Malignant Melanoma: Current Management

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MedNet21
Center for Continuing Medical Education

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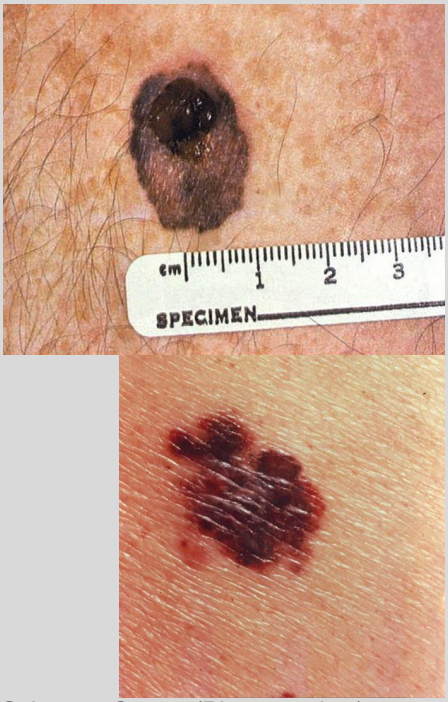
I have nothing to disclose

Outline

- Epidemiology
- Pathophysiology
- Evaluation and Diagnosis
- Interpretation of a Pathology Report
- Surgical Management
- Role of Surgery for Metastatic Disease

Malignant Melanoma

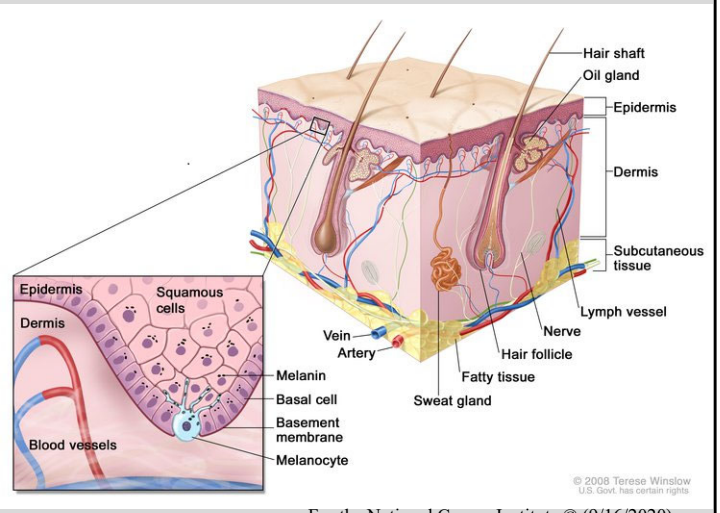
- Can affect any age, any ethnicity
  - More prevalent in older Caucasian patients
- Can affect nearly any anatomic site
  - Sun-exposed
  - Non-sun exposed areas
- Melanoma incidence is on the rise
- >100,000 new US diagnoses/year
- >6,800 US deaths/year



Laurence Meyer, MD, PhD, University of Utah Health Sciences Center (Photographer)

Pathophysiology

- Melanocytes at the dermoepidermal junction
  - Accumulation of UV mutations
  - Uncontrolled/dysregulated growth into the epidermis



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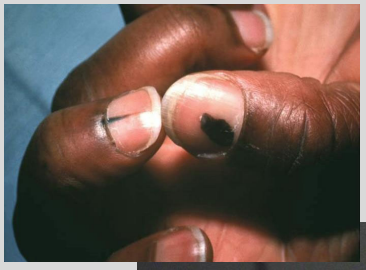
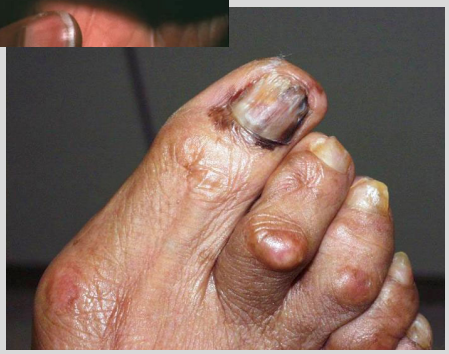
Subtypes of Melanoma

- Superficial spreading
  - Most common, good prognosis
- Lentigo maligna
  - Slow growing, good prognosis
- Nodular- more aggressive
- Acral- rare
  - Palms, soles, nailbeds
- Desmoplastic
- Mucosal





CDC/ Carl Washington, M.D., Emory Univ. School of Medicine; Mona Saraiya, MD, MPH

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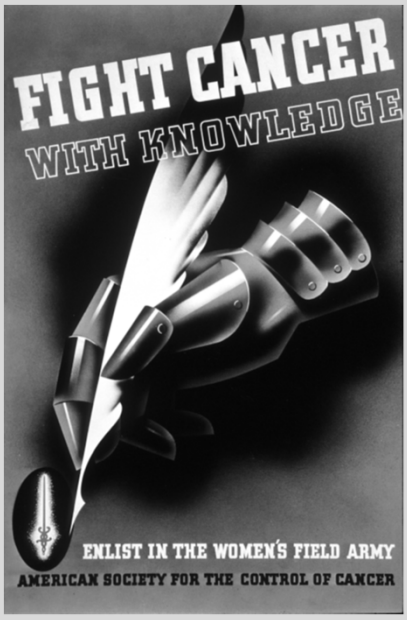
Evaluation and Diagnosis-The History

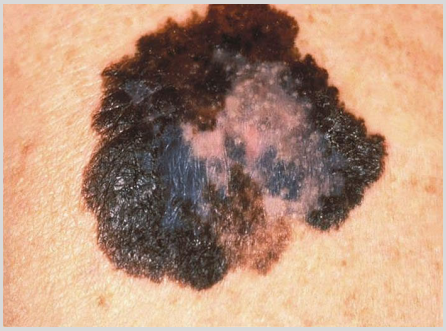
- **When was the lesion first noticed and has it changed?**
- **Does the patient have a personal or family history of melanoma or other skin cancers?**
- **Does the patient have a history of excessive sun exposure or tanning bed use?**
- **Did the patient suffer severe sunburns during their childhood or teenage years?**
- **Does the patient have a familial cancer syndrome (eg, familial atypical mole and melanoma syndrome or xeroderma pigmentosum)?**
- **Is the patient immunosuppressed?**



G. Terry Sharrer, Ph.d. National Museum Of American History.

Evaluation and Diagnosis-The Physical Examination

- Skin Examination
  1. Pattern Recognition
     - Asymmetry
     - Border irregularities
     - Color variegation
     - Diameter ≥6 mm
     - Evolution
  2. Comparative Analysis
     - The ugly duckling sign
  3. Dynamic analysis
- Examination of lymph node basins



Garbe et al. Eur J Cancer. 2020;126:141. Epub 2020 Jan 9.

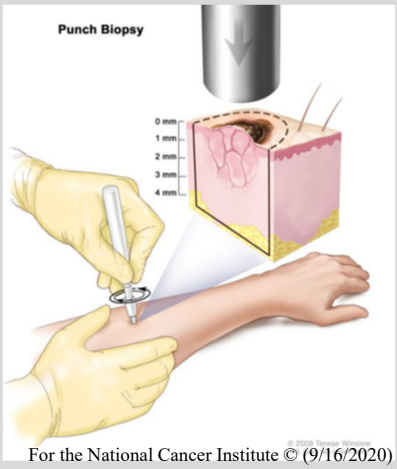
Indications for referral (or biopsy):

- A new mole appearing after the onset of puberty that is changing in shape, color, or size
- A long-standing mole that is changing in shape, color, or size
- Any mole that has three or more colors or has lost its symmetry
- A mole that is itching or bleeding
- Any new, persistent skin lesion, especially if growing, pigmented, or vascular in appearance, and if the diagnosis is not clear
- A new, pigmented line in a nail, especially where there is associated damage to the nail
- A lesion growing under a nail

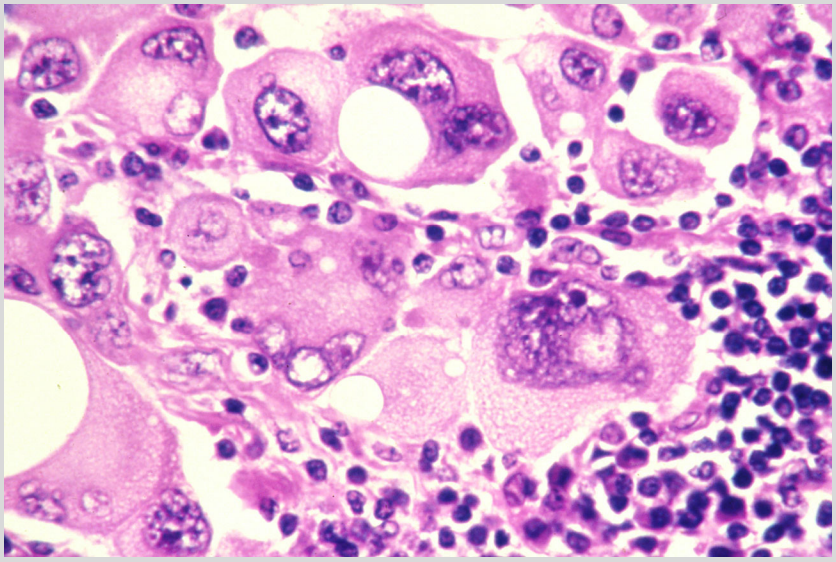
Marsden et al. Br J Dermatol. 2010;163(2):238. Epub 2010 Jul 1.

Diagnostic Evaluation—The Biopsy

- Punch biopsy is preferred
  - Provides full thickness specimen to pathology
- If it's shave biopsy versus no biopsy, always prefer shave



Zager, *J American College of Surgeons* 212.4 (2011): 454-460.



Courtesy of Dr. Lance Liotta Laboratory

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SPECIMEN	
Procedure	Biopsy, shave
Specimen Laterality	Left
TUMOR	
Tumor Site	Skin of upper limb and shoulder: Left proximal dorsal forearm
Histologic Type	Superficial spreading melanoma (low-cumulative sun damage (CSD) melanoma)
Maximum Tumor (Breslow) Thickness (Millimeters)	1.0 mm
Ulceration	Not identified
Anatomic (Clark) Level	IV (melanoma invades reticular dermis)
Mitotic Rate	None identified
Microsatellite(s)	Not identified
Lymphovascular Invasion	Not identified
Neurotropism	Not identified
Tumor-Infiltrating Lymphocytes	Present, nonbrisk
Tumor Regression	Not identified
MARGINS	
Peripheral Margins	Negative for invasive melanoma
Distance of Invasive Melanoma from Closest Peripheral Margin (Millimeters)	0.6 mm
Status of Melanoma in situ at Peripheral Margins	Negative for melanoma in situ
Distance of Melanoma in situ from Closest Peripheral Margin (Millimeters)	0.5 mm
Deep Margin	Negative for invasive melanoma
Distance of Invasive Melanoma from Deep Margin (Millimeters)	0.1 mm

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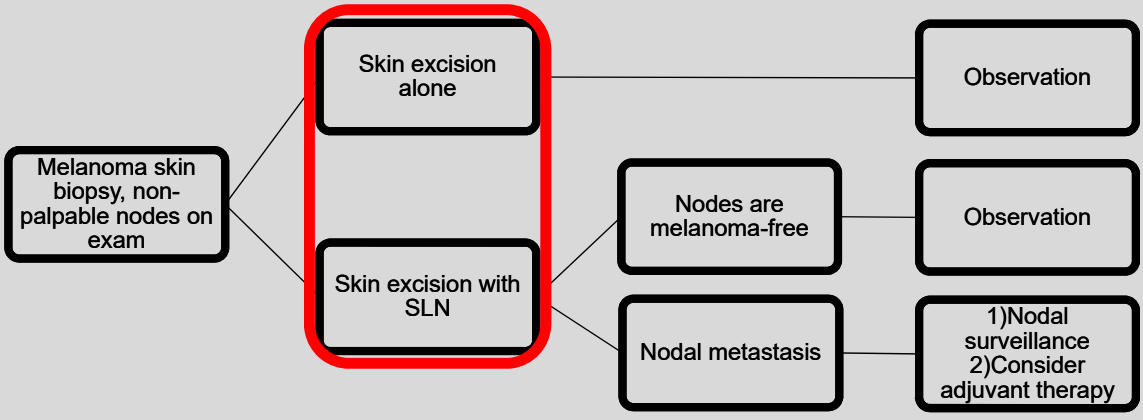
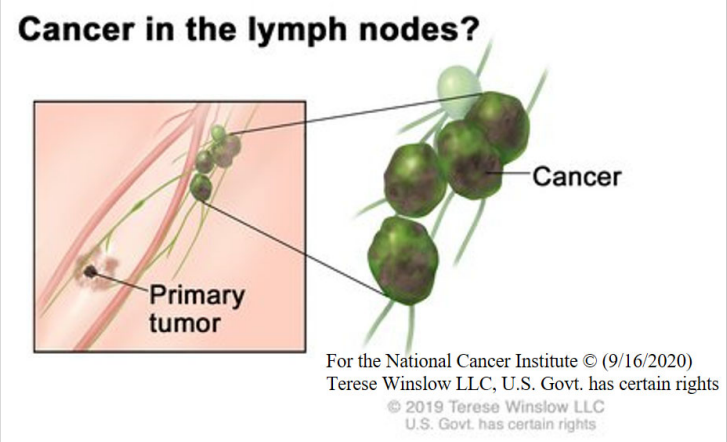
Management of Malignant Melanoma



Melanoma depth	Recommended gross surgical margin
< 1 mm	1 cm
1 mm – 2 mm	1 cm – 2 cm
> 2 mm	2 cm

- The sentinel lymph node is the most important predictor of survival in patients who present without palpable lymphadenopathy
- Is there microscopic spread of melanoma to lymph nodes?
  - Lymphoscintigraphy defines the specific lymph nodes that are most at risk for melanoma involvement

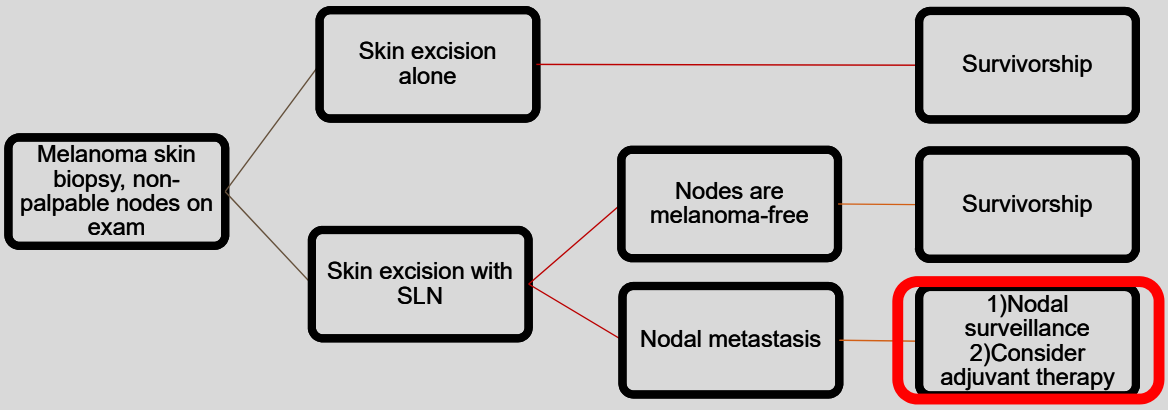


Gershenwald, *NEJM* 364.18 (2011): 1738-1745.

When do we perform sentinel lymph node biopsy?

- Which patients?
  - ≥ 0.8 mm depth (no other high-risk features)
  - ≤ 0.8 mm depth (ulcerated lesion, mitotic index ≥ 2/mm^2, "young" age)
- Sentinel lymph node biopsy should be considered when probability of lymph node metastasis ~5%
- Sentinel lymph node biopsy is safe, but not risk-free

Management of Malignant Melanoma



Management of patients with positive sentinel lymph nodes

- Completion lymph node dissection
  - Nearly 20% of patients have additional melanoma-containing lymph nodes
  - Risk of lymphedema
  - Large, painful incisions
  - High risk of postoperative wound complications

MSLT-2 trial

- Randomized patients with SLN metastasis to completion lymph node dissection versus observation
- **No difference in melanoma survival!**

Faries, *NEJM* 376.23 (2017): 2211-2222.

Therapy for Stage III or IV disease

Oral tyrosine kinase inhibitors	IV immunotherapy	Regional immunotherapy
• Vemurafenib, dabrafenib, etc • Optimally paired with an oral MEK inhibitor (trametinib) • Quick tumor response, issues with resistance	• Pembrolizumab (Keytruda) • Nivolumab (Opdivo) • Longer time to clinical response, some toxicities irreversible • Contraindicated in immunosuppression	• TVEC (Imlygic) • Requires intralesional administration every 2 weeks for 6 months

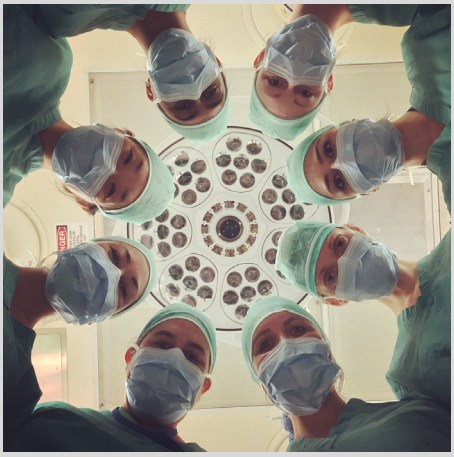
Survivorship: skin surveillance

- Regular complete skin exams
  - Melanoma in situ: every 12 months
  - Stage IA-IIA: every 6-12 months for 5 years, then annually
  - Stage IIB-IV: every 3-6 months x 2 years, then every 3-12 months x 3 years, then annually

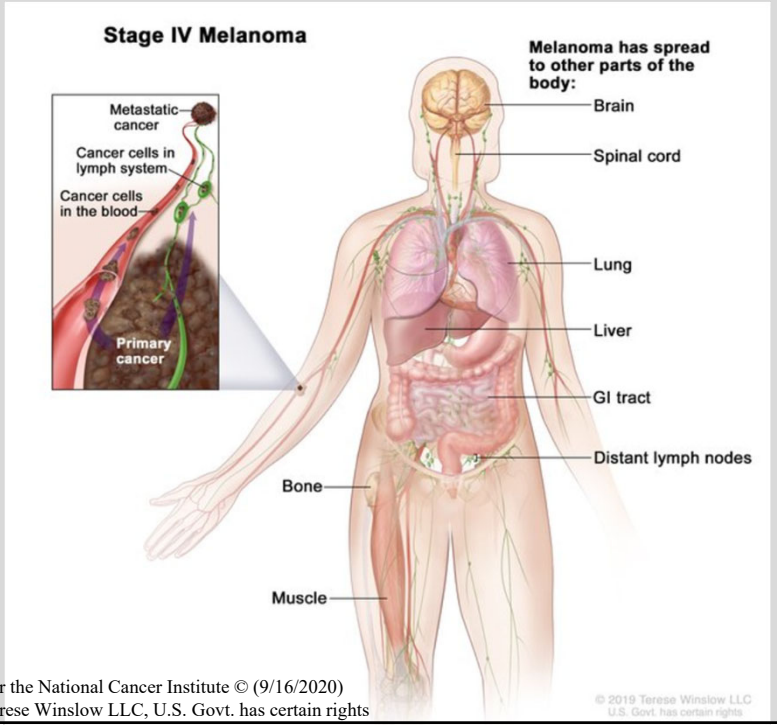
- **Low risk invasive melanoma: excision alone**
- **Higher risk melanoma : excision with sentinel lymph node biopsy**

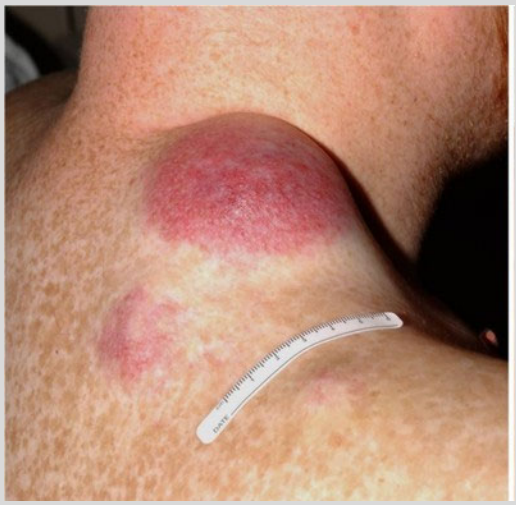
- **Patients who present with clinically palpable lymphadenopathy or concern for distant disease: biopsy of suspicious sites**
- **If proven nodal or distant spread: staging work up and multidisciplinary management**

Surgical Management of Stage IV Disease

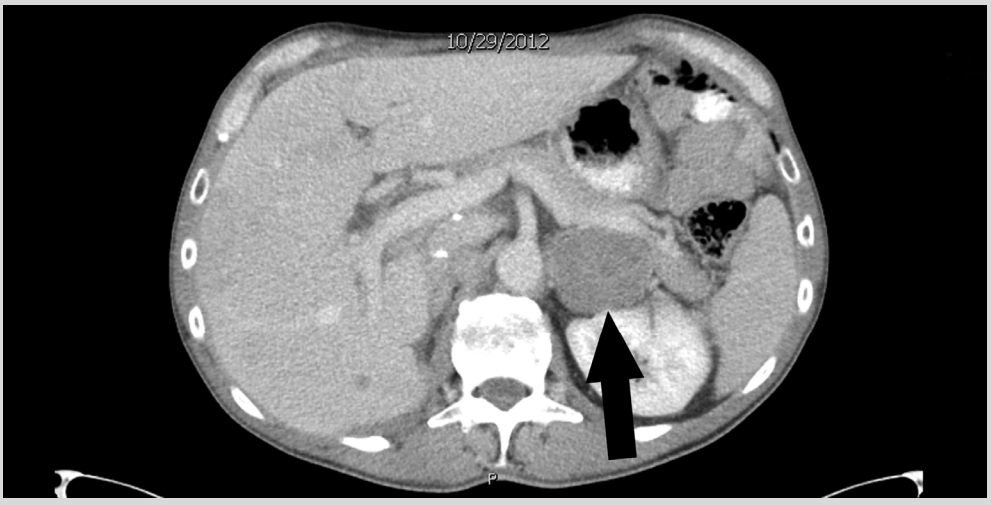


Courtesy of Jeremy Davis (photographer)

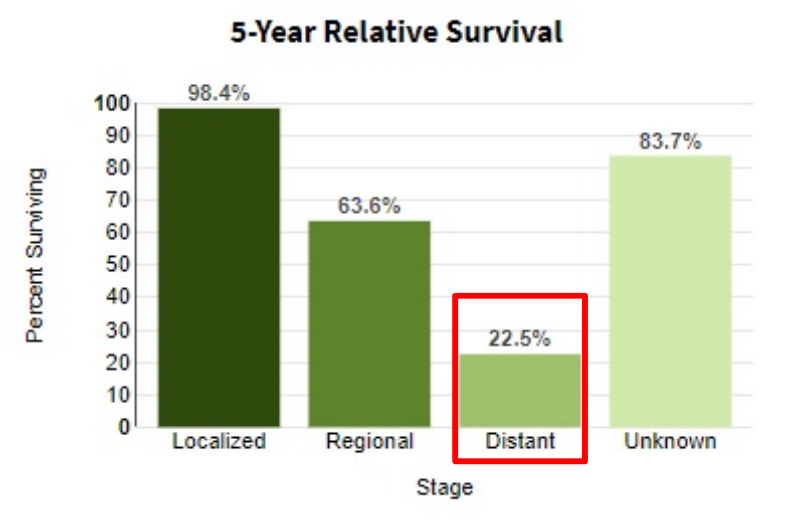




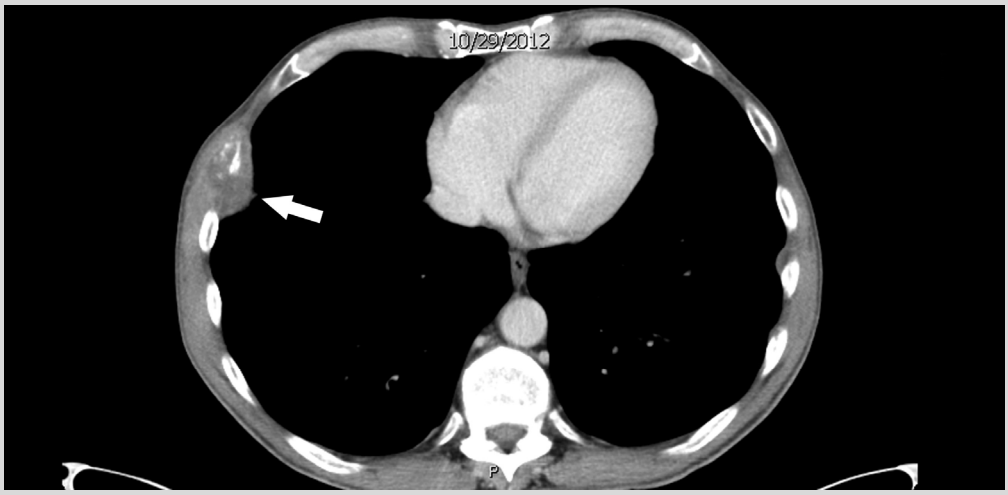
Courtesy of Steven A. Rosenberg, Mark Dudley



Courtesy of Dr. Peter Choyke, Molecular Imaging Program



By Cancer.gov - https://seer.cancer.gov/statfacts/html/melan.html, Public Domain, https://commons.wikimedia.org/w/index.php?curid=71472707



Take-Home Points

- Melanoma is the deadliest form of skin cancer and the incidence is increasing
- Suspicious lesions should be referred to a specialist and biopsied
- Surgical resection is the mainstay of treatment for cutaneous melanoma and may be combined with sentinel node biopsy to provide important prognostic information
- Patients with advanced melanoma should be managed by a multidisciplinary team
- Surgical resection in patients with Stage IV disease can improve survival in select patients
- Patients with melanoma require lifelong surveillance

THANK YOU!

The role of surgery in advanced melanoma

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Section Head for Melanoma/Sarcoma,
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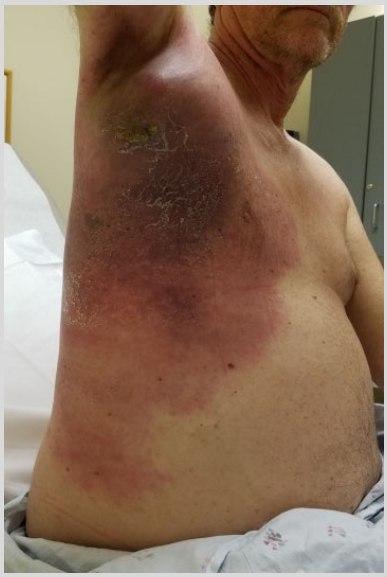
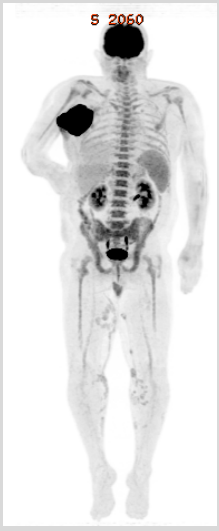
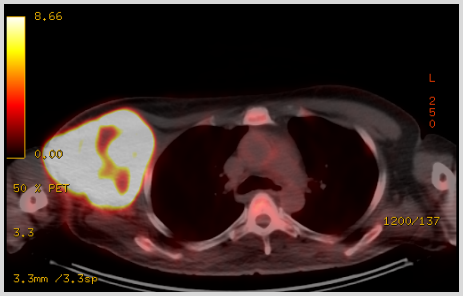
Topics

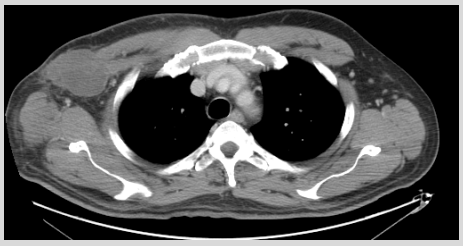
- Role of neoadjuvant therapy for patients with resectable Stage III/IV disease
- Role of metastasectomy in advanced melanoma

Challenging case





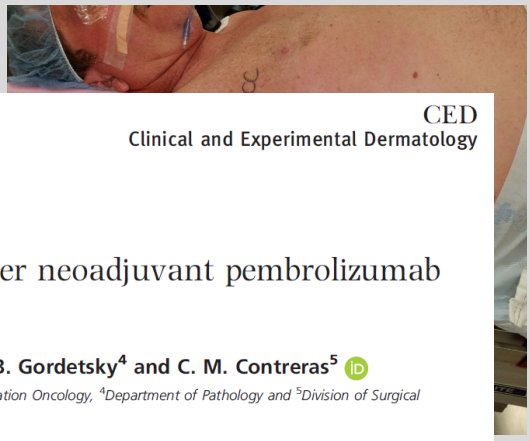




Neoadjuvant therapy

COMPLETE PATHOLOGIC RESPONSE

- Neoadjuvant pembrolizumab with concurrent radiation therapy



CPD • Therapeutic vignette

CED
Clinical and Experimental Dermatology

CPD

Pathological complete response after neoadjuvant pembrolizumab and radiation

J. N. Mynard,[1] R. M. Conry,[2] J. De Los Santos,[3] J. B. Gordetsky[4] and C. M. Contreras[5]

[1]School of Medicine, [2]Division of Hematology-Oncology, [3]Department of Radiation Oncology, [4]Department of Pathology and [5]Division of Surgical Oncology, University of Alabama at Birmingham, Birmingham, AL, USA

doi: 10.1111/ced.13820

Objectives

- Describe at least 2 advantages of neoadjuvant therapy in patients with resectable Stage III/IV melanoma
- List the 2 main classes of neoadjuvant therapy in patients with resectable Stage III/IV melanoma
- State at least 2 roles for metastasectomy in patients with Stage IV melanoma

Rationale for neoadjuvant therapy

- Earlier systemic therapy for tumors with high risk for systemic disease
- Opportunity to determine if the tumor is responsive
- Surgical complications, multi-stage resection/reconstruction can delay initiating systemic therapy
- Neoadjuvant therapy can facilitate a less morbid operation
- Having a complete pathologic response may predict favorable long-term outcome

Types of melanoma therapy

Immune checkpoint inhibitors	BRAF/MEK inhibitors	Intralesional therapies
• IV medications • Remove the "brakes" of the immune system • Pembrolizumab • Nivolumab • Ipilimumab	• Oral medications • Effective only for tumors with BRAF mutations • Paired with MEK inhibitors • Vemurafenib, dabrafenib, encorafenib	• A diverse set of agents • Injected directly into tumors • Viral • Immunomodulators

Neoadjuvant BRAF/MEK inhibitors: NeoCombi trial

Study design

- Single institution, Phase II study
- Stage IIIB-C melanoma
  - All patients BRAF mutant
- ECOG performance status 0-1
- 35 patients:
  - BRAF/MEK inhibitor x 12 weeks
  - Surgical resection
  - BRAF/MEK inhibitor x 40 weeks

Findings

Primary endpoint	**Proportion with a pathologic complete response**	**49%**
Secondary endpoint	Grade 3-4 adverse events	29%

Long, et al. *Lancet Oncology* 20.7 (2019): 961-971.

NeoCombi trial limitations

- Small sample size
- Despite impressive complete pathologic response rate…
  - Significant short-interval recurrence (57% = 20/35 patients)
    - 8 of 20 patients (40%) recurred within the first year
    - 12 of 20 patients (60%) recurred after first year
  - 55% of these recurrences were local and/or regional
- No predictors of which patients:
  - Achieve a pathologic complete response
  - Develop recurrence

Long, et al. *Lancet Oncology* 20.7 (2019): 961-971.

Even one dose of immunotherapy helps

Study design

- Single institution, Phase Ib trial
- 27 patients, stage III/IV resectable melanoma
- One dose of neoadjuvant pembrolizumab
- Surgical resection
- Post-op pembrolizumab x 1 year

Findings

- Major or complete pathological response in 30% of patients (8 of 27)
- Decrease in tumor diameter via PET after 3 weeks
- Detectable immune response in blood:
  - 3 weeks after the single pre-op dose
  - 1 week after the single preop dose

Huang, et al. Nature Med 25.3 (2019): 454-461.

Are 2 neoadjuvant IO agents better than 1?

Study design

- Single institution, Phase II trial
- 23 total patients, randomized to:
  - Arm A: Neoadj nivolumab
  - Arm B: Neoadj ipi + nivo
- All patients: surgical resection + adjuvant nivolumab

Findings

	Overall response	Pathologic complete response	Treatment related adverse events
Arm A	73%	45%	73%
Arm B	25%	25%	8%

- Toxicity concerns contributed to premature trial conclusion

Amaria, et al. Nature Med 24.11 (2018): 1649-1654.

Long-term outcome after neoadjuvant immunotherapy

Study design

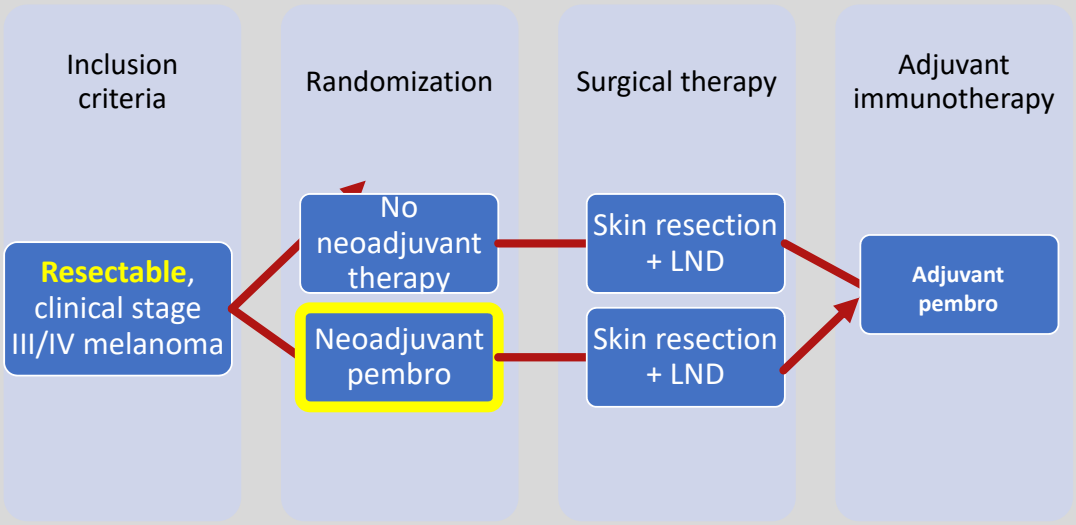
- Single institution, retrospective
- 59 patients (2011-2018) immunotherapy and resection
  - 18 (31%) adjuvant immunotherapy
  - 41 (69%) neoadjuvant immunotherapy
- Patients well-balanced in preop features

Findings

- No difference in disease-free survival
- Adjuvant therapy associated with worse 3-year disease-free survival vs pathologic response to neoadjuvant therapy
  - Adjuvant group: 31%
  - Neoadjuvant group: 73%
  - Hazard ratio 1.19, p=0.02

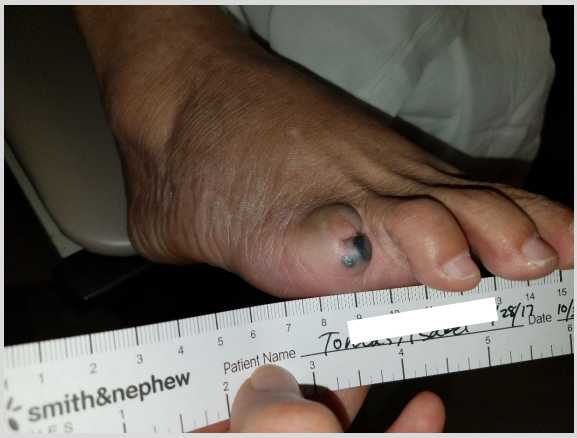
Song, et al. *Ann Surgical Oncology* (2020): 1-12.

Neoadjuvant therapy for resectable melanoma: SWOG 1801



https://www.swog.org/clinical-trials/s1801

Challenging case #2

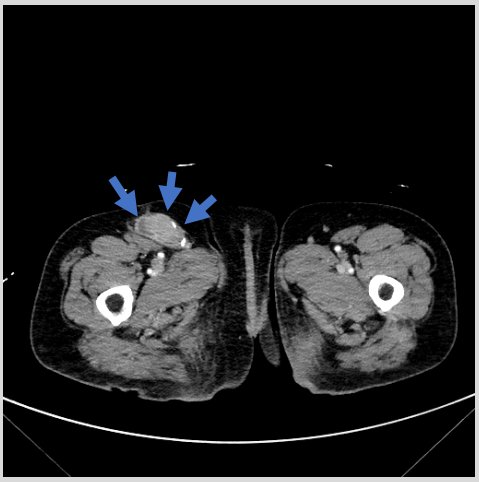


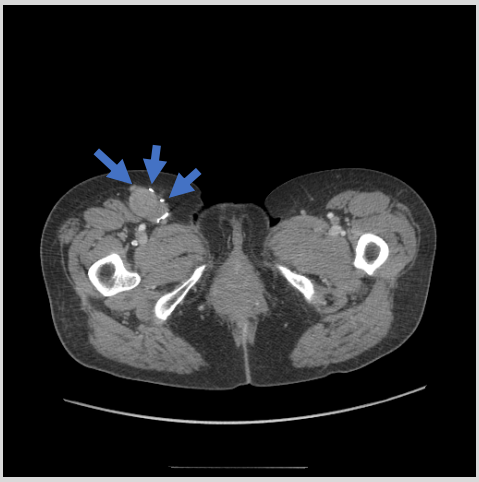
- 56 year old Hispanic woman
- 2015 melanoma of the right 5th toe diagnosed, s/p partial toe amputation
- Several months later, a right groin mass is excised
- 3 months later, the mass recurs
  - Core needle biopsy confirms metastatic melanoma
  - No other sites of disease

Nodal response

Started pembrolizumab June 2017

Finished pembrolizumab + Imlygic Oct 2018

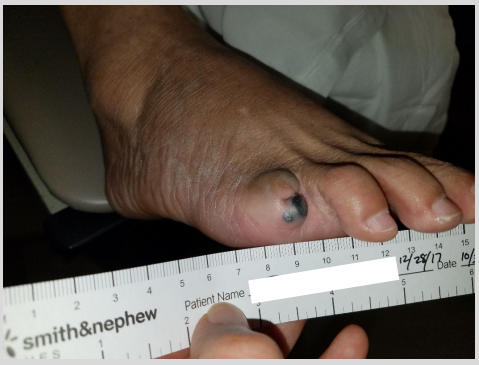


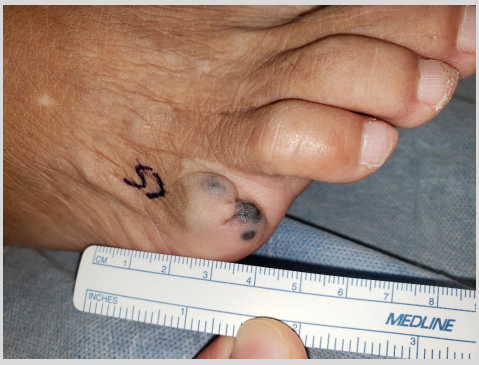


Foot response

Initial

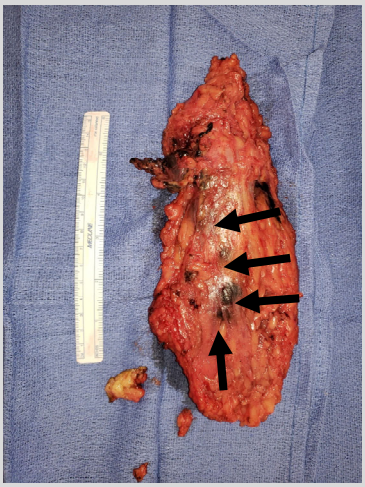
After therapy



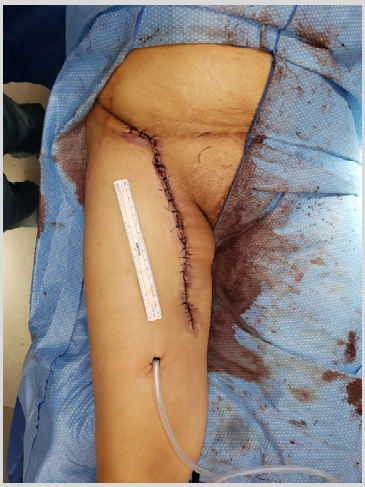


Operative findings

Inguinal specimen



Incision



Pathology report

A. Right foot, fifth toe, amputation:

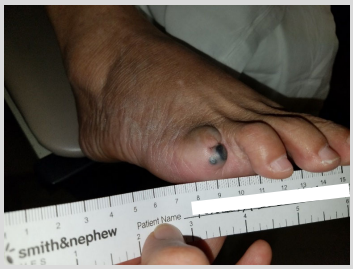
- Prominent melanophage deposition and fibrosis involving dermis and subcutaneous adipose tissue, consistent with tumor bed changes.
- **No viable melanoma is identified.**
- Mature bone uninvolved by tumor.
- Margins uninvolved by tumor bed.

B. Skin and lymph nodes, right inguinal, excision:

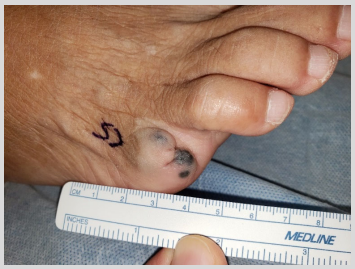
- Prominent melanophage deposition and fibrosis involving six of seventeen lymph nodes, dermis, and

Long-term follow-up

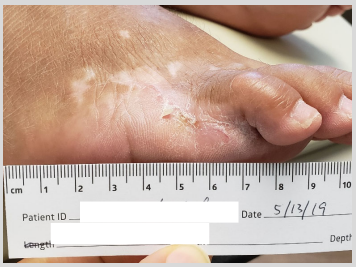
Initial



After therapy



2 years after presentation

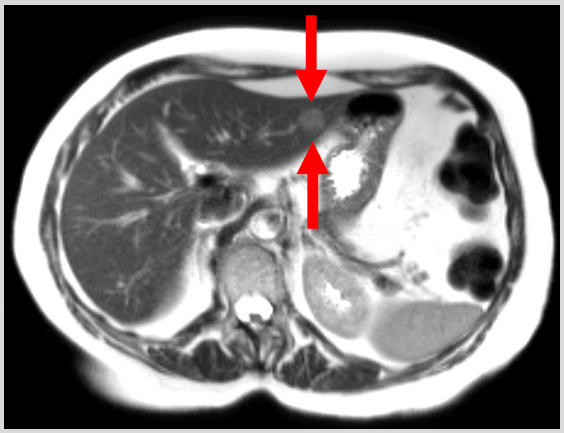


Intent of metastasectomy

- Curative intent
  - For patients with limited disease, and limited candidacy for systemic therapy
    - BRAF wild-type patients
    - Transplant patients
    - Patients treated with underlying autoimmune disease
- Palliative intent

Isolated ocular melanoma metastasis

- 67 year old woman
- 2016: pigmented lesion, left eye
- 2017: s/p ^{125}I plaque therapy
- 2020: surveillance imaging shows liver lesion, biopsy proves metastatic melanoma.
- s/p robotic resection, home on POD #1.
- No post-discharge narcotics



Rationale for palliative metastasectomy

- Provide analgesia
- Provide wound control
- Relieve intestinal obstruction or bleeding
- Only modality remaining after extensive pre-treatment
- The only modality that can make a patient a candidate for systemic therapy
- Isolated site of disease following effective therapy

Role for metastasectomy

- Single institution retrospective study
- 2,353 patients with metastatic melanoma
  - Two eras
    - 1967-2007
    - 2008-2015
- 45.2% underwent metastasectomy
- Proportion of patients undergoing resection higher in current era vs previous era (54.5% vs 44.7%, *p*=0.02)
- Patient selection is important
  - Age
  - Single-organ involvement

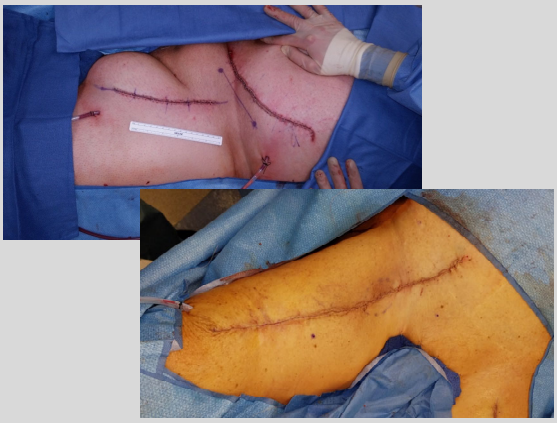
Nelson, et al. *Ann Surg Onc* 26.13 (2019): 4610-4618.

Why is metastasectomy successful?

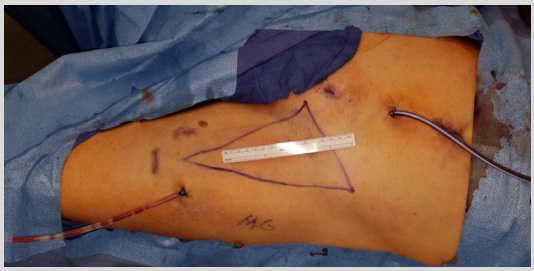
- Improved imaging improves patient selection
  - Contrast-enhanced CT and MRI
  - PET imaging
- Multidisciplinary melanoma care
  - Communication and coordination is essential
  - Has the patient exhausted all standard therapies and clinical trial options?
- Improved anesthesia techniques, enhanced recovery after surgery
- Minimally invasive approaches
  - Laparoscopic, robotic

Surgical approach matters

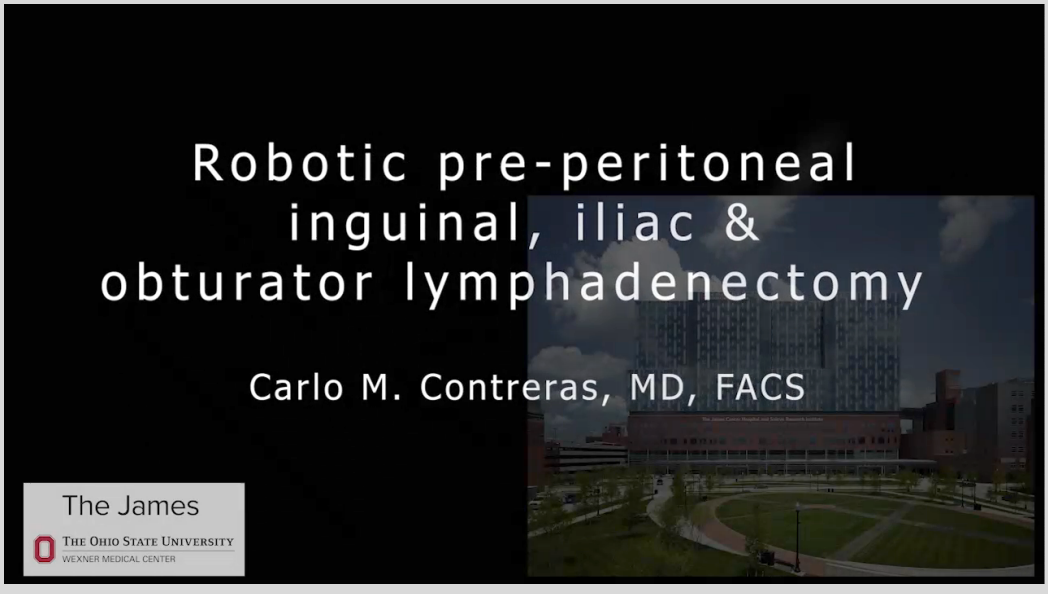
Standard technique



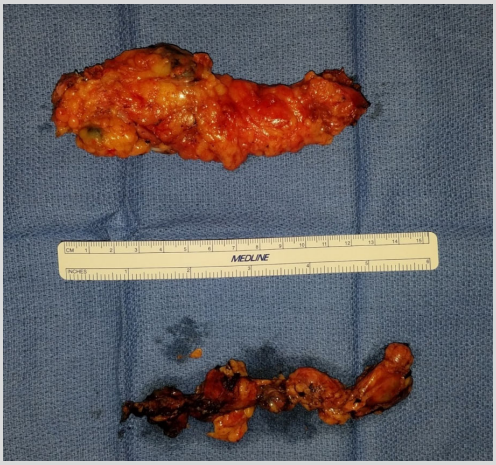
Minimally invasive technique



Robotic inguinal lymphadenectomy



Endoscopic LND specimens

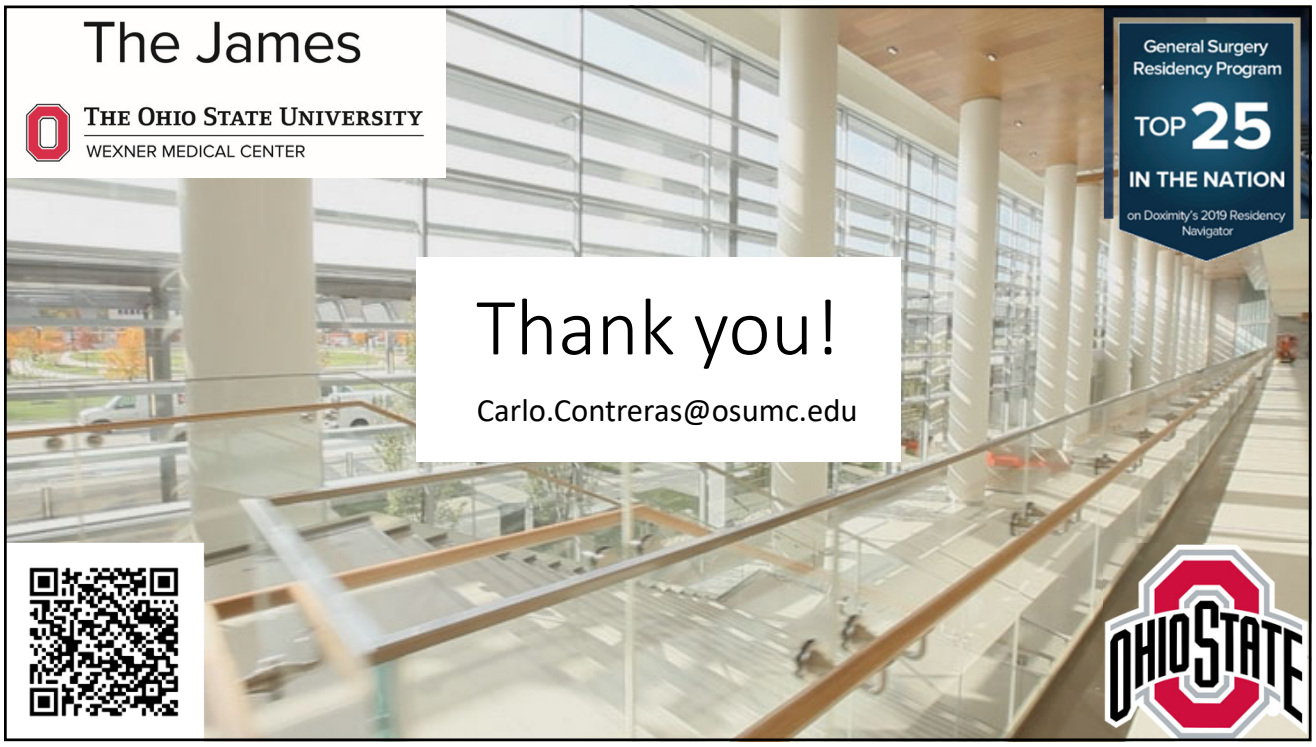


Inguinal LND specimen

Iliac/obturator LND specimen

Summary

- Neoadjuvant therapy has an increasing role in patients with resectable Stage III/IV melanoma
- The two main classes of neoadjuvant therapies are BRAF/MEK inhibition and immunotherapy
- The optimal neoadjuvant regimen is yet to be defined
- There is a role for surgical resection in patients with Stage IV melanoma
  - Curative intent
  - Palliative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Thank you!
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