Original Article

Hospitalizations in elderly glioblastoma patients

Claire Moroney, James R. Perry, Derek S. Tsang, Denise Bilodeau, Chris Mueller, Hany Soliman, Sten Myrehaug, Arjun Sahgal, Chia-Lin Tseng, May N. Tsao

Odette Cancer Centre, University of Toronto, Toronto, ON, Canada

Contributions: (I) Conception and design: C Moroney, JR Perry, MN Tsao; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: C Moroney, DS Tsang, MN Tsao; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: May N. Tsao, MD, FRCP(C). University of Toronto, Department of Radiation Oncology, Odette Cancer Centre, 2075 Bayview Ave., Toronto, ON M4N 3M5, Canada. Email: may.tsao@sunnybrook.ca.

Background: Elderly glioblastoma (GB) patients are at risk of hospitalizations due to the morbidity of the disease and possible treatment toxicity.

Methods: In this observational cohort study, 255 newly diagnosed GB patients age 65 years and older were included. Survival, emergency room visits and admissions to an acute care hospital were determined. Mean and median total health care costs were calculated. Risk factors for Emergency room visits and acute care hospital admissions were determined.

Results: Median overall survival was 6 months. The majority of patients (68%) had at least one visit to the emergency department and 77% had at least one admission to acute care. The mean and median total costs (hospital, ambulatory, physician billing, other health care costs) per patient were $162,479.78 (CAN) and $125,511.00 (CAN), respectively. Treatment with radiation or treatment with radio-chemotherapy was associated with a relative risk (RR) of 2.31 (95% CI: 1.44–3.7; P=0.0005) and 2.19 (95% CI: 1.28–3.74; P=0.004), respectively for emergency department visits as compared to patients who were managed with comfort measures only. Patients with a baseline ECOG 0 had a RR of 1.71 (95% CI: 1.06–2.77; P=0.0289) and patients with baseline ECOG 1 had a RR of 1.49 (95% CI: 0.98–2.26; P=0.0623) for hospital admission as compared to patients with ECOG 4.

Conclusions: A large proportion of elderly GB patients (particularly those with good baseline performance status who underwent active treatment) presented to the emergency department and had at least one admission to acute care.

Keywords: Glioblastoma (GB); elderly; hospitalizations; costs; palliative

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Introduction

Approximately half of all patients diagnosed with glioblastoma (GB) are aged 65 years or older (1) and it is well known that the survival outcomes are worse for elderly patients with GB than for younger GB patients (2,3). A population-based study in the USA from the years 2000–2010 reported survival outcomes of 14,675 GB patients. In this study, the median overall survival among age groups was 29 months for ages 19–34, 18 months for ages 35–49, 13 months for ages 50–64, 8 months for ages 65–74 and 5 months for ages 75 and older (4).

Studies suggest that GB patients spend significant amounts of time in both acute and chronic care settings. Rahman *et al.* (5) found that the most common reason for hospital admission was weakness and immobility. Factors associated with hospitalization were older age and poorer performance status. Paszat and colleagues (6) reported in 2001 that 45% of patients with GB aged 60–69 years old

spent at least half of their remaining survival after diagnosis as an inpatient with rates as high as 59% in 70–79 years old and 76% for those over 80 years of age. Out of 5,000 GB patients aged 65 and older, 21% were hospitalized for at least 30 cumulative days between diagnosis and death. Twenty-two percent of all patients spent at least one quarter of their remaining lives as an inpatient with the risk increasing with increasing age (1).

The management for patients age 65 and older for GB ranges from optimal supportive care alone, short course radiotherapy (1), temozolomide alone (7), short course radiotherapy with temozolomide chemotherapy (8), and protracted course radiotherapy (60 Gy in 30 daily fractions) with temozolomide chemotherapy (2). Management decisions are based on prognostic features such as age (65–70 years, 70 years and older), MGMT methylation status (9) and performance status (10). In general, patients who have poor performance status and poor survival, unlikely to benefit from treatment are considered for optimal supportive care alone. However, a randomized trial reported that for patients 70 years and older with anaplastic astrocytoma or GB patient and with Karnofsky performance status 70 or higher, radiation improves survival as compared to comfort measures (11). For patients age 65 years and older with Eastern Co-operative Oncology Group (ECOG) performance status 0–2, short course radiotherapy and temozolomide improves survival as compared to short course radiotherapy alone, based on a recently published trial (8). However, for patients who have excellent performance status in the lower end of the elderly age group (less than 70 years old), protracted radiation with temozolomide chemotherapy may be given based on the Stupp trial (2) which included patients up to the age of 70. For GB patients over the age of 70, either short course radiotherapy with (8) or without temozolomide or temozolomide alone may be considered (12). The use of temozolomide may be favoured in methylated MGMT GB (12).

Even with aggressive therapy (e.g., protracted radiation with temozolomide), survival for GB patients over the age of 65 is still short. The morbidity associated with GB and the potential toxicity of treatment puts this vulnerable group of patients at risk of hospitalizations.

The primary purpose of this study was to describe the proportion of survival spent in hospital in GB patients over the age of 65, initially managed at a tertiary cancer centre. The secondary objectives were to explore possible risk factors for admission and to explore costs.

Methods

Patients with newly diagnosed GB seen at a tertiary cancer centre from December 2006 to December 2014 were included. Demographic information (age at diagnosis, sex), baseline characteristics (performance status), treatment information (date of craniotomy, extent of surgical resection or biopsy, radiation dose fractionation, chemotherapy) and survival were linked anonymously with provincial administrative databases through the Institute of Clinical Evaluative Sciences (ICES).

The following sources and associated data were used:

(I) The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD): dates of acute hospital admission;

(II) National Ambulatory Care Reporting System Database (NACRS): dates of care (includes emergency room visits, day procedures and cancer clinic visits) and resource utilization (based on resource intensity weights) (13). A resource intensity weight (RIW) is assigned to each hospital inpatient and represents the average amount of hospital resources (including administration, staff, supplies, technology and equipment) used by patients with a particular condition relative to the average resources used by other patients. For example, a patient with a RIW of 2.0 used twice as many resources as a patient with a RIW of 1.0;

(III) Ontario Health Insurance Plan (OHIP) Schedule of Benefits Claims Database: Physician services, date provided, fee paid. We used the palliative care fee codes (K023; C945; C882; C982; A902; A771; A945; W882; W982; W872; W972; G511; K700) as a surrogate for patient access to palliative care.

We determined patient costs for acute inpatient hospitalizations, ambulatory care, and physician services costs. Patient costs for acute hospitalizations (CIHI-DAD) and ambulatory care (NACRS) were calculated as the product of the resource weight, reflecting the intensity of service utilization for the specific episode and the appropriate unit cost (13).

Bivariate associations between baseline characteristics [age, sex, ECOG performance status, initial treatment type (biopsy, subtotal resection, gross total resection, chemotherapy, radiation, comfort measures only)] were identified using the chi-square and Fisher exact tests. Negative binomial regression modelling was performed using backward elimination of variables at $P \geq 0.2$, with

Table 1 Demographics (N=255 glioblastoma patients)

Demographics	Number (range or percentage)
Age	
Mean ± SD	72.48±5.65
Median [IQR]	72 [67–77]
Sex	
Female	124 (48.6%)
Male	131 (51.4%)
ECOG performance status	
0	23 (9.0%)
1	82 (32.2%)
2	55 (21.6%)
3	54 (21.1%)
4	41(16.1%)
Surgical extent	
Biopsy	61 (23.9%)
Subtotal resection	41 (16.1%)
Gross total resection	153 (60.0%)
Year of diagnosis	
2006–2009	71 (27.8%)
2010–2011	90 (35.3%)
2012–2014	94 (36.9%)
Treatment	
Radiation alone	145 (56.9%)
Radiation and chemotherapy	56 (21.9%)
Chemotherapy alone	1 (0.4%)
Comfort measures	53 (20.8%)

SD, standard deviation; IQR, interquartile range; ECOG, Eastern European Cooperative Oncology Group.

the outcomes of interest being at least one visit to the emergency department, at least one admission to an inpatient acute care unit and length of stay. For the regression analyses, age and length of stay were treated as continuous variables. A P value of less than 0.05 was considered significant. All tests were 2-tailed and were performed using the SAS software application (version 9.2; SAS Institute, Cary, NC, USA).

The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre (Project Identification Number 013-2016). Due to the retrospective anonymized nature of this study, expressed written informed study consent from patients was not required.

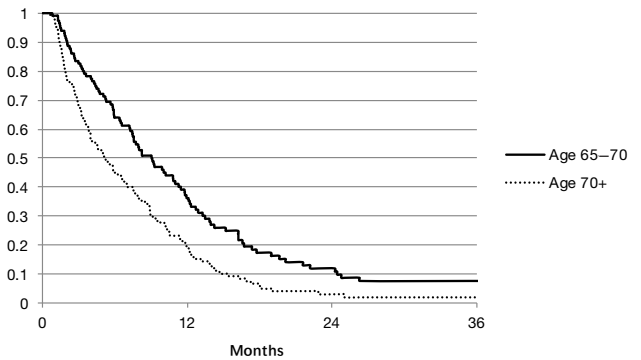

Figure 1 Overall survival by age intervals 65–70 years, 70+ years.

Results

Demographics (Table 1)

Two-hundred and fifty-five consecutive newly diagnosed GB patients aged 65 and older seen at a tertiary cancer centre from December 2006 to December 2014 were included. The median age was 72 years (range, 67–77 years). About 51% of patients were males and 49% were females. The percentage of patients with the following baseline ECOG performance status was as follows: 9%, 32%, 22%, 21%, and 16% for ECOG 0, 1, 2, 3, 4 respectively.

The majority of patients (60%) had a gross total resection based on the operative report and postoperative imaging. Twenty-four percent of patients underwent a biopsy and the remaining 16% had a subtotal resection.

In general, patients who had poor performance status and who were unlikely to derive significant survival or quality of life benefit with active therapy were managed with comfort measures (n=53). Other patients were treated with radiation alone (n=145), radiation and chemotherapy (n=56) or chemotherapy alone (n=1) with the intent to improve survival.

Survival

Overall median survival was 6 months (with an interquartile range of 1–19 months). *Figure 1* shows survival by the following age intervals: 65–70 years, 70+ years. *Figure 2*

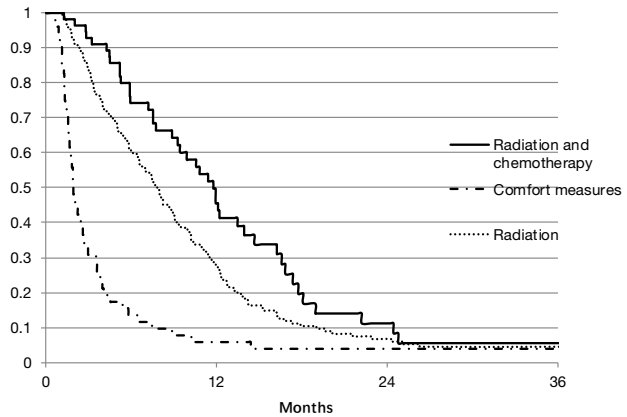

Figure 2 Overall survival for glioblastoma age 65 and over, by treatment.

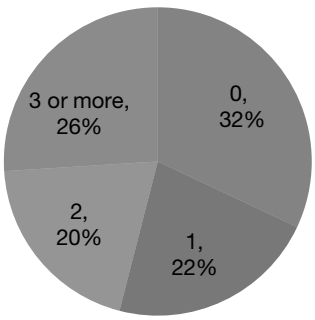

Figure 3 Emergency department (ED) visits.

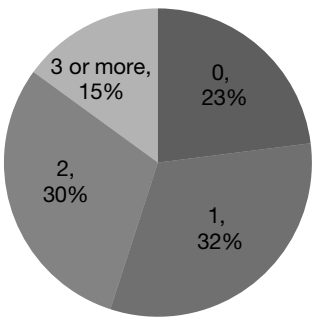

Figure 4 Admissions to acute care.

shows survival by treatment (comfort measures, radiation, radiation and chemotherapy).

Hospitalizations

The majority of patients (68%) had at least one visit to the emergency department (*Figure 3*) and 77% had at least one admission to acute care (*Figure 4*), after diagnosis (taken as the date of first surgery showing GB).

Specific reasons for emergency department visits and admission to acute care were not adequately captured in the databases used.

The mean and median length of acute hospital stay per patient was 20.5 and 14 days respectively. The breakdown of duration of inpatient admission as a fraction of patient survival time is shown in *Table 2*.

There was a mean of 79.7 days and a median of 43 days from the last emergency department visit to death (*Table 2*).

Table 2 Length of hospital stay, percentage of total follow-up spent as an inpatient, last ED visit to death

Characteristics	Data
Length of Stay, days	
Mean ± SD	20.52±24.54
Median (10^{th}, 90^{th} percentile)	14 [0–56]
% of total follow-up spent as inpatient, n (%)	
<5%	109 (42.7%)
5–<10%	48 (18.8%)
10–<20%	39 (15.3%)
20–<30%	21 (8.2%)
30–<70%	30 (11.8%)
70+%	8 (3.1%)
Last ED visit to death, days	
Mean ± SD	79.67±101.86
Median (IQR)	43 [18–101]

ED, emergency department; SD, standard deviation; IQR, interquartile range.

Palliative care

Based on physician services billing fee codes as palliative care, 60% of patients accessed physician services for palliative care.

Costs (all in Canadian dollars)

The mean and median hospitalization costs per patient was $87,625.79 and $47,673.00 respectively. The mean and median ambulatory costs per patient were $22,371.33 and $14,803 respectively. Mean and median OHIP billing costs per patient were $24,672.72 and $16,568.00 respectively.

Table 3 Costs of care per patient

Costs of care per patient*	Canadian dollars (range)
Ambulatory cost ($)	
Mean ± SD	22,371.33±23,172.66
Median (IQR)	14,803 (7,468–30,134)
Hospitalization cost ($)	
Mean ± SD	87,625.79±114,043.37
Median (IQR)	47,673 (22,767–97,449)
OHIP cost ($)	
Mean ± SD	24,672.72±22,884.68
Median (IQR)	16,568 (11,003–28,524)
Other cost ($)	
Mean ± SD	27,809.94±38,999.28
Median (IQR)	12,380 (2,031–33,187)
Total cost ($)	
Mean ± SD	162,479.78±135,029.10
Median (IQR)	125,511 (73,553–208,926)

*, all in Canadian dollars. OHIP, Ontario Health Insurance Plan.

The mean and median costs for other health care per patient were $27,809.94 and $12,380, respectively. The mean and median total costs per patient were $162,479.78 and $125,511.00, respectively (*Table 3*).

Risk factors for admission

Table 4 summarizes the risk factors for emergency department visits and hospital admission. Treatment with radiation or treatment with radiation and chemotherapy was associated with a relative risk of 2.31 (95% CI: 1.44–3.7; P=0.0005) and 2.19 (95% CI: 1.28–3.74; P=0.004), respectively for emergency department visits. Patients with baseline ECOG performance status of 0 or 1 had a RR of 2.73 (95% CI: 1.49–4.98; P=0.0011) and 1.75 (95% CI: 1.03–2.96; P=0.0372) for emergency department visits during the course of their illness as compared to patients with baseline ECOG performance status of 4. The majority of patients with ECOG performance status 4 were managed with comfort measures. Similarly, patients with a baseline ECOG 0 had a RR of 1.71 (95% CI: 1.06–2.77; P=0.0289) and patients with baseline ECOG 1 had a RR of 1.49 (0.98–2.26; P=0.0623) for hospital admission during the course of their illness as compared to patients with ECOG 4.

Table 4 Model results of risk factors for emergency department visits, hospital admission ED visits

Characteristics	RR (95% CI)	P value
ED visits		
Age	0.97 (0.95–1)	0.0209
Sex		
Male	1.07 (0.82–1.39)	0.612
Initial treatment		
None	REF	
Both treatment	2.19 (1.28–3.74)	0.004
Chemotherapy	1.62 (0.15–17.8)	0.6944
Radiation	2.31 (1.44–3.7)	0.0005
ECOG		
0	2.73 (1.49–4.98)	0.0011
1	1.75 (1.03–2.96)	0.0372
2	1.67 (0.97–2.86)	0.0636
3	1.57 (0.91–2.7)	0.1072
4	REF	
Surgery type		
STR	REF	
GTR	1.23 (0.88–1.72)	0.2266
Biopsy	0.78 (0.56–1.1)	0.1558
Hospital admission		
Age	0.99 (0.97–1.01)	0.4317
Sex		
Male	1.02 (0.82–1.25)	0.8873
Initial treatment		
None	REF	
Both treatment	1.3 (0.85–1.98)	0.2244
Chemotherapy	1.04 (0.14–7.67)	0.9725
Radiation	1.38 (0.97–1.98)	0.0765
ECOG		
0	1.71 (1.06–2.77)	0.0289
1	1.49 (0.98–2.26)	0.0623
2	1.26 (0.82–1.94)	0.2959
3	1.17 (0.76–1.81)	0.4647
4	REF	

Table 4 (*continued*)

Table 4 (*continued*)

Characteristics	RR (95% CI)	P value
Surgery type		
STR	REF	
GTR	1.02 (0.77–1.35)	0.8878
Biopsy	0.78 (0.59–1.03)	0.078

ED, emergency department; REF, reference; ECOG, Eastern Co-operative Oncology Group; STR, subtotal resection; GTR, gross total resection.

Discussion

Hospitalizations in GB patients

Although there have been publications on hospitalization in GB patients, ours is the only study which has examined hospitalizations and costs in GB patients 65 years and older from the time of diagnosis to death.

Rahman *et al.* (14) reported on 5,029 patients age 65 and older diagnosed with GB between 1999–2007 using SEER/Medicare-linked data in the United States. The authors reported that 21% were hospitalized at least 30 cumulative days between diagnosis and death. However, the study did not quantify the number of admissions or costs.

Rahman *et al.* (5) reported on 196 consecutive newly diagnosed GB patients age 23–90 years who underwent chemoradiation. Hospitalization outcomes were reported only during the period of chemoradiation and costs were not explored. The authors reported that 43% of patients were hospitalized during the chemoradiation period. Hospitalizations during the chemoradiation period were associated with shorter survival (adjusted hazard ratio 1.47; 95% CI: 1.01–2.13, P=0.043).

Diamond *et al.* (15) reported on GB patients, at least 18 years of age admitted within 1 month of death. They found that out of 385 GB patients, 42.6% were admitted within a month of death. Of these, 34% had ICU care.

In the present study, the proportion of patients who were hospitalized for a large fraction of their remaining survival time was low, as compared to prior reports in the literature. It may be hypothesized that strong palliative care supports in the community may have contributed to lowering this value as compared to published reports from other groups. However, despite the fact that GB is a uniformly terminal diagnosis, only 60% of our patients had a palliative care-associated billing code associated with their care. Opportunity exists to improve access to home palliative care supports and to evaluate whether this strategy lowers emergency room visits, acute care hospitalizations, quality of life and health care costs.

We found that the risk of emergency department visits and hospitalizations was associated with good baseline performance status and active treatment. This suggests that the morbidity of progressive disease and treatment puts these patients at risk of emergency room visits and hospitalizations, as compared to patients with shorter survival who are managed with comfort measures only.

These data underscore the magnitude of emergency department visits, hospitalization risk and health care costs associated with GB patients age 65 and older, particularly those who are selected for active therapy with the intent to improve survival.

Hospitalizations and goals of care

Challenges in the hospitalization of advanced cancer patients have also been highlighted by Bostanci *et al.* (16). The authors focused on the medical records of 39 advanced cancer patients who died in an acute care hospital. All the included patients had well established and predictably worsening disease and significant symptoms. In almost every case, admission to hospital followed advice from a doctor. Broader goals of care for these terminally ill patients were rarely documented at the time of hospital admission. The authors also noted that hospital discharge planning was frequently associated with family and inter-professional conflict. For some, it was difficult to transition from active investigations and treatments to end-of-life care. For others, although patients expressed a wish to have palliative care at home and to die at home, barriers included lack of home care supports and late recognition of dying with discharge planning delayed due to on-going investigations and considerations for further active therapies.

Wright *et al.* (17) examined a multi-site prospective cohort of 332 advanced cancer patients and their caregivers in the United States. Patients were followed from the time of enrollment to death. End of life discussions were associated with less aggressive medical care near death and earlier hospice referrals. Aggressive care was associated with worse patient quality of life and worse caregiver bereavement. Cancer patients who died in hospital or in the intensive care unit (ICU) were found to have worse quality of life compared to those who died at home. Bereaved caregivers for these cancer patients who died in hospital or

in ICU were also found to be at increased risk of developing psychiatric illness (18).

Advanced care planning (ACP)

ACP allows patients to assign a substitute or surrogate decision maker to make clinical decisions on their behalf if they are not capable of making these decisions themselves (19). Due to the potentially rapid neurologic and cognitive decline of patients with GB, early discussions of ACP can have impact on treatment and care decisions (20). Incorporating ACP into the care of GB patients allows the patient, their family and their health care team to understand their unique concerns and preferences. ACP discussions can provide the patient and family with a better understanding of their illness and prognosis (19). This knowledge may lead to earlier Palliative Care referrals as well as less need for emergency room visits and acute care stays. ACP may ultimately improve both GB patients' symptoms and their overall quality of life (20).

Home palliative care

A pilot project of palliative home care for primary brain tumour patients was reported in Italy (21). From 2000–2009, 572 patients were followed by a team of home care staff consisting of 1 neurologist, 2 physiotherapists, 2 psychologists, one social worker and 4 specialty nurses. Seventy percent of patients were managed at home until death. The hospitalization rate was lower (16.7%) in those who received the home care described above versus 38% of patients who did not. Costs of hospitalizations were also significantly lower in the group who received the specialized home care 517 € (95% CI: 512–522€) versus 24,076 € (95% CI: 24,040–24,112€) in those who did not.

For the subset of 197 patients with GB who received the specialized home care, 53.1% died at home, 34.4% died in hospice and 12.5% died in hospital. In 97% of cases, caregivers reported satisfaction with the home assistance. After 3 months, the Barthel Index (a measure of activities of daily living) improved in 43% of patients and 72% had an improvement in their quality of life scores in at least one item compared to baseline scores (22).

Limitations

The limitations of the present study are that the decision to hospitalize a patient is based on clinical judgment and that may vary among institutions and across communities based on palliative home care supports. Although we had detailed patient information such as performance status, extent of resection and treatment details in the patient database, we relied on a provincial database for hospitalizations and costs. As such, only hospitalizations and costs captured within the province were reported. Furthermore, the provincial database was inadequate with respect to reasons for emergency room visits and hospitalizations. The most common International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD10) codes was C719 (Brain, unspecified) for emergency department visits and C71 (malignant neoplasm brain) for hospital admissions.

The cost analysis only accounts for direct medical costs incurred by the single-payer universal provincial government health care system. Indirect costs such as income forgone because of impairment, disability or illness for the patient and caregiver(s) and other costs incurred by patients (such as copayment for medications, hospitalizations, canes/walkers/wheelchairs, transportation) are not addressed.

Future directions

In January 2014, a provincial palliative care integration project was initiated at our tertiary cancer centre. Hospital staff involved in the care of GB patients, were educated in a classroom setting with respect to approaches to palliative care. All GB patients were identified and since 2014, advanced care planning discussions are now initiated within the first few months of treatment. The process also involves integrating home care referrals earlier.

Whether strategies such as earlier palliative care discussions, improved palliative home care services and planning for direct palliative care unit or hospice placement when clinically relevant, will decrease emergency room visits, hospitalizations and quality of life requires further investigation.

Future directions include analyzing whether hospitalizations and costs have changed with the introduction of this provincial palliative care integration initiative at our cancer centre. As well, hospitalization rates and costs among different cancer centres can be compared using the existing administrative databases.

In addition, the development/use of a pretreatment Comprehensive Geriatric Assessment (CGA) tool may help to predict prognosis and toxicity (23). This tool is

a multidimensional assessment that determines medical, functional, and psychosocial aspects of elderly patients. It is anticipated that the CGA will add to our present use of age and performance status to help guide GB management, especially in elderly patients. Furthermore, the CGA may help identify patients who have a higher risk of complications from treatment, emergency room visits and hospital admissions.

Conclusions

A large proportion of patients with GB over the age of 65 years will present to the emergency department and will have at least one admission to acute care during their illness. Most patients spent their post-diagnosis survival time as outpatients. However, the cost of inpatient care still contributes to approximately half of total costs of care for elderly GB patients. Whether strategies such as earlier palliative care discussions, improved palliative home care services and planning for direct palliative care hospital or hospice placement will decrease emergency room visits and hospitalizations requires further investigation.

Acknowledgements

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Footnote

Conflicts of Interest: Dr. Arjun Sahgal has received honorarium for past educational seminars from Medtronic, Elekta AB, Accuray Inc., and Varian Medical Systems and research grants from Elekta AB. Dr. Sahgal also belongs to the Elekta MR Linac Research Consortium. The other authors have no conflicts of interest to declare.

Disclaimer: The results, opinions and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES, CCO or the Government of Ontario is intended or should be inferred.

Ethical Statement: The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre (Project Identification Number 013-2016). Due to the retrospective anonymized nature of this study, expressed written informed study consent from patients was not required.

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