Anti-metastatic Effect of Short-term Postoperative Anticoagulation for Patients Undergoing Curative Resection of Colorectal Cancer

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Abstract. *Background:* The purpose of this study was to examine the efficacy of anticoagulant fondaparinux postoperatively for preventing recurrence after curative resection of colorectal cancer with lymphnode metastasis. *Patients and Methods:* The records of 279 patients who underwent curative resection of colorectal cancer with lymphnode metastasis between 2006 and 2013 were reviewed. Patients were divided into two groups based on the type of prophylaxis for postoperative venous thromboembolism: the FPX group, treated with subcutaneous fondaparinux plus intermittent pneumatic compression; and the IPC group, treated with intermittent pneumatic compression alone. Recurrence-free survival was compared using propensity score matching. *Results:* In the propensity score-matched cohort, the 3-year recurrence-free survival rate was 74.9% and 74.4% in the FPX (n=61) and IPC groups (n=61), respectively (p=0.830). *Conclusion:* Our results do not suggest that short-term postoperative anticoagulation as prophylaxis for venous thromboembolism prevents colorectal cancer recurrence after curative resection.

Patients undergoing surgery for colorectal cancer (CRC) are at high risk of venous thromboembolism (VTE) because of cancer-associated activation of the hemostatic system (1, 2).

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Postoperative anticoagulation therapy is recommended as VTE prophylaxis (3).

On the other hand, one experimental study demonstrated that surgical stress promotes cancer metastasis via postoperative hypercoagulability (4). Therefore, the perioperative period may be an optimal time to influence the development of metastatic disease using anticoagulation therapy (5). However, little is known about the effect of perioperative anticoagulation therapy on prognosis after cancer resection. This study was conducted using propensity score matching to determine the efficacy of postoperative fondaparinux (FPX) in preventing recurrence after curative resection of CRC with lymph-node metastasis, which has a high risk of recurrence.

Materials and Methods

Study population. The present study included 273 patients with primary CRC with pathologically diagnosed lymph-node metastasis who underwent curative (R0) resection between April 1, 2006 and March 31, 2013 at Osaka National Hospital. Patients who received neoadjuvant chemotherapy or preoperative radiotherapy, received postoperative unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), or underwent a concomitant surgical procedure for another type of cancer, such as gastrectomy, esophagectomy, hepatectomy, splenectomy, or pancreatectomy, were excluded.

Treatment. All patients underwent elective resection of CRC under general anesthesia and received intermittent pneumatic compression (IPC) from the beginning of anesthesia until they were fully ambulatory. Beginning in 2010, our Institutions adopted FPX, a synthetic selective inhibitor of factor Xa, for thromboprophylaxis after CRC surgery. The patients were divided into two groups. The FPX group was treated with IPC and subcutaneous FPX (1.5 or 2.5 mg) once daily for 4 days or more. The IPC group was treated with

IPC alone as a control. In principle, 5-fluorouracil-based adjuvant chemotherapy was administered to patients younger than 75 years of age without any severe comorbidities.

Recurrence-free survival (RFS) was compared between the two groups. RFS was defined as the time between curative resection and the first recurrence confirmed by pathology or progressively increasing tumor size in imaging studies.

Statistical analysis. We performed propensity score matching to reduce the possibility of selection bias and to adjust for significant differences in baseline characteristics between patients in the FPX and IPC groups. To estimate the propensity score, logistic regression was performed with the following 10 variables: gender; age; American Society of Anesthesiologists (ASA) grade; tumor location; pathological T category; pathologic N category; histological type; preoperative serum carcinoembryonic antigen (CEA) level; type of surgery (laparoscopic or open); and adjuvant chemotherapy. T and N categories were based on the seventh version of the Union for International Cancer Control TNM classification system (6). Each patient in the FPX group was matched to a patient in the IPC group based on these variables. One-to-one pair matching was performed without replacement, and propensity scores were matched with a caliper of 0.001.

We compared the clinical characteristics of the patients, follow-up duration, and RFS in the two groups. In the propensity score-matched cohort, Cox proportional hazards regression was used to identify predictors of RFS. Continuous variables were expressed as medians and compared using Student's *t*-test. RFS was determined from Kaplan–Meier curves and compared using the log-rank test. Categorical variables were compared using the χ^2 test or Fisher's exact test in the full cohort. They were compared using McNemar's test in the propensity score-matched cohort. All statistical analyses were performed using JMP software, version 11.0 (SAS Institute Inc., Cary, NC, USA) and the statistical program R (<http://www.r-project.org/>), with advice from an experienced statistician. A *p*-value of less than 0.05 was considered statistically significant.

Results

Baseline variables of the patients in the FPX (n=118) and IPC (n=161) groups are shown in Table I. No statistically significant differences were observed in gender, age, ASA grade, tumor location, pathological T category, pathological N category, histological type, preoperative CEA level, or the proportion of patients receiving adjuvant chemotherapy. A higher proportion of patients in the FPX group (60%) underwent laparoscopic surgery compared to the IPC group (29%) ($p<0.001$). After propensity score matching, there were no significant differences in any of the baseline variables between the FPX (n=61) and IPC (n=61) groups. The median duration of FPX therapy was 4 days (range=1-5 days).

For the full cohort, the 3-year RFS rate was 68.3% in the FPX group and 72.7% in the IPC group (Figure 1a). The median follow-up duration was 47.8 months in the FPX group and 61.2 months in the IPC group ($p<0.001$). In the propensity score-matched cohort, the 3-year RFS rate was 74.9% in the FPX group and 74.4% in the IPC group (Figure

1b). The median follow-up duration was longer in the FPX group (50.4 months) than in the IPC group (61.2 months) ($p<0.001$). In both cohorts, there were no significant differences in RFS between the two groups.

Predictors of RFS in propensity score-matched cohort in the univariate and multivariate analyses are shown in Table II. Among the 11 variables investigated, multivariate analysis identified only pathological T category of T4a or T4b (hazard ratio=4.64, 95% confidence interval=1.55-13.9; $p=0.006$) as an independent predictor of poorer RFS.

Discussion

In patients with cancer, an activated coagulation system can facilitate tumor progression and metastasis *via* several mechanisms, including tumor cell spreading, direct stimulation of tumor growth and angiogenesis by platelets, inhibition of natural killer cells, and recruitment of macrophages (7, 8). LWMH was reported to have a favorable influence on survival in patients with advanced cancer as a result of its anticancer effect (9, 10). On the other hand, surgery activates platelets and the extrinsic coagulation pathways, leading to formation of thrombin and fibrin clots. Patients undergoing surgery are in a hypercoagulable state (11-13). Seth *et al.* demonstrated that surgical stress promotes cancer metastasis *via* activated platelets and fibrin clots, which impaired the ability of natural killer cells to clear tumor cells in an experimental study (4). Therefore, perioperative anticoagulation therapy has the potential to prevent tumor recurrence as well as VTE.

FPX is a synthetic selective inhibitor of factor Xa. Its safety and efficacy in VTE prophylaxis after CRC resection have been reported (14). Battinelli *et al.* demonstrated that FPX and LMWH exert anticancer effects by suppressing tumor cell-mediated release of platelet angiogenic proteins and diminishing the platelet angiogenic response (15). In order to examine the anti-metastatic effect of postoperative FPX given as VTE prophylaxis, we examined patients undergoing curative resection of CRC with lymphnode metastasis who were at higher risk of recurrence. However, there were no significant differences in RFS between the FPX and IPC groups when considering the full and propensity score-matched cohorts. Only pathological T4a or T4b status was, not surprisingly, identified as an independent predictor of poorer RFS in the multivariate analysis.

To the best of our knowledge, there have been only three clinical studies evaluating the anticancer effect of perioperative anticoagulation therapy (16-18). Kingston *et al.* showed that perioperative administration of UFH results in significant improvements in both 5-year overall and disease-free survival in patients with stage III CRC undergoing curative resection in a *post hoc* analysis of a randomized trial evaluating adjuvant razoxane (16). A

Table I. Clinical characteristics of the study patients.

	Full cohort (n=279), n (%)			Propensity score-matched cohort (n=122), n (%)		
	FPX (n=118)	IPC (n=161)	p-Value*	FPX (n=61)	IPC (n=61)	p-Value**
Gender			0.49			0.763
Male	64 (54.2)	94 (58.2)		36 (59.0)	37 (60.7)	
Female	54 (45.8)	67 (41.6)		25 (41.0)	24 (39.3)	
Age			0.847			0.248
<75 Years	86 (72.9)	119 (73.9)		47 (77.0)	43 (70.5)	
≥75 Years	32 (27.1)	42 (26.1)		14 (23.0)	18 (29.5)	
ASA grade			0.894			0.317
I, II	114 (96.6)	156 (96.9)		61 (100)	60 (98.4)	
III	4 (3.4)	5 (3.1)		0 (0)	1 (1.6)	
Tumor location			0.415			1
Colon	71 (60.2)	89 (55.3)		36 (59.0)	36 (59.0)	
Rectum	47 (39.8)	72 (44.7)		25 (41.0)	25 (41.0)	
Pathological T category			0.532			0.655
T1, 2, 3	94 (79.7)	133 (82.6)		54 (88.5)	55 (90.2)	
T4a, T4b	24 (20.3)	28 (17.4)		7 (11.5)	6 (9.8)	
Pathological N category			0.939			0.763
N1	86 (72.9)	118 (73.3)		50 (82.0)	51 (83.6)	
N2	32 (27.1)	43 (26.7)		11 (18.0)	10 (16.4)	
Histological type			0.101			0.317
Well, moderate	112 (94.9)	144 (89.4)		59 (96.7)	58 (95.1)	
Poor, mucinous	6 (5.1)	17 (10.6)		2 (3.3)	3 (4.9)	
Preoperative serum CEA			0.841			0.491
<5 ng/ml	63 (53.4)	84 (52.2)		34 (55.7)	37 (60.7)	
≥5 ng/ml	55 (46.6)	77 (47.8)		27 (44.3)	24 (39.3)	
Operative procedure type			<0.001			1
Open	47 (39.8)	114 (70.8)		34 (55.7)	34 (55.7)	
Laparoscopic	71 (60.2)	47 (29.2)		27 (44.3)	27 (44.3)	
Adjuvant chemotherapy			0.365			0.655
Yes	28 (23.7)	46 (28.6)		11 (18.0)	10 (16.4)	
No	90 (76.3)	115 (71.4)		50 (82.0)	51 (83.6)	
Included oxaliplatin	8 (8.9)	9 (7.8)		4 (8.0)	2 (3.9)	

FPX, Group receiving fondaparinux and intermittent pneumatic compression; IPC, group receiving intermittent pneumatic compression; ASA, American Society of Anesthesiologists; Well, well-differentiated adenocarcinoma; Moderate, moderately differentiated adenocarcinoma; Poor, poorly differentiated adenocarcinoma; Mucinous, mucinous adenocarcinoma; CEA, carcinoembryonic antigen. * χ^2 test or Fisher's exact test. **McNemar's test.

subgroup analysis of a randomized trial revealed that patients receiving perioperative LMWH for 7 days after surgery for pelvic gynecological cancer had better overall survival than those who received perioperative UFH (17). Currently, a large multicenter randomized controlled trial evaluating the anticancer effect of perioperative LMWH for 8 weeks after surgery in patients with resectable CRC is ongoing (18) after a pilot study had demonstrated its feasibility (5). Unlike those studies, administration of FPX in our study began postoperatively, not preoperatively. The median duration of FPX therapy (4 days) was shorter than in other studies. These factors might account for why we did not observe differences in RFS between the FPX and IPC groups. Several experimental studies have demonstrated that UFH and LMWH have anti-metastatic effects, not as a result of their anticoagulant activity, but by inhibition of selectins.

Selectins contribute to metastasis by mediating interactions among tumor cells, platelets, leukocytes and endothelial cells (19-21). However, an experimental study showed that FPX does not inhibit selectins because of its different structure in binding them (22). FPX is a pentasaccharide that binds to anti-thrombin and specifically inhibits factor Xa, not thrombin (23). It may have no antitumor effect because it has very specific anticoagulant activities.

This study has several limitations. Firstly, this was a retrospective study, hence the primary end-point, RFS, could not be defined in advance. Secondly, patients were compared over two time periods. Our Institution adopted FPX in 2010. The number of patients receiving FPX gradually increased until FPX was routinely used in 2011. Thirdly, overall survival was not evaluated because the standard chemotherapy for recurrent CRC changed during our study period (24, 25).

Figure 1. Recurrence-free survival curves for the group receiving fondaparinux and intermittent pneumatic compression (FPX) and the group receiving intermittent pneumatic compression alone (IPC) considering the full (a) and propensity score-matched (b) cohorts. The 3-year recurrence-free survival rates were 68.39% and 72.7%, respectively, in the full cohort and 74.9% and 74.4%, respectively, in the matched cohort.

Table II. Predictors of recurrence-free survival in the propensity score-matched cohort (n=122).

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% confidence interval)	p-Value	Hazard ratio (95% confidence interval)	p-Value
Gender				
Male/female	1.503 (0.733-3.084)	0.266	1.361 (0.641-2.888)	0.423
Age				
<75 Years/≥75 years	0.822 (0.393-1.719)	0.602	0.778 (0.309-1.958)	0.593
ASA grade				
III/I, II	NA	0.998	NA	0.997
Tumor location				
Rectum/colon	1.658 (0.846-3.253)	0.141	2.217 (0.935-5.258)	0.071
Pathological T category				
T4a, 4b/T1, 2, 3	3.823 (1.648-8.869)	0.002	4.642 (1.551-13.892)	0.006
Pathological N category				
N2/N1	1.179 (0.513-2.708)	0.698	0.970 (0.377-2.498)	0.950
Histological type				
Poor, mucinous/well, moderate	0.844 (0.115-6.176)	0.867	0.593 (0.072-4.903)	0.628
Preoperative serum CEA				
≥5 ng/ml/<5 ng/ml	2.227 (1.124-4.413)	0.022	1.425 (0.658-3.084)	0.369
Operative procedure				
Open surgery/laparoscopic surgery	1.959 (0.952-4.021)	0.067	1.509 (0.673-3.385)	0.318
Adjuvant chemotherapy				
Present/absent	0.829 (0.343-2.004)	0.677	0.940 (0.299-2.959)	0.916
Postoperative anticoagulation therapy				
FPX/none	0.929 (0.472-1.829)	0.832	1.009 (0.508-2.003)	0.980

ASA, American Society of Anesthesiologists; Well, well-differentiated adenocarcinoma; Moderate, moderately differentiated adenocarcinoma; Poor, poorly differentiated adenocarcinoma; Mucinous, mucinous adenocarcinoma; CEA, carcinoembryonic antigen; FX, fondaparinux; NA, not applicable.

Our results do not suggest that short-term postoperative use of FPX as VTE prophylaxis prevents CRC recurrence after curative resection. The retrospective nature of this study performed in a single Institution and the relatively small size of the study population warrant further studies on this issue.

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