Completeness of required site-specific factors for brain and CNS tumors in the Surveillance, Epidemiology and End Results (SEER) 18 database

Quinn T. Ostrom, Haley Gittleman, Carol Kruchko, Lynne Penberthy, Valentina Petkov, Jill S. Barnholtz-Sloan

The Central Brain Tumor Registry of the United States

Background

- Cancer classification and diagnosis are becoming increasingly based on molecular features, or ‘biomarkers’
- With increasing focus on ‘precision medicine,’ it is critical to measure tumor markers on a population level
- Brain tumors are highly heterogeneous, and relevant biomarkers vary significantly by histology

2007 WHO Classification and Grading Scheme

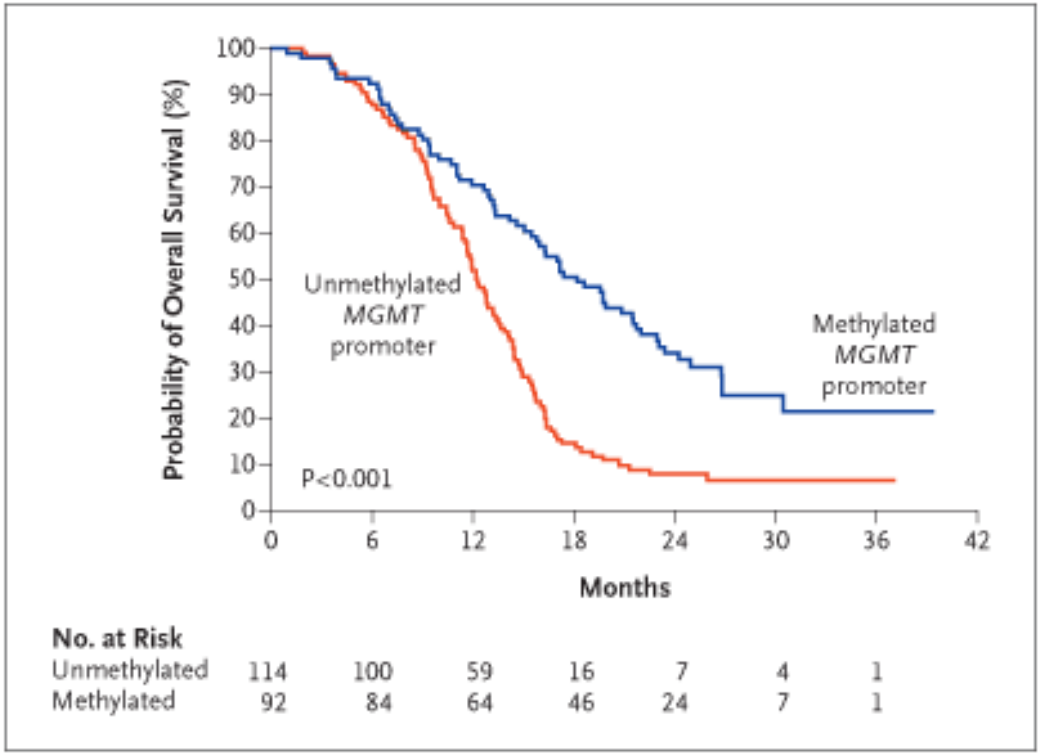
	I	II	III	IV
Astrocytic tumours				
Subependymal giant cell astrocytoma	•			
Pilocytic astrocytoma	•			
Pilomyxoid astrocytoma		•		
Diffuse astrocytoma		•		
Pleomorphic xanthoastrocytoma		•		
Anaplastic astrocytoma			•	
Glioblastoma				•
Giant cell glioblastoma				•
Gliosarcoma				•
Oligodendroglial tumours				
Oligodendroglioma		•		
Anaplastic oligodendroglioma			•	
Oligoastrocytic tumours				
Oligoastrocytoma		•		
Anaplastic oligoastrocytoma			•	
Ependymal tumours				
Subependymoma	•			
Myxopapillary ependymoma	•			
Ependymoma		•		
Anaplastic ependymoma			•	
Choroid plexus tumours				
Choroid plexus papilloma	•			
Atypical choroid plexus papilloma		•		
Choroid plexus carcinoma			•	
Other neuroepithelial tumours				
Angiocentric glioma	•			
Chordoid glioma of the third ventricle		•		
Neuronal and mixed neuronal-glial tumours				
Gangliocytoma	•			
Ganglioglioma	•			
Anaplastic ganglioglioma			•	
Desmoplastic infantile astrocytoma and ganglioglioma	•			
Dysembryoplastic neuroepithelial tumour	•			
Central neurocytoma		•		
Extraventricular neurocytoma		•		
Cerebellar liponeurocytoma		•		
Paraganglioma of the spinal cord	•			
Papillary glioneuronal tumour	•			
Rosette-forming glioneuronal tumour of the fourth ventricle	•			
Pineal tumours				
Pineocytoma	•			
Pineal parenchymal tumour of intermediate differentiation		•	•	
Pineoblastoma				•
Papillary tumour of the pineal region		•	•	
Embryonal tumours				
Medulloblastoma				•
CNS primitive neuroectodermal tumour (PNET)				•
Atypical teratoid / rhabdoid tumour				•
Tumours of the cranial and paraspinal nerves				
Schwannoma	•			
Neurofibroma	•			
Perineurioma	•	•	•	
Malignant peripheral nerve sheath tumour (MPNST)		•	•	•
Meningeal tumours				
Meningioma	•			
Atypical meningioma		•		
Anaplastic / malignant meningioma			•	
Haemangiopericytoma		•		
Anaplastic haemangiopericytoma			•	
Haemangioblastoma	•			
Tumours of the sellar region				
Craniopharyngioma	•			
Granular cell tumour of the neurohypophysis	•			
Pituicytoma	•			
Spindle cell oncocytoma of the adenohypophysis	•			

- The World Health Organization (WHO) grading scheme is an essential element of diagnosis for CNS tumors
- Developed and updated by expert neuro-pathologists
- Used to estimate prognosis and determine appropriate course of treatment

Louis et al, 2007

BT Prognostic Biomarkers: Methylation of MGMT

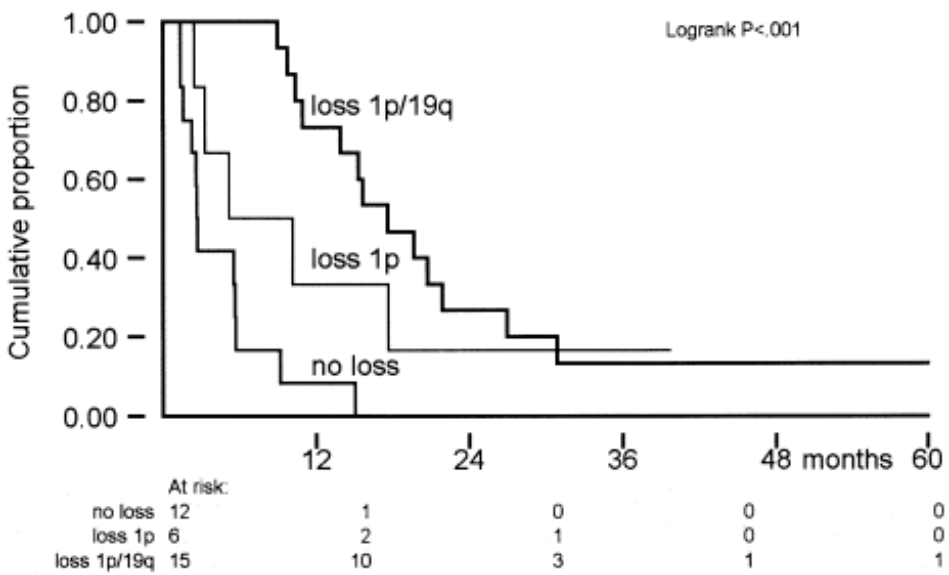
- Hypermethylation at MGMT – responsive to alkylating agents (i.e. Temozolomide)
- More responsive to both chemo and radiation if methylated



Hegi et al., NEJM 2005

BT Prognostic Biomarkers: Codeletion of 1p and 19q

- Concurrent loss of 1p and 19q is common in oligodendrogliomas
  - Also known as loss of heterozygosity (LOH)
- Collection is part of standard clinical care in LGG
- WHO has revised histologic criteria to include these markers as necessary for diagnosis of oligodendroglioma



Van den Bent et al, Cancer 2003

Are these markers complete at the population level?

- SEER registries have collected information on several tumor markers shown to be relevant in brain tumors since 2004
  - WHO grade (2004+)
  - MGMT Methylation (2008+)
  - 1p/19q deletion (2008+)
- Not all of these factors are relevant to all brain tumor histologies

AJCC Collaborative Staging Site-Specific Factors

- The AJCC Collaborative Staging system identified site-specific factors (SSF) for each cancer site that are relevant to determining stage of cancer

- Brain tumors are **not** staged, but AJCC includes several factors that are significantly associated with prognosis and survival in brain tumor

CoC and SEER Required Site-Specific Factors (SSF) for Collaborative Staging Version 02.04

Blue Already coded in CSv01 **Green** Additional clinically significant **White** Not required at this time

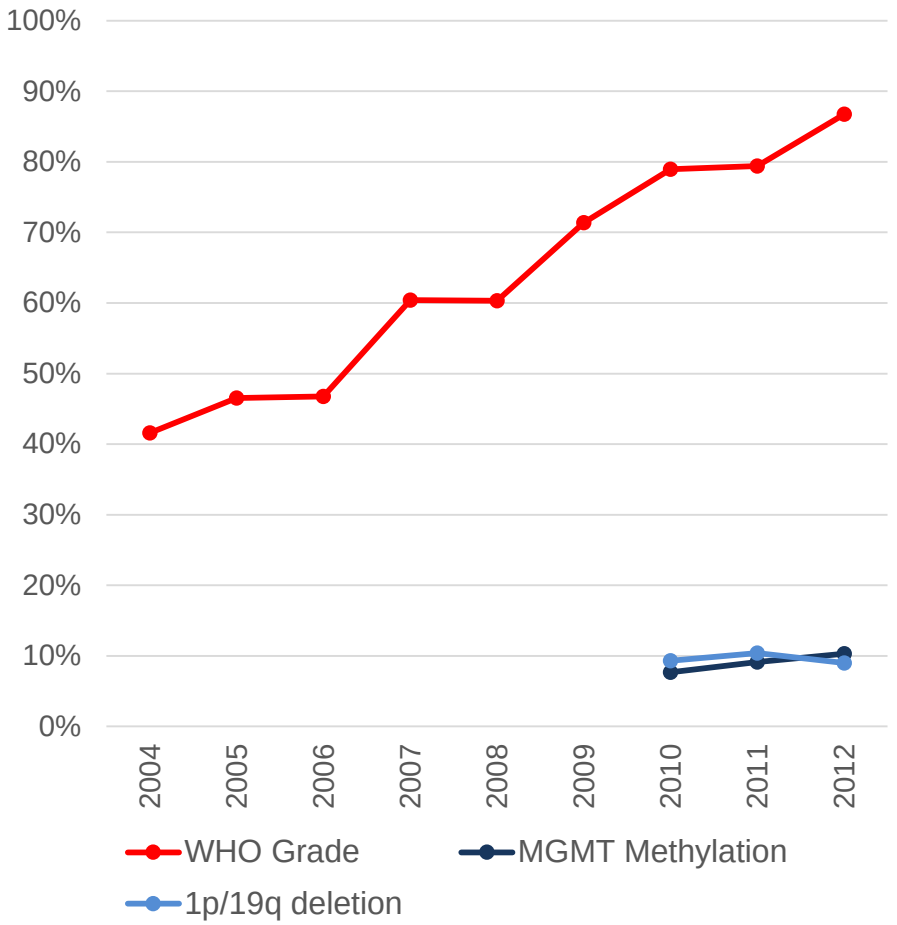
Schema Name	ICD-O-3 Primary Sites	SSF 1	SSF 2	SSF 3	SSF 4	SSF 5	SSF 6	SSF 7	SSF 8
Brain	C70.0, C71.0-C71.9	World Health Organization (WHO) Grade Classification	Ki-67/MIB-1 Labeling Index (LI): Brain	Functional Neurologic Status - Karnofsky Performance Scale (KPS)	Methylation of O6-Methylguanine-Methyltransferase (MGMT)	Chromosome 1p: Loss of Heterozygosity (LOH)	Chromosome 19q: Loss of Heterozygosity (LOH)	Surgical Resection	Unifocal vs Multifocal Tumor
Other CNS	C70.1, C70.9; C72.0-C72.5, C72.8-C72.9	World Health Organization (WHO) Grade Classification	Ki-67/MIB-1 Labeling Index (LI): Brain	Functional Neurologic Status - Karnofsky Performance Scale (KPS)	Methylation of O6-Methylguanine-Methyltransferase (MGMT)	Chromosome 1p: Loss of Heterozygosity (LOH)	Chromosome 19q: Loss of Heterozygosity (LOH)	Surgical Resection	Unifocal vs Multifocal Tumor
Intracranial Gland	C75.1-C75.3	World Health Organization (WHO) Grade Classification	Ki-67/MIB-1 Labeling Index (LI): Brain						

Methods

- Data were obtained via a SEER custom data request for four required factors
  - World Health Organization (WHO) grade
  - SSF
  - MGMT Methylation
  - 1p/19q loss of heterozygosity (LOH)

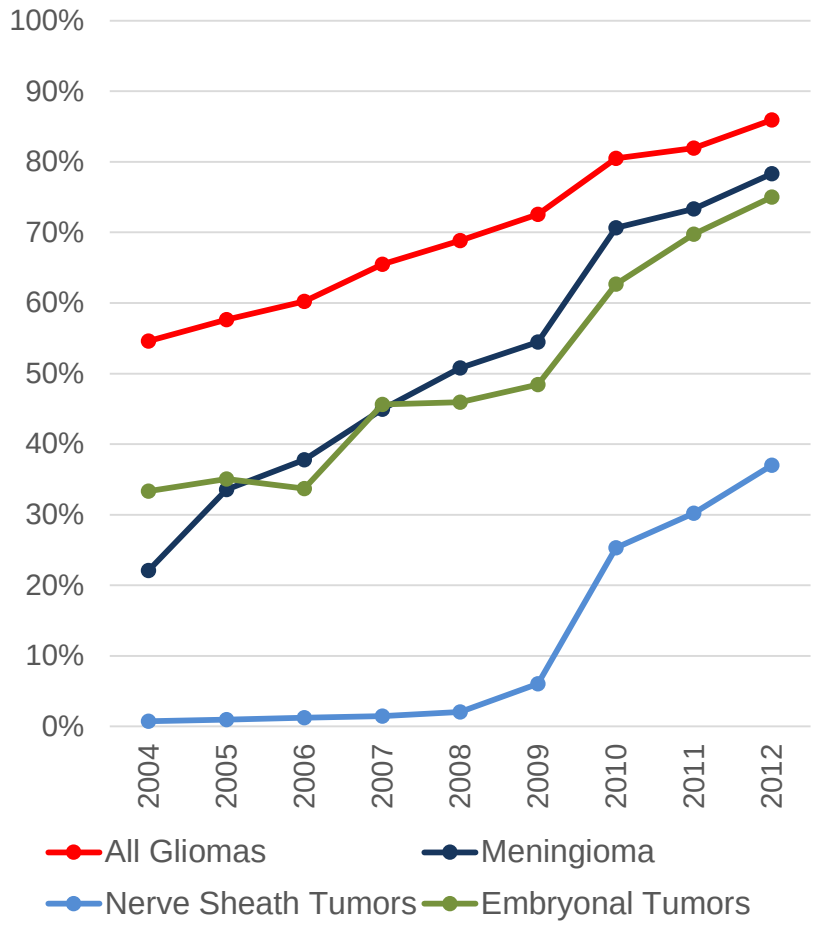
Overall Factor Completeness

- Overall percent complete:
  - WHO Grade: 46.5%
  - MGMT Methylation: 9.0%
  - 1p deletion: 9.5%
  - 19q deletion: 9.6%
- Completeness of all factors varied over time



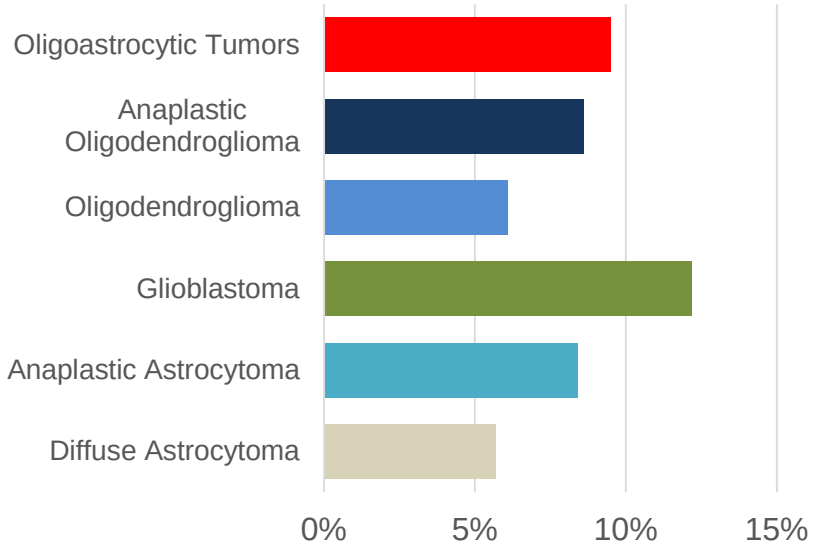
WHO Grade by Histology over Time

- WHO grade has been collected longest (2008-2012) and has shown significant increases over period of collection
- Completeness of WHO grade varied significantly by histology over time
  - Highest in gliomas



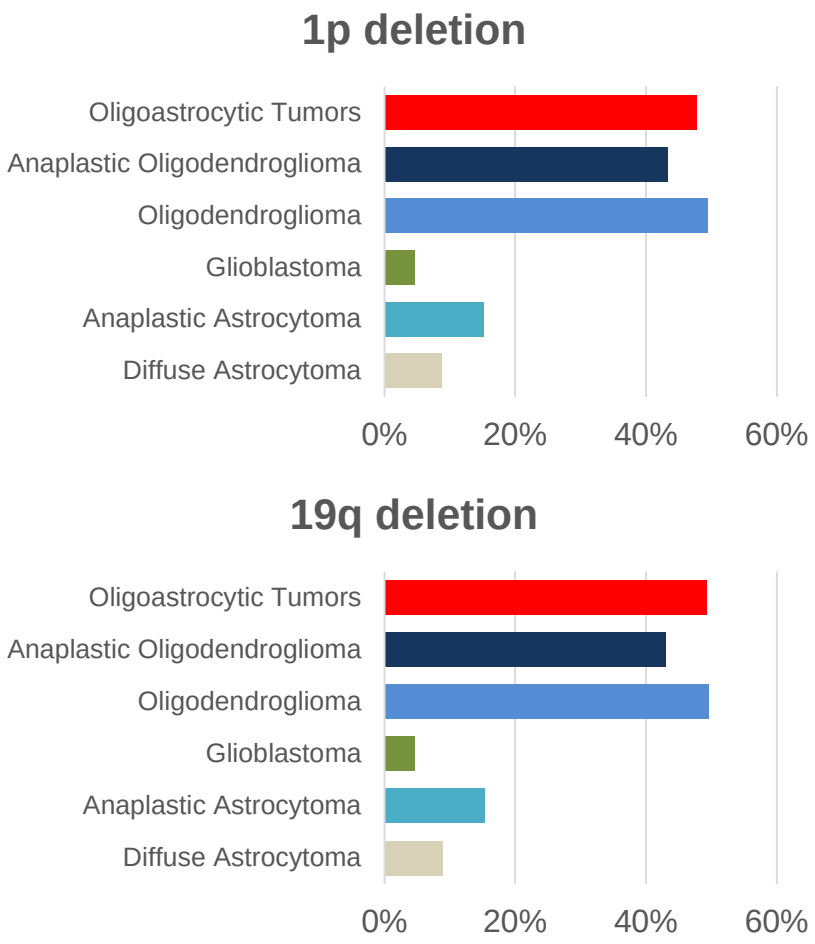
MGMT Methylation by Histology

- Completeness of MGMT methylation information varied significantly by histology
- Completeness was highest in histologies where factor is most clinically relevant
  - Glioblastoma



1p/19q Codeletion by Histology

- Completeness of 1p/19 codeletion status varied significantly by histology
- Completeness was highest in histologies where factor is most clinically relevant
  - Oligodendroglioma
  - Oligoastrocytoma



New WHO classification schema

- 2016 revision of WHO central nervous system tumor classification incorporates molecular markers
  - *IDH1/2* mutation
  - 1p/19q codeletion
- Cancer diagnosis is **increasingly molecular**, and it is **critical** that these data are incorporated in cancer registries

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*

Louis et al, 2016

Molecular Markers and Cancer Registration

- Population-based cancer surveillance data are a **critical resource** for measuring the impact of cancer on a population
- Availability of complete and accurate molecular markers by histology is **essential** for measuring clinical impact on a population
  - IDH1/2 mutation
  - 1p/19q codeletion

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