Abstract. Uni- and multivariate analyses were performed in order to assess the most valuable clinical features that were associated with the overall survival of 169 patients who underwent surgery for stage IV colorectal cancer (CRC). Univariate analyses demonstrated that tumor pathology (other/tub1, 2), the proportion of neutrophils and lymphocytes, serum level of C-reactive protein and albumin, neutrophil to lymphocyte ratio, and intraoperative bleeding volume were associated with overall survival. Multivariate analysis using these seven selected features disclosed that only tumor pathology was associated with the overall survival (p<0.001). In addition, tumor pathology was able to divide not only the patients as a whole (p<0.001), but also both patients with stage IVa (p=0.007) and IVb (p=0.007), into two groups for overall survival, respectively. Tumor pathology is not only associated with the overall survival but is also able to divide both patients as a whole and those sub-classified by stage, into two independent groups before surgery.

Although stage IV colorectal cancer (CRC) has been regarded as a lethal and final stage of the disease (1, 2), some patients are able to achieve long-term postoperative survival (3) with multidisciplinary treatments, including gold standard chemotherapy regimens such as Folinic acid (leucovorin)/Fluorouracil (5-FU)/Irinotecan (Camptosar) (FOLFIRI) (4) or Folinic acid (leucovorin)/Fluorouracil (5-FU)/Oxaliplatin (Elotuxin) (FOLFOX) (5-7). Furthermore, recent antibody agents have improved the survival of CRC patients who receive chemotherapy (8, 9). Therefore, it is necessary to investigate the clinical features of the patients in order, to rule out those for whom the outcome is likely to be poor (10, 11).

The latest revision of the TNM Classification of Malignant Tumors (seventh edition) (http://www.onconet. kiev.ua/ru/vremennaya/TNM%207.pdf) has indicated that there are two subclasses of stage IV CRC: stage IVa (M1a) and IVb (M1b). According to the definition, IVa (M1a) is defined as metastasis confined to one organ (liver, lung, ovary, non-regional lymph nodes), whereas IVb (M1b) is defined as metastasis in more than one organ or the peritoneum.

Nevertheless, it is acceptable that this definition might not be perfect for dividing stage IV CRC patients into two groups showing a significant difference in postoperative survival, because in each group there would be two types of patients: those for whom surgery would be relatively curative, and those for whom it would be non-curative. Clearly, stage IVb CRC patients undergoing curative surgery might expect longer postoperative survival than stage IVa CRC patients who undergo non-curative surgery.

In fact, patients undergoing surgery for primary CRC and resectable small single-peritoneal disseminated nodules (curative surgery for stage IVb CRC) would expect longer postoperative survival than patients undergoing surgery for primary CRC and unresectable multiple metastatic liver tumors (non-curative surgery for stage IVa CRC). Due to this heterogeneity of operative curability, there might be stage migration within this new classification (12).

On this regard, we tried to explore the clinical features that are most closely associated with the overall survival of patients with stage IV CRC and to evaluate whether those features are able to divide such patients into two independent groups.

Patients and Methods

A retrospective review was performed using a database of patients who had undergone elective surgery for CRC. All procedures were performed by the same surgical team at the Department of...
Gastroenterological Surgery, Dokkyo Medical University Hospital, between March 2000 and November 2011. Among these patients, 169 were enrolled in this study. All the patients were diagnosed as having stage IV CRC, and all underwent CRC resection to evaluate the primary tumor. Therefore, patients who underwent only stoma formation and bypass-surgery because the primary tumor was unsectable were excluded, as were patients for whom data were insufficient for analysis.

Routine laboratory measurements, including the levels of tumor markers such as carcinoembryonic antigen (CEA) (upper physiological value: 5 ng/ml) (13, 14), were carried out on the day of admission. None of the patients had clinical evidence of infection or other inflammatory conditions such as obstructive colitis, and none had undergone preoperative chemotherapy or irradiation. All patients underwent preoperative colonoscopy examinations to clarify the pathological characteristics of their tumors.

Univariate analysis was performed to evaluate clinical features including age (>70 years versus <70 years), sex (male versus female), tumor site (rectum versus colon), tumor type (3, 4, 5 versus 0, 1, 2) (invasive type/non-invasive type), number of tumors (>2 versus 1), maximum tumor size (>40 mm versus ≤40 mm), tumor pathology (other versus tub1, tub2) (other types of carcinoma/differentiated adenocarcinoma), lymphatic invasion (presence versus absence), venous invasion (presence versus absence), lymph node metastasis (presence versus absence), white blood cell (WBC) count, neutrophil ratio, lymphocyte ratio, monocyte ratio, platelet count (15), serum levels of C-reactive protein (CRP) (16), albumin (17) and CEA (14), body mass index (BMI) (18), subclass of stage IV CRC (Vib* versus Vla), neutrophil to lymphocyte ratio (NLR) (19), operative time and intraoperative bleeding volume, to select those features that were associated with overall survival (*reference group).

Multivariate analysis was performed using clinical features selected by univariate analysis with a p-value of <0.05.

**Definition of curability.** On the basis of the Japanese Classification of Colorectal Carcinoma (Japanese Society for Cancer of the Colon and Rectum, Second English Edition) (20), absence of residual tumor is diagnosed as R0, absence of residual tumor but tumor suspected at the resection margin as R1, and macroscopically evident residual tumor as R2 (20).

On the basis of this definition, operative curability is defined as: curability A (Cur A), R0 at TNM stage I, II or III; curability B (Cur B), R0 at TNM stage IV or R1 at any TNM stage; and curability C (Cur C), R2 at any TNM stage. Therefore, there is Cur B or C in patients with stage IV CRC (20).

**Definition of macroscopic tumor types and pathological findings.** Similarly, macroscopic tumor types are classified as: Type 0, superficial type; type 1, polypoid type; type 2, ulcerated type with a clear margin; type 3, ulcerated type with infiltration; type 4, diffusely infiltrating type; type 5, unclassified type (20).

According to these definitions, we classified patients into two disease groups: non-invasive type (0, 1, 2) and invasive type (3, 4, 5).

The pathological types of tumors are defined as: tub1, well-differentiated adenocarcinoma; tub2, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma; sig, signet-ring cell carcinoma (20).

According to these definitions, we classified patients into two groups: those with differentiated adenocarcinoma (tub1, 2) and those with other types of carcinomas (por, muc and sig).

Invasion of vessels, i.e. lymphatic invasion (ly) and venous invasion (v), is diagnosed as: ly0 (v0), no invasion; ly1 (v1), minimal invasion; ly2 (v2), moderate invasion; ly3 (v3), severe invasion (20).

According to these definitions, we classified patients into two groups: those without invasion (ly0, v0) and those with invasion (ly1-3, v1-3).

**Administration of chemotherapy.** Most patients with stage IV disease undergoing surgery were considered for postoperative chemotherapy. Recently formulated chemotherapy regimens such as FOLFIRI (4) and FOLFOX (5-7) were introduced in our Department in January 2005, and patients who had undergone surgery before that time were orally administered anticancer drug regimens based on 5-fluorouracil as postoperative chemotherapy (21, 22).

**Statistical analysis.** Data are presented as the mean±standard deviation (SD). Differences between groups were analyzed using the chi-squared test and the Mann-Whitney U-test. Odds ratios with 95% confidence interval (95% C.I.) were calculated by univariate and multivariate analysis using the Cox proportional hazards model.

Kaplan-Meier analysis and log-rank test were used to compare the survival curves of the two groups. Deaths prior to November 31st 2011 were included in this analysis.

Statistical analyses were performed using the SPSS statistical software package, version 16.0 (SPSS Inc., Chicago, IL, USA), at a significance level of p<0.05.

**Results.**

The relationships between clinical background features of the 169 patients who underwent surgery for stage IV CRC (stage IVa/IVb) are shown in Table I. There were 77 patients with stage IVa and 92 patients with stage IVb, 112 males and 57 females, 119 colon carcinomas and 50 rectal carcinomas. There were no significant inter-group differences between the clinical background features and the subclass of stage IV CRC, except for tumor type (p=0.017), lymphatic invasion (p=0.017) and operative curability (p<0.001) (chi-squared test).

Table II shows the relationship between the clinical laboratory features in patients with stage IV CRC and the subclass of stage IV CRC. There were no significant inter-group differences between the clinical features and the subclass of stage IV CRC except for the serum levels of albumin (p=0.037), BMI (p=0.024), operative time (p<0.001) and intraoperative bleeding volume (ml) (p=0.038) (Mann-Whitney U-test).

Table III shows the results of univariate analysis. During the observation period, 96 patients died, of whom, 86 died of cancer-related disease. Univariate analysis was performed to evaluate the influence of clinical features on overall survival, but this revealed no significant features except for tumor pathology (other versus tub1, tub2) (p<0.001), neutrophil ratio (p=0.004), lymphocyte ratio (p=0.004), the serum levels of CRP (p=0.003) and albumin (p=0.011), NLR (p=0.006) and intraoperative bleeding volume (p=0.020) (*reference group).
Multivariate analysis using the seven clinical features selected by univariate analyses, i.e., tumor pathology (other* versus tub1, tub2) (*reference group), neutrophil ratio, lymphocyte ratio, the serum level of CRP and albumin, NLR, and intraoperative bleeding volume to assess those most closely associated with overall survival disclosed that only tumor pathology had such an association (odds ratio 0.280; 95% CI 0.150-0.524; p<0.001) (Table IV).

The median and maximum follow-up periods for survivors were 420 and 3529 days, respectively, and the mean±SD postoperative survival period was 572±584 days. There was no significant difference in the postoperative survival period between patients with stage IVa (636±577 days) and those with Vb (518±588 days) disease (p=0.073). Similarly, Kaplan-Meier analysis and log-rank test revealed no significant difference in overall survival between these two patient groups (p=0.057) (Figure 1). On the other hand, tumor pathology was able to divide stage IV CRC patients into two independent groups (p<0.001) (Figure 2).

Subclass analyses using tumor pathology were performed for patients with stage IVa and IVb, respectively. There was a significant difference between the two groups divided by tumor pathology for both patients with stage IVa (p=0.007) (Figure 3a) and those with stage IVb (p=0.007) (Figure 3b) disease for which patients with tub1 or tub2 had significantly better survival.

**Discussion**

Although the recent revision of the TNM classification now divides stage IV CRC into two subgroups, i.e., stage IVa and IVb, based on the formation of metastases, including M1a and M1b, Kaplan-Meier analysis and log-rank test revealed that there was no significant difference in overall survival between these subgroups. Because stage IV is regarded as the final stage of CRC, most patients at that stage cannot expect long-term survival, even if they undergo surgical resection. In the present study, comparison of patients with stage IVa and IVb disease revealed no significant differences in their clinical background features except for tumor type and
lymphatic invasion. This suggested that invasive tumors and tumors with lymphatic invasion might have a tendency for peritoneal metastasis (23), because patients with stage IVb had a higher ratio of Cur C operations for peritoneal dissemination than did patients with stage IVa (data not shown). Similarly, patients with stage IVb had a significantly lower serum albumin level and BMI than did patients with stage IVa. Because these two clinical features reflect cachexia (24), it was obvious that patients with stage IVb were in poorer general condition than patients with stage IVa disease.

In fact, patients with stage IVb disease had a shorter operation time and lower intraoperative bleeding volume than did patients with stage IVa disease, indicating that the degree of surgical insult would be reduced in the former patients, who included a higher proportion of Cur C cases. Therefore, the fact that there were significant differences in the above two surgical parameters between patients with stage IVa and IVb CRC is not surprising.

Among numerous clinical background features, uni- and multivariate analyses clearly demonstrated that only tumor pathology was associated with the overall survival of patients undergoing surgery for stage IV CRC. In addition, Kaplan-Meier analysis and log rank test revealed that tumor pathology was able to divide not only patient group as a whole, but also both groups of patients with stage IVa and IVb disease into two independent groups.

Most patients with CRC generally have almost the same common pathological types of tumor: well-(tub1) or moderately differentiated adenocarcinoma (25, 26). In fact, in the present study, 88.8% (150/169) of patients had tub1 or 2 tumor pathology, and only 11.2% (19/169) had other types of tumor pathology. Therefore, tumor pathology could be a
useful parameter for screening patients likely to have a poor prognosis because survival curve analyses demonstrated that patients with a pathological type other than tub 1/2 had poorer overall survival than patients with tub 1 or 2.

Although the final diagnosis of tumor pathology should be based on the surgically resected specimen, most biopsy specimens are easily obtained by colonoscopy before surgery. Therefore, tumor pathology determined from such specimens, would be valuable in determining before surgery whether or not patients with stage IV CRC would have a poor prognosis.

In addition, because patients diagnosed as having stage IV CRC without the common tumor pathological types would definitively have a poorer prognosis than stage IV patients with the common tumor pathological types, such patients would require systemic chemotherapy before surgery to improve their chance of survival (27-29). However, because most of the current study patients had undergone multidisciplinary treatments after surgery, it might be difficult to improve the overall survival of these patients even if preoperative intensive treatment were to be implemented.

Therefore, a prospective randomized trial would be required in order to clarify the effect of preoperative systemic chemotherapy (27) for such patients with a poor prognosis (1, 2), because in the present study no patients with stage IV CRC without the common types of tumor pathology survived for more than 1,000 days after surgery.

Thus, in comparison with the TNM subclasses of stage IV CRC (IVA/IVB), tumor pathology is a significant feature, allowing for the preoperative division of patients with stage IV CRC into two subclasses, based on their expected postoperative survival.
Conflicts of Interest

We have no conflicts of interest to declare.

Acknowledgements

We received no funding/grant support for this study.

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Received April 15, 2012
Revised June 21, 2012
Accepted June 22, 2012