Characterization of therapy-related acute myeloid leukemia: increasing incidence and prognostic implications

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Supplement

Supplementary Methods

Data Collection

Data were collected from three nationwide registries: the Swedish AML Registry (SAMLR), the Swedish Cancer Registry (SCR) and the Swedish Rheumatology Quality Register (SRQ).

SAMLR started in 1997 and contains approximately 250 variables including extensive patient and disease characteristics, data on diagnosis, treatment, treatment response and allogeneic hematopoietic cell transplantation (HCT). Clinicians report to the registry at regular and well-defined follow-up time points.

SCR was founded in 1958 and covers basic patient information, medical data including date of cancer diagnosis, ICD codes for site of tumor and histological type as well as follow-up data. SCR is based on a dual reporting system where it is compulsory for both clinicians and pathologist to report all new diagnoses of cancer, based on clinical, morphological, and/or other laboratory examinations.

SRQ was initiated in 1996 and covers over 100 rheumatic diagnoses and includes 89,000 patients with ICD codes on diagnoses, patient information, treatment and follow-up.[1]

All registries use national unique personal identification numbers enabling identification of individuals across registries. All data reported to SAMLR with a diagnosis of AML between the start of the registry in 1997 until the end of 2015 were extracted for this study. Data on all malignant diseases on individuals in SAMLR also reported to SCR were retrieved, and information about rheumatic and system inflammatory diseases reported to SRQ was added to the data set.

Patients

The primary disease was explicitly stated in SAMLR in 265 (39%) of the patients with t-AML. Among the remaining 421 (61%), the primary disease was unambiguously defined in 275 cases (40%), and selected by high clinical likelihood in 48 cases (7%). We were unable to define the primary disease in 98 cases (14%). In 18 of these, it was possible to deduce that the primary

disease was a solid cancer, but the particular diagnosis was not reported. In 10 cases it was not possible to determine either the diagnosis or the type of disease, and in 70 cases the type of disease was non-malignant but the specific diagnosis was lacking.

Intensively treated non-acute promyelocytic leukemia (non-APL) patients received induction and consolidation therapy according to Swedish guidelines.[2] Induction treatment consisted of 1 g/m^2 cytosine arabinoside twice daily on days 1 to 5 and daunorubicin 60 mg/m^2 on days 1 to 3. Before 2006, cytarabine and daunorubicin doses varied based on local guidelines, but were always equivalent to classical 3+7 intensive AML induction. Consolidation treatment consisted of 1 to 3 courses of combination therapy, including intermediate or high-dose Ara-C followed by HCT in eligible patients. APL patients were treated with all-*trans*-retinoic acid, plus daunorubicin or idarubicin with or without Ara-C, depending on risk and age according to national treatment protocols.[2]

Additional definitions

The primary disease was defined as the malignant or non-malignant diagnosis for which chemo- or radiation therapy was given. The primary disease was explicitly stated in SAMLR for patients with t-AML diagnosed between 1997-2006. For patients diagnosed after 2006, the primary disease was deduced from records in SCR or SRQ. In cases of multiple diseases preceding AML, where information on treatment was unclear, the most likely diagnosis based on timing and known treatment traditions was selected as primary.

The latency period was defined as the time between the date of the primary diagnosis and the date of AML diagnosis. In cases where only the year of diagnosis of the primary disease was known, the date was approximated to June 30th. Overall survival (OS) was measured from the date of AML diagnosis to death or to last follow-up.

Additional information about statistical analyses

To adjust for changes in age distribution over time, incidence rates were age-standardized based on the 2006 (mid-study) Swedish population. The annual percentage change in incidence rate was estimated by fitting a linear regression model to the natural logarithm of the age-standardized rates over time. Kruskal-Wallis test by ranks was used to compare latency periods between multiple groups. Median follow-up time was calculated using the reverse Kaplan-Meier method.

REFERENCES

1. Register SRQ. Swedish Rheumatology Quality Register. 2018.
2. The Swedish AML group. Swedish national AML care program for adult patients. Akut myeloisk leukemi (AML) - Nationellt vårdprogram 2019.

Supplementary Tables

Supplementary Table S1. Comorbidities of patients with t-AML and de novo AML diagnosed between 1997-2015.

	Overall	*de novo* AML	t-AML	p
No. of patients	5492	4806	686	
Comorbidities (reported on 50% of cases)				
Inflammatory arthritis / systemic disease (%)	130 (5)	77 (3)	53 (13)	<0.001
Lung disease (%)	177 (6)	145 (6)	32 (8)	0.241
Diabetes (%)	248 (9)	215 (9)	33 (8)	0.557
Gastrointestinal disease / liver disease (%)	98 (4)	88 (4)	10 (2)	0.248
Cardiovascular disease including stroke (%)	754 (27)	648 (28)	106 (26)	0.557
Kidney disease (%)	73 (3)	60 (3)	13 (3)	0.567
Unspecified chronic disease (%)	308 (11)	216 (9)	92 (23)	<0.001

Abbreviations: AML, acute myeloid leukemia; t-AML, therapy-related AML.

Note: Comorbidities were not reported until 2007 and thus data are missing in 49.7% of cases.

Supplementary Table S2. Contribution by different diagnoses to the increase in incidence of t-AML. Leftmost columns show the average number of t-AML cases per year per 10 million inhabitants per primary disease during the time periods 1997-2002, 2003-2008 and 2009-2015. Middle columns show the change in average number of t-AML cases per year per year per 10 million inhabitants per primary disease between 1997-2002 and 2009-2015. Rightmost columns show the contribution of each primary diagnosis to the total increase in cases per year per 10 million inhabitants per primary disease between 1997-2002 and 2009-2015.

	Average t-AML cases / year / 10 million			Change between 97-02 and 09-15		Contribution to the total increase in cases / year between 97-02 and 09-15
Primary disease	1997-2002	2003-2008	2009-2015			
Lymphoma	10,1	9,3	10,7	0,6	6%	3%
Breast cancer	6,2	8,1	11,8	5,6	89%	27%
Gynecological malignancies	5,8	3,3	4,3	-1,5	-25%	-7%
Prostate cancer	1,2	1,6	6,4	5,2	430%	25%
Non-malignant diseases	4,3	7,2	12,5	8,2	190%	40%
Gastrointestinal malignancies	1,0	2,6	3,7	2,8	290%	13%
Multiple myeloma	3,6	2,1	1,9	-1,7	-48%	-8%
Other malignant diseases	6,2	7,0	7,9	1,6	26%	8%
Total	38,4	41,2	59,2	20,8	54%	100%

Supplementary Table S3. Prior diseases in the 686 patients with t-AML.

	Overall	Male	Female	p
No. of patients	686	294	392	
Number of prior malignancies				0.239
0	116 (17)	48 (16)	68 (17)	
1	434 (64)	194 (66)	240 (61)	
2	109 (16)	38 (13)	71 (18)	
3	17 (2)	8 (3)	9 (2)	
4	5 (1)	4 (1)	1 (0)	
5	1 (0)	0 (0)	1 (0)	
6	1 (0)	0 (0)	1 (0)	
Age at diagnosis of primary prior disorder				0.439
(median [range])	62 [0, 95]	63 [10, 95]	61 [0, 93]	
Type of primary prior disorder				<0.001
Solid cancer	378 (55)	135 (46)	243 (62)	
Hematological malignancy	176 (26)	102 (35)	74 (19)	
Non-malignant disease	122 (18)	53 (18)	69 (18)	
Undecidable	10 (1)	4 (1)	6 (2)	
Treament for primary prior disorder				0.008
Chemotherapy	337 (49)	165 (56)	172 (44)	
Chemo- and radiation therapy	178 (26)	66 (22)	112 (29)	
Radiation therapy	170 (25)	62 (21)	108 (28)	
Unknown	1 (0)	1 (0)	0 (0)	
Intermediate hematological disorder				0.277
MDS incl CMML	118 (17)	61 (21)	59 (15)	
MPN nos	12 (2)	3 (1)	9 (2)	
PCV	4 (1)	1 (0)	3 (1)	
ET	3 (0)	2 (1)	1 (0)	
Aplastic anemia	2 (0)	1 (0)	1 (0)	
None	551 (80)	229 (78)	322 (82)	
Solid cancers, n=378 (55%)				
Breast	124 (18)	1 (0)	123 (31)	
Gynecological (n=60)				
Uterine	30 (4)	0 (0)	30 (8)	
Ovarian	14 (2)	0 (0)	14 (4)	
Cervical	11 (2)	0 (0)	10 (3)	
Fallopian tube	4 (1)	0 (0)	4 (1)	
Vulvar	1 (0)	0 (0)	1 (0)	
Prostate	47 (7)	47 (16)	0 (0)	
Gastrointestinal (n=36)				
Colon	17 (2)	8 (3)	9 (2)	
Rectal	16 (2)	10 (3)	6 (2)	
Small intestine	1 (0)	1 (0)	0 (0)	
Peritoneal	1 (0)	0 (0)	1 (0)	
Gastric	1 (0)	1 (0)	0 (0)	
Lung	15 (2)	8 (3)	7 (2)	
Bladder	13 (2)	8 (3)	5 (1)	
Testicular	12 (2)	12 (4)	0 (0)	
Head and neck	12 (2)	8 (3)	4 (1)	
Sarcoma and osteosarcoma	10 (1)	5 (2)	5 (1)	
Skin	7 (1)	4 (1)	3 (1)	
CNS	3 (0)	2 (1)	1 (0)	
Eye	3 (0)	2 (1)	1 (0)	
Anal	3 (0)	1 (0)	2 (1)	
Thyroid	4 (1)	1 (0)	3 (1)	
Cancer of unknown primary	3 (0)	3 (1)	0 (0)	
Esophageal	2 (0)	2 (1)	0 (0)	
Adrenal	1 (0)	1 (0)	0 (0)	
Kidney	1 (0)	1 (0)	0 (0)	
Pancreatic	1 (0)	0 (0)	1 (0)	
Thymus	1 (0)	1 (0)	0 (0)	
Malignancy nos	2 (0)	1 (0)	1 (0)	
Undecidable	18 (3)	7 (2)	11 (3)	

Supplementary Table S3. Continued.

Hematologcal malignancies, n=176 (26%)				
Multiple myeloma		33 (5)	13 (4)	20 (5)
Lymphoma (n=139)				
	Hodgkin lymphoma	22 (3)	13 (4)	9 (2)
	Diffuse large B-cell lymphoma	20 (3)	13 (4)	7 (2)
	Follicular lymphoma	19 (3)	4 (1)	15 (4)
	Malignant lymphoma nos	15 (2)	10 (3)	5 (1)
	B-cell lymphoma nos	12 (2)	9 (3)	3 (1)
	Non Hodgkin lymphoma nos	12 (2)	9 (3)	3 (1)
	Chronic lymphocytic leukemia	10 (1)	9 (3)	1 (0)
	Mantle cell lymphoma	6 (1)	5 (2)	1 (0)
	Lymphoma nos	6 (1)	4 (1)	2 (1)
	T-cell lymphoma nos	4 (1)	2 (1)	2 (1)
	Indolent non Hodgkin lymphom	4 (1)	3 (1)	1 (0)
	Waldenström's Macroglobuliner	3 (0)	3 (1)	0 (0)
	Marginal zone lymphoma	3 (0)	0 (0)	3 (1)
	Burkitt lymphoma	2 (0)	1 (0)	1 (0)
	Aggressive non-Hodgkin lymph	1 (0)	0 (0)	1 (0)
Acute lymphoblastic leukemia		2 (0)	2 (1)	0 (0)
Langerhans cell histiocytosis		1 (0)	1 (0)	0 (0)
Systemic mastocytosis		1 (0)	1 (0)	0 (0)
Non-malignant diseases, n=122 (18%)				
Rheumatic/inflammatory (n=48)				
	Rheumatoid arthritis	30 (4)	6 (2)	24 (6)
	Vasculitis incl. GPA	8 (1)	5 (2)	3 (1)
	Arteritis	2 (0)	0 (0)	2 (1)
	Psoriasis / psoriatic arthritis	2 (0)	1 (0)	1 (0)
	Ankylosing spondylitis	2 (0)	0 (0)	2 (1)
	SLE / systemic inflammatory dis	2 (0)	2 (1)	0 (0)
	Still's disease	1 (0)	0 (0)	1 (0)
	Ulcerative colitis	1 (0)	1 (0)	0 (0)
Thyrotoxicosis		3 (0)	0 (0)	3 (1)
Hemangioma		1 (0)	0 (0)	1 (0)
Not specified		70 (10)	38 (13)	32 (8)
Not known, n=10 (1%)				
Undecidable		10 (1)	4 (1)	6 (2)

Abbreviations: t-AML, therapy-related acute myeloid leukemia; MDS, myelodysplastic syndromes; CMML, chronic myelomonocytic leukemia; MPN, myeloproliferative neoplasms; nos, not otherwise specified; PCV, polycythemia vera; ET, essential thrombocythemia; CNS, central nervous system; GPA, granulomatosis with polyangiitis; SLE, systemic lupus erythematosus.

Supplementary Table S4. Multivariable Cox regression analysis of the latency period from diagnosis of primary disease to the diagnosis of t-AML.

	HR	p
Risk		
Intermediate vs adverse	1.11 [0.90, 1.37]	0.327
Intermediate vs favorable	1.35 [0.95, 1.90]	0.090
Primary treatment		
Chemotherapy vs combination therapy	1.12 [0.87, 1.43]	0.380
Chemotherapy vs radiation alone	0.59 [0.45, 0.78]	<0.001
Type of primary disease		
Hematological disease vs non malignant disease	0.46 [0.27, 0.78]	0.004
Hematological disease vs solid cancer	0.95 [0.75, 1.21]	0.699
Age at primary diagnosis	1.04 [1.03, 1.05]	<0.001

Supplementary Table S5. Impact of a diagnosis of MDS prior to t-AML.

	HR	p
Unadjusted		
MDS vs no MDS	1.52 [1.09, 2.12]	0.013
Adjusted for age		
MDS vs no MDS	1.41 [1.01, 1.97]	0.042
Age	1.03 [1.02, 1.04]	<0.001
Adjusted for cytogenetic risk		
MDS vs no MDS	1.42 [0.98, 2.07]	0.064
Intermediate vs adverse	0.52 [0.40, 0.67]	<0.001
Favorable vs adverse	0.22 [0.14, 0.35]	<0.001
Adjusted for age and cytogenetic risk		
MDS vs no MDS	1.28 [0.89, 1.87]	0.185
Age	1.03 [1.02, 1.04]	<0.001
Intermediate vs adverse	0.51 [0.39, 0.65]	<0.001
Favorable vs adverse	0.21 [0.13, 0.34]	<0.001

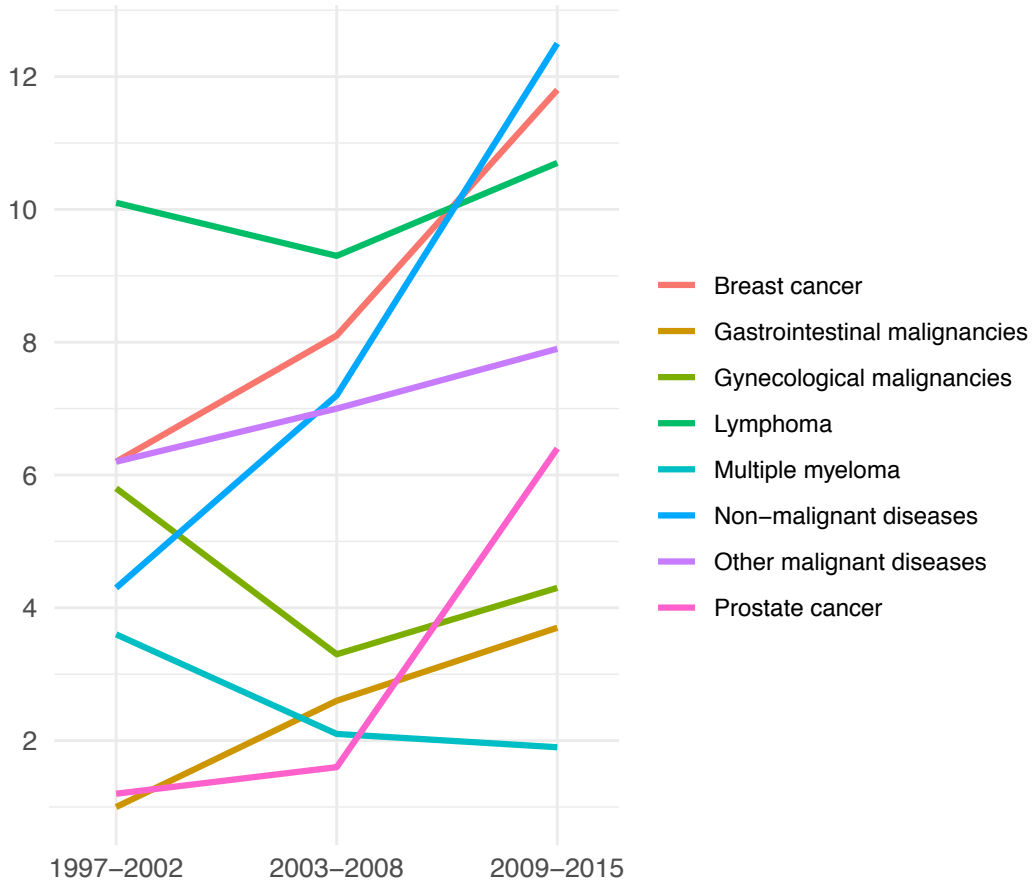
Supplementary Table S6. Multivariable regression analyses for overall survival and complete remission in the largest diagnostic groups in t-AML compared to *de novo* AML.

	Overall survival		Complete remission	
	HR [95% CI]	p	OR [95% CI]	p
Primary disease (compared to *de novo* AML)				
Breast cancer	1.40 [1.06, 1.84]	0.017	0.46 [0.28, 0.79]	0.004
Gastrointestinal malignancies	1.36 [0.78, 2.34]	0.275	0.38 [0.13, 1.08]	0.069
Gynecological malignancies	1.70 [1.12, 2.57]	0.012	0.31 [0.13, 0.75]	0.009
Lymphoma	1.48 [1.13, 1.93]	0.004	0.44 [0.26, 0.75]	0.003
Multiple myeloma	1.97 [0.98, 3.95]	0.057	0.36 [0.08, 1.62]	0.169
Prostate cancer	1.09 [0.66, 1.78]	0.738	1.29 [0.47, 4.14]	0.638
Rheumatic and inflammatory disease and vasculitis	1.39 [0.89, 2.16]	0.144	0.52 [0.23, 1.22]	0.123
Age	1.04 [1.03, 1.04]	<0.001	0.96 [0.95, 0.96]	<0.001
Cytogenetic risk (compared to intermediate)				
Adverse	1.79 [1.63, 1.98]	<0.001	0.45 [0.37, 0.55]	<0.001
Favorable	0.52 [0.45, 0.61]	<0.001	1.52 [1.13, 2.07]	0.007
ECOG PS 2-4 vs 0-1	1.53 [1.37, 1.70]	<0.001	0.46 [0.37, 0.57]	<0.001

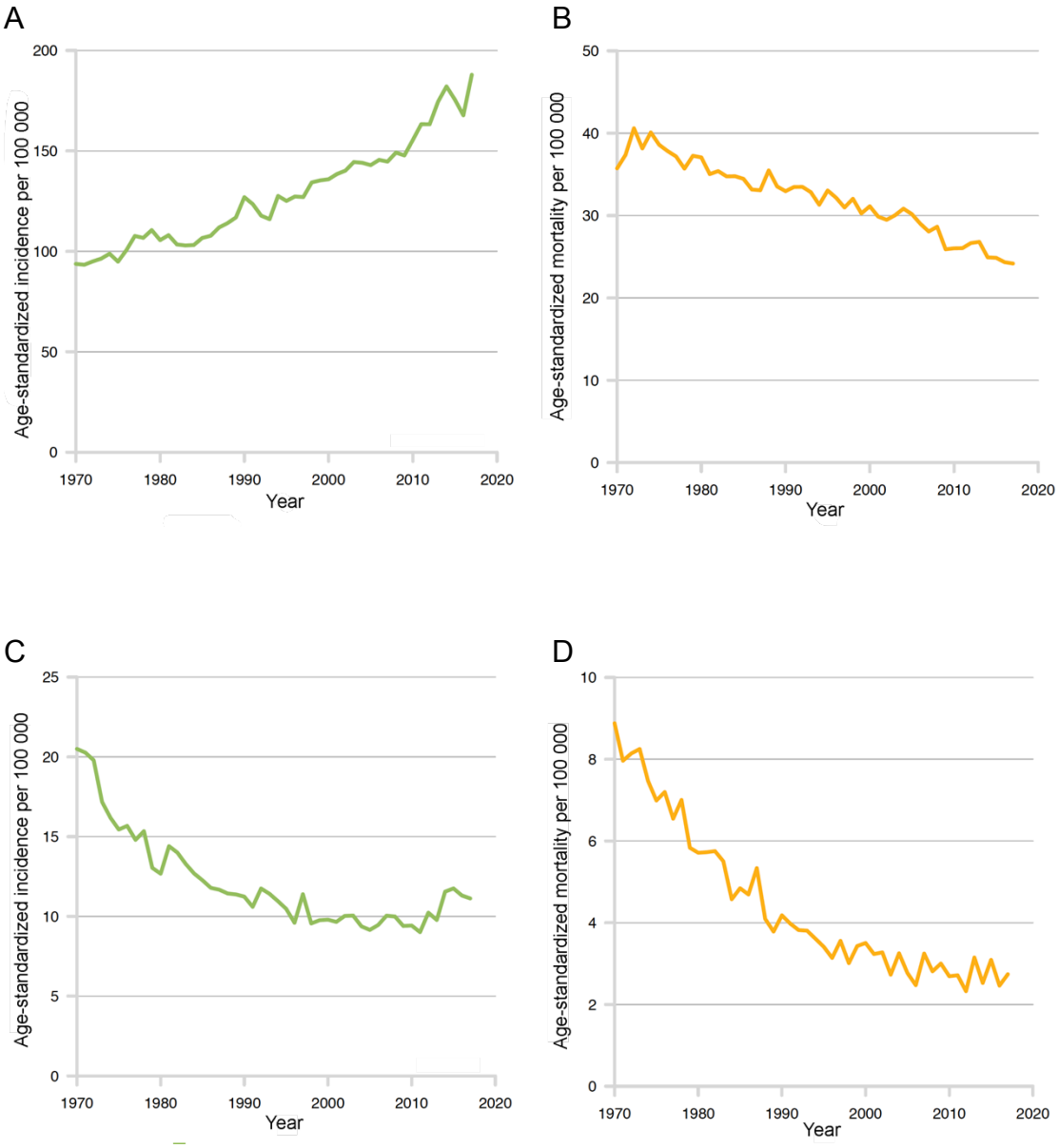
Abbreviations: AML, acute myeloid leukemia; t-AML, therapy-related AML; ECOG, Eastern Cooperative Oncology Group; PS, performance status; HR, hazard ratio; OR, odds ratio; CI, confidence interval.

Supplementary Figures

Supplementary Figure S1. Average number of t-AML cases per year per 10 million inhabitants during the three time periods 1997-2002, 2003-2008 and 2009-2015.



Supplementary Figure S2. Official data on incidence and mortality rates from The Swedish Cancer Society. Shows age adjusted yearly incidence per 100,000 inhabitants to the left and age adjusted mortality rates per 100,000 inhabitants to the right for breast cancer (A, B), cervical cancer (C, D), corpus cancer (E, F), ovarian carcinoma (G, H) and prostate cancer (I, J). Panel K shows age adjusted yearly incidence of all lymphomas per 100,000 inhabitants (men yellow and women blue lines) and observed (right) and age adjusted (right) survival per time period. Panel L shows the observed and relative survival after year of diagnosis of lymphoma. *(Figures used with permission from Regionala Cancercentrum i Samverkan, "Cancer i Sverige Registerdata över förekomst och dödlighet 1970-2017" and "Nationella kvalitetsregistret för lymfom - Nationell kvalitetsrapport för diagnosperioden 2000-2015", http://cancercentrum.se/samverkan)*



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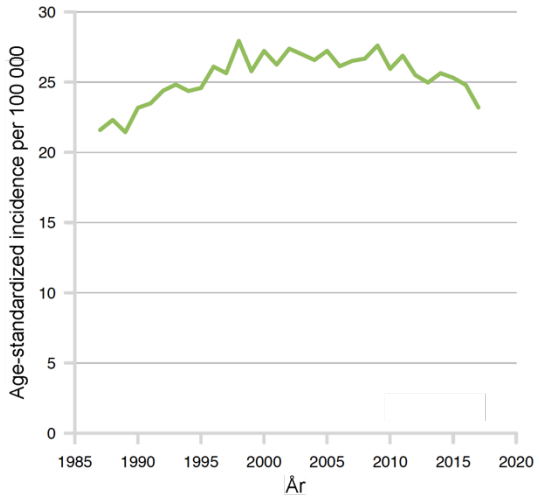
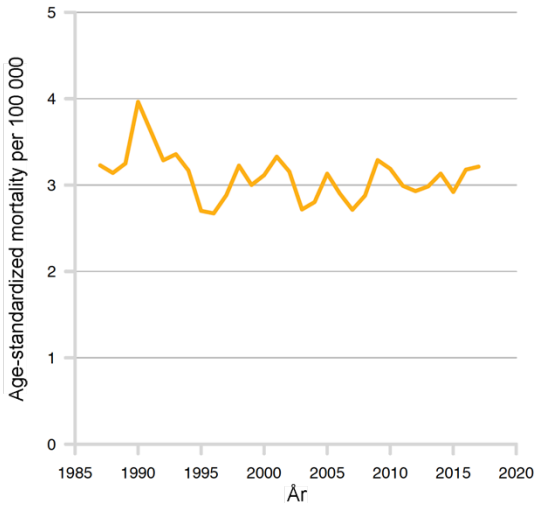

Age-standardized incidence per 100 000
30
25
20
15
10
5
0
1985
1990
1995
2000
2005
2010
2015
2020
År

F


Age-standardized mortality per 100 000
5
4
3
2
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1985
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1995
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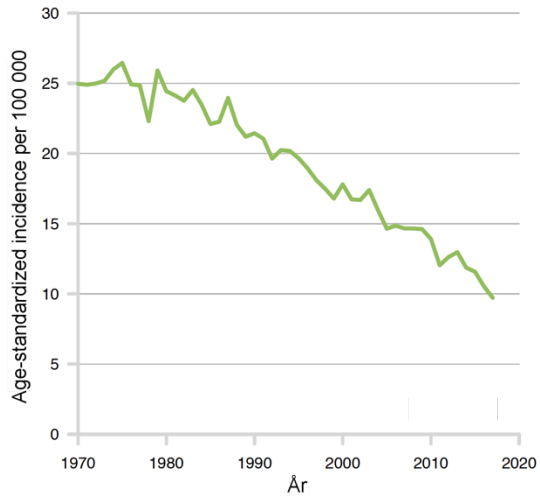
G


Age-standardized incidence per 100 000
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25
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15
10
5
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1970
1980
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2020
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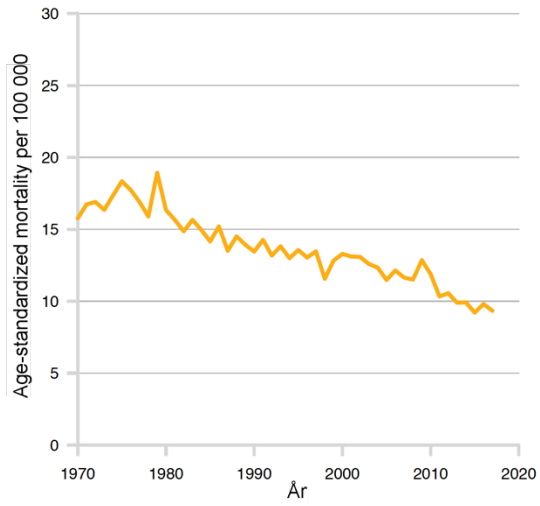
Age-standardized mortality per 100 000
30
25
20
15
10
5
0
1970
1980
1990
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2010
2020
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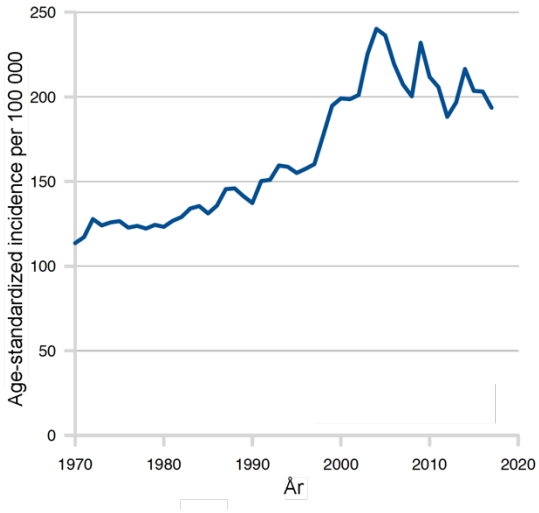
Age-standardized incidence per 100 000
250
200
150
100
50
0
1970
1980
1990
2000
2010
2020
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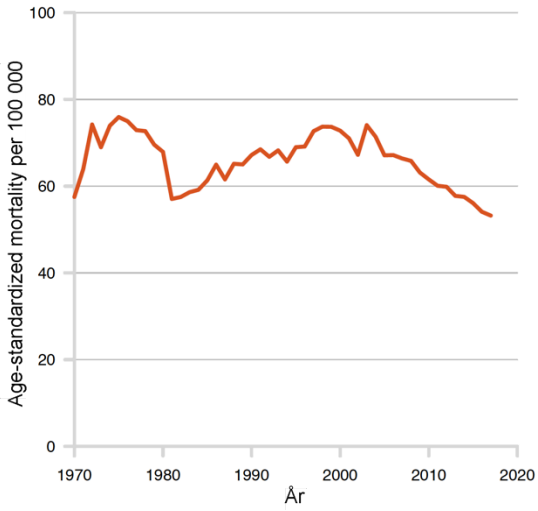
Age-standardized mortality per 100 000
100
80
60
40
20
0
1970
1980
1990
2000
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2020
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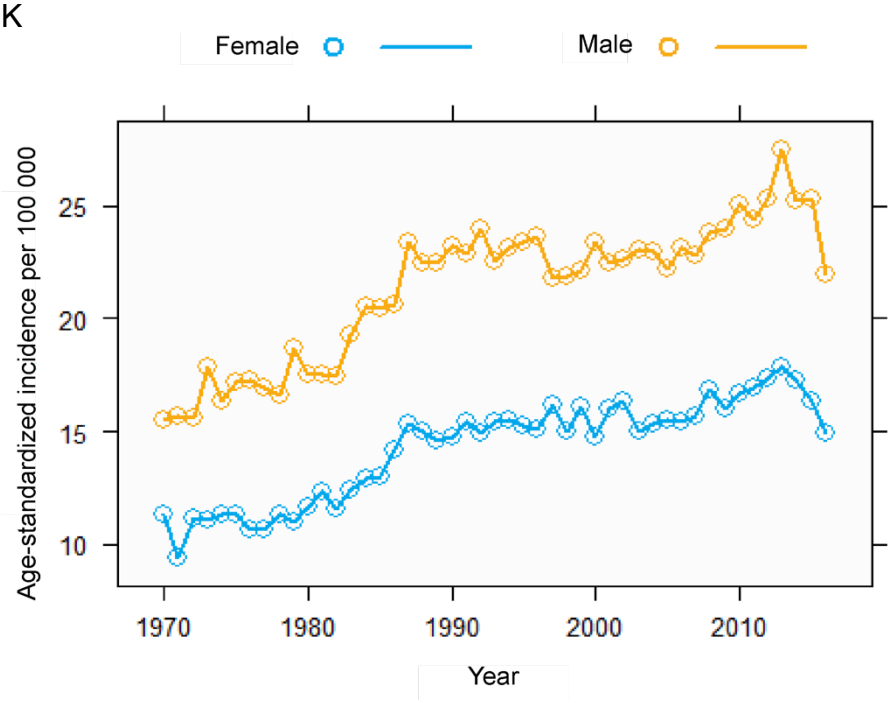
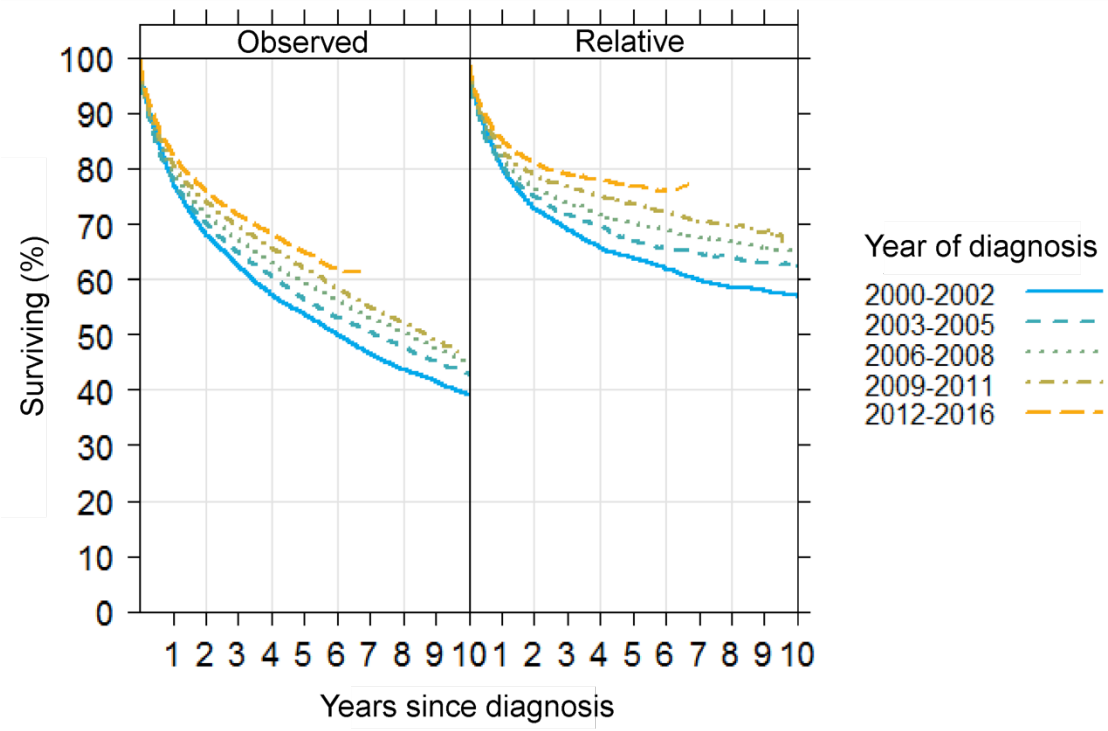
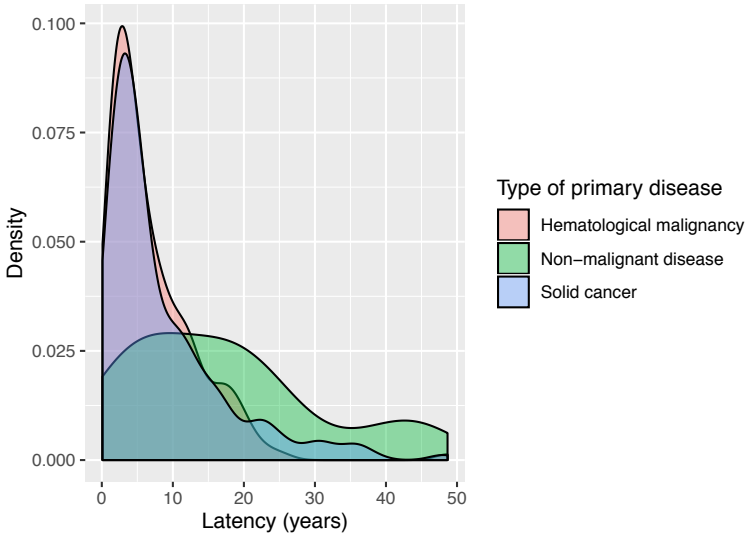

Female
Male
Age-standardized incidence per 100 000
10
15
20
25
1970
1980
1990
2000
2010
Year

L

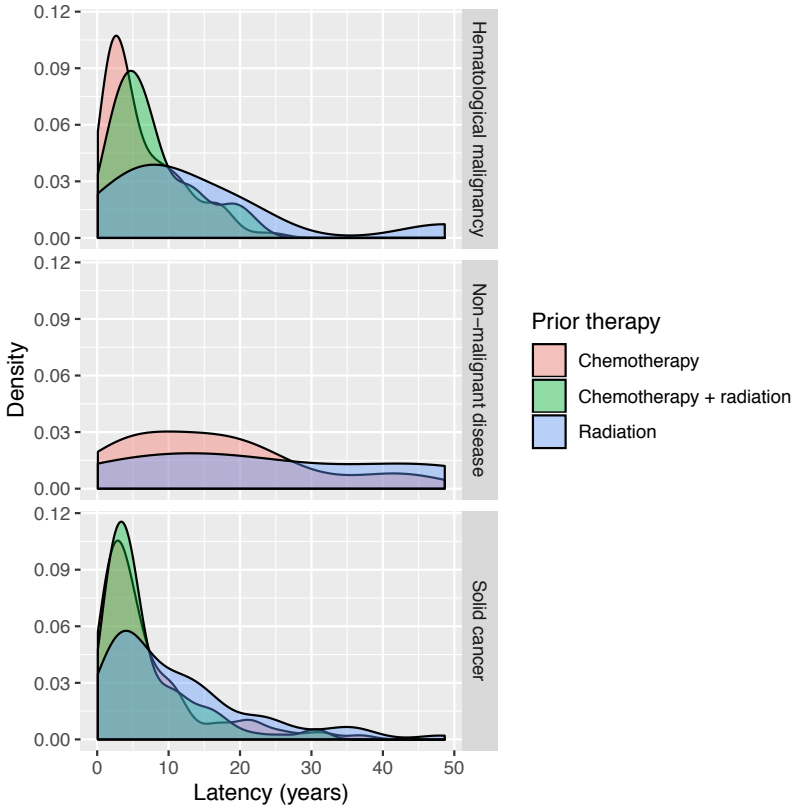

Observed
Relative
Surviving (%)
0
10
20
30
40
50
60
70
80
90
100
1 2 3 4 5 6 7 8 9 10 1 2 3 4 5 6 7 8 9 10
Years since diagnosis
Year of diagnosis
2000-2002
2003-2005
2006-2008
2009-2011
2012-2016

Supplementary Figure S3. Latency periods between primary disease and t-AML (A) grouped by type of primary disease (hematological cancer, non-malignant disease or solid tumor) and (B) grouped by both type of primary disease and type of cytotoxic treatment (chemotherapy, radiation, chemotherapy+radiation).

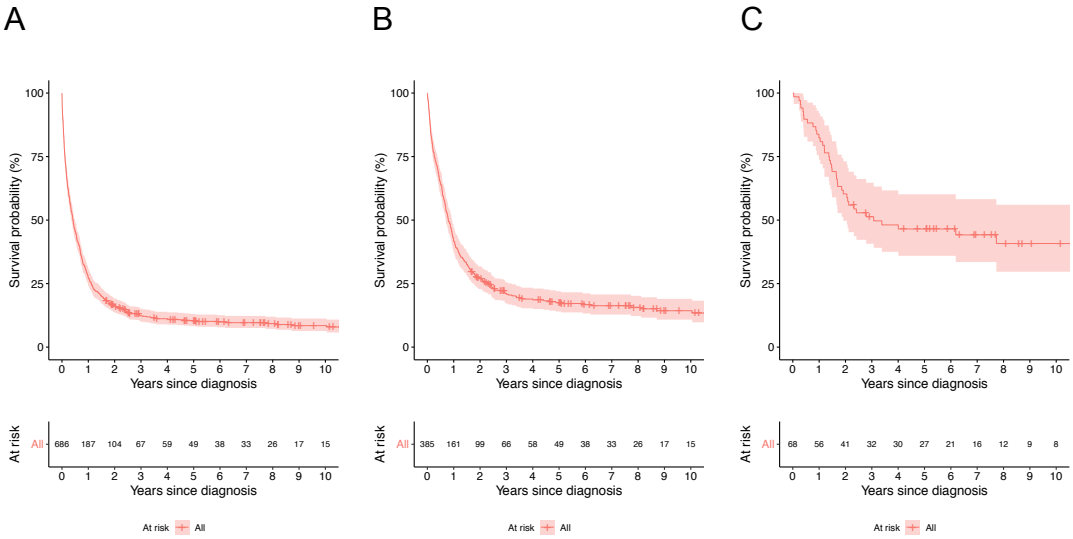
A



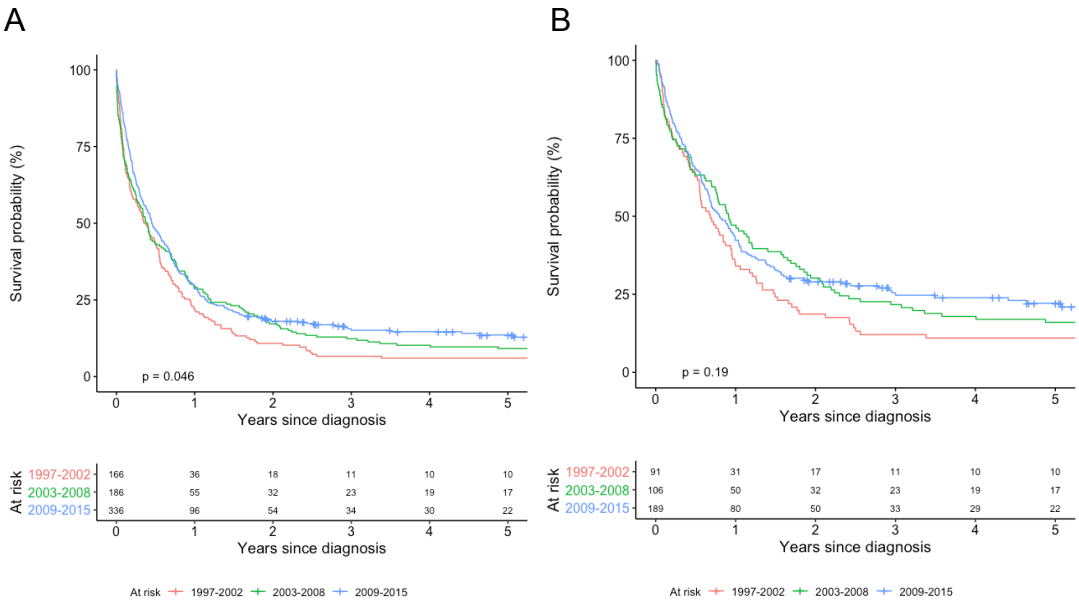
B



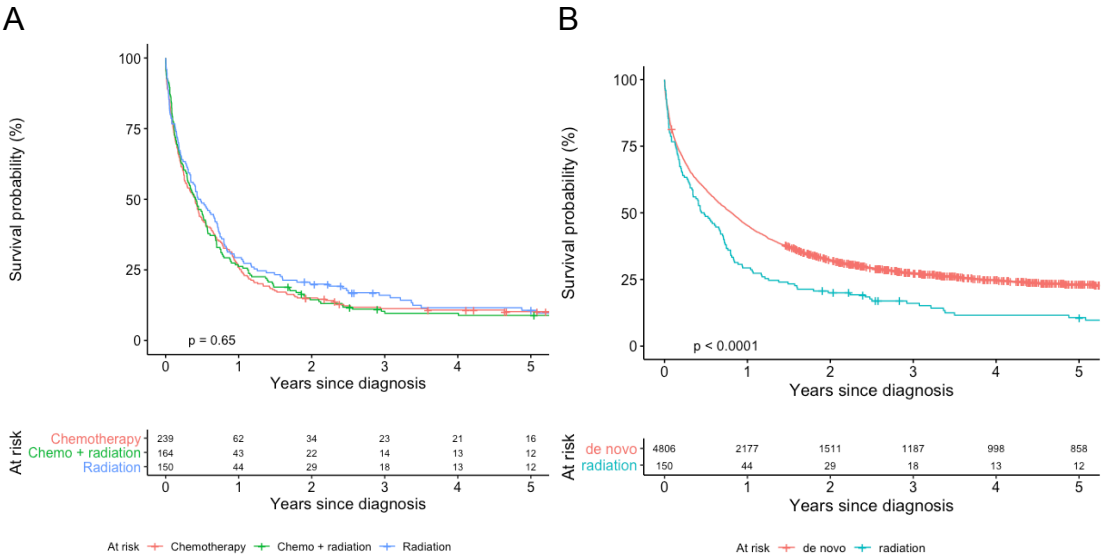
Supplementary Figure S4. (A) Overall survival in the 686 patients with t-AML diagnosed in Sweden between 1997-2015. (B) OS in the 386 intensively treated patients. (C) OS in the 68 patients who underwent HCT. Red area denotes 95% confidence interval.



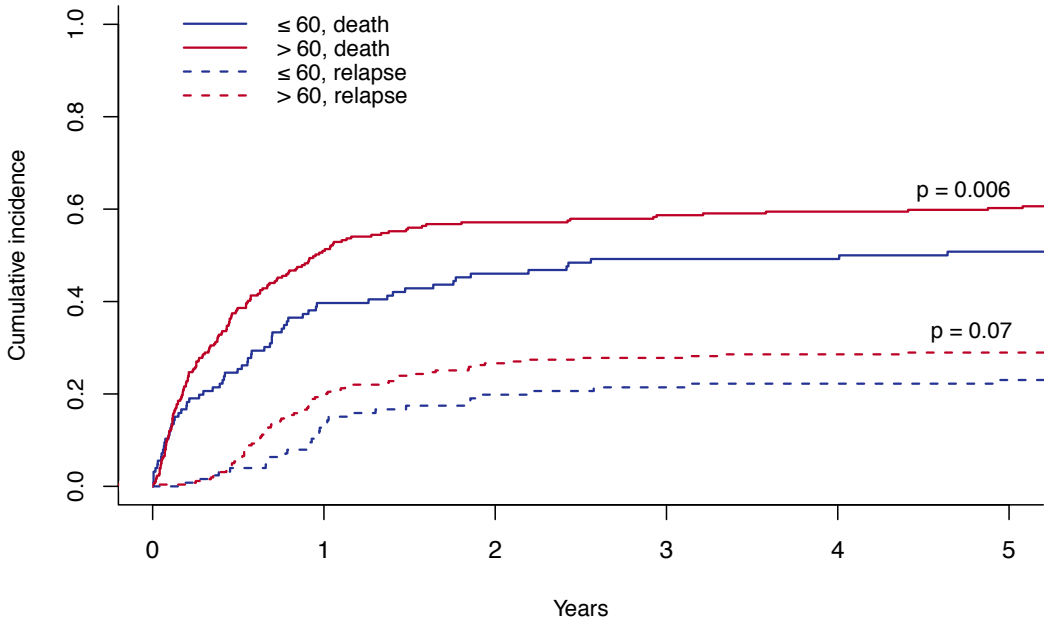
Supplementary Figure S5. Changes over time in OS in t-AML (A) in all patients and (B) in the subset of intensively treated patients.



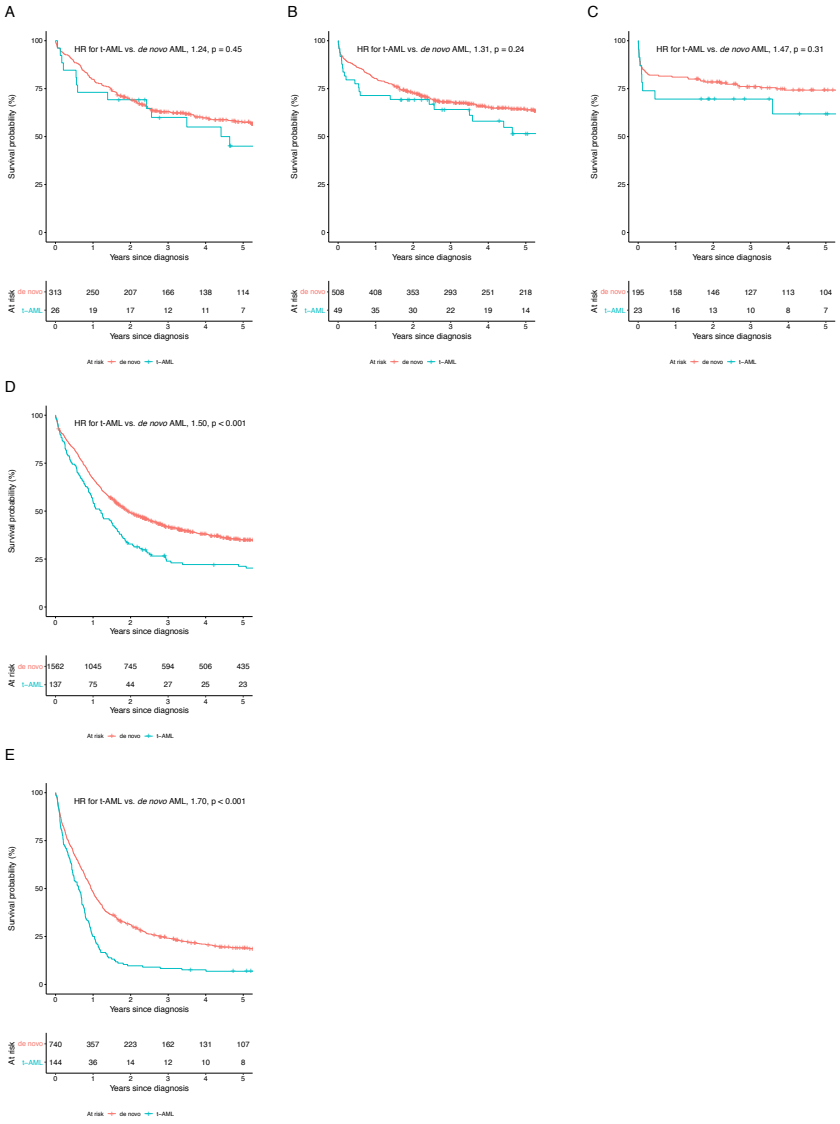
Supplementary Figure S6. (A) Overall survival was similar regardless if treatment for the primary disease was chemotherapy, radiotherapy or both chemo- and radiotherapy. (B) Patients with t-AML had inferior OS compared to de novo AML regardless of the primary treatment modality. Only t-AML with previous exposure to radiotherapy is shown.



Supplementary Figure S7. Cumulative incidence of death and relapse according to age in intensively treated patients with t-AML.



Supplementary Figure S8. Comparison of OS between t-AML and de novo AML in intensively treated patients with (A) favorable risk cytogenetics excluding patients with APL, (B) favorable risk cytogenetics including patients with APL, (C) APL only, (D) intermediate risk cytogenetics, and (E) adverse risk cytogenetics.



Supplementary Figure S9. Oncoplot displaying the mutation frequencies in a subset of 58 of the t-AML patients with NGS data available.