Impact of Pegfilgrastim Approval on Relative Dose Intensity and Outcomes of R-CHOP for Diffuse Large B-Cell Lymphoma

Yuka Morita
Department of Medical Oncology, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital

Yusuke Kanemasa (y-kanemasa@cick.jp)
Department of Medical Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital https://orcid.org/0000-0002-9809-2008

Yuki Sasaki
Department of Clinical Research Support, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital

An Ohigashi
Department of Medical Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital

Taichi Tamura
Department of Medical Oncology, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital

Shohei Nakamura
Department of Medical Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital

Yu Yagi
Department of Medical Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital

Akihiko Kageyama
Department of Medical Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital

Yasushi Omuro
Department of Medical Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital

Tatsu Shimoyama
Department of Medical Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Komagome Hospital

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Abstract

Maintaining the relative dose intensity (RDI) of chemotherapy with R-CHOP improves the prognosis of patients with diffuse large B-cell lymphoma (DLBCL). Pegfilgrastim was approved for use in Japan in November 2014 to prevent febrile neutropenia (FN) and maintain RDI. We herein reviewed 334 patients with DLBCL who received six or more courses of R-CHOP and retrospectively analyzed the difference in the RDI, overall survival (OS), and progression-free survival (PFS) between patients whose treatment started after November 2014 (the post-approval group) and those whose treatment started before October 2014 (the pre-approval group). The incidence of FN was lower (39.2% vs. 62.2%, $P < 0.001$) and the RDI of R-CHOP was higher (86.8% vs. 67.8%, $P < 0.001$) in the post-approval group. The RDI of patients aged < 70 years was maintained at a high level even if their RDI was predicted to be low based on the model derived from the pre-approval group. Pegfilgrastim was administered to many of these patients and was thought to have contributed to the high RDI maintenance in the post-approval group. The 5-year OS (85.7% and 69.9%, $P = 0.009$) and PFS (81.4% and 64.4%, $P = 0.011$) were superior in the post-approval group. In this group, improved survival outcomes were observed among patients with Ann Arbor stage 3/4 (5-year OS: 83.7% vs. 61.3%, $P = 0.019$) and high risk on the NCCN-IPI (5-year OS: 80.7% vs. 32.4%, $P = 0.014$). Maintenance of high RDI of R-CHOP and significant improvement in clinical outcomes, especially in high-risk groups, were observed after pegfilgrastim approval.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma (NHL) and accounts for approximately 30–40% of NHL cases. Standard therapy for DLBCL is combination chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Several, retrospective studies have reported that maintaining the relative dose intensity (RDI) of R-CHOP significantly improved clinical outcomes in patients with DLBCL, and that the RDI was an independent factor associated with response and survival prognosis [1–3]. Although DLBCL is a potentially curable disease, approximately one-third of patients will eventually experience a relapse, and the prognosis is extremely poor for those who relapse after front-line therapy [4].

Pegfilgrastim, a long-acting granulocyte-colony stimulating factor (G-CSF), was approved for use in Japan in November 2014 and has been administered to patients with various types of malignant tumor. Several studies have shown that prophylaxis with G-CSFs reduces the incidence of febrile neutropenia (FN) and mortality and increases the RDI, and that pegfilgrastim is more effective than short-acting G-CSFs, such as filgrastim or lenograstim [5–8]. Pegfilgrastim is used in clinical practice not only to prevent chemotherapy-induced FN but also to maintain the RDI of chemotherapy, especially in elderly patients, and is thought to enable a higher RDI necessary for achieving better clinical outcomes. However, it is unclear whether pegfilgrastim actually contributes to better survival outcomes in patients with DLBCL.

The present retrospective study evaluated the effect of pegfilgrastim on the RDI of R-CHOP and clinical outcomes in patients with DLBCL by comparing the clinical data before and after approval of the drug.

Materials And Methods

Patients

The medical records of patients in whom DLBCL was newly diagnosed between August 2004 and March 2018 at our hospital were reviewed. Data on patients who received more than six courses of R-CHOP were analyzed. The study population was divided into those who started receiving chemotherapy after pegfilgrastim approval in November 2014 (the post-approval group) and those who began receiving chemotherapy before October 2014 (the pre-approval group).

DLBCL was pathologically diagnosed in accordance with the World Health Organization (WHO) classification [9, 10], and clinical staging was performed using the Ann Arbor classification. Performance status (PS) was evaluated using the Eastern Cooperative Oncology Group (ECOG) criteria. The National Comprehensive Cancer Network-International Prognostic Index (NCCN-IPI) scores were calculated based on age, serum lactate dehydrogenase (LDH), PS, Ann Arbor stage, and extranodal involvement at diagnosis [11].

This retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tokyo Metropolitan Cancer and Infectious Diseases Center at Komagome Hospital. Written informed consent was waived because this study used retrospective data obtained from the hospital medical records.

Treatment

Standard R-CHOP therapy consisting of rituximab (375 mg/m^2 on day 1), cyclophosphamide (750 mg/m^2 on day 2), doxorubicin (50 mg/m^2 on day 2), vincristine (1.4 mg/m^2 (maximum 2 mg/body) on day 2), and prednisone (100 mg/day on days 2–6) was administered every three weeks. The dosage was often reduced to 5/6 in patients aged 70–79 years and to 7/12 in patients aged over 80 years in accordance with a previous report [12]. The dosage, timing of the start of subsequent cycles, and preparations for G-CSF administration were determined at the physician's discretion.

Outcome measures

The delivered dose intensity was calculated as the total delivered dose divided by the total time until completion of the chemotherapy. The RDI was calculated as the percentage of the delivered dose intensity divided by the standard intensity The average RDI for cyclophosphamide and doxorubicin was used for statistical analysis. Overall survival (OS) was defined as the period from the initiation of chemotherapy to the last follow-up or death from any cause. Progression-free survival (PFS) was defined as the period from the initiation of chemotherapy to progression, relapse, last follow-up or death from any cause.

Statistical analysis

OS and PFS were estimated using the Kaplan-Meier method and were compared using univariate analysis with the log-rank test. Multivariate analysis was performed for OS using the Cox proportional hazards model. The differences in the characteristics between the two groups were assessed by Fisher's exact test or Student's t-test. Multivariate analysis of factors associated with RDI ≥ 85% was performed using logistic regression analysis. Multiple linear regression analysis was performed to explore the association between RDI and other clinical factors, and backward stepwise selection was applied to choose the factors included in the prediction model. Pearson correlation coefficient analysis was used to analyze associations between two parameters. All *P* values were two sided, and $P < 0.05$ was considered to indicate statistical significance. Statistical analyses were performed with R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Between August 2004 and March 2018, DLBCL was newly diagnosed in 604 patients. In total, 334 patients met the inclusion criteria and were analyzed (Supplementary Fig. 1). The patients were classified into the post-approval (n = 125) and pre-approval (n = 209) groups. Table 1 shows the patient characteristics. Patients with Ann Arbor stage 3/4 (46.4% vs. 62.2%, $P = 0.006$), high-intermediate or high risk on the NCCN-IPI (40% vs. 57.4%, $P = 0.002$), and serum albumin < 3.7 g/dL (29.6% vs. 43.1%, $P = 0.015$) were fewer in the post-approval group than in the pre-approval group. The two groups did not differ significantly in terms of the other factors.

Table 1
Patient characteristics

	Post-approval (n = 125)	Pre-approval (n = 209)	*P* value
	n (%)	n (%)	
Age (> 60 years)	89 (71.2)	146 (69.9)	0.81
Sex (male)	65 (52.0)	126 (60.3)	0.17
B-symptoms (+)	31 (24.8)	62 (29.7)	0.38
ECOG-PS (≥ 2)	18 (14.4)	47 (22.5)	0.086
LDH (> ULN)	58 (46.4)	120 (57.4)	0.055
Ann Arbor stage (3/4)	58 (46.4)	130 (62.2)	0.006
Extranodal involvement (≥ 2)	31 (24.8)	59 (28.2)	0.53
NCCN-IPI (HI/H)	50 (40.0)	120 (57.4)	0.002
CCI (≥ 3)	51 (40.8)	66 (31.6)	0.098
Serum albumin (< 3.7 g/dL)	37 (29.6)	90 (43.1)	0.015

ECOG-PS Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *NCCN-IPI* National Comprehensive Cancer Network-International Prognostic Index, *CCI* Charlson Comorbidity Index

RDI

RDI was higher in the post-approval group than in the pre-approval group (86.8% vs. 67.8%, $P < 0.001$) (Fig. 1a). Similar results were obtained when the patients were divided into three age groups (≤ 69 years: 95.6% vs. 71.5%, $P < 0.001$; 70–79 years: 82.4% vs. 64.1%, $P < 0.001$; ≥ 80 years: 54.6% vs. 44.7%, $P < 0.001$) (Fig. 1b). Multivariate analysis revealed that patients with younger age, good PS, and a low Charlson Comorbidity Index (CCI), and patients in the post-approval group were significantly associated with RDI ≥ 85% (age ≥ 70 years, odds ratio [OR]: 0.09, 95% confidence interval [CI]: 0.04–0.20, $P < 0.001$; ECOG-PS ≥ 2, OR: 0.33, 95% CI: 0.14–0.81, $P = 0.016$; CCI ≥ 3, OR: 0.51, 95% CI: 0.27–0.98, $P = 0.044$; post-approval group, OR: 15.3, 95% CI: 7.45–31.40, $P < 0.001$) (Table 2).

Table 2
Univariate and multivariate analyses of factors associated with RDI ≧ 85%

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age (≧ 70 years)	0.17 (0.09–0.31)	< 0.001	0.09 (0.04–0.20)	< 0.001
Sex (male)	0.98 (0.61–1.58)	1		
B-symptoms (+)	0.58 (0.33–1.01)	0.043	0.71 (0.36–1.38)	0.32
ECOG-PS (≧ 2)	0.25 (0.11–0.53)	< 0.001	0.33 (0.14–0.81)	0.016
LDH (> ULN)	0.68 (0.42–1.08)	0.090		
Ann Arbor stage (3/4)	0.65 (0.41–1.04)	0.068		
Extranodal involvement (≧ 2)	0.62 (0.35–1.07)	0.074		
NCCN-IPI (HI/H)	0.27 (0.16–0.44)	< 0.001	0.77 (0.39–1.51)	0.44
CCI (≧ 3)	0.59 (0.35–0.98)	0.033	0.51 (0.27–0.98)	0.044
Serum albumin (< 3.7 g/dL)	0.52 (0.31–0.85)	0.007	1.25 (0.64–2.44)	0.52
Initial chemotherapy (Post-approval)	6.82 (4.06–11.62)	< 0.001	15.3 (7.45–31.40)	< 0.001

CI confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *NCCN-IPI* National Comprehensive Cancer Network-International Prognostic Index, *CCI* Charlson Comorbidity Index

Some patients in both groups received a G-CSF, such as filgrastim or lenograstim, daily for neutropenia treatment. While no patients in the post-approval group received G-CSF daily as a prophylaxis for FN or for RDI maintenance, 13 patients (6.2%) in the pre-approval group received G-CSF daily. In the post-approval group, 96 patients (76.8%) received pegfilgrastim at least once during R-CHOP. The patients who received pegfilgrastim had a significantly lower RDI than those who did not (85.2% vs. 92.0%, $P = 0.039$) (Fig. 2a). This was considered to be due to the high frequency of elderly patients among those who received pegfilgrastim. In fact, there was no significant difference in the RDI between patients with or without pegfilgrastim when stratified by age group (≧ 69 years: 95.0% vs. 96.9%, $P = 0.21$; 70–79 years: 83.3% vs. 76.5%, $P = 0.27$; ≧ 80 years: 54.4% vs. 57.0%, $P = 0.54$) (Fig. 2b). More patients in the older age groups received pegfilgrastim as primary prophylaxis (14%, 62%, and 80% in patients ≦ 69 years, 70–79 years, and ≧ 80 years, respectively, $P < 0.001$) (Fig. 2c, d). Of the patients who did not receive primary prophylaxis using pegfilgrastim, those with poor PS and a low albumin level were more likely to need secondary prophylaxis (Table 3).

Table 3
Univariate analysis of factors associated with secondary prophylaxis using pegfilgrastim in the post-approval group

	Odds ratio (95% CI)	*P* value
Age (> 60 years)	1.26 (0.45–3.49)	0.64
Age (≥ 65 years)	1.16 (0.42–3.26)	0.82
Sex (male)	1.16 (0.42–3.20)	0.82
B-symptoms (+)	2.58 (0.71–11.93)	0.17
ECOG-PS (≥ 2)	Inf (1.23-Inf)	0.023
LDH (> ULN)	1.01 (0.37–2.81)	1
Ann Arbor stage (3/4)	0.61 (0.22–1.67)	0.35
Extranodal involvement (≥ 2)	0.99 (0.32–3.21)	1
NCCN-IPI (HI/H)	1.56 (0.51–5.22)	0.45
CCI (≥ 3)	0.57 (0.20–1.61)	0.24
Serum albumin (< 3.7 g/dL)	6.62 (1.38–64.10)	0.007

CI confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *NCCN-IPI* National Comprehensive Cancer Network-International Prognostic Index, *CCI* Charlson Comorbidity Index

To examine the impact of pegfilgrastim administration on the RDI of each patient, we estimated the RDI from baseline clinical factors before pegfilgrastim became available. The significant factors associated with RDI in the pre-approval group were age, CCI, and serum albumin (71.5% vs. 61.3% in age < 70 and ≥ 70 years, $P < 0.001$; 70.4% vs. 62.0% in CCI < 3 and ≥ 3, $P = 0.001$; 70.5% vs. 64.1% in albumin ≥ 3.7 and < 3.7 g/dL, $P = 0.009$) (Supplementary Table 1), which were included as explanatory variables in the multiple linear regression analysis while age and CCI were retained in the prediction model (Table 4). The formula for the latter was predicted RDI (%) = 111.65–0.58×(age) – 2.38×(CCI). We found a significant correlation between the predicted RDI and actual RDI not only in the pre-approval group but also in the post-approval group ($r = 0.42$, $P < 0.001$ in pre-approval group; $r = 0.61$, $P < 0.001$ in pre-approval group). The actual RDI was higher than the predicted RDI in most patients in the post-approval group (Fig. 3a). Among patients aged < 70 years in the post-approval group, the difference between the actual RDI and predicted RDI was remarkable, especially in those with a low predicted RDI. In these patients, the actual RDI was maintained at a high level regardless of the predicted RDI. Many patients with a risk of low predicted RDI were given pegfilgrastim (Fig. 3b).

Table 4
Multivariate logistic regression analysis and backward stepwise selection of factors associated with relative dose intensity in the pre-approval group

	Multiple linear regression analysis		Backward stepwise selection	
	Coefficient (95%CI)	*P* value	Coefficient (95%CI)	*P* value
Age	-0.0055 (-0.0077-0.0033)	< 0.001	-0.0058 (-0.0080-0.0037)	< 0.001
CCI	-0.0232 (-0.0450-0.0015)	0.036	-0.0238 (-0.0456-0.0021)	0.032
Serum albumin	0.0290 (-0.0080-0.0661)	0.12		

CI confidence interval, *CCI* Charlson Comorbidity Index

Febrile neutropenia

The incidence of FN was lower in the post-approval group (39.2% vs. 62.2%, $P < 0.001$). Patients with serum albumin < 3.7 g/dL and those in the post-approval group were significantly associated with FN occurrence, according to multivariate analysis (serum albumin < 3.7 g/dL; OR: 1.94, 95% CI: 1.14–3.30, $P = 0.014$ and post-approval group; OR: 0.45, 95% CI: 0.28–0.72, $P = 0.001$) (Table 5).

Table 5
Univariate and multivariate analysis of factors associated with febrile neutropenia incidence

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age (≥ 60 years)	1.00 (0.61–1.65)	1		
Sex (male)	1.45 (0.92–2.31)	0.097		
B-symptoms (+)	1.97 (1.17–3.36)	0.007	1.41 (0.82–2.43)	0.218
ECOG-PS (≥ 2)	2.70 (1.45–5.21)	< 0.001	1.74 (0.90–3.38)	0.10
LDH (> ULN)	1.67 (1.06–2.65)	0.021	0.94 (0.56–1.58)	0.82
Ann Arbor stage (3/4)	1.82 (1.15–2.90)	0.008	1.32 (0.81–2.14)	0.27
Extranodal involvement (≥ 2)	1.52 (0.90–2.57)	1.52		
NCCN-IPI (HI/H)	1.46 (0.93–2.31)	0.10		
CCI (≥ 3)	0.91 (0.57–1.47)	0.73		
Serum albumin (< 3.7 g/dL)	2.71 (1.67–4.45)	< 0.001	1.94 (1.14–3.30)	0.014
RDI (≥ 85%)	0.78 (0.48–1.24)	0.78		
Initial chemotherapy (Post-approval)	0.39 (0.24–0.63)	< 0.001	0.45 (0.28–0.72)	0.001

CI confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *NCCN-IPI* National Comprehensive Cancer Network-International-Prognostic Index, *CCI* Charlson Comorbidity Index, *RDI* relative dose intensity

Prognosis

Five-year OS and PFS were significantly superior in the post-approval group (five-year OS: 85.7% and 69.9%, respectively, $P = 0.009$; five-year PFS: 81.4% and 64.4%, respectively, $P = 0.011$) (Fig. 4). A significant difference was observed in the patients with Ann Arbor stage 3/4 between the two groups (five-year OS: 83.7% vs. 61.3%, respectively, $P = 0.019$; five-year PFS: 75.2% vs. 55.8%, respectively, $P = 0.034$) (Fig. 5) and among those with a high risk on NCCN-IPI (five-year OS: 80.7% vs. 32.4%, respectively, $P = 0.014$; five-year PFS: 75.6% vs. 27.5%, respectively, $P = 0.010$) (Fig. 6) although no significant difference was observed among the other subgroups. Multivariate analysis showed that a high RDI and low LDH were associated with superior OS (RDI ≥ 85%, hazard ratio: 0.48, 95% CI: 0.27–0.87, $P = 0.016$; LDH > institutional upper limit of normal, hazard ratio: 2.38, 95% CI: 1.31–4.33, $P = 0.005$) (Table 6).

Table 6
Univariate and multivariate analyses of clinical factors of overall survival

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (> 60 years)	1.62 (1.06–2.48)	0.044	1.57 (0.91–2.68)	0.10
Sex (male)	1.35 (0.91–2.02)	0.15		
B-symptoms (+)	1.63 (1.03–2.56)	0.021	0.99 (0.63–1.55)	0.97
ECOG-PS (≧ 2)	2.49 (1.46–4.26)	< 0.001	1.45 (0.90–2.34)	0.13
LDH (> ULN)	2.93 (1.97–4.37)	< 0.001	2.38 (1.31–4.33)	0.005
Ann Arbor stage (3/4)	2.06 (1.38–3.07)	< 0.001	1.37 (0.78–2.43)	0.28
Extranodal involvement (≧ 2)	1.99 (1.23–3.22)	< 0.001	1.17 (0.71–1.90)	0.54
NCCN-IPI (IH/H)	2.82 (1.90–4.21)	< 0.001	0.91 (0.45–1.83)	0.79
CCI (≧ 3)	1.16 (0.76–1.76)	0.49		
Serum albumin (< 3.7 g/dL)	2.25 (1.48–3.42)	< 0.001	1.27 (0.79–2.02)	0.32
RDI (≧ 85%)	0.36 (0.23–0.54)	< 0.001	0.48 (0.27–0.87)	0.016
Initial chemotherapy (Post-approval)	0.52 (0.33–0.81)	0.009	0.72 (0.40–1.29)	0.27
Pegfilgrastim administration (+)	1.02 (0.64–1.61)	0.94		

CI confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *NCCN-IPI* National Comprehensive Cancer Network-International Prognostic Index, *CCI* Charlson Comorbidity Index, *RDI* relative dose intensity

Supplementary Table 1. Univariate analysis of factors associated with relative dose intensity in the pre-approval group

Discussion

The present study demonstrated that the RDI of the post-approval group was able to be maintained at a high level even in patients whose RDI tended to be low based on the prediction model, and that the OS and PFS improved after pegfilgrastim approval, especially in the clinically high-risk groups. To the best of our knowledge, the present report is the first to demonstrate a significant association between pegfilgrastim approval and the prognosis of patients with DLBCL.

Pegfilgrastim, a long-acting G-CSF, was approved for use in Japan in November 2014 to prevent FN induced by chemotherapy. The American Society of Clinical Oncology guidelines clearly state that the

reduction of FN is an important clinical outcome [14]. Moreover, FN can lead to infection-related mortality as well as dose reduction during chemotherapy, which in turn can lead to poorer outcomes. Three systematic reviews and meta-analyses demonstrated that the administration of G-CSF, including pegfilgrastim, resulted in better clinical outcomes. In one of these studies, the relative risk of infection-related mortality, early mortality (all-cause mortality during the chemotherapy period), and FN decreased, and that the average RDI significantly increased, in patients receiving G-CSF than in control patients [5]. Another study reported not only a reduction in FN after G-CSF administration, but also the superiority of pegfilgrastim over daily filgrastim, a short-acting G-CSF [7]. Another systematic review demonstrated that primary G-CSF prophylaxis reduced the relative risk of all-cause mortality, particularly in clinical trials with longer follow-up periods where the treatment was for curative intent and survival was the primary outcome [8].

In terms of the relationship between malignant lymphoma and G-CSF, a meta-analysis of 13 RCTs for malignant lymphoma concluded that G-CSF/GM-CSF prophylaxis significantly reduced the incidence of FN, neutropenia, and infection but did not significantly improve freedom from treatment failure (FFTF) or OS [15]. A randomized prospective trial reported that primary prophylaxis with pegfilgrastim reduced FN incidence and hospitalizations resulting from neutropenia or FN in patients with NHL aged 65 years or older [16].

As far as could be ascertained, no clear evidence indicates that the introduction of pegfilgrastim into DLBCL treatment has improved patients' prognosis. To investigate the impact of pegfilgrastim, the present study compared clinical outcomes before and after approval of the drug. Our study found that the FN incidence decreased while the RDI of R-CHOP increased, as previously reported, and that the OS and PFS significantly improved after pegfilgrastim approval. Moreover, multivariate analysis of OS found that high RDI led to improved prognosis, in line with previous reports [1, 2, 17].

The major guidelines recommend primary G-CSF prophylaxis for patients with a high FN risk (≧ 20%) receiving chemotherapy and patients classified as intermediate risk (10–19%) with risk factors of FN, such as older age, bone marrow invasion, poor PS, malnutrition, etc. [14, 18, 19]. The FN incidence in patients with DLBCL receiving R-CHOP is reportedly 18–19%, which is considered to be intermediate-risk [19]. Therefore, administration of pegfilgrastim as primary prophylaxis is recommended from the first R-CHOP cycle in patients with risk factors of FN. In the present study, pegfilgrastim was more often administered as a secondary prophylaxis to patients with poor PS and a low albumin level. Furthermore, it was also shown that the incidence of FN was higher in patients with a low albumin level. Based on these findings, primary prophylaxis with pegfilgrastim may be considered as a viable option for these patients.

Our analysis of the pre-approval group demonstrated that the RDI of patients with older age, high CCI, and low albumin was low. However, patients aged < 70 years in the post-approval group maintained high RDI, even if they were likely to have low RDI based on the prediction model consisting of age and CCI. The fact that many of these patients received pegfilgrastim suggested that this drug may have contributed to

maintaining a high RDI in patients whose RDI tended to be low without pegfilgrastim. On the other hand, there were also some patients who were able to maintain a high RDI without pegfilgrastim administration. As a result, the RDI of the entire post-approval group was maintained at a high level although the RDI of the patients who received pegfilgrastim was not higher than that of patients who did not receive the drug.

In the present study, improved OS and PFS in the post-approval group were observed only in the advanced stage and NCCN-IPI high-risk groups. While maintaining a high RDI may be important to achieve good survival outcomes in the clinically high-risk groups, it may be possible to reduce the intensity of R-CHOP in the clinically low-risk groups. In fact, some recent studies reported that four cycles of R-CHOP were sufficient for patients with localized or low-risk DLBCL [20, 21].

This study has some limitations. First, it was a retrospective study, making it impossible to assess all the factors that might have influenced the clinical outcomes. Furthermore, there were fewer patients with advanced stage DLBCL or a high-intermediate or high risk on the NCCN-IPI in the post-approval group. However, multivariate analysis showed that these factors had no statistically significant effect on OS. Moreover, evaluating the impact of pegfilgrastim could be difficult if there were a substantial number of patients receiving G-CSF daily for FN prophylaxis or RDI maintenance. However, such patients comprised only 6.2% of the pre-approval group. Pegfilgrastim was shown to have a prophylactic effect superior to that of short-acting G-CSFs as described above [7]. Moreover, the standard therapeutic strategy for DLBCL has not changed for more than 15 years. Based on these facts, it is likely that the pre-approval group served as a good historical control for investigating the impact of pegfilgrastim approval on clinical outcomes in patients with DLBCL. Second, patients who did not complete six cycles of R-CHOP were excluded. Because these patients were considered to have a poor prognosis, their exclusion might also have impacted the results. For reference, the treatment completion rate and clinical outcomes of all patients with DLBCL receiving R-CHOP improved after pegfilgrastim approval (treatment completion rate: 78.5% vs. 65.9%, $P = 0.003$; 5-year OS: 82.3% vs. 61.7%, $P < 0.001$; 5-year PFS: 73.0% vs. 56.0%, $P = 0.007$, in the post-approval and pre-approval groups, respectively). Despite these limitations, the present study is the first to demonstrate that pegfilgrastim has the potential to contribute to improving survival outcomes in patients with DLBCL.

In conclusion, after pegfilgrastim approval, the RDI of R-CHOP was able to be maintained at higher levels, and significantly better clinical outcomes were achieved, especially in clinically high-risk groups, suggesting that maintaining a high RDI in R-CHOP by administering pegfilgrastim to those who need it is important for achieving favorable outcomes in patients with DLBCL.

Declarations

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Availability of data and material

Datasets are available upon reasonable request.

Code availability

Not applicable.

Authors' contributions

YM contributed to designing the study, collecting and analyzing the data, and drafting the manuscript. YK helped with designing the study and drafting the manuscript and approved the final draft. YS helped with the data collection and approved the final draft. AO, TT, SN, YY, AK, TS, and YO provided materials and approved the final draft.

Ethics approval

This study was approved by the Institutional Review Board of Tokyo Metropolitan Cancer and Infectious Diseases Center at Komagome Hospital and performed in accordance with the Declaration of Helsinki and its later amendments.

Consent to participate

Written informed consent was waived because this study used retrospective data obtained from the hospital medical records.

Consent for publication

Not applicable.

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Figures

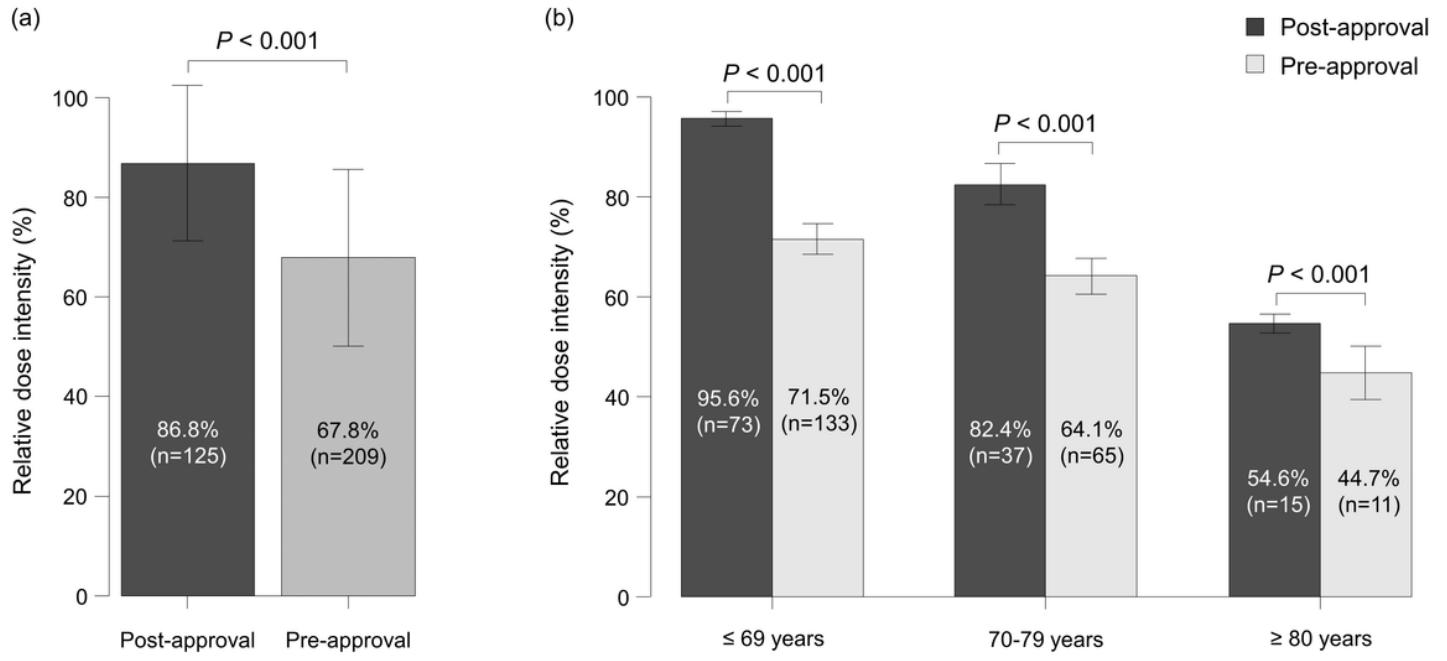

Figure 1

Relative dose intensity in the post- and pre-approval groups in the whole study cohort (a) and after stratification by age (b).

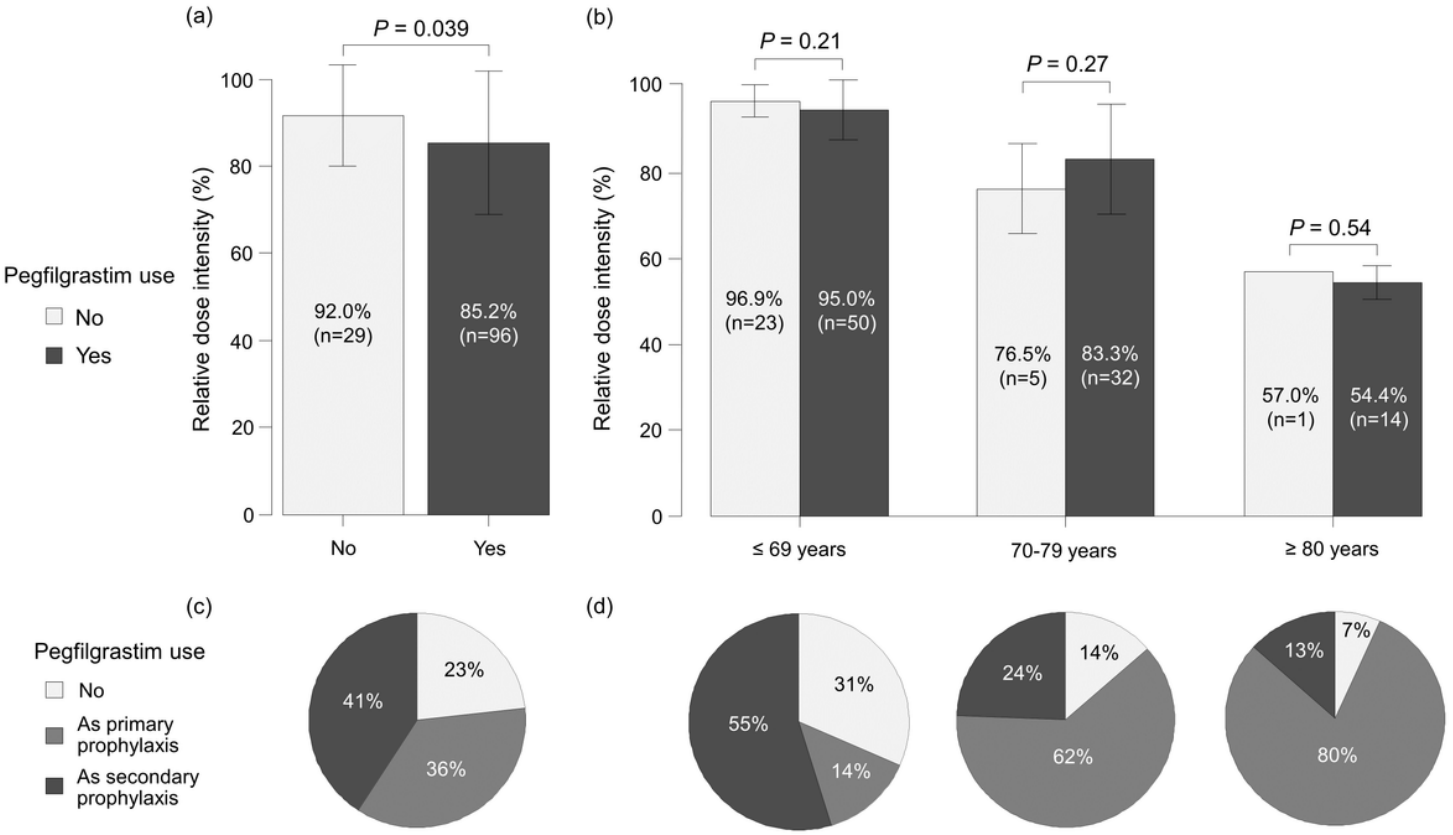

Figure 2

Relative dose intensity in the post-approval group in terms of pegfilgrastim use in the whole cohort (a) and after stratification by age (b). Breakdown of pegfilgrastim use and prophylaxis type in the whole cohort (c) and after stratification by age (d).

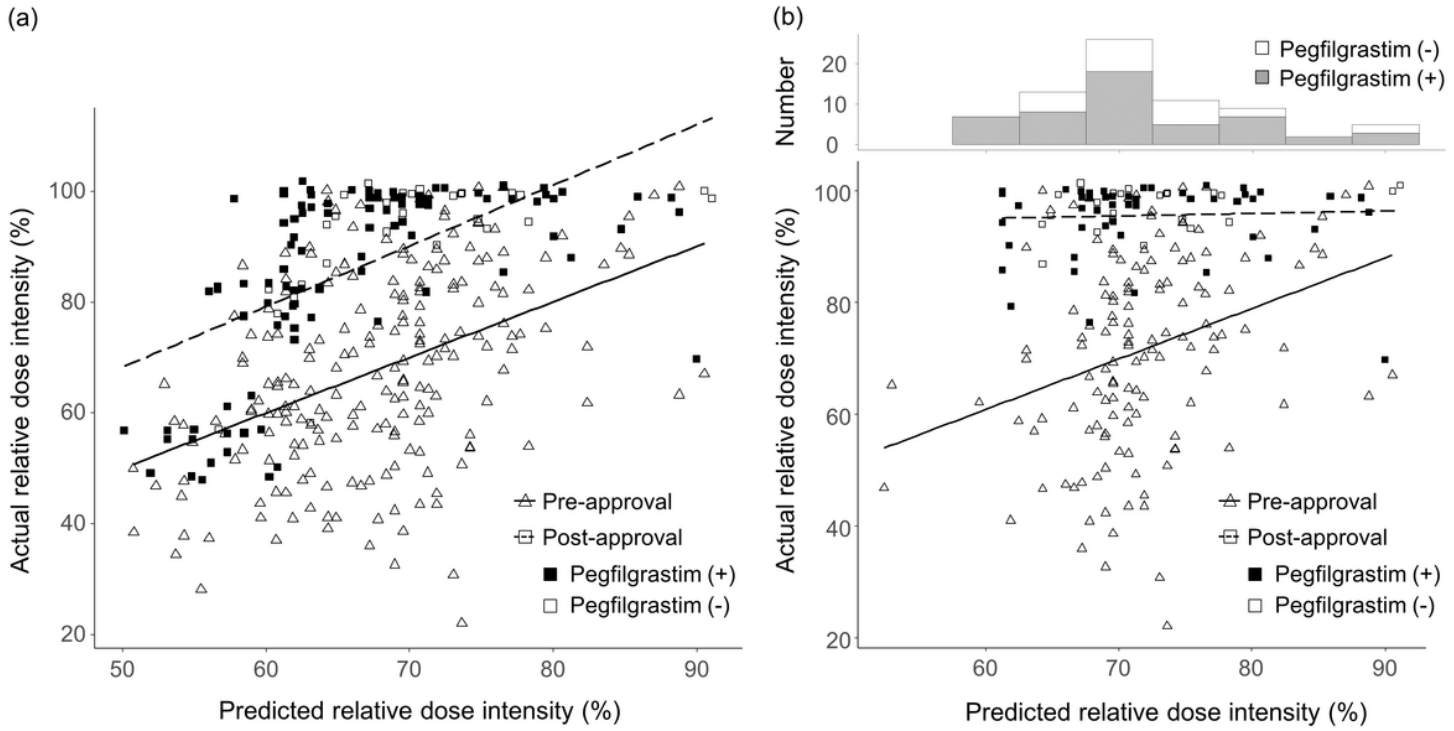

Figure 3

Scatter plots of predicted relative dose intensity and actual relative dose intensity among the entire cohort (a) and patients aged <70 years (b). The histogram in (b) shows the number of patients who received or did not receive pegfilgrastim.

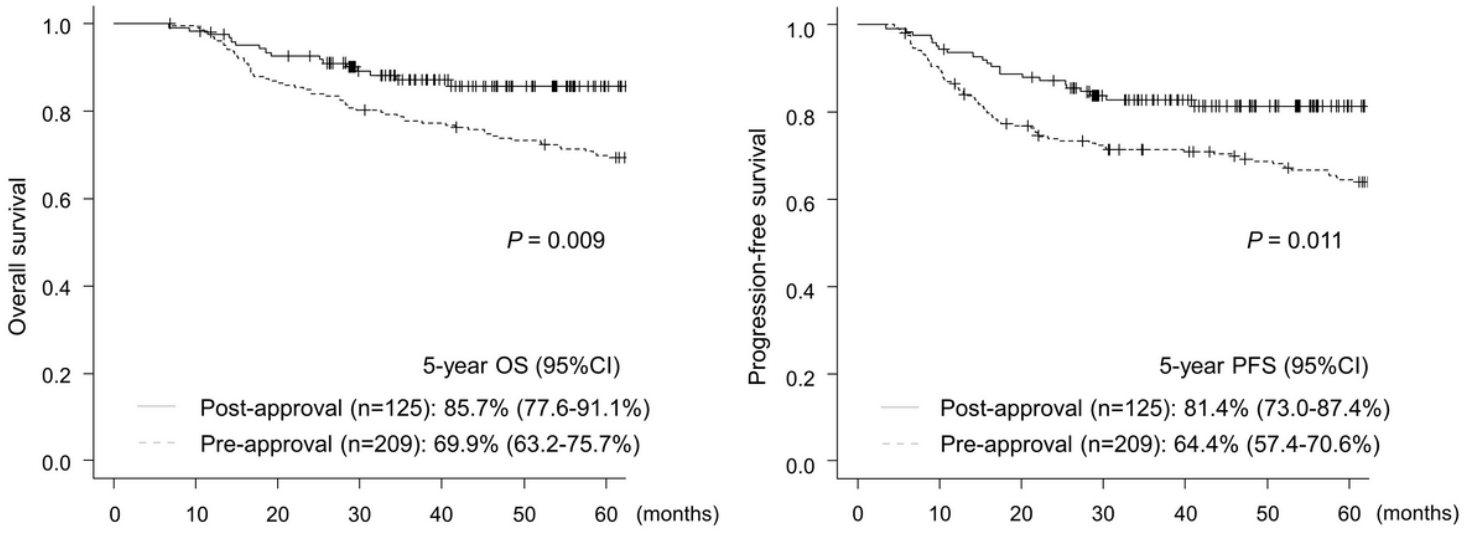

Figure 4

Kaplan-Meier curves of overall survival and progression-free survival in the whole cohort.

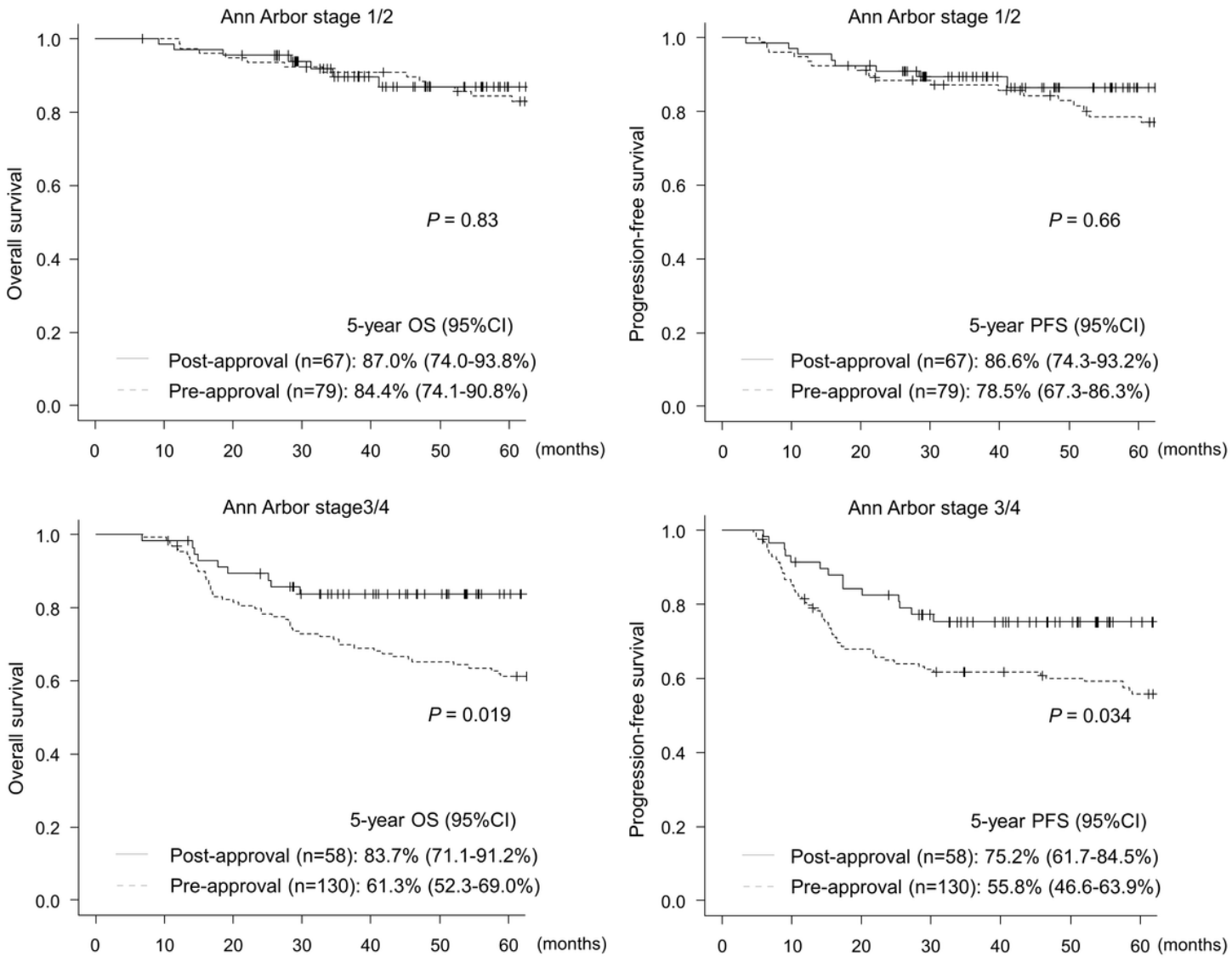

Figure 5

Kaplan-Meier curves of overall survival and progression-free survival stratified by Ann Arbor stage.

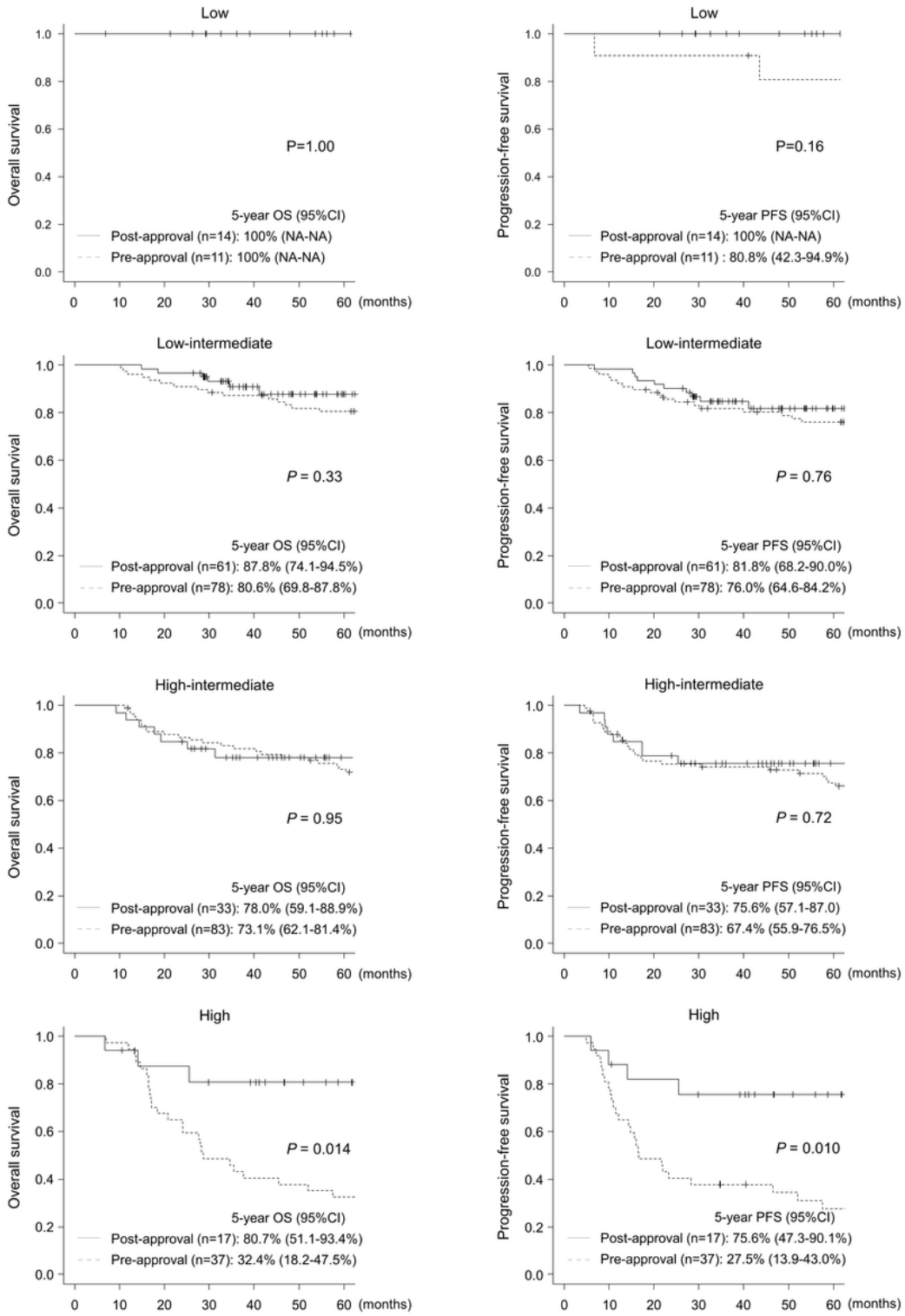

Figure 6

Kaplan-Meier curves of overall survival and progression-free survival stratified by NCCN-IPI.

Supplementary Files

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- SupplementaryFig1.tif
- SupplementaryTable1.docx