THE UNIVERSITY OF CHICAGO MEDICINE

Therapy-related Myeloid Neoplasms Following Radiation Therapy Only

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FIFTH
INTERNATIONAL SYMPOSIUM ON SECONDARY LEUKEMIA AND LEUKEMOGENESIS

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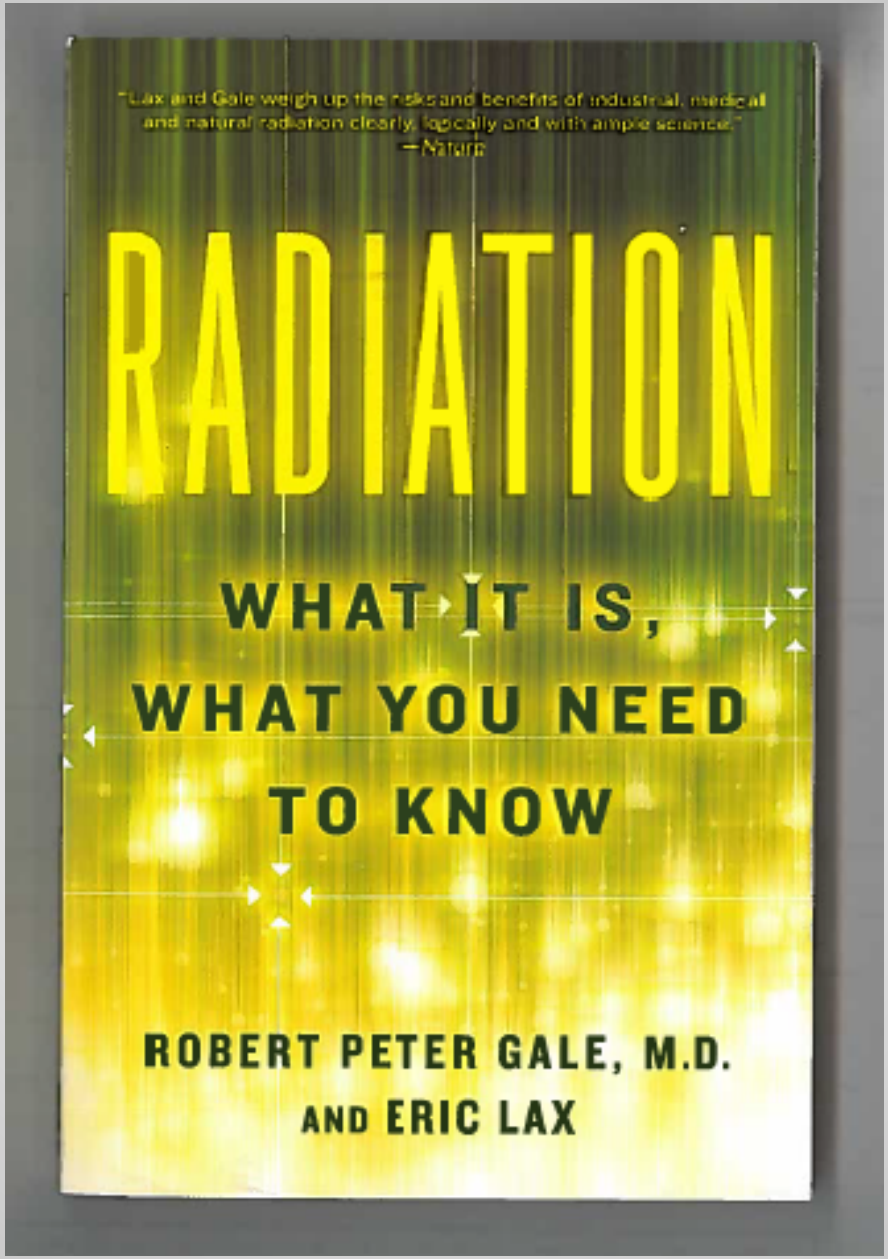
Astellas	X						
BristolMyers							DSMB
Celgene	X		X				DSMB
CVS			X				
Daiichi Sankyo	X						
Erytech	X		X				
Novartis	X		X				
Pfizer			X				


"Lax and Gale weigh up the risks and benefits of industrial, medical and natural radiation clearly, logically and with ample science."
—Nature
RADIATION
WHAT IT IS, WHAT YOU NEED TO KNOW
ROBERT PETER GALE, M.D.
AND ERIC LAX

Radiation therapy & t-MN

- Does exposure to ionizing radiation cause leukemia?
- How?
  - Stochastic DNA damage
  - Germline predisposition
  - Clonal selection
- How much absorbed radiation is necessary to cause leukemia?
  - Therapeutic exposure
  - Medical diagnostic exposure
  - Environmental / occupational exposure

Radiation therapy & t-MN

- Have modern RT techniques [mega-voltage linear accelerators; intensity-modulated radiation therapy (IMRT)] decreased the generation of leukemia?
- Do radiation-related myeloid neoplasms differ from those that follow alkylating agents and other cytotoxic drugs?
- How should patients with t-MN that occurs after radiation be managed?

Low dose irradiation is leukemogenic.

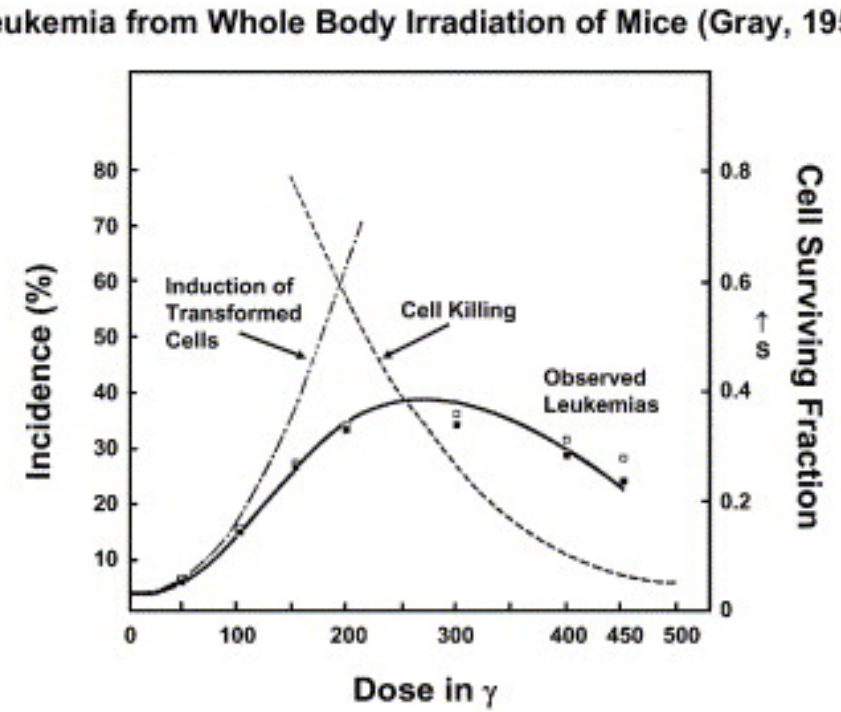


Illustration of the concept, introduced by Gray, that the incidence of radiation-induced cancer follows a “bell” shape because of the balance between the induction of transformed cells and cell killing.

EJ Hall. Internat Journal Rad Oncol 2006; 65 (1): 1–7

A single brief exposure to radiation is leukemogenic.

BLOOD *The Journal of Hematology*
MARCH, 1960 VOL. XV, NO. 3

Leukemia in Hiroshima Atomic Bomb Survivors

By Robert Heyssel, A. Bertrand Brill, Lowell A. Woodbury, Edwin T. Nishimura, Tarunendu Ghose, Takashi Hoshino and Mitsuru Yamasaki

A CAUSAL RELATION between radiation and leukemia has been well demonstrated.[1-12] The reported cases of leukemia in people exposed to radium,[13] thorotrast,[14,15] occupational x-ray,[16-18] therapeutic x-ray to the thyroid region in childhood[19,20] and possibly in utero diagnostic x-ray,[21] have been few in number. Estimates of the increased risk associated with exposure of man to radiation depend heavily upon studies of the survivors of the atomic bombing of Hiroshima and Nagasaki,[1-11] and of patients with ankylosing spondylitis[12] treated with high doses of x-radiation directed principally to the spinal marrow. Since the earlier reports from Hiroshima and Nagasaki established the increased incidence of leukemia in survivors, the number of cases has increased, and knowledge of population groups upon which to base analyses has improved. For the first time it is now possible to present analyses of incidence based on fixed samples of survivors. The present report summarizes the findings observed in the Hiroshima survivors from 1945 to 1958. A similar report is being prepared[22] on the survivors of the Nagasaki atomic explosion.

Materials and Methods

Immediately following the bombing, and intermittently for two years thereafter, teams of scientists entered Hiroshima to render assistance and to obtain information on the effects of radiation on humans. They, as well as members of the local medical community, were cognizant of the potential significance of hematologic findings resulting from irradiation. With improvement of local conditions and medical facilities, a systematic investigation became possible, and a routine hematologic survey was instituted.[23] Since 1948, scientists of the Atomic Bomb Casualty Commission in cooperation with physicians in the community have made intensive efforts to detect hematologic and other abnormalities in both the exposed and the nonexposed segments of the population. To collect information on patients with hematologic abnormalities before 1950, lists of patients and any available slides and related materials were exchanged by the ABCC and local physicians and continuously reviewed. Since 1950 these efforts have been intensified, so that few if any leukemia cases among survivors remaining in Hiroshima or its immediate environs can have been missed. Even for the first four years after the bombing, the likelihood of missing cases of leukemia is probably small.

From the Atomic Bomb Casualty Commission, Hiroshima-Nagasaki, Japan, a research agency of the U. S. National Academy of Sciences–National Research Council, under a grant from U. S. Atomic Energy Commission administered in co-operation with the Japanese National Institute of Health of the Ministry of Health and Welfare.
Submitted June 8, 1959; accepted for publication Aug. 12, 1959.

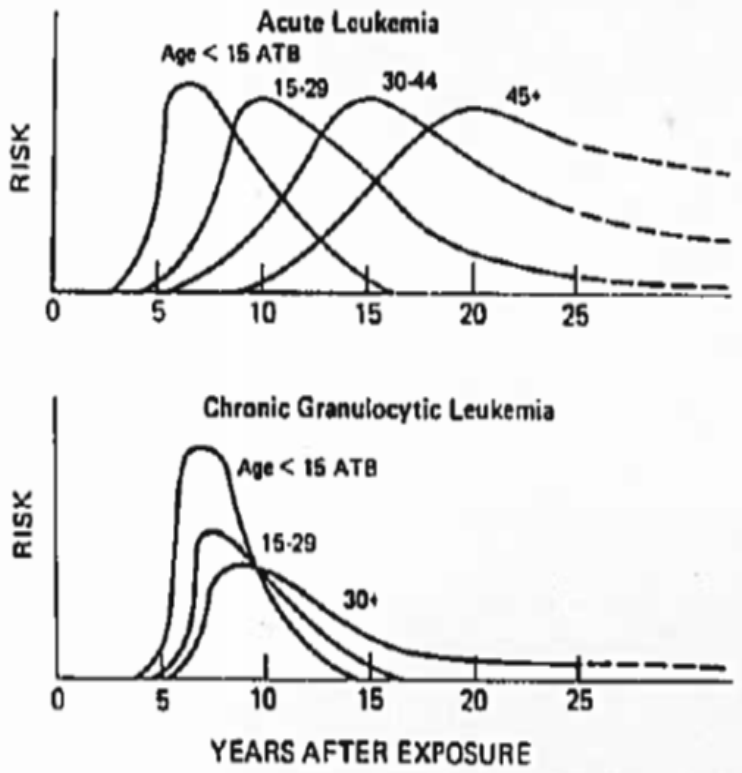


Figure 2. Influence of age at time of irradiation on latent period and period at risk for the development of leukemia among heavily exposed survivors of Hiroshima and Nagasaki. ATB = at time of bombing. (*From* Health Effects of Exposure to Low Levels of Ionizing Radiation: BEIR III. Committee on the Biological Effects of Ionizing Radiations, National Research Council, Washington, National Academy Press, 1980.)

Lifetime probability of fatal secondary malignancy

Organ site	Probability of fatal cancer (%/ Sv)
Bladder	0.3
Bone marrow	0.5
Bone surface	0.05
Breast	0.2
Esophagus	0.3
Colon	0.85
Liver	0.15
Lung	0.85
Ovary	0.1
Skin	0.02
Stomach	1.10
Thyroid	0.08
Remainder of body	0.5
Total	5

EJ Hall. Internat Journal Rad Oncol 2006; 65 (1): 1–7

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Health effects of ionizing radiation on man

- The gray - quantity "D"
- 1 Gy = 1 joule/kilogram - a physical quantity. 1 Gy is the deposition of a joule of radiation energy in a kg of matter or tissue. [Deterministic effect -- e.g., 40 Gy to treat NHL]
- The sievert - quantity "H"
- 1 Sv = 1 joule/kilogram - a biological effect. The sievert represents the equivalent biological effect of the deposit of a joule of radiation energy in a kilogram of human tissue.

Health effect of ionizing radiation on man

- The sievert - a biological effect.
- One sievert is equal to 100 rem (Roentgen equivalent man).
- One sievert carries with it a 5.5% chance of eventually developing cancer.
- For occupational exposure, the limit is 50 mSv in a single year.
  - A maximum of 100 mSv in a consecutive 5-year period.
  - For the public, an average of 1 mSv (0.001 Sv) of effective dose per year.

Wikipedia 2016

Occupational & accidental exposures

- 1.5 to 1.7 mSv: annual dose for flight attendants
- 2 to 7 mSv: barium fluoroscopy, e.g. Barium meal
- 10 to 30 mSv: single full-body CT scan
- 68 mSv: estimated maximum dose to evacuees who lived closest to the Fukushima I nuclear accidents
- 80 mSv: 6 months stay on the International Space Station
- 250 mSv: 6-month trip to Mars - radiation due to difficult-to-shield cosmic rays
- 500 mSv: The U.S. occupational dose limit, shallow-dose equivalent to skin, per annum
- 670 mSv: highest dose received by a worker responding to the Fukushima emergency
- 1 Sv: Maximum allowed radiation exposure for NASA astronauts over their career
- 4.5 to 6 Sv: fatal acute doses during Goiânia accident

Wikipedia 2016

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Wikipedia 2016

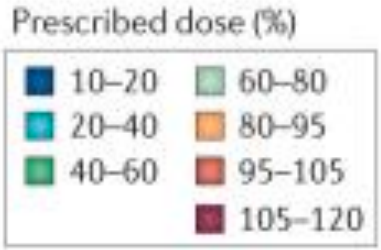
Intensity-modulated radiation therapy

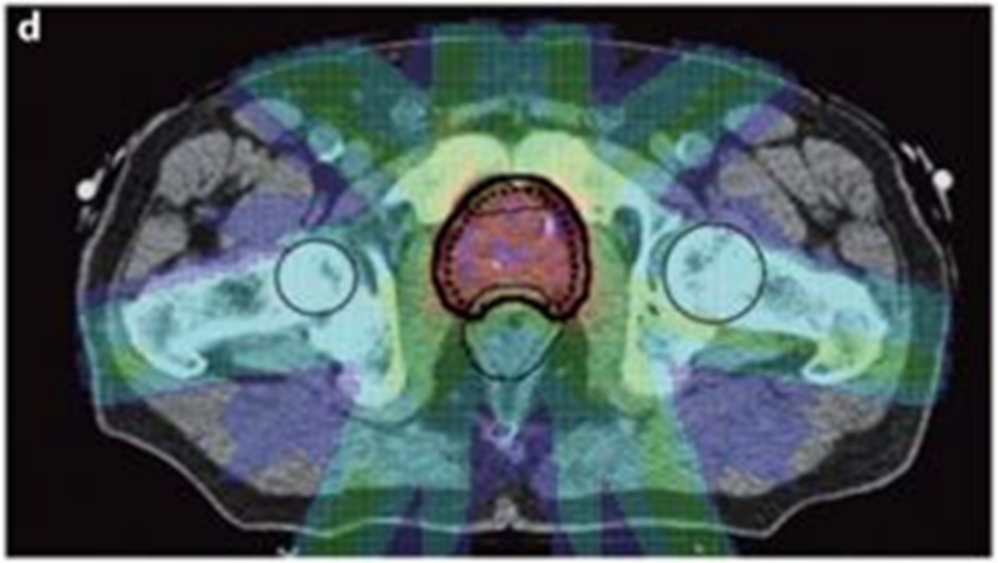
- IMRT delivers higher energies to tumor masses by using multiple angled beams.
- IMRT spreads out the radiation dose so that a larger volume of surrounding tissues receives a lower, less toxic, but more leukemogenic dose.
- It is estimated that IMRT is associated with a 3-fold increased risk for a second cancer compared with 3-dimensional confocal RT.

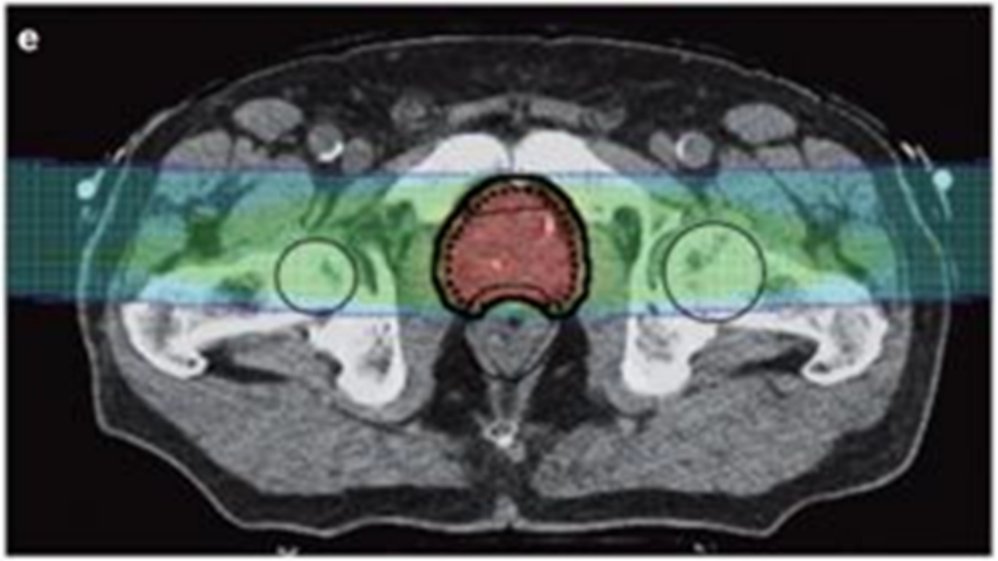
Sountoulides et al. Ther Adv Urol 2010; 2(3): 119-125.
Ruben et al. Int J Radiation Oncol Biol Phys 2008; 70(5): 1530-1536.
Kry et al. The calculated risk of fatal secondary malignancies from intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2005 Jul 15;62(4):1195-203.

Intensity Modulated Radiation Therapy: multiple beams

3-D Confocal RT: parallel opposed ports





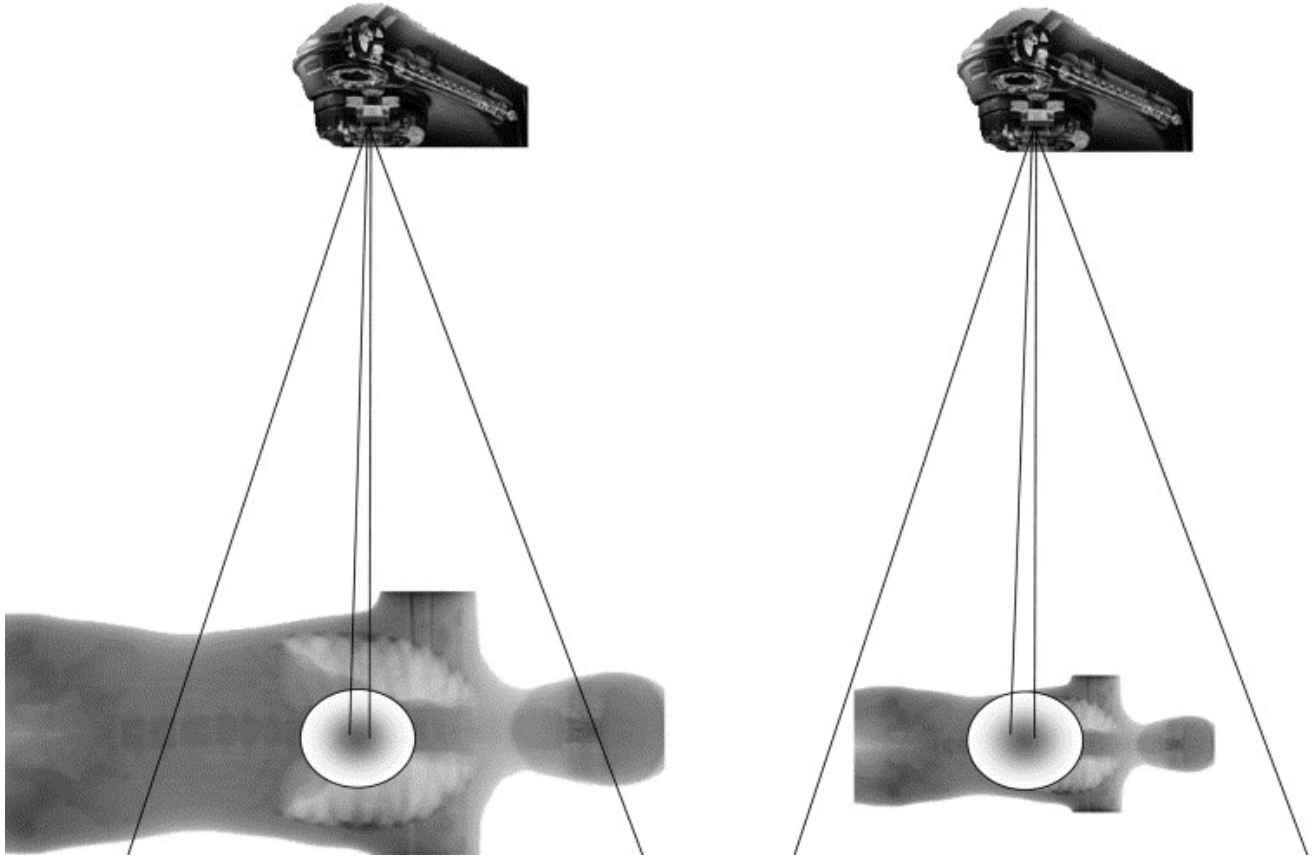


Radiation scatter & penumbra effects

- Cortical bone causes radiation to scatter, thus spreading the effect into surrounding tissues.
- Mega-voltage techniques deliver more energy to the targeted tumor mass. These doses would be lethal to hematopoietic stem cells.
- However, leakage from the collimator and the spreading of the photon beam results in much lower doses to the immediate surrounding tissues. These low doses are in the leukemogenic range.

Radiation leakage from the collimator

Same Leakage for Adult RT vs. Pediatric RT — But in Pediatric RT Scatter from the Treatment Volume Is More Significant



Adult

Child

VOLUME 30 · NUMBER 19 · JULY 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Acute Myeloid Leukemia and Myelodysplastic Syndromes After Radiation Therapy Are Similar to De Novo Disease and Differ From Other Therapy-Related Myeloid Neoplasms

VOLUME 30 · NUMBER 19 · JULY 1 2012

JOURNAL OF CLINICAL ONCOLOGY

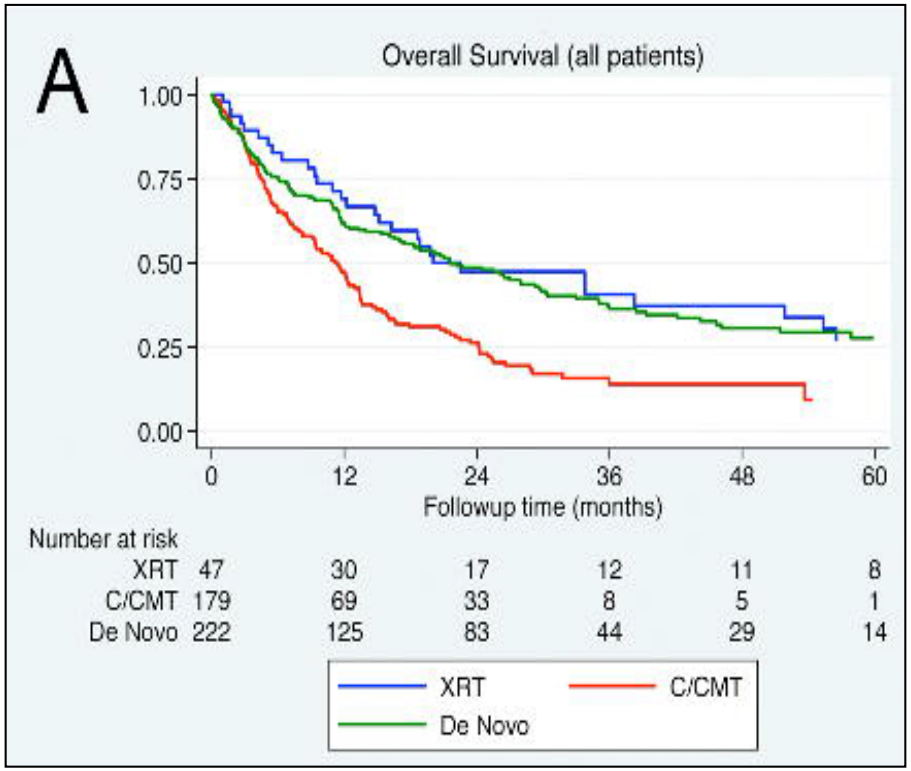
EDITORIAL

Cytogenetics, Not Just Previous Therapy, Determines the Course of Therapy-Related Myeloid Neoplasms

Richard A. Larson, *University of Chicago, Chicago, IL*

Is Survival for t-MN after RT similar to *de novo* AML?

	RT	CT/CMT	De novo
No. of Patients	47	181	222
Median age (range)	74 (40-87)	65 (14-88)	66 (18-93)
Median Latency, months	60	57	



RT = radiation therapy only
CT = chemotherapy only
CMT = combined modality therapy (CT+RT)

Nardi et al. J Clin Oncol 2012: 30: 2340

Is Survival for t-MN after RT similar to *de novo* AML?

	RT	CT/CMT	De novo
No. of Patients	47	181	222
Karyotypes:			
Normal (%)	20 (43)	26 (14)	99 (45)
Abnormal (%)	24 (51)	150 (83)	113 (51)
Deletion of chr. 5	9 (19)	95 (52)	38 (17)
Deletion/loss of chr. 7	9 (19)	92 (51)	35 (16)
Deletion/loss of either chromosome 5 or 7	12 (26)	115 (63)	50 (23)

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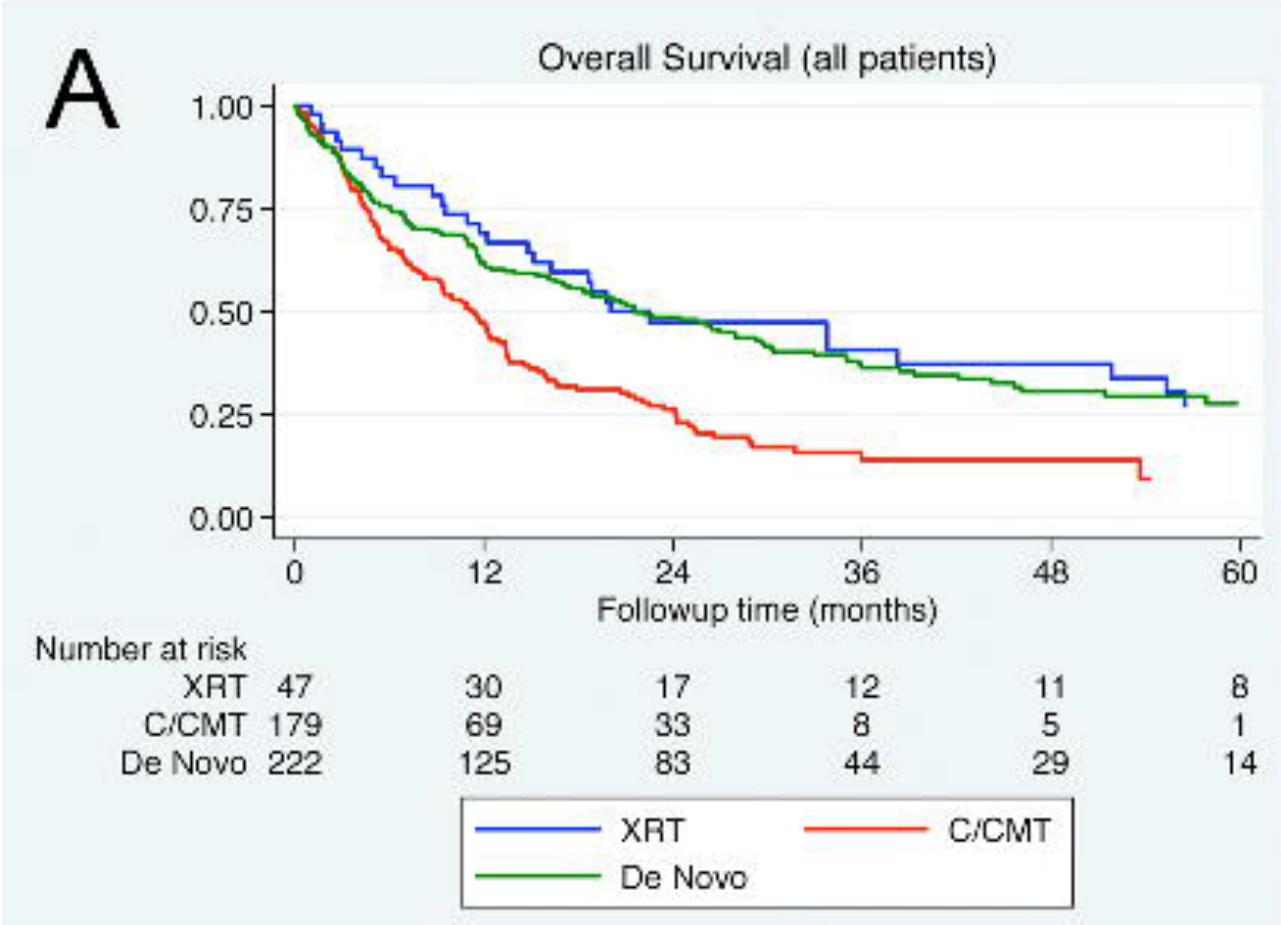
Survival is similar when matched for cytogenetics.

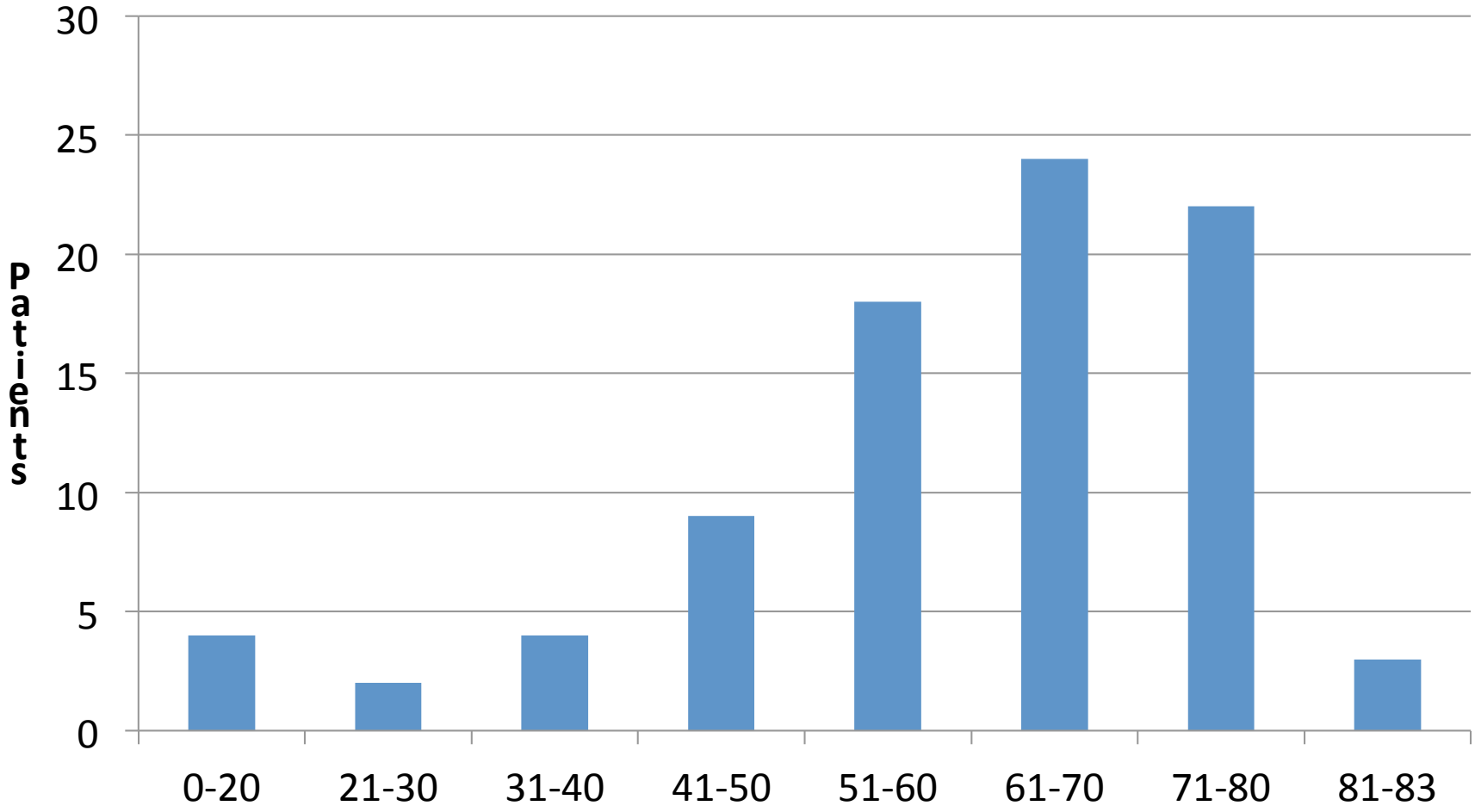


Nardi et al. J Clin Oncol 2012: 30: 2340

86 Patients with t-MN after RT only

- Consecutive cases at University of Chicago (1972-2015)
- 41 females; 45 males
- 62 white (72%); 13 African American (15%); 1 Asian (1%); 10 not recorded (12%)
- Median age at primary diagnosis: 64 years (range, 1-83)
- Median latency from RT to t-MN: 71 months (IQR, 31-126)

Age at Radiation Treatment



86 Patients with t-MN after RT only

Primary Diagnosis	No. of Patients	Percent	
Hematologic Cancer	5	6	4 HD; 1 NHL
Prostate/testicular	36	42	2 testis
Breast Cancer	19	20	
Gynecologic	15	19	6 uterus; 5 cervix
Head and Neck	4	4	
Thyroid Cancer	2	2	
Lung Cancer	2	2	
Meduloblastoma	1	1	
Non-malignant	2	2	Acne; HyperThyroid

86 Patients with t-MN after RT only

- 42 presented with t-MDS
  - 13 of these later developed >20% blasts
- 44 presented with t-AML (>20% blasts)

Karyotype	No. of Patients	Percent
Normal	16	19
Abnormal chromos. 5 and/or 7	45	52
Recurring balanced translocation	12	14
Other clonal abnormalities	13	15

Clonal cytogenetic abnormalities in 86 t-MN patients after RT

Clonal abnormality	No. of patients (%)	
Del (5q) sole	13 (15)	Abnl 5
Del (5q), del (7q)	11 (13)	
Del (5q) + other abnormalities	10 (12)	
Del (7q) sole	6 (7)	Abnl 7
-7 sole	3 (3)	
-7 + other abnormalities	2 (2)	
t(8;21) or t(21q)	3 (3)	Balanced
Inv (16) or t(16;16)	5 (6)	
t(15;17)	4 (5)	
+8 sole	3 (3)	Other clonal
+8 + other abnormalities	4 (5)	
Other clonal abnormalities	6 (7)	

75 Patients with t-MN after RT only

Latency in months (excluding cases >20 years)			
Karyotype	No. of Patients	Mean Latency	Minimum - Maximum
Normal	14	58 mos.	17 – 115
Abnormal chrom. 5 or 7	41	77	10 – 204
Recurring Balanced	12	39	11 – 95
Other clonal abnormal.	8	103	21 - 194

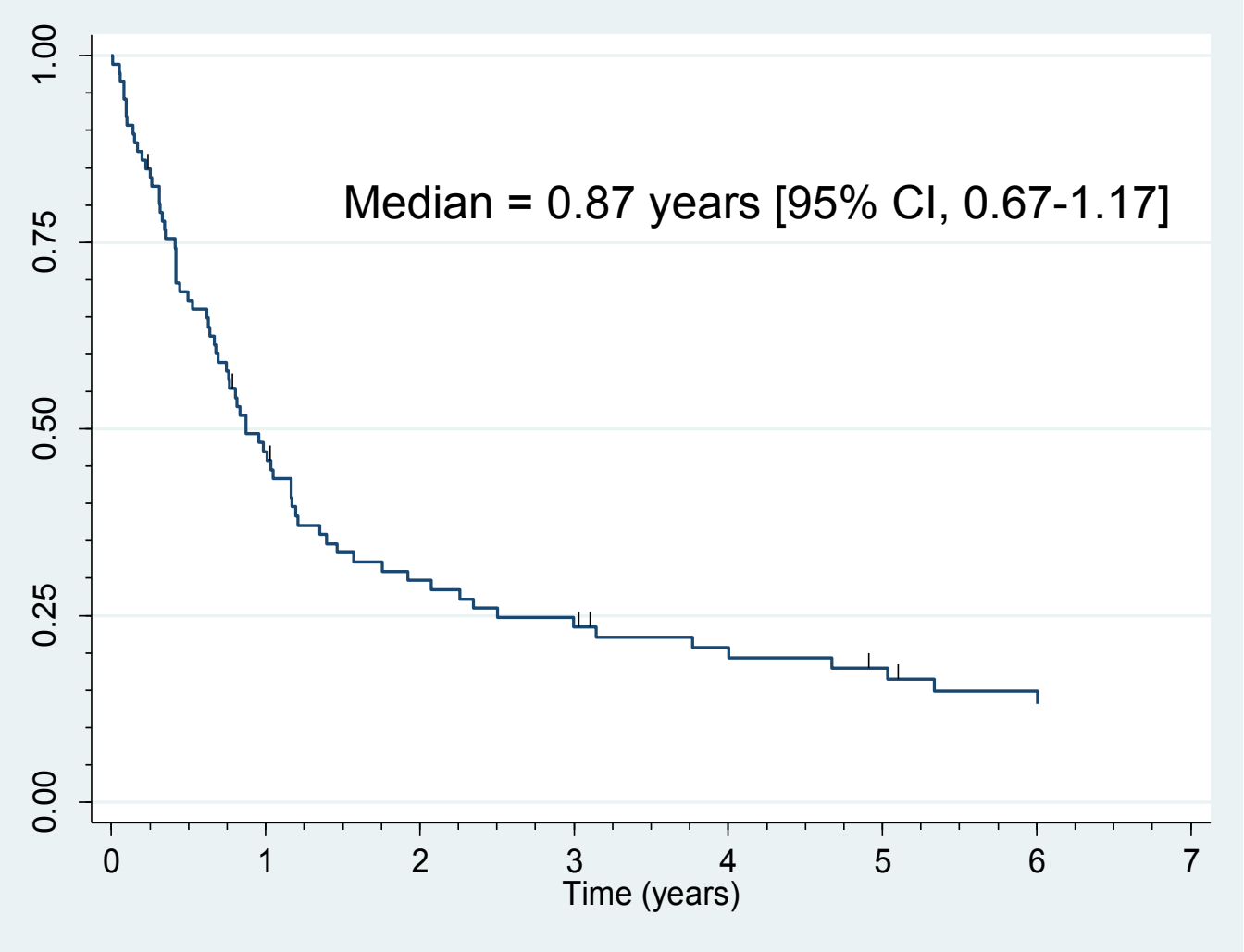
P = 0.009 overall;
P = 0.055 between Abnormal 5/7 and Recurring balanced

86 Patients with t-MN after RT only

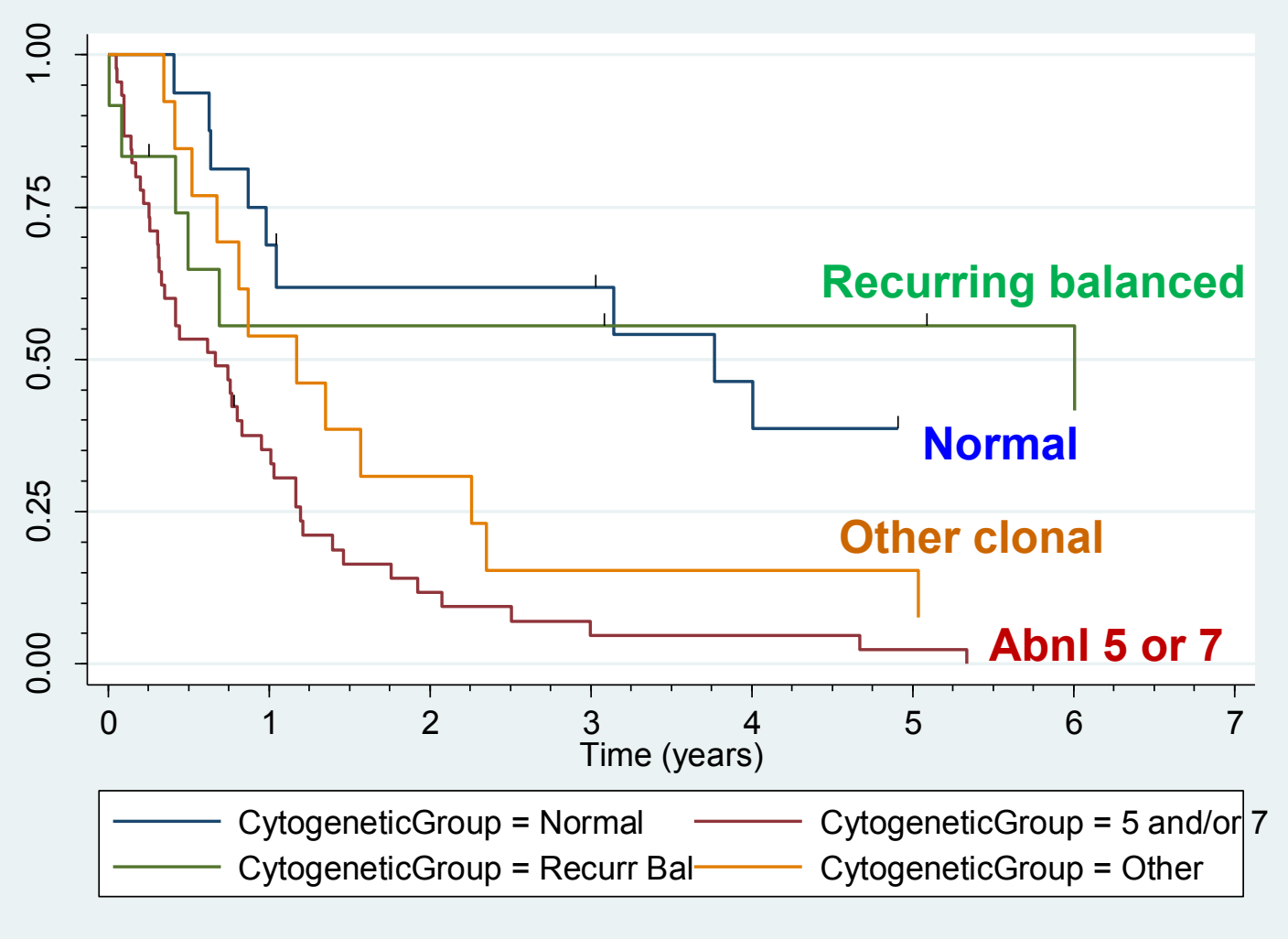
Treatment for t-MN	No. of Patients
Supportive care only	11
Chemotherapy	34
Chemotherapy followed by allogeneic transplantation	16 [10 had abnormal chr 5 or 7]
Unknown	25

- Median survival: 318 days (IQR, 150 – 916)
- 10 patients remain alive:
  - 4 with inv(16) or t(16;16)
  - 1 with t(15;17)
  - 1 with del(5q), t(1;3)
  - 4 with normal karyotypes [2 had alloHCT]

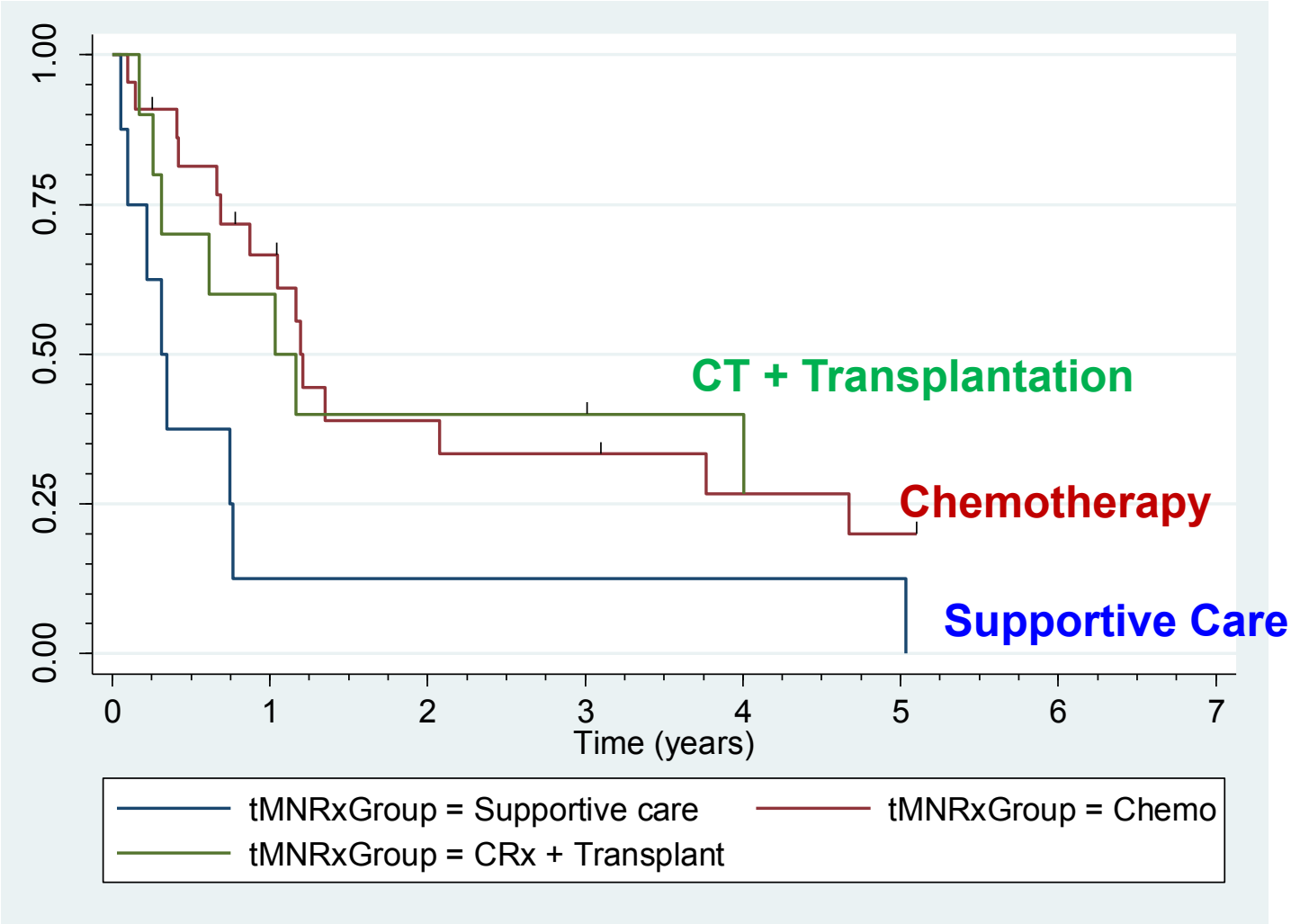
Survival of 86 t-MN patients after RT only



Survival by cytogenetic subgroup



Survival by treatment modality (n=61)

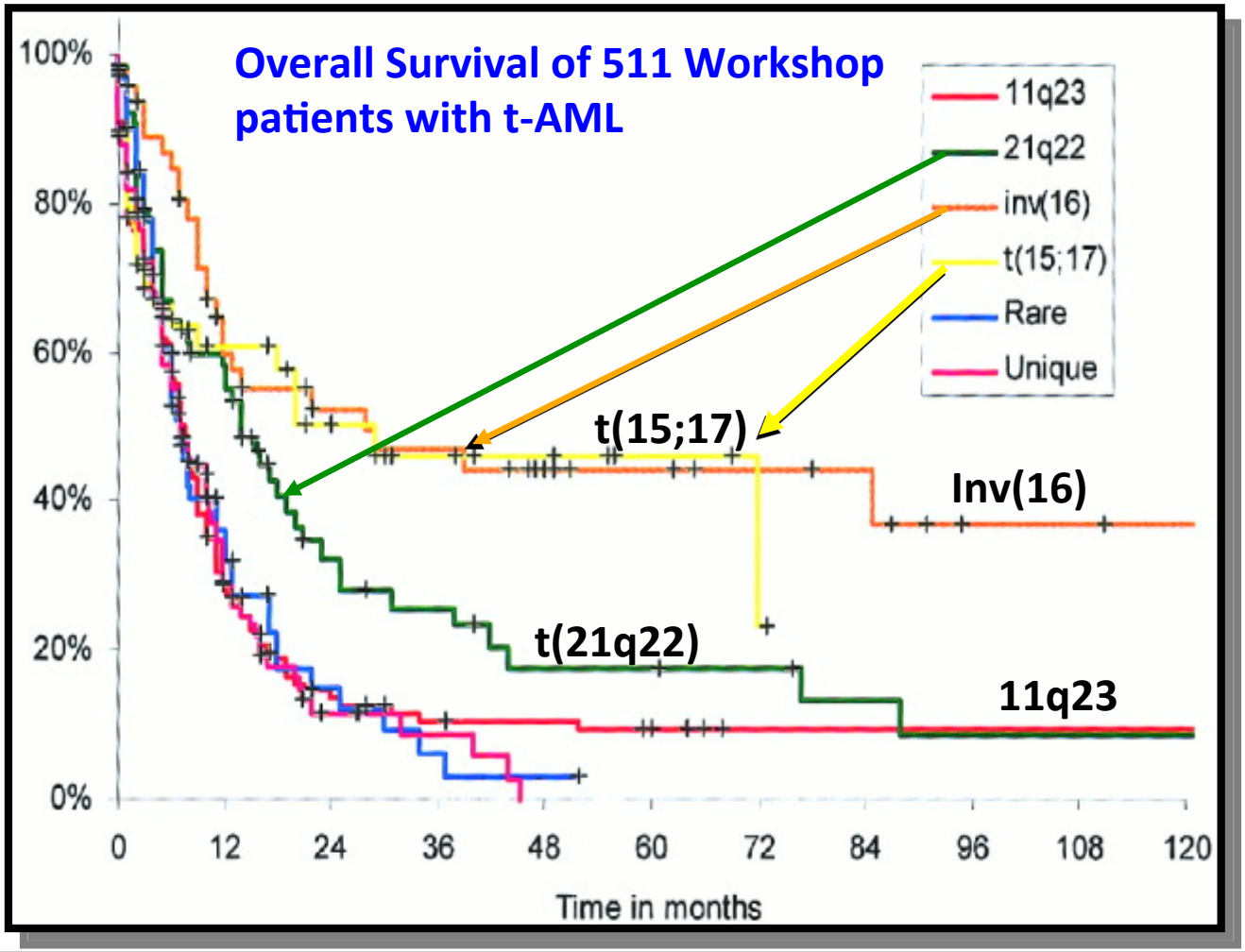


International Workshop on the Relationship of Prior Therapy to Balanced Chromosome Aberrations in Therapy-Related Myeloid Leukemia

	inv(16) N=48	t(15;17) N=41
Male : Female	18 : 30	15 : 26
Age at primary diagnosis: median (range), years	43 (6-75)	46 (18-79)
Cytotoxic exposure:		
Radiation only	10 (21%)	12 (29%)
Chemotherapy only	14 (29%)	7 (17%)
Combined RT + chemo	24 (50%)	22 (54%)
Age at t-MN: median (range)	48 (13-77)	49 (19-81)
Latency: Median (range), months	22 (8-533)	29 (9-175)

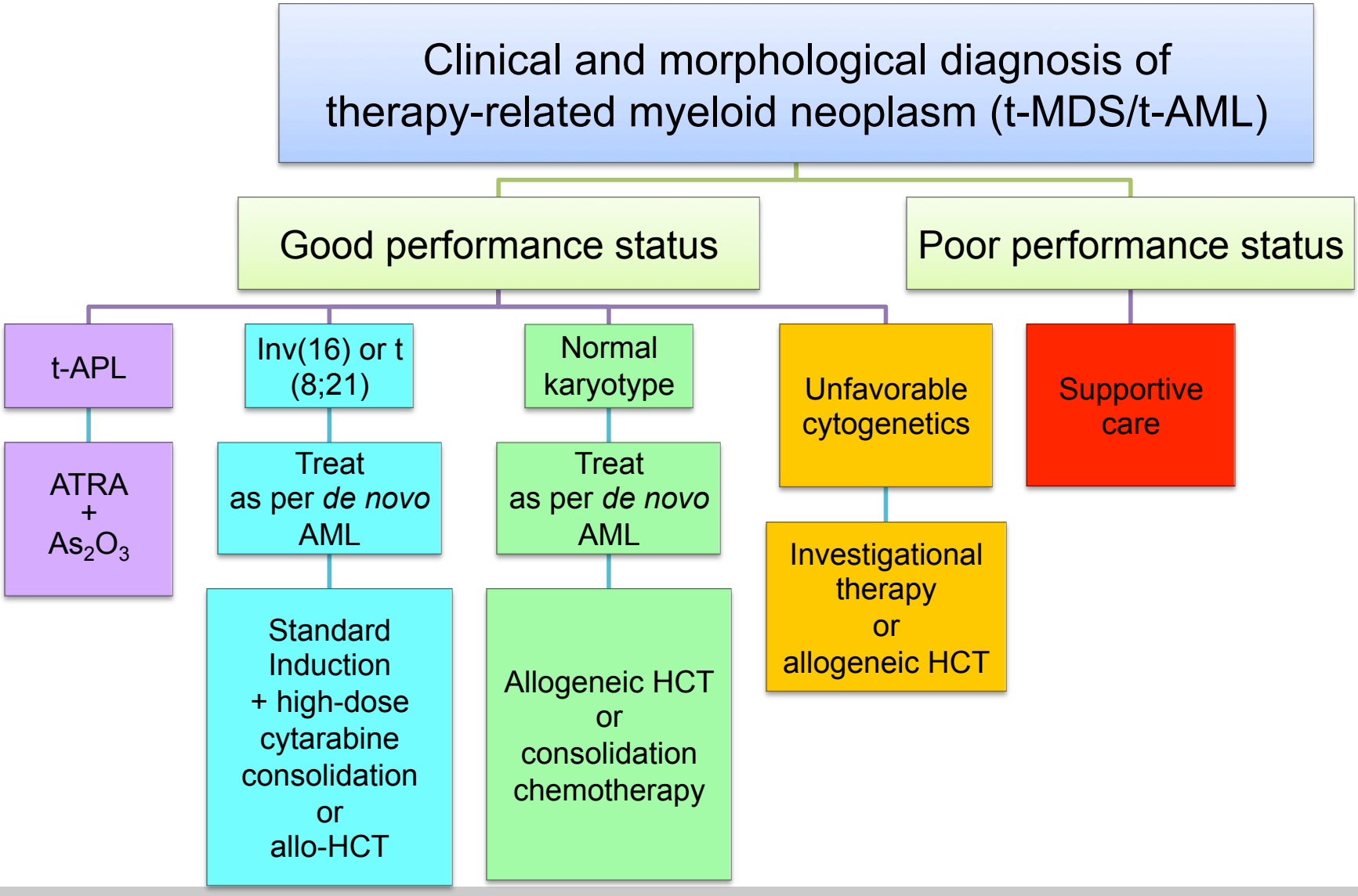
MK Andersen et al. Genes Chromos Cancer 2002; 33: 395-400

International Workshop on the Relationship of Prior Therapy to Balanced Translocations in t-AML



Genes Chromos Cancer, April 2002

Management of t-MN



Larson RA, Le Beau MM. Prognosis and therapy when acute promyelocytic leukemia and other "good risk" acute myeloid leukemias occur as a therapy-related myeloid neoplasm. Mediterr J Hematol Infect Dis. 2011;3(1): e2011032.

Summary

- Ionizing radiation is leukemogenic.
- Balanced chromosomal rearrangements occur after RT.
- t-MN following RT alone often has striking clinical and cytogenetic similarities to alkylator-associated t-MN.
  - Frequent clonal abnormalities of chromosomes 5 and 7.
  - Relatively long latencies (5-10 years).
  - Poor outcomes even with intensive therapy.
- Cytogenetics and not just previous cytotoxic therapy determine the course of t-MN
  - Some patients with recurring translocations or normal karyotypes have a better response to treatment and longer survival.

The Leukemia Program at The University of Chicago

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