

Sex Differences Between cT4b and pT4b Rectal Cancers

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We retrospectively evaluated rectal cancer surgery cases in which resection had been performed for invasion of other organs in terms of pathologic findings from the viewpoint of sex differences. We enrolled 61 consecutive patients with rectal cancer who had undergone curative surgery with resection of invaded adjacent organs. We investigated invasion of adjacent organs in terms of pathologic findings according to sex differences. Among males, 4 cases (13.8%) had received combined radical resections of more than 2 organs, while the number of such female cases was 15 (46.9%). The difference between males and females was statistically significant ($P = 0.006$). Among male cases, histopathologic invasion was present in 4 (13.8%), while 9 female cases (28.1%) showed this feature. Nevertheless, there was not a statistically significant difference between males and females ($P = 0.08$); the rate in females was roughly twice that in males. No significant difference was recognized in the overall survival rates between males and females, but more females than males experienced local recurrence. In cases with rectal cancer invading neighboring organs, the effect of the invasion must be carefully determined, and the most appropriate operative approach selected accordingly.

Key words: Rectal cancer – Invasion of other organs – Sex differences

It is important to prevent local recurrences of rectal cancer. Obtaining a sufficient circumferential resection margin (CRM) is thus a critical surgical procedure.^{1,2} This is especially true for local advanced rectal cancer with distant invasion of adjacent organs (pT4b). Total pelvic exenteration

remains the first-line surgical treatment for pT4b cases,³ but recently organ-sparing therapy has also frequently been chosen.⁴ However, the mode of invasion in highly aggressive rectal cancer has been less well studied. We retrospectively evaluated rectal cancer surgery cases in which resection had

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Table 1 Clinicopathological findings

	Male cases (%), N = 29	Female cases (%), N = 32
Age	60 ± 9	63 ± 12
Size (cm)	3.5 ± 2.0	5.9 ± 1.9
Figure		
Polypoid type	1 (3.4)	1 (3.1)
Ulcerated with clear margin type	24 (82.8)	22 (68.8)
Ulcerated with infiltration type	4 (13.8)	8 (25.0)
Diffuse infiltrating type	0 (0.0)	1 (3.1)
Unclassified type	0 (0.0)	0 (0.0)
Histology		
Well-differentiated and moderately differentiated	27 (93.1)	30 (93.8)
Others (poorly differentiated, mucinous, and Signet-ring cells)	2 (6.9)	2 (6.3)
Surgical procedure		
Low anterior resection	14 (48.4)	14 (43.8)
Hartmann's procedure	1 (3.4)	5 (15.6)
Abdominoperineal resection	11 (37.9)	10 (31.3)
Total pelvic exenteration	3 (10.3)	3 (9.3)
TNM		
IIA	0 (0.0)	0 (0.0)
IIB	11 (37.9)	8 (25.0)
IIC	0 (0.0)	2 (6.2)
IIIA	0 (0.0)	0 (0.0)
IIIB	7 (24.2)	6 (18.8)
IIIC	11 (37.9)	16 (50.0)

been performed for invasion of other organs in terms of pathologic findings from the viewpoint of sex differences.

Materials and Methods

We enrolled 61 consecutive patients with rectal cancer who had undergone curative surgery with resection of invaded adjacent organs at the Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan, between January 1990 and December 2001. Intraoperatively, if we recognized the primary rectal cancer as having invaded adjacent organs, combined radical resection was performed. None of our patients had received either chemotherapy or radiation therapy prior to surgery. Complete dissection of all regional lymph nodes with mesorectal excision was carried out in all cases. In Japan, lateral lymph node dissection is generally indicated if the lower margin of the primary cancer is located below the peritoneal reflection or anal canal with invasion into the muscularis propria or beyond. There were no cancer cells in the CRM in any of our cases. The resected specimens were fixed in 10% formalin for several days, and sections were prepared across the maximum diameter of the tumor and stained with hematoxylin and eosin (HE), without specific

immunostaining. The slides were then evaluated by simple light microscopy.

We conducted a review of the relevant hospital records to obtain clinicopathologic information about the patients, including sex and age, macroscopic configuration of the tumor, maximum tumor size, and histologic type of the tumor. Adenocarcinomas of the rectum are graded predominantly on the basis of their glandular appearance and are classified as well/moderately differentiated (W/M) or others (poorly differentiated, mucinous, and Signet-ring cells), according to the World Health Organization (WHO) histopathologic classification of tumors of the colon and rectum,⁵ and the Japanese Classification of Colorectal Carcinoma.⁶

This study included cases with rectal cancer defined as a tumor whose lowest border is located between the anal verge and the sacral promontory and the rectosigmoid colon. Tumors are classified into 5 types on the basis of their macroscopic appearance: (1) polypoid, (2) ulcerated with clear margin, (3) ulcerated with infiltration, (4) diffuse infiltrating, and (5) unclassified. Surgical procedures are classified into 4 approaches: (1) low anterior resection, (2) Hartmann's procedure, (3) abdominoperineal resection, and (4) total pelvic exenteration. In terms of the TNM staging system, all cases were classified as having stage II or stage III tumors. Most notably, we investigated invasion of adjacent organs

Table 2 The resected organs in males and females

Male: Resection 29 cases	Resection cases		Histopathological invasion (+)
Seminal vesicles	14 (48.3%)	25 (86.2%)	0 (0.0%)
Prostate	2 (6.9%)		0 (0.0%)
Urinary Bladder	9 (31.0%)	4 (13.8%)	1 (3.4%): Urinary Bladder
Seminal vesicles + Prostate	1 (3.4%)		1 (3.4%): Seminal vesicles
Seminal vesicles + Urinary bladder + Ureter	1 (3.4%)		1 (3.4%): Ureter
Seminal vesicles + Prostate + Ureter	1 (6.9%)		0 (0.0%)
Prostate+ Urinary bladder + Ileum	1 (6.9%)		1 (3.4%): Ileum
Total			4 (13.8%) ^c

Female: Resection 32 cases	Resection cases		Histopathological invasion (+)
Uterus	5 (15.6%)	17 (53.19%)	0 (0.0%)
Ovary	5 (15.6%)		0 (0.0%)
Vagina	6 (18.8%)	15 (46.9%)	2 (6.3%): Vagina
Ureter	1 (3.1%)		0 (0.0%)
Uterus + Ovary	4 (12.5%)		1 (3.4%): Uterus
Uterus + Vagina	7 (21.9%)		2 (6.3%): Vagina
Uterus + Urinary bladder + Sigmoid colon	1 (3.1%)		1 (3.1%): Sigmoid colon
Vagina + Urinary bladder	2 (6.3%)		2 (6.3%): Vagina + Urinary bladder
Uterus + Ovary+ Urinary bladder	1 (3.1%)		1 (3.1%): Uterus + Urinary bladder
Total			9 (28.1%) ^d

^aSignificantly different, $P = 0.006$.^bSignificantly different, $P = 0.006$.^cSignificantly different, $P = 0.08$.^dSignificantly different, $P = 0.08$.

in terms of pathologic findings, according to sex differences (Table 1). After the operation, TNM stage III cases were administered oral chemotherapy, with oral 5-fluorouracil, 5'-doxifluridine, carmofur, or uracil-tegafur with leucovorin being the most commonly used drugs, for approximately 6 to 12 months.⁷⁻⁹ None of the patients received radiation therapy.

All data are expressed as mean \pm SD. The χ^2 test was subsequently performed to identify factors possibly influencing pathologic invasion and recurrence. The log-rank test was used to evaluate the difference in local disease-free survival rates between groups. Statistical significance was set at $P < 0.05$.

Results

Table 2 shows the resected organs and whether histopathologic invasion was present (pT4b). In male cases, combined radical resections involved the seminal vesicles, prostate, urinary bladder, and/or ileum. The seminal vesicles were the most commonly resected adjacent organs (14 of 29 cases; 48.3%). Four cases (13.8% of males) underwent combined radical resection of more than 2 organs. In female cases, combined radical resection involved the uterus, ovaries, vagina, urinary bladder, ureters, and sigmoid colon. The vagina was the most

commonly resected adjacent organ (6 of 32 cases; 18.8%). Fifteen cases (46.9% of females) underwent combined radical resection of more than 2 organs. There was a statistically significant difference between males and females in the number of patients undergoing combined radical resection ($P = 0.006$). The results (Table 2) for histopathologic invasion are shown. Histopathologic invasion was present in only 4 males (13.8%). Yet, among females, histopathologic invasion was observed in 9 cases (28.1%). The difference between males and females was not statistically significant ($P = 0.08$), but the rate in females was roughly twice that in males. Figure 1 shows the partially resected posterior wall of the vagina. The cancer had spread showing discontinuity, and the shortest distance between the deepest part of the cancer and the incised surface was only 500 μ m.

Figure 2 shows the overall survival rates of the patients enrolled in this study. No significant differences in the overall survival rate were observed between T4a cases in males with and in females ($P = 0.561$), or T4b cases in males with and in females ($P = 0.728$). But there was a statistically significant difference between T4a cases and T4b cases in males ($P = 0.005$), and in T4a cases and T4b cases in females ($P < 0.001$) in the overall survival rate.

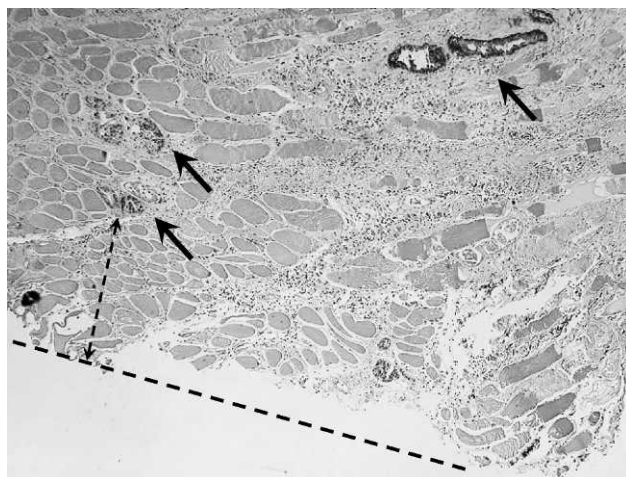


Fig. 1 This figure shows the partially resected posterior wall of the vagina. The cancer shows discontinuous spread (black arrow), and the shortest distance between the deepest part of the cancer and the incised surface (dotted line) was only 500 μm (dotted black arrow). H&E ($\times 100$).

Table 3 shows the organs affected by recurrence in males and females. While no significant difference was recognized in local recurrence rates between males and females undergoing resection ($P = 0.220$), the number of local recurrences in females receiving resection exceeded that in males.

Discussion

Previously, we reported pathologic studies of combined radical resection of seminal vesicles in the treatment of rectal cancer, and we emphasized that it is possible to ensure a sufficiently large CRM and to thereby attenuate local recurrence.¹⁰ However, most previously published reports do not make reference to sex differences. This study is the first, to our knowledge, to demonstrate sex differences in response to combined radical resection for the treatment of rectal cancer. Our data therefore have prognostic significance. Bonfanti *et al* report extensively on the organs resected for invasive colorectal cancer, providing considerable detail, but do not mention sex differences.¹¹

Recently, many studies have examined neoadjuvant treatment with chemotherapy and pelvic radiotherapy for locally advanced rectal cancer. Neoadjuvant treatment, employing chemotherapy and pelvic radiotherapy, contributes to better outcomes, with the former inhibiting distant metastases and the latter inhibiting local recurrences.¹² How-

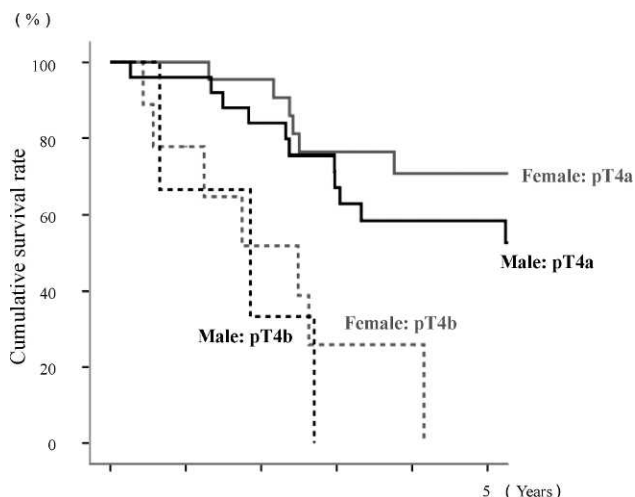


Fig. 2 This figure shows the overall survival rates of the study patients. Male: pT4a vs. Female pT4a : $p=0.561$; Male: pT4b vs. Female pT4b : $p=0.728$; Male: pT4a vs. Male pT4b : $p=0.005$; Female: pT4a vs. Female pT4b : $p<0.561$.

ever, because of the lack of pathologic findings without neoadjuvant treatment (*i.e.*, the spread of rectal cancer in the absence of other factors), this study provides data critical for determining the optimal treatment of pT4b cases.

It is of major interest that the rate of histopathologic invasion in females exceeded that in males. The reason is unclear, but in 15 female cases (46.9%) multiple organs were resected based on an intraoperative diagnosis of cT4b, making it reasonable to speculate that female anatomic structures are more susceptible to tumor invasion. This study showed tumors to be in proximity to the incised surface.

The local recurrence rate in females was approximately twofold that in males, such that the surgical margins in females were apparently insufficient. The many recurrences in our female patients prompted us to speculate that the operative method employed might be less than optimal in women. When rectal cancer invaded the posterior wall of the vagina, partial resection of the vagina was often deemed necessary, but this procedure was found to be insufficient to prevent recurrence. If intraoperative cT4b is recognized, it is essential that adequate combined resection be performed. Harris *et al* report that an aggressive surgical strategy with complete resection is predictive of long-term survival.¹³ And, the high-potency adjuvant treatment with chemo-

Table 3 The organs affected by recurrence in males and females

	Male cases (%), N = 29	Female cases (%), N = 32
All recurrence cases	9 (31.0)	10 (31.3)
Local	1 (3.4)	4 (12.5)
Anastomosis line	1 (3.4)	1 (3.4)
Distant (lung, liver, bone)	5 (17.2)	4 (12.5)
Distant peritoneum	1 (3.4)	1 (3.4)
Lymph nodes	1 (3.4)	0 (0.0)

^aSignificantly different, $P = 0.220$.

^bSignificantly different, $P = 0.220$.

therapy is essential for pT4b cases in males and females.¹³

Our data showed that no pathologic invasion cases account for about 80% of resected adjacent organs in males and females. So, it is essential to rule out the cases except pT4b, but it is very difficult intraoperatively. The reasonably accurate diagnostic imaging is essential before operation.

In rectal cancer cases with invasion of neighboring organs, the effect of the invasion must be carefully determined, and the most appropriate operative approach selected accordingly.

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