

## Retrospective Study

# Stage at diagnosis of colorectal cancer through diagnostic route: Who should be screened?

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## Abstract

### BACKGROUND

Colorectal cancer (CRC) is a global health concern, with advanced-stage diagnoses contributing to poor prognoses. The efficacy of CRC screening has been well-established; nevertheless, a significant proportion of patients remain unscreened, with > 70% of cases diagnosed outside screening. Although identifying specific subgroups for whom CRC screening should be particularly recommended is crucial owing to limited resources, the association between the diagnostic routes and identification of these subgroups has been less appreciated. In the Japanese cancer registry, the diagnostic routes for groups discovered outside of screening are primarily categorized into those with comorbidities found during hospital visits and those with CRC-related symptoms.

### AIM

To clarify the stage at CRC diagnosis based on diagnostic routes.

## METHODS

We conducted a retrospective observational study using a cancer registry of patients with CRC between January 2016 and December 2019 at two hospitals. The diagnostic routes were primarily classified into three groups: Cancer screening, follow-up, and symptomatic. The early-stage was defined as Stages 0 or I. Multivariate and univariate logistic regressions were exploited to determine the odds of early-stage diagnosis in the symptomatic and cancer screening groups, referencing the follow-up group. The adjusted covariates were age, sex, and tumor location.

## RESULTS

Of the 2083 patients, 715 (34.4%), 1064 (51.1%), and 304 (14.6%) belonged to the follow-up, symptomatic, and cancer screening groups, respectively. Among the 2083 patients, CRCs diagnosed at an early stage were 57.3% (410 of 715), 23.9% (254 of 1064), and 59.5% (181 of 304) in the follow-up, symptomatic, and cancer screening groups, respectively. The symptomatic group exhibited a lower likelihood of early-stage diagnosis than the follow-up group [ $P < 0.001$ , adjusted odds ratio (aOR), 0.23; 95% confidence interval (95%CI): 0.19-0.29]. The likelihood of diagnosis at an early stage was similar between the follow-up and cancer screening groups ( $P = 0.493$ , aOR for early-stage diagnosis in the cancer screening group *vs* follow-up group = 1.11; 95%CI = 0.82-1.49).

## CONCLUSION

CRCs detected during hospital visits for comorbidities were diagnosed earlier, similar to cancer screening. CRC screening should be recommended, particularly for patients without periodical hospital visits for comorbidities.

**Key Words:** Colorectal neoplasms; Cancer registry; Diagnostic route; Cancer screening; Stage at diagnosis

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**Core Tip:** Colorectal cancer (CRC) screening reduces CRC deaths, yet several patients remain unscreened. To encourage more individuals to participate in screening, identifying subgroups at high risk is crucial. This study used cancer registries from two Japanese facilities to clarify the stage at diagnosis in three groups: cancer screening, follow-up (patients detected during follow-up for other comorbidities), and symptomatic. The proportion of early-stage diagnoses was higher in the follow-up group than in the symptomatic group and was comparable to that in the cancer screening group. Therefore, CRC screening should be recommended, particularly for patients without periodical hospital visits for comorbidities.

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## INTRODUCTION

Colorectal cancer (CRC) is a commonly diagnosed cancer and is a leading cause of cancer-related deaths worldwide[1]. CRC has a poor prognosis when diagnosed at an advanced stage, and screening can lead to more early-stage diagnoses, potentially improving patient survival[2-5]. Despite evidence showing the effectiveness of CRC screening, some (30%-50%) of the eligible population does not undergo the process, with over 70% of all CRC cases discovered through non-screening routes[6-8]. Although encouraging individuals to participate in CRC screening is essential, there remains insufficient guidance on effectively and efficiently recommending screening for the non-adherent population.

Understanding the individuals for whom screening should be particularly recommended is crucial for its efficient promotion. Screening should be recommended for all eligible individuals; however, personalized messages for all eligible individuals are impractical due to limited human and financial resources[9-13]. Targeted interventions to increase cancer screening are considered cost-effective[14]. Therefore, identifying individuals for whom CRC screening should be particularly recommended based on the subgroup to which the screening-eligible population belongs is beneficial. However, few reports have appreciated the value of the diagnostic route to clarify subgroups of patients that are more likely to be diagnosed at a later stage.

CRC is diagnosed through various routes besides screening, leading to different stages at diagnosis. In Western countries, diagnostic routes for CRC are primarily classified into emergency and non-emergency pathways, with emergency cases typically diagnosed at more advanced stages than those of non-emergency[8,15,16]. Conversely, the Japanese cancer registry categorizes CRC cases other than those in the screening pathway into two primary groups: Those discovered during hospital visits owing to comorbidities and those found through symptom-driven medical consultations[17]. CRC cases detected during hospital visits for comorbidities are those detected during the monitoring or management of other chronic diseases or pre- and post-operative examinations for unrelated benign or malignant diseases or malignant tumors. They may be discovered at an earlier stage compared with those of patients with CRC-

related symptoms. However, there are no reports on the comparison regarding the stages at diagnosis between the two groups to determine which group is more likely to be diagnosed at a later stage.

This study aimed to clarify the stages at diagnosis based on the diagnostic routes of CRC using hospital-based cancer registries from two Japanese facilities. We evaluated the diagnostic stage distribution and compared the proportion of early-stage cases among three groups: (1) Patients detected during hospital visits for other comorbidities; (2) patients detected following presentation with CRC-related symptoms; and (3) patients detected during cancer screening.

## MATERIALS AND METHODS

### Study population

This retrospective observational study was conducted at Kyoto University Hospital (KU) in Kyoto Prefecture and Japanese Red Cross Wakayama Medical Center (WMC) in Wakayama Prefecture. Both facilities are among the hospitals that have treated the largest CRC cases in each prefecture and are designated cancer care hospitals. KU covers approximately 20% of patients with CRC in Kyoto Prefecture, and WMC covers approximately 40% of these patients in Wakayama Prefecture[18]. All patients with CRC registered in the hospital-based cancer registry at both institutions between January 2016 and December 2019 were included in this study.

### Assessments

Data from each registry were extracted from cancer registrars based on medical records according to the standard registry definition. The diagnostic routes were primarily classified into three groups: Cancer screening, follow-up (patients detected during the follow-up of comorbidities), and symptomatic[19]. The two other groups were CRC cases with unknown diagnostic routes and those discovered at autopsy. However, the total number is less than 5% nationwide[18]. The cancer screening group included patients who underwent a population-based or opportunistic screening. In the cancer screening group, almost all patients were estimated to undergo an immunochemical fecal occult blood test (iFOBT) because iFOBT is strongly recommended for population-based and opportunistic screening in the Japanese CRC screening guidelines[20]. The follow-up group comprised patients detected during examinations conducted as part of the follow-up for existing comorbidities (lifestyle-related diseases, such as hypertension and diabetes, heart disease, other organ cancers, and benign digestive disorders). Cases in which CRC was discovered due to CRC-related symptoms during a hospital visit for comorbidity follow-up were classified as the follow-up group. Patients with CRC who presented to the hospital primarily for CRC-related symptoms were classified as “other group” in the cancer registry, distinguished from the patients with CRC detected *via* screening or during hospital visits for comorbidities[17,19]. Stages were recorded according to the tumor-node-metastasis staging system of the Union for International Cancer Control (8<sup>th</sup> edition). If the patient had undergone surgery, the post-operative stage was used; if the patient had not, the preoperative stage was used. Data on age, sex, diagnostic routes, tumor location, clinical and pathological stages, and pathological findings were obtained from a hospital-based cancer registry. No data were missing. We excluded patients with non-epithelial or neuroendocrine tumors, those whose stage or route of discovery was unknown, and autopsy-detected cases. Patients with multiple CRCs were considered to have advanced-stage disease. Regarding tumor location, we defined right-sided CRC as tumors from the cecum to the splenic flexure, whereas left-sided CRC was defined as tumors from the descending colon to the rectum. For advanced lesions on both sides of the colorectum, left-sided lesions were excluded because previous reports indicated a poorer prognosis in right-sided primary CRC than in left-sided[21]. Localized disease, corresponding to Stages 0 and I, is associated with a 5-year survival rate of over 90%, making its prognosis more favorable than that in the regional or distant stages[2]. Hence, as in previous reports, we categorized Stages 0 and I as early stages in this study[22,23]. The stage distribution and proportion of patients with early-stage CRC were evaluated using the diagnostic routes. We compared the proportion of patients with early-stage CRC between the follow-up, symptomatic, and cancer screening groups.

### Statistical analysis

Pearson’s Chi-square test was used to compare the proportion of early-stage CRCs in the follow-up group with those in the symptomatic and screening groups. Differences were considered statistically significant at  $P < 0.05$ . Logistic regression analysis was used to determine the odds of early-stage diagnosis in the symptomatic and cancer screening groups using the follow-up group as a reference. Univariate logistic regression analysis was used to calculate the crude odds ratios of early-stage detection, comparing the follow-up group with the symptomatic and cancer screening groups. Multivariate logistic regression analysis was also used to calculate adjusted odds ratios (aORs), adjusted for age, sex, and tumor location. Statistical results were calculated as point estimates with a 95% confidence interval (95%CI). All statistical analyses were performed using JMP Pro® 16.1.0 (SAS Institute Inc., Cary, NC, United States).

## RESULTS

A flowchart of the participants is shown in Figure 1. Of the 2575 lesions and 2435 patients, the study included 2083 patients (879 at KU and 1204 at WMC). Table 1 presents patient characteristics for each discovery route. Among the 2083 patients included in the study, 715 (34.4%), 1064 (51.1%), and 304 (14.6%) belonged to the follow-up, symptomatic, and cancer screening groups, respectively. Patient characteristics at each hospital are presented in Table 2. The stage distri-

**Table 1 Characteristics of the patients and colorectal lesions according to diagnostic routes in two hospitals**

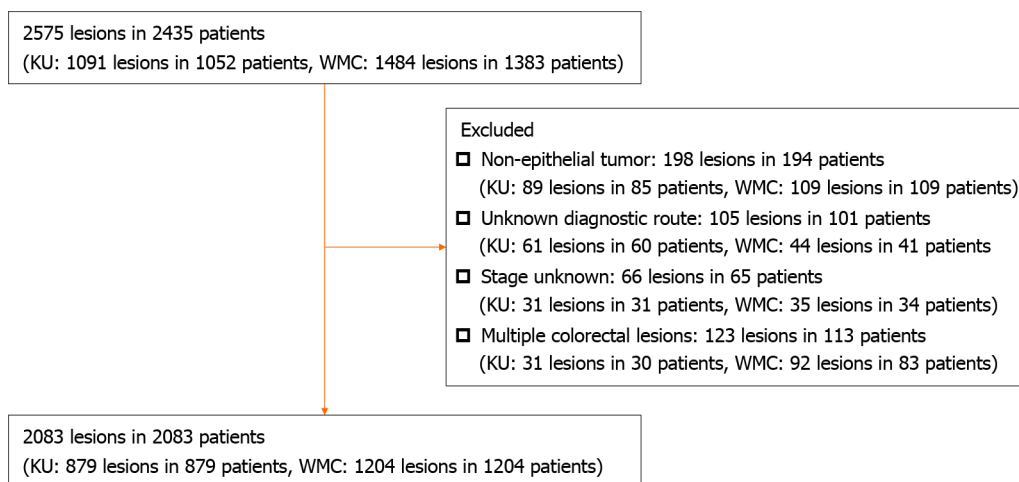
Variable	Follow-up group (n = 715)	Symptomatic group (n = 1064)	Cancer screening group (n = 304)
Age (median, IQR)	74 (68-79)	71 (62-78)	64 (56-71)
Sex, male, n (%)	444 (62.1)	559 (52.5)	172 (56.6)
Right side, n (%)	318 (44.5)	302 (28.4)	96 (31.6)

Follow-up group: Patients with cancer detected during follow-up for other comorbidities; symptomatic group: Patients with complaints associated with colorectal cancer-related symptoms; cancer screening group: Patients detected by screening or medical check-up. IQR: Interquartile range; Right side: Tumors from the cecum to the splenic flexure.

**Table 2 Characteristics of the patients and colorectal lesions according to diagnostic routes at each hospital**

Variable	KU			WMC		
	Follow-up group (n = 271)	Symptomatic group (n = 480)	Cancer screening group (n = 128)	Follow-up group (n = 444)	Symptomatic group (n = 584)	Cancer screening group (n = 176)
Age (median, IQR)	72 (66-79)	69 (59-76)	64 (54-70)	74 (69-79)	72.5 (64.3-80.0)	64.0 (56.3-71.8)
Sex, male, n (%)	168 (62.0)	251 (52.3)	71 (55.5)	276 (62.2)	308 (52.7)	101 (57.4)
Right side, n (%)	116 (42.8)	125 (26.0)	41 (32.0)	202 (45.5)	177 (30.3)	55 (31.3)

KU: Kyoto University Hospital; WMC: Japanese Red Cross Wakayama Medical Center.



**Figure 1 Flow diagram of colorectal lesions and patients from two hospitals.** Between January 2016 and December 2019, cancer registries listed 2575 colorectal lesions in 2435 patients. Of these, 198 non-epithelial tumors in 194 patients were excluded. From the remaining 2377 lesions, 105 lesions in 101 patients with unknown diagnostic routes were excluded. Further, 66 lesions in 65 patients with unknown stages were excluded. Of the remaining 2206 lesions, 123 lesions in 113 patients were identified as synchronous colorectal cancers, and after excluding early-stage lesions, 2083 lesions in 2083 patients remained. KU: Kyoto University Hospital; WMC: Japanese Red Cross Wakayama Medical Center.

bution and early-stage diagnosis proportions for each diagnostic route are presented in Table 3. In each hospital, as for the early-stage diagnosed proportion, the follow-up, symptomatic, and cancer screening groups had 55.7%, 21.7%, and 54.7%, respectively, in KU, and 58.3%, 25.7%, and 63.1%, respectively, in WMC, indicating similar trends at both institutions (Table 4). The proportion of patients with CRC diagnosed at an early stage was 57.3% (410 of 715), 23.9% (254 of 1064), and 59.5% (181 of 304) in the follow-up, symptomatic, and cancer screening groups, respectively. The symptomatic group exhibited a lower likelihood of early-stage diagnosis than the follow-up group ( $P < 0.001$ ; aOR: 0.23; 95%CI: 0.19-0.29). The likelihood of being diagnosed at an early stage was similar between the follow-up and cancer screening groups ( $P = 0.493$ ; aOR for early-stage diagnosis in the cancer screening group *vs* the follow-up group = 1.11, 95%CI = 0.82-1.49) (Table 5).

**Table 3 Stage distribution of colorectal cancer by diagnostic route in two hospitals, n (%)**

Tumor stage	Follow-up group (n = 715)	Symptomatic group (n = 1064)	Cancer screening group (n = 304)
Stage 0	216 (30.2)	92 (8.7)	81 (26.6)
Stage I	194 (27.1)	162 (15.2)	100 (32.9)
Stage II	106 (14.8)	240 (22.6)	39 (12.8)
Stage III	109 (15.2)	297 (27.9)	54 (17.8)
Stage IV	90 (12.6)	273 (25.7)	30 (9.9)
Early-stage	410 (57.3)	254 (23.9)	181 (59.5)

Follow-up group: Patients with cancer detected during follow-up for other comorbidities; symptomatic group: Patients with complaints associated with colorectal cancer-related symptoms; cancer screening group: Patients detected by screening or medical check-up. Early stages: 0 and I.

**Table 4 Stage distribution according to diagnostic routes at each hospital, n (%)**

Tumor stage	KU			WMC		
	Follow-up group (n = 271)	Symptomatic group (n = 480)	Cancer screening group (n = 128)	Follow-up group (n = 444)	Symptomatic group (n = 584)	Cancer screening group (n = 176)
Stage 0	62 (22.9)	22 (4.6)	20 (15.6)	154 (34.7)	70 (12.0)	61 (34.7)
Stage I	89 (32.8)	82 (17.1)	50 (39.1)	105 (23.7)	80 (13.7)	50 (28.4)
Stage II	39 (14.4)	113 (23.5)	14 (10.9)	67 (15.1)	127 (21.8)	25 (14.2)
Stage III	43 (15.9)	120 (25.0)	23 (18.0)	66 (14.9)	177 (30.3)	31 (17.6)
Stage IV	38 (14.0)	143 (29.8)	21 (16.4)	52 (11.7)	130 (22.3)	9 (5.1)
Early-stage	151 (55.7)	104 (21.7)	70 (54.7)	259 (58.3)	150 (25.7)	111 (63.1)

KU: Kyoto University Hospital; WMC: Japanese Red Cross Wakayama Medical Center.

**Table 5 Univariate and multivariate analyses of early-stage detection rate comparing follow-up group vs symptomatic group and cancer screening group**

Variable	Early-stage detection rate (%)	Univariate		Multivariate	
		cOR (95%CI)	P value	aOR (95%CI)	P value
Follow-up group	57.3	Reference		Reference	
Symptomatic group	23.9	0.23 (0.19-0.29)	< 0.001	0.23 (0.19-0.29)	< 0.001
Cancer screening group	59.5	1.09 (0.83-1.44)	0.516	1.11 (0.82-1.49)	0.493

Adjusted covariates are age, sex, and tumor location. cOR: Crude odds ratio; CI: Confidence interval; aOR: Adjusted odds ratio.

## DISCUSSION

In this study, we conducted a comparative analysis of stages at diagnosis of CRC based on diagnostic routes. This study had two major findings. First, patients with CRC, which was detected during hospital visits for existing comorbidities, exhibited a higher proportion of early-stage diagnoses than those who presented with CRC-related symptoms. Second, the proportion of early-stage CRC diagnoses detected during hospital visits for comorbidities was comparable to that in the cancer screening group.

Patients with CRC detected at a comorbidity visit had a higher rate of early-stage diagnosis than those who presented with CRC-related symptoms. The first potential explanation for this derived from the fact that asymptomatic patients were included among the patients with CRC who were detected during hospital visits for other comorbidities. The frequency of symptomatic early-stage cancer is low, and the proportion of symptomatic cases increases with cancer progression[23]. Follow-up testing for comorbidities would incidentally detect asymptomatic CRC at an earlier stage compared to CRC detected in symptomatic patients. Second, the increased frequency of hospital visits owing to



comorbidities likely results in early-stage cancer diagnosis due to incidental detection (surveillance hypothesis)[24]. Previous studies have shown that certain chronic diseases, such as end-stage kidney disease and high levels of comorbidities, are correlated with the detection of CRCs in earlier stages owing to frequent visits to healthcare providers [25,26]. In our study, patients with comorbidities were more likely to undergo imaging studies and colonoscopies because of abnormal tests and some symptoms, which could lead to an earlier diagnosis. Therefore, CRC detection during hospital visits for comorbidities may have been at an earlier stage than that in symptomatic patients.

We also found that the proportion of early-stage CRCs detected during hospital visits for comorbidities was comparable to that in the cancer screening group. The proportion of early-stage detection was 57.3% in the follow-up group compared with 59.5% in the screening group ( $P = 0.493$ ). The odds of early detection were similar between groups, with an OR of 1.11 (95%CI: 0.82-1.49) (screening *vs* follow-up), and no significant differences were observed between the two groups. There have been no reports comparing the proportion of early-stage CRC diagnoses detected during hospital visits for comorbidities with those detected through regular screening. Our findings can be attributed to the unique medical context seen in Japan, characterized by unrestricted access to medical facilities facilitated by the universal insurance system[27]. The swift examinations during hospital visits potentially increase the chances of rapid diagnosis and early detection. Extended diagnosis periods are reportedly correlated with later detection stages[28]. Notably, Japan's healthcare infrastructure facilitates easy access to advanced diagnostic technologies, such as colonoscopies and computed tomography, potentially contributing to early detection. Therefore, patients regularly monitored for comorbidities may have an increased early-stage diagnosis rate, which is comparable to that of patients who undergo cancer screening, even if they present with CRC-related symptoms.

Therefore, CRC screening should be recommended, particularly for patients without periodical hospital visits for comorbidities. Our study suggests that, in clinical practice, CRC is detected relatively early when it is found in patients presenting for follow-up for existing comorbidities. To date, no report has demonstrated that CRC detection during the follow-up of comorbidities is at an earlier stage than that after presenting with symptoms and that it occurs as early as that during cancer screening. Previous studies suggest that patients who visit hospitals for comorbidities can be recommended for cancer screening during consultation with their family physician[29,30]. Conversely, individuals without underlying conditions or those who do not undergo CRC screening may harbor undiagnosed CRC owing to a lack of hospital visits. CRC screening should be recommended for all screening-eligible individuals. Tailored message interventions for screening recommendations targeting segmented individuals reportedly increase screening attendance rates[9]. However, the resources required for screening outreach are limited, and colonoscopies for diagnostic testing require financial and human resources[10-13]. CRC detected at late stages contributes to higher medical costs[31]. Therefore, recommending screening would be essential, particularly for populations at a high risk of diagnosis with late-stage cancer, to take advantage of limited resources. Hence, it would be beneficial to develop policies that specifically encourage cancer screening for those who do not regularly visit the hospital due to comorbidities, considering the barriers to acceptance of screening and the causes of lack of access to healthcare facilities in this population. Encouraging populations other than those who regularly visit the hospital for any comorbidities to undergo screening could increase the earlier-stage detection, which would further contribute to an improved prognosis for patients with CRC.

Our study has some limitations in interpreting the results. First, the type and number of comorbidities and frequency of hospital visits in patients with CRC detected during follow-up for other comorbidities in this study have not been considered. Second, whether individuals presenting with CRC-related symptoms include those who undergo regular cancer screening is unclear. However, in Japan, approximately half of the eligible candidates do not undergo screening, and it is presumed that most individuals exist within the symptomatic group who do not undergo regular cancer screening[6]. Third, our study was conducted at two designated cancer care hospitals in Japan and may not apply to other regions or countries. Healthcare systems and classification of CRC routes for diagnosis may differ in other countries; however, there were no significant differences in the proportions and stage distributions of each population between our study population and the Japanese cohort[18]. While our study only had access to cancer registration data from two facilities, using cancer registration data from other facilities or nationwide cancer registration data in Japan would aid in investigating whether the trends observed in this study are universally applicable.

## CONCLUSION

This study suggests that CRC detection during hospital visits for comorbidities is likely at earlier stages than those detected *via* the symptomatic route. Furthermore, CRCs detected during hospital visits for comorbidities may be detected as early as those detected through cancer screening. While CRC screening should be recommended for all eligible individuals, particular attention could be directed towards populations without periodical hospital visits for comorbidities as they may not derive early CRC detection benefits due to fewer opportunities for hospital visits.

## ARTICLE HIGHLIGHTS

### Research background

Colorectal cancer (CRC) screening reduces CRC mortality, yet several patients remain unscreened.

### Research motivation

Although identifying specific subgroups at high risk is crucial to encourage more individuals to participate in screening, the association between the diagnostic routes and identification of these subgroups has been less appreciated.

### Research objectives

To determine the stage at diagnosis of CRC based on various diagnostic routes.

### Research methods

A retrospective observational study was conducted using data from the cancer registry of two hospitals to clarify the stage at diagnosis in three groups: Follow-up (patients detected during follow-up for other comorbidities), symptomatic (patients detected following presentation with CRC-related symptoms), and cancer screening.

### Research results

In a study of 2083 patients, early-stage CRCs were diagnosed in 57.3% of the follow-up group, 23.9% of the symptomatic group, and 59.5% of the cancer screening group. The symptomatic group had a lower likelihood of early-stage diagnosis compared to the follow-up group, while the follow-up and cancer screening groups showed similar likelihoods of early-stage diagnosis.

### Research conclusions

CRCs detected during hospital visits for comorbidities were diagnosed earlier, similar to cancer screening.

### Research perspectives

Encouraging CRC screening in individuals who do not make regular hospital visits for comorbidities could enhance early detection and improve patient prognoses.

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## FOOTNOTES

**Author contributions:** Agatsuma N, Utsumi T, Nishikawa Y, and Horimatsu T contributed to conception and design; Agatsuma N, Utsumi T, Nishikawa Y, Horimatsu T, Seta T, Yamashita Y, Tanaka Y, Inoue T, Nakanishi Y, Shimizu T, Ohno M, Fukushima A, Nakayama T, and Seno H contributed to data analysis and interpretation; Agatsuma N, Utsumi T, and Nishikawa Y contributed to manuscript drafting; Horimatsu T, Seta T, Yamashita Y, Tanaka Y, Inoue T, Nakanishi Y, Shimizu T, Ohno M, Fukushima A, Nakayama T, and Seno H contributed to critical article revision for important intellectual content; and all authors have read and agreed to the final version of the manuscript.

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**Institutional review board statement:** The study protocol was approved by the Institutional Review Boards of Kyoto University Hospital (approval No. R3472), and the Japanese Red Cross Wakayama Medical Center (approval No. 1004).

**Informed consent statement:** Anonymized data were used in this study. The board approved an opt-out approach for the research use of the data. Information about the study's purpose and data usage was posted on the hospital's website rather than obtaining patient informed consent, ensuring patients' right to withdraw.

**Conflict-of-interest statement:** Yoshitaka Nishikawa reports a donation from Datack outside the submitted work. Takeo Nakayama reports the following potential conflicts of interest outside the submitted work: Grants from I&H Co., Ltd, Cocokarafine Group Co., Ltd, Konica Minolta, Inc., and NTT DATA.; consulting fees from Ohtsuka Pharmaceutical Co., Takeda Pharmaceutical Co., Johnson & Johnson K.K., and Nippon Zoki Pharmaceutical Co., Ltd.; honoraria from Pfizer Japan Inc., MSD K.K., Chugai Pharmaceutical Co., Takeda Pharmaceutical Co., Janssen Pharmaceutical K.K., Boehringer Ingelheim International GmbH, Eli Lilly Japan K.K., Maruho Co., Ltd, Mitsubishi Tanabe Pharma Co., Novartis Pharma K.K., Allergan Japan K.K., Novo Nordisk Pharma Ltd, Toa Eiyo Ltd, Dentsu Co., Ono Pharmaceutical Co., Ltd, GSK, Alexion Pharmaceuticals, Inc., Canon Medical Systems Co., Kowa Company Ltd, Araya, and AbbVie Inc.; stock option from BonBon Inc.; and donation from CancerScan and YUYAMA Co., Ltd. All the other authors declare no competing interests.

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