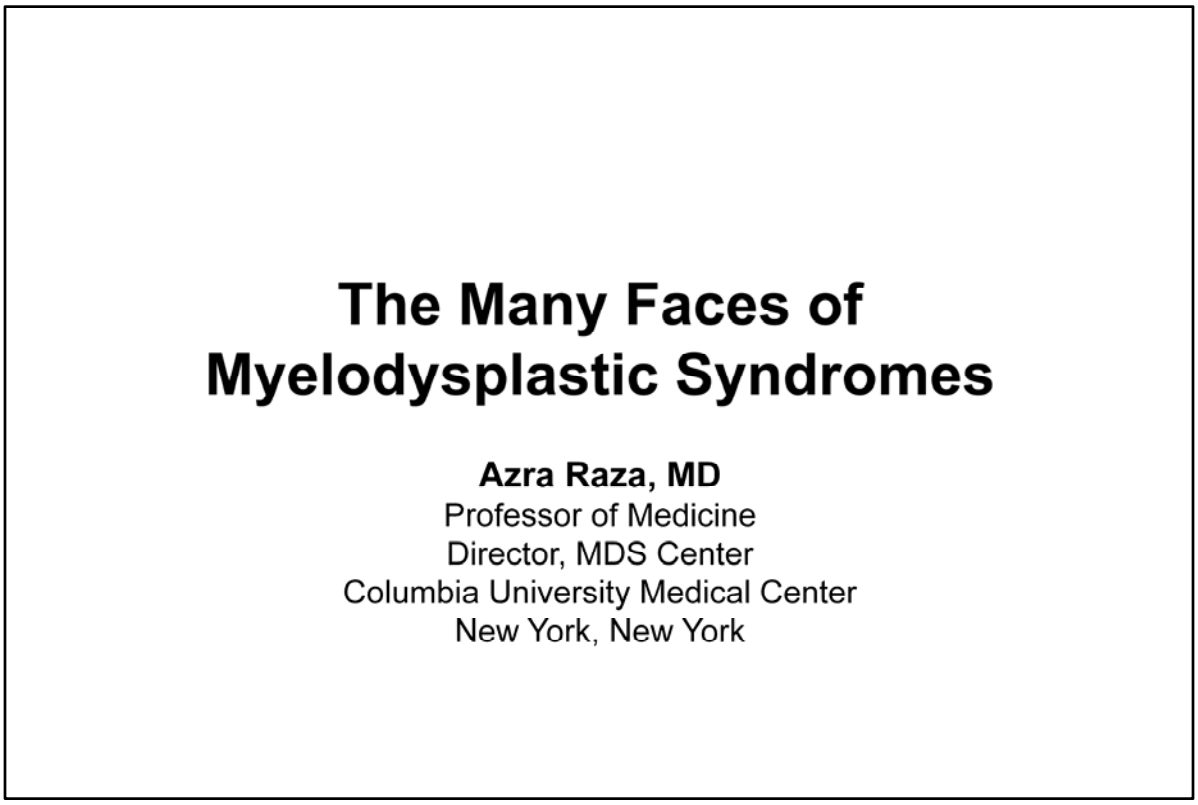
The Many Faces of Myelodysplastic Syndromes



Hi, my name is Azra Raza, and I am a professor of medicine and director of the MDS Center at Columbia University in New York. I am speaking to you today about managing MDS (myelodysplastic syndromes), and more specifically, in the next few minutes, I would like explain to you the different types of MDS that exist. So, just as the name connotes, myelodysplastic syndromes, it is not any single disease, it is a collection of syndromes. There is great heterogeneity in this disease, both in terms of morphologic classification as well as survival for patients, and attempts have been made for the last 35 to 40 years to bring some method to this madness and classify these syndromes into specific subtypes.

Milestones in Disease Characterization and Treatment

Development	Description	Year(s)
FAB	Morphologic classification	1982
IPSS	Prognostic stratification	1997
WHO	Morphologic classification	2000
IWG	Response criteria	2000
FDA approvals	AZA, DAC, LEN	2004-2005
IWG revised	Response criteria	2006
WPSS	Prognostic stratification	2007
WHO revised	Morphologic classification	2008

AZA=azacitidine; DAC=decitabine; FAB=French-American-British; FDA=US Food and Drug Administration; IPSS=International Prognostic Scoring System; IWG=International Working Group; LEN=lenalidomide; WHO=World Health Organization; WPSS=WHO-based Prognostic Scoring System.

Ault J, et al. *Clin J Oncol Nurse*. 2009;13(5):511-517.; Gattermann N. *Int J Hematol*. 2008;88(1):24-29; Cheson BD, et al. *Blood*. 2006;108(2):419-425.; Ghoshal K, et al. *Drugs Today (Barc)*. 2007;43(6):395-422.; Hazarka M, et al. *Oncologist*. 2008;13(10):1120-1127.; Alessandrino EP, et al. *Blood*. 2008;112(3):895-902.; Weinberg OK, et al. *Blood*. 2009;113(9):1906-1908.

It is not easy, but the first real classification of trying to see how many types of MDS there are was attempted by a group of investigators from France, America, and Britain—and this is known as a FAB classification, which really became universally accepted in the Western countries in 1982. This was a purely morphologic classification, but over time, it was realized that there were some issues with it.

FAB Classification of MDS

FAB Subtype	Blast (%)		Other Features
	Blood	Bone Marrow	
Refractory anemia (RA)	<1	<5	
Refractory anemia with ringed sideroblasts (RARS)	<1	<5	>15% ringed sideroblasts
Refractory anemia with excess blasts (RAEB)	<5	5-20	
Chronic myelomonocytic leukemia (CMML)	<5	5-20	Monocytosis >1,000/mcL
RAEB in transformation (RAEB-T)	≥5	21-30	±Auer rods

MDS=myelodysplastic syndromes
Bennett JM. *Semin Oncol.* 2005;32(4 Suppl 5):S3-10.; 1982; NCCN Guidelines. Myelodysplastic Syndromes. 2009.

So, according to FAB type, for example, a patient who presented with cytopenia could be described as *refractory anemia*, whereas the cytopenia was really low platelet count, and hemoglobin was perfectly normal in 14-gram range, but we could only call them *refractory anemia* patients. So, because of that, the World Health Organization (WHO) introduced the WHO classification—first in 2000, and it was revised in 2008.

FAB Versus WHO Classification

FAB	WHO	Dysplasia	Blast (%)
RA	5q- syndrome	Erythroid + mega	<5
	RA	Erythroid	<5
	RCMD	Erythroid + other	<5
	MDS-U	Nonerythroid	<5
RARS	RARS	Erythroid only	<5
	RCMD-RS	Erythroid + other	<5
RAEB	RAEB-1	≥1 lineage	5-9
	RAEB-2	≥1 lineage	10-19
RAEB-T	AML	Myeloid ± other	≥20
CMML	MDS/MPD	Variable	<20

AML=acute myeloid leukemia; MPD=myeloproliferative disorder; RCMD=refractory cytopenias with multilineage dysplasia
Mufti G, et al. *Hematology Am Soc Hematol Educ Program*. 2003;176-199.

And the difference between the FAB and the WHO classification was both are morphologic, but the WHO is now taking into account more details. For example, what used to be refractory anemia according to FAB was now divided into refractory anemia with 5q- or 5q-syndrome. Refractory cytopenia—which meant that patient could have just low platelet count or low white count also in addition to having just the anemia—but in this category, they were two subtypes or refractory cytopenia with either unilineage dysplasia or multilineage dysplasia at the bone marrow. The second classification according to FAB type used to be RARS, refractory anemia with ringed sideroblasts, anyone having more than 15% of ringed sideroblasts in the marrow and dysplasia were then RARS. But WHO further divided into RARS and then a category of refractory cytopenia with multilineage dysplasia and ringed sideroblasts—so RCMD-RS. Another type of MDS is that which presents with excess blasts. It used to be just straightforward RAEB according to FAB, but it was divided into two: RAEB-1, with 5%-9% blasts, and RAEB-2, 10%-19% blasts in the WHO classification. In FAB, we used to have a type of MDS called RAEB-T—that is, refractory anemia with excess blasts and transformation—and those were the patients who had blast counts of 20%-30%. But according to WHO, this is now called *acute myeloid leukemia* (AML). So, anyone over 20% blasts is AML according to WHO. And CMML (chronic myelomonocytic leukemia) that was considered as part of MDS according to the original FAB is now reclassified as an overlap syndrome, which is MDS/MPD—so myelodysplastic/myeloproliferative overlap syndrome. It is no longer considered just straightforward MDS.

IPSS for Risk Stratification

	Score Value				
Prognostic Variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone marrow blasts	<5%	5%-10%	--	11%-20%	21%-30%
Karyotype[a]	Good	Intermediate	Poor	--	--
Cytopenias[b]	0/1	2/3	--	--	--

	Total Score					
	0	**0.5**	**1.0**	**1.5**	**2.0**	**≥2.5**
Risk	Low	Intermediate I		Intermediate II		High
Median survival, y	5.7	3.5		1.2		0.4

[a] Good=normal, -Y, del(5q), del(20q); intermediate=other karyotypic abnormalities; poor=complex (≥3 abnormalities) or chromosome 7 abnormalities
[b] Hemoglobin <10 g/dL; absolute neutrophil count <1800/mcL; platelets <100,000/mcL

Greenberg P, et al. *Blood*. 1997;89(6):2079-2088.

Now, when a patient walks in, we want to know what is the prognosis. And in terms of finding the types of MDS by prognosis, the IPSS, or International Prognostic Scoring System, has been used, and this uses three variables: bone marrow blasts, cytogenetics, and number of cytopenias. A score is assigned, and if the score is low, then the patient has lower-risk disease, risk of transformation to leukemia, or risk of dying; and if the score is high, it is high-risk disease. And it was shown that median survival was related to risk. So, low-risk disease in original IPSS median survival is 5.7 years, whereas for patients who had high-risk disease it was only 0.4 years. However, this had its own problems and it was only accurately predictive in about 40%-50% of the patients.

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IPSS-R—2012

Table 3. IPSS-R prognostic score values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤ 2	—	> 2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50-< 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

— indicates not applicable.

Survival by IPSS-R

	No. of patients	Very low	Low	Intermediate	High	Very high
Patients, %	7012	19	38	20	13	10
Survival, all*		8.8	5.3	3.0	1.6	0.8

IPSS-R=revised IPSS
Greenberg PL, et al. *Blood*. 2012;120(12):2454-2465.

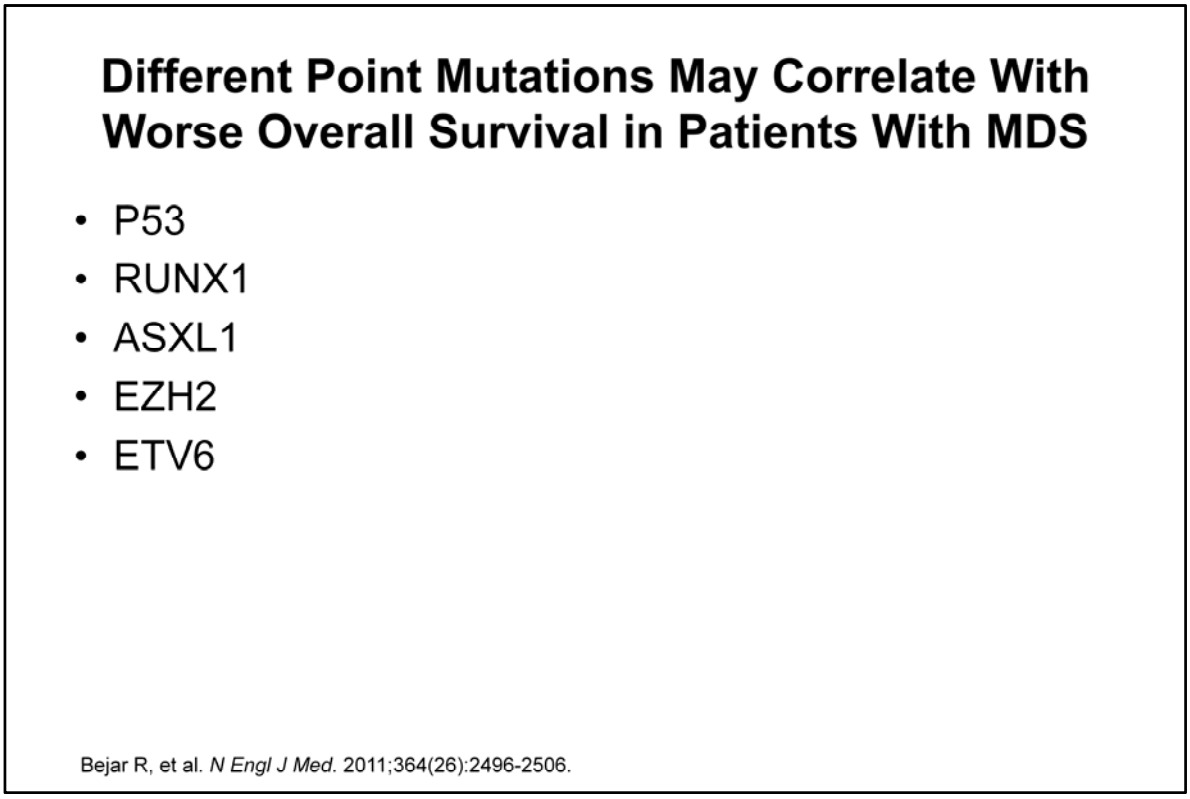
So, a IPSS system was then introduced in 2012, which just takes these three parameters in a more elaborate manner, so that cytogenetics have groups now ranging from very good to very poor cytogenetics, and a score is assigned on the basis of that. And in addition to looking at just the number of cytopenias, now you have to look at the profundity of cytopenia. So, sure, the hemoglobin is low, but is it below 8, or is it between 8 and 10, or is it above 10? What about platelets? Are they below 50,000 or above? So, with all of these looking at more elaborate ways, this revised IPSS system has been introduced using 7,000 patients who were followed first to make sure that they had stable disease for three months—and then if they had stable disease, these patients were included in developing the classification system.

Mortality of MDS Patients With or Without AML Evolution

Risk Category	No. (%) of Patients	Patients Who		
		Survival, Median (y)	Died From AML, n (%)	Died Without AML, n (%)
Very low	1,313	8.8	46 (13)	304 (87)
Low	2,646	5.3	174 (17)	861 (83)
Intermediate	1,433	3	205 (26)	568 (74)
High	898	1.6	207 (33)	421 (67)
Very high	722	0.8	193 (31)	422 (69)

Greenberg PL, et al. *Blood*. 2012;120(12):2454-2465.

And according to revised IPSS, now we have five categories: patients range from very low-, low-, intermediate-, to high-, and very high-risk disease. So, once again, you can see that these are various types of MDS. The problem that exists now is that none of these systems are going to be terribly accurate until we are able to take into account the biology of the disease into these classifications into types of MDS.



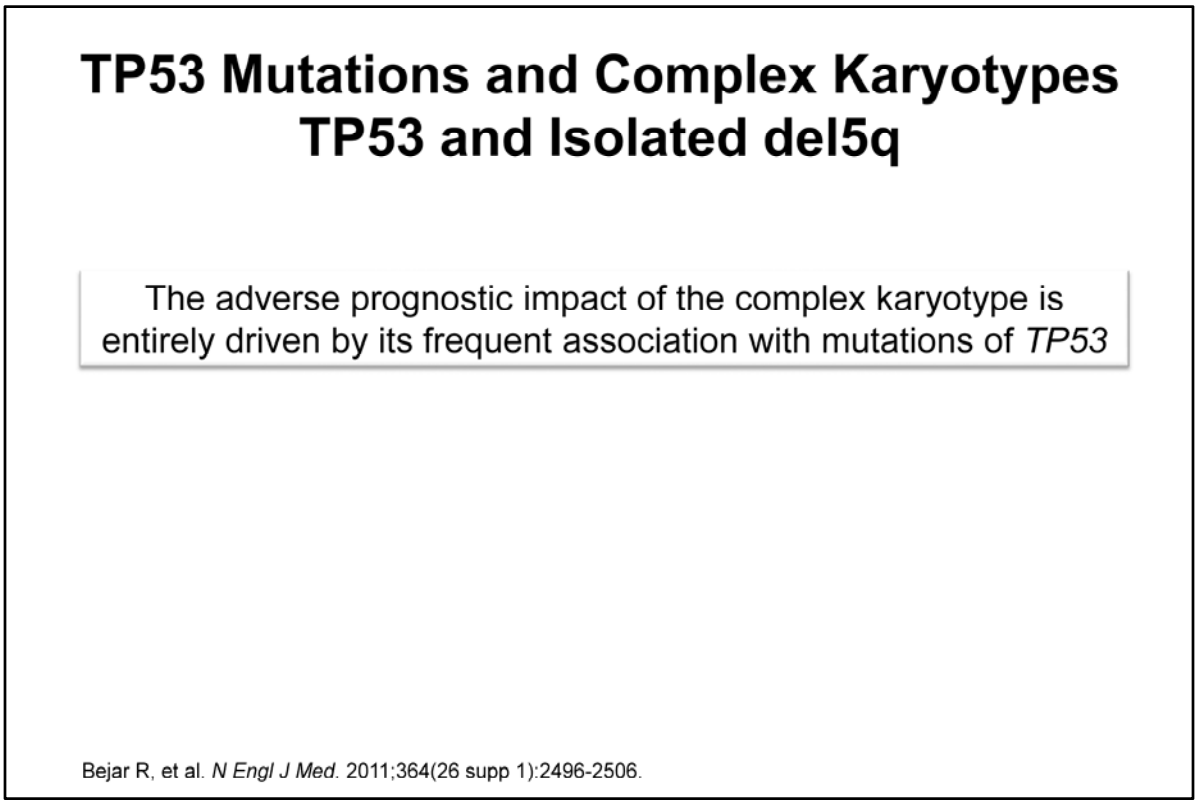
And so, in terms of finding biologic parameters, a paper was published in 2011 in *The New England Journal of Medicine* which showed that if there is a mutation in 1 of 5 genes—P53, RUNX1, ASXL1, EZH2, or ETV6—then survival of the patient is affected. In fact, what happens is that the presence of one or more mutations reclassifies the patient into the next-higher IPSS risk category.

Therapeutic Shift Based on Risk Reclassification From IPSS

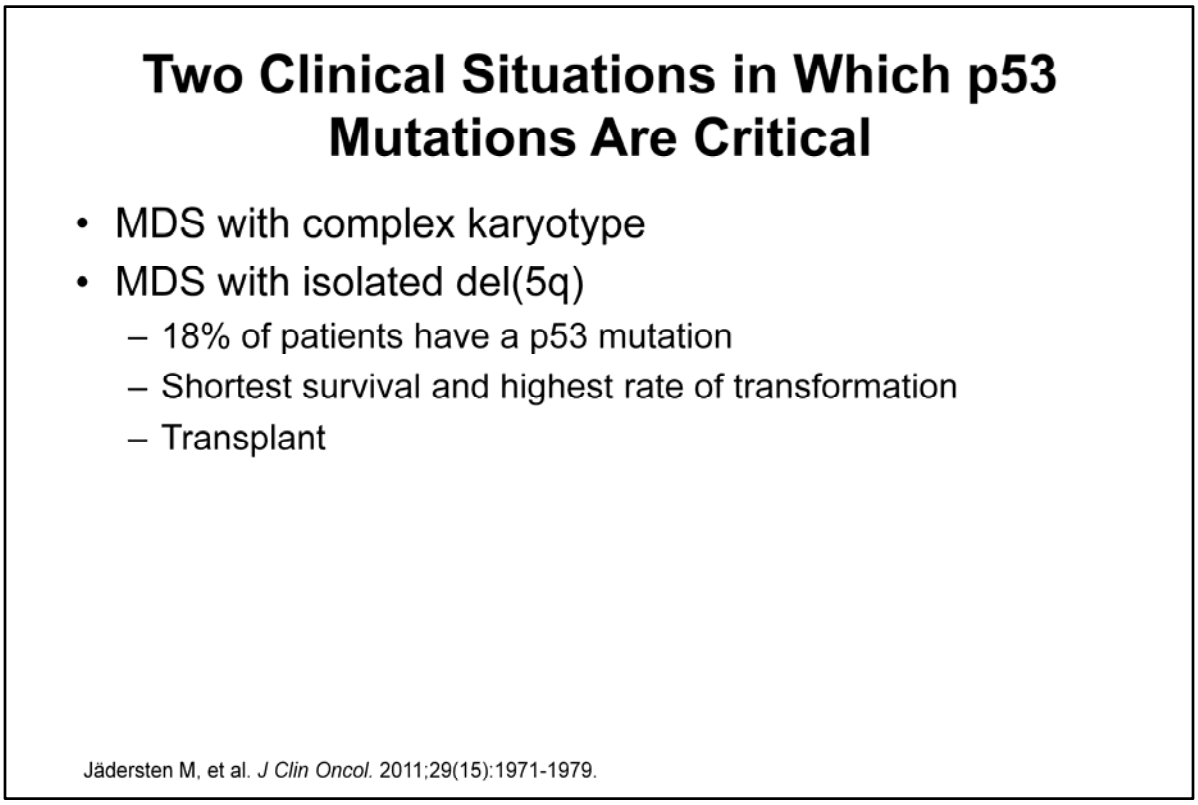
- The presence of one or more mutations would reclassify patients into the next highest IPSS risk group
- Example: Intermediate-1 patient with identified mutation shifts to Intermediate-2
  - According to National Comprehensive Cancer Network® guidelines, this could call for more aggressive therapies to be undertaken

Adapted from Bejar R, et al. *N Engl J Med.* 2011;364(26):2496-2506.

So, for example, if a patient is intermediate-1 risk disease but you find a mutation in ASXL1, then the patient is reclassified as having intermediate-2 risk disease.

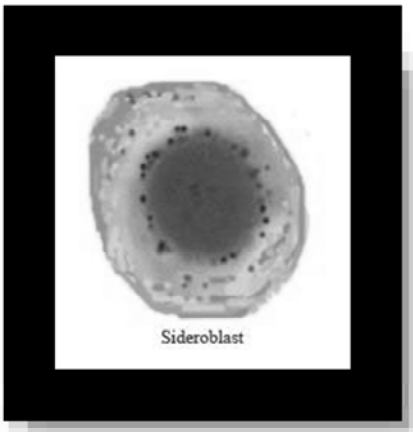


Another important thing to come out of this study was the fact that when a patient presents with complex cytogenetics we get very worried that this looks like an unstable genome and the patient is likely to progress rapidly. It turns out not to be the case always because if the patient has a complex karyotype and p53 mutation then sure, it seems that median survival is very low—half the patients are dead by 6 months, and everyone is dead by 2 years. So, it is not good to have complex cytogenetics and p53 mutations. On the other hand, if patients have complex karyotype but no p53 mutation they will be having really like lower-risk disease patients. So it seems that the adverse prognostic impact of the complex karyotype is almost entirely driven by mutation in p53.



In addition to this, on the opposite end of the spectrum, patients who present with an isolated deletion 5q are supposed to have a lower risk of transformation to leukemia and longer survival—but not so if they have a mutation in p53. Those are the patients who have isolated deletion 5q and p53 mutation who are going to progress rapidly to leukemia. So, now, if you have a patient with either a complex karyotype or, on the other hand, with an isolated deletion 5q—in both those circumstances, before giving prognostic information to the patient—it is important that you get the molecular profiling done. And you can also act on the basis of the molecular profile. So, patients with deletion 5q and p53 you know are at risk of transformation rapidly, so you should start a conversation and start making contingency plans about transplant or more aggressive therapies in these patients. So, I am just trying to show how different types of MDS are an evolving and a moving target right now as we are adding more and more clinical information.

Unique Case of RARS

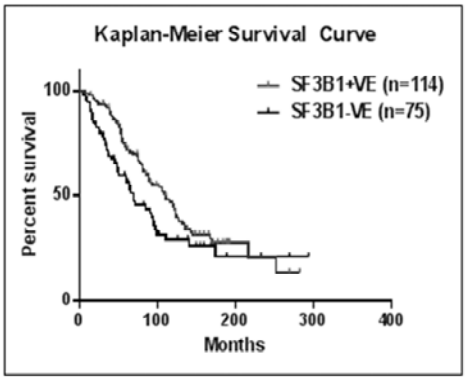


- SF3B1 mutation associated with ringed sideroblasts (60%-88%)
- 20%-35% of RARS do not have mutations in RNA splicing machinery
- Mutations cluster in exons 12-15 with hot spot K700E
- SF3B1 mutation related to survival

Papaemmanuil E, et al. *N Engl J Med*. 2011;365(15):1384-1395.; Yoshida K, et al. *Nature*. 2011;478(7367):64-69.; Malcovati L, et al. *Blood*. 2011:118(24):6239-6246.

Now, in terms of refractory anemia with ringed sideroblasts, they are supposed to have a long and good survival also, but recently, it has been shown that a mutation in splicing factor 3B1, SF3B1, is associated with the presence of ringed sideroblasts. This mutation, there is a hot-spot case, K700E, which seems to be present in up to 88% of patients with refractory anemia and ringed sideroblasts.

Survival and SF3B1 in 209 Patients With RARS

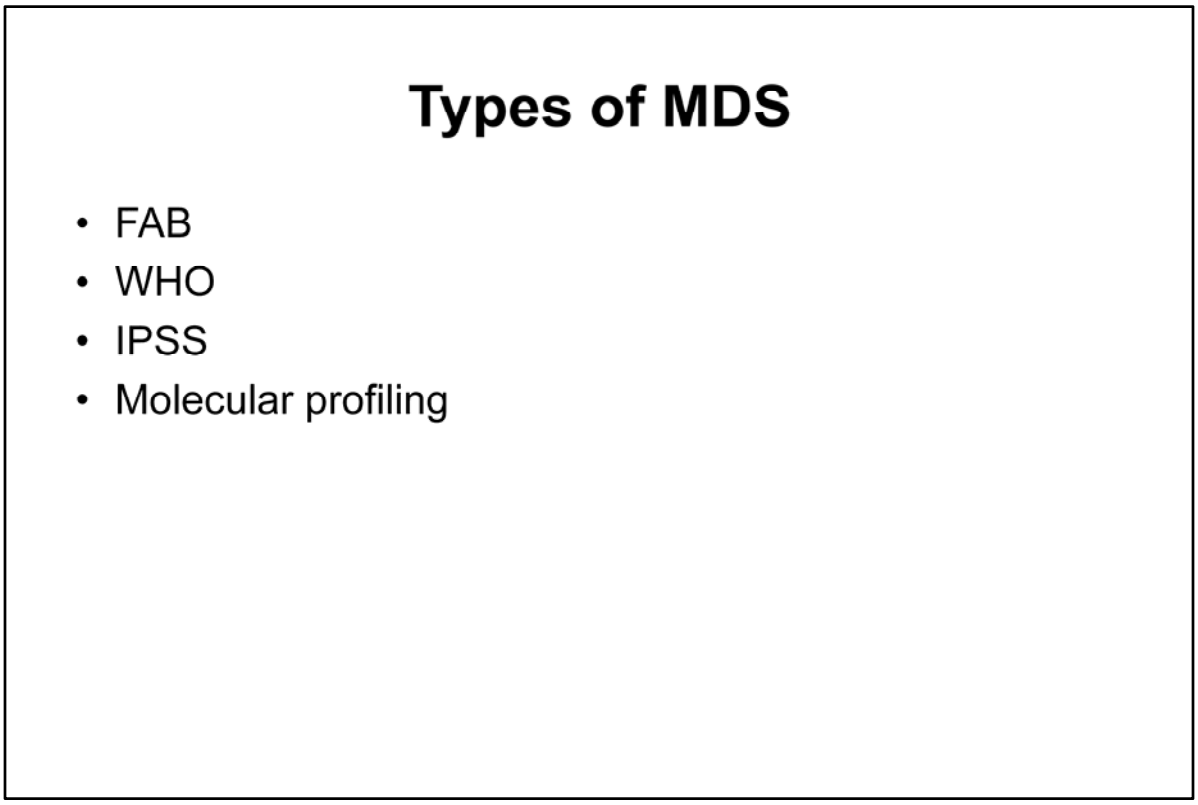


Mutated cases: median survival, 110 months
Wild-type cases: median survival, 70 months
(P <.0014)

Ali AM, et al. *Blood*. 2014;124(21):Abstract 3237.

In our experience, and we reported this in the ASH (American Society of Hematology) meetings in 2014. We sequenced the SF3B1 gene in 209* RARS patients and found that there is a mutation present in 60% of those patients; 40% of patients did not have the mutation. And so, what was important was that survival for patients with the mutation is almost twice as good, or statistically significantly longer, compared to those RARS patients who do not have the mutation. So, I am not saying that this mutation is giving a better survival to patients who have it; what I am saying is those RARS patients who do not have the mutation must have some other mutation which is making them have a worse prognosis, and we need to find that mutation. So, this is another interesting type of MDS.

*Dr. Raza misspeaks when she says 204, the correct number is 209



So, in summary, I have told you that MDS is being classified and what are the types of MDS since 1970s; attempts have been made by the FAB group, by the World Health Organization, by the IPSS group; and now, the latest thing is molecular profiling which is allowing us to bring more clarity to this kind of issue.

Summary

- Types of MDS vary by morphology, cytogenetics, IPSS, and mutational profiles
- At the moment, the accepted types of MDS are those defined by the revised WHO classification of 2008
- For prognostic assessment, the IPSS-R is being used but is still limited because it lacks biologic information
- A molecular classification is needed to more distinctly stratify patients into various types of MDS

And so, I think, in the next 5 years, as more and more mutational information becomes available, then we are going to start adding this information to the classification system. And eventually, it may happen that myelodysplastic syndromes will not be classified at all on the basis of morphology or cytogenetics, but rather entirely on the basis of *omics*—whether it is genomics, RNA sequencing, transcriptomic, or metabolomics and we are going to have a mutational profiling and genomic classification and types of MDS, rather than morphologic or cytogenetic. Thank you very much.