (Rb, rectum/below the peritoneal reflection). Then the 5Y-RFS and 5Y-OS were calculated for each category or subcategory. The 5Y-RFS/5Y-OS was 80.3/80.6% for Stage II patients and 63.7% ($p<0.001$)/66.2% ($p<0.001$) for Stage III patients. In the Stage II group, the survival rates were 82.9/81.2% for CC, 77.6/74.8% for RSC, and 72.9/80.5% for RC, with no significant differences between each category. In the Stage III group, the survival rates were 69.3/72.8% for CC, 71.6/77.7% for RSC, and 46.5/46.2% for RC. There was no significant difference of survival for CC vs. RSC, but significant differences were noted for CC vs. RC ($p<0.001$/$p<0.001$) and RSC vs. RC ($p=0.008$/$p=0.007$). In the Stage III group, survival rates were 71.6/77.7% for RSC, 47.6/44.8% for Ra, and 45.7/51.3% for Rb, with significant differences for RSC vs. Ra ($p=0.013$/$p=0.005$) and RSC vs. Rb ($p=0.026$/$p=0.180$), but not for Ra vs. Rb. These results suggest that Stage II/III RS cancer should be classified as colon cancer and should not be considered an independent tumor type.

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Abbreviations: CRC, colorectal cancer; RS, rectosigmoid junction; RSC, rectosigmoid junction cancer; CC, colon cancer; RC, rectal cancer; Ra, rectum/above the peritoneal reflection; Rb, rectum/below the peritoneal reflection; 5Y-RFS, 5-year relapse-free survival; 5Y-OS, 5-year overall survival; GRCPSC, General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus; 5FU, 5-fluorouracil; LV, leucovorin; CPT-11, irinotecan; UFT, tegafur/uracil; PSK, krestin

Key words: colorectal cancer, rectosigmoid junction, stage II/III cancer, TNM classification, GRCPSC (Japanese classification)

Introduction

Cancer is the number one cause of death in Japan. For women, colorectal cancer (CRC) is the leading cause of death, followed by lung, breast, and gastric cancer. For men, lung cancer ranks first, followed by gastric, colorectal, and hepatobiliary cancer (1). Although CRC is currently ranked third among men, it is expected to rank first for both men and women in the near future due to its rapid rate of increase. Of note, there has also been an increase of other cancers such as breast cancer and prostate cancer, both of which affect specific organs and are associated with hormonal factors. Consequently, the profile of fatal malignancies in Japan is becoming similar to that in the USA and Europe. While gastric cancer was the leading cause of death among all cancers for both men and women until around the year 2000, early diagnosis and treatment have led to significant improvement in the overall outcome for gastric cancer, with a decline in both morbidity and mortality. Meanwhile, the number of patients with CRC has increased dramatically as a result of adoption of a westernized diet and lifestyle (1). In recent years, there has been marked improvement of the outcome of treating primary CRC in Japan due to advances in surgery and the development of adjuvant treatments such as chemotherapy and radiation therapy. In fact, the reported 5-year survival rate is ~80-85% (colon: 84.5±2.8%, rectum: 79.8±4.0%) for patients who have undergone curative resection of Dukes' B/Stage II CRC without lymph node metastases (2-4). On the other hand, the 5-year survival rate of patients with Dukes' C/Stage III cancer and lymph node metastases decreases to ~60-70% (colon: 74.0±3.5%, rectum: 64.7±4.3%), indicating that 30-40% of these patients will suffer from life-threatening metastases/recurrence despite curative resection (2-4).

CRC is usually classified as colon cancer (CC) and rectal cancer (RC). According to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum

and Anus (GRCPSC; Japanese classification), cancer of the rectosigmoid junction (RS) was classified with RC up to the 6th edition (5). The RS is defined as the part of the large bowel between the sacral promontory and the lower margin of S2 where the sigmoid mesocolon terminates. Although it is anatomically considered to be part of the sigmoid colon, the RS shares the surgically important vascular system with the rectum above the peritoneal reflection, suggesting it would be better considered as part of the rectum. In fact, this is noted in the section on the sigmoid colon of the GRCPSC (5).

The 7th edition of the GRCPSC published in 2006 was revised to include a note stating that the RS should be classified as part of the sigmoid colon from an anatomical point of view, but should be treated surgically as the RS (6), indicating that it is an independent section of the bowel and is no longer classified as part of the colon [International Classification of Disease for Oncology (ICD-O), 3rd edition; C-18, (0-7)] or part of the rectum (ICD-O; C-20) (7). This classification is consistent with the TNM classification (ICD-O; C-19) (7). While it is more common now to classify the RS as an independent part of the large bowel, there have been no studies on patients who have undergone curative resection of Stage II/III primary CRC to determine whether they should be categorized as having CC or RC based on the TNM classification or the GRCPSC. Therefore, the purpose of the present study was to examine whether the RS category of Stage II/III CRC should be classified as CC or RC.

Patients and methods

In the 15-year period between January 1995 and January 2010, 1,014 patients underwent curative resection of primary CRC. Among them, a total of 766 patients (pathological stage II in 397 patients and stage III in 369 patients) met the following criteria: i) age ≤75 years, ii) performance status of 0 or 1, iii) availability of complete medical records that allowed assessment of recurrence as well as survival, and iv) identification of lymph node metastasis based on the GRCPSC criteria. The stage II patients were categorized as follows: 283 had CC, 40 had RS cancer (RSC, between the sacral promontory and the lower margin of S2), and 74 had RC. In addition, of the stage III patients, 226 had CC, 52 had RSC, and 91 had RC (5,6). Moreover, Stage III RC patients were subcategorized into 68 Ra cases (Ra, rectum/below the lower margin of S2 above the peritoneal reflection) and 23 Rb cases (Rb, rectum/below the peritoneal reflection) (5,6). Subsequently, the 5-year relapse-free survival rate (5Y-RFS) and 5-year overall survival rate (5Y-OS) were calculated for patients in each stage/category.

Postoperative treatment and follow-up. In general, Stage II patients received postoperative adjuvant chemotherapy with oral UFT/PSK (Krestin) for 12 months or longer (8-10). Stage III patients received intravenous 5FU/LV or 5FU/LV in combination with CPT-11 for 6 months after surgery, and then received oral UFT/Uzel (an oral calcium folinate) or UFT/PSK for 12 months or longer (11-13). In principle, surgical resection was chosen as the first-line treatment for postoperative recurrence/metastasis. In patients who were not indicated for surgery, anticancer agents other than those mentioned above were administered as second-line treatment. Radiotherapy

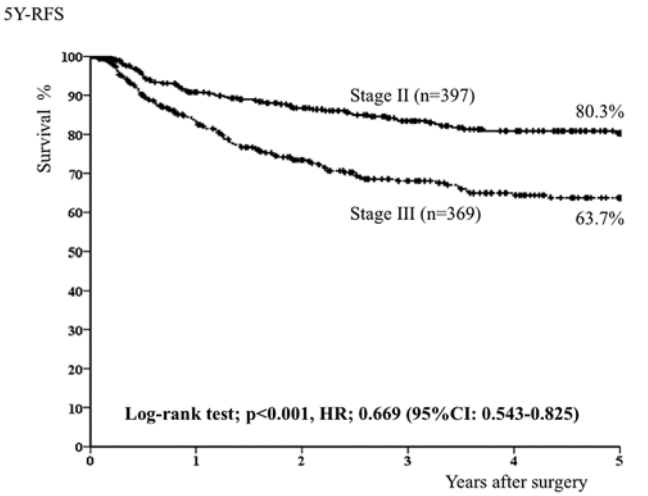

Figure 1. 5Y-RFS of patients with Stage II/III cancer (766 cases). Stage II (397 cases, 80.3%). Stage III (369 cases, 63.7%). Stage II vs. III, p<0.001; HR=0.669 (95% CI: 0.543-0.825).

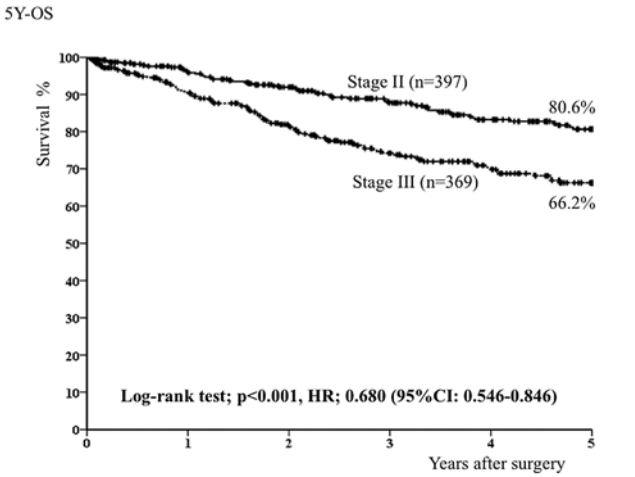

Figure 2. 5Y-OS of patients with Stage II/III cancer (766 cases). Stage II (397 cases, 80.6%). Stage III (369 cases, 66.2%). Stage II vs. III, p<0.001; HR=0.680 (95% CI: 0.546-0.846).

was added in the case of rectal cancer for the local recurrence involving the pelvic floor (12-14). As a general rule, outpatient follow-up included measurement of tumor markers 3-4 times per year and ultrasonography/computed tomography (US/CT) 3-4 times a year, with recurrence/metastasis being confirmed by both US and CT (10,13).

Statistical analysis. The 5Y-RFS and the 5Y-OS were calculated by the Kaplan-Meier method and compared with the log-rank test, and hazard ratios (HR, 95% CI) were also calculated for comparisons between two groups. A p-value <0.05 was considered to indicate significance in all analyses, which were performed with SPSS 17.0 J software (SPSS Japan, Inc., Tokyo, Japan).

Results

The 5Y-RFS was 80.3% for Stage II patients and 63.7% for Stage III patients (p<0.001, HR=0.669, 95% CI: 0.543-0.825)

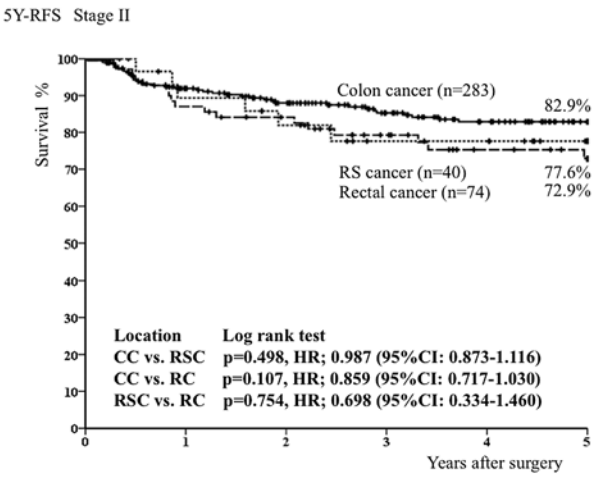

Figure 3. Detailed 5Y-RFS of patients with Stage II cancer (397 cases). The breakdown was: colon cancer (CC) (283 cases, 82.9%); RS cancer (RSC) (40 cases, 77.6%); and rectal cancer (RC) (74 cases, 72.9%). No significant differences were found between any of these subgroups. CC vs. RSC, p=0.498; CC vs. RC, p=0.107; and RSC vs. RC, p=0.754.

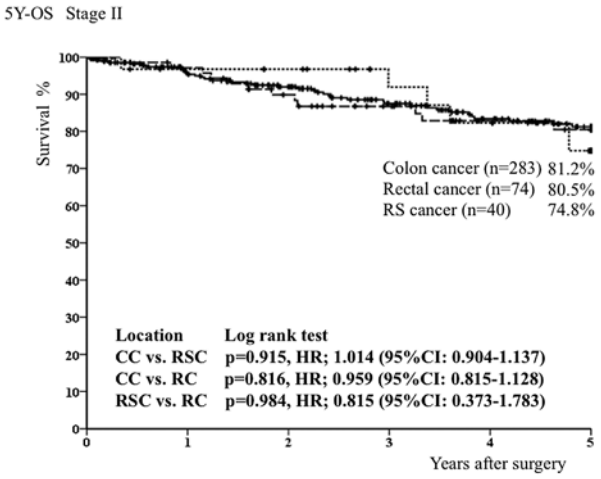

Figure 4. Detailed 5Y-OS of patients with Stage II cancer (397 cases). The breakdown was: colon cancer (CC) (283 cases, 81.2%), RS cancer (RSC) (40 cases, 74.8%), and rectal cancer (RC) (74 cases, 80.5%). No significant differences were found between any of these subgroups. CC vs. RSC, p=0.915; CC vs. RC, p=0.816; and RSC vs. RC, p=0.984.

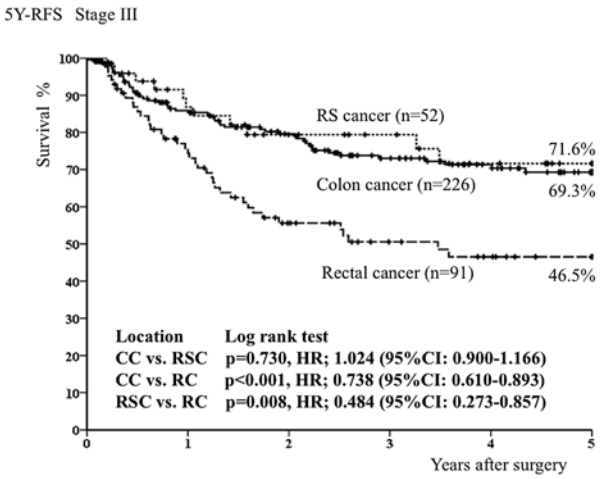

Figure 5. Detailed 5Y-RFS of patients with Stage III cancer (369 cases). The breakdown was: colon cancer (CC) (226 cases, 69.3%), RS cancer (RSC) (52 cases, 71.6%); and rectal cancer (RC) (91 cases, 46.5%). No significant difference was found for CC vs. RSC: p=0.730. However, significant differences were found for CC vs. RC, p<0.001 and RSC vs. RC, p=0.008.

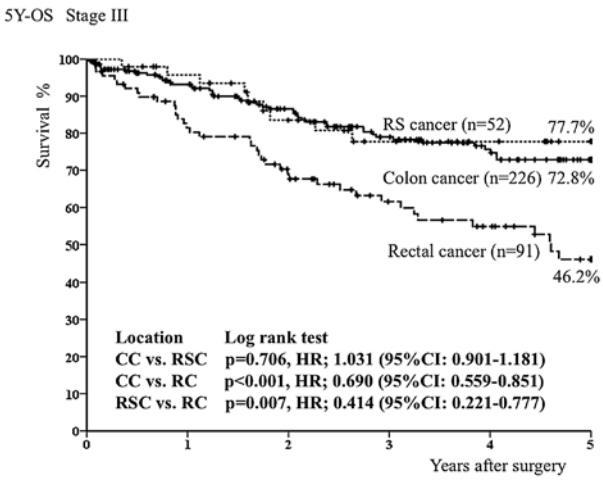

Figure 6. Detailed 5Y-OS of patients with Stage III cancer (369 cases). The breakdown was: colon cancer (CC) (226 cases, 72.8%), RS cancer (RSC) (52 cases, 77.7%); and rectal cancer (RC) (91 cases, 46.2%). No significant difference was found for CC vs. RSC, p=0.706. However, significant differences were found for CC vs. RC, p<0.001 and RSC vs. RC, p=0.007.

(Fig. 1). The 5Y-OS was 80.6% for Stage II patients and 66.2% for Stage III patients (p<0.001, HR=0.680, 95% CI: 0.546-0.846) (Fig. 2).

The 5Y-RFS/5Y-OS for patients in each Stage II category were: CC, 82.9%/81.2%; RSC, 77.6%/74.8%; and RC, 72.9%/80.5%. For the 5Y-RFS, the results of statistical comparison were: CC vs. RSC; p=0.498, HR=0.987 (95% CI: 0.873-1.116), CC vs. RC; p=0.107, HR=0.859 (95% CI: 0.717-1.030), and RSC vs. RC; p=0.754, HR=0.698 (95% CI: 0.334-1.460). There were no significant differences between any of these subgroups (Fig. 3). With regard to the 5Y-OS, the results were: CC vs. RSC; p=0.915, HR=1.014 (95% CI: 0.904-1.137), CC vs. RC; p=0.816, HR=0.959 (95% CI: 0.815-1.128), and RSC vs. RC; p=0.984, HR=0.815 (95% CI: 0.373-1.783). Again there were no significant differences between any of the subgroups (Fig. 4).

The 5Y-RFS/5Y-OS for patients in each Stage III category were: CC, 69.3/72.8%; RSC, 71.6/77.7%; and RC, 46.5%/46.2%. Statistical comparison of 5Y-RFS between CC and RSC revealed p=0.730, HR=1.024 (95% CI: 0.900-1.166) (Fig. 5), while comparison of 5Y-OS revealed p=0.706, HR=1.031 (95% CI: 0.901-1.181) (Fig. 6). Thus, there were no significant differences between these two groups. However, statistical comparison of CC with RC revealed a p<0.001, with HR=0.738 (95% CI: 0.610-0.893) for the 5Y-RFS (Fig. 5), as well as p<0.001, HR=0.690 (95% CI: 0.559-0.851) for the 5Y-OS (Fig. 6). Thus, there were significant differences between these two subgroups. Similarly, statistical comparison of RSC vs. RC gave p=0.008, HR=0.484 (95% CI: 0.273-0.857) for the 5Y-RFS (Fig. 5), as well as p=0.007, HR=0.414 (95% CI: 0.221-0.777) for the 5Y-OS (Fig. 6), again revealing significant differences between these two subgroups.

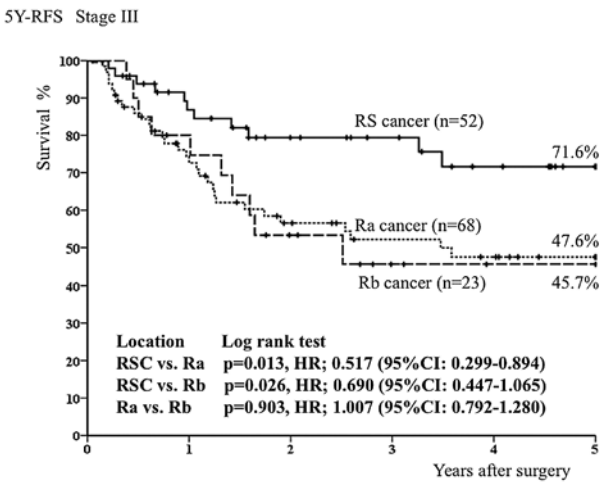

Figure 7. Detailed 5Y-RFS of Stage III patients with RS cancer (RSC, 52 cases) or rectal cancer (RC, 91 cases). The breakdown was: RSC, 71.6%; Ra cancer (Ra, 68 cases), 47.6%; and Rb cancer (Rb, 23 cases), 45.7%. Significant differences were found for RSC vs. Ra, p=0.013 and RSC vs. Rb, p=0.026. No significant difference was found for Ra vs. Rb, p=0.903.

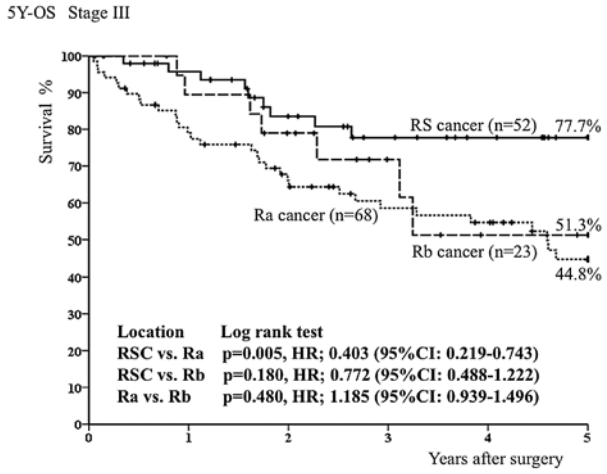

Figure 8. Detailed 5Y-OS of Stage III patients with RS cancer (RSC, 52 cases) or rectal cancer (RC, 91 cases). The breakdown was: RSC, 77.7%; Ra cancer (Ra) (68 cases, 44.8%); and Rb cancer (Rb) (23 cases, 51.3%). A significant difference was found for RSC vs. Ra, p=0.005. However, no significant differences were found for RSC vs. Rb, p=0.180 and Ra vs. Rb, p=0.480.

The 5Y-RFS/5Y-OS for each Stage III subgroup was: RSC=71.6%/77.7%, Ra cancer=47.6%/44.8%, and Rb cancer=45.7%/51.3%. Statistical comparison of RSC with Ra gave p=0.013, HR=0.517 (95% CI: 0.299-0.894) for the 5Y-RFS (Fig. 7), as well as p=0.005, HR=0.403 (95% CI: 0.219-0.743) for the 5Y-OS (Fig. 8). For RSC vs. Rb, statistical analysis showed p=0.026, HR=0.690 (95% CI: 0.447-1.065) for the 5Y-RFS (Fig. 7), as well as p=0.180, HR=0.772 (95% CI: 0.488-1.222) for the 5Y-OS (Fig. 8). Finally, for Ra vs. Rb, the statistical analysis revealed p=0.903, HR=1.007 (95% CI: 0.792-1.280) for the 5Y-RFS (Fig. 7), as well as p=0.480, HR=1.185 (95% CI: 0.939-1.496) for the 5Y-OS (Fig. 8). There were no significant differences between these subgroups.

Discussion

Among gastrointestinal cancers, gastric cancer was the leading cause of death in Japan until around the year 2000. However, early diagnosis and treatment have led to significant improvement of the overall outcome for patients with gastric cancer, so that both morbidity and mortality are declining. In contrast, there has been a significant increase of patients with colorectal cancer (CRC) due to adoption of a westernized diet and lifestyle by the Japanese (1). Esophageal cancer and gastric cancer are often poorly differentiated or undifferentiated tumors that are highly malignant, with their modes of recurrence including peritoneal dissemination, mediastinal lymph node metastasis, and bone metastasis. On the other hand, CRC is usually moderately differentiated or well differentiated adenocarcinoma, and the main sites of recurrence/metastasis are the liver and lungs for colon cancer. In patients with rectal cancer, local recurrence involving the pelvic floor is also common (3,4), but initial recurrence due to peritoneal dissemination or bone metastasis is rare. It has been suggested that recurrence and hematogenous metastasis are closely associated with involvement of the portal vein and the inferior vena cava. Therefore, we speculated that liver metastases, which are also associated with involvement of the portal vein, would be more common in RS patients, while lung metastasis associated with involvement of the inferior vena cava would be more common in Ra/Rb patients. Although we did not review a large number of subjects, there were no significant differences in the site of recurrence between RS patients and Ra/Rb patients, suggesting that the location of the primary tumor did not influence the mode of recurrence (data not shown). Although RSC resembles the cancer of the sigmoid colon from an anatomical point of view, such tumors share surgically important vessels with the cancer of the rectum located above the peritoneal reflection, which has led to the suggestion that RSC should be classified with cancer of the rectum (5). In our series, the percentage of rectal cancer patients (Ra/Rb) who had the first recurrence localized to the pelvic floor was 27.5% (11/40) vs. 36.4% (4/11) for RSC patients (N.S., data not shown). The data indicate that detailed studies on the influence of the portal vein/inferior vena cava involvement as well as the sites of local recurrence are necessary, which would require accumulation of more cases in the future.

It is expected that the prognosis will become worse as the location of cancer moves from Ra to Rb, i.e., in the direction closer to the anus. However, we found no significant differences of 5Y-RFS/5Y-OS between Ra and Rb cases. In Japan, it is considered that patients with cancer located closer to the anus have an increased risk of lateral lymph node metastasis because the lymphatics run from the rectum to the external and internal iliac vessels including obturator lymph nodes as well as to the inguinal lymph nodes. Therefore, the Japanese treatment guidelines for primary rectal cancer recommend that lateral lymph node dissection should be performed prophylactically on one side or both sides in patients with localized Rb cancer (3,4). The most serious problem for patients with Ra/Rb cancer is the excisional wedge-positive infiltration of the sacral periosteum by tumors on the posterior wall of the rectum. Invasion of adjacent organs is another problem for patients with Ra cancer located on the anterior wall of the rectum. Since men have a narrower pelvic cavity than women, male patients with lesions occupying the trigone of the bladder

or sites near the ureteral junctions often require excision of the bladder as well as the ureters. In women, if infiltration into the posterior vaginal wall or the uterus is confirmed, combined resection of these organs may be required. In patients with Rb cancer, the most important issue is whether resection of the rectum with total mesorectal excision can be performed with an adequate margin of 2-3 cm at the distal border of the tumor, and successfully achieving this is particularly difficult in male patients with a high BMI with narrow pelvises (14-16). Invasion of adjacent organs, such as the prostate and the vagina is another problem for patients with Rb cancer located on the anterior wall of the lower rectum. Aside from consideration of prophylactic lateral lymph node dissection and laparoscopy-assisted colorectal surgery, reports on local recurrence involving the pelvic floor or the anterior surface of the sacrum suggest that this is related to an inadequate resection and extranodal mesorectal spread, which are problems unique to the lower rectal cancer (17,18). Detection of such tumor spread is considered to be extremely difficult by macroscopic examination during surgery or even by pathological examination of intraoperative frozen sections for verification of the resection margin. Therefore, it is most important to perform detailed examination of the surgical specimens from patients with Ra/Rb cancer and lymph node involvement (e.g., by immunohistochemical staining of the mesorectum and surgical margins) and to identify patients with a high risk of recurrence in the early postoperative period (19,20). Patients in the high-risk group need stronger chemoradiotherapy as postoperative adjuvant therapy, additional radiotherapy for the pelvic floor or sacrum, and molecular-targeting agents combined with FOLFOX to control tumor growth (17-20). Thus, treatment is clearly more complicated for patients with Ra/Rb cancer located deep in the pelvic floor than for patients with RS cancer. Therefore, as far as both anatomy and the surgical procedures are concerned, it seems to be more suitable to classify RS cancer with colon cancer, in addition to their similar prognosis.

Acknowledgements

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