

The Role of Metastasectomy for Melanoma in an Era of Effective Systemic Therapy.



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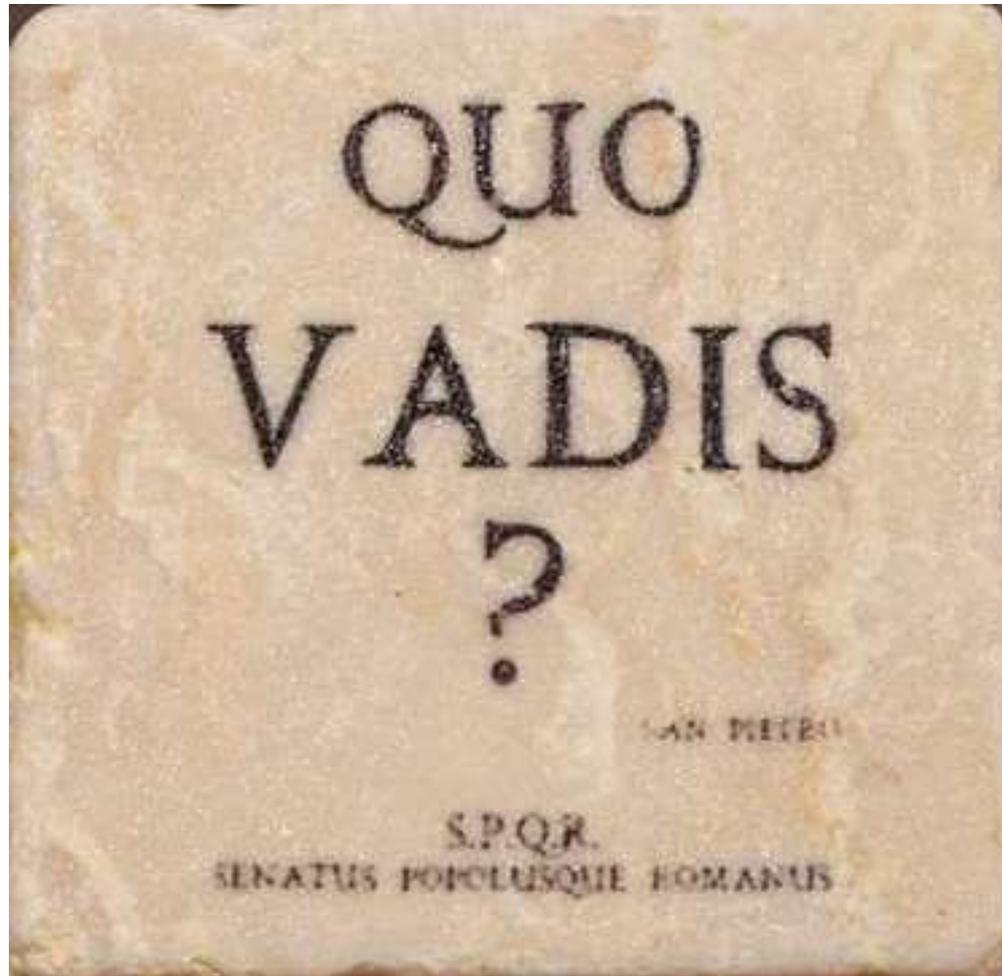
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The Role of Metastasectomy for Melanoma in an Era of Effective Systemic Therapy.

Disclosure:

- I have no actual or potential conflict of interest in relation to this program/presentation.

The Role of Metastasectomy for Melanoma in an Era of Effective Systemic Therapy.



Introduction:

- Up to 10% of patients with melanoma present with stage IV disease at the time of primary diagnosis.
- Two thirds of the patients who develop distant metastasis will have already experienced another type of disease recurrence such as local/in transit or regional lymph node metastasis.
- Up to 86% of patients with stage IV melanoma have initially only one metastatic site, which would be theoretically amenable to locoregional treatment.

Mervic L. PLoS One 2012;7:32955. Essner R et al. Arch Surg 2004; 139:961–6.

Barth A et al. J Am Coll Surg 1995;181: 193–201. Lee ML et al. Melanoma Res 2000;10:81–92.

Several factors appear to predict a better outcome following surgery for stage IV melanoma patients:

- Non-visceral sites of disease.
- Fewer numbers of organs involved.
- Longer intervals from primary or regional disease to the development of metastatic disease.

Metastasectomy in cutaneous melanoma.

These patients have poor prognosis with a median survival of approximately 9 months.

- Five year survival of 5–15%.

Predictors of outcome in stage IV melanoma:

- Age.

- Male gender.

- Oligometastatic disease.

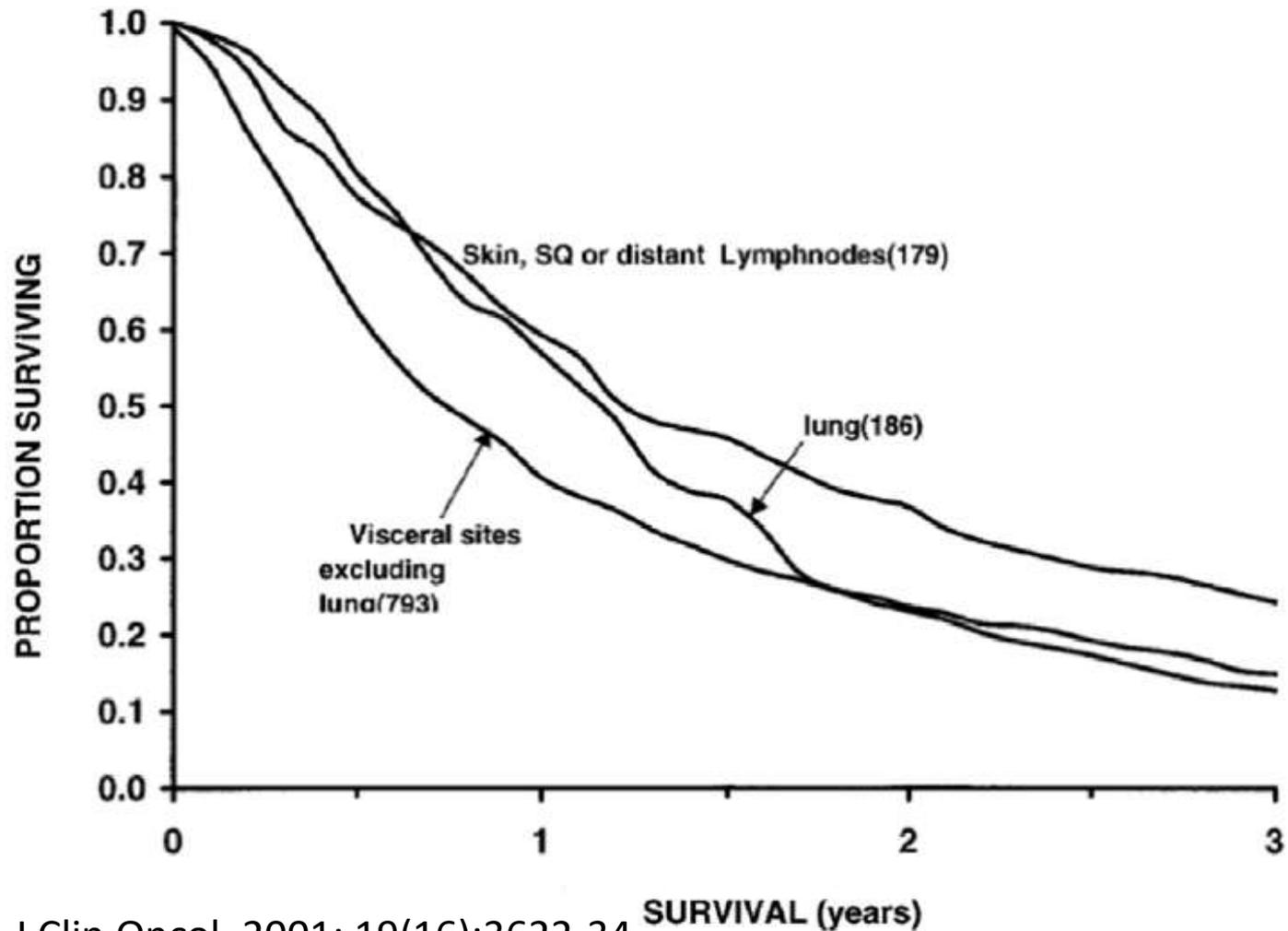
- High levels of serum lactate dehydrogenase (LDH).

Lasithiotakis K et al. Cancer 2008;112:1795–804. Staudt M et al. Br J Cancer 2010;102:1213–8.

Neuman HB et al. Ann Surg Oncol 2008;15:2034–41.

Metastasectomy in cutaneous melanoma.

Survival curves of 1158 patients with metastatic melanomas at distant sites.



Surgical Therapy for Metastatic Melanoma in the Era Before Effective Systemic Therapy.

- Systemic therapies in melanoma have not achieved meaningful results for more than 30 years.
- DTIC, the reference chemotherapeutic agent for melanoma, induced response rates not exceeding 15–20%, less than 5% being complete response.
- The duration of the responses was also quite short, usually not exceeding 6 months.

Surgical Therapy for Metastatic Melanoma in the Era Before Effective Systemic Therapy.

- Most of the evidence for metastasectomy in stage IV melanoma comes from single center case series.
- These studies have an inherent selection bias with only the best candidates from the aspect of tumor biology and physiological status of the patients were chosen for surgery.
- Complete resection of distant metastatic melanoma has been reported to be associated with a median survival of 15–20 months and an average 5-year survival rate of ~ 20%.

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Morton D, et al. *CA Cancer J Clin.* 1999;49(2):101–16.

Hsueh E, et al. *J Clin Oncol.* 2002;20(23):4549–54.

Karakousis C, et al. *Surgery.* 1994;115(3):295–302.

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Essner R, et al. *Arch Surg.* 2004;139(9):961–6

Does metastasectomy improve survival in patients with Stage IV melanoma? A cancer registry analysis of outcomes.

National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database (1988–2006):

- 4229 patients diagnosed with Stage IV melanoma.
- 1422 patients (33.6%) underwent metastasectomy for either M1a or M1bc disease.
 - Median survival was 12 months.
 - Overall survival at five years: 16%.

Does metastasectomy improve survival in patients with Stage IV melanoma? A cancer registry analysis of outcomes.

Improvement in median and overall survival at 5 years by n

	Median survival (months)	Overall survival at 5 years	p-value
Entire cohort (n = 4229)	7 mos	10%	
No Surgery	5 mos	7 %	<i><0.001</i>
Metastasectomy	12 mos	16%	
M1a only (n =1994)	8 mos	13%	<i><0.001</i>
No Surgery	6 mos	9%	
Metastasectomy	14 mos	20%	
M1bc only (n = 2235)	6 mos	8%	<i><0.001</i>
No Surgery	4 mos	5%	
Metastasectomy	10 mos	13%	

Metastasectomy for distant metastatic melanoma: Analysis of data from the first Multicenter Selective Lymphadenectomy Trial (MSLT-I)

- The MSLT-I database was queried for patients who developed stage IV recurrence.
- 291 (15% of the entire cohort) patients with complete data for stage IV recurrence.
- Stage IV recurrence involved only one organ in 242 (83%).
- 226 (78%) patients had only one solitary distant metastasis.

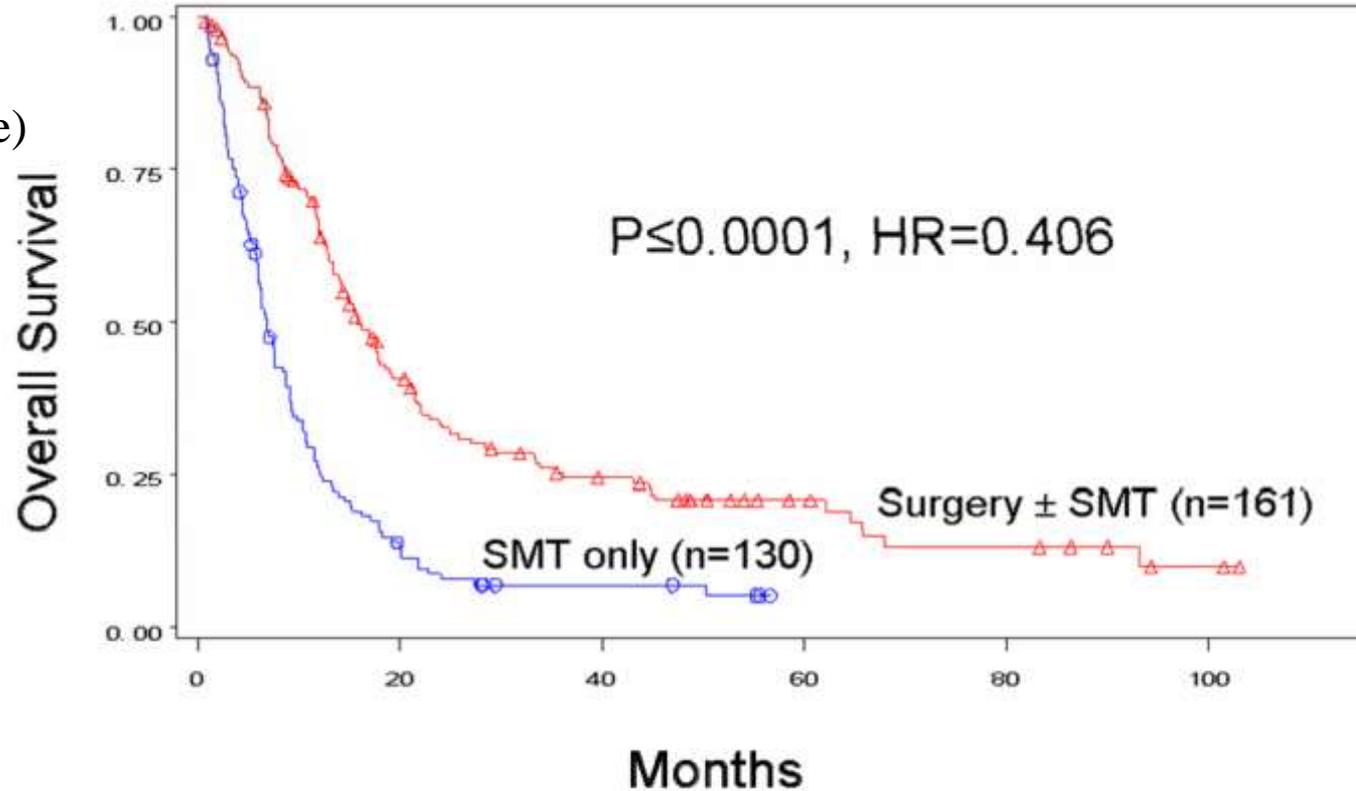
Metastectomy for distant metastatic melanoma: Analysis of data from the first Multicenter Selective Lymphadenectomy Trial (MSLT-I)

Median survival after stage IV diagnosis:

- 15.8 months (surgery).
 - 6.9 months (SMT alone)
- ($p < 0.0001$)

Four-year survival:

- Surgery: 20.8%.
- Without surgery: 7%.



Metastasectomy for distant metastatic melanoma: Analysis of data from the first Multicenter Selective Lymphadenectomy Trial (MSLT-I)

Surgical treatment was associated with improved survival for any M category:

M1a	Median survival (p = 0.0106)	4 Y survival
Surgery	> 60 months	69.3%
SMT alone	12,4 months	0.0%

M1b	Median survival (p = 0.1143)	4 Y survival
Surgery	17.9 months	24.1%
SMT alone	9.1 months	14.3%

M1c	Median survival (p <0.0001)	4 Y survival
Surgery	15months	10.5%
SMT alone	6.3 months	4.6%

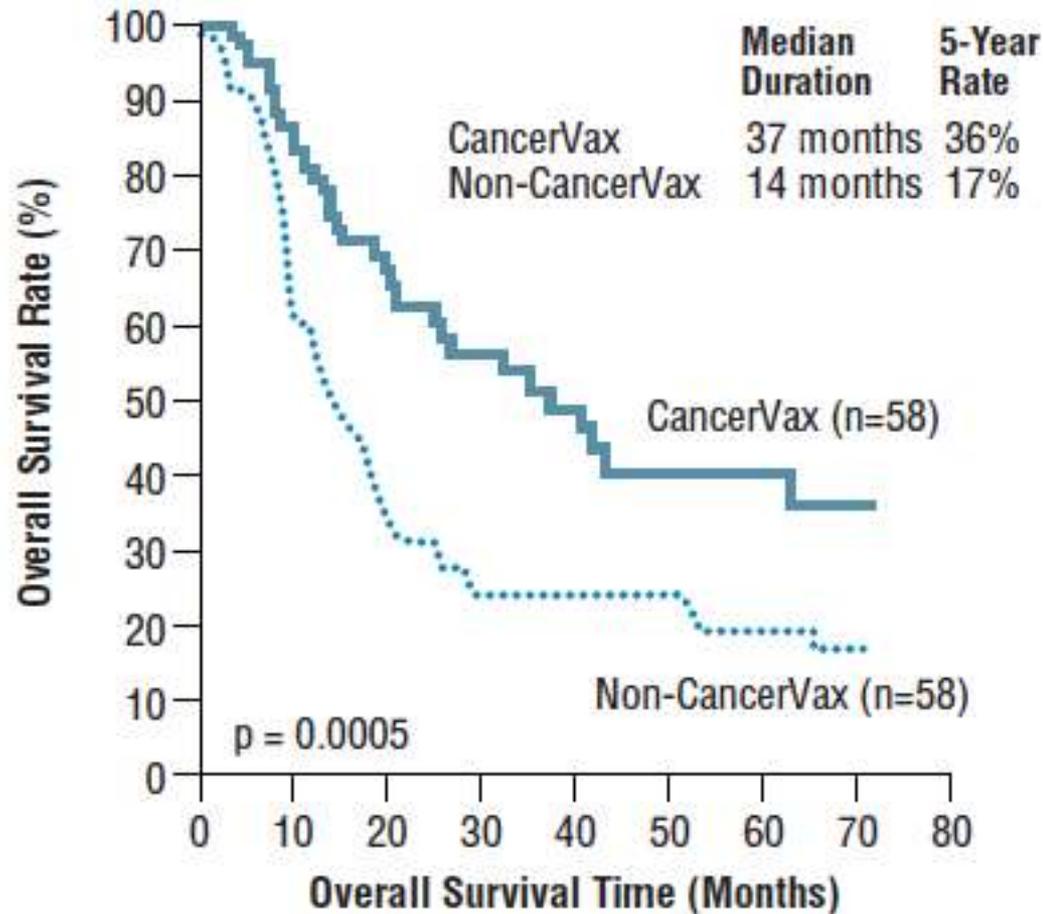
Metastasectomy in cutaneous melanoma.

Surgical Therapy for Metastatic Melanoma in the Era Before Effective Systemic Therapy.

There are three prospective trials which have used standardized procedures and quality control in surgery for stage IV melanoma.

Cytoreductive surgery and adjuvant immunotherapy: a new management paradigm for metastatic melanoma.

Postoperative Adjuvant CancerVax Therapy



An international, randomized, phase III trial of bacillus Calmette-Guerin (BCG) plus allogeneic melanoma vaccine (MCV) or placebo after complete resection of melanoma metastatic to regional or distant sites.

Objective: Show the effectiveness of a polyvalent melanoma vaccine in patients who underwent complete metastasectomy with tumor free surgical margins.

- The study failed to show a survival advantage of the use adjuvant tumor vaccine.
- 5-year overall survival of the entire cohort of 454 patients was 40%.
- This survival rate has never been achieved in any randomized study of any systemic treatment of metastatic melanoma.

Long-Term Survival after Complete Surgical Resection and Adjuvant Immunotherapy for Distant Melanoma Metastases.

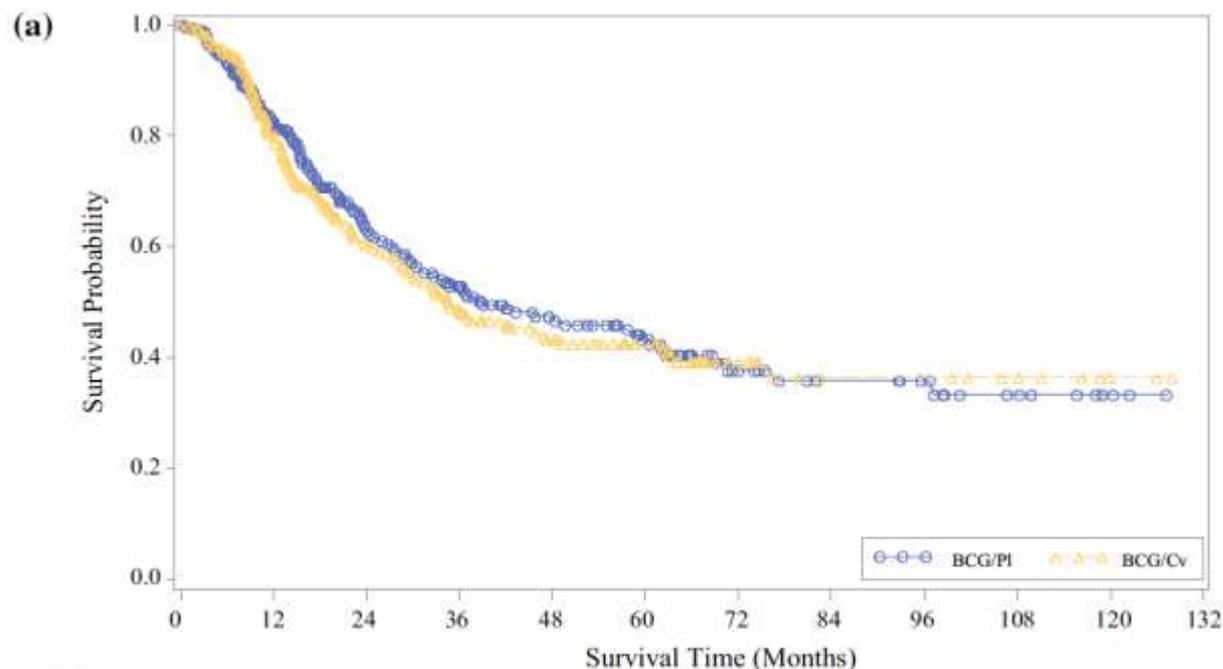
- Patients could have no more than five metastases in no more than two visceral organ sites at the time of definitive surgery.
- 496 patients were enrolled and randomized at 69 centers.
- Despite a clear biological rationale and strong Phase 2 trial data, there was no indication of either benefit or harm from adjuvant treatment with vaccine compared to placebo in this study.
- The study was terminated after the second interim analysis indicated a low probability of a significant survival benefit for the BCG/Cv arm.

Long-Term Survival after Complete Surgical Resection and Adjuvant Immunotherapy for Distant Melanoma Metastases.

This is the highest 5-year survival ever reported in a phase III trial for Stage IV melanoma.

5-year Overall survival:

- 44.9%.



at Risk:

Group	N	12	24	36	48	60	72	84	96	108	120	132
BCG/Cv	246	167	109	84	61	43	21	11	11	7	2	
BCG/PI	250	165	109	84	63	48	25	18	15	9	4	

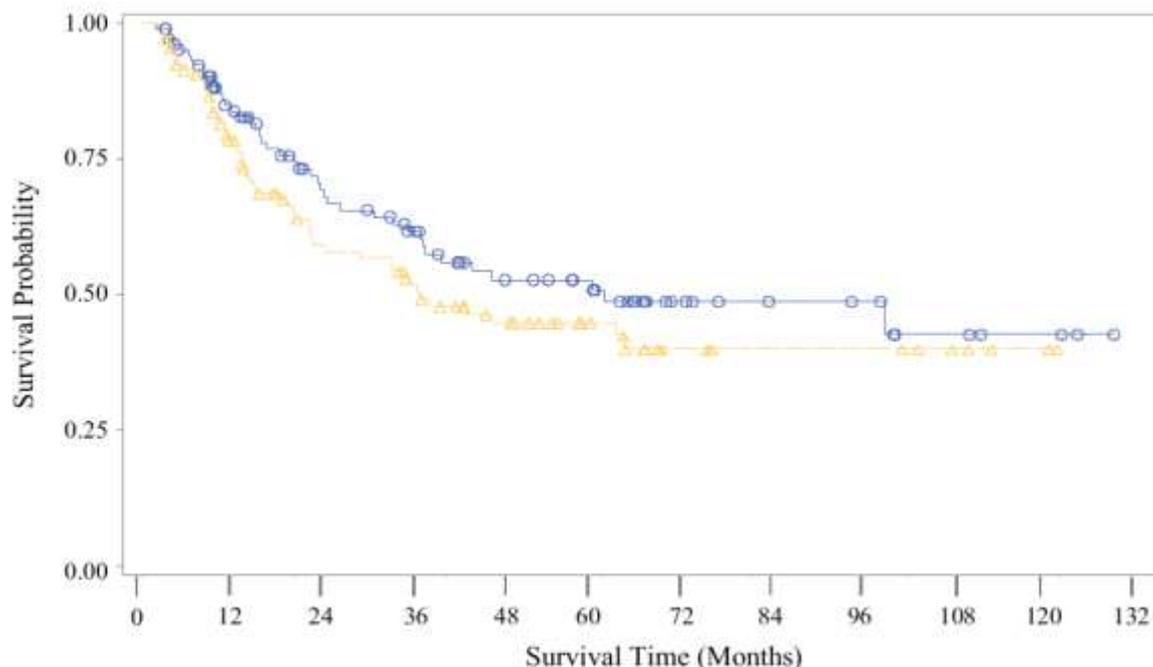
Long-Term Survival after Complete Surgical Resection and Adjuvant Immunotherapy for Distant Melanoma Metastases.

This is the highest 5-year survival ever reported in a phase III trial for Stage IV melanoma.

5-year Overall survival:

- M1a: 60.6 months.

(b)



at Risk:

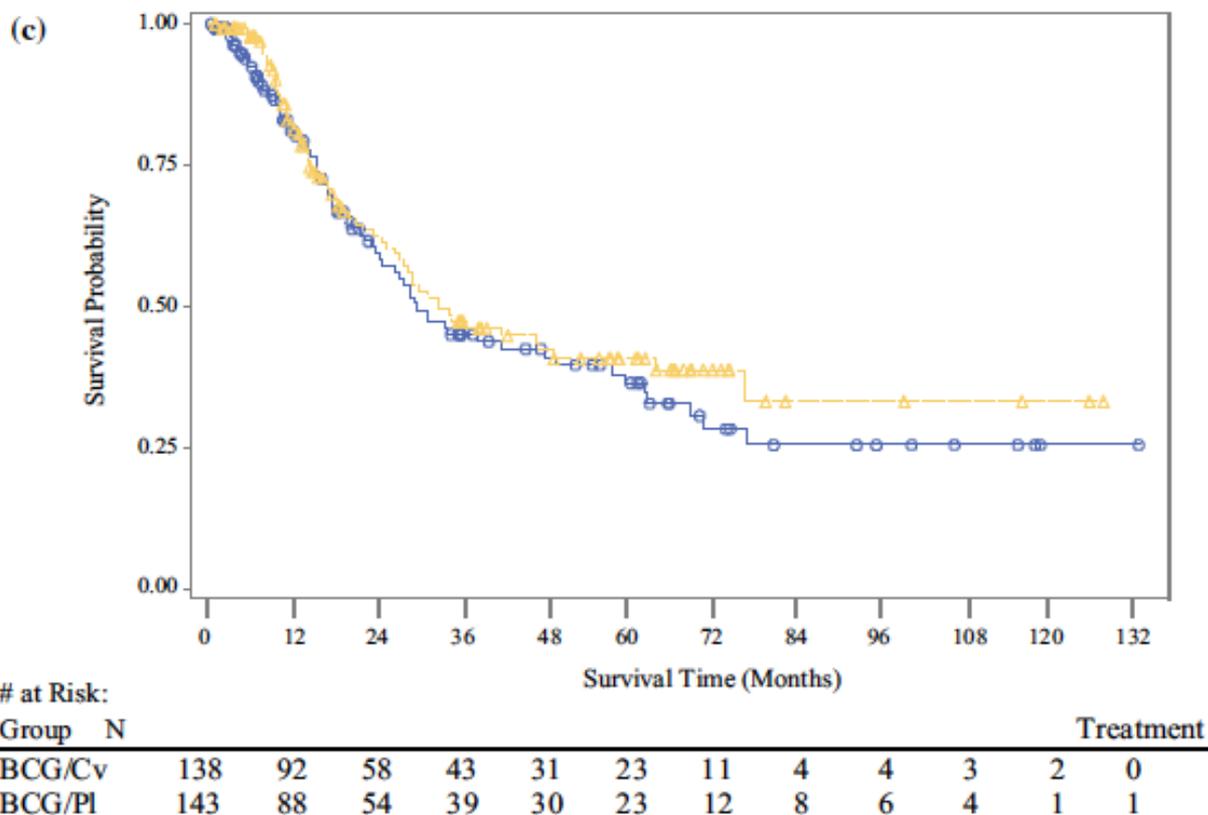
Group	N	0	12	24	36	48	60	72	84	96	108	120	132
BCG/Cv	108	108	74	49	40	29	19	10	7	7	4	0	0
BCG/PI	107	107	76	54	44	32	24	13	10	9	5	3	0

Long-Term Survival after Complete Surgical Resection and Adjuvant Immunotherapy for Distant Melanoma Metastases.

This is the highest 5-year survival ever reported in a phase III trial for Stage IV melanoma.

Median OS:

- M1b: 33 months



Long-Term Survival after Complete Surgical Resection and Adjuvant Immunotherapy for Distant Melanoma Metastases.

This is the highest 5-year survival ever reported in a phase III trial for Stage IV melanoma.

Two possible explanations can be considered:

- Selection bias.
- Beneficial effect of metastasectomy.

A phase II trial of complete resection for stage IV melanoma: results of Southwest Oncology Group Clinical Trial S9430.

- 64 patients were enrolled from 18 different centers.
- SWOG performance status 0–2.

Preoperative imaging:

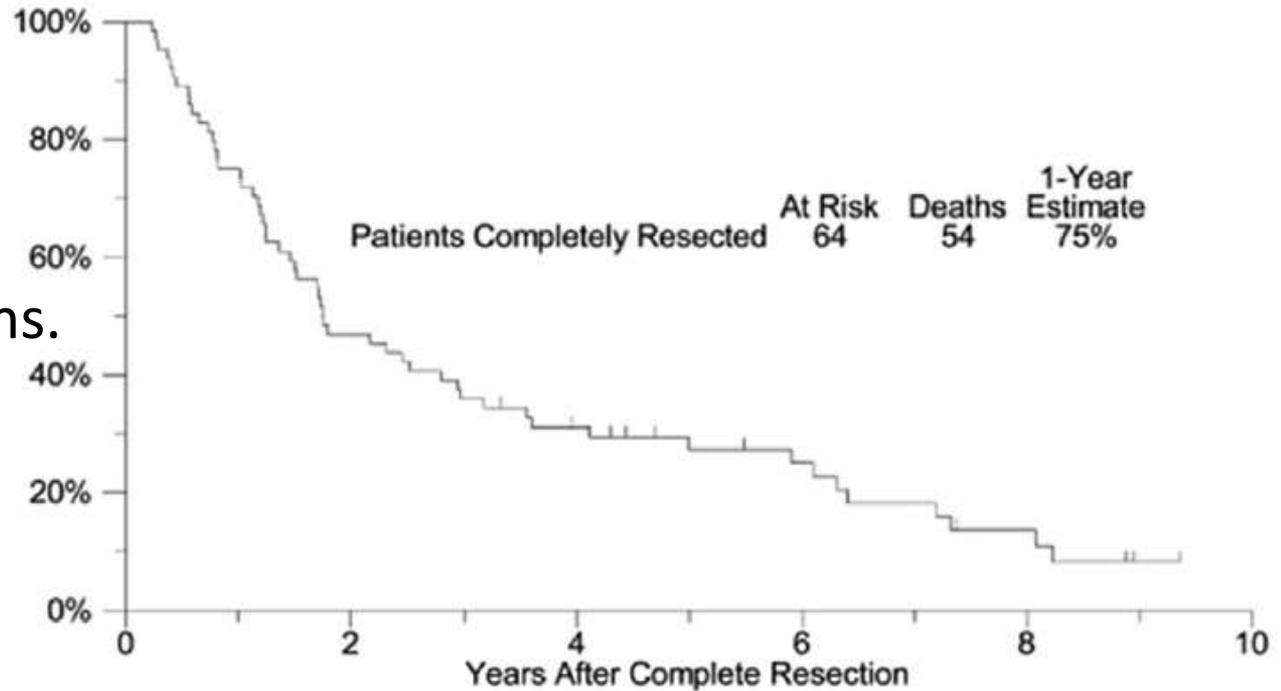
- CT chest, abdomen.
- PET/CT scan.
- Brain CT or MRI

A phase II trial of complete resection for stage IV melanoma: results of Southwest Oncology Group Clinical Trial S9430.

- 64 patients were enrolled from
18 different centers.

Overall Survival for those patients who
were completely resected of all disease.

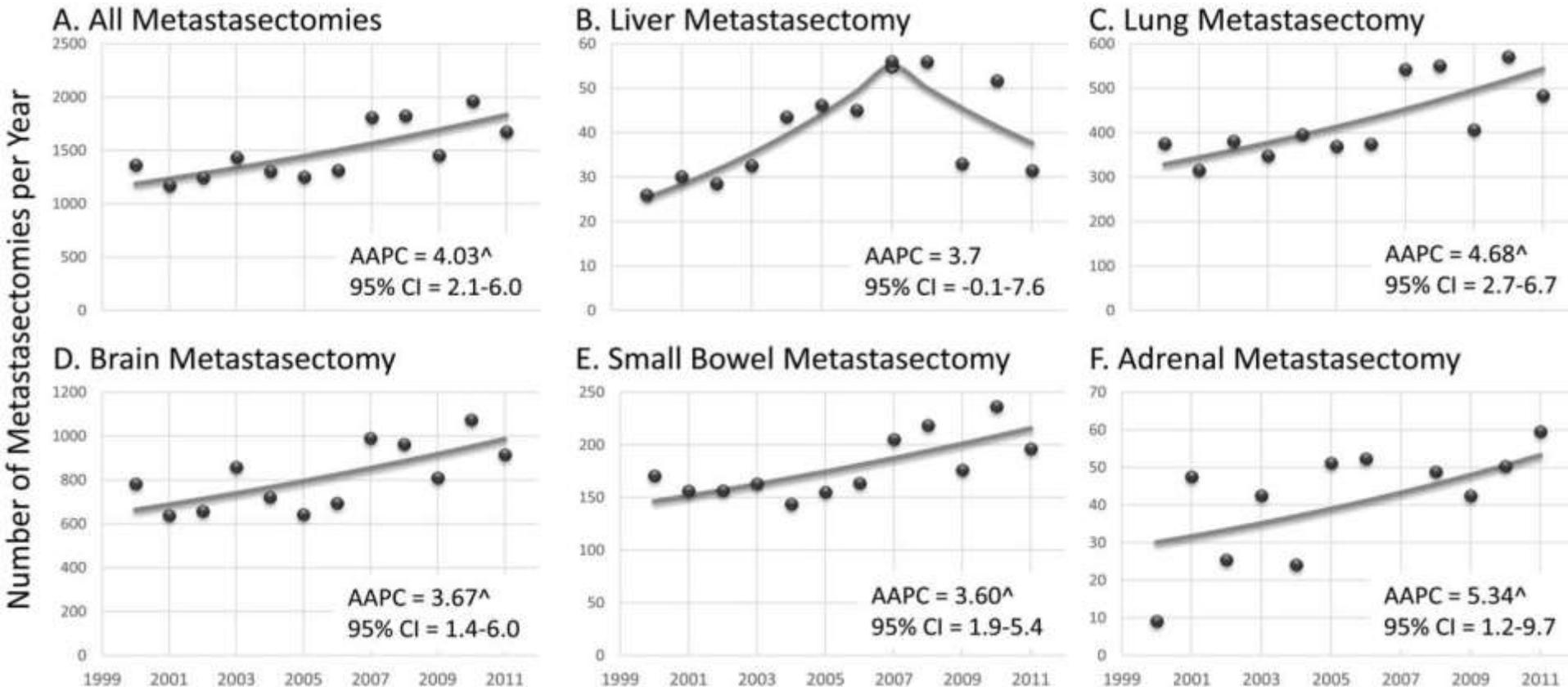
- Median overall
survival time: 21 months.



1-year :	75%	(95% CI : 64% - 86%)
2-year:	47%	(95% CI: 35% - 59%)
3-year:	36%	(95% CI: 24% - 48%)
4-year:	31%	(95% CI: 20% - 42%)

The Rise in Metastasectomy Across Cancer Types Over the Past Decade.

- Admissions from the National (Nationwide) Inpatient Sample (NIS) (2000-2011) involving a metastasectomy for melanoma were included.



Surgical Therapy for Metastatic Melanoma in the Era Before Effective Systemic Therapy.



Metastasectomy in cutaneous melanoma.

Surgical Therapy for Metastatic Melanoma in the Era Before Effective Systemic Therapy.

A large majority of research examining the efficacy of metastasectomy for malignant melanoma predates the era of effective systemic therapy. As a result, much of the data is biased due to patient selection.

Introduction of targeted treatments in melanoma:

- Inhibitor of the BRAF kinase.
- MEK inhibitors.
- Immune check point inhibitors.

Unprecedented advancement in the treatment of metastatic melanoma.

The Role of Metastasectomy for Melanoma in an Era of Effective Systemic Therapy.

The increased efficacy of drug therapy may increase the number of patients who undergo initial systemic therapy, rather than up-front surgery.

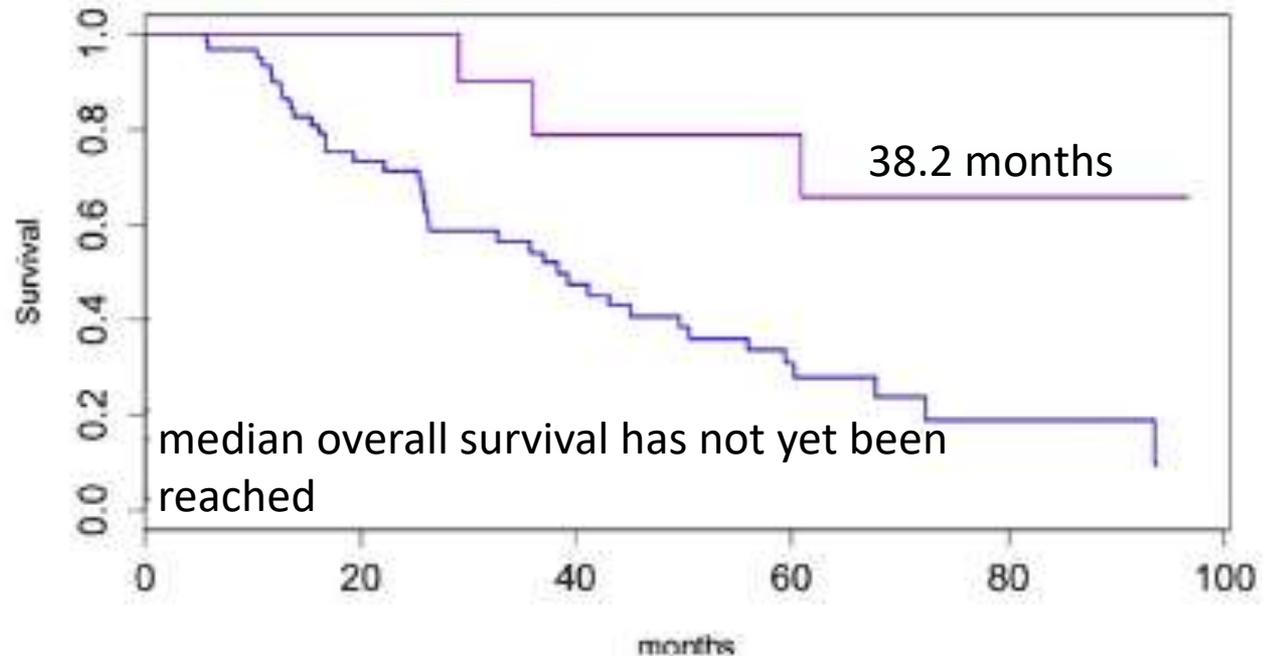
Ultra Selection!

Patients who experience a partial or mixed response to drug treatment may now be candidates for resection either to consolidate their response or to eliminate specific tumors with demonstrated treatment resistance.

Metastasectomy following incomplete response to high-dose interleukin-2.

- 305 patients had metastatic melanoma or renal cell carcinomas/15 metastasectomies.

Surgical resection of incomplete metastatic disease is associated with improved survival



5- year OS of 36% for melanoma patients.

Post-Operative Survival Following Metastasectomy for Patients Receiving BRAF Inhibitor Therapy is Associated With Duration of Pre-Operative Treatment and Elective Indication.

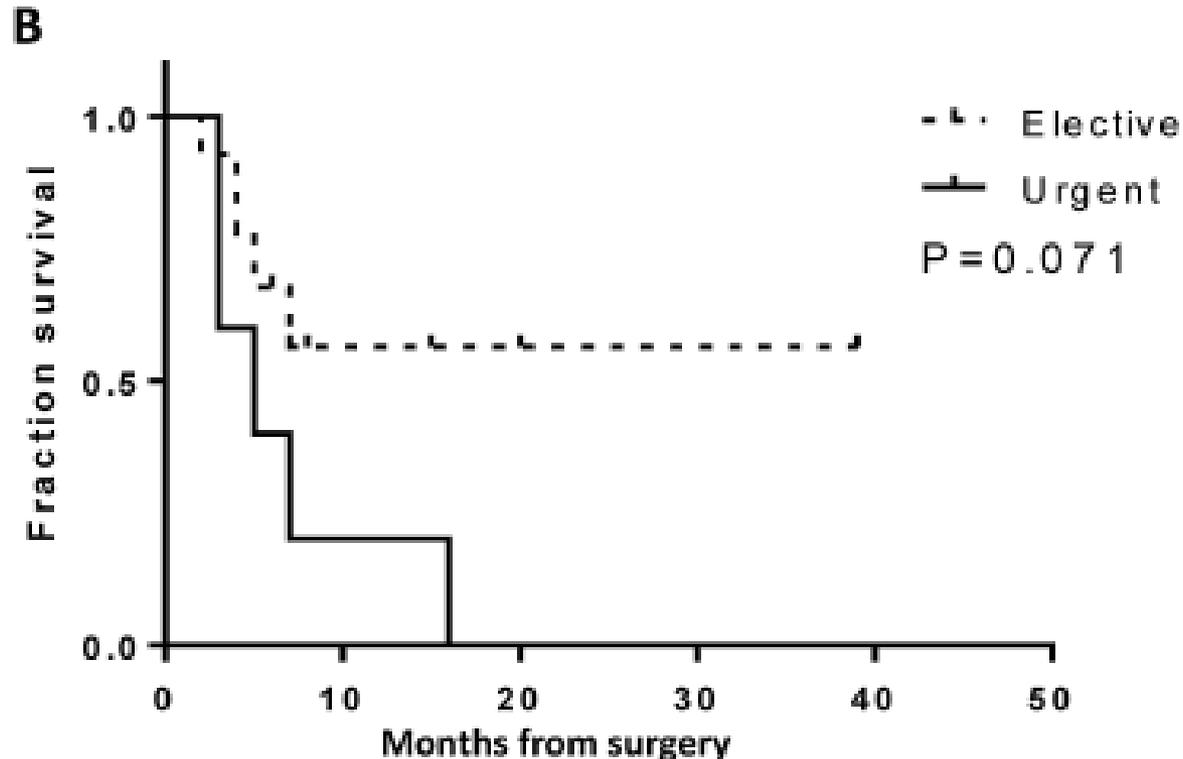
- 148 patients treated with vemurafenib. 18 (12.2%) underwent surgical resection.
- Indications for surgery:
 - Solitary residual focus of disease .
 - New focus after complete response to vemurafenib at all other sites.
 - Solitary site of progressive disease in the setting of otherwise stable or responding disease.
 - Symptomatic disease (surgery was required irrespective of disease response status)

Post-Operative Survival Following Metastasectomy for Patients Receiving BRAF Inhibitor Therapy is Associated With Duration of Pre-Operative Treatment and Elective Indication.

- 80% ECOG 0-1.
- 90% stage IV M1c.
- 1 death (sepsis).
- Most operations (80%) had no complications or only minor deviations.
- Median survival was 7.4 months.

Post-Operative Survival Following Metastasectomy for Patients Receiving BRAF Inhibitor Therapy is Associated With Duration of Pre-Operative Treatment and Elective Indication.

Kaplan–Meier survival curve from date of surgery for patients who had elective versus emergency surgery.



Elective surgery for asymptomatic lesions represented only 8% of 148 patients treated with vemurafenib.

He M et al. Journal of Surgical Oncology 2015;111:980–984.

Metastasectomy Following Immunotherapy with Adoptive Cell Transfer for Patients with Advanced Melanoma.

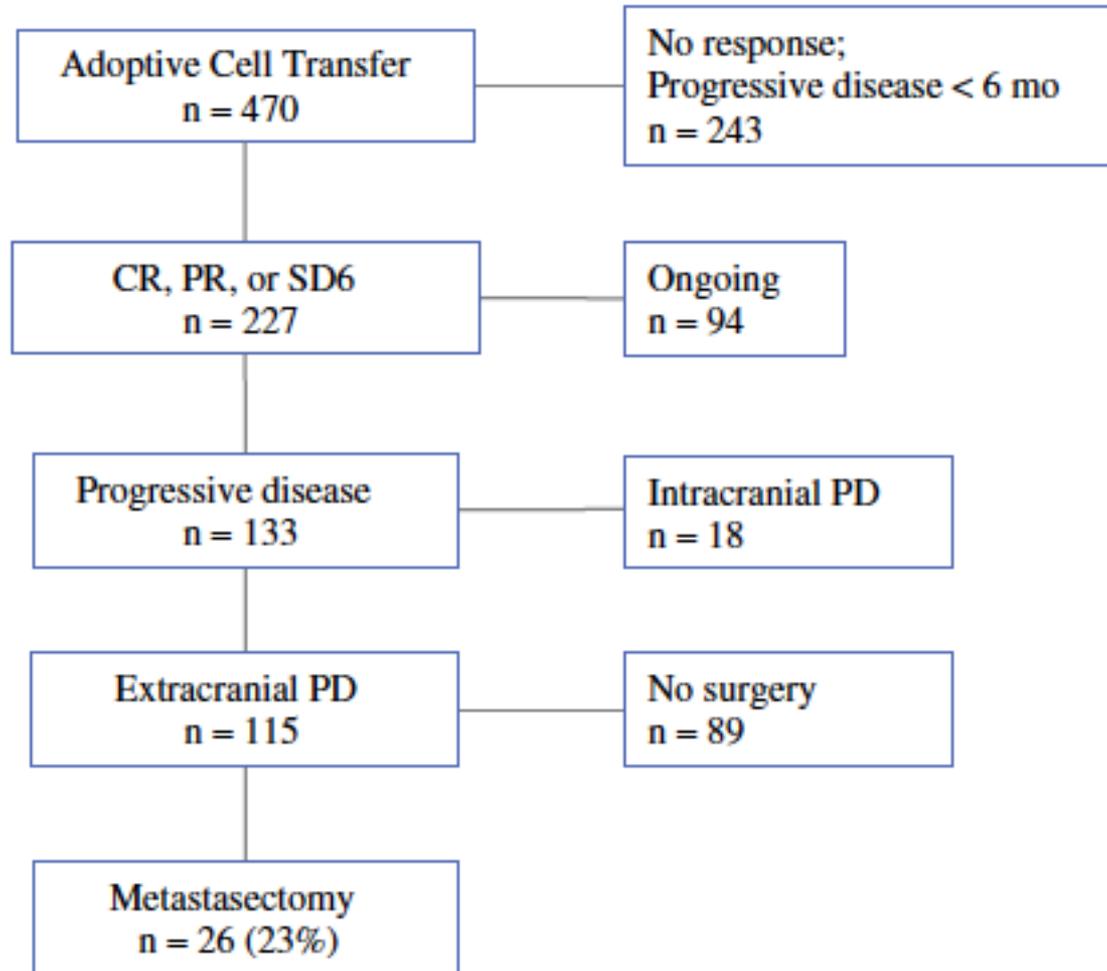
Surgery Branch, National Cancer Institute (NCI)

Adoptive cell transfer (ACT) of autologous lymphocytes:

- Complete response: 24%.
- Partial response (PR): 30%.
- 70 % of patients with only a PR subsequently developed progressive disease.
- Metastasectomy can be considered if tumor progression is limited.

Metastectomy Following Immunotherapy with Adoptive Cell Transfer for Patients with Advanced Melanoma.

Surgery Branch, National Cancer Institute (NCI)



Metastasectomy Following Immunotherapy with Adoptive Cell Transfer for Patients with Advanced Melanoma.

Surgery Branch, National Cancer Institute (NCI)

- 26 patients. No mortalities related to metastasectomy.
- 5-year OS was 57 % for all 26 patients.
- Longer PFS and OS were significantly associated with the resection of a pre-existing site of metastasis compared with a new site of disease.
- The 5-year OS rates following surgery on pre-existing lesions versus new lesions were 73 and 0 % respectively.

The option of metastasectomy was reconsidered only after a strong response to immunotherapy, which was often associated with the resolution of multiple tumors

The Role of Metastectomy for Melanoma in an Era of Effective Systemic Therapy.

There is little debate that patients with substantial disease burden should be offered palliative metastectomy only in cases of bleeding, obstruction, or pain to address their symptoms



The Role of Metastasectomy for Melanoma in an Era of Effective Systemic Therapy.

Asymptomatic patients with oligometastatic disease.

Given the current therapeutic options (immunotherapy and/or targeted therapy), the role for surgery in metastatic melanoma remains complicated and nuanced.

Currently, the role of surgery in this modern era remains to be determined...

Asymptomatic patients with oligometastatic disease.

Analyses of larger patient cohorts will be required to improve the identification of asymptomatic patients who may benefit from surgery in the challenging and rapidly changing clinical contexts of modern melanoma treatment.

Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial.
(NCT 02231775)

- Surgically resectable clinical stage III or oligometastatic stage IV *BRAF V600 mutated melanoma*.
- Dabrafenib and trametinib combination.

Groups	N	Median event free survival ($p < 0.0001$)
Upfront surgery	7	2.9 months
Neoadjuvant plus adjuvant	14	19.7 months

The Role of Metastasectomy for Melanoma in an Era of Effective Systemic Therapy.

Who's gonna win?



The Role of Metastasectomy for Melanoma in an Era of Effective Systemic Therapy.

Take Home Message

“Biology is King; selection of cases is Queen, and the technical details of surgical procedures are princes and princesses of the realm who frequently try to overthrow the powerful forces of the King and Queen, usually to no long-term avail, although with some temporary apparent victories.”

Blake Cady MD.