Our study is limited by the retrospective design, a small cohort size, and a possible selection bias; however, it reinforces the fact that signet ring histology is associated with poor prognosis and as such may benefit from the use of total neoadjuvant therapy. Total neoadjuvant therapy also ensures more compliance and more treatment completions, as a significant proportion of patients do tend to default adjuvant chemotherapy. On this background and in view of higher progression rate on NACTRT, alternative neoadjuvant protocols like Short Course Radiation Therapy (SCRT) followed by neoadjuvant chemotherapy may be considered in this subtype. However, randomized trials with a higher number of patients will be needed to definitively answer these questions.

Disclosure statement

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ORCID

RajeshS. Shinde http://orcid.org/0000-0001-9478-8676
Ninad Katdare http://orcid.org/0000-0001-8858-6883

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LETTER TO THE EDITOR

Risk factors and patterns of local recurrence in T3 rectal cancer treated with short-course hyperfractionated accelerated chemoradiotherapy with delayed surgery

Naohito Beppu[a,b], Ryo Okamoto[a], Yoshihiko Nakamoto[a], Fumihiko Kimura[a], Masataka Ikeda[b], Naohiro Tomita[b], Hidenori Yanagi[a] and Naoki Yamanaka[a]

[a]Department of Surgery, Meiwa Hospital, Hyogo College of Medicine, Nishinomiya City, Hyogo, Japan; [b]Department of Surgery, Hyogo College of Medicine, Nishinomiya City, Hyogo, Japan

Introduction

Down-staging can be expected with prolonged waiting period from radiotherapy to surgery of rectal cancer. In our institution, a short-course hyperfractionated accelerated chemoradiotherapy with delayed surgery (SC-HART-delay) (25 Gy/10 fraction/5 days) regimen has been applied to T3 rectal cancer, and this study examined the risk factors and patterns of local recurrence associated with this treatment regimen.

Methods

Patients

The inclusion criteria of this retrospective consecutive cohort study were biopsy-proven T3 M0 rectal cancer located below the peritoneum reflexion and treatment with total mesorectal excision (TME) following SC-HART-delay between 2003 and 2016. Prior to the preoperative treatment, all patients underwent a staging work-up including digital rectal examinations,

CONTACT Naohito Beppu n_beppu@yahoo.co.jp Department of Surgery, Meiwa Hospital Department of Surgery, Hyogo College of Medicine 4-31, Agenaruo-cho, Nishinomiya City, Hyogo 663-8186, Japan

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measurement of the tumor marker levels (CEA and CA19-9), chest radiography, abdominal and pelvic computed tomography (CT), pelvic magnetic resonance imaging (MRI) and colonoscopy with a biopsy.

Treatment

The radiation regimen was a total dose of 25 Gy of radiotherapy administered in 10 fractions of 2.5 Gy each for 5 days (25 Gy/10 fractions/5 days). The radiotherapy regimen included S-1 (Taiho®; Pharmaceutical Co., Tokyo, Japan; 60 mg/m^2/day) or capecitabine (Xeloda®; Roche Ltd., Basel, Switzerland; 825 mg/m^2/day) as a radiosensitizer from days 1 to 10. The target interval between the completion of radiotherapy and surgery was four weeks. Our regimen involved two modifications of the original SRT-delay protocol: (1) fractionated accelerated radiotherapy to decrease the predicted risk of late toxicity and (2) the concomitant use of a radiosensitizer to increase the treatment effect because the biologically effective dose (BED) of SC-HART-delay (2.5 Gy $\times$ 10 fractions) is 31.3 Gy, which was inferior to the original SRT-delay (5 Gy $\times$ 5 fractions) BED of 37.5 Gy [1]. The details of this regimen have been described previously [2,3].

At the surgical procedure, all patients received TME with sphincter preservation or a permanent stoma. In addition, lateral lymphadenectomy was appended for lateral nodes $\geq$10 mm in diameter based on the initial MRI findings. The pathological findings were recorded according to the Japanese colorectal guidelines, 8th edition [4].

Patient follow-up

All cases except for the ypT0-1N0 cases were recommended to receive adjuvant oral 5FU-based chemotherapy. Patient surveillance was subsequently performed as follows: chest–abdominal CT every six months, colonoscopy annually and blood tests (including measurement of the CEA and CA 19-9 levels) at three-month intervals. In addition, patients suspected of having local recurrence underwent pelvic MRI and positron emission tomography (PET).

Local recurrence was defined as the detection of a recurrent tumor within the pelvis and classified into two subgroups: lateral pelvic recurrence and other types of pelvic recurrence [5,6]. Lateral pelvic recurrence was defined as recurrence involving invasion of the bony pelvic sidewall or sidewall structures, including the iliac vessels, pelvic ureters, lateral lymph nodes, pelvic nerves, and sidewall musculature. Other type of pelvic recurrence was defined as anastomotic recurrence; anterior-side recurrence adjacent to the bladder, vagina, uterus, seminal vesicles or prostate; and posterior-side recurrence, including presacral recurrence.

Statistical analyses

A chi-squared test with Yates correction was used to compare individual variables. A multivariable analysis was performed using the Cox proportional hazards model to identify factors associated with the risk of local recurrence. All variables in the univariate analysis with a $p < 0.10$ were entered into a multiple logistic regression model, and $p < 0.05$ were considered to indicate statistical significance. The five-year local recurrence rate (5-y-LRR), local recurrence-free survival (LFS), recurrence-free survival (RFS) and overall survival (OS) were estimated using the Kaplan-Meier method, and differences were assessed using the log-rank test. The data were analyzed using the JMP 10.0 software program (SAS Institute Inc., Cary, NC, USA).

Table 1. Patients characteristics of T3M0 rectal cancer.

	Total $n = 216$ (%)
Age (years)	
Mean ± SD	62 ± 11
Median (Range)	64 (34–89)
Sex	
Male	144 (67)
Female	72 (33)
Clinical N stage	
−	95 (44)
+	121 (56)
Distance from anal verge (cm)	
Mean ± SD	4 ± 2
Median (Range)	4 (0–8)
Tumor size (cm)	
Mean ± SD	3 ± 2
Median (Range)	3 (1–8)
MRF	
Negative	178 (82)
Positive	38 (18)
Type of operation	
DST	94 (44)
ISR	106 (49)
APR	14 (7)
Hartmann	2 (1)
Pelvic sidewall node resection	
No	203 (94)
Yes	13 (6)

SD: standard deviation; MRF: mesorectal fascia involvement; DST: double stapling technique; ISR: intersphincteric resection; APR: abdominoperineal resection.

Results

Patients' characteristics

The characteristics of the 216 included patients are shown in Table 1, and the pathological data are shown in Supplementary Table 1. A pathological compete response was confirmed in 14 (7%). Thirteen patients (6%) underwent additional pelvic sidewall node resection, and 2 (15%) had pathologically positive nodes, while the other 11 (85%) had negative nodes.

Long-term oncologic outcomes

The median follow-up period was 70 months (range: 1–153 months). The five-year LFS, DFS and OS were 92%, 78% and 84%, respectively (5-y-LRR: 8%). The incidence of local recurrence was observed in 16 patients, including 10 cases (63%) with lateral pelvic recurrence and six cases (38%) with other types of local recurrence.

Table 2. Risk factors associated with local recurrence by clinical factors.

Factor	Total (n = 216)	Local recurrence Univariate analysis HR (95% CI)	*p*	Multivariate analysis HR (95% CI)	*p*
Age (years)					
≤64	120	1			
>64	96	1.3 (0.5–3.6)	0.6		
Sex					
Male	144	1			
Female	72	0.7 (0.3–2.2)	0.6		
Clinical N					
−	95	1			
+	121	1.2 (0.4–4.2)	0.7		
Distance from anal verge					
≥4 cm	109	1			
≺4 cm	107	1.3 (0.5–3.9)	0.6		
Tumor size					
≤3 cm	111	1			
>3 cm	105	1.2 (0.4–3.2)	0.8		
MRF					
Negative	178				
Positive	38	3.6 (1.2–10.9)	0.02	4.0 (1.5–10.6)	0.006
Histology					
Tub	203	1			
por/muc	13	2.3 (0.5–8.5)	0.2		
Type of operation					
Sphincter preservation	200	1			
Permanent stoma	16	2.9 (0.6–11.2)	0.2		
Pelvic sidewall node resection					
No	203	1			
Yes	13	1.4 (0.08–7.7)	0.8		

MRF: mesorectal fascia involvement.

Table 3. Patterns of local recurrence according to the MRF status.

	Positive MRF *n* = 38 (%)	Negative MRF *n* = 178 (%)	*p* value
Lateral lymphadenectomy	5 (13)	8 (5)	0.1
Positive lateral nodes	1/5 (20)	1/8 (13)	0.7
Positive pCRM	3 (8)	5 (3)	0.3
Local recurrence	7 (18)	9 (5)	0.01
Lateral type	5 (13)	5 (3)	0.02
Other type	2 (5)	4 (2)	0.6

MRF: mesorectal fascia involvement; pCRM: pathological circumferential resection margin.

The details of the 10 patients with lateral pelvic recurrence were as follows: nine patients (90%) showed no lateral lymph node swelling on the initial findings and therefore did not undergo lateral lymphadenectomy; the remaining one patient (10%) showed lateral node swelling and received lateral lymphadenectomy of pathologically negative lateral nodes. Of the six patients with other types of local recurrence, 4 (67%) showed positive pathological circumferential resection margin (pCRM). Distant recurrence was noted in 45 patients (21%), including 30 (14%) with lung metastasis, 24 (11%) with liver metastasis, 6 (3%) with brain metastasis and 5 (2%) with bone metastasis (with some overlap).

Risk factors associated with local recurrence

Local recurrence was significantly associated with the mesorectal fascia involvement (MRF) status (negative/positive, hazard ratio [HR]: 4.0 $p = 0.006$) in a multivariate analysis (Table 2). The 5-y-LRR of the MRF-positive patients was 18% with an incidence of 7 among 38 (18%), whereas that of the MRF-negative patients was 5% with an incidence of 9 among 178 (5%) ($p = 0.01$) (Table 3; Figure 1).

Patterns of local recurrence according to the MRF status

The incidence of patients who received lateral lymphadenectomy (5/38 [13%] vs. 8/178 [5%]; $p = 0.1$), positive lateral nodes following lateral lymphadenectomy (1/5 [20%] vs. 1/8 [13%]; $p = 0.7$) and positive pCRM (3/38 [8%] vs. 5/178 [3%]; $p = 0.3$) were not markedly different between the MRF-positive and MRF-negative patients (Table 3).

In this setting, lateral pelvic recurrence was significantly more frequent in MRF-positive patients than in MRF-negative patients (5/38 [13%] vs. 5/178 [3%]; $p = 0.02$). However, other types of pelvic recurrence were not markedly different between the two groups (2/38 [5%] vs. 4/178 [2%]; $p = 0.6$).

Discussion

This study identified the risk factors and patterns of local recurrence in rectal cancer treated with SC-HART-delay. The major benefit of delayed surgery is down-staging of the tumor while waiting for surgery; however, our results showed that MRF positivity, which requires down-staging in order to achieve R0

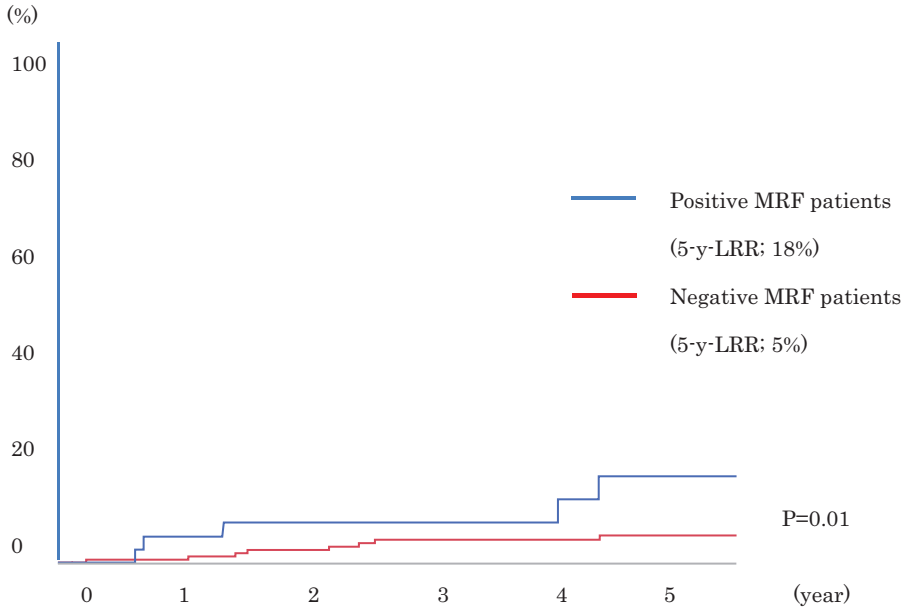

Figure 1. Five-year LRR according to the MRF status.

resection by TME, remains a risk factor for local recurrence, and the 5-y-LRR of MRF-positive patients was 18%.

This study further investigated the patterns of local recurrence. The incidence of other types of pelvic recurrence did not differ significantly between the MRF-positive and MRF-negative patients (5% vs. 2%, $p = 0.6$). Other types of pelvic recurrence tend to develop into or adjacent to the TME resection plane, so the aim of preoperative therapy with this type of local recurrence is tumor downsizing and reducing the viability of cancer cells. Consequently, the incidence of positive pCRM between MRF-positive and MRF-negative patients was not markedly different (8% vs. 3%, $p = 0.3$), indicating a reduced risk of other types of pelvic recurrence in MRF-positive patients.

In contrast, lateral pelvic recurrence was significantly more frequent in MRF-positive patients than in MRF-negative patients (13% vs. 3%, $p = 0.02$). In Western countries, preoperative therapy is the only treatment for cancer in the lateral pelvic area, as lateral lymphadenectomy has not been standardized, and total regression of positive lateral nodes is required. In the present study, selective lateral lymphadenectomy was appended for cases of node swelling, even in patients treated with SC-HART-delay. However, most lateral nodes (11/13; 85%) following lateral lymphadenectomy were found to be negative, and most cases of lateral pelvic recurrence (9/10; 90%) developed from occult metastasis (no lateral node swelling showing at the initial staging), so predicting lateral pelvic recurrence based on the initial lateral node status would have been difficult. Therefore, when considering the management of MRF-positive patients, who are at a high risk of lateral pelvic node metastasis, SC-HART-delay (BED: 31.3Gy) appears to be insufficient, necessitating radiation treatment with a higher BED.

Several limitations associated with the present study warrant mention. First, this study was a retrospective study performed in a limited number of patients. Prospective randomized trials are needed to obtain strong evidence. Second, our regimen is quite different from the originally designed Swedish SRT-delay schedule. Third, a prospective study involving another patient group for a comparison is needed in order to discuss the optimum treatment strategy for MRF-positive patients, as these patients are also at a high risk of local recurrence even when treated with 45 Gy of conventional chemoradiotherapy.

In conclusion, our retrospective study demonstrated that MRF positivity is a risk factor for local recurrence in T3 rectal cancer treated with SC-HART-delay. Furthermore, while delayed surgery results in R0 resection and subsequently reduces the risk of other types of pelvic recurrence, lateral pelvic recurrence is still common in MRF-positive patients. Prospective randomized trials are needed to obtain strong evidence supporting the optimum treatment strategy of MRF-positive rectal cancer.

Disclosure statement

No potential conflict of interest was reported by the authors.

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LETTER TO THE EDITOR

KRAS mutation status, comorbidity, and mortality in patients with metastatic colorectal cancer in Denmark

Anne Gulbech Ording[a], Buket Öztürk[a], Karen-Lise Garm Spindler[b,c], Henrik Toft Sørensen[a], Margaret McCusker[d] and Vera Ehrenstein[a]

[a]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [b]Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark; [c]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; [d]Diagnostics Information Solutions, F Hoffmann-La Roche AG, Pleasanton, CA, USA

Comorbid conditions are common in patients with colorectal cancer and are associated with worse overall survival [1–3]. KRAS mutations in tumor may be associated with differential mortality in patients with metastatic colorectal cancer (mCRC) [4,5]. It is unclear, however, whether KRAS mutation testing in tumor vary with comorbidity level and whether any putative prognostic impact of KRAS mutations among mCRC patients differs by levels of comorbidity.

Methods

The Danish National Health Service provides tax-funded medical care for all Danish residents and maintains clinical databases for monitoring quality of care [6]. Using data linked from several nationwide databases and registries, we established a cohort of adults with mCRC identified between 1 January 2009 and 31 December 2013. The cohort included patients with primary mCRC and patients with distant metastasis at CRC recurrence. Patients with other primary cancers (except non-melanoma skin cancer) were excluded. The index date was the later of the dates of KRAS testing or of mCRC diagnosis to ensure that all patients were included in the analysis at a time that they were eligible for third line treatment, because in recent years of the study period, KRAS testing was conducted on primary surgical specimens also for patients with non-metastatic disease. Earlier, KRAS testing took place at the start of third-line treatment using specimens from earlier resections or resections for metastatic lesions.

KRAS mutation status was defined as wild type (WT) or as mutant (MT). Testing for BRAF and NRAS mutations was not routine during the study period, and thus not assessed.

Comorbidity was measured using the Charlson Comorbidity Index (CCI) [7,8], and summarized as score of 0 (no comorbidity), 1–2 (low comorbidity), and $\geq$3 (moderate to severe comorbidity) using a modified version of the CCI, which excluded colorectal and other malignancies.

Follow-up

The study outcome was death from any cause at one year after index to ensure that all patients had potential for at least one year of followup. The followup started on the index date and ended on the earliest of the date of death, emigration, one year post-index date, or the study end, 31 December 2014.

Statistical analysis

We tabulated distributions of demographic characteristics. We then constructed one-year cumulative mortality curves. Proportional hazards regression was used to calculate one-year hazard rate ratios as a measure of the mortality rate ratio (MRR) for KRAS MT patients vs. KRAS WT patients, disaggregated by comorbidity burden, with adjustment for sex, age group, and calendar period.

To examine if the putative KRAS mutation-mortality association varied by comorbidity, we calculated the interaction contrast (IC). The IC represented a measure of the absolute impact on mortality risk of interaction between comorbidity and KRAS mutation status that deviated from the sum of each factor acting alone.

All analyses were performed using SAS version 9.4® (SAS Institute Inc., Cary, NC, USA).

The study was approved by the Danish Data Protection Agency (record number: 2007-58-0010, case no. 1-16-02-517-14).

Results

We identified 7245 mCRC patients between 2009 and 2013; 63% had distant metastases at their primary incident diagnosis, and 37% had metastases at recurrence (Supplemental Table 1). In the mCRC cohort, 2471 (34%) patients had a record of KRAS tumor testing (Supplemental Table 1).

CONTACT Anne Gulbech Ording ao@clin.au.dk Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark

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