Melanoma in Childhood
Growing Problem or Fairy Tale?

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Disclosures

• Dr. Sondak is a compensated consultant for Array, Genentech, Merck, Novartis, Pfizer, Polynoma and Provectus

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The Pediatric Melanoma Journey

It’s Not Just One Size Fits All

IN UTERO  BIRTH  ONE YEAR  PUBERTY (~10 YRS)  18-21 YRS

- Perinatal
- Infantile
- Childhood
- Adolescent/Young Adult

Pediatric melanoma

- Incidence of pediatric melanoma is increasing ~2.9% per year over the last 3 decades (50% from 1988 to 2007)
- ~ 500 cases of melanoma estimated to be diagnosed in patients <21 in the US this year
  - 1-3% of all pediatric malignancies
  - 1-4% of all cases of melanoma
- Total US melanoma cases 87,100 in 2017, so 871 – 3484 pediatric cases

Siegel et al. CA Cancer J Clin 2017;67:7-30
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It’s Not Just One Size Fits All

IN UTERO  BIRTH  ONE YEAR  PUBERTY (~10 YRS)  18-21 YRS

Perinatal  Infantile  Childhood  Adolescent/Young Adult

Pediatric melanoma

- 11% of pediatric melanomas
- Clinical and pathologically distinct from adolescent melanoma, relationship to UV exposure less clear
- Conflicting data on survival outcomes compared to adolescent melanoma but generally considered more favorable

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It’s Not Just One Size Fits All

IN UTERO  BIRTH  ONE YEAR  PUBERTY (~10 YRS)  18-21 YRS

Perinatal  Infantile  Childhood  Adolescent/Young Adult

Pediatric melanoma

- Pediatric melanoma category rising most rapidly in incidence

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Before and After Puberty

- IN UTERO
- BIRTH
- ONE YEAR
- PUBERTY (~10 YRS)
- 18-21 YRS

- Perinatal
- Infantile
- Childhood
- Adolescent/Young Adult

Pediatric melanoma

Melanoma in situ
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Before and After Puberty

IN UTERO  BIRTH  ONE YEAR  PUBERTY (~10 YRS)  18-21 YRS

Perinatal   Infantile   Childhood   Adolescent/Young Adult

Pediatric melanoma

Age 14

Melanoma 10.8 mm, sentinel node positive
"A journey of a thousand miles begins with a single step"
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Starting With A Single Step

- Someone had to notice an odd bump, changing mole or some other skin lesion
- Someone had to go to the doctor
- Some doctor had to look at that skin lesion and decide that a biopsy should be performed

Wong et al. *Pediatrics* 2013;131:846-54
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Starting With A Single Step

• Someone had to notice an odd bump, changing mole or some other skin lesion
• Someone had to go to the doctor
• Some doctor had to look at that skin lesion and decide that a biopsy should be performed

• What signals a skin lesion to worry about in a child, adolescent or young adult?
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Should Kids Learn Their ABCDs?

After the Biopsy – More Questions!

I DON'T KNOW WHAT THE Heck IS GOING ON

AND I'M A GENIUS
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What the Heck is That?

• Once biopsied, the pathologist had to look at the specimen under the microscope and try to figure out what it was.

• That’s not as easy as it sounds, and two pathologists might easily disagree about what they think the diagnosis is.

• Why can’t they agree? How does the pathologist figure out what something is? How do they communicate it to other doctors?
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Beware the “Ivory Tower”
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Beware the “Ivory Tower”

• Some degree of diagnostic uncertainty is inevitable in many pediatric cases, but it can and should be minimized by good communication between clinician and pathologist.

• Diagnostic uncertainty in and of itself contributes to a disproportionate amount of anxiety among patients and family.

• An integrated approach requires clear communication among the medical team and with the patient and family, and commitment to manage the “worst case scenario”
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Enter the Detective
The Running Man
Innocent Bystander or Master Criminal?

Sondak et al. *Crit Rev Oncogenes*is*is 2015; in press*
The Running Man
Innocent Bystander or Master Criminal?

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Enter the Detective

• Like a detective, the pathologist searches for clues and looks for more evidence at the scene of the crime

• This can include the modern equivalent of fingerprints – DNA testing (CGH, FISH)

• Sometimes guilt or innocence can’t be determined just from the biopsy, but wider removal and checking the sentinel node can provide critical information – but unlike the detective we can say something is “guilty until proven innocent”
The Running Man
Innocent Bystander or Master Criminal?

Atypical Spitz Tumors

What Are They?

• Many cutaneous neoplasms, particularly in children and young adults, have pathologic features reminiscent of but not diagnostic for the benign Spitz nevus

• Some of these are clearly melanoma, termed “Spitzoid melanoma”

• Lesions lacking unequivocal diagnostic criteria for either a benign Spitz nevus or a Spitzoid melanoma are termed “atypical Spitz tumors”

Messina JL. Presentation at 2015 New York Melanoma Symposium
Atypical Spitz Tumors

Recently discovered genetic abnormalities

- 34% unknown
- BAP-1 loss
- HRAS
- NTRK
- ALK
- ROS-1
- BRAF
- RET
- Unknown

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“The Worst Case Scenario”
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“The Worst Case Scenario”

• If there is a chance a lesion could be melanoma, we treat it the way we would treat a melanoma.
• For kids, even the “worst case” scenario is not always really bad.
• But how does the pathologist communicate the chance the lesion could be melanoma to other doctors?
Atypical Spitz Tumors

Five Shades of Gray

S1
Benign Spitz nevus

S2
Atypical, favor benign

HRAS mutation
6q23 loss

S3
Atypical, uncertain biologic potential

S4
Atypical, favor malignant
6p25 gain
11q13 gain

S5
Spitzoid melanoma

9p21 deletion

Combination of morphologic, IHC, genetic, and chromosomal features can convey the best assessment of risk

Sreeraman Kumar et al. *Clin Oncol AYA* 2015;5:75-86
Atypical Spitz Tumors

Putting it all together

- Combination of morphologic, IHC, genetic, and chromosomal features can convey best assessment of risk

S1
Benign Spitz nevus
HRAS mutation
6q23 loss

S2
Atypical, favor benign

S3
Atypical, uncertain biologic potential

S4
Atypical, favor malignant
6p25 gain
11q13 gain

S5
Spitzoid melanoma
9p21 deletion or abn. CGH

Sreeraman Kumar et al. Clin Oncol AYA 2015;5:75-86
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“Prediction is very difficult...”

So if it IS melanoma, and my child is fine right now, what does the future hold?

“...especially if it's about the future.”

Niels Bohr
Nobel laureate in Physics (1922)
Positive sentinel lymph node was a significant predictor of recurrence on multivariate analysis.

45.5% of recurrences occurred after 5 years.

Han et al. *Ann Surg Oncol* 2012;19:3888-95
The period at risk of recurrence is defined as the age at diagnosis plus 9 months of gestation. According to Collins' law, a patient who has no clinical evidence of recurrence within this time period is considered cured.

Sure et al. Clin Neurol Neurosurg 1997;99:113-6
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Another Explanation?

| Subjects   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 |
|------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Age        |   |   |   |   |   |   |   |   |   |    |   |   |   |   |    |   |   |   |   |    |   |   |   |   |   |   |    |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SLN Metastasis |   |   |   |   |   |   |   |   |   |    |   |   |   |   |    |   |   |   |   |    |   |   |    |   |   |   |    |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| BRAF       |   |   |   |   |   |   |   |   |   |    |   |   |   |   |    |   |   |   |   |    |   |   |    |   |   |   |    |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| NRAS       |   |   |   |   |   |   |   |   |   |    |   |   |   |   |    |   |   |   |   |    |   |   |    |   |   |   |    |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| ROS1       |   |   |   |   |   |   |   |   |   |    |   |   |   |   |    |   |   |   |   |    |   |   |    |   |   |   |    |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| ALK        |   |   |   |   |   |   |   |   |   |    |   |   |   |   |    |   |   |   |   |    |   |   |    |   |   |   |    |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| NTRK1      |   |   |   |   |   |   |   |   |   |    |   |   |   |   |    |   |   |   |   |    |   |   |    |   |   |   |    |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| RET        |   |   |   |   |   |   |   |   |   |    |   |   |   |   |    |   |   |   |   |    |   |   |    |   |   |   |    |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| CDKN2A     |   |   |   |   |   |   |   |   |   |    |   |   |   |   |    |   |   |   |   |    |   |   |    |   |   |   |    |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| TERT promoter |   |   |   |   |   |   |   |   |   |    |   |   |   |   |    |   |   |   |   |    |   |   |    |   |   |   |    |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Outcome    |   |   |   |   |   |   |   |   |   |    |   |   |   |   |    |   |   |   |   |    |   |   |    |   |   |   |    |   |   |    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

Lee et al. *Science Rep* 2015;5:11200
Welcome to The Future

I see trees of green... red roses too
I see 'em bloom... for me and for you
And I think to myself... what a wonderful world.
The colors of a rainbow so pretty in the sky
Are also on the faces of people going by
I see friends shaking hands... saying how do you do
They're really saying... I love you.
I hear babies cry... I watch them grow
They'll learn much more... than I'll never know
And I think to myself... what a wonderful world.

The Future

The Pediatric Melanoma Journey
The Pediatric Melanoma Journey

Welcome to The Future

they'll learn much more

than I'll ever know
Conclusions

• Sentinel node biopsy is indicated in pediatric melanoma, and may be useful in at least some atypical melanocytic neoplasms
  ➢ As in adults, the additional value of CLND after a positive sentinel node biopsy is poorly defined
• Despite higher incidence of nodal metastases, survival is comparable to or better than what is historically reported for adults with melanoma
• Recurrences and deaths are seen beyond 5 years and long term follow-up is necessary
Conclusions

• Pediatric melanoma is no fairy tale – it is a growing problem facing pediatricians, dermatologists, surgeons and especially dermatopathologists

• All of us working together is imperative for optimum results in these challenging cases – where “Failure is Not an Option”
FAILURE IS NOT AN OPTION
MISSION CONTROL FROM MERCURY TO APOLLO 13 AND BEYOND

GÉNÉE KRAHNZ
FORMER FLIGHT DIRECTOR, NASA
HELPING KIDS WITH MELANOMA
Hi, My Name is Lacie.
I have had an amazing time at Moffit. Dr. Sandoval was so great when he removed a bump that was on my head. Just keep growing and growing. Moffit is a great place to come and have any surgery. Because the Doctors are great and the Nurses are very very nice.
I have had an excellent time at Moffit and I hope you have too. Thanks Moffit for everything you do!

Lacie Wilber
Pediatric melanoma patient

Presented at age 17 with axillary nodal metastasis after multiple recurrences of an “atypical blue nevus”
YOUR COURAGE INSPIRES OURS.