Journal of Clinical Neuroscience 22 (2015) 474–478

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

In-hospital outcomes of thrombolysis for acute ischemic stroke in patients with primary brain tumors

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ARTICLE INFO

Article history:
Received 4 July 2014
Accepted 14 September 2014

Keywords:
Acute stroke
Nationwide inpatient sample
Primary brain tumors
Thrombolysis

ABSTRACT

Data on thrombolysis outcomes in patients with primary brain tumors are limited. Our aim was to study stroke outcomes following thrombolysis in these patients in a population-based study. Patients with acute ischemic stroke who received thrombolysis were identified from the 2002–2011 USA Nationwide Inpatient Sample. We compared demographics, comorbidities, and outcomes between primary brain tumor-associated strokes (BTS) and non-brain tumor associated strokes (NBTS). The main outcomes were inpatient mortality, home discharge and intracranial hemorrhage (ICH) rate. Of the 124,083 thrombolysis-treated stroke patients, 416 (0.34%) had brain tumors. In adjusted analysis, inpatient mortality (odds ratio [OR]: 0.98; 95% confidence interval [CI]: 0.77–1.26, $p = 0.918$), rate of home discharge (OR: 1.15; 95% CI: 0.87–1.53, $p = 0.40$) and rate of ICH (OR: 0.94; 95% CI: 0.62–1.44, $p = 0.801$) were similar between BTS and NBTS. Analysis of brain tumor subtypes showed that compared to NBTS, malignant BTS were independently associated with higher in-hospital mortality (OR: 2.51; 95% CI: 1.66–3.79, $p < 0.001$), lower home discharge (OR: 0.36, 95% CI: 0.18–0.72, $p = 0.004$), and increased risk of ICH (OR: 2.33, 95% CI: 1.49–3.65, $p < 0.001$). Additionally, among the BTS, intraparenchymal location of tumor was associated with higher mortality (OR: 2.51; 95% CI: 1.20–5.23, $p = 0.014$) and lower home discharge (OR: 0.26; 95% CI: 0.13–0.53, $p < 0.001$). Thrombolytic therapy for acute stroke appears to be safe in patients with primary brain tumors, with similar rates of ICH. Malignant BTS have worse outcomes, while benign BTS have outcomes comparable to NBTS. Careful consideration of tumor pathology may aid selection of patients with poor thrombolysis outcomes.

1. Introduction

The incidence of acute ischemic stroke (AIS) in patients with primary brain tumors is about 1.3% [1]. Among the brain tumor-associated strokes (BTS), glioblastoma, meningioma, anaplastic glioma, low-grade gliomas, and primary central nervous system lymphomas account for the vast majority of tumor pathologies [1]. Thrombolytic treatment is underutilized for AIS [2], partly as a result of stringent exclusion criteria used in earlier stroke trials [3–5]. Off-label thrombolysis use in patients with some of these exclusion criteria has been shown to have acceptable outcomes [6]. Patients with systemic malignancies and brain tumors are generally perceived to have a higher risk of intracerebral hemorrhage (ICH) and worse outcomes, and are therefore usually excluded from intravenous thrombolysis. Recent retrospective observational studies have suggested that thrombolysis outcomes may be favorable in patients with systemic malignancies, with no difference in ICH rates among liquid, solid or metastatic tumors [7,8]. On the other hand, literature on outcome of stroke thrombolysis in patients with brain tumors is limited to case reports with possible publication bias for favorable outcomes [9]. Therefore, we aimed to compare the outcomes of thrombolysis in patients with BTS with non-brain tumor-associated strokes (NBTS) in a population-based cross-sectional study using a large national health database.

2. Methods

2.1. Data source

The discharge data of patients were obtained from the Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization

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http://dx.doi.org/10.1016/j.jocn.2014.09.016
0967-5868/

Project (HCUP) from years 2002–2011 [10]. NIS, the largest inpatient health dataset in the USA, is an all-payer dataset that provides cross-sectional data on approximately 8 million inpatient hospitalizations yearly from 1000 US hospitals, and represents a 20% stratified sample of all non-federal hospitals. Discharge weighting is provided to extrapolate population estimates from the sampled data. Detailed information regarding the design and contents of NIS is available on the HCUP website [10].

2.2. Patient selection

Patients admitted with AIS were selected using the *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 433.x1, 434.x1 and 436. Patients receiving intravenous thrombolysis were identified using the procedure code 99.10. In addition, patients who received thrombolysis using the "drip and ship" paradigm were identified using the code V45.88. Benign and malignant brain tumors were identified using ICD-9 codes 191.x, 192.0, 192.1, 192.8, 192.9, 225.0, 225.1, 225.2, 225.8, and 225.9. Extraparenchymal tumors were identified using the ICD-9 codes 192.0, 192.1, 225.1 and 225.2. The exclusion criteria were age $\leqslant$17 years, patients with missing data on discharge disposition, and metastatic brain tumors. To avoid uncertainty of indication for thrombolysis, we excluded patients with acute myocardial infarction or pulmonary embolism and those on hemodialysis (with possibly clotted access) from the analyses.

We used the Elixhauser point scale index, a validated weighted score of 21 different comorbidities with van Walraven modification for comorbidity adjustment [11–14]. These scores were grouped into the following quartiles: <5, 5–7, 8–14, and $\geqslant$15. Premorbid and current anticoagulant use was quantified using the ICD-9 code V58.61. Initiation of palliative care was identified using the code V66.7. Due to significant missing data (18%), race was recoded to include a separate category for missing data. The primary outcomes of the study were inpatient mortality, and home discharge/self-care was used as a surrogate for good functional outcome. The safety outcome of interest was ICH defined by the following ICD-9 codes: 431 (ICH); 432.0 (non-traumatic extradural hemorrhage); 432.9 (unspecified intracranial hemorrhage); 430 (subarachnoid hemorrhage); and 997.02 (iatrogenic cerebrovascular infarction or hemorrhage).

2.3. Statistical analysis

Wilcoxon–Mann–Whitney and Pearson chi-squared tests were used for comparison of continuous and categorical variables respectively. Logistic regression models were constructed to assess stroke outcomes following thrombolysis, after adjusting for age, sex, race, Elixhauser comorbidity quartiles, coronary artery disease, seizure, status epilepticus, hospital teaching status, insurance status, and anticoagulant use. Analyses were two-tailed, and statistical significance was defined as $p < 0.05$. Analyses were performed using the Statistical Package for the Social Sciences version 21.0 (SPSS, Chicago, IL, USA). Standard weights provided by HCUP were applied to obtain national estimates.

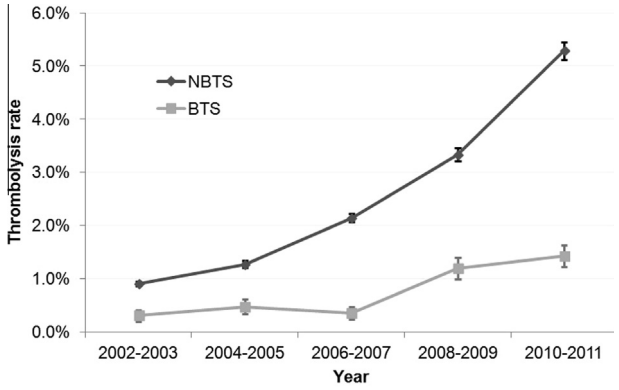

Fig. 2. Trends in thrombolysis utilization from 2002 to 2011 in the USA. Error bars indicate standard error of population estimate. BTS = brain tumor associated strokes, NBTS = non-brain tumor associated strokes.

3. Results

3.1. Demographics

We identified 124,083 patients with AIS who received thrombolysis, including 416 (0.34%) patients with BTS (297 with benign BTS, and 119 with malignant BTS). The thrombolysis utilization rate was 2.6% for NBTS and 0.8% for BTS. Only 1.3% of patients with benign BTS and 0.4% of patients with malignant BTS received thrombolysis (Fig. 1). The overall trend in thrombolysis rates for BTS increased from 0.3% in 2002 to 1.4% in 2011 as shown in Figure 2. The BTS cohort had more patients over 65 years of age ($p = 0.005$), more females (66.9% *versus* 49.0%, $p < 0.001$), and higher proportion of Caucasian patients (65% *versus* 59.9%, $p < 0.006$) as shown in Table 1. There were no differences in the hospital characteristics between the two groups.

3.2. Comorbidities and in-hospital complications

The BTS cohort had more patients with Elixhauser scores $\geqslant$15 (28% *versus* 19.6%, $p < 0.001$) as shown in Table 2. The rates of diabetes, hypertension, hyperlipidemia, valvular heart disease,

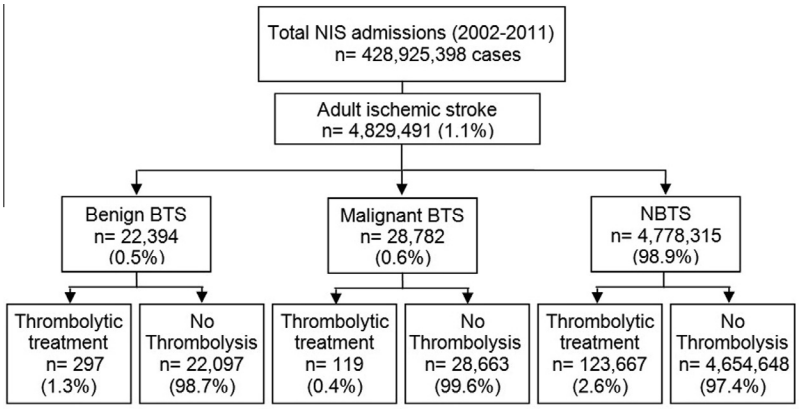

Fig. 1. Case selection of acute ischemic stroke patients treated with thrombolysis. BTS = brain tumor strokes, NBTS = non-brain tumor strokes, NIS = Nationwide Inpatient Sample.