Prognostic Significance of Circulating Basophil Counts in Patients Who Underwent Esophagectomy for Esophageal Cancer

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Abstract

Purpose: Recent reports have suggested that basophils influence allergic reactions and tumor immunity. In this study, we aimed to elucidate the association between preoperative circulating basophil (CB) counts and the outcomes of patients who underwent esophagectomy for esophageal cancer.

Methods: A total of 783 consecutive patients who underwent esophagectomy for esophageal cancer were eligible. The clinicopathological factors and prognoses were compared between the groups stratified by the preoperative counts of CB.

Results: There were more advanced clinical T and N stages in the low CB group than in the high CB group (P = 0.01 and = 0.04, respectively). The incidences of postoperative complications were comparable between the groups. The low CB count was associated with unfavorable overall and recurrence-free survivals (P = 0.04 and 0.01, respectively). In the multivariate analysis, low CB count was one of the independent prognostic factors for poor recurrence-free survival (HR 1.30; 95% CI 1.02–1.66; P = 0.04). In addition, hematogenous recurrence occurred more frequently in the low CB group than in the high CB group (57.6% vs. 41.4%, P = 0.04).

Conclusion: A preoperative low CB count was an unfavorable prognosticator in patients who underwent esophagectomy for esophageal cancer.

Introduction

Esophageal cancer is one of the most aggressive cancers and the sixth leading cause of cancer-related death worldwide [1]. With the recent advances in multidisciplinary treatment strategies, surgical techniques, and perioperative management, the prognosis of patients has gradually improved. Nevertheless, the long-term outcomes remain poor even after curative treatment [2].

In 1879, Paul Ehrlich discovered basophils, which are rare circulating leukocytes [3]. Basophils play critical roles in eliciting potent effector functions in allergic diseases. They release powerful inflammatory mediators such as histamine and cytokines under the stimulus of immunoglobulin E (IgE) [4, 5]. Recently, their activation states have been reported to influence not only allergic reactions but also tumor immunity [6, 7]. IgE-mediated immune responses against tumors are known as allergo-oncology [8].

Although basophils have beneficial roles in survival outcomes of several cancers, including lung, ovarian and colorectal cancers [9–11], only a few studies have investigated the association between basophils and prognosis of esophageal cancer. We hypothesized that basophils are also associated with favorable long-term outcomes after esophageal cancer surgery. Thus, this study aimed to explore the association between circulating basophil (CB) count and outcomes of esophagectomy for esophageal cancer.

Materials And Methods

Patients and data collection

We retrospectively reviewed data from 818 consecutive patients who underwent esophagectomy for esophageal cancer between 2009 and 2016 at the Cancer Institute Hospital of Japanese Foundation for Cancer Research. After excluding 35 patients with inadequate data, 783 patients were eligible for this study. Preoperative blood tests including CB count were performed within 1 week before esophagectomy.

The clinical and pathological tumor stages of esophageal cancer were classified based on the Union for International Cancer Control TNM staging, 8th Edition [12]. Performance status was categorized based on the American Society of Anesthesiologists-Physical Status (ASA-PS) [13]. Comorbidities were categorized according to the Charlson Comorbidity Index (CCI), which is an established tool for the numerical conversion of comorbidities [14].

This study was approved by the institutional review board (Approval No. 2022-GB-020) and performed under the ethical standards of the Declaration of Helsinki and its later amendments.

Esophageal cancer treatment, esophagectomy, and postoperative follow-up

The treatment strategy for esophageal cancer was decided by a multidisciplinary tumor board based on the Japanese Guidelines for the Treatment of Esophageal Carcinoma [15, 16]; surgery alone for stage I tumors, neoadjuvant treatment followed by surgery for stage II/III tumors, definitive chemoradiotherapy for T4b tumors or refusal of surgery irrespective of the stage, and salvage surgery for the failure of chemoradiotherapy. Supraclavicular lymph node metastases (clinical M1 tumors) were also the implication of surgery.

McKeown esophagectomy was the first choice of esophagectomy. Considering the tumor location, histological subtype, and patient's comorbidities, we occasionally chose the Ivor-Lewis or transhiatal esophagectomy. The esophagus was dissected along with the regional lymph nodes.

Patients were followed up every 4 months for at least 1 year and every 6 months after that. Follow-up included physical examination, blood test, and computed tomography.

Statistical analysis

The software package EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), was used for all statistical analyses [17]. All data were presented as medians (range) or numbers (%). We decided on the optimal cutoff value of CB count based on the survival analysis by the quartile stratification. Overall survival (OS) was evaluated from the date of surgery to either death or last follow-up. Recurrence-free survival (RFS) was assessed from the date of surgery to either recurrence, death, or last follow-up. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Patient characteristics were statistically compared between the low and high CB groups using Fisher's

exact test and the Mann–Whitney U test, as appropriate. Multivariable Cox regression analysis was performed, including the following potential confounders; age at surgery (< 65, 65–74, and ≥ 75 years), sex (female vs. male), preoperative body mass index (BMI; <20, 20–22, and ≥ 23 kg/m^2), ASA-PS (1 vs. 2–3), CCI (0 vs. 1–7), serum albumin (< 4 vs. ≥4 g/dL), preoperative therapy (yes vs. no), main tumor location (upper, middle, and lower), histology (squamous cell carcinoma, adenocarcinoma, and others), clinical T stage (T1–T2 vs. T3–T4), clinical N stage (N0 vs. N1–N3), clinical M stage (M0 vs. M1), surgical approach (open thoracic, thoracoscopic, and transhiatal), operative time (< 540 vs. ≥540 min), blood loss (< 300 vs. ≥300 mL), anastomotic leakage (yes vs. no), and pneumonia (yes vs. no). Hazard ratio (HR) and 95% confidence interval (CI) were calculated. Simultaneously, interactions were also assessed, in which the effect of the CB count on the prognosis was evaluated according to the state of other causal variables. A two-sided probability level of < 0.05 was considered to indicate a significant difference.

Results

Cutoff value of CB count from quartile stratification analysis

The median value of CB count was 33/mm^3 (range, 0–499), and the distribution of CB count is described in Supplemental Fig. 1. When stratifying the patients according to the quartiles of CB count, the OS and RFS rates of the patients in the first-quartile group were significantly worse than those in any other groups (Fig. 1, P = 0.04 and = 0.01, respectively). Based on these findings, we decided on the cutoff value of CB count and classified the patients into the low CB (CB count ≤ 22/mm^3, n = 204) and high CB groups (CB count > 22/mm^3, n = 579).

Comparison of patient characteristics between the low and high CB groups

Patient characteristics were compared between the low and high CB groups (Table 1). Preoperative BMI and serum albumin levels were lower in the low CB group than in the high CB group (P< 0.01 and < 0.01, respectively). The low CB group included tumors with more advanced clinical T and N stages than the high CB group (P= 0.01 and = 0.04, respectively). Consequently, preoperative therapy was more frequently given in the low CB group than in high CB group (P< 0.01). In the low CB group, open transthoracic esophagectomy and three-field lymph node dissection were performed more frequently (P< 0.01, and = 0.02, respectively). Postoperatively, there were no significant differences in the incidences of pneumonia, anastomotic leakage, and surgical site infection.

Table 1
Patient characteristics and short-term outcomes

Characteristics	Low basophil n = 204 (26.1%)	High basophil n = 579 (73.9%)	P value
Age (years) [a]	66 (32−84)	65 (31−88)	0.13
Sex [b]			
Male	166 (81.4)	489 (84.5)	0.32
Female	38 (18.6)	90 (15.5)	
Preoperative BMI (kg/m^2) [a]	21.2 (14.3−31.5)	22.0 (13.5−31.6)	< 0.01**
ASA-PS [b]			
1	73 (35.8)	194 (33.5)	0.86
2	125 (61.3)	365 (63.0)	
3	6 (2.9)	20 (3.5)	
CCI [a]	1 (0−7)	1 (0−7)	0.78
Serum albumin (g/dL) [a]	4.0 (2.7−4.8)	4.1 (2.0-5.1)	< 0.01**
Preoperative therapy [b]			
None	67 (32.8)	277 (47.8)	< 0.01**
Chemotherapy	117 (57.4)	270 (46.6)	
Chemoradiotherapy	20 (9.8)	32 (5.5)	
Pathological therapeutic effect [b]			
pGrade 0/1a/1b	96 (84.9)	217 (82.2)	0.78
pGrade 2/3	17 (15.1)	47 (17.8)	
Not available	91	315	
Main Tumor location [b]			
Upper	33 (16.2)	89 (15.4)	0.06

Data expressed as number (%) or median (range). BMI: body mass index. ASA-PS: American Society of Anesthesiologists-physical status. CCI: Charlson Comorbidity Index. SCC: squamous cell carcinoma. AC: adenocarcinoma.

[a] Mann-Whitney U test. [b] Fisher's exact test. *P< 0.05. **P< 0.01.

Characteristics	Low basophil n = 204 (26.1%)	High basophil n = 579 (73.9%)	P value
Middle	98 (48.0)	229 (39.6)	
Lower	73 (35.8)	261 (45.1)	
Histology [b]			
SCC	182 (89.2)	475 (82.0)	0.02*
AC	16 (7.8)	89 (15.4)	
Others	6 (2.9)	15 (2.6)	
Clinical T stage [b]			
T1−T2	99 (48.5)	342 (59.1)	0.01*
T3−T4	105 (51.5)	237 (40.9)	
Clinical N stage [b]			
N0	96 (47.1)	322 (55.6)	0.04*
N1−N3	108 (52.9)	257 (44.4)	
Clinical M stage [b]			
M0	196 (96.1)	556 (96.0)	1.00
M1	8 (3.9)	23 (4.0)	
Pathological T stage [b]			
T1−T2	125 (61.3)	387 (66.8)	0.17
T3−T4	79 (38.7)	192 (33.2)	
Pathological N stage [b]			
N0	93 (45.6)	313 (54.1)	0.07
N1−N3	111 (54.4)	266 (45.9)	
Pathological M stage [b]			

Data expressed as number (%) or median (range). BMI: body mass index. ASA-PS: American Society of Anesthesiologists-physical status. CCI: Charlson Comorbidity Index. SCC: squamous cell carcinoma. AC: adenocarcinoma.

[a] Mann-Whitney U test. [b] Fisher's exact test. *$P < 0.05$. **$P < 0.01$.

Characteristics	Low basophil n = 204 (26.1%)	High basophil n = 579 (73.9%)	P value
M0	194 (95.1)	535 (92.4)	0.26
M1	10 (4.9)	44 (7.6)	
Surgical approach [b]			
Open transthoracic	127 (62.3)	253 (43.7)	< 0.01**
Thoracoscopic	71 (34.8)	274 (47.3)	
Transhiatal	6 (2.9)	52 (9.0)	
Field of dissection [b]			
Two-field	84 (41.2)	296 (51.1)	0.02*
Three-field	120 (58.8)	283 (48.9)	
Operation time (min) [a]	537 (274−1047)	555 (132−1019)	0.21
Blood loss (mL) [a]	330 (30-18350)	280 (0-2450)	0.06
Pneumonia [b]	49 (24.0)	142 (24.5)	0.93
Anastomotic leakage [b]	16 (7.8)	56 (9.7)	0.48
Surgical site infection [b]	39 (19.1)	84 (14.5)	0.15

Data expressed as number (%) or median (range). BMI: body mass index. ASA-PS: American Society of Anesthesiologists-physical status. CCI: Charlson Comorbidity Index. SCC: squamous cell carcinoma. AC: adenocarcinoma.

[a] Mann-Whitney U test. [b] Fisher's exact test. *P< 0.05. **P< 0.01.

Influence of low CB count on patient survival

As shown in Table 2, low CB count was significantly associated with poor OS (HR 1.32, 95% CI 1.01−1.73, P = 0.04) and RFS (HR 1.44, 95% CI 1.09−1.90, P = 0.01) in the unadjusted analysis. In addition, a low CB count was one of the independent poor prognostic factors for RFS after multivariable adjustment (HR 1.30; 95% CI 1.02−1.66; P = 0.04), along with higher age, male, lower BMI, advanced clinical T and N stages, large amounts of operative blood loss, and anastomotic leakage. Interaction analyses revealed that any clinicopathological variables did not influence the effect of a low CB count on poor RFS (Supplemental Fig. 2).

Table 2
Clinical impact of basophils on patient survival

Characteristics	Reference	OS		RFS	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Univariate					
Basophils					
Low	High	1.32 (1.01–1.73)	0.04*	1.44 (1.09–1.90)	0.01*
Multivariate					
Basophils					
Low	High	1.15 (0.88–1.51)	0.30	1.30 (1.02–1.66)	0.04*
Age (years)					
65−75	< 65	0.93 (0.70–1.24)	0.63	0.84 (0.65–1.09)	0.20
≥ 75		1.59 (1.07–2.37)	0.02*	1.54 (1.06–2.25)	0.02*
Sex					
Male	Female	1.89 (1.22–2.93)	< 0.01**	1.53 (1.05–2.25)	0.03*
Preoperative BMI (kg/m^2)					
20−23	< 20	0.55 (0.40–0.74)	< 0.01**	0.58 (0.44–0.76)	< 0.01**
≥ 23		0.55 (0.40–0.76)	< 0.01**	0.49 (0.36–0.66)	< 0.01**
ASA-PS					
2, 3	1	1.05 (0.80–1.38)	0.72	0.94 (0.73–1.21)	0.65
CCI					

OS: overall survival. RFS: recurrence-free survival. HR: hazard ratio. CI: confidence interval. BMI: body mass index. ASA-PS: American Society of Anesthesiologists-physical status. CCI: Charlson Comorbidity Index. SCC: squamous cell carcinoma. AC: adenocarcinoma.

*P < 0.05. **P < 0.01.

Characteristics	Reference	OS		RFS	
		HR (95% CI)	P value	HR (95% CI)	P value
1–7	0	1.29 (0.99–1.67)	0.06	1.19 (0.93–1.51)	0.16
Serum albumin (g/dL)					
< 4	≥ 4	1.13 (0.86–1.48)	0.38	1.05 (0.82–1.36)	0.69
Preoperative therapy					
Yes	No	0.70 (0.50–0.99)	0.04*	0.91 (0.67–1.25)	0.57
Main tumor location					
Upper	Lower	1.20 (0.82–1.78)	0.35	1.05 (0.72–1.52)	0.82
Middle		1.15 (0.85–1.55)	0.38	1.29 (0.97–1.70)	0.08
Histology					
SCC	AC, others	0.86 (0.57–1.30)	0.48	0.85 (0.54–1.12)	0.24
Clinical T stage					
T3, T4	T1, T2	1.94 (1.43–2.64)	< 0.01**	1.84 (1.39–2.43)	< 0.01**
Clinical N stage					
N1, 2, 3	N0	1.89 (1.39–2.56)	< 0.01**	1.67 (1.26–2.20)	< 0.01**
Clinical M stage					
M1	M0	1.18 (0.70–2.01)	0.53	1.11 (0.67–1.86)	0.68
Surgical approach					
Open transthoracic	Thoracoscopic	1.47 (1.06–2.05)	0.02*	1.31 (0.98–1.77)	0.07

OS: overall survival. RFS: recurrence-free survival. HR: hazard ratio. CI: confidence interval. BMI: body mass index. ASA-PS: American Society of Anesthesiologists-physical status. CCI: Charlson Comorbidity Index. SCC: squamous cell carcinoma. AC: adenocarcinoma.

*P< 0.05. **P< 0.01.

Characteristics	Reference	OS		RFS	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Transhiatal		0.94 (0.49–1.80)	0.86	0.96 (0.52–1.75)	0.88
Operation time (min)					
≥ 540	< 540	1.01 (0.77–1.34)	0.92	1.18 (0.91–1.52)	0.22
Blood loss (mL)					
≥ 300	< 300	1.29 (0.96–1.72)	0.09	1.45 (1.10–1.89)	< 0.01**
Anastomotic leakage					
Yes	No	1.17 (0.78–1.76)	0.44	1.52 (1.07–2.16)	0.02*
Pneumonia					
Yes	No	1.28 (0.97–1.69)	0.08	1.27 (0.98–1.63)	0.07
OS: overall survival. RFS: recurrence-free survival. HR: hazard ratio. CI: confidence interval. BMI: body mass index. ASA-PS: American Society of Anesthesiologists-physical status. CCI: Charlson Comorbidity Index. SCC: squamous cell carcinoma. AC: adenocarcinoma.					
*P< 0.05. **P< 0.01.					

Recurrence patterns and CB count

Table 3 shows the association between the recurrence patterns and CB count. Among the 206 patients who experienced disease recurrence, hematogenous recurrence was more frequent in the low CB group than in the high CB group (57.6% vs. 41.4%, *P* = 0.04). Meanwhile, there were no significant differences in other recurrence patterns such as lymphatic, dissemination, and local recurrence patterns.

Table 3
Patterns of recurrence

Characteristics	Low basophil n = 66 (32.4%)	High basophil n = 140 (24.2%)	P value
Lymphatic [a]	35 (53.0)	86 (61.4)	0.29
Hematogenous [a]	38 (57.6)	58 (41.4)	0.04*
Dissemination [a]	7 (10.6)	19 (13.6)	0.66
Local [a]	4 (6.1)	15 (10.7)	0.44
Data expressed as number (%).			
[a] Fisher's exact test. *$P < 0.05$.			

Discussion

In this study, we investigated the association between preoperative CB count and the outcomes of esophageal cancer surgery. We found that a low CB count was significantly associated with advanced tumor stage and was an independent poor prognostic factor for RFS. In addition, hematogenous recurrence was more frequent in the low CB group than in the high CB group. To the best of our knowledge, this study is the first to demonstrate the association between preoperative CB count and outcomes after oncologic esophagectomy.

Thus far, basophils have not attracted intensive attention because of their sparse distribution and difficulty in exploring their function. Basophils play vital roles in allergic diseases and type 1 hypersensitivity. Also, they can be recruited to tissues in response to parasitic, bacterial, and viral infections. Recently, basophil-depleting antibodies and basophil-deficient mouse models have been established, leading to an understanding of basophil biology outside of the allergic response. As a result, the possible association between basophils and tumor immunity has been elucidated [18]. Basophils not only improve the function of humoral immunity but also the release intracellular substances, leading to anti-tumor immunity [18–20], in which chemokines CCL3 and CCL4 accelerate CD8 + T cell infiltration [18], and TNF-α and IL-6 augment the inflammatory anti-tumor reaction [21, 22]. Also, histamine could suppress inflammation associated with carcinogenesis and increase tumoral apoptosis [23, 24].

Studies have reported that basophils have beneficial roles in the survival outcomes of several cancers [9–11]. In ovarian cancer, endometrial cancer, and sarcoma, higher gene expression levels of activated basophil signatures in the tumor were associated with a favorable prognosis, whereas converse results were obtained in gastric cancer [7]. In pancreatic cancer, basophils were also reported to be associated with long-term tumor engraftment and reduced survival [25]. Meanwhile, it was reported that the association in breast cancer differed depending on the subtypes [26]. These indicate that the local

microenvironments may influence basophils, providing the juxtaposing pro-tumor or anti-tumor effects, which may have caused the varied effects on survival among cancer types [6].

We showed that esophageal cancer patients with a lower CB count had more advanced tumors. In addition, preoperative BMI and serum albumin levels were significantly lower in the low CB group than in the high CB group. These characteristics might be related to the poor prognosis and higher incidence of hematogenous recurrence in the low CB group. However, given that a low CB count was one of the independent poor prognostic factors for RFS after multivariable adjustment, basophils might have a crucial role in suppressing micro-metastasis.

Among the studies in the field of allergo-oncology, the biological characteristics of IgE are now interesting because IgE may have potential anti-tumor functions. Recently, a phase I study of anti-cancer IgE antibody for patients with advanced solid tumors revealed the safety of IgE as a treatment for cancer with potential efficacy [27]. One of the potential concerns associated with IgE applications as cancer treatment is the perceived risk of IgE-mediated anaphylaxis. However, activating basophils with IgE-based therapeutic agents may provide novel and more effective treatments for cancer.

Meanwhile, the inhibition of programmed death protein 1 (PD-1)/ PD-1 ligand 1 (PD-L1) axis with immune checkpoint inhibitors (ICIs) has been emerging as a novel treatment strategy for several types of cancers, including esophageal cancer [28–32]. PD-L1 is also expressed on the surfaces of various immune cells, including basophils in tumor microenvironments, and it was suggested that PD-L1 expressed in immune cells plays an essential role in ICI blockade therapy [9, 33, 34]. Therefore, further research on the role of PD-L1 + basophils in ICI blockade would also be attractive.

This study has several limitations. First, this is a retrospective, observational study at a single institution with a long study period. Second, this study included only a Japanese population, and the results need to be verified in a more representative global population. Third, the precise mechanism by which CB influenced prognosis remains unclear. Therefore, further prospective multicenter, large-scale studies are required to confirm the present findings. Also, elucidating the roles of basophils in cancer is still needed.

Conclusion

In conclusion, a low CB count was significantly associated with advanced tumor stage and was an independent poor prognosticator for RFS with a higher incidence of hematogenous recurrence. Basophils might have beneficial roles in the survival outcomes of esophageal cancer patients.

Declarations

Informed consent statement: All study participants provided informed written consent prior to their study enrollment.

This study was approved by the institutional review board and performed under the ethical standards of the Declaration of Helsinki and its later amendments.

Authors' Contributions

Study concept and design: MS, OA and WM. Performance of operation: OA, KJ, IY, WM. Draft the manuscript: MS, OA and WM. Acquisition of data: MS, KY, KK, and SK. Analysis and interpretation of data: MS, OA, and WM. All authors have revised and approved the manuscript.

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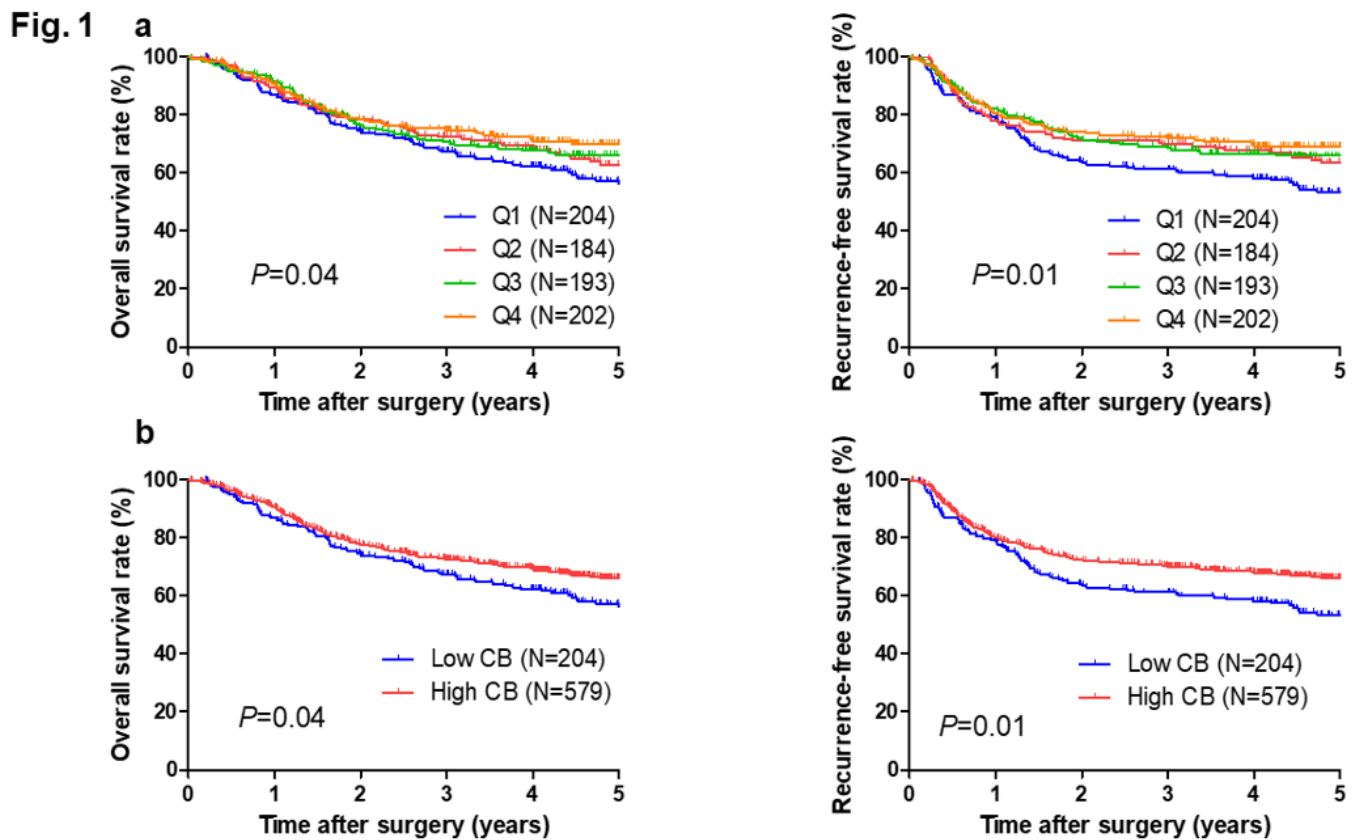
Figures

Figure 1

Kaplan-Meier curves of patients for overall survival and recurrence-free survival rates stratified by circulating basophil counts.

CB: circulating basophil

Supplementary Files

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