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Original article

Hypofractionated radiation therapy (HFRT) versus conventional fractionated radiation therapy (CRT) for newly diagnosed glioblastoma patients. A propensity score matched analysis

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ABSTRACT

Background: The current treatment for newly diagnosed glioblastoma consists of surgery followed by conventional radiotherapy (CRT) with concomitant and adjuvant chemotherapy. Hypofractionated radiation therapy (HFRT) has been investigated and it resulted feasible and safe. The aim of this study was to evaluate whether HFRT can be comparable to CRT.

Materials and methods: The analysis included newly diagnosed glioblastoma patients treated with CRT 60 Gy/30 fractions or HFRT 60 Gy/15 fractions. A propensity score matching analysis (PSM) was performed using a logistic regression that considered age, KPS, extent of surgery, MGMT and IDH status.

Results: A total of 267 patients were included; before PSM 169 were in CRT-group and 98 in HRFT-group. After 1:1 matching, 82 patients resulted in each group. The median OS time was 17.9 months for the CRT-group and 16.7 months for the HFRT-group; the 1, 2, 3-year OS rates were 75.6%, 32.7%, and 15.5% for the CRT-group, and 75.6%, 33.3%, and 18.9% for the HFRT-group (p value = 0.8). No statistically significant differences were recorded between the two radiation therapy treatments performed.

Conclusions: A short course of radiation therapy would seem comparable to CRT in terms of outcome and less burdensome for these poor prognosis patients.

 Radiotherapy and Oncology xxx (2017) xxx–xxx

The standard of care for newly diagnosed glioblastoma multiforme (GBM) patients consists of surgical resection followed by radiotherapy (RT) with concomitant and adjuvant temozolomide chemotherapy (TMZ-CHT) [1,2]. This approach affords a median overall survival (OS) time and a 2-year OS rate of 14.6 months and 26.5%, respectively. Conventional fractionated radiotherapy (CRT) to a total dose of 60 Gy in 30 daily fractions of 2 Gy each is employed [3]. The use of protracted RT schedules harbors the theoretical drawback of allowing a cell repopulation, which could be of relevance in tumors with a rapid doubling time such as GBM [4]. This effect may be seen in routine clinical practice as well, where a wide rate of patients, up to 10%, discontinues RT for disease progression [1]. The impact of hypofractionated radiation therapy (HFRT) has been investigated as well. The delivery of a higher dose per fraction over a shorter time frame has the advantages to achieve an increase in cells killing and a reduction in accelerated tumor cell repopulation. The initial experiences were carried out in elderly and frail patients with the aim to reduce the overall treatment time [5–8]. Results recorded were equivalent to CRT, although lower total doses were used. More recently, HFRT has been employed in newly diagnosed GBM patients with a curative aim [9–13]. Retrospective and prospective studies showed that this approach shares similar feasibility and safety results as standard RT schemes, without a growing incidence of neurological toxicity. A previous prospective phase II trial carried out in our institution (ClinicalTrials.gov NCT00006353) in newly diagnosed unselected GBM patients showed that HFRT is a feasible and safe approach with a median OS time, 1 and 2 years OS rate of 15.9 months, 72%, and 30%, respectively, affording a considerable decrease in the treatment time (from 6 to 3 weeks), without an increasing neurological deterioration [14]. However, no

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comparative data or randomized trials are available and no evidence has been provided if a short course of RT is comparable to standard ones in terms of survival and neurological impairment. Therefore, we utilized the database of newly diagnosed GBM patients treated in our institution with CRT or HFRT schedule, into a multimodal approach including concomitant and adjuvant TMZ-CHT. To explore whether HFRT can be comparable to CRT we sought to compare outcomes using propensity matching in patients receiving different schedules of RT at different times. This analysis was designed to simulate a possible comparison that could be undertaken in a prospective randomized trial.

Materials and methods

Data collection and population

All patients provided a written informed consent to the treatment and the use of their data for scientific purposes. The study population included newly diagnosed GBM patients, 18 years of age or older, with a Karnofsky performance scale (KPS) $\geq$60, tumor molecular profile available, a normal liver, kidney and bone marrow functions. All patients received different entities of surgical resection: gross total resection (GTR) defined as tumor removal between 90% and 100% of contrast enhancing tumor volume, subtotal resection (STR) between 78% and 89%, partial resection (PR) between 30% and 78%, and biopsy (B) between 0 and 30%. RT was performed within 4–6 weeks after surgery using volumetric modulated arc therapy (VMAT) in both groups. The dose prescribed was 60 Gy with daily fraction of 2 Gy on surgical cavity for 30 consecutive working days or 60 Gy with daily fraction of 4 Gy for 15 consecutive working days. For standard conventional RT group the target delineation was performed according to international guidelines. For HFRT the clinical target volume (CTV) corresponded to the entire surgical cavity plus eventual residual tumor after surgery or, to the abnormality on the T1-weighted post-contrast MPRAGE and 11CMETPET in case of biopsy. Planning target volume (PTV) was generated adding an isotropic margin of 5 mm. All patients received TMZ concurrently with RT. TMZ was administered orally, once daily, at 75 mg/m^2, starting on the first day of RT and continuing for the whole treatment. After a 4-week break adjuvant TMZ was administered at 150–200 mg/m^2 orally, once daily, for 5 consecutive days every 28 days up to 12 cycles, or until disease progression occurred. Corticosteroids were administered at low doses at the start of RT in both groups and progressively reduced during the course of RT in patients neurologically stable. In case of biopsy or gross residual tumor steroids were given at higher doses. Antiepileptic drugs (AEDs) were prescribed only in patients with a history of at least one seizure. The most frequently used AEDs were levetiracetam as first line instance followed by topiramate, lamotrigine or lacosamide. Clinical outcome was evaluated by neurological examination and MRI imaging 1 months after concurrent CHT-RT and every four months thereafter. Tumor progression was defined according to Response Assessment in Neuro-Oncology (RANO) working group [15]. In cases of doubt between disease progression are radionecrosis (RN) perfusion MRI and METPET were performed.

Propensity scoring and matching

Propensity scoring is a balancing technique whereby a numerical value is assigned for the probability of an intervention or treatment. The goal is to approximate the balance in measured covariates. In our investigation, we aimed to standardize the groups based on propensity to receive one RT treatment schedule over another. The following variables were selected: age at time of diagnosis, KPS, kind of surgery, MGMT and IDH status. The overall sample is described using measures of central tendency (mean and median) and variation (standard deviation), and compared by treatment group using two-sample *t* tests and Pearson's Chi square test, as appropriate. To minimize selection bias inherent in treatment group allocation, propensity score modeling was used to match the two groups using a logistic regression approach [16]. To evaluate the robustness of the choice of matching covariates, matches were compared in terms of bias reduction and standardized differences across each variable before and after matching. An absolute standard bias measure <0.20 is considered small, and sufficient overlap is required for the propensity scores [17]. The bias was reduced to <0.20 for all variables used in both of the matching analyses as shown in Fig. 1. Each patient was matched one-to-one based on propensity score, using the nearest neighbor matching algorithm.

Statistical analysis

Standard descriptive statistics was used to describe the data general behavior. Survival and recurrence time observations were evaluated according to the method of Kaplan and Meier, starting from the date of diagnosis. Variables considered were: gender, age, KPS, IDH and MGMT status, and EOR. Age of patients was divided into two groups, respectively, $\leq$65 and >65 years, and KPS $\leq$80 or 90–100. Statistical analysis was performed by the use of the SPSS v.22 (IBM, Armonk, USA) software.

Results

Patients

From 2011 to 2015 a total of 267 patients were treated, and included in this analysis. Before PSM, there were 169 patients in the former group and 98 in the latter. Significant differences were recorded in relation to KPS and EOR. In comparison with HFRT-group, more patients in CRT-group had KPS 60–80 and underwent PR or STR as shown in Table 1. After 1:1 matching there were 82 patients in each group, respectively. Distribution of covariates was adequately balanced in the matched data set, as shown in Table 2.

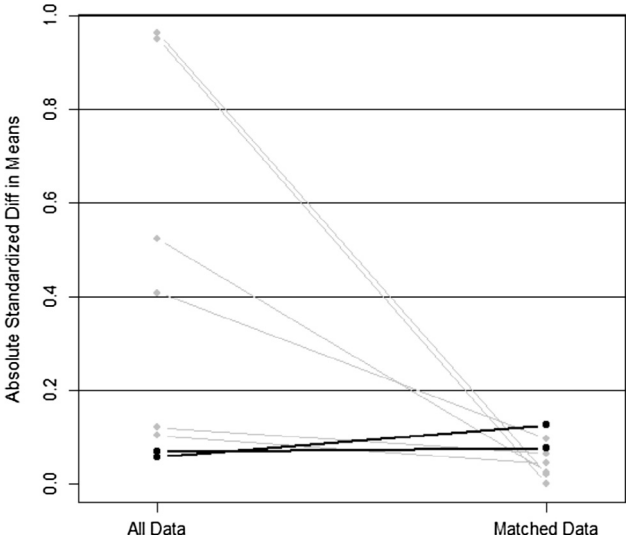

Fig. 1. Absolute standardized difference in means before and after propensity score matching. The plot illustrates the effect of weights on the magnitude of differences between groups on each pretreatment covariate. Substantial reductions in effect sizes are observed for most variables (light lines), with only two variables showing a small increase in effect size (dark lines), however under the value 0.2.

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