Surgical Management of Malignant Glioma
Evidence Summary Report #9-8

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and members of the Neuro-Oncology Disease Site Group

ORIGINAL EVIDENCE SUMMARY: January 14, 2004
MOST RECENT LITERATURE SEARCH: July 2004

Literature searches conducted since the completion of the original evidence summary have found no new evidence relevant to the evidence summary.

An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base practice recommendations.

SUMMARY

Question
What is the most appropriate surgical management at initial presentation of glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligoastrocytoma, and anaplastic oligodendroglioma (i.e. supratentorial malignant glioma) in adults? Outcomes of interest were survival, prognostic factors for survival, complications of surgical interventions, functional independence, and quality of life.

Target Population
This evidence summary applies to adult patients with supratentorial malignant glioma who have not received any prior therapy.

Opinions of the Neuro-oncology Disease Site Group
The lack of sufficient high quality evidence precludes definitive recommendations. Instead, the Neuro-oncology DSG offers the following opinions based on the evidence reviewed:

• There is no high quality evidence to support or refute the statement that resection is better than biopsy in terms of survival and quality of life.
• Patients who are young (less than 50 years) are more likely to undergo aggressive resection than older patients.
• Patients with ‘accessible’ tumours are more likely to undergo resections than biopsies.
• If resection is perceived to be safe and feasible in patients with malignant glioma, then resection, rather than biopsy, seems to be the preferred surgical procedure at this time.
• There are no high-quality randomized controlled trials examining the role of extent of resection in relation to overall survival and quality of life in patients with malignant glioma. Such trials would be of benefit to the neuro-oncology community and the patients they serve. Patients and surgeons should be encouraged to take part in such trials.
Methods

Entries to MEDLINE (1985 to June 2004), EMBASE (1985 to week 25, 2004), CANCERLIT (1985 to October 2002), and Cochrane Library (2004, Issue 2) databases were systematically searched for evidence relevant to this evidence summary report.

Evidence was selected and reviewed by three members of the Practice Guidelines Initiative’s Neuro-oncology Disease Site Group and methodologists. This evidence summary report has been reviewed and approved by the Neuro-oncology Disease Site Group, which is comprised of medical and radiation oncologists, neuro-oncologists, neurosurgeons, a neuroradiologist, an oncology nurse, and a patient representative.

External review by Ontario practitioners is obtained for all evidence summary reports through a mailed survey. Final approval of the evidence summary report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each evidence summary report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original evidence summary.

Key Evidence

- One systematic review, one randomized trial, six prospective studies, and 11 retrospective studies examined the extent of surgery on survival in adults with supratentorial malignant glioma. The most commonly identified prognostic factors for survival in adults with malignant glioma are extent of resection, age, and Karnofsky performance status.

- Most studies reported a significant improvement in median survival in patients undergoing resection compared to patients undergoing biopsies. However, these studies are of low quality and contain several biases, most predominantly selection bias, in which patients with poorer prognoses underwent biopsies and patients with better prognoses underwent resections.

- Patients undergoing gross total resection seem to have minimally improved measures of quality of life compared with patients undergoing any resection less than total.

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PREAMBLE: About Our Evidence Summary Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care (PEBC). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹

An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base a practice guideline. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. For example, the evidence comes from uncontrolled studies, from studies with control groups that are not relevant to current practice in Ontario, or from subgroup analyses, or the evidence consists solely of preliminary results from ongoing trials. The PEBC will monitor the scientific literature and will develop a practice guideline on this topic when more evidence becomes available.

This evidence summary report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of an evidence summary by the Coordinating Committee does not necessarily mean that the evidence summary has been adopted as a practice policy of CCO. The decision to adopt an evidence summary as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

For the most current versions of the evidence summary reports and information about the PGI and the Program, please visit our Internet site at:
http://www.cancercare.on.ca/access_PEBC.htm
For more information, contact our office at:
Phone: 905-525-9140, ext. 22055
Fax: 905-522-7681

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I. QUESTION
What is the most appropriate surgical management at initial presentation of glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligoastrocytoma, and anaplastic oligodendroglioma (i.e. supratentorial malignant glioma) in adults? Outcomes of interest were survival, prognostic factors for survival, complications of surgical interventions, and quality of life.

II. CHOICE OF TOPIC AND RATIONALE

In 2002, there were an estimated 2,400 new cases of brain cancer and 1,600 deaths due to brain cancer in Canada (1). The prognosis of patients with supratentorial malignant glioma, which includes glioblastoma multiforme and anaplastic astrocytoma, is poor and warrants an investigation into optimal surgical treatment (2). The role of surgery in the treatment of supratentorial malignant glioma remains unclear, and reports of surgical outcomes in the medical literature offer conflicting results (3). Some neurosurgeons recommend that gliomas be resected as extensively as possible (4); however, there is limited evidence to suggest that aggressive surgical management significantly prolongs survival in adults with malignant gliomas (5). There is also limited evidence to suggest that aggressive surgical management significantly improves quality of life or functional independence. Also, some studies that have attempted to compare biopsy versus resection have measured extent of resection according to a surgeon's impression, rather than using an objective measure, such as magnetic resonance imaging (MRI) or computed tomography (CT) scans (6). The extent of surgery (biopsy or resection) offered to patients with malignant glioma depends largely upon the surgeon and the hospital. The Neuro-oncology Disease Site Group (Neuro-oncology DSG) chose to develop an evidence summary on the appropriate surgical management of malignant glioma to attempt to establish the most appropriate surgical management for adults with malignant glioma. The most appropriate surgical management is the surgery that maximizes survival, functional status, and quality of life.

III. METHODS

Evidence Summary Development

This evidence summary report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario’s Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (7). Evidence was selected and reviewed by three members of the PGI’s Neuro-oncology DSG and methodologists. Members of the Neuro-oncology DSG disclosed potential conflict of interest information.

The evidence summary report is a convenient and up-to-date source of the best available evidence on the surgical management of malignant glioma developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. In contrast to the practice guidelines, the body of evidence in an evidence summary is less mature and is comprised of data primarily from non-randomized controlled trial data or data available only in abstract form. This precludes the development of definitive recommendations, and instead, opinions of the DSG are offered. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all evidence summaries through a mailed survey consisting of items that address the quality of the evidence summary report, the interpretation of the available evidence, and whether there is a need to develop an evidence-based practice guideline when sufficient evidence is available. Final approval of the evidence summary is obtained from the Practice Guidelines Coordinating Committee (PGCC).
The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

**Literature Search Strategy**

MEDLINE (1985 to June 2003), CANCERLIT (1985 to October 2002) and the Cochrane Library (2003, Issue 1) databases were searched using “glioma/su” (Medical subject heading (MeSH)), plus the keywords “glioma”, “glioblastoma”, “astrocytoma” combined with “surgical procedures, operative”. These terms were then combined with the search terms for the following study designs and publication types: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and controlled clinical trials. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (www.cancer.gov/clinicaltrials/finding) was searched for reports of new or ongoing trials. Relevant articles were selected and reviewed by three reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnsw/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/) were searched for existing evidence-based practice guidelines.

**Update**

The original literature search has been updated using MEDLINE (through June 2004), EMBASE (through week 25 2004), the Cochrane Library (Issue 2, 2004), and the 2004 proceedings of the annual meeting of the American Society of Clinical Oncology.

**Inclusion Criteria**

Articles were selected for inclusion in this evidence summary if they were:

1. Systematic reviews, meta-analyses, practice guidelines, or randomized controlled trials (RCTs) comparing extents of surgery (i.e. gross total resection versus biopsy) for supratentorial malignant glioma in adults or;

2. Prospective phase II trials or retrospective studies reporting on the outcome of surgery, resection or biopsy for supratentorial malignant glioma in adults, reporting at least one of the following outcomes: survival, prognostic factors for survival, quality of life, functional independence, or complications.

3. Explicit descriptions of the use of early postoperative imaging in order to judge the extent of resection as opposed to the surgeon’s impression.

**Exclusion criteria**

1. Letters, editorials and conference abstracts were not considered.

2. Papers published in a language other than English were not considered.

3. Trials where the majority of patients were being treated for conditions other than cancer or the proportion of patients with malignant glioma was not clearly described were not included.

4. Studies that included patients with malignant gliomas who were less than 15 years of age and that did not report results separately for patients older than 15 years were excluded.

**Synthesizing the Evidence**

Data from the studies included in this evidence summary were not pooled because of the heterogeneity of the presentation of the outcomes. Most of the studies indicated median survival time (MST), but they reported survival for a variety of dependent variables (various descriptions of extent of resection and size of residual tumour, described in Table 1); thus the results could not be pooled.
IV. RESULTS

Literature search results

Nineteen studies met the inclusion criteria of this evidence summary (2,8-25), including one Cochrane review (25). One small RCT compared biopsy to resection in elderly patients with malignant glioma (24). Eleven of the studies were retrospective (2,8-17), and the remaining six studies were prospective phase II trials (18-23). The studies included in this evidence summary are described in Table 1.

In 2002, Metcalfe & Grant (25) published a Cochrane review of biopsy versus resection for malignant glioma. Their inclusion criteria included only RCTs, and they were unable to locate any RCTs that compared biopsy to resection in adults with malignant glioma. They concluded that randomized trials need to be developed to establish recommendations.

In 1991, Quigley and Maroon (6) published a systematic review describing the relationship between survival and the extent of resection in patients with malignant gliomas. They found 20 studies with a total of 5,691 patients. Unfortunately, all the studies included in their systematic review used the surgeon’s impression to measure the extent of resection as opposed to using an objective measure of resection, like MRI or CT.

Update

No new studies that met the inclusion criteria for this evidence summary were identified in the update literature searches.
<table>
<thead>
<tr>
<th>Study [type of study]</th>
<th>No. of patients</th>
<th>Age of patients (years)</th>
<th>Preoperative KPS</th>
<th>Degree of resection</th>
<th>Postop imaging</th>
<th>Postop therapy</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vuorinen, 2003 (24) [RCT]</td>
<td>10 (grade IV) 13 (grade III, 10 grade IV)</td>
<td>median 70 (range 66-80) median 72 (range 67-79)</td>
<td>mean 78 mean 70</td>
<td>resection biopsy</td>
<td>CT/MRI</td>
<td>RT</td>
<td>24 weeks (95% CI 21-40) 12 weeks (95% CI 8-22)</td>
</tr>
<tr>
<td>Lacroix, 2001 (2) [RR]</td>
<td>416 (100% GBM) 82 (100% GBM)</td>
<td>mean 53 mean 57 (range 22-85)</td>
<td>75% &gt;70 mean 63.3 (range 30-90)</td>
<td>197 (47%) &gt;98% resection 219 (53%) &lt;98% resection</td>
<td>MRI</td>
<td>RT +/- chemoT</td>
<td>56 weeks &gt; 98% resection 38 weeks &lt; 98% resection p=0.02</td>
</tr>
<tr>
<td>Shinoda, 2001 (8) [RR]</td>
<td>416 (100% GBM) 82 (100% GBM)</td>
<td>mean 53 mean 57 (range 22-85)</td>
<td>75% &gt;70 mean 63.3 (range 30-90)</td>
<td>36 (44%) GTR 46 (56%) &lt; GTR</td>
<td>MRI</td>
<td>RT +/- chemoT</td>
<td>60 weeks GTR 43 weeks &lt; GTR p=0.0002</td>
</tr>
<tr>
<td>Keles, 1999 (9) [RR]</td>
<td>92 (100% GBM)</td>
<td>median 51 (range 15-80)</td>
<td>mean for all levels of resection &gt; 85 attempted GTR</td>
<td>41 (18%) GTR 85 (38%) PR 99 (44%) biopsy</td>
<td>CT/MRI</td>
<td>RT +/- chemoT</td>
<td>32 weeks &gt;25% resection 57 weeks 25-49% resection 63 weeks 50-74% resection 89 weeks 75-99% resection 93 weeks 100% resection p&lt;0.0005</td>
</tr>
<tr>
<td>Kreth, 1999 (10) [RR]</td>
<td>225 (100% GBM)</td>
<td>resection mean 57 biopsy mean 58</td>
<td>resection mean 72 biopsy mean 70</td>
<td>41 (18%) GTR 85 (38%) PR 99 (44%) biopsy</td>
<td>CT</td>
<td>RT</td>
<td>37 weeks resection 33 weeks biopsy p=0.09</td>
</tr>
<tr>
<td>Mohan, 1998 (11) [RR]</td>
<td>102 (100% GBM)</td>
<td>mean 75 (range 70-87)</td>
<td>mean 70.5</td>
<td>7 (7%) GTR 42 (41%) STR 53 (52%) biopsy</td>
<td>CT/MRI</td>
<td>RT +/- chemoT</td>
<td>75 weeks GTR 31 weeks STR 15 weeks biopsy p&lt;0.0001</td>
</tr>
<tr>
<td>Kowalczuk 1997 (12) [RR]</td>
<td>75 (69% GBM, 31% AA)</td>
<td>mean 53</td>
<td>mean 76</td>
<td>29 GTR 33 STR 13 biopsy</td>
<td>CT/MRI</td>
<td>RT +/- chemoT</td>
<td>116 weeks GTR 143 weeks STR 56 weeks biopsy p=0.039 (resection vs biopsy)</td>
</tr>
<tr>
<td>Kiwit, 1996 (13) [RR]</td>
<td>80 (68% GBM, 32% MG)</td>
<td>surgery mean 60 biopsy mean 58</td>
<td>surgery mean 54 biopsy mean 55</td>
<td>40 surgery 40 biopsy</td>
<td>CT/MRI</td>
<td>RT</td>
<td>42 weeks surgery 26 weeks biopsy p&lt;0.05</td>
</tr>
<tr>
<td>Slotman, 1996 (18) [Pros]</td>
<td>30 (100% GBM)</td>
<td>mean 56 (range 27-75)</td>
<td>26 (87%) &gt; 70</td>
<td>12 (40%) &gt;90% resection 8 (27%) 75-90% resection 8 (27%) &lt;75% resection 2 (6%) biopsy</td>
<td>CT/MRI</td>
<td>RT</td>
<td>42 weeks &gt;75% resection 31 weeks &lt;75% resection p&lt;0.05</td>
</tr>
<tr>
<td>Study [type of study]</td>
<td>No. of patients</td>
<td>Age of patients (years)</td>
<td>Preoperative KPS</td>
<td>Degree of resection</td>
<td>Postop imaging</td>
<td>Postop therapy</td>
<td>Median Survival</td>
</tr>
<tr>
<td>----------------------</td>
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</tr>
<tr>
<td>Nitta, 1995 (19) [Pros]</td>
<td>101 (68% GBM, 33% AA)</td>
<td>mean 55 (range 16-79)</td>
<td>100% &gt; 60</td>
<td>26 (26%) GTR 36 (36%) STR 39 (38%) PR</td>
<td>CT/MRI</td>
<td>RT + chemoT</td>
<td>87 weeks GTR 52 weeks STR 43 weeks PR (p&lt;0.01 for GTR vs STR, and GTR vs PR; p=0.428 for STR vs PR)</td>
</tr>
<tr>
<td>Quigley, 1995 (14) [RR]</td>
<td>63 (70% GBM, 30% AA)</td>
<td>mean 58</td>
<td>NR</td>
<td>9 (14%) GTR 31 (49%) STR 23 (37%) biopsy</td>
<td>CT/MRI</td>
<td>NR</td>
<td>116 weeks GTR 48 weeks STR 43 weeks biopsy GTR vs biopsy p&lt;0.001 STR vs biopsy p=0.35</td>
</tr>
<tr>
<td>Albert, 1994 (20) [Pros]</td>
<td>60 (95% GBM, 5% AA)</td>
<td>mean 53</td>
<td>NR</td>
<td>attempted GTR</td>
<td>CT/MRI</td>
<td>RT</td>
<td>46 weeks residual tumour 92 weeks without residual tumour p=0.0002</td>
</tr>
<tr>
<td>Kelly, 1994 (15) [RR]</td>
<td>128 (100% GBM)</td>
<td>resection mean 72 biopsy mean 70</td>
<td>mean 84</td>
<td>40 resection 88 biopsy</td>
<td>CT</td>
<td>RT</td>
<td>27 weeks resection 15 weeks biopsy p=0.008</td>
</tr>
<tr>
<td>Rostomily, 1994 (21) [Pros]</td>
<td>51 (61% GBM, 39% AA)</td>
<td>mean 42</td>
<td>mean &amp; median 80 (range 60-100)</td>
<td>31 resection 20 no resection</td>
<td>CT/MRI</td>
<td>chemoT</td>
<td>30 weeks resection GBM 40 weeks no resection GBM (no p level) 202 weeks resection AA 49 weeks no resection AA (no p level)</td>
</tr>
<tr>
<td>Bricolo, 1990 (22) [Pros]</td>
<td>107 (80% GBM, 20% AA)</td>
<td>NR</td>
<td>NR</td>
<td>66 (62%) GTR 41 (38%) PR</td>
<td>CT</td>
<td>RT</td>
<td>1 year survival for GTR 60%, PR 24%</td>
</tr>
<tr>
<td>Ammirati, 1987 (23) [Pros]</td>
<td>31 (68% GBM, 32% AA)</td>
<td>median 50</td>
<td>median 70</td>
<td>19 (61%) GTR 12 (39%) STR</td>
<td>CT</td>
<td>NR</td>
<td>90 weeks GTR 43 weeks STR p&lt;0.001</td>
</tr>
<tr>
<td>Ciric, 1987 (16) [RR]</td>
<td>42 (79% GBM or AA, 21% other)</td>
<td>median 58</td>
<td>median 70</td>
<td>27 (62%) GTR 10 (24%) STR 6 (14%) PR</td>
<td>CT</td>
<td>NR</td>
<td>NR by surgical intervention</td>
</tr>
<tr>
<td>Andreou, 1983 (17) [RR]</td>
<td>115 (100% AA)</td>
<td>mean 55</td>
<td>NR</td>
<td>attempted GTR</td>
<td>CT</td>
<td>NR</td>
<td>Length of survival increases, as extent of residual tumour decreases p&lt;0.01</td>
</tr>
</tbody>
</table>

Note: AA, anaplastic astrocytoma; chemoT, chemotherapy; CI, confidence interval; CT, computed tomography; GBM, glioblastoma multiforme; GTR, gross total resection; LGG, low-grade glioma; MG, malignant glioma; MRI, magnetic resonance imaging; MST, median survival time; NR, not reported; postop, postoperative; PR, partial resection; Pros, prospective study; RCT, randomized controlled trial; RR, retrospective study; RT, radiotherapy; STR, subtotal resection; vs, versus.
Outcomes

Prognostic Factors for Survival

Six retrospective studies (2,8-10,12,13) and one prospective phase II study (21) have attempted to define the best performing prognostic factors for survival in adult patients with malignant glioma. The most commonly identified prognostic factors for survival among these studies were extent of resection, age and Karnofsky performance status (KPS). Table 2 outlines the prognostic factors for survival in adult patients with malignant gliomas. The studies used both multivariate and univariate analyses to establish the independent contributions of the prognostic factors.

In Kreth et al’s (10) multivariate analyses, they reported that KPS, location of tumour, tumour size, and extent of resection were not significant predictors of survival. They identified age only as a predictor of survival. In their univariate analysis, KPS was a significant predictor of survival. However, it was not significant in the multivariate analyses because KPS was significantly correlated with age (p<0.01). Similarly, Shinoda et al (8) reported that both age and KPS were significant prognostic factors of survival on univariate analyses. However, they also reported that KPS was a significant prognostic factor of survival in multivariate analyses (p=0.04), and age was not a significant prognostic factor (p=0.06).

Table 2. Prognostic factors of survival in adult patients with malignant glioma using multivariate analyses.

<table>
<thead>
<tr>
<th>Study</th>
<th>Extent of resection</th>
<th>Age</th>
<th>KPS</th>
<th>Tumour location</th>
<th>Postoperative tumour volume</th>
<th>Postoperative complications</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacroix, 2001 (2)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>✓ degree of necrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓ pre-operative MRI</td>
</tr>
<tr>
<td>Shinoda, 2001 (8)</td>
<td>✓</td>
<td>--</td>
<td>✓</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Keles, 1999 (9)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>--</td>
<td>✓</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Kreth, 1999 (10)</td>
<td>--</td>
<td>✓</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Kowalczuk 1997 (12)</td>
<td>--</td>
<td>✓</td>
<td>✓</td>
<td>--</td>
<td>--</td>
<td>✓</td>
<td>✓ RT dose</td>
</tr>
<tr>
<td>Kiwit, 1996 (13)</td>
<td>--</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Rostomily, 1994 (21)</td>
<td>✓</td>
<td>--</td>
<td>✓</td>
<td>--</td>
<td>✓</td>
<td>--</td>
<td>✓ prior chemotherapy</td>
</tr>
</tbody>
</table>

Note: KPS, Karnofsky performance status; MRI, magnetic resonance imaging; RT, radiation therapy

Biopsy versus Resection

One randomized controlled trial (24), six retrospective studies (10-15), and one prospective phase II study (18) compared biopsy to resection in adults with malignant gliomas.

The randomized trial by Vuorinen et al (24) compared resection to biopsy in 30 elderly patients (>65 years) with malignant glioma. Seven of the patients included in the trial did not have malignant glioma on further investigation. Thus, the results for 23 patients with malignant glioma were presented. Ten patients were randomized to undergo resection, and 13 were randomized to undergo biopsy. Vuorinen et al observed longer median survival for the patients undergoing resection compared with those undergoing biopsy (24 weeks versus 12 weeks, respectively, p=0.035). There are several problems with this randomized trial, including concerns regarding the patients that were included (23% did not have malignant glioma) and a small sample size.
Vuorinen et al do not specify in the study design if the study was powered to detect a significant difference between groups.

The retrospective study by Kreth et al (10) was the only one to report no significant difference in median survival favouring resection over biopsy (p=0.09). Quigley et al's retrospective study (14) compared gross total resection (GTR) to biopsy and subtotal resection (STR) to biopsy. When they compared GTR to biopsy, there was a significant difference in median survival in favour of patients undergoing GTR (p<0.001). However, when Quigley et al (14) compared STR to biopsy, they did not report a significant difference in median survival (p=0.35). All the other studies that compared resection to biopsy showed significant differences in favour of resection (11-13,15,18). The results of these studies need to be interpreted cautiously, because four of these studies are retrospective (11-13,15), and the prospective study only included 30 patients (18).

In the past, there has been some bias regarding the elderly and surgery. It was thought the elderly could not tolerate resection, and thus biopsy was the alternative. Two of the studies that compared survival in patients undergoing either resection or biopsy focused on elderly patients (11,15). According to the results from Mohan et al's retrospective study (11), patients older than 70 years with a KPS score greater than 70 should be treated aggressively because they have an increased chance of survival. However, in their retrospective study, the extent of surgery was based on tumour location, size, patient's medical condition, and past medical history. Thus, the more prognostically favourable patients underwent resection, and the prognostically less favourable patients underwent biopsy. It is not surprising that the patients who underwent resection had a longer median survival than the patients undergoing biopsies (p<0.001). Kelly et al (15) found a statistically significant improvement in median survival benefit for resection compared with biopsy in patients older than 65 years (p=0.008); however, they acknowledged several potential biases using retrospective data, including the method of selecting patients for resection versus biopsy.

**Gross Total Resection versus Subtotal or Partial Resection**

Five retrospective studies (2,8,9,11,14) and five prospective studies (18-20,22,23) compared GTR to STR or partial resection (PR) in terms of survival (Table 3). STR and PR are terms that are used relatively interchangeably; however, STR often implies greater resection than PR. All the studies, except for a preliminary prospective analysis by Bricolo et al (22), reported a significant improvement in survival in the GTR patients compared to the patients undergoing STR or PR (p<0.05). Although no p levels were reported, Bricolo et al (22) found that 60% of patients undergoing GTR were alive one year after surgery compared to only 24% after undergoing STR. Quigley et al (14) reported that patients undergoing GTR had significantly longer median survivals than patients undergoing STR (p<0.001); however, there were only nine patients in the GTR group and 31 patients in the STR group.

The retrospective study by Keles et al (9) reported survival for five separate resection groups: 100%, 75% to 99%, 50% to 74%, 25% to 49%, and <25% resection. Keles et al stated that the greater the extent of resection, the greater the median survival (p<0.0005). However, Keles et al did not report the point at which the extent of resection was insignificant. For instance, Keles et al did not report if median survival was significantly different between the 25% to 49% resection and the 75% to 99% resection groups.

Of the 10 studies, only two studies (22,23) explicitly stated that prior to surgery the patients undergoing GTR were comparable to those undergoing STR or PR in terms of age and functional status (measured by KPS). Both Quigley et al (14) and Mohan et al (11) indicated that the choice of surgical treatment was dependent upon tumour size, tumour location and perceived surgical risk. It is not surprising, therefore, that younger patients with smaller, accessible tumours were more likely to undergo GTR and live longer than were older patients with larger tumours in less accessible (higher risk) locations.
Shinoda et al (8) reported the extent of surgery according to stage of disease. Gross total resection was performed in over 60% of the stage I and II patients, but in none of the stage III patients. Shinoda et al concluded by recommending that stage III patients should not undergo GTR, but they did not present any results of any stage III patients undergoing GTR.

The remaining studies attempted GTR in all patients but did not report the preoperative characteristics (age, KPS, tumour location, size) of the patients who underwent GTR compared to those who underwent STR or PR. As would be expected, Slotman et al (18) reported that younger patients (<50 years) were more likely to have GTR than were older patients.

Nitta et al (19) observed that GTR significantly increased survival in patients with glioblastoma multiforme when compared to patients with glioblastoma multiforme who underwent PR or STR (p<0.01). However, there was no survival difference between GTR, PR and STR in patients with anaplastic astrocytoma (19). Rostomily et al (21) compared patients who had undergone resections with patients who did not undergo any surgery and found the opposite effect of Nitta et al. Rostomily et al (21) who reported that glioblastoma patients with resection survived a median of 30 weeks versus 40 weeks for glioblastoma patients without resection. Anaplastic astrocytoma patients who had undergone resection survived a median of 202 weeks versus 49 weeks for anaplastic astrocytoma patients without resection (no p level reported) (21).

Table 3. Studies comparing gross total resection to subtotal or partial resection: median survival.

<table>
<thead>
<tr>
<th>Study [type of study]</th>
<th>No. of patients</th>
<th>Median survival GTR (n)</th>
<th>Median survival STR/PR (n)</th>
<th>p level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacroix, 2001 (2) [RR]</td>
<td>416</td>
<td>56 weeks (197) [≥ 98% resection]</td>
<td>38 weeks (219) [&lt;98% resection]</td>
<td>0.02</td>
</tr>
<tr>
<td>Shinoda, 2001 (8) [RR]</td>
<td>82</td>
<td>60 weeks (36)</td>
<td>43 weeks (46)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Keles, 1999 (9) [RR]</td>
<td>92</td>
<td>93 weeks (23) [100% resection]</td>
<td>32 weeks (25) [≥25% resection]</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>57 weeks (21) [25-49% resection]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>63 weeks (18) [50-74% resection]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>89 weeks (20) [75-99% resection]</td>
<td></td>
</tr>
<tr>
<td>Mohan, 1998 (11) [RR]</td>
<td>102 (53 biopsy)</td>
<td>75 weeks (7)</td>
<td>32 weeks (42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Slotman, 1996 (18) [Pros]</td>
<td>30</td>
<td>42 weeks (20) [≥75% resection]</td>
<td>31 weeks (10) [&lt;75% resection]</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Nitta, 1995 (19) [Pros]</td>
<td>101</td>
<td>87 weeks (26)</td>
<td>52 weeks (36) [STR]</td>
<td>&lt;0.01 b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>43 weeks (39) [PR]</td>
<td></td>
</tr>
<tr>
<td>Quigley, 1995 (14) [RR]</td>
<td>63 (23 biopsy)</td>
<td>116 weeks (9)</td>
<td>48 weeks (31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albert, 1994 (20) [Pros]</td>
<td>60</td>
<td>92 weeks (NR) [no residual tumour]</td>
<td>46 weeks (NR) [residual tumour]</td>
<td>0.0002</td>
</tr>
<tr>
<td>Bricolo, 1990 (22) [Pros]</td>
<td>107</td>
<td>60% 1 year survival (66)</td>
<td>24% 1 year survival (41)</td>
<td>NR</td>
</tr>
<tr>
<td>Ammirati, 1987 (23) [Pros]</td>
<td>31</td>
<td>90 weeks (19)</td>
<td>43 weeks (12)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: GTR, gross total resection; NR, not reported; PR, partial resection; Pros, prospective study; RR, retrospective review; STR, subtotal resection

* Keles et al (9) do not report which extents of resection were compared.

b GTR vs STR or PR

Complications of Surgical Procedures

There was only one study identified that reported the complications of surgical procedures in adults with malignant glioma. In Kelly et al’s study (15), three of 88 (3%) patients undergoing biopsies had hematomas postoperatively; two of these patients died within two weeks of surgery.
Two additional (2%) biopsy patients died within 30 days of surgery (15). In the same study, one of 40 (2%) patients undergoing resection died of pulmonary emboli within 30 days of surgery (15).

**Quality of Life or Functional Independence**

There were four retrospective studies (8,9,13,15) and one prospective study (23) that addressed quality of life or functional status. The study by Ammirati et al (23) was the only one to use the term “quality of life”. The four retrospective studies reported measures of functional status pre- and postoperatively (8,9,13,15). Ammirati et al did not report measures of emotional status (e.g. depression) but did report measures of functional independence.

Ammirati et al (23) included 31 patients in their study, 19 of whom underwent GTR and 12 STR. Pre-operatively, all the patients were comparable in terms of age, sex, KPS, and tumour location. Ammirati et al reported that 21 patients were independent postoperatively (KPS>80). However, they did not specify how many of these independent patients underwent GTR versus STR. Ammirati et al reported that the independent patients who underwent GTR were independent longer than the patients who underwent STR (185 weeks and 12.5 weeks, respectively, p=0.007). This is a large difference in functional independence; however, there was probably an immense selection bias. Patients who were functionally well, with tumours in non-eloquent brain, would have total resections as compared to patients with poor function, with tumours in hard to reach/eloquent brain, who would be selected for biopsy only. The latter group would be predicted to have a poorer outcome based on their clinical presentation and KPS, thus obscuring the value of surgery. Similarly, the patients who were semi-independent postoperatively (KPS>60) and had undergone GTR were semi-independent longer than the patients who were semi-independent postoperatively who had undergone STR (68 weeks and 20 weeks, respectively, p=0.001). These results are also most likely biased on the ability to perform resection versus biopsy. This was a very small study that was subject to several biases, including extent of surgery completed. Ammirati et al did not specify how patients were selected to undergo GTR or STR.

Keles et al (9) measured both preoperative and postoperative KPS in 92 patients with glioblastoma multiforme. They reported results for five separate subgroups: 100%, 75% to 99%, 50% to 74%, 25% to 49%, and <25% resection. KPS scores decreased in every subgroup after surgery by a median of five points, except in the 100% resection group where there was no change observed in KPS scores. However, the median pre- and postoperative KPS scores were above 80 in all subgroups. Kiwit et al’s (13) comparison of pre- and postoperative KPS scores reported that the mean KPS for the 40 patients undergoing biopsy decreased by two points from 55 to 53. In the group of 40 patients undergoing resection, KPS increased from 54 to 58. The statistical or clinical significance of these findings is uncertain and was not presented.

Shinoda et al (8) measured neurological deterioration in patients with malignant glioma undergoing surgery. They defined deterioration as decreased motor, verbal, or cognitive function for more than three weeks after surgery. They reported that two of 36 patients undergoing GTR suffered from neurological deterioration and seven of 46 patients who underwent less than GTR suffered from neurological deterioration postoperatively. The study by Shinoda et al was a small retrospective study that was subject to several biases, including extent of surgery completed. Shinoda et al did not specify how patients were selected to undergo GTR or STR. In Kelly et al’s (15) retrospective study, they reported that three of 80 (4%) patients undergoing biopsy and two of 40 (5%) patients undergoing resection experienced “worsening neurological deficit” postoperatively. However, Kelly et al did not define how they established neurological function.

V. **INTERPRETIVE SUMMARY**

In spite of an extensive literature review on the value of cytoreductive surgery for malignant gliomas, there are no clear conclusions. Although many of the publications discussed above purport to show a survival advantage when gross total resection is achieved, there are
currently no high quality published studies in which the extent of surgery was randomized. The randomized trial by Vuorinen et al (24) included too few participants to draw conclusions. Young patients with good KPS scores and superficial tumours are more likely to receive a gross total resection, as compared to older, more disabled patients with deep tumours, who are likely to receive stereotactic biopsies. The different natural history of these subsets of malignant glioma likely eclipses the effect of current therapies, including surgery, and confounds the currently available data. At present, the relative value of biopsy, subtotal resection and gross total resection of malignant gliomas in terms of extended life, and quality of life remain unknown. The evidence is also limited for functional independence because of biases in the available retrospective literature. For those few malignant glioma patients who present \textit{in extremis} due to high intracranial pressure or with herniation syndromes (i.e. a large temporal lobe glioblastoma causing transtentorial herniation), the role of surgery will probably never be tested as it would be unethical to randomize these patients to biopsy alone. The value of cytoreductive surgery for malignant glioma that present electively awaits a clinical trial in which patients are randomized at the outset to either maximal safe resection or biopsy.

VI. ONGOING TRIALS
No ongoing clinical trials were identified.

VII. OPINIONS OF THE NEURO-ONCOLOGY DISEASE SITE GROUP
The lack of sufficient high quality evidence precludes definitive recommendations. Instead, the Neuro-oncology DSG offers the following opinions based on the evidence reviewed:

- There is no high quality evidence to support or refute the statement that resection is better than biopsy in terms of survival, quality of life and functional independence.
- Patients who are young (less than 50 years) are more likely to undergo aggressive resection than older patients.
- Patients with ‘accessible’ tumours are more likely to undergo resections than biopsies.
- If resection is perceived to be safe and feasible in patients with malignant glioma, then resection, rather than biopsy, seems to be the preferred surgical procedure at this time.
- There are no high quality randomized controlled trials examining the role of extent of resection in relation to overall survival and quality of life in patients with malignant glioma. Such trials would be of benefit to the neuro-oncology community and the patients they serve. Patients and surgeons should be encouraged to take part in such trials.

VIII. EXTERNAL REVIEW OF THE EVIDENCE SUMMARY REPORT
Practitioner Feedback
A draft version of this report was reviewed by Ontario practitioners. Any changes made to the report as a result of practitioner feedback are described in the ‘Modifications’ section below.

\textit{Methods}
Practitioner feedback was obtained through a mailed survey of 38 practitioners in Ontario (8 medical oncologists, 21 surgeons, 1 hematologist, 2 pathologist and 6 neurologists). The survey consisted of items evaluating the methods, results, and interpretive summary. Written comments were invited. The practitioner feedback survey was mailed out on August 28, 2003. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Neuro-oncology DSG reviewed the results of the survey.
Results
Nineteen responses were received out of the 38 surveys sent (50% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 16 indicated that the report was relevant to their clinical practice and they completed the survey. Results of the practitioner feedback survey are summarized in Table 4.

Table 4. Results of the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
<th>Strongly agree or agree</th>
<th>Neither agree nor disagree</th>
<th>Strongly disagree or disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing an evidence summary, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>16 (100%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>There is a need for an evidence summary on this topic.</td>
<td>16 (100%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>The literature search is relevant and complete in this evidence summary.</td>
<td>15 (100%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I agree with the methodology used to summarize the evidence.</td>
<td>16 (100%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I agree with the overall interpretation of the evidence in the evidence summary.</td>
<td>15 (94%)</td>
<td>0</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>The Opinions of the Disease Site Group section of this evidence summary is useful.</td>
<td>15 (94%)</td>
<td>0</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>An evidence summary of this type will be useful for clinical decision making.</td>
<td>12 (80%)</td>
<td>2 (13%)</td>
<td>1 (7%)</td>
<td></td>
</tr>
<tr>
<td>At present, there is insufficient evidence to develop a practice guideline on this topic.</td>
<td>14 (88%)</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available.</td>
<td>13 (81%)</td>
<td>3 (19%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Summary of Written Comments
Five respondents (31%) provided written comments. The main points contained in the written comments were:

1. The recommendations are non directive which reflects the lack of hard data. Listing that young patients are more likely to undergo resection isn’t really a recommendation.
2. Patients do best with more aggressive resection independent of age and KPS.
3. This is a longstanding issue where a clear cut trial to guide strict clinical practice is not present and most likely will not occur in the future. However just this knowledge of ambiguity as per findings of this study is useful for our practice and teaching to residents.

Modifications/Actions
The evidence summary report was not modified as per the comments from the practitioners. There is a lack of high quality evidence surrounding the surgical management of patients with malignant glioma. The Neuro-oncology DSG wants to clarify that they have offered their opinions, not recommendations. Until there is high quality evidence (as one practitioner indicated, this may never happen) the Neuro-oncology DSG will not make recommendations.
Practice Guidelines Coordinating Committee Approval Process

The evidence summary report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Eight of 13 members of the PGCC returned ballots. One member did not review the report for approval as he is a member of the Neuro-oncology Disease Site Group. All eight of the PGCC members approved the evidence summary report as written. One member encouraged the development of a clinical trial regarding surgery for malignant glioma. The members of the Neuro-oncology DSG agree that there is a need for a clinical trial.

IX. JOURNAL REFERENCE

A manuscript of this evidence summary has been accepted for publication by *Current Oncology*. Taylor M, Chambers A, Perry J, Bernstein M. Evidence-based review of the role of surgery for malignant glioma. *Current Oncology* (in press).

X. ACKNOWLEDGMENTS

The Neuro-oncology Disease Site Group would like to thank Dr. Michael Taylor, Dr. Mark Bernstein, Dr. Susan Brien, Dr. James Perry, and Ms. Alexandra Chambers for taking the lead in drafting, revising and updating this evidence summary report.

*For a complete list of the Neuro-oncology Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the CCO Web site at http://www.cancercare.on.ca/access_PEBC.htm.*
REFERENCES

Appendix 1. Literature search terms used for MEDLINE, CANCERLIT and COCHRANE.

1. random:sh,pt,tw.
2. controlled:sh,tw,pt.
3. clinical trial?:sh,tw,pt.
4. prospective?:sh,tw,pt.
5. or/1-4
6. exp guidelines
7. (practice guidelines or guideline?).tw,pt.
8. consensus.sh,tw,pt.
9. or/5-7
10. meta-analysis.sh,pt.
11. (meta-anal: or metaanal: or metanal:).tw.
12. (systematic: review? or systematic: overview?).tw.
13. or/10-12
14. 5 or 9 or 13
15. glioma
16. glioblastoma
17. astrocytoma
18. or/15-17
19. surgery
20. biopsy
21. surgical procedures, operative
22. resection.mp.
23. or/19-22
24. 14 and 18 and 23