RESEARCH ARTICLE

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Skin Disorders and Primary Tumor Location as Prognostic Factors in Patients with Metastatic Colorectal Cancer Treated with Cetuximab and Chemotherapy

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Abstract

Background: Cetuximab-induced skin disorder is common in colorectal cancer (CRC), and is known to affect prolonged overall survival (OS). Patients with left-sided CRC survive longer than those with right-sided CRC, among those treated with combination cetuximab and chemotherapy. However, no study has evaluated patient prognosis in terms of OS and progression-free survival (PFS) in relation to both tumor location and skin disorder. This study aimed to determine the incidence of skin disorder according to tumor location and analyze the relationship of tumor location and skin disorder with OS. **Methods:** Patients with metastatic colorectal cancer (mCRC) treated with standard chemotherapy and cetuximab as first-line therapy were included. Differences in the incidence of skin disorders due to the location of the primary tumors were compared in the same patient. The OS and PFS in relation to the location of the primary tumors and presence or absence of skin disorder were also compared. **Results:** Total frequency of each skin disorder as rash acneiform, paronychia, and dry skin in patients with left- and right-sided mCRC was 70%, 70%, and 43% and 27%, 36%, and 27%, respectively. The median OS was 8.9 months for mCRC on the left-sided without skin disorder and 56.3 months for mCRC on the left-sided with skin disorder. In comparison, the median OS was 10.4 months for mCRC on the right-sided without skin disorder and 11.3 months for mCRC on the right-sided with skin disease (left-sided with skin disorder versus other three group; P<0.001). **Conclusions:** Primary tumor location and the presence of skin disorder are important factors in patients with mCRC who receive cetuximab. In particular, our results show the new fact that the left-sided and right-sided mCRC survival time were comparable if there is no skin disorder caused by cetuximab.

Keywords: Colorectal cancer- cetuximab- skin disease

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Introduction

The number of newly-diagnosed cases of metastatic colorectal cancer (mCRC) and mCRC-related mortality ranks third and fourth worldwide, respectively (Ferlay et al., 2015). The European Society for Medical Oncology (ESMO) guidelines for the treatment of mCRC have been developed based on data from six clinical trials of cetuximab as first-line treatment for mCRC (Van Cutsem et al., 2016; Arnold et al., 2017). Cetuximab, an immunoglobulin G1 monoclonal antibody, has demonstrated efficacy for RAS wild-type mCRC in many clinical studies (Huang et al., 2013; Sommeijer et al., 2014; Bokemeyer et al., 2012). Previous clinical trials have reported skin disorders as a common characteristic side effect associated with cetuximab (Van Cutsem et al., 2013; Petrelli et al., 2013). Epidermal growth factor receptor (EGFR) is overexpressed in approximately 84% of patients with mCRC (Huang et al., 2013). EGFR is highly expressed in the epidermis, basal cell layer, sebaceous glands, and keratinocytes (Holcmann et al., 2015; Dahlhoff et al., 2014). Cetuximab primarily induces skin disorders via EGFR inhibition. First, EGFR inhibition causes inflammation due to chemokine and cytokine production in the keratinocytes. Then, keratinocyte differentiation impairs tight junction and barrier functions. With the invasion of immune cells such as macrophages and neutrophils and impaired barrier function, bacterial infection occurs, leading to skin disorders (Dahlhoff et al., 2014) that may lead to discontinuation of chemotherapy and decreased quality of life. However, a positive correlation between skin disorder and survival time has been reported (Jonker et al., 2007; Abdel-Rahman et al., 2015). Therefore, it is important to maximize the effect of cetuximab by managing skin disorders, as skin disorders

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during cetuximab treatment are considered to be predictors of treatment efficacy. In the STEEP trial, Lacouture et al. reported that the incidence of >grade 2 skin disorders can be reduced by performing preventive skin care (Lacouture et al., 2010). Patients without skin disorders have low benefit from cetuximab. Therefore, we considered switching of therapy as one of the strategic possibilities, in the absence of skin disorder. Treatment with cetuximab is known to significantly increase overall and progression-free survival (PFS) in patients with left-sided colorectal cancer (CRC), but not in patients with right-sided CRC (Jonker et al., 2007; Hansen et al., 2012; Tejpar et al., 2016; Arnold et al., 2017). A meta-analysis reported that cetuximab significantly prolonged the overall survival (OS) of patients with left-sided CRC when compared to patients with right-sided CRC (Holch et al., 2017). In addition, multivariate Cox regression analyses of OS and PFS in the FIRE-3 trial demonstrated that left-sided tumor location is a predictor of favorable outcomes in patients with RAS wild-type mCRC who receive first-line FOLFIRI plus cetuximab (Tejpar et al., 2016). Sagawa et al., (2017) reported that left-sided tumor has a predictive value in the OS of patients receiving cetuximab therapy. Although the location of the primary tumor and the presence of skin disorders are correlated with the PFS and OS of patients with mCRC, no report has evaluated OS and PFS according to both tumor location and the presence of skin disorder in mCRC. Therefore, this study investigated the frequency of rash according to the primary tumor location (left sided versus right sided) and evaluated the PFS and OS according to both factors.

Materials and Methods

Patient background

This study was a retrospective trial conducted in a single hospital. A total of 50 patients with mCRC were enrolled between January 2011 and December 2015 in Hokkaido Cancer Center, Japan. Steroid ointment was applied to the hands, face, and body to prevent skin disorders once cetuximab treatment was started. Oral administration of antibiotics and prevention of skin disorders were also performed. This was based on clinical trials reporting the preventive effect of steroid ointment for skin disorder in patients receiving anti-EGFR treatment (Lacouture et al., 2010). Patients who did not use prophylactic steroid ointment were excluded. We evaluated the associations between tumor location, survival parameters (PFS, OS), and skin disorder in patients with previously untreated mCRC who were receiving first-line chemotherapy (FOLFOX or FOLFIRI) plus cetuximab in the same patients. This study was approved by the ethics committee of Hokkaido Cancer Center (Approval No: 29-66). All patients provided written informed consent to participate in the study.

Definition of skin disorders and primary tumor location

Skin disorder was defined as the appearance of at least one of the following symptoms: acneiform rash, paronychia, or dry skin. These side effects were evaluated by CTCAE Ver. 4.

Primary tumor location was categorized based on the method of Sagawa et al., (2017). Right-sided mCRC was defined as a primary tumor located in the caecum, ascending colon, hepatic flexure, and transverse colon. Left-sided mCRC was defined as a primary tumor located in the splenic flexure, descending colon, sigmoid colon, and rectum.

Comparison of incidence of skin disorders according to primary tumor location

Primary tumor location was defined as left-sided mCRC and right-sided mCRC. Skin disorders was defined as acneiform rash, paronychia, or dry skin. The incidence of skin disorder at primary tumor location was compared.

Relationship between skin disorders according to primary tumor location and progression-free survival and overall survival

We evaluated the relationship of OS or PFS with the tumor location and the presence of skin disorders in the same patient.

Relationship between overall survival according to each skin disorders

Overall survival was compared for each skin disorder of acneiform rash, paronychia, and dry skin.

Statistical analysis

A chi-squared test analysis was used to compare the frequency of skin disorders symptoms.

Landmark analyses using the Kaplan-Meier method were conducted to assess whether tumor location and skin disorder were associated with either PFS or OS. Two-sided P-values of less than 0.05 were considered significant. All analyses were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd.).

Results

Patient characteristics

The patient characteristics are summarized in Table 1. Among the 50 patients, 41 who used prophylactic steroid ointment and Oral administration of antibiotics were analyzed. The total number of patients with left-sided mCRC was 30, while those with right-sided mCRC was 11.

The average age of the patients with right-sided mCRC and those with left-sided mCRC was 60 and 61 years, respectively. The left-sided mCRC group comprised 16 men and 14 women, while the right-sided mCRC group comprised 4 men and 7 women. The histologic classification was divided into adenocarcinoma and mucinous. In the right-sided mCRC group, all 11 patients had adenocarcinoma. In the left-sided mCRC group, 28 patients had adenocarcinoma and 2 had mucinous type. The genetic classification was divided into KRAS and RAS. In the right-sided mCRC group, the genetic type was KRAS and RAS in 7 and 4 patients, respectively. Meanwhile, in the left-sided mCRC group, the genetic type was KRAS in 27 patients and RAS in 3 patients.

Table 1. Patient Characteristics

Characteristic	Tumor location N (%)	
	Left-sided (n=30)	Right-sided (n=11)
Sex		
Male	16	4
Female	14	7
Age (Years)		
Median		
<61	15	6
≥61	15	5
Histologic type		
Adenocarcinoma	28	11
Mucinous	2	0
Chemotherapy regimen		
FOLFOX*1	15	7
FOLFIRI*2	15	4
KRAS/RAS status		
KRAS wild/ RAS wild	27/3	7/4

*1, mFOLFOX-6, oxaliplatin; 5-fluorouracil bolus; 5-fluorouracil continuous infusion. *2, FOLFIRI, irinotecan; 5-fluorouracil bolus; 5-fluorouracil continuous infusion

The chemotherapy regimen was divided into two regimens: leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) and leucovorin, 5-fluorouracil, and irinotecan (FOLFIRI). In the right-sided mCRC group, FOLFOX and FOLFIRI were administered in 7 and 11 patients, respectively. Meanwhile, in the left-sided mCRC group, FOLFOX and FOLFIRI were administered in 15 patients each. In all patients the median PFS and OS were 12.6 months (range, 8.6-16.6) and 50.6 months (range, 18.7-82.5), respectively.

Comparison of incidence of skin disorder according to primary tumor location

Thirty patients had left-sided mCRC, while 11 had right-sided mCRC. The total incidence of acneiform rash, paronychia, and dry skin was higher in the left-sided mCRC group at 77%, 70%, and 43% than that in the right-sided mCRC group at 23%, 36%, and 27%, respectively (Table2).

Relationship between skin disorders according to primary tumor location and progression-free survival and overall survival

The median PFS was 2.7 months for mCRC on the left-sided without skin disorder and 16.3 months for mCRC on the left-sided with skin disorder. In comparison, the median PFS was 2.0 months for mCRC on the right-sided without skin disorder and 7.7 months for mCRC on the right-sided with skin disease (left-sided with skin disorder versus other three group; P<0.001, Figure 1-a). The median OS was 8.9 months for mCRC on the left-sided without skin disorder and 56.3 months for mCRC on the left-sided with skin disorder. In comparison, the median OS was 10.4 months for mCRC on the right-sided without skin disorder and 11.3 months for mCRC on the right-sided with skin disease (left-sided with skin disorder versus other three group; P<0.05, Figure 1-b).

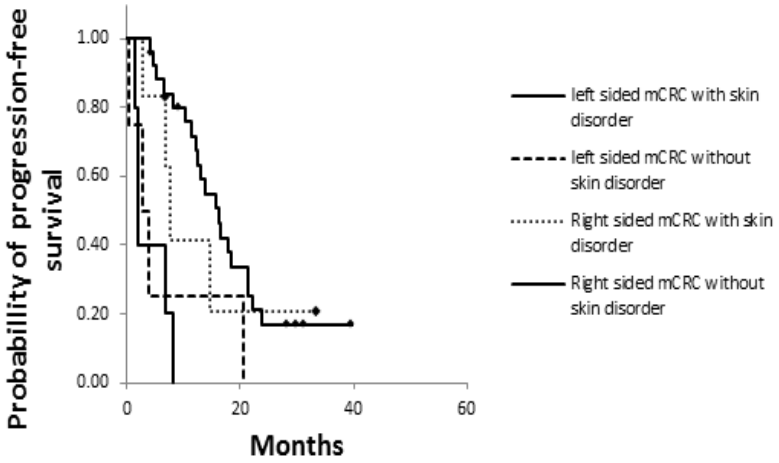

Figure 1-a. Kaplan-Meier Curves for Progression-free Survival According to Primary Tumor Location and Skin Disorder

Table 2. Frequency of Skin Disorders by CTCAE Grade Classification

	Left-sided mCRC				Right-sided mCRC			
Skin disorder	Gr1	Gr2	Gr3	All Gr	Gr1	Gr2	Gr3	All Gr
Acneiform	10%	47%	13%	70%*1	0%	27%	0%	27%*1
Paronychia	10%	47%	13%	70%*2	9%	18%	9%	36%*2
Dry skin	20%	23%	0%	43%*3	0%	27%	0%	27%*3

*1, Left-sided vs Right-sided:(Acneiform) P<0.05; *2, Left-sided vs Right-sided, (Paronychia) P<0.05; *3, Left-sided vs Right-sided, (Dry skin) P<0.05

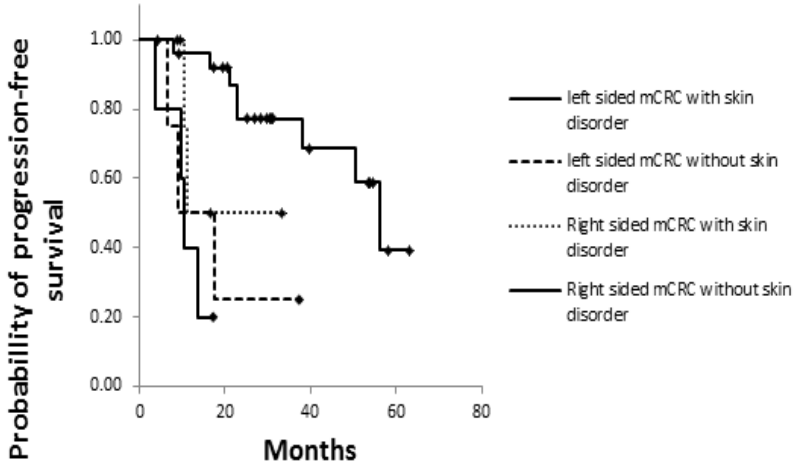

Figure 1-b. Kaplan-Meier Curves Indicate the Primary Tumor Location and Skin- Disorder for Overall Survival

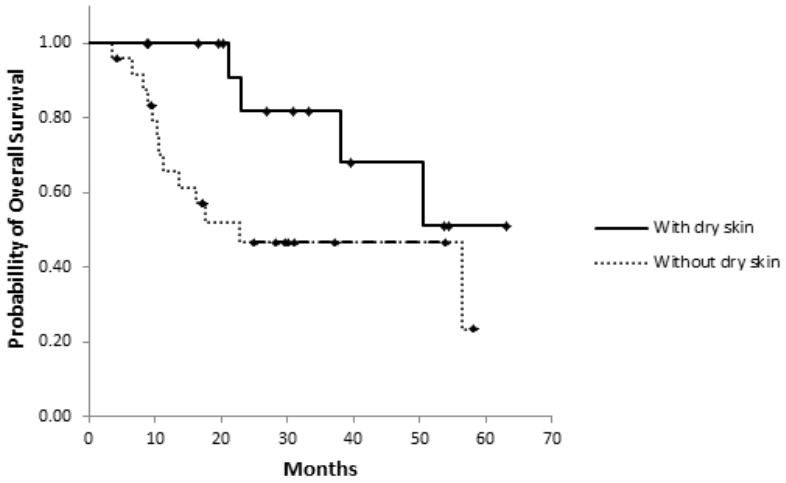

Figure 2-a. Kaplan-Meier Curves for Overall Survival According to Dry Skin

Relationship between overall survival according to each skin disorders

The median OS was not reached in patients with dry skin, 22.8 months in patients without dry skin. (P<0.05) (Figure 2-a). The median OS was 56.3 months in patients with acneiform, 16.3 months in patients without acneiform. (P<0.05) (Figure 2-b). The median OS was 56.3 months in patients with paronychia, 17.6 months in patients without paronychia. (P<0.05) (Figure 2-c).

Discussion

In our study, we compared the occurrence of skin disorders according to primary tumor location in patients undergoing first-line chemotherapy with cetuximab in combination with oxaliplatin or irinotecan-based regimen. It has been recently reported that differences

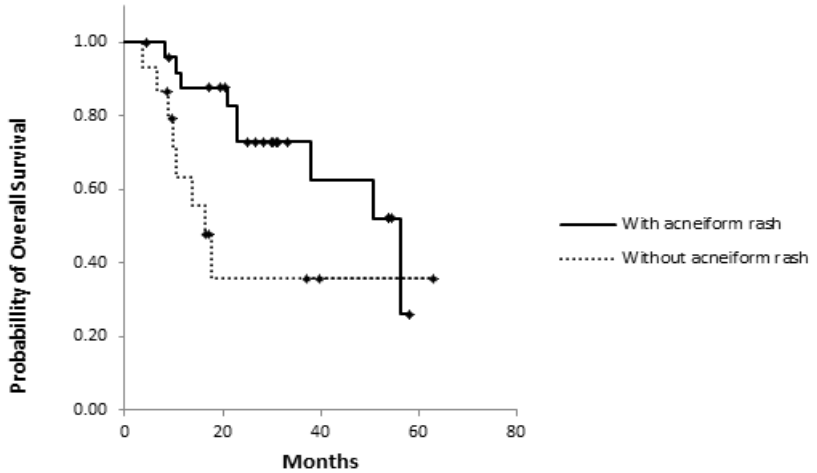

Figure 2-b. Kaplan-Meier Curves for Overall Survival According to Acneiform

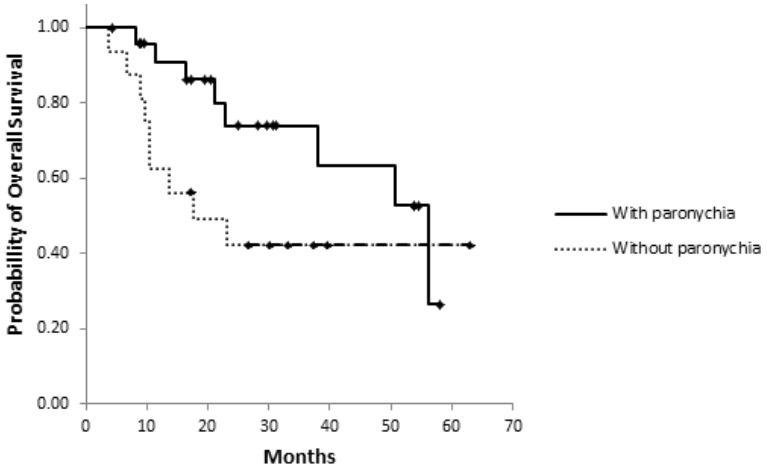

Figure 2-c. Kaplan-Meier Curves for Overall Survival According to Paronychia

in the primary tumor location (right-sided and left-sided) contribute to prolonged PFS and OS. Previous studies have reported that if cetuximab treatment is administered, the survival time on the left-sided will be longer than on the right -sided. Moreover, the degree of skin disorder caused by cetuximab has also been reported to be related to prolong OS (Jonker et al., 2007; Abdel-Rahman et al., 2015). Some have studies shown the relationship between the degree of OS and skin disorder caused by cetuximab treatment (Petrelli et al., 2013; Abdel-Rahman et al., 2015). In previous clinical trials, the degree of relevance of PFS and OS for primary tumor location and skin disorders was not evaluated. Therefore, we conducted a retrospective survey to evaluate the relationship of OS or PFS with the tumor location and the presence of skin disorder in the same patient. Our study is the first report confirming that the left-sided and right-sided mCRC survival time were comparable if there is no skin disorder caused by cetuximab. In view of these information, in mCRC, the two important factors contributing to prolonged PFS and OS are the presence of skin disorder and the primary tumor location.Recently, several studies reported that the tumor location (left side versus right side) can be a possible predictor of prognosis (Tejpar et al., 2016; Arnold et al., 2017; Sunakawa et al., 2017; Wang et al., 2015). Sagawa et al., (2017) reported that left-sided tumor has a predictive value in the OS of Japanese patients with mCRC patients receiving cetuximab therapy. Another meta-analysis reported that left-sided mCRC had better OS than did right-sided mCRC (Holch et al., 2017). Multivariate Cox regression analyses of OS and PFS in the FIRE-3 trial demonstrated that left-sided mCRC is a predictor of outcomes in patients with RAS wild-type mCRC who receive first-line FOLFIRI plus cetuximab (Tejpar et al., 2016). The JACCRO CC-05/06 trial reported that the OS of patients with left-sided mCRC is significantly better than that of patients with right-sided mCRC among those who receive FOLFOX/SOX plus cetuximab (median OS: 36.2 versus 12.6 months, HR=0.28, P<0.001) (Sunakawa et al., 2017). Similarly, in our study the PFS and OS of patients with left-sided mCRC were significantly longer than that of those with right-sided mCRC (median PFS: 15.8 versus 6.8 months, P=0.07; median OS: 56.3 versus 11.3 months, P=0.01). Moreover, another study that compared cetuximab versus best supportive care reported the relationship between overall survival and the extent of skin disorder; in that study, the median survival time of patients with grade 0, 1, and ≥2 rash was 2.6 months, 4.8 months, and 8.4 months, respectively (Jonker et al.,2007). Two meta-analyses reported that skin disorders caused by cetuximab treatment are related to prolonged OS (Petrelli et al., 2013; Abdel-Rahman et al., 2015). In this study, the type of skin disorder identified acneiform, paronychia, and dry skin and survival was prolonged when one or more of those symptoms developed. As results of comparing OS by three types of skin disorders, the OS significantly extended when each symptom appeared. Our study showed that the PFS and OS were significantly longer in mCRC patients with skin disorder (median PFS: 14.6 versus 2.7 months, P<0.001; median OS: 56.3 versus 10.4 months, P<0.01). This result reproduces the previous report. Treatment strategy for patients with right-sided mCRC, and left-sided mCRC without skin disorder, who do not benefit from cetuximab, are important for their prognosis. Because our trial is retrospective by design, more reliable results will be obtained from prospective studies. This study has limitation. Only KRAS mutations were analyzed in the majority of patients, and RAS analysis was performed in only 17% of patients. In RAS analysis, the main mutation was located in KRAS exon 2. Because RAS gene analysis is not conducted in Japan, only KRAS analysis was performed at the start of this study. At the end of this study, since RAS analysis was approved in Japan, those who are performing RAS analysis are also included. We believe that this verification will prove more reliable results by carrying out RAS analysis and conducting jointly with multiple facilities. However, in the previous studies, the extension of the OS was expected in the case of the left mCRC, however, it was a new finding that if the skin symptoms do not appear, even if it is on the left side, extension of the OS was not confirmed. In addition, when skin disorder due to cetuximab was given, OS was expected to be extended, but on the right mCRC, it was new finding that even if skin disorder appeared, extension of OS was not

confirmed. In conclusion, the results of our study indicated that patients with left-sided mCRC with skin disorder benefitted from cetuximab treatment. The survival rate was comparable between patients with left-sided mCRC without skin disorder and those with right-sided mCRC.

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Conflict of interest

The authors declare that they have no conflict of interest.

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