Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Improved cost-effectiveness of short-course radiotherapy in elderly and/or frail patients with glioblastoma

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ARTICLE INFO

Article history:
Received 13 April 2017
Received in revised form 4 December 2017
Accepted 30 January 2018
Available online xxxx

Keywords:
Cost-effectiveness
Radiotherapy
Short-course
Elderly
Frail
Glioblastoma

ABSTRACT

Background and purpose: Short-course radiotherapy (25 Gy in five fractions) was recently shown in a randomized phase III trial to be non-inferior to 40 Gy in 15 fractions in elderly and/or frail patients with glioblastoma multiforme. This study compared the cost-effectiveness of the two regimens.
Material and methods: The direct unit costs of imaging, radiotherapy (RT), and dexamethasone were collected from the five primary contributing countries to the trial, constituting the data of 88% of all patients. Effectiveness was measured by the restricted mean overall survival (RMOS) and progression free survival (RMPFS). The incremental cost-effectiveness ratio (ICER) was calculated. Indirect costs were also estimated for comparison.
Results: The median OSs for the short-course and commonly used RTs were 8.2 (95% confidence interval [CI] 6.1–10.3) and 7.7 (95% CI 5.5–9.9) months, respectively (log rank $p = 0.340$). Median PFSs were also not different ($p = 0.686$). The differences in the RMOS and the ICER, however, were +0.11 life-years and -$3062 United States dollars (USD) per life-year gained, respectively. The differences in the RMPFS and the ICER were +0.02 PFS and -$17,693 USD, respectively.
Conclusion: The ICER of -$3062 per life-year gained and -$17,693 per PFS gained indicates that the short-course RT is less costly compared to the longer RT regimen.

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults. It is predominantly a disease of the elderly, with a median age of diagnosis of 64 years and the highest incidence in those aged 75–84 years [1]. The age-standardized incidence continues to increase and it is expected that two-thirds of GBM patients will be over the age of 65 years by 2030 [2]. Outcomes remain poor, with median survival approximately 12–15 months. In elderly and/or frail patients, survival time is in the order of approximately 6 months [3–5].

The landmark EORTC-NCIC trial established combination radiotherapy (RT) and temozolomide (TMZ) as the standard of care for patients with good performance status under the age of 65 years [6]. The trial was limited to patients under the age of 70 years and with Eastern Cooperative Oncology Group performance status of 0–2. Subgroup analyses showed no survival benefit for patients aged 65–70 [7] or for patients with performance status of 2 (Supplemental material from [6]). The recently published NCIC CE.6 trial showed that combination RT/TMZ also benefits patients ≥ 65 years of age with good performance status (ECOG 0-2), extending median OS from 7.6 months with RT alone to 9.3 months with the addition of TMZ ($p < 0.0001$). The benefit was more pronounced in patients with O6-methylguanine-DNA methyltransferase gene (MGMT) methylated tumors, although a modest improvement was also seen in patients with MGMT non-methylated tumors [8].

Prior to the publication of CE.6, two randomized phase III trials showed promising outcomes with RT or TMZ monotherapy in elderly GBM patients [9,10]. Additionally, a hypofractionated regimen consisting of 40 Gy in 15 fractions was shown to be non-inferior to 60 Gy in 30 fractions in elderly patients [11], and this more convenient regimen was utilized as the RT schedule in CE.6. More recently, 25 Gy in 5 fractions was shown in a

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https://doi.org/10.1016/j.radonc.2018.01.017
0167-8140/

randomized phase III clinical trial to be non-inferior to 40 Gy in 15 fractions in elderly and/or frail patients [12]. There was no difference in overall survival (OS), progression free survival (PFS), or quality of life between arms after a median follow-up time of 6.3 months.

In recent years, there has been an increasing awareness of the escalating costs of oncology care in addition to the traditional endpoints of clinical efficacy and treatment toxicity [13,14]. The impact on patients in terms of the inconvenience and time associated with treatment is another consideration which may be particularly important in malignancies with short overall survival times such as GBM; shorter courses of treatment may maximize the survival to treatment time ratio [15]. This study aimed to compare the cost-efficacy of the two treatment regimes.

Materials and methods

Patients

Patients eligible for the phase III trial included elderly and/or frail patients diagnosed with GBM. Frail patients were defined as ≥50 years old with a Karnofsky performance status (KPS) of 50–70%; elderly and frail patients were defined as ≥65 years old with a KPS of 50–70%; and elderly patients were defined as ≥65 years old with a KPS of 80–100%. Patients were randomly allocated in a 1:1 ratio to either short-course RT (25 Gy in five fractions delivered in 1 week) or commonly used RT (40 Gy in 15 fractions delivered in 3 weeks). Patients were stratified by age (< and ≥65 years), KPS, and extent of surgery (near total/complete/gross total or incomplete/partial resection). Details on trial conduct and clinical outcomes have previously been reported [12].

In total, 98 patients from ten countries were randomized between 2010 and 2013. The economic evaluation was based on data of 88% of all patients accrued ($n = 86$) from the five primary contributing countries to the trial, Brazil – Porto Alegre, Belarus, India, Poland and Georgia. To facilitate comparisons between treatment arms and between centers, data from centers contributing fewer than 5 patients were not included in analysis. The data on the individual cost of CT, MRI of the brain, three-dimensional conformal RT (3DCRT) in 5 fractions, 3DCRT in 15 fractions and dexamethasone 4 mg tablet were collected retrospectively. Baseline characteristics and recurrence and survival data were collected prospectively as previously described [12].

Measurement of effectiveness

Effectiveness was measured by overall survival (OS) and progression free survival (PFS). OS was calculated as the time between randomization and death. PFS was calculated as the time between treatment received and death or disease progression. Progression was defined as clinical or radiological evidence of tumor progression. Patients who were still alive or did not have tumor progression at the date of last follow-up were censored for the time to event analysis. The difference in OS and PFS between the two study arms was calculated using the restricted mean survival method [16], and expressed in life years gained (LYG) and PFS gained. Irwin's restricted mean method is used when censoring prevents the estimation of the mean survival time. Irwin proposed the estimation of mean lifetime may be restricted to a suitable chosen time [17]. For this analysis, the time frame was restricted to 1.97 years for OS and 1.40 years for PFS, time points chosen as they approximated the last observed event time for OS and PFS, respectively.

Effectiveness was also assessed as quality-adjusted life-years gained (QALYs). Quality of life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the brain module QLQ-BN20 at baseline prior to RT, four weeks after completion of RT, and every three months thereafter until disease progression. Because the QLQ-C30 lacks a utility scoring system (i.e. it lacks quantified weights to reflect the preferences for a health state relative to others, which is necessary for the quality adjustment for QALY calculation), QLQ-C30 scores were converted to the preference-based Euro QOL 5D (EQ-5D) using existing mapping algorithms [18].

Resource use and costs

The direct unit costs of imaging, RT, and dexamethasone were collected in equitable United States dollars (USD) from contributing countries. Costs were calculated by multiplication of each resource by its unit price (Table 1). The base year for costs was 2015. Evaluation of costs associated with severe adverse events (e.g. hospitalization) was not undertaken as there were no grade 3 or 4 toxicities. Patients were assessed weekly during treatment and then 4 weeks after completing RT with repeat history, physical examination, imaging of the brain, and mini-mental state examination (MMSE). Thereafter, patients were assessed every 3 months until death.

Statistical and economic analysis

Total cost was compared between the two treatment arms in the study group as a whole as well as by individual center. The life years gained and progression-free life-years gained were calculated using the following formula:

$$\text{Incremental cost effectiveness Ratio (ICER)} = \frac{cost_A - cost_B}{\text{life year gain}_A - \text{life year gain}_B}$$

where $cost_A$ refers to the total cost for the short course RT arm (5 fractions) and $cost_B$ refers to the total cost for the standard course RT arm (15 fractions), and life year gain_A refers to restricted mean life/progression years for the short course RT arm and life year gain_B represents the restricted life/progression years for the standard course RT arm.

Fieller's method was planned to calculate the 95% confidence intervals [19], however, negative cost differences were generated

Table 1
Direct unit cost of resources associated with radiotherapy treatment for glioblastoma.

	Unit cost (USD)				
	Dexamethasone 4 mg tablet	CT	MRI	RT in 5 fractions	RT in 15 fractions
Belarus	$0.27	$269	$330	$600	$1,800
Brazil (PA)	$0.06	$119	$293	$1,046	$1,985
Georgia	$0.30	$130	$230	$2,900	$3,800
India	$0.01	$25	$58.3	$25	$42
Poland	$1.36	$57	$130	$3,472	$3,472

Abbreviations: USD United States dollar; CT computed tomography; MRI magnetic resonance imaging; RT radiotherapy; PA Porto Alegre.
Base year for costs: 2015.

Please cite this article in press as: Ghosh S et al. Improved cost-effectiveness of short-course radiotherapy in elderly and/or frail patients with glioblastoma. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.01.017