Po ASTRO - OUN

60. Doroczna Konferencja ASTRO, San Antonio

Jacek Fijuth

UNIWERSYTET MEDYCZNY W ŁODZI

Katedra Onkologii U.M.

KOPERNIK

Regionalny Ośrodek Onkologii i Hematologii

Łódź

3R, Warszawa, 15.11.2018 r.

Glioma WHO III

NRG ONCOLOGY

Advancing Research. Improving Lives.™

Elevated *MGMT* Gene Expression Is Independently Associated With Worse Overall Survival In NRG Oncology/RTOG 9813

A Phase III Study of Radiation Therapy (RT) and Temozolomide Versus RT and Nitrosourea in Anaplastic Grade III Glioma

Jessica Fleming, Joseph P McElroy, Erica H Bell, Susan M Chang, Emad Youssef, Grant K Hunter, W K Alfred Yung, Steven P Howard, Joseph A Bovi, Jean-Paul Bahary, Helen A Shih, Rachel A Rabinovitch, Yuhchyau Chen, Peixin Zhang, and Arnab Chakravarti

ASTRO 2018
October 22, 2018

Wzmożona ekspresja genu MGMT jest niezależnym czynnikiem prognostycznym skorelowanym z krótszym OS chorych na glejaka WHO III

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma (Hegi M i wsp. N Engl J Med. 2005) Based on study of Stupp et al.

206 ch.,

hipermetylacja promotora genu MGMT obecna u ok. 45% ch.

- hamuje mechanizm naprawy DNA po TMZ i RT

śr. przeżycie 21.7 m. vs. 15.3 m. (p=0.007) (MGTM”+”)

2-letnie przeżycie po TMZ+RT 46% (MGMT”+”) vs. 14% (MGMT”-”)

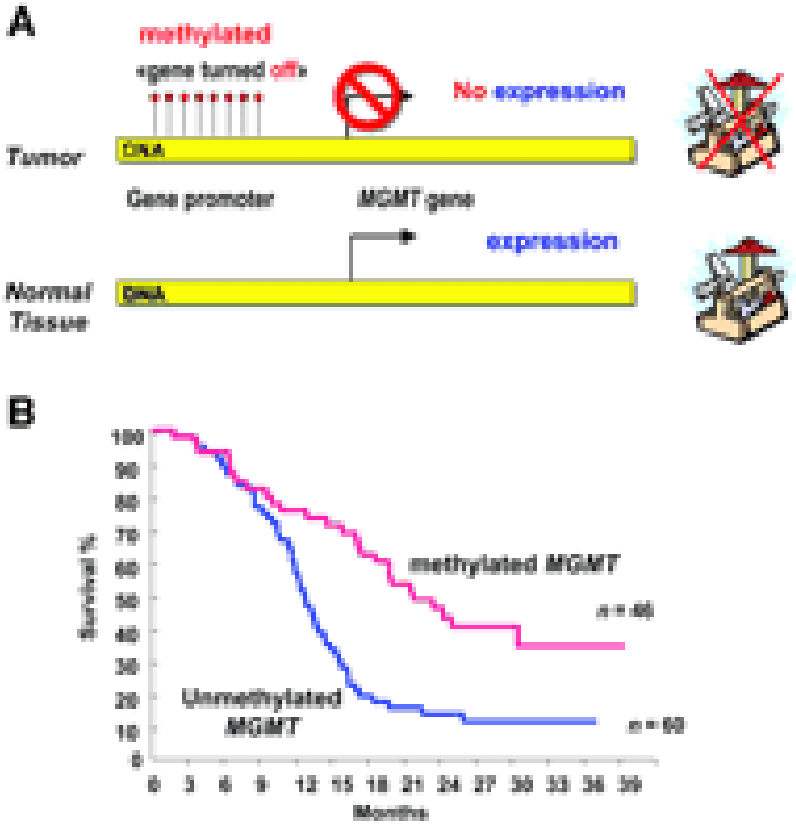


TABLE 1

Correlation of *MGMT* Methylation Status With Survival Benefit in Glioblastoma Multiforme Patients

	Radiation Therapy (n = 100)	Temozolomide/Radiation Therapy (n = 106)
Methylated	n = 46	n = 46
Median overall survival	15.3 months	21.7 months
2-Year overall survival	23%	46%
Hazard ratio	1.00	0.51
P value	.007	
Unmethylated	n = 54	n = 60
Median overall survival	11.8 months	12.7 months
2-Year overall survival	< 2%*	14%
Hazard ratio	1.00	0.69
P value	.06	

* No patient followed up for 2 years
Abbreviation: MGMT = O^6-methylguanine-DNA methyltransferase

!!!

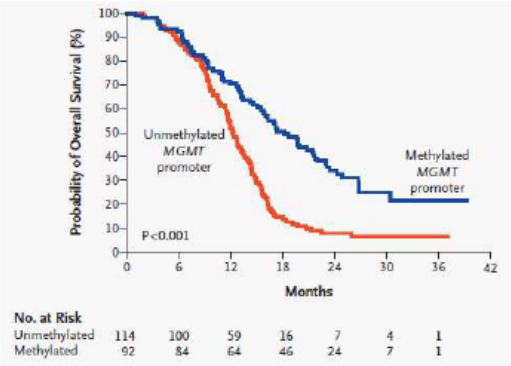
Inhibiting DNA Repair Mechanisms to Improve Treatment for Brain Tumours: A Look to the Future. Calvert HA World Federation of Neuro-Oncology/ European Association for Neuro-Oncology, Edinburgh, 2005

Glioma WHO III

MGMT: O6-methylguanine-DNA methyltransferase

- *MGMT* promoter methylation is a well-established prognostic biomarker in glioblastoma.
- Previously, we've shown upon unimarker multivariable analysis, *MGMT* promoter methylation significantly correlated with better overall survival in NRG 9813.
- However, methylation is an upstream regulatory mechanism that leads to gene expression silencing.

gene switched "off":
no transcription



Hypothesis: Patients with **elevated** levels of *MGMT* gene expression would have significantly worse survival rates.

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Hegi M et al. (2005) *NEJM* 352: 997-1003
Bell et al. (2017) ASTRO

Metylacja promotora MGMT jest czynnikiem skorelowanym z wydłużeniem OS chorych na GBM i Anapl. Glioma WHO III (Stupp, Hegi, NRG 9813)
Metylacja jest mechanizmem regulatorowym prowadzącym do wyciszenia ekspresji genu MGMT

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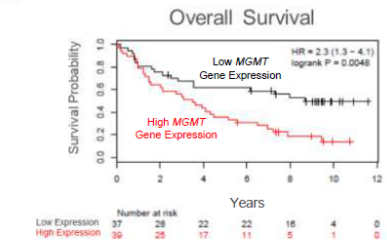
Wzmożona ekspresja genu MGMT jest istotnie związana z gorszym OS, niezależnie od metylacji promotora MGMT

Elevated *MGMT* Gene Expression Is Significantly Associated With Worse Overall Survival, Independent of *MGMT* Promoter Methylation



Overall Survival: Long-Term Effect		
Univariate Cox Proportional Hazards Model		
Variable	HR (95% CI)	p-value
MGMT gene expression (continuous)	1.56 (1.17-2.08)	0.003
Multivariable Cox Proportional Hazards Model Co-variates: age, surgery, *IDH* mutation, and KPS		
Variable	HR (95% CI)	p-value
MGMT gene expression (continuous)	2.04 (1.32-3.13)	0.001
Multivariable Cox Proportional Hazards Model Co-variates: age, surgery, *IDH* mutation, KPS, and *MGMT* promoter methylation		
Variable	HR (95% CI)	p-value
MGMT gene expression (continuous)	1.74 (1.02-2.97)	0.043

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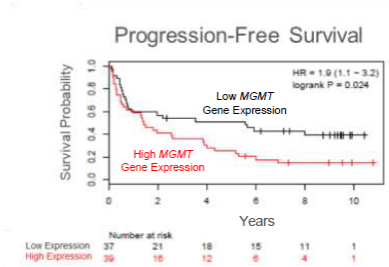
Wzmożona ekspresja genu MGMT jest istotnie związana z gorszym PFS, niezależnie od metylacji promotora MGMT

Elevated *MGMT* Gene Expression Is Significantly Associated With Worse Progression-Free Survival, Independent of *MGMT* Promoter Methylation



Progression-Free Survival: Long-Term Effect		
Univariate Cox Proportional Hazards Model		
Variable	HR (95% CI)	p-value
MGMT gene expression (continuous)	1.39 (1.06-1.82)	0.019
Multivariable Cox Proportional Hazards Model Co-variates: age and *IDH* mutation		
Variable	HR (95% CI)	p-value
MGMT gene expression (continuous)	3.07 (1.61-5.88)	0.001
Multivariable Cox Proportional Hazards Model Co-variates: age, *IDH* mutation, and *MGMT* promoter methylation		
Variable	HR (95% CI)	p-value
MGMT gene expression (continuous)	2.34 (1.22-4.49)	0.010

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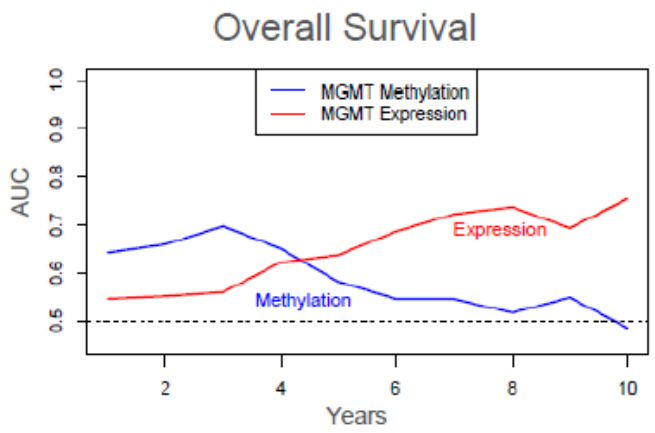
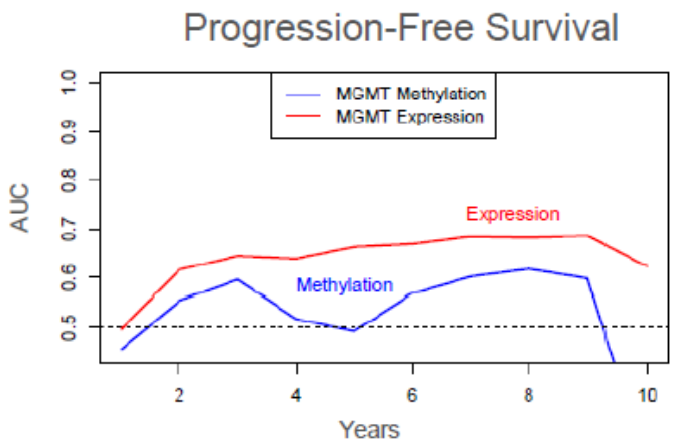
MGMT Gene Expression Is A Superior Prognostic Biomarker for Long-Term Survival Over *MGMT* Promoter Methylation in NRG Oncology/RTOG 9813





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MGMT Expression = Continuous
MGMT Methylation = Continuous

W dłuższej obserwacji wzmożona ekspresja genu MGMT jest lepszym biomarkerem dla OS od metylacji promotora MGMT

Glioma WHO III

Clinical and Molecular Associations with Overall Survival

Univariate Overall Survival

	Variable (**Bolded** value has favorable outcome)	Hazards Ratio (95% CI)	p-value	
*	Age (**< 50** vs ≥ 50)	3.50 (1.90-6.30)	< 0.001	*
*	*IDH* mutation status (**Mutant** vs Non-mutant)	2.30 (1.30-4.10)	0.004	*
*	*MGMT* promoter methylation status (Methylated vs Unmethylated)	1.73 (0.87-3.43)	0.110	*
*	*MGMT* gene expression (Increased vs Decreased) (continuous)	1.56 (1.17-2.08)	0.003	*
*	Surgery (**Resection** vs Biopsy)	0.45 (0.26-0.80)	0.005	*
*	KPS (60-80 vs **90-100**)	0.52 (0.28-0.98)	0.041	*
	Gender (Male vs **Female**)	0.78 (0.44-1.36)	0.379	
	Treatment (**RT + TMZ** vs RT + NU)	0.85 (0.49-1.48)	0.569	

Clinical and Molecular Associations with Progression-Free Survival

Univariate Progression-Free Survival

	Variable (**Bolded** value has favorable outcome)	Hazards Ratio (95% CI)	p-value	
*	Age (**< 50** vs ≥ 50)	2.90 (1.60-5.20)	< 0.001	*
*	*IDH* mutation status (**Mutant** vs Non-mutant)	2.10 (1.20-3.60)	0.008	*
*	*MGMT* promoter methylation status (**Methylated** vs Unmethylated)	1.36 (0.71-2.60)	0.350	*
*	*MGMT* gene expression (Increased vs **Decreased**) (continuous)	1.39 (1.06-1.82)	0.019	*
	Surgery (**Resection** vs Biopsy)	0.64 (0.37-1.10)	0.104	
	KPS (60-80 vs **90-100**)	0.61 (0.32-1.13)	0.114	
	Gender (Male vs **Female**)	0.95 (0.56-1.62)	0.857	
	Treatment (**RT + TMZ** vs RT + NU)	0.67 (0.39-1.14)	0.138	

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MVA: No Split Overall Survival

Variable (**Bolded** value has favorable outcome)	Hazards Ratio (95% CI)	p-value
Age (**< 50** vs ≥ 50)	2.56 (1.33-4.92)	0.005
IDH mutation status (**Mutant** vs Non-mutant)	0.78 (0.40-1.53)	0.473
MGMT gene expression (Increased vs Decreased) (continuous)	1.45 (1.05-2.01)	0.026
Surgery (**Resection** vs Biopsy)	0.55 (0.27-1.11)	0.097
KPS (60-80 vs **90-100**)	0.59 (0.28-1.25)	0.167

MVA: No Split Progression-Free Survival

Variable (**Bolded** value has favorable outcome)	Hazards Ratio (95% CI)	p-value
Age (**< 50** vs ≥ 50)	2.44 (1.30-4.57)	0.005
IDH mutation status (**Mutant** vs Non-mutant)	0.72 (0.38-1.35)	0.304
MGMT gene expression (Increased vs **Decreased**) (continuous)	1.27 (0.93-1.74)	0.129

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OS

wiek, ekspresja genu MGMT

PFS

wiek

Glioma WHO III

- Univariate analyses indicated that elevated *MGMT* gene expression was significantly associated with worse OS and PFS.
- In the multivariate analyses, it was determined that **elevated *MGMT* gene expression** significantly correlated with **worse OS and PFS**, independent of *age, IDH mutation, resection status, Karnofsky performance status, and most importantly, MGMT promoter methylation*.
- **This study suggests that *MGMT* gene expression may provide additional prognostic value for patients beyond the clinical and molecular biomarkers currently utilized.**

Glioma WHO III

Conclusions

- We found that elevated *MGMT* gene expression is significantly associated with worse overall survival and progression-free survival, **independent** of *MGMT* promoter methylation and *IDH* mutation status.
- We found *MGMT* promoter methylation was significantly associated with better overall survival, but not progression-free survival in our univariate analysis; however, this significance was lost in our multivariable analyses.

- Wzmożona ekspresja genu MGMT jest niezależnym czynnikiem wpływającym negatywnie na OS w glejakach WHO III po RT/TMZ, niezależnie od statusu metylacji promotora MGMT (NRG Oncology/RTOG 9813)

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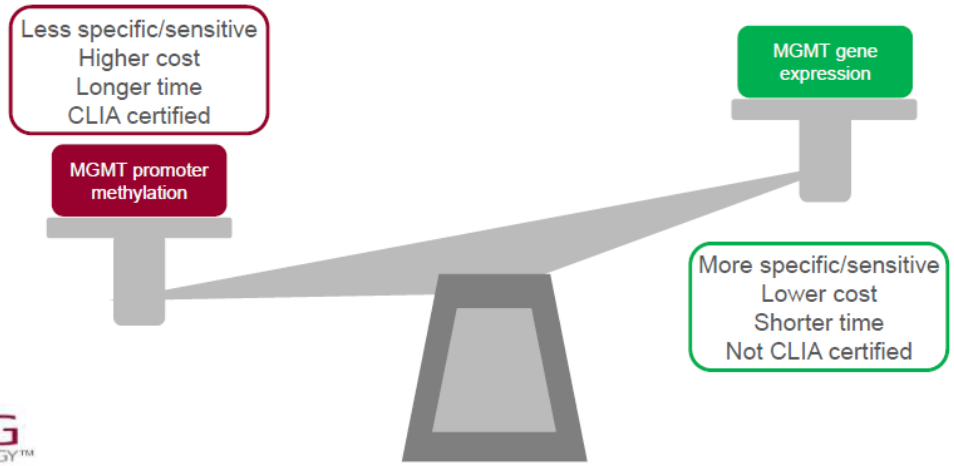
MGMT Gene Expression Versus Methylation



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Analogiczna obserwacja dot. ekspresji genu dla MGMT w odniesieniu do GBM

GBM

MGMT protein expression adds prognostic value beyond *MGMT* promoter methylation and stratifies survival prognoses of un-methylated glioblastoma patients.

The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

Aline Paixao Becker[1], Erica H. Bell[1], Joseph McElroy[1], Tiantian Cui[1], Marjolein Geurts[2], Ziyan Liu[1], S. Jaharul Haque[1], Pierre Robe[2], Arnab Chakravarti[1]

1- The Ohio State University, Columbus, OH, USA.
2- University Medical Center Utrecht, Utrecht, the Netherlands.

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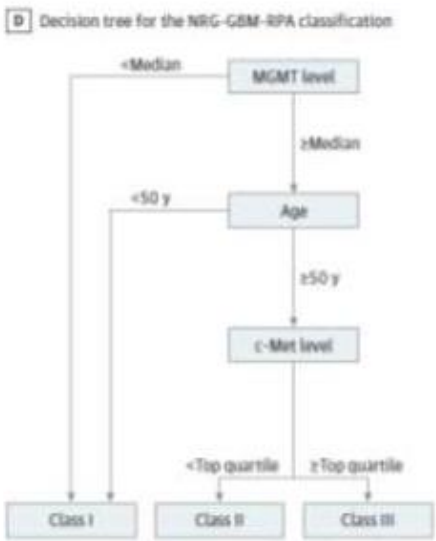
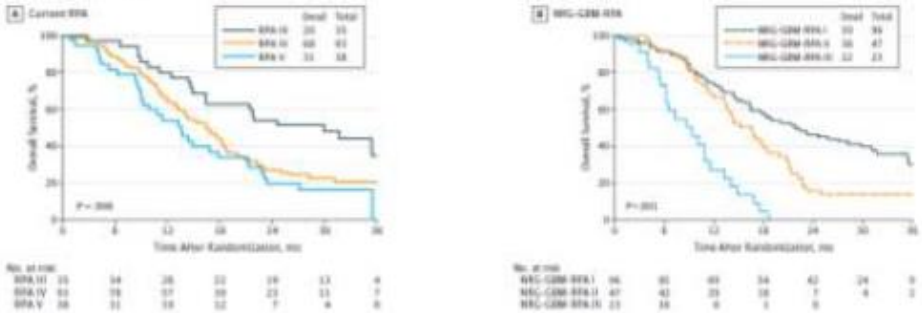
Background

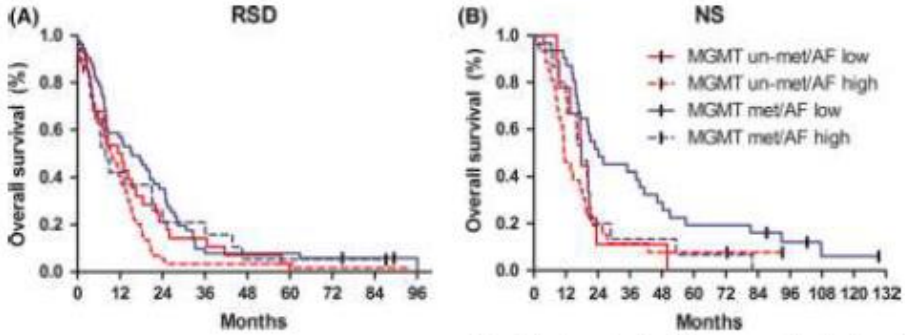
- MGMT protein expression refines the RPA classification for risk assessment of glioblastoma patients.



Bell et al, JAMA Oncology 2017

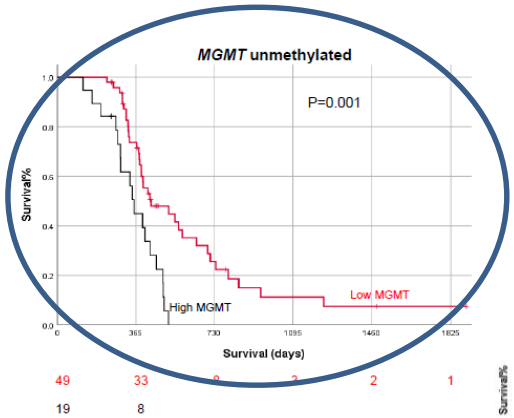


Bell et al, *JAMA Oncology*, 2017

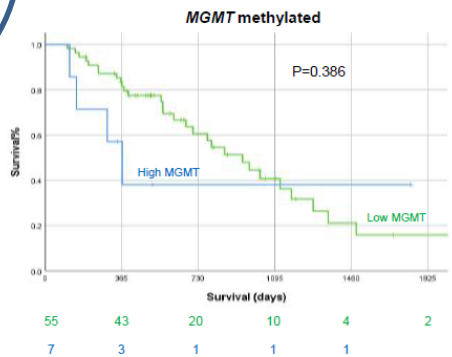


Dahlrot et al, *Neuropathol Appl Neurobiol*, 2018

GBM

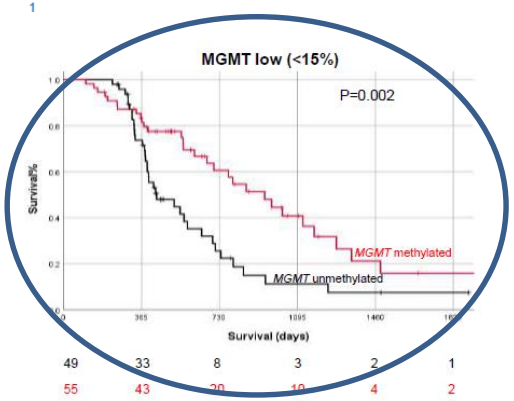


MGMT protein level determined significant difference in OS in *MGMT* un-methylated glioblastomas

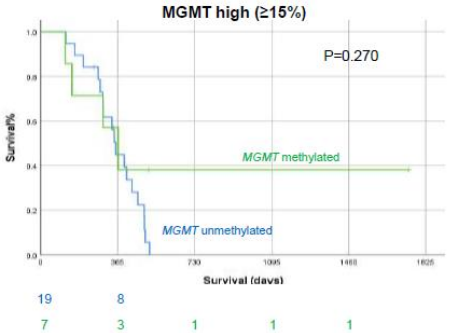


W GBM bez metylacji, niska ekspresja genu MGMT pozytywnie koreluje z OS

Metylacja MGMT pozytywnie koreluje z OS tylko w przypadku niskiej ekspresji genu MGMT



***MGMT* methylation was significantly related to OS only in low MGMT expressing tumors**



GBM

Take Home Messages

•More than 70% of un-methylated glioblastomas had low MGMT expression and significantly better OS after Stupp protocol than glioblastomas with high MGMT expression (p=0.001).

•*MGMT* promoter methylation significantly split OS only in the tumors with inherent low MGMT expression (p=0.002), but not when MGMT expression was ≥15% (p=0.270).

•MGMT protein expression is a prognostic biomarker independent of *MGMT* methylation for newly diagnosed glioblastomas.

•The immunohistochemistry test may identify, upfront, at a lower cost and shorter turn-around-time [after CLIA validation], patients who may not respond to the Stupp protocol and impact clinical decision-making/trials design.

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>70% GBM bez metylacji promotora MGMT ma niską ekspresję genu dla MGMT
W glejakach bez metylacji, niska ekspresja genu MGMT pozytywnie koreluje z OS lecz nie w przypadku ekspresji ≥15%
Metylacja promotora MGMT pozytywnie koreluje z OS tylko w przypadku niskiej ekspresji genu MGMT
Ekspresja genu MGMT jest czynnikiem prognostycznym niezależnym od metylacji promotora MGMT (Ohio, Utrecht)

Neoadjuwantowa chth TMZ
(2 tyg.)
Przyspieszona RT+TMZ

GBM

Long Term Outcomes Of A Phase II Trial Of Neo-adjuvant Temozolomide (TMZ) Followed By Accelerated Hypofractionated Radiotherapy And Concomitant TMZ Followed By Adjuvant TMZ In Patients With Newly Diagnosed Glioblastoma (GBM)

Clinical.trials.gov NCT01702610

G. Shenouda[1], L. Souhami[1], K. Petrecca[2], S. Owen[3], M-C. Guiot[4], V. Panet-Raymond[1], T. Carvalho[1], B. Abdulkarim[1].

Department of Radiation Oncology[1], Neurosurgery[2], Medical Oncology[3], Pathology[4], McGill University

GBM

NEO-ADJUVANT TMZ PHASE II STUDY IN GBM

SCHEMA

- **Neo-Adjuvant TMZ** <--2 weeks-->
  - TMZ =75 mg/m²
- **Con TMZ + HART** <--4 weeks-->
  - TMZ =75 mg/m²
  - AHRT = 60 Gy/20 fractions
    - CTV60 = residual disease + surgical cavity (T1 Gad MRI)
    - CTV40 = CTV60 + 15 mm
    - PTV = CTV + 5 mm
- **Adjuvant TMZ** <-- 6 to 12 cycles-->
  - TMZ = 150 to 200 mg/m²
  - Depending on tolerance and continued improvement

CTV60 - loża w T1RM
60 Gy/20 fr
CTV60/CTV40
CTV40=CTV60+15mm
PTV=CTV+5mm

TMZ wzmaga swoją aktywność w kolejnych kursach poprzez redukcję aktywności MGMT

TMZ zmniejsza migrację komórek GBM wywołanych RT

GBM

Temozolomide

- Freidman et al (2000) and Tolcher et al (2003) showed that protracted courses of TMZ lead to **auto-enhancement** of TMZ itself by depleting already existing cellular MGMT activity, and thereby increasing the efficiency of a subsequent TMZ exposure

- TMZ reduces ionizing radiation-induced **GBM cell migration** Wick W et al, Cancer Res 2002;62: 1915–1919

GBM

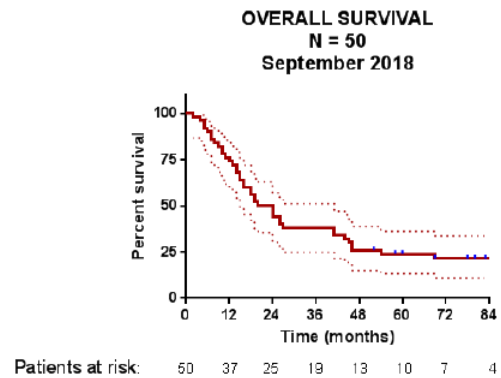
Overall Survival

Fifty patients were accrued 2009-2014

Median F/U patients at risk 79 m (52.3-84.8)

Overall Survival

Median	3y	5y	7y
22 m	34%	24%	21%



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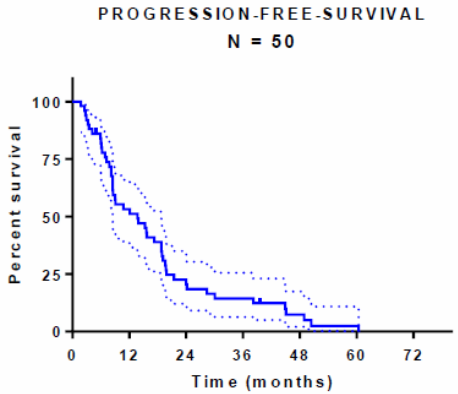
Progression-Free-Survival

- Median PFS 13.7 months
- 80% Central
- 5% Peripheral
- 15% Distant



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Stupp et al, Lancet Oncology 2009

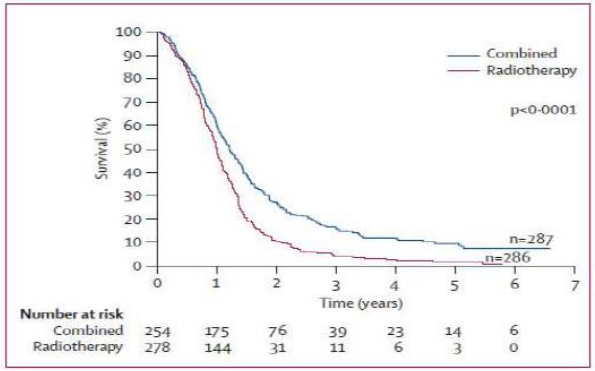

Figure 2: Kaplan-Meier estimates of overall survival by treatment group

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3-, 5-, 7-letnie OS korzystniejsze niż w badaniu Stupp'a

Główną przyczyną niepowodzenie wznowa centralna – zawężenie marginesów bezpieczne

GBM

Discussion

- Fifty patients were accrued with standard eligibility criteria similar to large RCT for patients with newly diagnosed GBM
- A median OS of 22.3 months compares favourably with median OS reported in the literature
- Long-term OS at 3, 5, and 7 years are very encouraging at 38%, 24% and 21%, respectively
- Toxicity is acceptable with an 82% actuarial freedom of necrosis at 3 years
- Possible mechanisms:
  - Early intervention
  - Hypofractionation
  - MGMT silencing by pre-irradiation neo-adjuvant TMZ exposure
  - Reduction of radiation-induced glioma cell migration by TMZ
  - Limited margins radiotherapy volumes allowing accelerated hypo-fractionation with acceptable toxicity

CONCLUSIONS

Neo-adjuvant TMZ followed by accelerated hypofractionated limited-margin radiotherapy and concomitant TMZ and adjuvant TMZ is feasible and safe

The overall and Progression Free Survival compare favourably to conventionally fractionated radiotherapy schedules

The pattern of failure remains central similar to approaches using larger margins for radiotherapy planning with significant sparing of normal brain tissues

Toxicity is acceptable with shortening of overall treatment time with significant reduction of time and resources to both patients and health care providers

Why change the dosing/sequencing of the Stupp regimen?

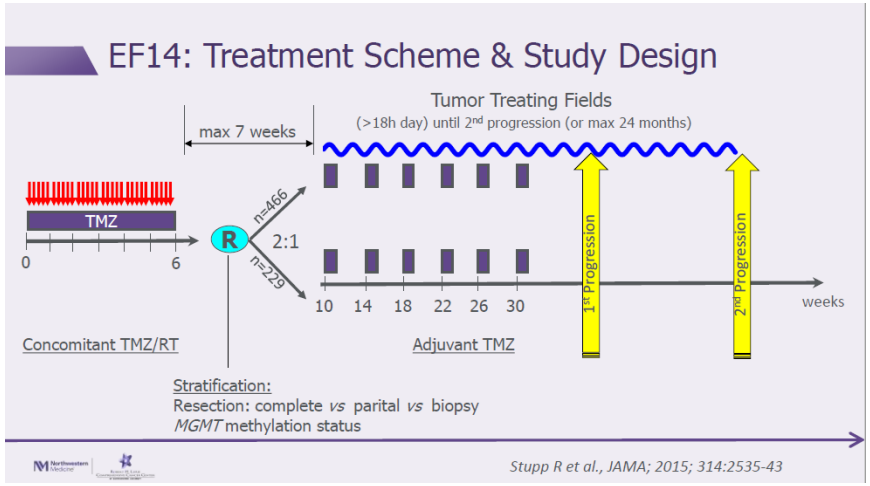
1. Why accelerated hypofractionated RT (AHRT)?
   - -Increase tumor cell killing/repopulation
   - -Possibly enhanced interactions with TMZ
2. Why give neoadjuvant TMZ?
   - -Prevent early tumor cell spread after surgery and before RT
   - -Reduce MGMT levels in unmethylated tumors
3. Why shrink margins?
   - -Facilitate the use of larger fraction sizes
   - -Reduce normal tissue exposure and thus toxicity

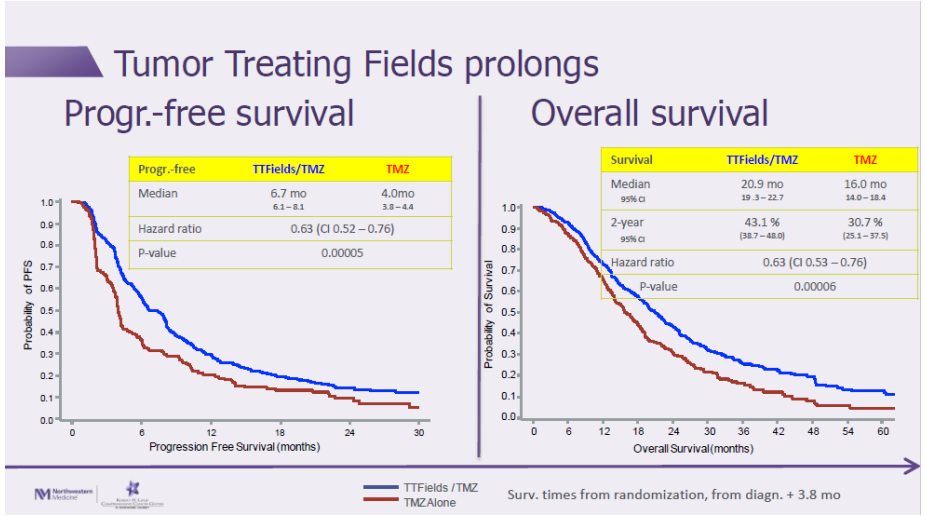
Neoadjuwantowa chth TMZ (2 tyg.)
+ przyspieszona RT+TMZ

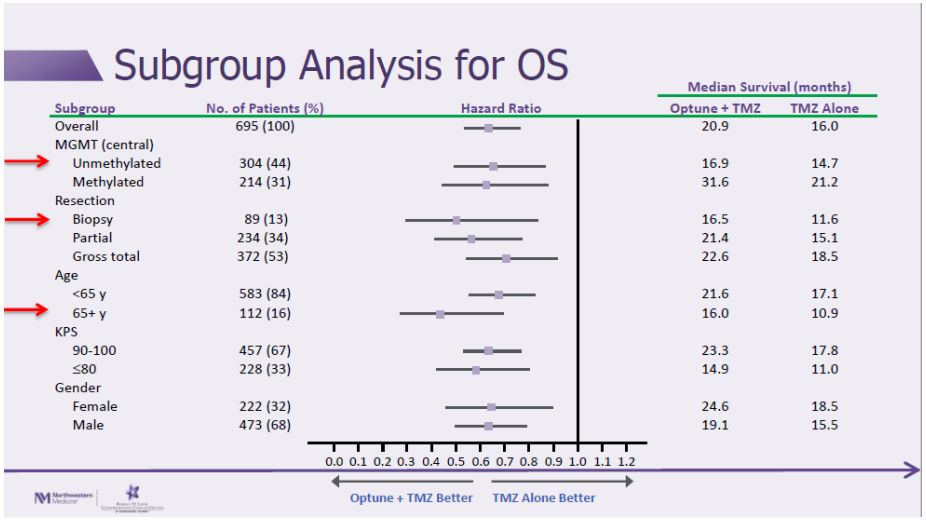
- **korzystną opcją terapeutyczną o uzasadnieniu farmakokinetycznym i biologicznym**

This study suggests this approach is feasible, safe, and possibly favorable to conventional regimens…

GBM







Zmienne pole elektryczne w skojarzeniu z RT/TMZG w GBM – standard terapeutyczny 2018

BM
– SRS + inhibitory punktów kontrolnych

Treatment of Brain Metastases with Stereotactic Radiosurgery and Immune Checkpoint Inhibitors: An International Meta-Analysis of Individual Patient Data

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BM

1570 BM
głównie MM, NSCLC, RCC

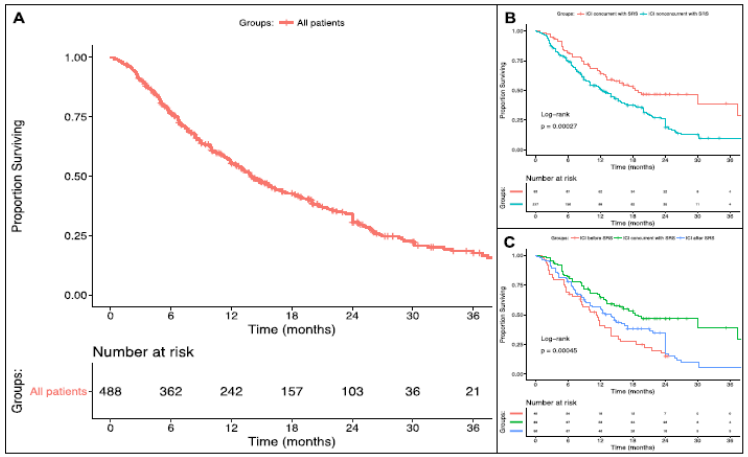
Background

- Combination stereotactic radiosurgery and immune checkpoint inhibitors have shown great promise in treating brain metastases
- Data are largely limited to single institution retrospective studies
- We aim to characterize safety, efficacy, and the optimal administration of these therapies relative to one another

Results

- 17 Studies
  - 3 Countries
  - Published between 2013-2018
  - Melanoma in 16, NSCLC in 2, RCC in 1
- 1,570 metastases
- Concurrent
  - SRS/ICI given within 4 weeks of one another

Results: 1-year OS



Results: 1-year OS

- 1-Year OS for all patients
  - 56.7%
- Concurrent vs Non-concurrent
  - 64.6% vs. 51.6% ($p<0.001$)
- ICI before SRS vs Concurrent vs ICI after SRS
  - 40.7% vs. 65% vs. 56%
  - All $p<0.01$ (vs. concurrent therapy)

Jednoczesne zastosowanie SRS i ICI najkorzystniejszą opcją terapeutyczną (głównie MM)

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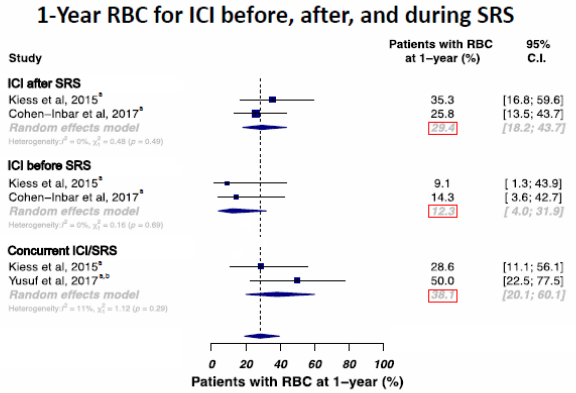
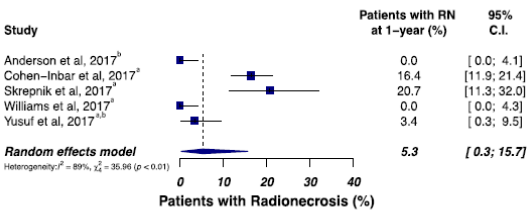
Results: 1-Year Regional Brain Control



38.1% vs. 12.3% (p=0.049)

a=ipilimumab; b=pembrolizumab or nivolumab

Results: Radionecrosis



- Too few studies stratified by timing
- Ipilimumab > Nivolumab/Pembrolizumab
  - SRS + checkpoint inhibitors in metastatic melanoma 2.5x increased risk of RN (Martin, JAMA Onc)
    - SRS + ipilimumab 4.7x increased risk

a=ipilimumab; b=pembrolizumab or nivolumab

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Summary

- 1-Year OS of 56%
- Radionecrosis more common with ipilimumab
- Concurrent over sequential therapy may be associated with improved 1-year OS, 1-year LC, and 1-year regional brain control
- Prospective data are needed

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BM

Authors

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ASTRO'S 60TH ANNUAL MEETING

Translating Discovery to Cure

Improved survival following immunotherapy in patients with lung and melanoma primaries metastatic to the brain treated with upfront stereotactic radiosurgery

2018 Nobel Prize in Physiology or Medicine

James Allison

Tasuku Honjo

Background

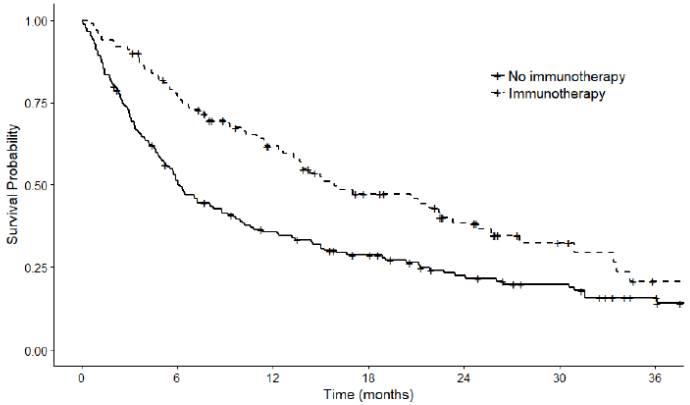
- Unclear effects of immunotherapy on brain met populations receiving SRS because:
  - 1) excluded from clinical trials
  - 2) unclear penetration of BBB
  - 3) reports of increased radiation necrosis

Objectives

- Single institution retrospective study of 271 consecutive metastatic NSCLC or melanoma patients treated with upfront SRS from 2013-2018
- Evaluate survival, patterns of failure, and cause of death in NSCLC and melanoma patients receiving SRS
- Compare a population receiving immunotherapy with a control population

Results

Figure 1: Kaplan-Meier plot of overall survival by immunotherapy



271 BM - SRS + inhibitory punktów kontrolnych w NSCLC i MM

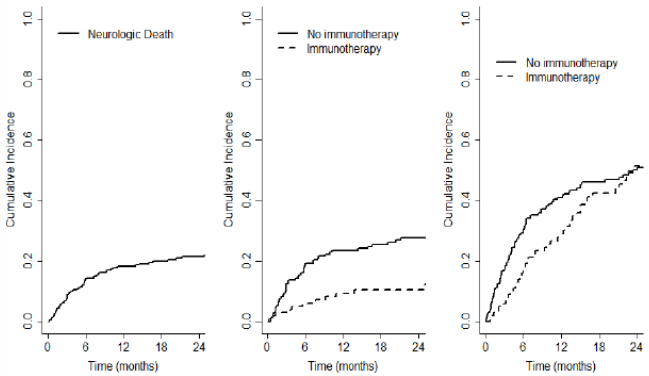
BM

Zgon z powodów neurologicznych

DBF

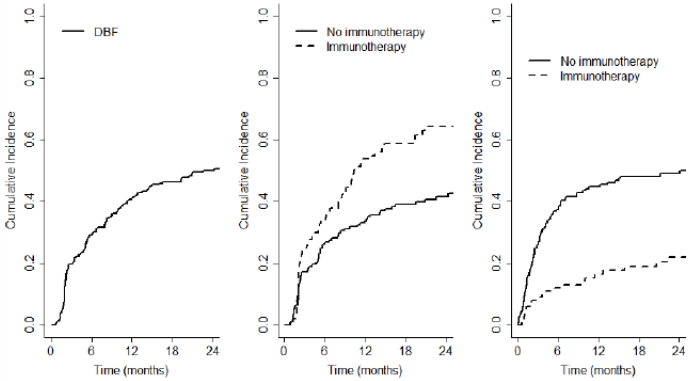
Results

Figure 2: Cumulative incidence of neurologic death for the overall cohort (left), neurologic death stratified by immunotherapy (middle) and non-neurologic death stratified by immunotherapy (right)



Results

Figure 3: Cumulative incidence of DBF for the overall cohort (left), DBF stratified by immunotherapy (middle), and death without DBF (right)



Multivariate analysis of neurologic death

	sHR	95% CI	P-value
Primary (Melanoma v. lung)	3.97	2.30-6.85	<0.001
KPS	0.97	0.95-1.0	0.05
Symptoms	1.97	1.07-3.63	0.03
Immunotherapy	0.35	0.19-0.66	0.001
HR, hazard ratio; KPS, Karnofsky Performance Status; sHR, subdistribution hazard ratio			

Multivariate analysis of non-neurologic death

	sHR	95% CI	P-value
Primary (Melanoma v. lung)	0.41	0.24-0.72	0.002
KPS	0.98	0.97-1.00	0.12
Symptoms	0.62	0.43-0.91	0.02
Immunotherapy	1.00	0.71-1.40	0.98
HR, hazard ratio; KPS, Karnofsky Performance Status; sHR, subdistribution hazard ratio			

Po ICI – zmniejszenie ryzyka zgonu z powodów neurologicznych

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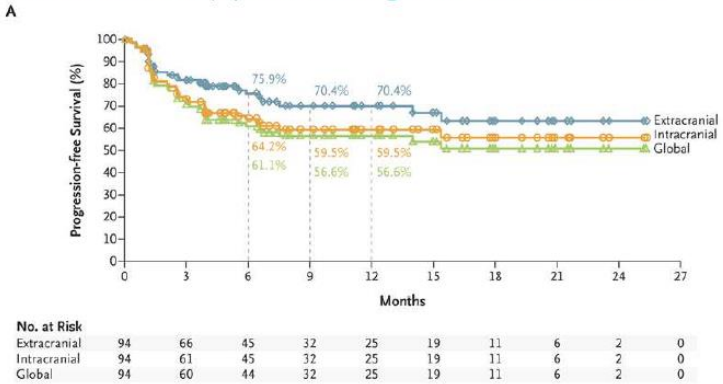
Evidence of Immunotherapy Affecting CNS Outcomes

Kaplan–Meier Estimates of Survival. "Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain."



No. at Risk										
Extracranial	94	66	45	32	25	19	11	6	2	0
Intracranial	94	61	45	32	25	19	11	6	2	0
Global	94	60	44	32	25	19	11	6	2	0

Tawbi, et al. N Engl J Med (2018).

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Conclusion

- Immunotherapy improves survival in melanoma/NSCLC brain metastasis patients receiving SRS
- Immunotherapy *improved neurologic death*, but had a *non-significant effect on non-neurologic death*

Poprawa przeżycia po skojarzeniu SRS i ICI
Skojarzenie – pozytywny wpływ na zmniejszenie ryzyka zgonu z powodów neurologicznych , nie istotny statystycznie wpływ na zmniejszenie ryzyka zgonu z innych powodów

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Przedoperacyjna SRS w BM

BM

Preoperative Stereotactic Radiosurgery For Resected Brain Metastases: Updated Analysis of Efficacy and Toxicity Of A Novel Treatment Paradigm

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*Accepted for publication in *Journal of Neurosurgery* July 16, 2018

Preoperative SRS

Atrium Health Levine Cancer Institute

Rationale:

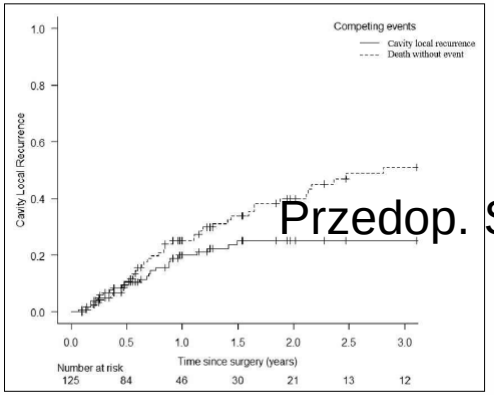
- Treat intact brain metastasis and avoid difficulty in delineating cavity volume and need for additional margin into normal brain
- Radiate tumor cells prior to surgery and potential spillage to reduce risk of surgery related leptomeningeal disease (LMD)
- Potentially increase compliance by delivering SRS prior to surgery and avoiding variable clinical course and delay after surgical resection
- Applied 10 - 20% dose reduction due to the need to control microscopic residual disease only
  - Allows all treatments to be single fraction, even to large lesions, in order to not delay surgery

Preoperative SRS

	Design	Patients	Cavity Local Recurrence	Symptomatic Rad Nec	LMD
Asher et al. 2014	Combined prospective and retrospective	47	1 year: 14%	NR	0%
Patel et al. 2016	Retrospective Pre-op SRS vs. Post-op SRS	66 pre-op / 114 post-op SRS	2 year: 23% vs. 16% (p=0.33)	**2 year: 5% vs. 16% (p=0.02)**	**2 year: 3% vs. 17% (p=0.01)**
Patel et al. 2017	Retrospective Pre-op SRS vs. post-op WBRT	66 pre-op / 36 post-op WBRT	2 year: 25% vs. 25% (p=0.81)	Crude: 6% vs. 0% (p=0.29)	**2 year: 4% vs. 9% (p=0.66)**

Local cavity recurrence

Atrium Health Levine Cancer Institute



Przedop. SRS

1-year cavity LR: 19.9%
2-year cavity LR: 25.1%

*2-year cavity LR from 2016 study (n=66): 23%

Przedop. SRS: mniejsze ryzyko LMD, martwicy, łatwiejsze planowanie, niższa dawka całk.

BM

Local cavity recurrence: Multivariable analysis

	Hazard ratio	95% confidence interval	p-value
Active systemic disease:			
No	reference		
Yes	0.44	0.16 – 1.17	0.1
SRS dose	0.91	0.7 – 1.18	0.48
GPA	0.99	0.48 – 2.05	0.98
Gross tumor volume (quartiles)	1.2	0.8 – 1.81	0.37
Resection status:			
Gross total	0.15	0.04 – 0.58	**0.008**
Subtotal	reference		
Primary site:			
NSCLC	reference		
Breast	1.28	0.52 – 3.16	0.6
Melanoma	0.21	0.03 – 1.68	0.14
Renal Cell	0.1	0.02 – 0.16	**<0.001**
Gastrointestinal	2.23	0.39 – 1.27	0.37
Other	1.79	0.62 – 5.21	0.29

Leptomeningeal disease (LMD) and Radiation Necrosis (RN)

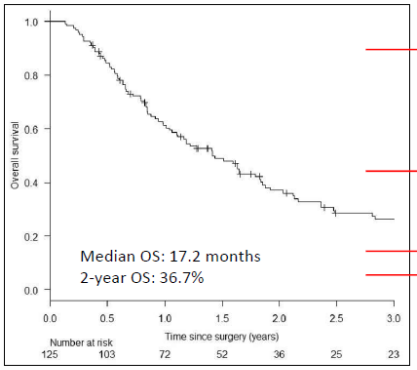
Atrium Health Levine Cancer Institute

	Current study (n=117/125)	2016 study (n=66/71)
2-year LMD	4.3%	3.2%
2-year RN	8.1%	8.2%
2-year symptomatic RN	4.8%	4.9%

3 patients experienced grade 3 toxicity:
- Symptomatic RN requiring surgery (n=1)
- Post-operative wound complications (n=1)
- Cavity hematoma requiring evacuation (n=1)

2-letnie OS: 56,7%

Overall Survival



	Hazard ratio	95% CI	p-value
Active systemic disease:			
No	reference		
Yes	1.04	0.57 – 1.89	0.9
SRS dose	0.91	0.78 – 1.06	0.21
GPA	0.54	0.33 – 0.89	**0.02**
Gross tumor volume (quartiles)	1.01	0.77 – 1.31	0.95
Resection status:			
Gross total	0.38	0.14 – 0.99	**0.05**
Subtotal	reference		
Primary site:			
NSCLC	reference		
Breast	0.55	0.29 – 1.03	0.06
Melanoma	0.52	0.25 – 1.08	0.08
Renal Cell	0.62	0.3 – 1.25	0.18
GI	1.9	0.72 – 5.04	0.2
Other	1.07	0.42 – 2.71	0.89
Age (years)	1	0.98 – 1.02	0.6

Conclusions

Atrium Health Levine Cancer Institute

- Preoperative single fraction SRS continues to be associated with excellent cavity local control with notably low incidence of LMD and RN in this expanded patient cohort with more imaging and clinical patient-years analyzed.
- In the setting of GTR, pre-op SRS dose reduction and larger tumor size are not associated with worse cavity local control
- STR was rare (4.8%), but these patients are at significantly higher risk of cavity LR and death compared with GTR
  - We do not recommend dose reduced pre-op SRS in cases where STR is likely
  - In cases of unexpected STR after dose reduced preoperative SRS, consider re-resection or additional boost RT.
- A phase IIR cooperative group trial of pre-op vs. post-op SRS is currently being designed

Przedop. SRS – doskonała LC zwłaszcza po GTR guza, niskie ryzyko LMD i RN

BM

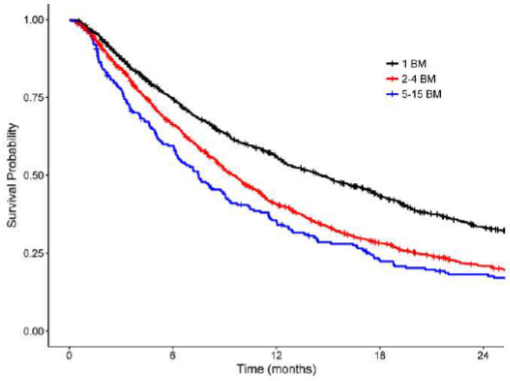
Initial SRS for patients with 5-15 brain metastases: results of a multi-institutional experience

Ryan T. Hughes MD[1], Adrianna H. Masters MD PhD[1], Emory R. McTyre MD MS[1], Michael K. Farris MD[1], Caroline Chung MD MSc[2], Brandi R. Page MD[3], Lawrence R. Kleinberg MD[3], Jaroslaw Hepel[4], Joseph N. Contessa MD PhD[5], Veronica Chiang MD[6], Jimmy Ruiz MD[7], Kounosuke Watabe PhD[8], Jing Su PhD[9], John B. Fiveash MD[10], Steve Braunstein MD PhD[11], Samuel Chao MD[12], Albert Attia MD[13], Diandra N. Ayala-Peacock MD[13], Michael D. Chan MD[1]

Background

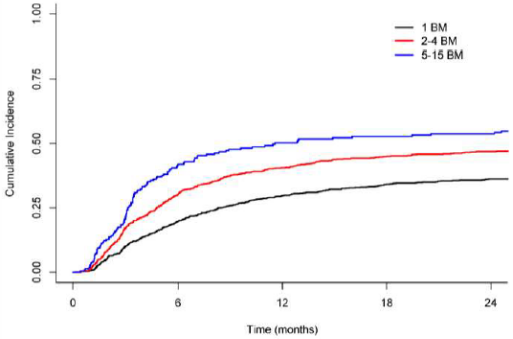
- Stereotactic radiosurgery (SRS) is an accepted standard for patients with 1-4 brain metastases
- Whole brain radiotherapy (WBRT) reduces distant brain failure (DBF) and decreases salvage therapy requirements
- Cognitive decline is more frequent in patients treated with WBRT
- The role for SRS for 5-15 brain metastases remains controversial

Overall Survival



Number of BM	Median OS (months)	HR (95% CI)	p value
1	14.6	0.72 (0.65-0.79)	<0.01
2-4	9.5	Reference	-
5-15	7.5	1.13 (0.96-1.32)	0.14

Distant Brain Failure

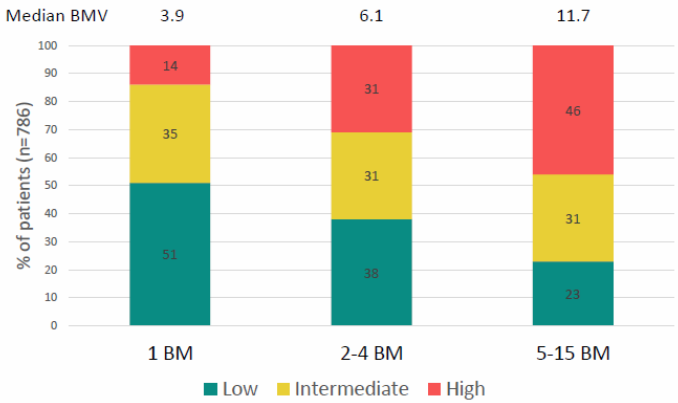


Number of BM	1-year DBF	HR (95% CI)	p value
1	30%	0.73 (0.63-0.83)	<0.01
2-4	41%	Reference	-
5-15	50%	1.29 (1.04-1.59)	0.02

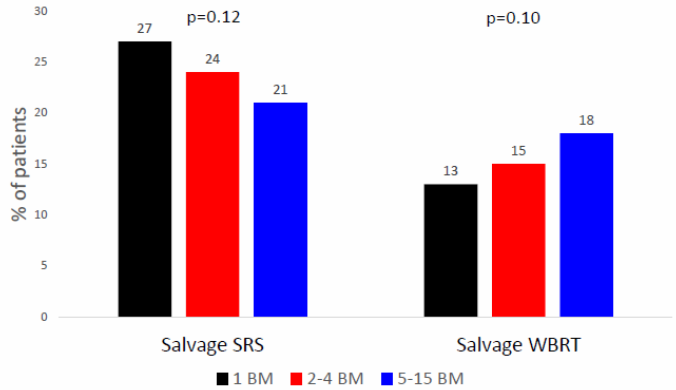
Zastosowanie SRS w przypadku 5-15 BM jako wyłącznej metody leczenia

BM

Brain Metastasis Velocity



Salvage Radiotherapy



Conclusions

- Overall survival did not differ between patients with 2-4 and 5-15 brain metastases
- 5-15 brain metastases treated was associated with higher rates of DBF and higher BMV
- Trend toward fewer salvage SRS and more salvage WBRT procedures

Brak istotnej statystycznie różnicy w OS (p=0,14) pomiędzy 5-15 i 2-4 BM
Wyższe ryzyko DBF i wyższe BMV
Trend w kierunku ograniczenia powtórnej SRS, większa potrzeba WBRT

BM - ratująca RT; SRS vs WBRT

Salvage SRS is associated with improved OS compared to WBRT in the setting of progressive brain metastases

Michael H. Soike,[1] Emory R. McTyre,[1] Michael Farris,[1] Diandra N. Ayala-Peacock,[2] Jaroslaw T. Hepel,[3] Brandi R. Page,[4] Lawrence Kleinberg,[4] Joseph N. Contessa,[5] Veronica Chiang,[5] Christina K. Cramer,[1] Jimmy Ruiz,[7] Boris Pasche,[7] Stephen B. Tatter,[7] John B. Fiveash,[8] Manmeet Ahluwalia,[9] Samuel T. Chao,[9] Steve E. Braunstein,[10] Albert Attia,[2] Caroline Chung,[15,16] Michael D. Chan[1]

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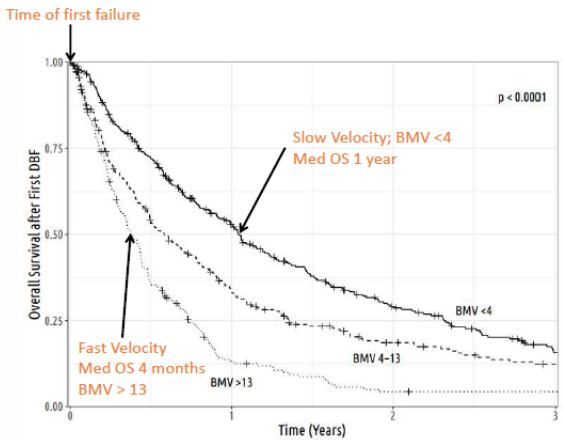
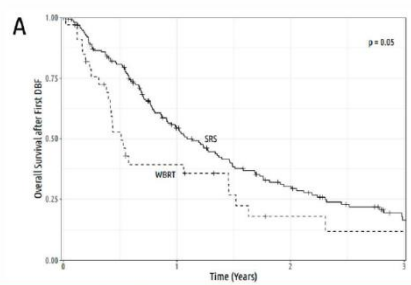
Multi-institutional database

- N=2,083 patients
- Risk stratification for failure after SRS
- Multiple histologies

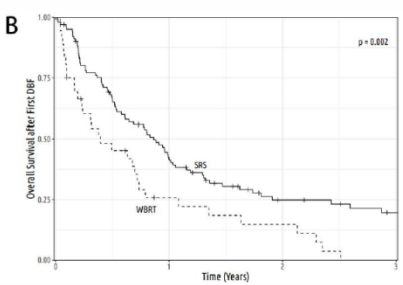


Low BMV <4 BM/year



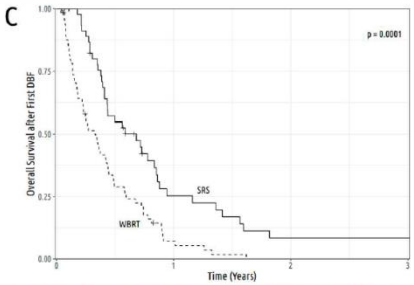
HR 1.67 (1.07-2.61)

Intermediate BMV 4-13 BM/yr



HR 2.11 (1.3

High BMV >13 BM/year



HR 3.02 (1.89-4.83)

Conclusions

- SRS is associated with longer OS at time of salvage therapy for progressive disease
  - DS-GPA, Histology
- Patient selection bias within retrospective dataset
- Phase III RCT: WBRT vs SRS for new progressive brain metastases

Przeżycie chorych uzależnione od BMV (brain mets velocity) – 2 lata vs 4 mies.

SRS skuteczniejsza vs WBRT we wszystkich kategoriach BMV

BM

Brain Metastases: From Promising to Proven

October 24, 2018

Ayal Aizer MD, MHS
Assistant Professor
Department of Radiation Oncology
Brigham and Women's Hospital / Dana-Farber Cancer Institute
Harvard Medical School

BM

DF/HCC
DANA-FARBER/HARVARD CANCER CENTER

RCTs of local brain directed therapy +/- WBRT

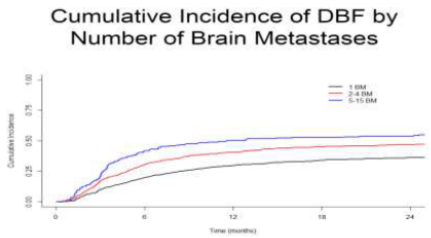
Study	N	Num BM	Arms	Years of Accrual	Intracranial Recurrence with WBRT	OS with WBRT	QoL with WBRT	Neurocog with WBRT
Patchell *JAMA 1998*	95	1	1. Surgery 2. Surgery + WBRT	1989-1997	Lower	No difference	No difference (KPS)	N/A
JROSG 99-1 *JAMA 2006*	132	1-4	1. SRS 2. SRS + WBRT	1999-2003	Lower	No difference	No difference (KPS)	No difference (MMSE)
MDACC *Lancet Oncol 2009*	58	1-3	1. SRS 2. SRS + WBRT	2001-2007	Lower	Worse	No difference	Inconclusive
EORTC 22952 *JCO 2011,2013*	359	1-3	1. Local Therapy 2. Local Therapy + WBRT	1996-2007	Lower	No difference	Trend to worse	Worse
NCCTG N0574 *JAMA 2016*	213	1-3	1. SRS 2. SRS + WBRT	2002-2013	Lower	No difference	Worse	Worse
JCOG0504 *JCO 2008*	271	1-4	1. Resection + SRS 2. Resection + WBRT	2006-2014	Lower	No difference	N/A	Generally worse
Polish *Rad and Oncol 2016*	59	1	1. Resection + SRS 2. Resection + WBRT	2011-2015	No difference	Better	No difference	Unclear
NCCTG 107C *Lancet Oncol 2017*	194	1-4	1. Resection + SRS 2. Resection + SRS + WBRT	2011-2015	Lower	No difference	No significant difference	Worse

Dodatek WBRT do leczenia miejscowego
– niższe ryzyko wznowy wewnątrzmózgowej, bez wpływu na OS (większość), bez wpływu na QoL (większość), pogorszenie funkcji poznawczych

BM

DF/HCC
DANA-FARBER/HARVARD CANCER CENTER

Expanded role of SRS/SRT



Hughes et al. ASTRO 2018

	New lesions	LM disease
1 BM	HR 0.55, p<.001	HR 0.71, p=.09
2-4 BM	REF	REF
5-10 BM	HR 1.22 p=.07	HR 1.58, p=.04

Yamamoto et al. Lancet Onc. 2014

DF/HCC
DANA-FARBER/HARVARD CANCER CENTER

Expanded role of SRS/SRT

	OS
BMV <4	SRS > WBRT (p=.005)
BMV 4-13	SRS > WBRT (p=.005)
BMV >13	SRS > WBRT (p=.0006)

Soike et al. ASTRO 2018

Study	OS with WBRT
Patchell *JAMA 1998*	No difference
JROSG 99-1 *JAMA 2006*	No difference
MDACC *Lancet Oncol 2009*	Worse
EORTC 22952 *JCO 2011,2013*	No difference
NCCTG N0574 *JAMA 2016*	No difference
JCOG0504 *JCO 2008*	No difference
Polish *Rad and Oncol 2016*	Better
NCCTG 107C *Lancet Oncol 2017*	No difference

BWH/DFCI Study

PATIENTS WITH 5-20 BRAIN METASTASES

↓

STRATIFY: 1. HISTOLOGY 2. CRANIOTOMY

↓

RANDOMIZE

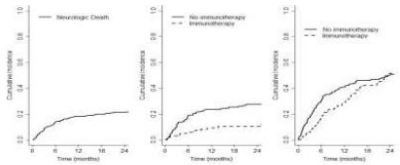
↓

WBRT | SRS/SRT

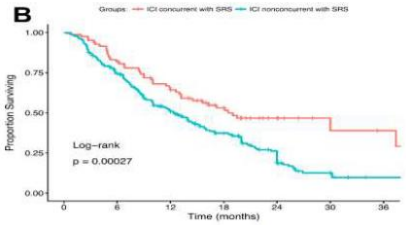
PRIMARY ENDPOINT: QUALITY OF LIFE

DF/HCC
DANA-FARBER/HARVARD CANCER CENTER

SRS + IO



Hughes et al. ASTRO 2018



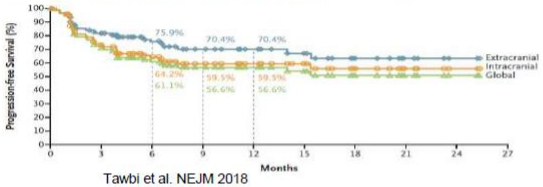
Lehrer et al. ASTRO 2018

Wzrastająca rola SRS w BM

BM

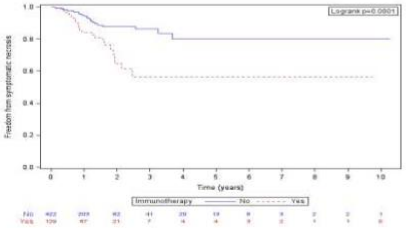
DF/HCC
DANA-FARBER/HARVARD CANCER CENTER

IO alone vs SRS + IO



Tawbi et al. NEJM 2018

"Although current practice is to start with surgery, stereotactic radiotherapy, or both followed by immunotherapy or targeted agents, our results support the initiation of immunotherapy to achieve prompt control of both extracranial and brain metastases"



Martin et al. JAMA ONC. 2018

Proposed Study

PATIENTS WITH MELANOMA AND BRAIN METASTASES

RANDOMIZE

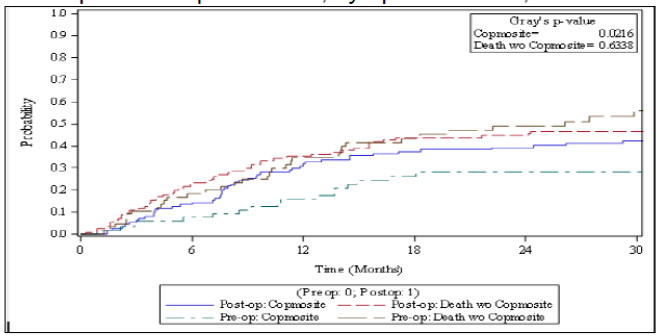
IPI/NIVO | IPI/NIVO + SRS/SRT

PRIMARY ENDPOINT: OS

DF/HCC
DANA-FARBER/HARVARD CANCER CENTER

Pre-op vs post-op RT

Composite endpoint of LR, symptomatic RN, or LMD



Prabhu et al. ASTRO 2018

DF/HCC
DANA-FARBER/HARVARD CANCER CENTER

Pre-op vs post-op SRS/SRT: Trial Design

Post-op SRS vs Post-op WBRT

CAVITY CONTROL	SRS	WBRT
3 mo	96%	94%
6 mo	80%	87%
12 mo	61%	81%

Post-op: SRS vs SRT

OUTCOME	SRS	SRT
LR	++	
NECROSIS	++	
LMD	-	-

Brown et al. Lancet Oncol. 2017

LMD – wzrost ryzyka po resekcji chirurgicznej

Leptomeningeal Disease After Surgical Resection and Radiosurgery for Brain Metastases: A Multi-Institutional Analysis of the Presentation, Patterns of Failure, and Outcomes Based on Type of Salvage Treatment

Roshan S. Prabhu[1,2], Brandon E. Turner[3], Anthony L. Asher[1,4], Samuel R. Marcrom[5], John B. Fiveash[5], Paul M. Foreman[5], Robert H. Press[6], Kirtesh R. Patel[7], Walter J. Curran Jr[6], William Breen[8], Paul D. Brown[8], Krishan R. Jethwa[8], Inga S. Grills[9], Jessica D. Arden[9], Lauren M. Foster[10], Matthew A. Manning[11], Joseph D. Stern[4,11], Katherine R. Miller[1], Scott G. Soltys[3*], Stuart H. Burri[1,2*]

*Both senior authors contributed equally to this work

[1]Levine Cancer Institute, Atrium Health, Charlotte, NC, [2]Southeast Radiation Oncology Group, Charlotte, NC
[3]Department of Radiation Oncology, Stanford University, Stanford, CA, [4]Carolina Neurosurgery and Spine Associates, Charlotte, NC
[5]University of Alabama at Birmingham, Birmingham, AL, [6]Winship Cancer Institute of Emory University, Atlanta, GA
[7]Yale University School of Medicine, New Haven, CT, [8]Mayo Clinic, Rochester, MN, [9]Beaumont Health, Royal Oak, MI
[10]Oakland University William Beaumont School of Medicine, Auburn Hills, MI, [11]Cone Health Cancer Center, Greensboro, NC

Atrium Health
Levine Cancer Institute

LMD after Postoperative SRS

Institution(s)	Study Design	# of Patients	Median Marginal SRS Dose (Gy)	1 year LMD (%)	Risk factors for LMD
Johnson (Beaumont) 2016	Retrospective	112	16	16.9	Prior surgical resection Breast primary
Patel (Emory) 2016	Retrospective	114	18	16.6 (2-year)	Multiple brain metastases
Atalar (Stanford) 2013	Retrospective	165	NR	11	Breast primary (24% vs. 9%)
Ojerholm (Penn) 2014	Retrospective	86	16	14 (crude)	Breast primary Posterior fossa location
Foreman (UAB) 2017	Retrospective	91	16	31	Multiple brain metastases Breast primary
Mahajan (MDACC) 2017	Prospective	63 (SRS arm)	16	28	NR
Brown (N107C) 2017	Prospective	98 (SRS arm)	NR	7	NR

Atrium Health
Levine Cancer Institute

LMD after post-operative SRS

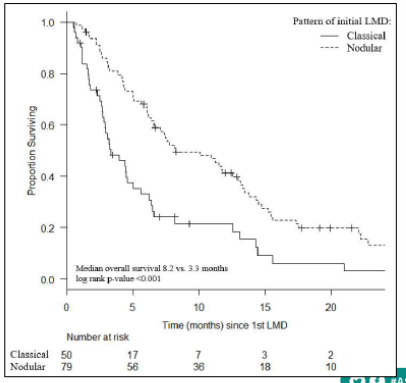
- Risk factors for LMD include:
  - Surgical resection of brain metastases*
  - Breast primary*
  - Multiple brain metastases
  - Piecemeal resection (vs. en bloc)
  - Hemorrhagic brain metastases
  - Posterior fossa location
- Thought to be caused by tumor spillage into the CSF at the time of surgical resection that was not as apparent when adjuvant WBRT was routine

Atrium Health
Levine Cancer Institute

Survival Outcomes

Median OS for all 147 patients: 5.4 months
Median OS for treated (n=129) vs. untreated (n=18) patients:
- 6.4 vs. 0.9 months, p<0.001

Median OS for nLMD vs. cLMD among patients who received LMD salvage treatment (n=129):
- 8.2 vs. 3.3 months, p<0.001



SRS w LMD – 1 roczne przeżycie 7-31 %
Czynniki ryzyka nawrotu LMD po SRS: resekcja chirurgiczna BM, rak piersi, liczne BM, wycięcie we fragmentach, krwawiące BM, lokalizacja w tylnym dole czaszki
Powtórna SRS po SRS jest korzystną opcją terapeutyczną pozwalającą uniknąć WBRT

SBRT - Spine

JOHNS HOPKINS MEDICINE
RADIATION ONCOLOGY & MOLECULAR RADIATION SCIENCES

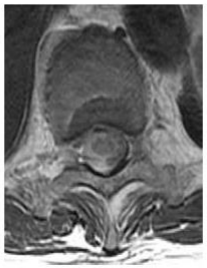
A Phase II Study of Post-Operative Spine SBRT for Solid Tumor Spine Metastases

Kristin Redmond, D Sciubba, B Leaf, M Khan, L Kleinberg, J Grimm, C Gui, Z Gokaslan, X Ye, M Lim

Spinal Cord Delineation

JOHNS HOPKINS MEDICINE RADIATION ONCOLOGY & MOLECULAR RADIATION SCIENCES

T2 weighted MRI +2 mm radial margin or thecal sac if below conus



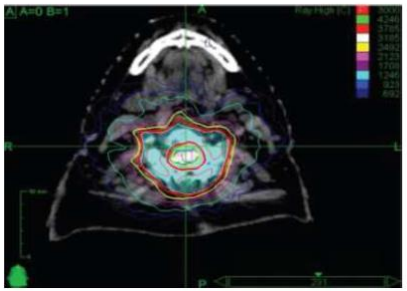
Axial

Sagittal

Prescription Dose

JOHNS HOPKINS MEDICINE RADIATION ONCOLOGY & MOLECULAR RADIATION SCIENCES

30 Gy in 5 fractions
Median prescription isodose line: 61% (range 53-71)
Median PTV coverage: 90.2% (range 85.1-96.2)

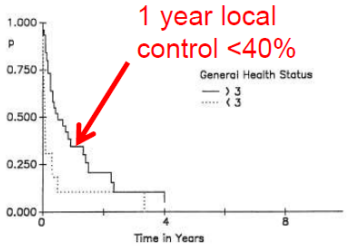


Conclusion

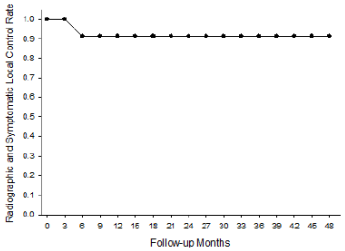
JOHNS HOPKINS MEDICINE RADIATION ONCOLOGY & MOLECULAR RADIATION SCIENCES

- Randomized study warranted

HISTORICAL KLEKAMP 1998



CURRENT STUDY



Prospective clinical trial demonstrates excellent local control following post-operative spine SBRT with low toxicity

Dosimetry,
Local Control and Toxicity of Spine SBRT

Scott G. Soltys, M.D.

Department of Radiation Oncology
Stanford Cancer Institute - Stanford University

ASTRO 2018 San Antonio
Panel 33: SBRT for Spine Metastases: What Can Be Offered When Conventional RT Fails?
Oct 24, 2018

SBRT - Spine

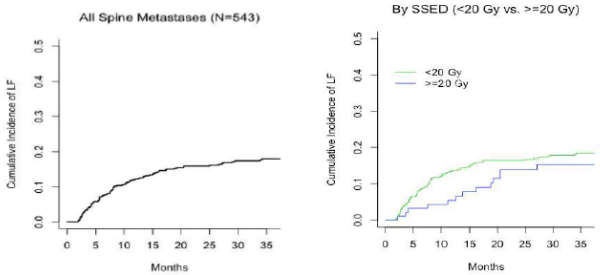
Spine SBRT Planning: Prescription Dose

- Dosing is Variable (Typically 18-24 Gy or equivalent):
  - RTOG 0631 — 16 or 18 Gy
  - Cleveland Clinic — 18 Gy
  - MSKCC — 24 Gy
  - Stanford — 20 Gy (usually the D95% to PTV)
  - MDACC — 24 Gy to GTV, 16 Gy to CTV
  - Sunnybrook — 24 Gy in 2 fractions
  - Johns Hopkins — 24 Gy in 2 fractions

Dose and Local Control

- Stanford
- n=543 lesions

Local Failure	Overall	<20 Gy	≥20 Gy
1 Year	12%	14%	5%



Kumar et al., submission in 2018

Spinal SBRT – De Novo Lesions

ISRS Systematic Review
14 articles 1024 spinal lesions

Median OS:	15-19 months
Local Control:	85-90% at 1 year
Complete pain response (only 3 studies):	~50%
Vertebral Compression Fracture:	9%

Conclusion: Spinal SBRT is effective and durable but need more prospective, better quality data

Husain JNS Spine June 9, 2017

Conclusion: Dose and Coverage

Prescription Dose is not standardized
- Typical range: 18-24 Gy in 1 fraction or equivalent
  - 24 Gy in 2 → SFED of 18.5 Gy_{10}
  - 27 Gy in 3 → SFED of 18.2 Gy_{10}

Coverage not standardized, but usually >90% at that dose
3 large data sets suggest want Dmin > 14-15 Gy
- Ideally a GTV D95 of 18 Gy

In the current era, publications are now reporting dosimetry
- Can then do multi-institutional TCP modeling

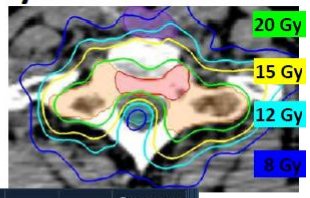
SFED = Single Fraction Equivalent Dose

SBRT - Spine

Dose to PTV and OARs: 20 Gy x 1

Goals:

Cord V14 < 0.03 cc
Cord V10 < 0.35 cc
GTV Dmin >15 Gy
Esophagus V16 < 0.03 cc (RTOG)
Esophagus V14 < 2.5cc, Dmax 22Gy (Cox)



Name	Min (cGy)	Mean (cGy)	Max (cGy)	CI	nCI	HI	Coverage (%)
T1 GTV	1550	2296	2495	2.14	2.22	1.25	96.38
T1 CTV	1550	2284	2500	1.41	1.46	1.25	96.72
T1 cord	361	710	1312	n/a	n/a	n/a	n/a
Esophagus	49	918	1978	n/a	n/a	n/a	n/a

Name	Dose (cGy)	Dose (%)	Volume (cm³)	Volume (%)
T1 cord	**1400**	56.0	0.00	0.0
T1 cord	**1000**	40.0	0.36	12.8
Esophagus	**2000**	80.0	0.00	0.0
Esophagus	**1400**	56.0	1.52	17.9
Esophagus	**1200**	48.0	2.54	29.9

OAR Constraints: Nerve Roots

n=557 treatments 24Gy x 1 in 88%

n=14 peripheral nerve injuries: 2.5%

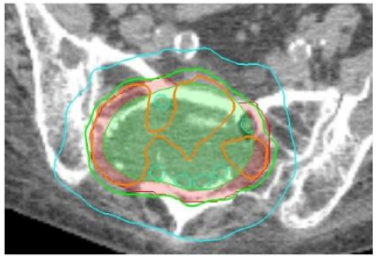
if exclude the T spine: 4.5%

Median time after SRS: 10 months (range 4-32)

No dose relationship (per prescription dose)

– But no nerve dosimetry available
- Is the injury from the prescription dose of 24 Gy?
- Is the injury from 120-130% dose from plan heterogeneity?

Stubblefield, Bilsky NSurg Focus 42, 2017



Conclusions – Spine SBRT Planning

Contouring – Per Consensus Guidelines

Dose – Typically 18-24 Gy x 1, 24 Gy in 2, 27-30 Gy in 3

– Dmin >14-15 Gy in 1. -GTV D95 > 18.3 Gy

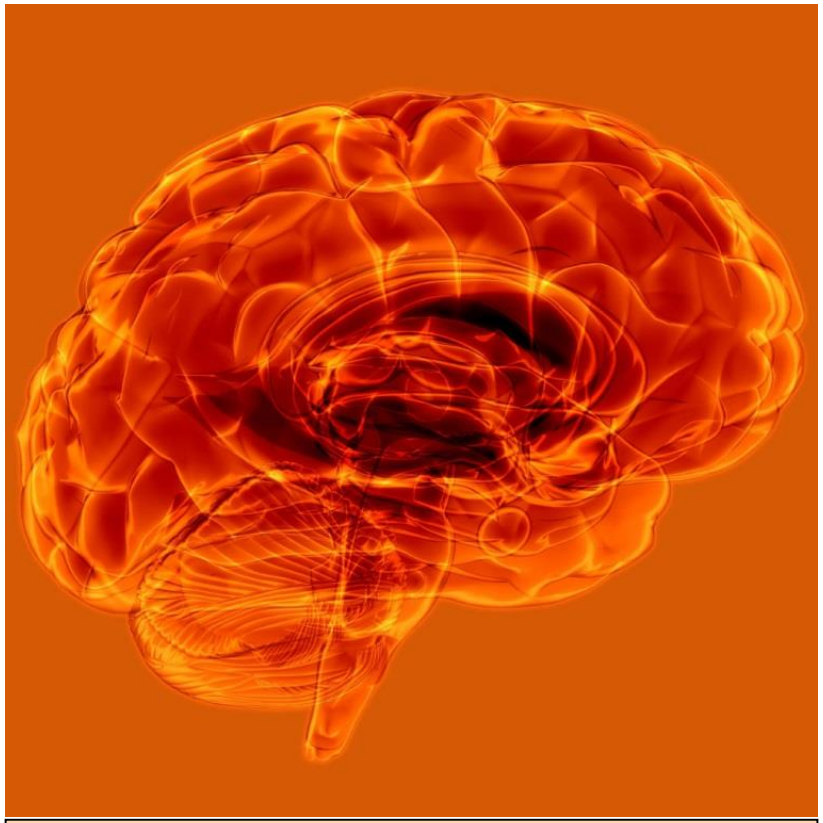
Cord: Dmax 14, V10 0.35 (RTOG 0631)

Esophagus: Dmax 22 Gy, V14 < 2.5 cc

Nerve Roots: Less than 105% of plan

Rekomendacje dozymetryczne dla SBRT w guzach rdzenia

20 Gy – LC 2,5%
1 r. LC – 85-90%
CR ból – ok. 50%
Kompresyjne złamanie – 9%



Dziękuję za uwagę !