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Research paper

Prognostic impact of a suboptimal number of analyzed metaphases in normal karyotype lower-risk MDS

Louise de Swart[a], Alex Smith[b], Detlef Haase[c], Pierre Fenaux[d], Argiris Symeonidis[e], Jaroslav Cermak[f], Guillermo Sanz[g], Reinhard Stauder[h], Moshe Mittelman[i], Eva Hellström-Lindberg[j], Luca Malcovati[k], Saskia Langemeijer[a], Mette Skov-Holm[l], Krzysztof Mądry[m], Ulrich Germing[n], Antonio Medina Almeida[o], Aurelia Tatic[p], Aleksandar Savic[q], Njetočka Gredelj Šimec[r], Corine van Marrewijk[a], Agnes Guerci-Bresler[s], Laurence Sanhes[t], Elisa Luño[u], Dominic Culligan[v], Odile Beyne-Rauzy[w], Sonja Burgstaller[x], Nicole Blijlevens[a], David Bowen[y], Theo de Witte[z,*]

[a] Dep. of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands
[b] Epidemiology and Cancer Statistics Group, Department of Health Sciences, University of York, York, United Kingdom
[c] Dep. of Haematology and Oncology, Georg August University of Göttingen, Göttingen, Germany
[d] Service d'Hématologie, Hôpital Saint-Louis, Assistance Publique des Hôpitaux de Paris (AP-HP) and Université Paris 7, Paris, France
[e] Dep. of Medicine, Div. Hematology, University of Patras Medical School, Patras, Greece
[f] Dep. of Clinical Hematology, Inst. of Hematology & Blood Transfusion, Praha, Czech Republic
[g] Dep. of Haematology, Hospital Universitario y Politécnico La Fe, Valencia, Spain
[h] Dep. of Internal Medicine V (Haematology and Oncology), Innsbruck Medical University, Innsbruck, Austria
[i] Dep. of Medicine A, Tel Aviv Sourasky (Ichilov) Medical Center and Sackler Medical Faculty, Tel Aviv University, Tel Aviv, Israel
[j] Dep. of Medicine, Div. Hematology, Karolinska Institutet, Stockholm, Sweden
[k] Dep. of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy
[l] Dep. of Haematology, Aarhus University Hospital, Aarhus, Denmark
[m] Dep. of Haematology, Oncology and Internal Medicine, Warszawa Medical University, Warszawa, Poland
[n] Dep. of Haematology, Oncology and Clinical Immunology, Universitätsklinik Düsseldorf, Düsseldorf, Germany
[o] Serviço de Hematologia – Instituto Português de Oncologia de Lisboa, Francisco Gentil, Lisbon, Portugal
[p] Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest, Romania
[q] Clinic of Hematology – Clinical Center of Vojvodina, University of Novi Sad, Novi Sad, Serbia
[r] Dep. of Internal Medicine, Division of Hematology, Merkur University Hospital, Zagreb, Croatia
[s] Service d'Hématologie, Centre Hospitalier Universtaire Brabois Vandoeuvre, Nancy, France
[t] Service d'Hématologie, Centre Hospitalier de Perpignan, Perpignan, France
[u] Servicio d'Hematología, Servicio de Salud del Principado de Asturias, Oviedo, Spain
[v] Dep. of Haematology, Aberdeen Royal Infirmary, Aberdeen, United Kingdom
[w] Service d'Hématologie, Centre Hospitalier Universitaire de Purpan, Toulouse, France
[x] Dep. of Internal Medicine IV, Klinikum Wels-Grieskirchen, Wels, Austria
[y] St. James's Institute of Oncology, Leeds Teaching Hospitals, Leeds, United Kingdom
[z] Dep. of Tumor Immunology – Nijmegen Center for Molecular Life Sciences, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

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ABSTRACT

Conventional karyotype is one of the most relevant prognostic factors in MDS. However, about 50% of patients with MDS have a normal karyotype. Usually, 20–25 normal metaphases (nMP) are considered to be optimal to exclude small abnormal clones which might be associated with poor prognosis. This study evaluated the impact of examining a suboptimal number of metaphases in patients recruited to the EUMDS Registry with low and intermediate-1 risk according to IPSS. Only 179/1049 (17%) of patients with a normal karyotype had a suboptimal number of nMP, defined as less than 20 metaphases analyzed. The outcome (overall survival and progression-free survival) of patients with suboptimal nMP was not inferior to those with higher numbers of analyzed MP both in univariate and multivariate analyses. For patients with an abnormal karyotype, 224/649 (35%) had a suboptimal number of MP assessed, but this did not impact on outcome. For patients with a normal karyotype and suboptimal numbers of analyzable metaphases standard evaluation might be acceptable for

* Corresponding author.
E-mail address: Theo.dewitte@radboudumc.nl (T. de Witte).

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general practice, but we recommend additional FISH-analyses or molecular techniques, especially in candidates for intensive interventions.

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal myeloid disorders characterized by peripheral blood cytopenias and increased risk of transformation to acute myelogenous leukemia (AML) [1]. Classical karyotype analyses detect clonal chromosome abnormalities in about 50% of patients with MDS [2]. The karyotype is one of the strongest prognostic parameters in the currently applied prognostic models, including the revised International Prognostic Scoring System (IPSS-R) [3]. In general, the aim is to analyze 20 or more metaphases (MP) before a karyotype is considered to lack specific clonal abnormalities. A lower number of MP analyzed (< 20) is associated with a higher chance of missing small clones [2]. The prognostic relevance of these smaller clones remains to be elucidated in lower-risk MDS [4].

The primary aim of the present study was to assess whether the number of MP examined in patients with normal karyotype provide any additional prognostic information about overall survival (OS) and progression-free survival (PFS) in patients with lower-risk MDS participating in the European MDS Registry Study [5]. The secondary aim was to assess the impact of the number of analyzed metaphases on outcome in patients with an abnormal karyotype. To the best of our knowledge, this is the first prospective study in this field. We hypothesized that a higher number of analyzed nMP does have a positive impact on survival in patients with lower-risk MDS.

2. Design and methods

2.1. Eligibility

Patients were eligible for inclusion if they were newly diagnosed with MDS according to the WHO 2001 classification [6] and had a low or intermediate-1 risk score according to the IPSS [7]. Patients with post-cytotoxic MDS have been excluded from this Registry. The ethics committees of all participating countries and centers have approved the EUMDS registry (trial number NCT00600860). Patient-specific (including bone marrow morphology, histology and cytogenetics), intervention and outcome data were collected at baseline and at each 6-monthly out-patient follow-up visit for the routine clinical care of patients with MDS. All subjects were prospectively followed until death, progression to higher-risk MDS or leukemia, loss to follow-up or withdrawal of informed consent.

2.2. Assignment of IPSS(-R) score

Both the IPSS cytogenetic score and the IPSS-R cytogenetic score were determined from the diagnostic cytogenetic reports at registration. The local investigator assigned the IPSS cytogenetic scores. The IPSS-R cytogenetic scores were retrospectively assigned by one of the investigators of the EUMDS registry and verified by an independent expert of the international IPSS working group (D. Haase). IPSS and IPSS-R scores were calculated and the IPSS-R cytogenetic risk category of patients with only nMP was assigned as good-risk. In these cases no abnormal MP were reported. Patients with abnormal MP were categorized to the IPSS-R cytogenetic risk score: very good, good, intermediate, poor and very poor risk category [8].

2.3. Statistical analysis

Standard descriptive techniques were used to assess the distribution of baseline patient characteristics including chi squared test and Wilcoxon rank sum test. Overall survival (OS) was defined as the time from date of diagnosis to death, or for subjects still alive at the date of the last follow-up visit. Time to disease progression (TDP) was measured from date of diagnosis to date of disease progression to either higher-risk MDS or acute leukemia. Patients without disease progression were censored at date of death or date of last follow-up visit. Standard methods were used to assess time to event, namely Cox proportional hazards regression models and Kaplan–Meier survival curves. Hazard ratios (HR) and 95% confidence intervals (95% CI) are reported for univariate analyses, unadjusted and adjusted for sex and age at diagnosis. All analyses were undertaken in Stata 14 (StataCorp, College Station, TX).

3. Results

In total 2196 patients were registered to the study between 1st April 2008 to 31st March 2017 and patients were followed-up to the 1st June

Table 1
Number of metaphases by age at diagnosis and cytopenias for subjects with a normal karyotype only or an abnormal karyotype.

Metaphase category (n)	N (%)	Median age years (range)	Median (25–75 percentile)		
			Hemoglobin (g/dL)	Platelets (10^9/L)	Absolute Neutrophils Count (10^9/L)
	Normal karyotype				
Total	1225 (100)	73 (18–93)	10.3 (9.2–11.6)	171 (96–263)	2.4 (1.3–3.8)
1–9	42 (3.4)	72 (47–89)	10.3 (9.2–11.6)	179 (88–264)	2.6 (1.2–4.1)
10–19	137 (11.2)	72 (21–90)	9.8 (8.8–11.4)	169 (97–263)	2.4 (1.4–3.7)
20–24	634 (51.8)	74 (21–93)	10.2 (9.1–11.4)	173 (96–270)	2.4 (1.3–3.8)
25–29	164 (13.4)	73 (42–93)	10.6 (9.7–11.7)	160.5 (94–270)	2.2 (1.2–3.6)
30 +	72 (5.9)	74 (57–90)	10.8 (9.8–12.1)	181.5 (99–253)	2.4 (1.4–4.1)
Not recorded	176 (14.4)	74 (18–93)	10.6 (9.4–11.8)	169 (101–257)	2.4 (1.4–3.9)
	Abnormal karyotype				
Total	774 (100)	75 (21–97)	10 (9–11.1)	177.5 (103–283)	2.4 (1.4–3.8)
1–9	44 (5.7)	70 (39–93)	9.8 (8.9–10.9)	162 (67.5–236)	1.8 (1.2–3.3)
10–19	180 (23.3)	75 (21–93)	10 (9–11.1)	197 (114–296)	2.2 (1.4–3.5)
20–24	276 (35.7)	77 (33–93)	9.9 (9–11.1)	168 (103–290)	2.6 (1.5–4)
25–29	104 (13.4)	74 (34–89)	10.2 (9.1–11.4)	181 (106–292)	2.8 (1.5–4.4)
30 +	45 (5.8)	77 (27–91)	10.3 (9–11.2)	189 (98–258)	2.2 (1.4–3.7)
Not recorded	125 (16.1)	73 (46–97)	9.7 (8.5–10.9)	172 (102–275)	2.1 (1.4–3.6)

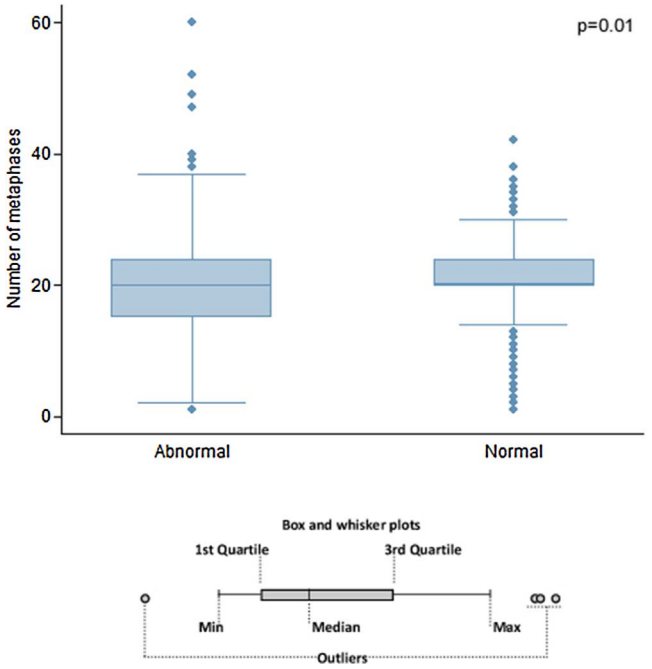

Fig. 1. Distribution of number metaphases by abnormal vs normal karyotype.
The *p*-value (=.01) shows a significant difference in median number of analyzed metaphases in the normal and abnormal karyotype groups. The aim in assigning an abnormal karyotype is not to analyze 20 or more metaphases (MP) compared to a normal karyotype where the aim is to analyze 20 or more metaphases (MP).

2017. The majority of patients had conventional cytogenetics performed (95%) and 1999 had a karyotype recorded. Sixty-one percent had a normal karyotype (1225/1999) at diagnosis and 39% an abnormal karyotype (774/1999). Patients were subdivided into six categories based on the number of reported MP (Table 1). The median number of MP examined was 20 for patients with normal and abnormal karyotypes, however, the distributions were very different as can be seen in Fig. 1 (p = .01). Whilst some patients with an abnormal karyotype had over 40 MP assessed, 35% had less than 20 MP assessed (suboptimal), this is in contrast to those with a normal karyotype where only 17.1% had less than 20 MP assessed (p < 0.0001). Patients with an abnormal karyotype were, on average, older (75 vs 73 years, p = .03), and in terms of cytopenias they lower hemoglobin values than those with a normal karyotype (p < .0001). However, there were no differences in hemoglobin, platelets or neutrophil counts by number of metaphases examined (Table 1).

Table 2 shows the number of normal MP were evenly distributed within the various categories with the exception of the participating countries. The median number of analyzed MP was significantly higher (p < .0001) in the two Scandinavian countries compared to the number of MP in Israel, Italy, Serbia, Croatia and Romania. As expected, there were differences between the normal and abnormal karyotypes groups in terms of WHO diagnosis and IPSS-R score; patients with an abnormal karyotype were more likely to have been transfused at diagnosis compared to those with a normal karyotype.

3.1. Overall survival and progression-free survival

Median follow-up was 2.1 years (range of 0.1–8.7 years) and 33% (669 of 1999) of patients had died during the observation period; median survival for patients with a normal karyotype was 5.2 years (95% Confidence Intervals (95% CI): 3.3–4.5) and abnormal karyotype (4.0 years (95% CI: 4.0 (4.8–5.9) log rank test = 15.63, p = .0001. The univariate overall survival (Fig. 2A and B) and progression-free survival estimates, as depicted in Fig. 3A and B, showed a similar outcome in the six categories throughout the whole observation period.

Table 2
Demographic parameters and impact on median number of metaphases.

Category	Normal karyotype		Abnormal karyotype	
	No. of patients	No. of nMP Median (range)	No. of patients	No. of MP Median (range)
Total	1049 (100)	20 (1–42)	649 (100)	20 (1–60)
Age				
< 60 years	130 (12.4)	20 (4–34)	50 (7.7)	20 (4–47)
60–70	247 (23.5)	20 (2–42)	138 (21.3)	20 (1–52)
70+	672 (64.1)	20 (1–38)	461 (71)	20 (1–60)
WHO-diagnosis				
RA	164 (15.6)	20 (3–42)	101 (15.6)	20 (6–52)
RARS	190 (18.1)	20 (1–34)	78 (12)	20 (9–34)
RCMD	429 (40.9)	20 (2–38)	245 (37.8)	20 (1–60)
RCMD-RS	73 (7)	20 (3–38)	33 (5.1)	21 (7–40)
RAEB-1	143 (13.6)	20 (2–35)	60 (9.2)	20 (1–47)
RAEB-2	6 (0.6)	20 (10–23)	–	–
MDS-U	44 (4.2)	20 (8–34)	29 (4.5)	14 (1–30)
5q-Syndrome	–		103 (15.9)	20 (3–37)
Country				
Austria	65 (6.2)	22 (4–34)	41 (6.3)	20 (1–31)
Croatia	2 (0.2)	20 (20–20)	5 (0.8)	16 (7–21)
Czech Republic	50 (4.8)	22 (2–25)	42 (6.5)	22 (8–40)
Denmark	36 (3.4)	25 (10–26)	20 (3.1)	25 (25–28)
France	291 (27.7)	20 (8–36)	162 (25)	21 (4–49)
Germany	27 (2.6)	22 (2–29)	21 (3.2)	22 (5–34)
Greece	70 (6.7)	20 (2–29)	58 (8.9)	20 (5–52)
Israel	60 (5.7)	10 (3–21)	37 (5.7)	10 (2–28)
Italy	40 (3.8)	17 (1–25)	22 (3.4)	14 (3–25)
Netherlands	45 (4.3)	20 (10–20)	22 (3.4)	10.5 (10–30)
Poland	29 (2.8)	22 (5–27)	26 (4)	21 (18–30)
Portugal	17 (1.6)	20 (20–30)	16 (2.5)	10 (6–29)
Romania	12 (1.1)	15 (8–24)	9 (1.4)	16 (9–22)
Serbia	8 (0.8)	15 (1–15)	8 (1.2)	30 (5–30)
Spain	80 (7.6)	20 (5–42)	37 (5.7)	20 (3–47)
Sweden	54 (5.1)	26 (20–38)	38 (5.9)	25 (20–30)
United Kingdom	163 (15.5)	20 (3–30)	85 (13.1)	10 (1–60)
IPSS-R* Cytogenetics				
Very Good	–	–	156 (24.0)	20 (1–60)
Good	1049 (100)	20 (1–42)	250 (38.5)	20 (1–39)
Intermediate	–	–	206 (31.7)	20 (1–49)
Poor	–	–	21 (3.2)	20 (1–60)
Very Poor	–	–	16 (2.5)	20 (4–28)
IPSS-R* Overall	986 (100)	20 (1–42)	610 (100)	20.0 (1–60)
Very low	309 (31.3)	20 (1–42)	166 (27.2)	20 (2–39)
Low	480 (48.7)	20 (1–38)	245 (40.2)	20 (1–60)
Intermediate	161 (16.3)	20 (2–35)	152 (24.9)	20 (1–40)
High	35 (3.5)	20 (10–32)	42 (6.9)	20 (1–30)
Very high	1 (0.1)	20	5 (0.8)	20 (5–20)
Transfused at registration				
No	761 (72.5)	20 (1–35)	427 (65.8)	20 (1–60)
Yes	288 (27.5)	20 (1–42)	222 (34.2)	20 (1–39)
Transfused > 1 unit/month				
No	886 (84.5)	20 (1–42)	504 (77.7)	20.0 (1–60)
Yes	163 (15.5)	20 (2–38)	145 (22.3)	20.0 (1–39)

*IPSS-R: Revised International Prognostic Scoring System.

Multivariate analyses were performed to adjust for the various relevant prognostic components: age at diagnosis, MDS WHO category, blast count, hemoglobin levels, platelets and neutrophil count, RBCT-dependency (> 1 unit/month for 6 months) and country. IPSS-R cytogenetic risk category was also included in the model in patients with an abnormal karyotype. The largest category of MP (20–24 MP) was used as the reference category. The number of MP, analyzed both as a continuous variable or as a categorical variable did not significantly influence survival nor progression-free survival. The group with MP not recorded in the database were included in all analyses (Table 3 and Figs. 2 and 3).

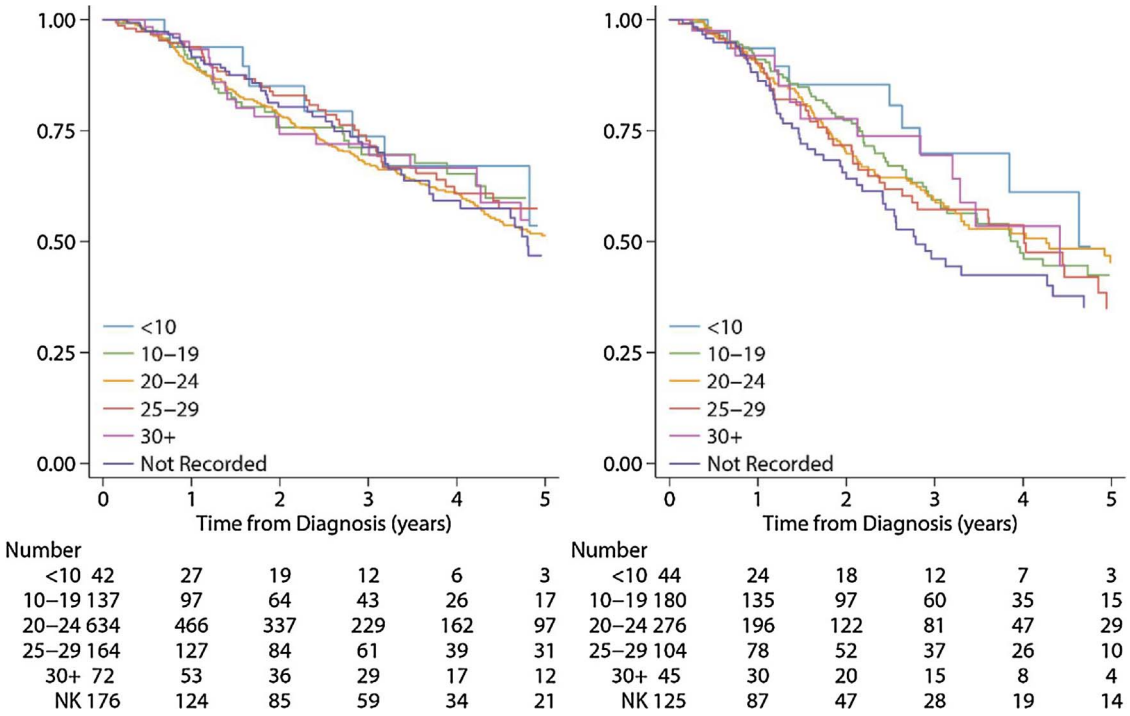

Fig. 2. Overall Survival.
Overall survival from date of diagnosis by the six analyzed categories based on the number of reported metaphases; normal karyotype 2A, and abnormal karyotype 2B. The columns under the figures represent the number of patients in each of the categories at that specific time point.

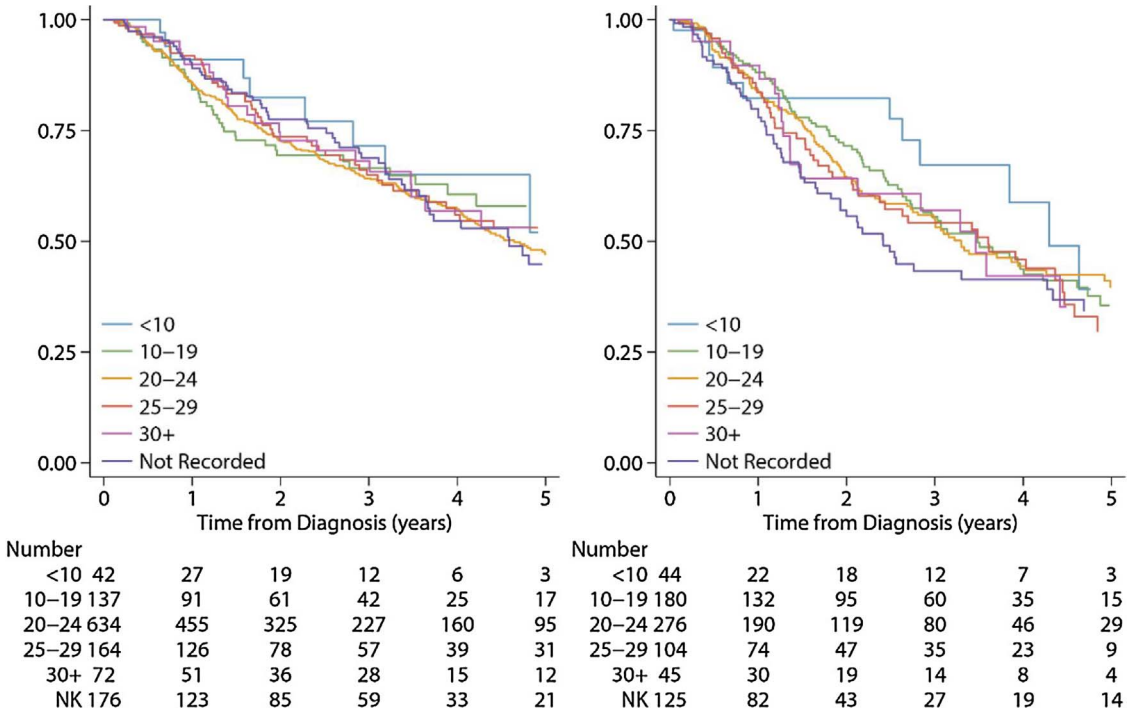

Fig. 3. Progression-free survival.
Progression-free survival from date of diagnosis by the six analyzed categories based on the number of reported metaphases; normal karyotype 2A, and abnormal karyotype 2B. The columns under the figures represent the number of patients in each of the categories at that specific time point.

4. Discussion

The analyses of this study were focused on the impact of analyzable metaphases in patients with a normal karyotype on outcome, including estimated overall survival and progression-free survival. Our recently published study on the first 1000 patients within the EUMDS registry confirmed established prognostic factors, such as age, gender and World Health Organization 2001 classification [5] in addition, with low health-related quality of life (EQ-5D visual analogue scale score) and a high co-morbidity index predicted poor outcome. The IPSS-R was superior to the original IPSS for predicting both disease progression and survival [5]. We identified 1225 patients with normal conventional

Table 3
Multivariate analyses on impact of number of normal and combined normal/abnormal metaphases on survival and progression-free survival.

Metaphase category (n)	Normal karyotype				
		Survival		Progression-free survival	
		HR (95% CI)	Adjusted HR (95% CI)[a]	HR (95% CI)	Adjusted HR (95% CI)[a]
Continuous	1225	1.00 (0.98–1.02)	1.00 (0.98–1.03)	1.00 (0.98–1.02)	1.01 (0.98–1.03)
1–9	42	0.83 (0.42–1.61)	1.06 (0.54–2.07)	0.77 (0.41–1.45)	0.98 (0.52–1.85)
10–19	137	0.85 (0.60–1.22)	0.94 (0.65–1.36)	0.88 (0.63–1.23)	0.96 (0.69–1.36)
20–24	634	1 (ref)	1 (ref)	1 (ref)	1 (ref)
25–29	164	0.90 (0.66–1.23)	1.02 (0.74–1.39)	0.93 (0.70–1.24)	1.04 (0.78–1.39)
30 +	72	0.87 (0.56–1.36)	1.05 (0.66–1.66)	0.84 (0.55–1.29)	1.00 (0.64–1.56)
Not Recorded	176	1.00 (0.74–1.35)	1.28 (0.94–1.75)	0.97 (0.73–1.29)	1.21 (0.91–1.62)
	Abnormal karyotype				
		HR (95% CI)	Adjusted HR (95% CI)[b]	HR (95% CI)	Adjusted HR (95% CI)[b]
Continuous	774	1.00 (0.98–1.02)	0.99 (0.98–1.01)	1.00 (0.98–1.02)	1.01 (0.98–1.03)
1–9	44	0.83 (0.53–1.33)	0.79 (0.41–1.53)	0.83 (0.47–1.47)	0.85 (0.47–1.51)
10–19	180	1.01 (0.81–1.26)	1.07 (0.77–1.47)	0.99 (0.74–1.31)	1.04 (0.78–1.39)
20–24	276	1 (ref)	1 (ref)	1 (ref)	1 (ref)
25–29	104	1.03 (0.82–1.29)	1.21 (0.84–1.72)	1.09 (0.79–1.52)	1.15 (0.82–1.60)
30 +	45	0.91 (0.64–1.29)	0.82 (0.47–1.45)	1.06 (0.65–1.73)	0.93 (0.57–1.51)
Not Recorded	125	1.13 (0.93–1.37)	1.27 (0.90–1.79)	1.31 (0.96–1.79)	1.20 (0.87–1.65)

[a] Age, transfused, WHO diagnosis, platelets counts, neutrophil counts, hemoglobin levels, country.
[b] Age, transfused, WHO diagnosis, platelets counts, neutrophil counts, hemoglobin levels, country, karyotype risk category.

karyotype in the EUMDS Registry, representing 61% of this lower-risk MDS patient population. The great majority of patients with normal karyotype had 20 or more MP analyzed, while 14% of the patients were registered with a normal karyotype, based on less than 20 analyzed MP. Estimated overall survival as well as the estimated progression-free survival of the patients with a normal karyotype and a suboptimal number of analyzed MP (< 20) was not inferior when compared with 20 or more analyzed MP. In our study, we found a complete absence of a trend towards an impaired prognostic risk when comparing the varying cohorts. This is not surprising, since the chance of missing a small abnormal clone increases by 25% if only 5 normal MP have been analyzed and between 10 and 15% in patients with 10–15 nMP analyzed [2]. This means that the majority of patients with a suboptimal number of analyzed MP (< 20) are expected to have a conventionally normal karyotype associated with a low risk MDS. In contrast, the size of abnormal clones may play a role in the prognosis [9]. In the study by Mallo et al. the outcome of patients with abnormal clones < 100%, assessed by FISH, was better when compared to patients with 100% abnormal clones [9]. Unfortunately, the impact of smaller clone sizes was not assessed in that study, similar to a large important study, performed by Schanz, et al. [10]. A study of 101 MDS patients with normal karyotype revealed small clones (ranging 15% to 32%) using FISH techniques in 18 patients [4]. FISH abnormalities were predictive for worse prognosis, but the majority of these 18 patients had higher-risk MDS and all three patients with refractory anemia were surviving at time of evaluation. It is also possible to apply FISH on circulating CD34-positive cells, in order to avoid another BM aspiration to obtain sufficient material for standard banding techniques [11].

Additionally, we analyzed the patients with abnormal karyotypes. As expected the number of analyzed metaphases is lower in this group of patients because the definition of clonality in patients with abnormal karyotype requires a lower number of analyzed metaphases. Also in this group of patients the number of analyzed metaphases does not influence the outcome after adjustment for relevant variables.

Currently, it is possible to detect MDS-specific mutations in more than 90% of patients with MDS [12]. These mutations will allow a better prognostication of all MDS cases with normal karyotype. Therefore, molecular testing should be seriously considered in all fit patients with MDS who are candidates for allogeneic stem cell transplantation or patients in investigational studies, in absence of poor-risk cytogenetic characteristics, as is the case in all patients with MDS, characterized by normal karyotype [13].

In summary: patients with lower-risk MDS with a normal karyotype and suboptimal numbers of analyzable metaphases (< 20) have a similar outcome when compared to patients with optimal numbers of analyzed metaphases (≥ 20). However, it should be a general aim to reach at least a complete analysis of 20 metaphases to be able to exclude clonal cytogenetic abnormalities, especially in patients who are eligible for intensive interventions. If this is not possible, we recommend to use complementary FISH-analyses covering the most frequent cytogenetic changes such as del(5q), monosomy 7/del(7q), trisomy 8, del(17p)/loss of TP53-alleles and del(20q), or additional or molecular techniques [13].

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