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Editorial

Long Term Survivors of Glioblastoma

Nezih OKTAR[1], Erkin ÖZGİRAY[1], Taner AKALIN[2]
1Ege University, Faculty of Medicine, Dept.(s) of Neurosurgery, Izmir, Turkey 2Ege University, Faculty of Medicine, Dept.(s) of Pathology, Izmir, Turkey

Abstract

There is no generally accepted definition of long-term GBM survivors (LTGBMS). Usually most authors define long-term GBM survivor as a patient who survives at least 3 years after the histological diagnosis of glioblastoma. LTGBMS are uncommon and are reported to occur in 0.5%-16% of cases. In our ENOK (Ege Neuro-Oncology Council) cases we have 12 out of 372 GBM patients who survived more than 3 years (3.2%). The clinical and molecular factors that contribute to long-term survival are still unknown. Authors underline the association of glioblastoma long-term survival with prognostically favorable clinical factors, in particular young age and good initial performance score (KPS) as well as MGMT promotor hypermethylation.

Key-words: Long survival, glioblastoma multiforme

Uzun Yaşam Süreli Glioblastomlar

Özet

Uzun yaşam süreli GBM ile ilgili genel olarak kabul edilmiş bir tanımlama yoktur. Genel olarak bu durum tüm GBM hastalarının yaklaşık %0,1 ila %16'sını oluşturur. Bizim ENOK (Ege Nöro-onkoloji Konseyi) olgularımızda 372 GBM tanılı hastadan sadece 12 hasta 3 yıldan fazla yaşamıştır (%3,2). Uzun yaşam süresine etki eden klinik ve moleküler faktörler hala bilinmemektedir. Ancak yazarlar genellikle uzun yaşam süresi gösteren GBM olgularının genç olması, Karnofsky performans başlangıç skalalarının yüksek olması ve MGMT metilasyonunun bulunmasının özellikle altını çizmektedirler.

Anahtar sözcükler: Uzun yaşam süresi, glioblastoma multiforme

INTRODUCTION

There is no generally accepted definition of long-term GBM survivor. Usually most authors define long-term GBM survivor as a patient who survives at least 3 years after the histological diagnosis of glioblastoma[45]. Some authors have chosen longer or shorter survivals after diagnosis[9,35,42]. In general, this occurs in about 2%-5% of patients with GBM[11,44].

The most obvious question when confronted with a LTGBMS is whether the histologic diagnosis is correct. The histopathologic diagnosis is revised in about half of putative LTGBMS when the long survival becomes apparent[30,41,44,55].

Not suprisingly, the most common entities confused with GBM are other malignant gliomas that also contain vascular and endothelial proliferation and necrosis. Histologic diagnoses that may be confused with a GBM is given in Table 1.

Table 1: Histologic diagnoses that may be confused with a GBM

Non-GBM, malignant brain tumors:
Malignant oligodendroglioma
Malignant oligoastrocytoma
Primitive neuroectodermal tumors (PNET)
Rare histologic subtypes of nonmalignant tumors:
Pilocytic astrocytoma
Dysembryoplastic neuroepithelial tumor (DNET)
Ganglioglioma
Pleomorphic xanthoastrocytoma
Central neurocytoma
Nonneoplastic processes:
Demyelinating disease
Infarction
Progressive multifocal leukoencephalopathy
Gliosis
Pineal cyst
Cerebral contusion

Scott et al.[5], Burger et al.[44]

These diagnostic errors are uncommon but can occur even in experienced hands when small pieces of tissue available from a stereotactic biopsy of a very heterogeneous tumor are examined. Unfortunately; there are as yet no reliable immunohistochemical markers that differentiate GBMs from other gliomas, such as oligodendrogliomas.

LTGBMS are uncommon and are reported to occur in 0.5%-16% of cases (Table 2). In a study of Tait et al. have concluded that overall survival of GBM remained poor and had not improved for more than a decade[(52)]. However, individual patient survival was very heterogenous. Their LTGBMS rate was 1.44% (9/625)[(52)]. The longest survival reported in the literature was 25 years[(4,13)]. In our ENOK (Ege Neuro-oncology Council) cases we have 12 cases out of 372 GBM patients who survived more than 3 years (3.2%) (Table 3). Our three cases are still alive without any treatment (Figure 1). Survival data of all GBM is given in Figure 2 as an Kaplan-Meier chart.

Table 2: Reported LTGBMS cases

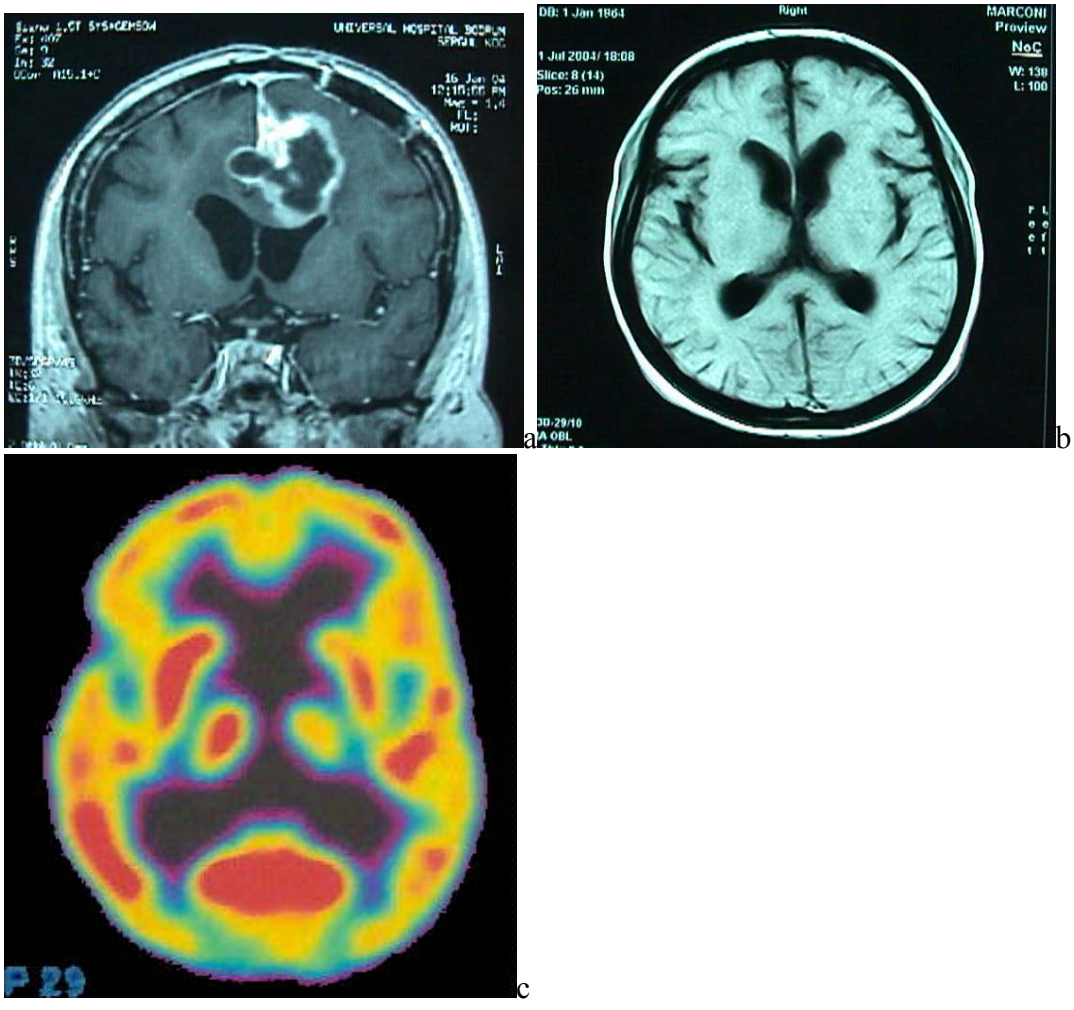
Ref. (year)	*n / (%)*	*Mean survival*	*Range (years)*	*Definition (yrs)*
Netsky et al., (1950)[31]	5/?	14	?	>5
Roth and Elvidge, (1960)[37]	3/?	12	10-15	>10
Bouchard & Peirce (1960)[3]	2/?	12.5	11-14	>10
Ley et al., (1962)[26]	3/?	?	?	?
Taveras et al., (1962)[54]	13/425 (**3.1%**)	?	?	?
Elvidge and Barone, (1965)[13]	2/?	21	17-25	>10
Gullotta and Bettag, (1967)[15]	1/?	11	11	>10
Jelsma and Bucy, (1967)[22]	6/?	?	?	?
Stage & Stein (1974)[50]	2/?	12.5	11-14	>10
Takeuchi (1975)[53]	1/?	10	10	>10
Dara et al., (1980)[10]	10/?	?	?	>2*AG3-4
Johnson AC(1981)[23]	1/?	?	?	>10
Bucy et al., (1985)[4]	1/?	25	25	?
Salford et al (1988)[41]	3 / ?	18.5	14-23	>10*AG3-4
Akslen et al., (1989)[1]	2/?	8	7-9	>5*GCGBM
Ishikura et al., (1989)[20]	1/?	?	?	>3*GCGBM
Margetts and Kalyan-Raman, (1989)[27]	3/?	?	?	>3
Imperato et al (1990)[19]	7 / 100 (**7%**)	6.3	2-10	>2
Shibamoto et al., (1990)[46]	1/135 (**0.9%**)	?	?	>5
Rutz et al., (1991)[38]	1/?	15	15	?*Turcot syndrome
Vertosick and Selker (1992)[58]	13 / ?	8.3	?-15	>4
Hiesiger et al., (1993)[16]	10/?	?	?	>3
Chandler et al (1993)[9]	22 / 449 (**5%**)	9.4	5.1-13.6	>5
Phuphanich et al., (1993)[33]	9/?	?	2-7.3	>2
Salcman et al (1994)[40]	33 / 213 (**15.5%**)	?	?	>3*AG4
Wester et al., (1994)[56]	1/?	?	?	>7
Archibald et al., (1994)[2]	7/?	?	?	>3
Morita et al (1996)[30]	6 / 521 (**1.2%**)	?	?-15	>7
Pollak et al., (1997)[34]	2/?	?	?-11	>10
New et al., (1997)[32]	1/?	7	?	?
Davis et al (1998)[11]	86 / 8581 (**1%**)	?	?	>5
Cervoni et al., (1998)[8]	1/?	14.9	?	>5
Klein et al., (1998)[24]	1/?	11	11	>10
Scott et al (1998)[44]	5 / 279 (**1.8%**)	7.2	3.2-15.8	>3
Salvati et al (1998)[42]	11 / ?	8.1	?-12	>5
Puzzilli et al (1998)[35]	1/?	11	11	>10
Scott et al (1999)[44]	15 / 689 (**2.2%**)	3.2-15.8	>11	>3
Yoshida et al., (2000)[60]	2/?	14.5	14-15	>10
Sabel et al (2001)[39]	1/?	17	17	>10*GCGBM
Burton (2002)[7]	41 / ?	4.9	?	>3
Burton (2002)[6]	39 / ?	4.9	3.1-15	>3
Valery et al., (2002)[57]	1/?	?	?	>3
Floeth et al., (2003)[14]	1/?	?	?	>7
Ho et al., (2003)[17]	34/249 (**13.7%**)	?	?	>2
McLendon and Halperin (2003)[28]	17/766 (**2.2%**)	?	?	>5
Schmidinger et al., (2003)[43]	5/13	?	?	>3>1
Jagannathan et al., (2004)[21]	4/?	?	?	>3
Rainov and Heidecke (2004)[36]	1/?	?	?	>3
Shinojima et al (2004)[47]	6/113 (**5.3%**)	6.9	5.2-8.3	>5
Deb et al. (2005)[12]	6/1296 (**0.5%**)	9	5-15	>5
Yamanaka et al. (2006)[59]	1/?	?	?	>3
Steinbach et al. (2006)[51]	10/?	?	?	>5
Tait et al.(2007)[52]	9/625 (**1.4%**)	?	2.7-4.9	>2.7
Midi A et al. (2008)[29]	7/650 (**1.1%**)	6	3.1-8.3	>3GCGBM 4 cases
Krex D et al (2007)[25]	55/?	4.6	3.0-15.3	>3
Sonoda et al. (2009)[48]	18/123 (**14.6%**)	4	3.3-7.8	>3
Sperduto et al. (2009)[49]	1/?	20	20	?
Hottinger & Yoon (2009)[18]	39/352 (**11%**)	9.15	3-18	>3
Present report (2009)	12 / 372 (**3.2%**)	4.5	3-7	>3

**GCGBM=Giant Cell GBM, AG3 AG4=Malignant astrocytoma*

Table 3: Data on Ege Adult Neuro-Oncology Council (=ENOK) LTGBMS cases

All GBM cases	372
All GBM cases mean survival	53.5 weeks (1.03yrs)
LTGBMS Definition	Who survives >3 yrs
LTGBMS cases only and % (in all GBMs)	12 cases (3.2%)
Mean age on diagnosis of LTGBMS cases	40.9 Range:20-67
GCGBM* case(s) among LTGBMS	1 case
Mean survival of LTGBMS cases	4.5+ yrs (range 3-7+yrs; three cases still alive)
Gender in LTBGMS cases	5F/7M
Surgical excision (total/partial/biopsy)	4/8/0
Radiotherapy & Chemotherapy	All cases received

**GCGBM=Giant Cell GBM*



a b c

Figure 1 a *Bi-frontal typical GBM on MRI, b after treatment 4 years later, and c a recent PET-CT brain scan of same LTGBMS case, who is still alive without any treatment.*

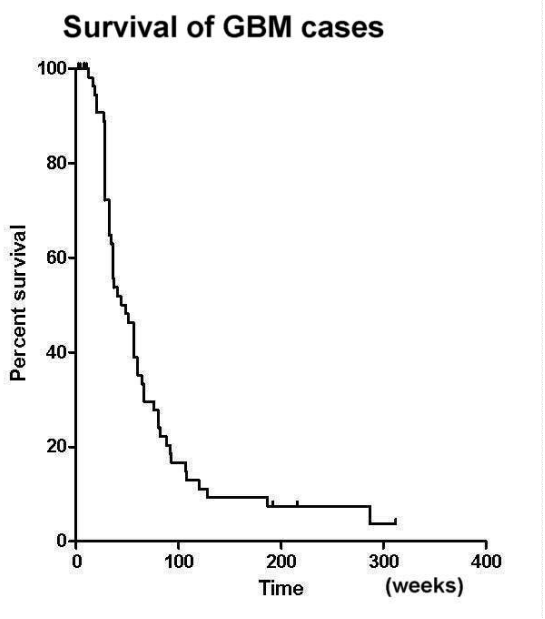


Figure 2. *Survival data of GBM cases. ENOK (=Ege Adult Neuro-Oncology Council) Cases: n=372; mean survival=53.5(wks); LTGBMS survived >3 yrs (>156 wks)= 12 cases; >5 yrs (>260 wks)=9 cases; >6 yrs (>312 wks)=3 cases still alive.*

The clinical and molecular factors that contribute to long-term survival are still unknown. Authors underline the association of glioblastoma long-term survival with prognostically favorable clinical factors, in particular young age and good initial Karnofsky performance score (KPS) as well as MGMT promotor hypermethylation[47].

Correspondence to:
Nezih Oktar
E-mail: editor@jns.dergisi.org

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