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Title: Therapy related myeloid neoplasm, same but different?

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Title: Therapy related myeloid neoplasm, same but different?**Abstract**

Therapy-related myeloid neoplasms (t-MNs) include therapy-related acute myeloid leukemia (t-AML) and therapy-related myelodysplastic syndromes (t-MDS), arising from exposure to cytotoxic chemotherapy and/or radiation therapy used to treat prior malignancies.

We conducted a retrospective study in a large cohort of patients at Gustave Roussy Institute, over the period extending from January 1st, 1995 to June 30th, 2018. We used the 2010 ELN prognostic classifications for AML and or IPSS for MDS.

404 patients with t-MN were referred to our institution, including 204 cases of t-AML and 200 cases of t-MDS. Based on the ELN 2010 classification 43%, 22% and 20% of t-AML were classified as adverse, intermediate (I/II) and favorable, respectively. Based on the IPSS classification 72% of t-MDS were considered as intermediate-2/high and 28% as Low/Intermediate-1 risk.

The median overall survival (OS) was 11.9 months for both t-AML and t-MDS (95% CI: 8.5-14.2 for t-AML and 9.3 -14.1 for t-MDS), but long-term survival was mainly demonstrated in t-AML patients (5 years OS 24.6% [19-31.3] in t-AML vs 10.6% [6.8-16.3] in t-MDS). In multivariate analysis for t-AML, intensive therapy (HR [95%CI]: 0.26 [0.15-0.46]), adverse ELN 2010 risk (1.57 [1.03-2.39]), cancer disease status (2.65 [1.53-4.57]) and performance status >1 (2.69 [1.72-4.14]) were a powerful markers of OS. For t-MDS only intermediate 2/high IPSS score (3.11 [2.06-4.79]) and performance Status >1 (3.13 [2.05-4.71]) remained independent markers of OS.

Despite some benefit from intensive therapies in selected t-MN cases, survival remains limited, particularly when adverse disease features or active malignancies are present.

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Introduction

Therapy-related myeloid neoplasms (t-MNs) represent a serious complication arising from exposure to cytotoxic chemotherapy and/or radiation therapy used to treat prior malignancies [1,2]. These secondary neoplasms, which include therapy-related acute myeloid leukemia (t-AML) and therapy-related myelodysplastic syndromes (t-MDS), are typically associated with poor clinical outcomes. T-MNs management present significant challenges regarding both treatment effectiveness and patient survival with markedly inferior overall survival (OS) compared to *de novo* counterparts [3,4]. The latest WHO classification did not consider t-MN as a distinct entity but rather as a diagnostic qualifier (myeloid neoplasm following cytotoxic therapy) despite some specificities [5]. **In contrast, the 2022 International Consensus Classification (ICC) does recognize therapy-related neoplasms as separate, well-defined entities, reflecting their unique clinical, biological, and prognostic features [6].**

One of the major obstacles to improving care for t-MN patients is the limited understanding of prognostic factors specific to this group. While molecular and cytogenetic markers have been extensively studied in *de novo* AML and MDS, the identification and validation of prognostic markers for t-MNs remain difficult. This challenge is compounded by the fact that patients with t-MNs are frequently excluded from clinical trials, resulting in a lack of robust, prospective data to inform risk stratification and therapeutic decision-making.

In this study, we present a large single-center cohort of t-MN patients and aim to identify prognostic factors linked to OS and treatment response, in order to determine whether the poor outcomes observed were related to the patients' clinical history and prior cancer or to the biological characteristics of the t-MN disease itself.

Patients and methods

In light of these challenges, we conducted a retrospective study in a large cohort of patients at Gustave Roussy Institute, over the period extending from January 1st, 1995 to June 30th, 2018 (data protection approval, CNIL GR-2018-01). We did not include prior autoimmune diseases (AID) as the recent WHO classification have excluded methotrexate (largely used in AID) as a qualifying criterion for myeloid neoplasm post cytotoxic therapy [5].

We collected clinical and biological data including age, sex, performance status, latency period since prior cancer diagnosis, preceding therapy lines, prior cancer state at t-MN diagnosis. T-MN treatment modalities were classified as best supportive care, low-dose treatment (low-dose cytarabine or hypomethylating agents), intensive treatment (including induction chemotherapy and allogeneic hematopoietic stem cell transplantation [HSCT], **regardless of the induction therapy preceding transplant**). We used the 2010 European LeukemiaNet (ELN) prognostic classifications for AML and or International Prognostic Scoring System (IPSS) for MDS, based on cytogenetics and molecular analyses when available (NPM1 and FLT3-ITD mutations were screened by PCR and fragment analysis, for all AML patients starting from April 2008). Acute promyelocytic leukemia (i.e., AML with t(15;17)) was included within the favorable category.

Statistical analysis

Database cutoff for survival analysis was on October first, 2024. Statistical analyses were performed with R software version 3.6.1. The comparison of percentages was carried out using a Pearson's Chi-square test or a Fisher's exact test. The distributions of a quantitative variable according to the modalities of a qualitative variable were compared according to the Mann-Whitney test. OS was calculated from the date of TRMN diagnosis to the date of death from any cause or censored at the last follow-up. The distributions of survival data were estimated using the Kaplan-Meier method, compared using the log-rank test and hazard ratios (HRs) with 95% confidence intervals (95% CIs). To identify

variables associated with OS, a Cox proportional hazards regression analysis of candidate prognostic factors was performed. All the tests were two-sided and considered to be significant when $P < 0.05$.

Results

Patient characteristics

404 patients with t-MN were referred to our institution, including 204 cases of t-AML and 200 cases of t-MDS, their clinical and biological characteristics are summarized in Table 1. The median age at t-MN onset was 62 years old (IQR: 51-70), significantly younger for t-AML (59 years, 46-69) than for t-MDS patients (64 years, 55-72) ($p < 0.001$). The percentage of women in our cohort is relatively high especially in t-AML (66% vs 56% in t-MDS, $p = 0.036$). Latency period between t-MN and cancer diagnosis was 5 years (3-10) with a trend for a longer latency period in t-MDS ($p = 0.070$). The most common primary cancers were breast cancer (26%), non-Hodgkin lymphoma (17%) and gynecological cancer (10%). Previous cancer treatments included combined chemo-radiotherapy accounting for 51% of cases ($n=205$), chemotherapy alone in 35% of cases ($n = 140$), and radiotherapy alone in 15% of cases ($n=59$). Forty-eight percent ($n=194$) of the patients received more than one treatment line for their primary cancer, with a significant difference between t-AML and t-MDS (42% vs 54% $p=0.017$). Thirty-three percent ($n=132$) of the patients presented an active cancer at the time of t-MN diagnosis, 38% in the t-MDS group compared to 27% in the t-AML group ($p=0.076$). An ECOG Performance Status of 0–1 was observed in 76% ($n=156$) of patients with t-AML and 80% ($n=159$) of those with t-MDS, yielding an overall proportion of 78% ($n=315$) across both cohorts ($p = 0.463$).

Based on the ELN 2010 classification 43%, 22% and 20% of t-AML were classified as adverse, intermediate (I/II) and favorable, respectively. The 23 cases (14%) of acute promyelocytic leukemia were combined with the favorable t-AML patients for latter survival analysis. Similarly, based on the IPSS classification 72% of t-MDS were considered as intermediate-2/high and 28% as Low/Intermediate-1 risk.

Survival analysis

Treatment approaches included intensive chemotherapy (43%, $n = 175$), low-dose therapy (24%, $n = 97$), and best supportive care (31%, $n = 126$). As expected, intensive treatment was restricted to t-AML compared to t-MDS (64% vs 22%, $p<0.001$) (Table 1). **Three of the APL patients received all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) combination, considered as intensive treatment in these specific cases.**

Only 12% ($n=48$) of the entire cohort underwent hematopoietic stem cell transplantation (HSCT), among which 63% had t-AML and 37% t-MDS, with a median latency of 4.2 years between initial cancer and t-MN onset. The most common primary cancers among these patients were breast (40%), and non-Hodgkin lymphoma (15%). Most patients had received radiotherapy (52%) or combined chemo-radiotherapy (35%) as initial treatment, with 71% having had only one prior treatment line. The median age at HSCT was 53 years, and the majority were female (83%) with good performance status (ECOG 0–1 in 92%). Ninety-four percent of the patients were in complete remission of their primary cancer, the remaining 6% ($n=3$) had a hematologic malignancy as their primary cancer (multiple myeloma, $n=2$, and Hodgkin's lymphoma, $n=1$). Among the t-AML patients ($n=27$), 37% had favorable ($n=10$), 26% intermediate ($n=7$), 37% adverse risk ($n=10$) according to the ELN 2010 classification. As expected, no patients with APL were transplanted. Among the favorable t-AML, 4 out of 10 underwent HSCT after achieving a second complete remission (CR2) after relapse. In t-MDS cohort, 78% had an intermediate-2/high- risk IPSS score (Table 2).

The median overall survival (OS) was 11.9 months for both t-AML and t-MDS (95% CI: 8.5-14.2 for t-AML and 9.3 -14.1 for t-MDS), but long-term survival was mainly demonstrated in t-AML patients

1 (5 years OS 24.6% [19-31.3] in t-AML vs 10.6% [6.8-16.3] in t-MDS) (Fig 1.A). Among transplanted
2 patients, the OS was more promising, with a median of 95.9 (24.5-NR) months and a 5-year OS of
3 51.4% (37.6-65) (Fig 1.F).

4 Although the ELN 2010 classification was a powerful score to distinguish between favorable AML
5 patients and other subgroups (with a median OS not reached and 5-years OS of 57.9% [44.6-70]), the
6 median OS was similar for intermediate (I/II) and adverse risk groups (9.7 months [IQR, 4.6-17.6] and
7 8.7 months [IQR: 5.1-12.2], respectively $p < 0.0001$) (Fig 1.B). Interestingly, cancer disease status
8 influenced OS of t-AML patients with a median OS of 15.9 months [95% CI: 12.5–23.9] for t-AML
9 patients in complete response (CR) of their previous cancer vs 3.6 months [95% CI: 2.1–5.1] for those
10 with active cancer ($p < 0.0001$). The difference was particularly significant in the subgroup of ELN
11 favorable category with a median OS of 6.4 months [95% CI: 2.5-54] for patients with active cancer
12 compared to a median OS not yet reached (Fig 1.C).

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15 Furthermore, in multivariate analysis (Table 3), intensive therapy (HR [95%CI]: 0.26 [0.15-0.46]),
16 adverse ELN 2010 risk (1.57 [1.03-2.39]) and performance status >1 (2.69 [1.72-4.14]) were maintained
17 as powerful markers of OS just like cancer disease status remained an independent risk factor of survival
18 (2.65 [1.53-4.57]). However, correlation test showed interaction between performance status and cancer
19 disease state with 81% of patients in CR having an ECOG 0-1 vs 64% of patients with active cancer
20 state having an ECOG > 1 ($p = 0.01$).

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23 Moving the focus to the t-MDS population, the poor OS of t-MDS was not only explained by the
24 proportion of the IPSS intermediate-2/high population having a poor OS (with a median OS of 9.2
25 months [95% CI: 7.2-11.9]), who represented more than 2/3 of the t-MDS population. Indeed, the OS
26 of the intermediate-1/low risk patients was relatively low, with a median OS 27.7 months [95% CI: 5.7-
27 42.7]) ($p < 0.0001$) (Fig 1.D) [6]. As described for t-AML, the cancer disease state influenced the survival
28 in t-MDS patients, with a median OS of 14.3 months in patients in CR of their cancer [95% CI: 11.6-
29 17.9] dropping to 6.4 months in patients with active cancer [95% CI: 4.9-11.1] ($p < 0.0001$). This impact
30 was also best described in the intermediate-1/low risk group where the median OS dropped from 42.7
31 months [95% CI: 24.3-108.9] in patients in CR of their cancer to 19.7 [95% CI: 3.6-26.9] in patients in
32 active disease. The median OS of high/intermediate-2 patients also dropped from 11.6 months [95%
33 CI: 8.9-14.3] to 6.3 months [95% CI: 4.7- 9.2] according to the cancer status ($p < 0.0001$) (Fig 1.E).

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36 Interestingly, in the multivariate analysis (Table 4), cancer disease state did not stand out as an
37 independent risk factor for OS in t-MDS patients (HR [95% CI]: 1.27 [0.86-1.89], $p = 0.2276$). Only
38 intermediate 2/high IPSS score (3.11 [2.06-4.79]) and performance Status >1 (3.13 [2.05-4.71])
39 remained independent markers of OS (Table 3).

40 41 42 43 44 Discussion

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46 Improvements in the life expectancy of cancer survivors, driven by novel therapies and optimized
47 cancer management protocols, are expected to increase the incidence of t-MNs, including among
48 patients with active malignancies (notably, one-third of our patients were not in complete remission of
49 their primary cancer at the time of t-MN diagnosis). While these innovative treatments contribute to
50 better cancer survival, they may also lead to the emergence of therapy-related hematologic
51 malignancies; for instance, PARP inhibitors (PARPi) have been associated with the development of
52 poor-prognosis t-MNs [8,9]. The status of the primary cancer plays a crucial role in influencing long-
53 term outcomes, particularly in t-AML. However, in cases of t-MNs with unfavorable prognosis,
54 prognostic classification of the myeloid neoplasm often carries greater weight for survival outcomes
55 than the status of the primary cancer.

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58 In fact, long-term survival was mainly observed in one particular category: t-AML patients with
59 favorable ELN classification who were also in complete remission (CR) of their primary cancer. This
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1 could be explained not just by their CR status, but also by the favorable prognosis of their AML and
2 their good performance status, which not only directly influences survival but also allows for intensive
3 therapy that increases the chances of long-term remission. Indeed, there is a tight relation between
4 performance status and cancer state, both of which critically shape therapeutic eligibility and outcomes.
5 **In select cases, these factors may enable patients with less favorable disease to become eligible for**
6 **HSCT, a curative option associated with prolonged survival but feasible only in a minority—typically**
7 **younger patients in remission and sufficiently distant from their initial malignancy [10].**

8
9 Moreover, in patients with t-MDS and good performance status, it was previously reported that the
10 presence of an active neoplastic disorder did not negatively affect overall survival (OS) when patients
11 were treated with 5-azacytidine (AZA), with most deaths primarily attributed to the progression of the
12 myeloid disorder [11]. The addition of Venetoclax (VEN) to AZA may also benefit unfit t-AML
13 patients, excluding those harboring *TP53* mutations, although dose reductions are often necessary to
14 manage the increased toxicity associated with VEN plus AZA [12]. In contrast, t-AMLs with favorable-
15 risk features, such as Core-Binding Factor (CBF) AML, may be curable with intensive chemotherapy
16 alone, without requiring HSCT. In this subgroup, the status of the primary cancer becomes a key factor
17 influencing treatment decisions: intensive therapy must be weighed against the expected OS related to
18 the initial malignancy. In some cases, it might even favor opting for less intensive approaches such as
19 VEN plus AZA, despite the limited data supporting its efficacy in CBF-AML, since these patients were
20 excluded from the VIALE-A study. Adding to that, unlike intensive chemotherapy, VEN plus AZA
21 requires continuous administration until relapse, potentially complicating long-term treatment strategies
22 [13]. Finally, comorbidities resulting from prior cancer or its treatment may further contribute to under-
23 treatment, highlighting the urgent need for management guidelines tailored specifically to this complex
24 patient population.
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28 One of the limitations of our study is that given the defined period of the collected data, the prognostic
29 classifications used were those of the ELN 2010 and IPSS, which lack large molecular panels included
30 in the most recent prognostic classifications (ELN 2022 and IPSS-M). In fact, with the next-generation
31 sequencing (NGS) molecular panels some myeloid neoplasms acquire different classifications
32 (becoming for instance of poorer prognosis, which could explain in part the poor OS of the different t-
33 MDS classes).
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36 Our patients did not benefit from the use of NGS panels at diagnosis, which are now mandatory for the
37 classification of t-AML according to the 2022 ELN recommendations. Moreover, given certain genetic
38 specificities, such as a higher incidence of *TP53* and *PPM1D* mutations, pertaining to t-MN, the
39 development of a dedicated classification encompassing both t-AML and t-MDS could be of particular
40 interest. Lindsley *et al.* proposed an ontogeny-based classification delineating three distinct subgroups,
41 including a *TP53*-mutated group associated with inferior clinical outcomes, which may be highly
42 relevant in the t-AML setting and potentially translatable to t-MDS [14,15].
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45 These distinct features have also been highlighted through the use of whole genome sequencing (WGS)
46 in t-MN. WGS enables comprehensive genomic analysis, revealing specific mutational footprints based
47 on single-base substitution signatures that reflect the underlying molecular mechanisms of t-MN
48 pathogenesis [16]. Chemotherapy-related mutational signatures, such as those associated with
49 melphalan or platinum exposure, have been characterized in t-MN. By using these signatures as
50 temporal barcodes, it has been suggested that chemotherapy may not only promote the clonal selection
51 of pre-existing mutated clones but also increase genomic complexity and actively drive the development
52 of t-MN [17].
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55 These findings underscore the notion that t-MN may differ from *de novo* MN, even when the driver
56 mutations are identical, a concept that paves the way to a potential therapeutic window before the onset
57 of t-MN. Indeed, incidental detection of clonal hematopoiesis via cell-free DNA testing, germline
58 testing or evaluation of cytopenia following cancer therapy is increasingly reported [18]. **Further**
59 **supporting this approach, recent studies demonstrated that the presence of clonal hematopoiesis in was**
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1 associated with a significantly increased risk of subsequent t-MN, particularly in cases involving high-
2 risk mutations such as *TP53* and *PPM1D* [19]. In the coming years, the development of a robust risk
3 prediction score could allow for more precise assessment of myeloid transformation risk, thereby
4 enabling the establishment of preventive strategies and potentially transforming the clinical course for
5 these patients.

6 **Conclusion**

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9 Therapy-related myeloid neoplasms constitute a growing clinical concern due to their poor prognosis
10 and increasing incidence among cancer survivors. Our study emphasizes the prognostic relevance of
11 established risk classifications, prior cancer status, and performance status at diagnosis. Despite some
12 benefit from intensive therapies in selected cases, survival remains limited, particularly when adverse
13 disease features or active malignancies are present.
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16 The distinct genetic landscape of t-MN, including frequent *TP53* and *PPM1D* mutations and
17 chemotherapy-related mutational signatures, highlights the need for specific diagnostic and prognostic
18 frameworks [20,21]. Advances in genomic profiling and the development of risk prediction models may
19 enable earlier detection and preventive strategies, ultimately improving the management and outcomes
20 of this challenging patient population.
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Conflict of interest:

The authors declare that they have no conflict of interest.

Tables and Figures

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Table 1. Patient's characteristics according to t-MN disease

	AML N = 204	MDS N = 200	Total N = 404	p-value[†]
First Cancer, n (%)				0.0010
Breast Cancer	70 (34)	37 (18.5)	107 (26)	
Gynecological Cancer	12 (6)	29 (14.5)	41 (10)	
Hodgkin's lymphoma	4 (2.0)	7 (3.5)	11 (3)	
Non-Hodgkin lymphoma	28 (14)	41 (20.5)	69 (17)	
Prostate Cancer	8 (4)	8 (4.0)	16 (4.0)	
Others	82 (40)	78 (39)	160 (40)	
First Cancer Treatment, n (%)				0,953
Chemotherapy	72 (35)	68 (34)	140 (35)	
Radiotherapy	29 (14)	30 (15)	59 (15)	
chemo-radiotherapy	103 (50)	102 (51)	205 (51)	
Number of preceding treatment lines				0,017
1 line	118 (58)	92 (46)	210 (52)	
> 1 line	86 (42)	108 (54)	194 (48)	
Median time between cancer and t-MN				0,070
Mean (SD), years	7 (7)	8 (8)	8 (8)	
Median (IQR), years	5 (2, 9)	6 (3, 11)	5 (3, 10)	
Age at TRMN				<0.001
Median age, years (IQR)	59 (46, 69)	64 (55,72)	62 (51, 70)	
Sex				0,036
Male, n (%)	69 (34)	88 (44)	157 (39)	
Female, n (%)	135 (66)	112 (56)	247 (61)	
Performance Status (ECOG)				0,463
PS 0-1, n (%)	156 (76)	159 (80)	315 (78)	
PS 2-3, n (%)	48 (24)	41 (21)	89 (22)	
Cancer status				0,076
Active Cancer, n (%)	56 (27)	76 (38)	132 (33)	
Cancer in remission, n (%)	148 (73)	124 (62)	272 (67)	
ELN 2010 AML Classification				
Favorable, n (%)	33 (20)	NA	NA	
Intermediate, n (%)	36 (22)	NA	NA	
Adverse, n (%)	70 (43)	NA	NA	
APL, n (%)	23 (14)	NA	NA	
MDS IPSS score				
Low/Intermediate-1, n (%)	NA	48 (24)	NA	
Intermediate-2/High, n (%)	NA	124 (62)	NA	
t-MN Treatment				<0.001
Best supportive care	38 (19)	88 (44)	126 (31)	
Intensive, n (%)	131 (64)	44 (22)	175 (43)	
Low dose, n (%)	32 (16)	65 (33)	97 (24)	

HSCT			0,091
n (%)	30 (15)	18 (9)	48 (12)

[†] Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test

Table 2. HSCT patients' characteristics

	(HSCT n = 48)
First Cancer, n (%)	
Breast Cancer	19 (40)
Gynecological Cancer	4 (8)
Hodgkin's lymphoma	3 (6)
Non-Hodgkin lymphoma	7 (15)
Prostate Cancer	1 (2)
Others	14 (29)
First Cancer Treatment, n (%)	
Chemotherapy	6 (13)
Radiotherapy	25 (52)
chemo-radiotherapy	17 (35)
Number of preceding treatment lines	
1 line	34 (71)
> 1 line	14 (29)
t-MN	
t-AML, n (%)	30 (63)
t-MDS, n (%)	18 (37)
Median time between cancer and t-MN	
Median (IQR), years	4,2 (2-8,2)
Age at TRMN	
Median age, years (IQR)	53 (39-58)
Sex	
Male, n (%)	8 (17)
Female, n (%)	40 (83)
Performance Status (ECOG)	
PS 0-1, n (%)	44 (92)
PS 2-3, n (%)	4 (8)
Cancer status	
Active Cancer, n (%)	3 (6)
Cancer in remission, n (%)	45 (94)
ELN 2010 AML Classification	n=27
Favorable, n (%)	10 (37)
Intermediate, n (%)	7 (26)
Adverse, n (%)	10 (37)
APL, n (%)	0
MDS IPSS score	
Low/Intermediate-1, n (%)	4 (22)

Intermediate-2/High, n (%)

14 (78)

Survival

Median OS (months, 95% CI)

95.9 (24.5-NR)

5-year OS, % (95% CI)

51,4 (37.6-65)

HSCT: hematopoietic stem cell transplantation, NR= Not Reach

Fig 1. Overall survival curves

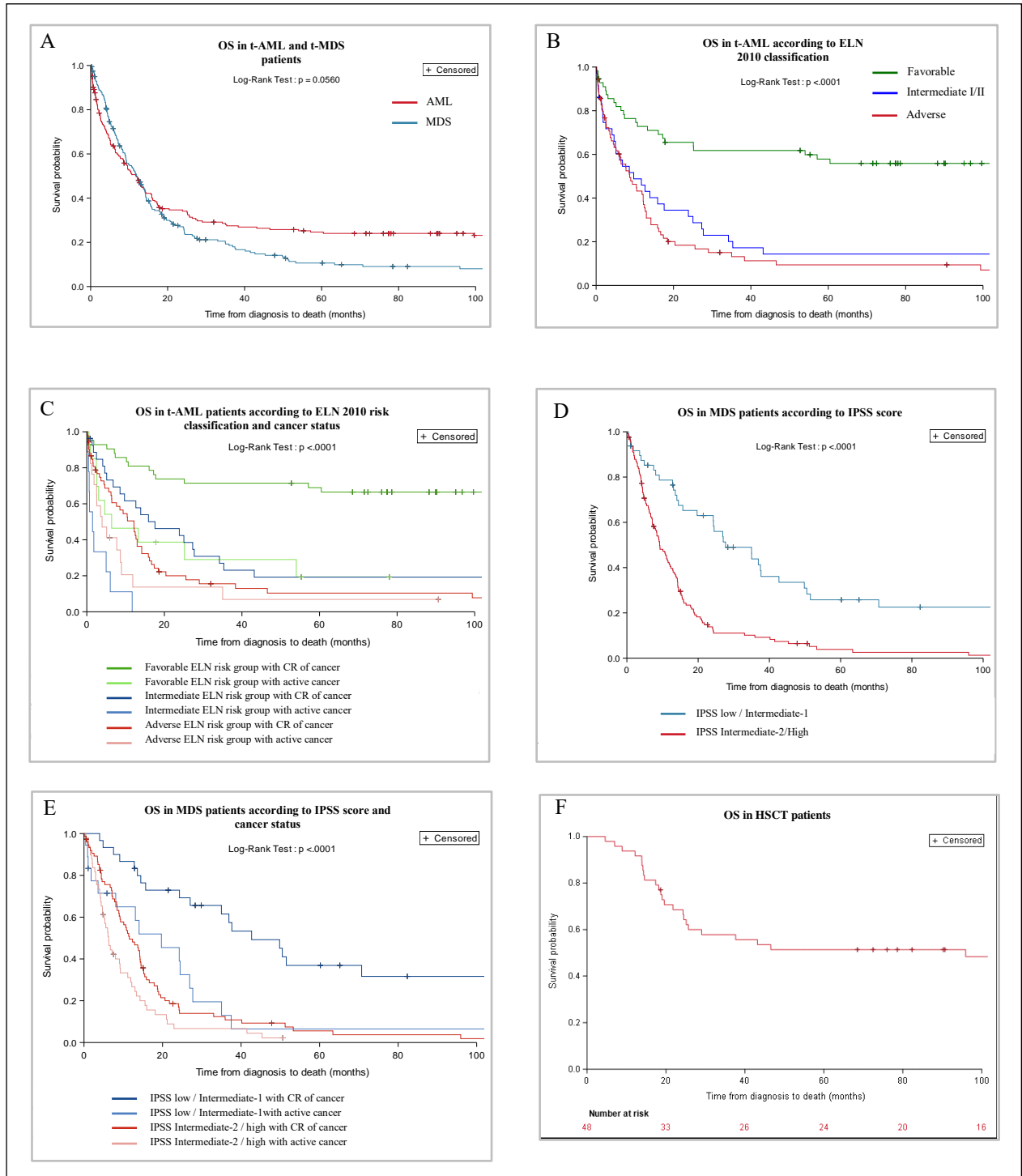


Fig 1. Overall survival based on variables:

A. Overall survival (OS) in t-AML and t-MDS: Kaplan-Meier survival curves highlighting significant survival differences among t-AML (red line) and t-MDS (blue line).

B. Overall survival (OS) in t-AML according to the 2010-ELN risk stratification: Kaplan-Meier survival curves highlighting significant survival differences among 2010 ELN risk groups, adverse (red line), intermediate (blue line) and favorable (including acute promyelocytic leukemia, green line).

C. Overall survival (OS) in t-AML according to the 2010-ELN risk stratification and the prior cancer status: Kaplan-Meier survival curves highlighting significant survival differences among 2010 ELN risk groups risk groups and prior cancer status. Adverse in CR of their previous cancer (red line) or not (light red line), intermediate in CR of their previous cancer (blue line) or not (light blue line) and favorable in CR of their previous cancer (including acute promyelocytic leukemia, green line) or not (light green line).

D. Overall survival (OS) in t-MDS according to the IPSS score: Kaplan-Meier survival curves highlighting survival differences among risk groups, with the IPSS intermediate-2/high showing the poorest outcomes (red line). However, a poor OS overrules both IPSS subgroups.

E. Overall survival (OS) in t-MDS according to the IPSS score and the prior cancer status: Kaplan-Meier survival curves highlighting significant survival differences among IPSS risk groups and prior cancer status. Intermediate-2/high in CR of their previous cancer (red line) or not (light red line); Low/Intermediate-1 risk in CR of their previous cancer (blue line) or not (light blue line).

F. Overall survival (OS) in t-MNs after HSCT: Kaplan-Meier survival curves highlighting representing the OS of patients with t-MNs who required HSCT as part of their treatment.

Table 3. Univariate and multivariate analysis for overall survival in AML (N=204)

	Univariate analysis		Multivariate analysis	
	Crude HR (95%CI)	p	Adjusted HR (95% CI)	p
Age > 60 years old	1.6 [1.16;2.21]	0,0043	1.03 [0.65;1.61]	0,9093
Latency period < 5 years	1.33 [0.96;1.83]	0,0847	1.20 [0.79;1.82]	0,5932
Sex (male)	0.54 [0.39;0.75]	0,0004	0.57 [0.38;0.86]	0,013
> 1 preceding therapy lines, mean (sd)	1.7 [1.23;2.35]	0,0015	0.95 [0.59;1.49]	0,9859
Performance Status (>1)	2.5 [1.72;3.56]	<0.0001	2.37 [1.46;3.78]	0,0006
Cancer disease (stable or active)	3.01 [2.01;4.41]	<0.0001	2.36 [1.27;4.36]	0,0109
ELN 2010 (Adverse)	4.51 [2.53;8.67]	<0.0001	3.09 [1.66;6.15]	0,0007
Intensive therapy	0.09 [0.06;0.14]	<0.0001	0.15 = [0.07;0.32]	<0.0001

Global logRank test p<0.0001

Table 4. Univariate and multivariate analysis for overall survival in MDS (N=200)

	Univariate analysis		Multivariate analysis	
	Crude HR (95%CI)	p	Adjusted HR (95% CI)	p
Age > 60 years old	0.86 [0.63;1.18]	0,3414	0.92 [0.63;1.36]	0,6751
Latency period < 5 years	0.77 [0.57;1.05]	0,0972	0.70 [0.50;1.00]	0,0516
Sex (male)	1.06 [0.78;1.44]	0,7162	0.92 [0.65;1.29]	0,6121
> 1 preceding therapy lines, mean (sd)	1.55 [1.14;2.11]	0,0047	1.29 [0.88;1.89]	0,196
Performance Status (>1)	3.18 [2.18;4.55]	<0.0001	3.13 [2.05;4.71]	<0.0001
Cancer disease (active)	2.52 [1.78;3.53]	<0.0001	1.27 [0.86;1.89]	0,2276
IPSS Int2/High	4.32 [2.53;8.13]	<0.0001	3.11 [2.06;4.79]	<0.0001
Intensive therapy	0.86 [0.59;1.21]	0,3873	0.73 [0.46;1.14]	0,1652

Global logRank test p<0.0001

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