



A PROSPECTIVE OBSERVATIONAL STUDY TO ASSESS WAITING TIMES TO FIRST TREATMENT IN PATIENTS DIAGNOSED WITH BRAIN TUMOR

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SUMMARY – The aim was to investigate and determine waiting intervals from diagnosis to first treatment in brain tumor patients. A prospective observational study was performed at the Department of Neurology, Split University Hospital Center, Split, Croatia, from February 21, 2016 until April 10, 2017. The inclusion criterion was the diagnosis of brain tumor confirmed by standard neuroimaging methods. The diagnosis-to-treatment interval (DTI) was defined as the time interval between the date of confirmed radiological diagnosis and the initiation of definitive treatment. Out of 73 patients diagnosed with brain tumor, 3 of them died, 16 were discharged for symptomatic treatment, and the rest were cured by surgical and/or oncologic procedures. The median DTI for any kind of treatment was 15.5 days. The median DTI for radio-guided and resection surgery was 14 days, while the median DTI for the initial oncologic treatment was 42 days. The median DTI of 15.5 days for brain tumors is still, by a wide margin, beyond the preferable one-digit number. When compared to the available data from other countries, however, it seems that the health system in Croatia provides the same, if not a slightly higher, level of efficiency. The median DTI for primary oncologic treatment did, however, indicate a substantial delay.

Key words: *Brain tumor; Brain neoplasms; Waiting time; Surgical therapy; Oncologic therapy*

Introduction

The devastating news of a brain tumor diagnosis marks a dramatic turning point in a patient's life. A quick and reasonable treatment decision is required to save or prolong life in response to the brain tumor inherent progressive nature. Some health systems have set standards for the diagnosis-to-treatment interval (DTI). The UK National Health System, for example, proclaims an operational standard of one-month wait

from diagnosis to first treatment for all cancers¹. To the best of our knowledge, such a standard has not yet been established in Croatia, although there have been some partial programs, under the government auspices, for early detection/prevention of colon, breast, and cervix cancers².

In public and political national life, this issue has occasionally become a matter of lively discussion. The best example was a debate announcing the national parliament elections in 2015, the same year in which the health administration introduced the so-called '72 Hour Program' for patients with malignant tumors, who had to be treated within 72 hours from the time of diagnosis³. A total of 2300 cancer patients were treated according to this standard that year, from

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Received February 28, 2019, accepted February 25, 2020

April until December, in the five largest Croatian public hospitals⁴. At the beginning of 2016, the newly elected health administration abolished the program, claiming that it had been designed to meet the goals of a political campaign, and that every patient with malignant disease should be the health system highest priority and their care should not require any additional legislative measures^{4,5}. The aim of this research was to obtain reliable data that would indicate how close or far the DTI in Croatia was from the implemented ideal standard of 72 hours.

Patients and Methods

This prospective observational study was conducted at the Department of Neurology, Split University Hospital Center (UHC) from February 21, 2016, until April 10, 2017. Inclusion criterion was the diagnosis of brain tumor confirmed by standard neuroimaging methods (computed tomography [CT] or magnetic resonance imaging [MRI]). In most cases, it was sufficient to classify tumors on an assumed histologic basis. A few patients were first referred to perform stereotactic biopsy, so the histopathologic diagnosis was determined before any specific treatment commenced. Initial radiological findings and detailed diagnostic follow-up, including consultations with other specialists, were required to determine and finally recommend the most effective therapeutic options for each patient. If the initial treatment required neurosurgery procedures, patients were referred to the Department of Neurosurgery. The therapy of choice for a few patients was gamma-knife radiosurgery, which was performed at the Zagreb University Hospital Center. After surgery, some patients continued with oncologic treatment. If oncologic treatment was chosen as the first-line therapeutic option, it consisted of radiotherapy, chemotherapy or concomitant chemoradiotherapy, in which case the patients were transferred to the Department of Oncology, Split UHC, or treated there as outpatients. Some patients were found not to be candidates for surgical resection or oncologic treatment, so they were discharged and symptomatic treatment was initiated. The clinical characteristics of patients and recommended therapies are shown in Tables 1, 2 and 3. DTI was defined as the time between the date of radiological diagnosis and date of the first treatment.

Results

A total of 73 patients diagnosed with brain tumor were involved in the research that was conducted at the Department of Neurology, Split UHC from February 21, 2016 until April 10, 2017. There were 38 (52.1%) female and 35 male (47.9%) patients. The median age at tumor presentation was 65 years.

Primary brain tumor was diagnosed in 50 (68.5%) patients, whereas 23 (31.5%) patients had metastatic tumors; the most common type of primary brain tumor was meningioma, and the second-ranking tumor was glioblastoma multiforme (Table 1). Out of 73 patients, three patients died during hospitalization and 16 were discharged for symptomatic treatment. Different types of treatment were recommended to the remaining patients; the most common treatment was surgery,

Table 1. Brain tumors diagnosed at Department of Neurology, Split University Hospital Center from February 21, 2016 to April 10, 2017

	n (%)
Meningioma	20 (27.4)
Glioblastoma multiforme	17 (23.3)
Glioma	5 (6.8)
Anaplastic astrocytoma	2 (2.7)
Hypophyseal macroadenoma	2 (2.7)
Lymphoma	1 (1.4)
Oligodendroglioma	1 (1.4)
Third ventricle colloid cyst	1 (1.4)
Multiple cavernomas	1 (1.4)
Metastases	23 (31.5)

Table 2. Recommended first-line treatment in patients diagnosed with brain tumors at Department of Neurology, Split University Hospital Center from February 21, 2016 to April 10, 2017

	n (%)
Surgery	35 (47.9)
Symptomatic therapy	16 (21.9)
Palliative radiotherapy	6 (8.2)
Radiosurgery (gamma knife)	5 (6.8)
Chemotherapy	5 (6.8)
Concomitant chemoradiotherapy	3 (4.2)
Died before any treatment	3 (4.2)

followed by different types of oncologic therapy (Table 2). The median DTI for any kind of treatment was 15.5 days (interquartile range [IQR] 10-28 days). The waiting time from diagnosis to first treatment was lowest in patients undergoing radiosurgery, followed by classic brain surgery, while concomitant chemoradiotherapy had the highest waiting time (median DTIs shown in Table 3). In general, primary oncologic therapies caused significant lengthening of DTI compared to surgery (Table 3). Definitive histopathologic diagnosis of brain tumor was required in a few patients before initiation of treatment, and therefore they underwent stereotactic biopsy. When completed, the histopathologic reports showed that out of these 12 patients, six were diagnosed with glioblastoma multiforme, two with brain metastases, and one patient each was diagnosed with meningioma, anaplastic astrocytoma, glioma, and lymphoma. In patients having undergone stereotactic diagnostic biopsy, median DTI was 24 days. Interestingly, two patients underwent brain surgery the day after they had been radiologically diagnosed with brain tumor.

Table 3. Waiting DTI for patients diagnosed with brain tumors at Department of Neurology, Split University Hospital Center from February 21, 2016 to April 10, 2017

	Median DTI days (IQR)
Gamma knife	8 (6-12)
Brain surgery	14 (9-18)
Palliative radiotherapy	23 (14-37)
Chemotherapy	42 (34-107)
Concomitant chemoradiotherapy	52 (42-79)
All types of oncologic treatment	42 (27-52)
All types of surgery	14 (8-17)
All types of treatment	15.5 (10-28)

DTI = diagnosis-to-treatment interval; IQR = interquartile range

Discussion

To the best of our knowledge, this is the first study assessing DTI for brain tumors in Croatia. Surprisingly, similar data on brain tumors are quite scarce in the literature, and it is more common to find data on DTI for cancers of the lungs, breast, colon, etc.⁶⁻⁹. The main finding of this study was that the median wait from

diagnosis to any kind of first treatment for brain tumor patients in Split, Croatia, was 15.5 days. This at first appears rather dispiriting, as it is 5 times longer than the standard of 72 hours implemented in 2015³.

This perspective changes, however, if this figure is observed in a broader context and compared to the available DTI data from other countries for brain or other tumors. The median DTI of 8 days (IQR 6-12 days) for radiosurgery and of 14 days (IQR 9-18 days) for surgical resection in Croatia should be considered pretty good if compared to the 18-21 day wait from radiological diagnosis to surgery in Sweden (analysis period 1999-2012)¹⁰. The second important finding of this study was that oncologic procedures, if recommended as the first-line therapeutic option, required significant prolongation of the DTI, i.e. median of 42 days (IQR 27-52 days) *vs.* median of 14 days (IQR 8-17 days) for combined radiotherapy and resection surgery. There are few papers dealing with primary radiotherapy DTI for brain tumors. Robinson *et al.*¹¹ report on 35 days as the median wait for primary radiotherapy for brain tumor, whereas our six patients waited for 23 days (IQR 14-37 days) for palliative radiotherapy.

Considering that planning oncologic therapy is sometimes very complex and requires additional time, frequent mismatches between the available oncologic resources and patient need, as well as the fact that patients, even after brain surgery, may wait for subsequent oncologic treatment for more than 4-8 weeks¹²⁻¹⁴, our median 6-week prolongation from diagnosis to primary oncologic treatment does not appear unexpected or unacceptably high. When compared to the waiting DTI for tumors in other localizations, such as the head and neck (which tend to proliferate rapidly), the data obtained seem rather promising as well. In France, for example, the median DTI for surgery of the head and neck cancers was 27 days and for radiotherapy treatment alone 54.5 days¹⁵, while in Portugal, the median wait for surgery of the head and neck cancers was 27 days and for radiotherapy treatment 62 days¹⁶. Finally, the median 8.5-day prolongation of the waiting DTI due to diagnostic stereotactic biopsy in our study seems plausible, given the time needed to make the histopathologic report.

From the psychosocial aspect of the individual patient diagnosed with a brain tumor, it is of enormous importance to reduce the waiting time from diagnosis to treatment. From the biological aspect, it also seems

quite reasonable that, with delay in treatment initiation, tumors tend to be more aggressive, harder to control, or almost incurable. Despite the relatively encouraging data on waiting DTI for brain tumor patients in Split, there is still room for further improvement, regardless of the primary therapy regimen chosen.

Neuroradiological procedures should be available and performed without hesitation. During this study, some scheduled daily appointments at the MRI unit were postponed because of public holidays, machine breakdowns, or regular repairs. It is important to point out that there is only one MRI unit *per* 450 000 population in the Split UHC, which is part of the National Health Insurance System. We also suggest that inpatient consultations and all diagnostic procedures required for brain tumor patients should be performed urgently.

Finally, because the data unequivocally support constraints relating to staff and equipment in national oncologic centers, this problem should be addressed promptly in the near future.

Study limitations

We measured DTI from radiological diagnosis to initial intervention. In general, waiting times include additional days from the patient's referral until hospitalization, but in everyday practice at Split UHC, it is rather common that a patient is admitted to hospital immediately after the appearance of the first presenting symptoms or signs of brain tumor.

The main limitation of this study was whether the diagnosis of brain tumor during the observed period was made in the Department of Neurology, Split UHC; some patients with brain tumor had been diagnosed in other clinical institutions or on emergency neurology wards, which referred these patients to other departments for further treatment.

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Sažetak

PROSPEKTIVNO OPSERVACIJSKO ISTRAŽIVANJE ZA PROCJENU VREMENA ČEKANJA NA POČETAK LIJEČENJA U BOLESNIKA S DIJAGNOSTICIRANIM TUMOROM SREDIŠNJEGA ŽIVČANOG SUSTAVA

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Cilj istraživanja bio je utvrditi vrijeme čekanja na kirurško i onkološko liječenje u bolesnika kojima je postavljena dijagnoza tumora središnjega živčanog sustava (SŽS). Prospektivno opservacijsko istraživanje je provedeno u Klinici za neurologiju KBC Split od 21. veljače 2016. do 10. travnja 2017. godine. Uključni kriterij je bio dijagnoza tumora SŽS postavljena standardnim neuroslikovnim metodama. Dijagnostičko-terapijski interval (DTI) je definiran kao vrijeme od postavljanja radiološke dijagnoze do početka liječenja. Od ukupno 73 bolesnika s dijagnozom tumora SŽS umrla su 3 bolesnika, 16 ih je otpušteno na simptomatsko liječenje, a kod ostalih je započeto liječenje kirurškim i/ili onkološkim postupcima. Sveukupni medijan DTI iznosio je 15,5 dana, medijan DTI za radiokirurške metode i ablativnu neurokirurgiju 14 dana, dok je medijan DTI za primarne onkološke postupke bio 42 dana. Sveukupni medijan DTI od 15,5 dana bio je značajno dulji od priželjkivanog jednoznamenkastog broja. Međutim, kad se naši podatci usporede s onima iz drugih zemalja čini se da hrvatski nacionalni zdravstveni sustav pokazuje istu, ako ne i višu razinu učinkovitosti. Naši rezultati upućuju na to da je u bolesnika s tumorima SŽS vrijeme čekanja na primarne onkološke terapijske postupke značajno dulje u usporedbi s kirurškim metodama liječenja.

Ključne riječi: Tumor središnjega živčanog sustava; Novotvorine središnjega živčanog sustava; Vrijeme čekanja; Kirurško liječenje; Onkološko liječenje