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Glioblastoma survival is improving despite increasing incidence rates: a nationwide study between 2000 and 2013 in Finland

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ABSTRACT

Background: We assessed population-level changes in glioblastoma survival between 2000 and 2013 in Finland, with focus on elderly patients (>70 years) in order to assess if changes in treatment of glioblastoma are reflected also in population-based survival rates.

Methods: We identified all patients (age ≥ 18 years) from the Finnish Cancer Registry (FCR) with a histopathological diagnosis of primary glioblastoma in 2000–2013. Patients were followed up until December 2015. The accuracy of register-based search of glioblastoma patients was internally validated. We report age-standardized relative survival ratios and relative excess risks of death (RER) between 2000–2006 (pre) and 2007–2013 (post-period).

Results: We identified 2,045 glioblastoma patients from the FCR. The accuracy of the FCR-based search was 97%. Median age was 63.3 years, and 42% were women. Incidence increased on average by 1.6% ($p=0.004$) and median age by 0.4 years per calendar year. Between the pre and post-period, the proportion of patients >70 years increased from 24% to 27%. In >70-year-old patients, the median survival time increased from 3.6 months in 2000–2006 to 4.5 months in 2007–2013 (RER 0.82, 95% CI 0.68–0.98). In ≤ 70 -year-old-patients, the median survival time increased from 9.3 months in 2000–2006 to 11.7 months in 2007–2013 (RER 0.74, 95% CI 0.67–0.82).

Conclusion: Despite the increased proportion of elderly glioblastoma patients, population-level survival of glioblastoma patients have improved since year 2000. However, increasing incidence, increasing age of patients, and poor survival in elderly are alarming, and future studies should perhaps focus more on elderly.

Key words: glioma; malignant glioma; glioblastoma; epidemiological study; elderly

Key points:

- Glioblastoma incidence has increased consistently from 2000 to 2013
- Survival has improved more in younger glioblastoma patients
- Poor survival in elderly glioblastoma patients is alarming

IMPORTANCE OF THE STUDY

Following the European Organization for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (EORTC-NCIC) trial in 2005, the standard of care for patients with glioblastoma have consisted of tumor resection followed by radiotherapy and temozolomide. In this study, we estimated population-level survival changes following the EORTC-NCIC trial. We found that patients diagnosed with glioblastoma after the EORTC-NCIC trial had a 24% lower relative risk of death compared to patients diagnosed before the trial. The relative risk of death decreased more in glioblastoma patients ≤ 70 years compared to glioblastoma patients >70 years (26% vs. 18%). Furthermore, median survival time increased only by 0.9 months in glioblastoma patients >70 years compared to 2.4 months in glioblastoma patients ≤ 70 years. We also found that the median age and incidence of glioblastoma, especially among the elderly, steadily increased. This study provides nationwide evidence showing that survival rates among glioblastoma patients have improved following the recent randomized controlled trial. Still, poor overall population-level survival in elderly glioblastoma patients raises concerns whether current treatment strategies for elderly patients are optimal. Given the rapidly aging population in many industrialized countries, studies focusing on elderly glioblastoma patients are urgently needed.

INTRODUCTION

Glioblastoma, classified according to the World Health Organization (WHO) as a grade IV glioma, is the most prevalent type of newly diagnosed primary malignant brain tumors in adults.¹⁻⁴ To date, no curative treatment exists for these rapidly progressing tumors and there is no deadlier form of cancer than glioblastoma (5-year mortality rate of 97%).⁵ Since the European Organization for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (EORTC-NCIC) trial published in 2005 (conducted in 2000–2002),⁶ standard treatment consists of surgical tumor resection followed by concomitant radiotherapy and temozolomide (chemoradiation). In more detail, the EORTC-NCIC trial⁶ showed that by adding temozolomide to radiotherapy, the median survival improved from 12.1 months to 14.6 months in glioblastoma patients between 18 and 70 years. In 2017, another trial (conducted in 2007–2013) showed that in glioblastoma patients 65-year-old or older glioblastoma patients, chemoradiation increased median survival time from 7.6 months to 9.3 months.⁷ Still, controversy exists whether elderly (>70 years) glioblastoma patients benefit from the more aggressive treatment.⁸

Nationwide results on cancer survival are among key indicators in assessing healthcare system effectiveness of care and management of cancer patients.^{5,9} Yet, nationwide epidemiological studies assessing the impact of these changes in treatment policies of glioblastoma reflected by survival are scarce. Finland has a government-subsidised social welfare and health care system, where socioeconomic factors and health inequalities are less likely to affect cancer treatments and treatment outcomes, which are shown to be among the best in the world.⁵ Since nationwide cancer registry can be used to reliably estimate the population-level changes, including treatment changes, the primary aim of our register-based study was to explore if nationwide glioblastoma incidence and survival rates have changed after the EORTC-NCIC trial⁶, with focus on elderly (>70 years) glioblastoma patients. We hypothesized that population-level glioblastoma survival has improved since standardization of chemotherapy.⁶

MATERIALS AND METHODS

Ethical Considerations

According to the Finnish law, individual level data with identifiers from the Finnish Cancer Registry (FCR) can only be used for scientific research with approval from authorities or for statistics. The FCR follows strict regulations to ensure absolute confidentiality and protection of the individuals. The data processing procedures were evaluated and approved by the Helsinki University Hospital's research committee (HUS/356/2017 §107) and the National Institute for Health and Welfare THL (THL/1009/6.02.00/2018). We conducted the study according to the STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) guidelines (Electronic Supplementary Material 1).

Finnish Health Care System

Finland's healthcare system offers equal and low-cost public healthcare for all citizens, also for those with or without income or insurances. For example, in 2017, the daily hospital fee for short-term institutional care in Helsinki University Hospital, one of the largest hospital organizations in industrialized countries, was €38.80. This out-of-pocket fee covers the whole treatment from all types of surgeries to intensive care stay, as medical care costs are tax-funded and paid by the municipality the patient lives in. The most specialized and high-level medical care is provided by five public and non-profit university hospitals, and for example all intracranial neurosurgical operations, including brain tumor surgeries, are performed exclusively in these five university hospitals. In the Finnish healthcare payment model, employees in academic hospitals do not have for example procedure or capitation-based financial incentives.

Finnish Cancer Registry

The FCR is a non-profit institute for statistical and epidemiological cancer research in Finland funded by the Cancer Society of Finland and National Institute for Health and Welfare (THL). The FCR maintains a nationwide database covering all incident cancers since 1953. It covers 95% of all solid tumors.¹⁰ As mandated by law, health care organizations are required to report cancer cases to the FCR, which collects demographic, diagnostic and treatment data on patients diagnosed and/or treated in Finland. Accordingly, laboratories of pathology, cytology and haematology send respective clinical (diagnostic) notifications (passive registration). Statistics Finland, which has archived all Finnish death certificates from 1936 onwards, provides causes of death of individuals registered in the FCR. In addition, also cases where the diagnosis of cancer is based solely on the death certificate, will be received

(death certificate only [DCO] cases). Coding of cancer cases is done by specifically qualified cancer coders and supervised by the FCR physician (pathologist). Since 2007, the FCR has used the International Classification of Diseases for Oncology Third Edition (ICD-O-3) nomenclature for cancer topography (primary site of cancer) and morphology (histological type). Older code combinations have been systematically converted into the ICD-O-3. For malignant gliomas, the conversion (ICD-O-3 nomenclature) is available from 2000 onwards.

Identification of glioblastoma patients from the Finnish Cancer Registry

All patients (≥ 18 years of age) with primary glioblastoma were identified through the FCR. Using the topography codes (ICD-O-3) "C71.0–C71.9" and morphology code "9440" (glioblastoma), we identified persons with a histopathological diagnosis of first primary glioblastoma obtained through either biopsy or resection. We excluded morphology codes "9441" (giant cell glioblastoma, N=25) and "9442" (gliofibroma/gliosarcoma, N=58), as we presumed that including these rare malignancies might decrease, not increase, external validity (generalisability). Secondary or recurrent glioblastomas (*i.e.* prior diagnosis of glioma or glioblastoma re-operation) were also excluded. As histopathological diagnosis was an inclusion criteria we did not include DCO cases.

Identification of glioblastoma patients from the hospital registry and treatment strategies

In order to evaluate the internal validity of the FCR in glioblastoma identification, all patients operated on in two separate years (2005 and 2010) at Helsinki University Hospital were identified through a prospective surgical log book, which includes every neurosurgical patient operated on in the Department of Neurosurgery (which covers more than one-third of all glioblastoma patients in Finland). We then compared the number of glioblastoma patients identified through the FCR with the number of operated glioblastoma patients identified through the hospital registries. We further scrutinized electronic health record (EHR) data of these patients treated in 2005 and 2010 and collected data regarding type of surgery performed (resection or biopsy), and whether the patient received adjuvant chemotherapy including temozolomide.

Survival and follow-up

Patients were followed up from the date of histopathological diagnosis until death, emigration or to the end of 2015. Due to the nationwide and obligatory registries including unique personal identifiers, follow-up was complete. Since

the randomized trial results were published in 2005,⁶ a one-year transition period was taken into account, and therefore 2 time periods, namely 2000-2006 and 2007-2013 were used in the comparative analyses.

Statistical Analysis

We calculated age-standardized glioblastoma incidence per 100,000 inhabitants using the European Standard Population 2013 (ESP2013). Incidence rates are also reported by age groups (<15, 15–24, five-year groups from 25–29 to 80–84, and ≥85 years). The relative annual change in age-standardized incidence rate was estimated by using the Poisson regression. The Davies' test was used as a significance test to detect a change in the incidence trend.¹¹

To estimate the accuracy of the FCR, we considered the hospital registry as the gold standard, and report the accuracy of the FCR-based search on persons with glioblastoma as percentage of cases found in FCR divided by cases found in the hospital registry.

We calculated age-standardized relative survival by using the Ederer II method.^{12,13} It summarizes patients' excess risk of death due to the cancer by comparing the survival of patients to that of their reference population (the population of Finland stratified by sex, age, and calendar year). In the age standardization, the age group specific numbers of patients diagnosed in 2000–2013 were used as weights based on 6 groups (18–40, 41–50, 51–60, 61–70, 71–80 and 81 years and older at diagnosis). To compare differences in relative survival between 2000–2006 and 2007–2013, we estimated relative excess risk (RER) of death by using the Poisson regression model for relative survival.¹⁴ In age group specific analyses, the model included 7 intervals of follow-up time since diagnosis (0 to <2 months, 2 to <6 months, 6 to <12 months, 12 to <18 months, 18 to <24 months, 2 to <3 years, 3 to <5 years) and the period of diagnosis. In analyses combining more than one age group, age at diagnosis (the same age groups as above) and interaction between follow-up time and age were also included in the model to allow for non-proportional excess risk of death by age. The first 5 years of follow-up was considered and longer survival times were censored at 5 years. An estimate of RER under one indicates that the excess risk of death among patients diagnosed in the 2007–2013 era was lower than that in the 2000–2006 era and vice versa. Subgroup-specific analysis was done by sex, age groups and separately for patients >70 years. We also report median survival times. P-values for the differences in excess mortality between the two time periods were based on the likelihood-ratio test, which was adjusted for multiple comparisons by using the

method of Benjamini and Hochberg.¹⁵ The adjustment was done for interactions between age and time period, and for the main effects of age and sex.

RESULTS

Glioblastoma incidence and age at diagnosis

Between 2000 and 2013, a total of 2,045 persons with a histopathological diagnosis of primary glioblastoma were recorded in the FCR. The median of age at diagnosis was 63.3 years, and 42% were women (Table 1). The average increase in patient median age was 0.4 years per calendar year. The proportion of elderly (>70 years) increased from 23.6% in 2000–2006 to 26.7% in 2007–2013. The ESP2013 standardized mean incidence of glioblastoma during the study period was 2.9 per 100,000 person-years. The age-standardized incidence of glioblastoma increased on average by 1.6% (95% CI 0.5% to 2.7%) per calendar year ($p=0.004$). The relative annual increase was 1.4% (95% CI 0.0% to 2.8%, $p=0.056$) in men and 1.9% (95% CI 0.2% to 3.6%, $p=0.028$) in women (Figure 1). This increase was unchanged during the study period ($p=0.640$). The incidence of glioblastoma increased sharply with age, being the highest among 65 to 79 year-olds (Electronic Supplementary Material 2).

Accuracy of glioblastoma patient identification

Of all 2,045 glioblastoma patients included in the study 761 patients (37%) were operated in Helsinki. The FCR-based search identified 113 persons who were diagnosed with primary glioblastoma in 2005 and 2010 in the Helsinki University Hospital catchment area. The search, which was based on Helsinki University hospital registries and EHR, identified 116 glioblastoma patients operated on in the same years. Therefore, the accuracy of FCR-based search was 97% in identifying operated (burr-hole biopsy or craniotomy) glioblastoma patients.

Survival and excess risk of death by period and age

Age-standardized cumulative relative survival ratios are shown in Table 2 and Figure 2. In 2000–2006, 1-year survival rate was 31%, 3-year survival rate was 5% and 5-year survival rate was 2%. In 2007–2013, 1-year survival increased rate to 41%, 3-year survival rate increased to 8% and 5-year survival rate increased to 3%. Even though 1-year survival increased in all age groups from 2000–2006 to 2007–2013, 3-year and 5-year survival remained poor, particularly in people older than 60 years (Table 2). When comparing ≤ 70 and >70 -year-old patients, 1-year survival for patients ≤ 70 years was approximately 3 times higher than in elderly. Three-year and 5-year survival remained overly poor in elderly patients. In fact, of elderly patients diagnosed in 2007–2013, only 3% and 1% survived 3 and 5 years, respectively.

Cumulative relative survival for patients ≤ 70 and >70 years are shown in Table 3 and Electronic Supplementary Material 3. In 2000–2006, median survival time for patients ≤ 70 years was 9.3 months compared to 11.7 months in 2007–2013. In men ≤ 70 years, median survival time increased from 9.8 months to 11.8 months; in women ≤ 70 years, median survival time increased from 8.9 months to 11.7 months. For patients >70 years, median survival time was 3.6 months in 2000–2006 compared to 4.5 months in 2007–2013. In men >70 years, median survival time increased from 3.6 months to 4.8 months; in women >70 years, median survival time increased from 3.7 months to 4.2 months.

Relative excess risks (RER) of death by sex and age group are shown in Table 2. Patients diagnosed in 2007–2013 had a smaller relative excess risk of death (RER 0.76, 95% CI 0.69–0.83, $p < 0.001$) as compared to patients diagnosed in 2000–2006. This reduction in RER of death between periods was evident for both patients ≤ 70 years (RER 0.74, 95% CI 0.67–0.82, $p < 0.001$) and >70 years of age (RER 0.82, 95% CI 0.68–0.98, $p = 0.032$). We found no evidence of the difference in the reduction of excess mortality from 2000–2006 to 2007–2013 between the age groups in men (adjusted p -value=0.670) nor in women (adjusted p -value=0.073). When analyzed by sex, RER of death decreased significantly for men and women ≤ 70 years. Among patients >70 years, the decrease was significant in men only. The decrease was the largest in ≤ 70 -year-old women (RER 0.64, 0.54–0.76), and significantly larger ($p = 0.048$) than that in older women (RER 0.88, 0.68–1.15). In an age group specific analysis, RER of death decreased significantly in patients aged 41–50 years (RER 0.70), 51–60 years (RER 0.70) and 61–70 years (RER 0.78) (Figure 3).

Treatment strategies in 2005 and 2010

Year 2005. Forty-eight glioblastoma patients were operated on in Helsinki University Hospital. Of these, 16 patients (33%) were >70 years. Of these 16 patients, 11 (69%) underwent craniotomy and tumor resection, and 5 (31%) underwent stereotactic tumor biopsy. Only 2 elderly patients (13%) received adjuvant chemoradiation including temozolomide. Of the 32 ≤ 70 -year-old patients, 30 (94%) underwent craniotomy and tumor resection, and only 2 (6%) underwent stereotactic tumor biopsy. Of these 32, 18 (56%) received adjuvant chemoradiation including temozolomide.

Year 2010. Of the 68 operated glioblastoma patients in Helsinki, 18 patients (26%) were >70 years. Of these 18 patients, 17 (94%) underwent craniotomy and tumor resection, and 1 patient (6%) underwent stereotactic tumor biopsy. Data on adjuvant radiation and chemotherapy of one elderly patient was missing. Six elderly patients (33%)

received adjuvant chemoradiation including temozolomide. Of the 12 elderly patients that did not receive temozolomide, 4 (33%) were treated with whole brain radiotherapy. Chemotherapy in the elderly was omitted mainly due to fast progression or poor overall condition following surgery. Of the 50 <70-year-old patients, 46 (92%) received adjuvant chemoradiation including temozolomide, and 44 patients (88%) underwent craniotomy and tumor resection (6 patients [12%] underwent stereotactic tumor biopsy only).

DISCUSSION

Key findings

In this nationwide study, we found that patients diagnosed in 2007–2013 had a 24% lower RER of death compared to patients diagnosed in 2000–2006. The RER of death decreased more in patients 70 years or younger (26%) compared to patients older than 70 years (18%). Median survival time increased by 2.4 months (from 9.3 to 11.7 months) in patients 70 years or younger but only by 0.9 months (from 3.6 to 4.5 months) in patients older than 70 years.

Furthermore, the incidence of glioblastoma and median age of glioblastoma patients increased in time.

Comparison with previous studies

To estimate population-wide survival effects from controlled trials, one should turn to population-based studies.^{5,9}

One of the first large epidemiological glioblastoma studies (before the EORTC-NCIC trial), including almost 17,000 patients, came from the Surveillance, Epidemiology, and End Results (SEER) database and showed no improvement in survival rates for glioblastoma patients during from the 1980s to 2001.¹⁶ A more recent study from the SEER database, including almost 7,000 patients, showed that survival times for glioblastoma patients increased from 12 to 15 months between 2000–2001 and 2005–2006.¹⁷ Another study from the SEER database, including almost 14,000 patients, showed an improvement in median survival time from 8.1 months in 2000–2003 to 9.7 months in 2005–2008.¹⁸ Still, it should be noted that the SEER database covers only 26% of the U.S. population and that access to neuro-oncological treatment is unequal and dependent for example upon socioeconomic factors.¹⁹

A study from the nationwide Norwegian Cancer Registry (covering the whole Norwegian population like the FCR in Finland), including included 1,157 patients, showed that median survival time increased from 8.3 months in 2000–2003 to 10.1 months in 2004–2007.²⁰ Median survival time was even higher among patients receiving adjuvant temozolomide compared to radiotherapy alone (16.2 months vs. 9.0 months).²⁰ A subgroup analysis showed that survival improved in patients 70 years or older, as well. However, this subgroup analysis was compromised by the low number of patients, as only 22 out of 271 (8%) elderly patients received adjuvant temozolomide chemoradiation. In the present study, we could not assess the effect of temozolomide on survival times for the whole population, as the nationwide registries do not contain detailed data on individual treatments. However, the median survival time increased from 7.5 months in 2000–2006 to 9.6 months in 2007–2013 in Finland. These figures are in line with the

previous population-based studies but lower than results from the Danish Neuro-Oncology Register (including 1,364 histopathological confirmed glioblastoma patients from 2009 to 2014), which showed a median overall survival time of 14.3 months for patients older than 70 years and a median survival of 18.6 months for glioblastoma patients between 18 and 59 years.²¹

As expected, we found a relationship between age and survival. For example, in 2007–2013, 1-year survival in patients 70 years or younger was 49% but only 16% in patients older than 70 years. The difference in 1-year mortality was notable even in patients between 61–70 years and older than 70 years (37% vs. 16%, respectively in 2007–2013). If comparing survival in patients between 41–50 years and older than 70 years, survival differences seem even more evident (1-year survival 70% vs 18% in 2007-2013). In two studies from the SEER database, one reported a 1-year survival rate of 19% for glioblastoma patients older than 70 years (study years 1999–2010)²² and a median survival time of 4 months (study years 1994–2002)²³. These figures are in line with our results.

We found that the incidence glioblastoma seems to be increasing, especially among women. The finding is in line with a report from the Central Brain Tumor Registry of the United States (CBTRUS) and the SEER database.^{2,16} The increase in the incidence is probably linked to the higher life-expectancy due to a reduction in cardiovascular deaths and other forms of cancer deaths in Finland.^{5,24} In the light of increasing incidence and population ageing, one question is of increasing importance, namely how to optimally treat elderly glioblastoma patients today and in future. A French RCT, showed that glioblastoma patients 70 years or older receiving adjuvant radiotherapy (50 Gy) had a median survival of 6.8 months compared to 3.9 months in patients receiving supportive care only.²⁵ Importantly, there were no differences in quality of life between patients receiving radiotherapy compared to supportive care only, although almost half of the increased survival time was spent receiving the treatment.²⁵ The NOA-08 trial showed no difference in overall survival for glioblastoma patients 65 years or older treated with adjuvant temozolomide compared to adjuvant conventional radiation therapy (60.0 Gy).²⁶ On the other hand, the Nordic trial showed that conventional radiotherapy (60.0 Gy) was associated with poorer outcomes in comparison to temozolomide monotherapy or hypofractionated radiotherapy (34.0 Gy) in glioblastoma patients ≥ 60 years.²⁷ Further, a recently published RCT, reported that glioblastoma patients 65 years or older had a survival advantage after receiving adjuvant radiotherapy (40.0 Gy) with concomitant temozolomide compared to adjuvant radiotherapy alone.⁷ Despite the fact that the above-mentioned studies were highly selected trials that excluded a number of potential elderly patients, median survival

times for elderly were only 6.8 months²⁵, 9.6 months²⁶, 8.3 months²⁸ and 9.3 months⁷. In contrast to these trials, the nationwide Norwegian Cancer Registry study reported that elderly patients (older than 70 years) receiving adjuvant temozolomide had an improved median survival time (13.4 months).²⁰ In comparison, glioblastoma patients older than 70 years not receiving any adjuvant therapy in the Norwegian study had a median survival of 2.8 months.²⁰ Still, as only 8% of elderly patients received adjuvant temozolomide therapy, this survival benefit is highly selected. In our nationwide study, median survival time was 4.5 months (in 2007–2013) for patients older than 70 years. In the Helsinki University Hospital subgroup analysis, the median survival time of 6 out of 18 elderly (>70 years) patients who received temozolomide was 13.2 months, and 2.5 months for patients who underwent tumor resection but did not follow the temozolomide protocol (results not shown). This suggests that only a minority of elderly (>70 years) patients are pre and postoperatively fit to tolerate and benefit from chemoradiation. A recent population-based study supports this notion by showing that less than half of all glioblastoma patients completes the standard of care.²⁹ Taken together, future studies should focus on defining the subpopulation of elderly, who have the best likelihood of benefitting from tumor resection and subsequent chemoradiation.

Brain tumor resection can be considered as major surgery, particularly for elderly. The only randomized trial looking at the role of tumor resection versus diagnostic biopsy for glioblastoma patients 65 years or older showed a survival benefit for resection as compared to diagnostic biopsy (5.7 months vs. 2.8 months).³⁰ In our subgroup analysis of Helsinki University Hospital patients, we found that in the years of 2005 and 2010, 82% of patients older than 70 years underwent craniotomy and tumor resection. Similar aggressive approaches have been reported elsewhere.³¹ On the other hand, some centers seem to have a more conservative approach. For example, in the Mayo Clinic during 2003–2008, only 50% of all glioblastoma patients 65 years or older underwent tumor resection.³² Further, a study using the SEER database from 1994–2002, showed that 61% of patients 65 years or older underwent tumor resection surgery.²³ Studies including comprehensive nationwide data looking at the role of surgery in elderly glioblastoma patients are lacking.

Following glioblastoma resection, temozolomide treatment is undoubtedly an aggressive treatment approach for elderly, who often have functional impairments already prior to treatment. A study investigated the role of temozolomide in elderly patients with lowered functional status (the ANOCEF phase II trial) in 2007–2009.³³ In the trial, glioblastoma patients 70 years or older with a Karnofsky performance score <70 (need of assistance) receiving

adjuvant temozolomide, had a median survival time of 5.8 months.³³ Patient selection for adjuvant chemotherapy and/or radiation therapy is essential, considering that a notable amount of elderly patient that receive chemoradiation, including temozolomide, experience significant toxicity.^{6,7,33,34} In the internal validation of the Helsinki University Hospital cohort in 2005 and 2010, the use of temozolomide increased from 56% to 92% in patients 70 years or younger and from 13% to 33% in patients older than 70 years. Thus, it is possible that the modest improvement in survival for patients older than 70 years is due to the increase of adjuvant temozolomide use. However, benefits of temozolomide in elderly should be weighed against treatment-related major side-effects, modest increase in survival time, amount of time spent in the hospital, and the high costs³⁵. Furthermore, aggressively treating elderly glioblastoma patients may shift the attention away from end of life care, causing unnecessary suffering.³⁶

Strengths and limitations

Strengths of this study include that it was performed in a country with government-subsided social welfare and healthcare system where socioeconomic factors and personal insurance status do not affect availability and implementation of glioblastoma treatment. Thus, our assessments of incidence of glioblastoma and population-level mortality and survival of glioblastoma patients provide a somewhat unbiased picture of the very recent situation in Finland. Furthermore, we assessed the accuracy of FCR¹⁰ in identifying glioblastoma cases, and the accuracy was high. Combining nationwide cancer registry and hospital information of glioblastoma treatment provides unique possibility to evaluate implications of changes in treatment policy. Some limitations should be acknowledged. First, as the FCR does not contain detailed data regarding treatments we are unable to directly compare pattern of care between groups. Still, the nested cohort analysis provides reliable data regarding treatment standards from one hospital, which can be applied to the other included hospitals as well. Second, the extent of glioblastoma resection is considered an important prognostic factor.³⁷ Routine post-operative MRI studies after glioblastoma surgery were introduced in the middle of the study period. Hence, it was not possible nor statistically sound to assess the role of surgery for all included patients. These are, however, common limitations of large epidemiological nationwide studies like this. Third, we only included patients with a histopathological diagnosis of glioblastoma. Thus, patients dying due to glioblastoma before a histopathological diagnosis could be obtained are not included in the present study (i.e. DCO cases that comprises 4,2% of recorded malignant CNS tumors in the FCR³⁸). Accordingly, the reported survival rates are probably slightly worse and incidence slightly higher than reported here. Fourth, due to the

observational nature of the study (retrospective register-based cohort), we cannot establish any causation between changes in treatment between periods and excess mortality .

In conclusion, In this nationwide study, we found that the incidence of glioblastoma and glioblastoma patient age are increasing and that the overall survival of glioblastoma patients has improved from 2000–2006 to 2007–2013. Survival improved only modestly in elderly glioblastoma patients compared to younger patients and poor overall population-level survival in elderly glioblastoma patients raises concerns whether current treatment strategies for elderly patients are optimal. Given the rapidly aging population in many industrialized countries, studies focusing on elderly glioblastoma patients are urgently needed.

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FIGURE CAPTIONS

Figure 1: Age-standardized (the European Standardized Population in 2013) incidence of glioblastoma (per 100,000 person-years) in Finland in 2000–2013 with 95% confidence intervals. To the left the incidence for men and women and to the right the incidence for men and women separately. Data from the Finnish Cancer Registry.

Figure 2: Comparison of age-standardized cumulative relative survival ratios between persons diagnosed in 2000–2006 (dashed line) compared to 2007–2013 (solid line). To the left all patients, men in the middle men and women to the right. Data from the Finnish Cancer Registry.

Figure 3: Comparison of age-standardized cumulative relative survival ratios between patients over and under 70 years of age diagnosed in during 2000–2006 (dashed line) and 2007–2013 (solid line). To the left all patients, in the middle men and to the left women. Data from the Finnish Cancer Registry.

Table 1: Patient characteristics in 2000–2006 and 2007–2013

Variable	All patients N=2,045	2000–2006 N=893	2007–2013 N=1,152
Age (y), median	63.3	61.4	64.3
Age (y), mean	62.8	61.7	63.6
18-40	83 (4%)	42 (5%)	41 (4%)
41-50	220 (11%)	115 (13%)	105 (9%)
51-60	566 (28%)	280 (31%)	286 (26%)
61-70	657 (32%)	245 (27%)	412 (36%)
71-80	427 (21%)	173 (20%)	254 (22%)
>80	92 (4%)	38 (4%)	54 (5%)
Sex			
Men	1,191 (58%)	524 (59%)	667 (58%)
Women	854 (42%)	369 (41%)	485 (42%)
Categorical variables shown as numbers with percentages. Data from the Finnish Cancer Registry.			

Table 2: Relative excess risk (RER) of death between 2007–2013 and 2000–2006, and relative survival ratios (with 95% confidence intervals) at 1, 3 and 5 years after diagnosis by age, sex and diagnosis period

Outcome	RER		One-year survival (%)		Three-year survival (%)		Five-year survival (%)	
	2007–13 vs. 2000–06	Adjusted p-Value	2000–2006	2007–2013	2000–2006	2007–2013	2000–2006	2007–2013
All patients	0.76 (0.69–0.83)	<0.001	31 (28–34)	41 (38–43)	5 (3–6)	8 (6–9)	2 (1–3)	3 (2–4)
≤70y	0.74 (0.67–0.82)	<0.001	39 (35–42)	49 (46–53)	6 (4–8)	9 (7–12)	3 (2–4)	4 (2–6)
>70y	0.82 (0.68–0.98)	0.053	8 (5–13)	16 (12–20)	1 (0–4)	3 (1–5)	1 (0–3)	1 (0–3)
Age groups								
18–40y	0.92 (0.57–1.48)	0.735	64 (48–77)	68 (52–80)	24 (12–37)	22 (11–36)	12 (4–24)	15 (6–29)
41–50y	0.70 (0.53–0.92)	0.021	49 (39–58)	70 (60–78)	11 (6–17)	16 (10–24)	4 (2–9)	6 (2–12)
51–60y	0.70 (0.59–0.83)	<0.001	40 (35–46)	53 (47–58)	3 (2–6)	8 (5–12)	1 (1–4)	3 (2–6)
61–70y	0.78 (0.66–0.92)	0.007	31 (25–37)	37 (32–42)	4 (2–7)	7 (4–10)	2 (1–4)	2 (1–5)
71–80y	0.83 (0.68–1.01)	0.092	10 (6–15)	18 (14–23)	1 (0–5)	3 (1–6)	1 (0–4)	1 (0–3)
>80y	0.78 (0.51–1.20)	0.335	3 (0–13)	4 (1–12)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Sex and age								
Men	0.79 (0.70–0.89)	<0.001	34 (31–38)	42 (38–45)	5 (3–7)	7 (5–9)	3 (1–4)	2 (1–5)
≤70	0.80 (0.70–0.92)	0.004	43 (38–47)	49 (45–54)	6 (4–9)	8 (6–11)	3 (2–5)	2 (1–4)
>70	0.75 (0.58–0.97)	0.048	6 (3–12)	16 (11–23)	1 (0–5)	3 (1–7)	1 (0–5)	1 (0–5)
Women	0.71 (0.61–0.82)	<0.001	26 (22–31)	39 (35–43)	4 (2–6)	9 (6–12)	1 (1–3)	4 (2–6)
≤70	0.64 (0.54–0.76)	<0.001	33 (27–38)	49 (43–54)	5 (3–8)	12 (8–15)	2 (1–4)	5 (3–9)
>70	0.88 (0.68–1.15)	0.400	11 (6–19)	16 (10–22)	1 (0–7)	3 (1–6)	0 (0–0)	0 (0–0)

Relative excessive risk of death (RER) for glioblastoma patients diagnosed in 2007–2013 compared to those diagnosed in 2000–2006. A RER less than one indicates that patients diagnosed in 2007–2013 had a lower excess risk of death compared to patients diagnosed in 2000–2006 and vice versa.

The estimates are age-standardized and can be compared between the two periods .

One-year, three-year and five-year survival rates are shown as percentages with 95% confidence intervals.

Adjusted p-Values refer to p-values adjusted for multiple testing.

Data from the Finnish Cancer Registry.

Table 3: Median survival times (point estimate with 95% confidence interval) in months

Outcome	Median survival time (95% CI)	
	2000–2006	2007–2013
All patients	7.5 (6.8–8.2)	9.6 (9.1–10.2)
≤70	9.3 (8.6–10.1)	11.7 (11.0–12.5)
>70	3.6 (3.2–4.1)	4.5 (3.8–5.1)
Age group		
18-40	17.0 (11.1–22.0)	19.7 (13.7–25.1)
41-50	11.8 (10.2–13.2)	17.3 (14.5–19.5)
51-60	9.9 (9.2–11.2)	12.4 (11.3–13.8)
61-70	6.7 (5.6–7.8)	9.3 (8.3–9.9)
71-80	4.2 (3.6–5.2)	5.2 (4.5–5.8)
>80	2.0 (1.3–2.6)	2.3 (1.4–3.1)
Sex and age		
Men	8.1 (7.1–8.9)	9.9 (9.2–10.8)
≤70	9.8 (8.6–11.1)	11.8 (10.9–12.7)
>70	3.6 (3.1–4.3)	4.8 (3.8–5.5)
Women	6.7 (5.7–7.8)	9.2 (8.2–10.1)
≤70	8.9 (7.8–9.8)	11.7 (10.3–13.3)
>70	3.7 (2.8–4.6)	4.2 (3.3–5.2)
The estimates are age-standardized and can be compared between the two periods. Survival time shown in months.		
Data from the Finnish Cancer Registry.		

Fig 1

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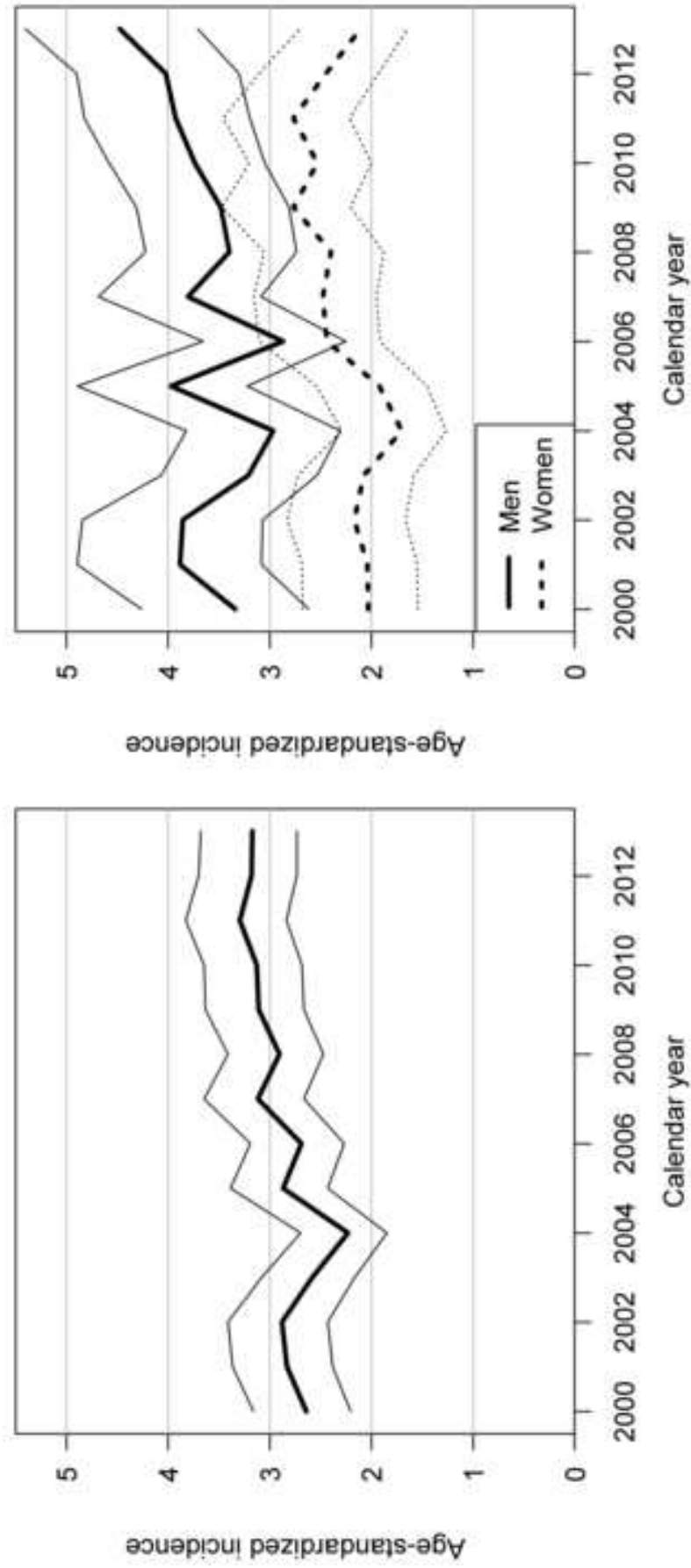
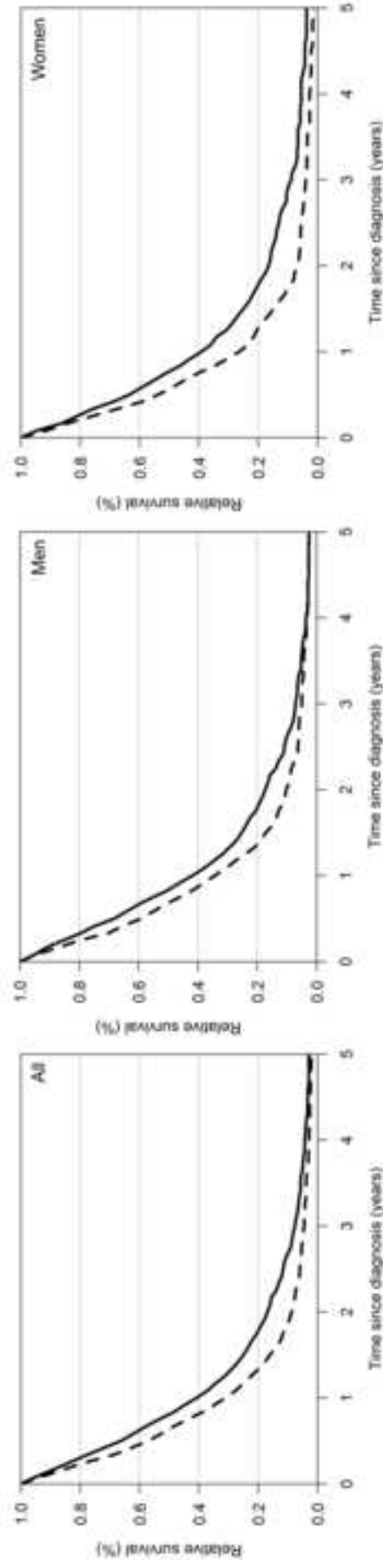
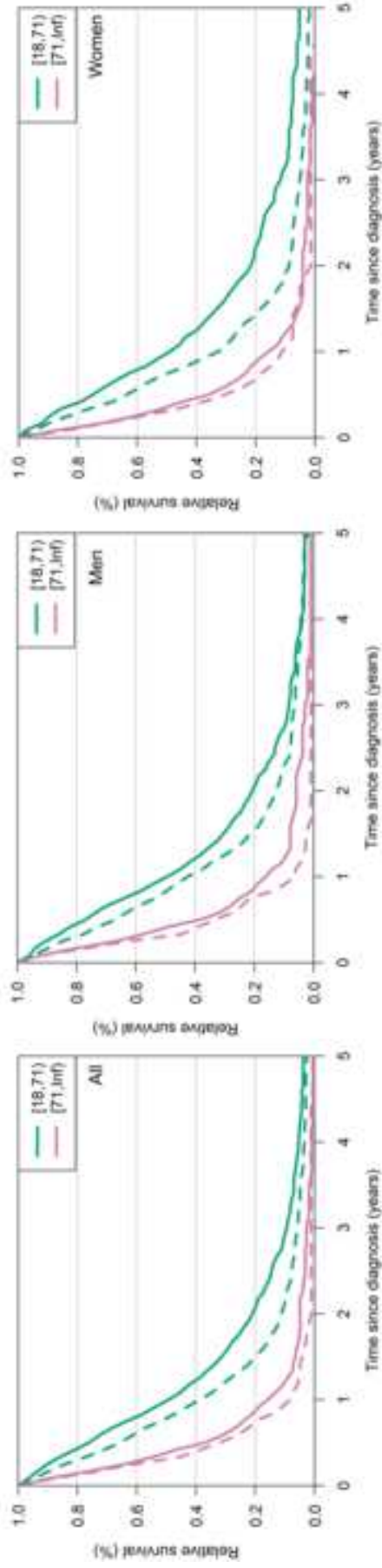


Fig 2

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Electronic Supplementary Material 1: Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

Electronic Supplementary Material 2: Age-specific incidence of glioblastoma (per 100,000 person-years) in Finland in 2000–2013.

Electronic Supplementary Material 3: Comparison of age-specific cumulative relative survival ratios between patients diagnosed during 2000–2006 (dashed line) compared to 2007–2013 (solid line). The relative excess risk (RER) of death decreased significantly ($p < 0.05$) in the 41–50 year, 51–60 year and 61–70 year age subgroups. No statistically significant change in RER of death was noted for the other age groups. Data from the Finnish Cancer Registry.

Electronic Supplementary Material 2: Age-specific incidence of glioblastoma (per 100,000 person-years) in Finland in 2000–2013.

Electronic Supplementary Table 1: Age-specific incidence of glioblastoma (per 100,000 person-years; point estimate with 95% confidence interval) in Finland in 2000–2013

Age group	Incidence (95% CI)			
	Men		Women	
<15	0.14	(0.07, 0.27)	0.08	(0.03, 0.20)
15-24	0.19	(0.10, 0.36)	0.22	(0.12, 0.42)
25-29	0.25	(0.11, 0.56)	0.27	(0.12, 0.59)
30-34	0.38	(0.20, 0.73)	0.31	(0.15, 0.65)
35-39	0.94	(0.62, 1.41)	0.55	(0.32, 0.95)
40-44	1.65	(1.23, 2.23)	0.75	(0.48, 1.18)
45-49	2.74	(2.18, 3.44)	1.96	(1.49, 2.57)
50-54	4.91	(4.15, 5.81)	2.51	(1.98, 3.18)
55-59	7.72	(6.73, 8.86)	4.51	(3.77, 5.39)
60-64	9.08	(7.92, 10.42)	5.32	(4.47, 6.34)
65-69	10.72	(9.27, 12.39)	8.37	(7.18, 9.77)
70-74	10.16	(8.59, 12.02)	6.55	(5.44, 7.89)
75-79	12.02	(10.04, 14.40)	6.69	(5.50, 8.14)
80-84	6.80	(4.99, 9.27)	3.88	(2.90, 5.20)
≥85	2.90	(1.56, 5.39)	1.88	(1.20, 2.94)

Incidence shown per 100,000 person-years with 95% confidence intervals.
Data from the Finnish Cancer Registry.

