

## Supplementary Online Content

Brown TJ, Brennan MC, Li M, et al. Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. *JAMA Oncol*. Published online June 16, 2016. doi:10.1001/jamaoncol.2016.1373.

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This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1. Included Study Characteristics**

| Study and year | Level of evidence | Years of patient accrual | N each group                  | Extent of resection determination           | Median follow up | Adjuvant therapies |
|----------------|-------------------|--------------------------|-------------------------------|---|------------------|--------------------|
| Ahmadloo 2013  | IV                | 1990-2008                | GTR: 15<br>STR: 150<br>Bx: 58 | MRI/CT GTR >98% resection                   | 11 mos           | RT, PCV, T         |
| Albert 1994    | IV                | 1989-1994                | GTR: 72<br>STR: 31            | CT/MRI EOR ND                               | 15 mos           | RT                 |
| Ammirati 1987  | IV                | NS                       | GTR: 19<br>STR: 12            | MRI GTR= no residual enhancement            | NS               | RT, Ch             |
| Butowski 2007  | III               | 1975-2003                | GTR: 153<br>STR: 740          | MRI GTR > 90% resection of enhancing tissue | NS               | Ch, Br             |
| Chaichana 2011 | III               | 1997-2007                | STR: 40<br>Bx: 40             | Defined by procedure                        | NS               | RT, T              |
| Chaichana 2014 | III               | 2007-2012                | STR: 29<br>Bx: 19             | Defined by procedure                        | NS               | RT, T              |
| Dea 2012       | IV                | 2004-2008                | GTR: 27<br>STR: 95            | MRI. GTR > 90% reduction                    | NS               | RT, T, Ch          |
| Devaux 1993    | IV                | 1984-1988                | STR: 63<br>Bx: 86             | Defined by procedure                        | NS               | RT                 |
| Ewelt 2011     | IV                | 2002-2007                | GTR: 23<br>STR: 37<br>Bx: 43  | MRI GTR = no residual enhancement           | NS               | RT, Ch, T          |
| Hrabalek 2015  | II                | 2007-2009                | GTR: 3<br>STR: 19<br>Bx: 16   | MRI GTR > 99% resection of enhancing tissue | NS               | RT + T             |

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|                       |                          |                                 |                                |   |                                |                           |
|-----------------------|--------------------------|---------------------------------|--------------------------------|---|--------------------------------|---------------------------|
| Jeremic 1994          | III                      | 1988-1991                       | GTR or STR: 61<br>Bx: 25       | Defined by procedure. No definition for GTR     | NS                             | RT + PCV/BCNU+H           |
| Kalita 2014           | IV                       | 2006-2012                       | GTR or STR: 63<br>Bx: 68       | Defined by procedure<br>Surgery > 70% resection | NS                             | RT, T                     |
| Keles 1999            | III                      | 1980-1991                       | GTR: 20<br>STR: 54             | MRI<br>GTR = no residual enhancement            | NS                             | RT, Ch                    |
| Kelly 1994            | III                      | 1984-1992                       | STR: 40<br>Bx: 88              | Defined by procedure                            | NS                             | RT                        |
| Kiwit 1996            | IV                       | 1986-1990                       | GTR: 26<br>STR: 28<br>Bx: 36   | Surgeon's opinion. CT and MRI                   | NS                             | RT                        |
| Kreth 1993            | III                      | 1986-1991                       | STR: 57<br>Bx: 58              | Defined by procedure                            | 35.6 w                         | RT                        |
| Kreth 1999            | II                       | 1991-1994                       | STR: 126<br>Bx: 99             | Defined by procedure                            | Until death (all died by 1999) | RT                        |
| Kreth 2013            | III                      | 2004-2009                       | GTR: 125<br>STR: 148<br>Bx: 72 | MRI<br>GTR = no residual enhancement            | NS                             | RT, At, T                 |
| <b>Study and year</b> | <b>Level of evidence</b> | <b>Years of patient accrual</b> | <b>N each group</b>            | <b>Extent of resection determination</b>        | <b>Median follow up</b>        | <b>Adjuvant therapies</b> |
| Kuhnt 2011            | IV                       | 2002-2008                       | GTR: 79<br>STR: 56             | MRI<br>GTR = no residual enhancement            | NS                             | RT, Ch                    |
| Li 2015               | II                       | 1993-2012                       | GTR: 876<br>STR: 353           | MRI<br>GTR = no residual enhancement            | NS                             | NS                        |
| Martinez              | IV                       | 1999-                           | GTR:                           | MRI   | NS                             | NS                        |

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|                    |     |               |   |   |                |                        |
|--------------------|-----|---------------|---|---|----------------|------------------------|
| 2007               |     | 2004          | 64<br>STR:<br>38<br>BX: 25                  | GTR = no<br>residual<br>enhancement               |                |                        |
| McGirt<br>2009     | III | 1996-<br>2006 | GTR:<br>330<br>STR:<br>619                  | MRI<br>GTR = no<br>residual<br>enhancement        | 18 mos         | RT, G, T               |
| Nitta 1995         | IV  | 1988-<br>1994 | GTR:<br>14<br>STR:<br>54                    | CT<br>GTR = no<br>residual<br>enhancement         | NS             | NS                     |
| Noorbakhsh<br>2014 | III | 1998-<br>2009 | GTR:<br>6018<br>STR:<br>5609<br>Bx:<br>3982 | Surgical code<br>according to<br>SEER<br>handbook | NS             | RT, Ch, T              |
| Oszvald<br>2012    | III | 2000-<br>2006 | GTR:<br>60<br>STR:<br>174<br>Bx: 127        | MRI<br>GTR = no<br>residual<br>enhancement        |                | RT, Ch, T,<br>ACNU     |
| Pichlmeier<br>2008 | II  | 1999-<br>2004 | GTR:<br>122<br>STR:<br>121                  | MRI<br>GTR = no<br>residual<br>enhancement        | 35.4<br>mos    | RT                     |
| Pirotte<br>2009    | IV  | 1997-<br>2004 | GTR:<br>10<br>STR:<br>21                    | MRI/PET<br>GTR = no<br>residual<br>enhancement    | Until<br>death | NS                     |
| Salvati<br>2012    | IV  | 2002-<br>2007 | GTR:<br>45<br>STR:<br>34<br>Bx: 25          | MRI<br>GTR = no<br>residual<br>enhancement        | NS             | RT, Ch, T              |
| Senft 2010         | IV  | 2004-<br>2005 | GTR:<br>29<br>STR:<br>12                    | MRI<br>GTR = no<br>residual<br>enhancement        | 82 wks         | RT, Ch, T              |
| Shinoda<br>2001    | III | 1989-<br>1998 | GTR:<br>36<br>STR:<br>36                    | MRI<br>GTR = no<br>residual<br>enhancement        | Until<br>death | RT, ACNU,<br>IFNB, Cis |
| Simpson<br>1993    | III | 1974-<br>1987 | GTR:<br>105                                 | Surgeon<br>impression                             | NS             | RT, BCNU,<br>MeCCNU    |

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|                           |                              |   |   |  |                                 |                               |
|---------------------------|------------------------------|---|---|--|---------------------------------|-------------------------------|
|                           |                              |   | STR:<br>413<br>Bx: 107                      |  |                                 |                               |
| Stark 2005                | IV                           | 1990-2001                               | GTR:<br>167<br>STR:<br>199                  | CT<br>GTR = no<br>residual<br>enhancement                      | NS                              | RT, Ch, T, Cis,<br>ACNU       |
| Stummer<br>2000           | IV                           | 1995-1998                               | GTR:<br>33<br>STR:<br>19                    | MRI<br>GTR = no<br>residual<br>enhancement                     | NS                              | RT, Ch, Br                    |
| Uzuka 2012                | III                          | 2000-2010                               | STR:<br>73<br>Bx: 34                        | CT or MRI<br>GTR = >90%<br>reduction of<br>enhancing<br>tissue | 12 mos                          | ACNU,<br>MeCCNU, T            |
| Vuorinen<br>2003          | III                          | 1992-2006                               | STR:<br>14<br>Bx: 16                        | Defined by<br>procedure  | Until<br>death                  | RT                            |
| <b>Study and<br/>year</b> | <b>Level of<br/>evidence</b> | <b>Years of<br/>patient<br/>accrual</b> | <b>N each<br/>group</b>                     | <b>Extent of<br/>resection<br/>determination</b>               | <b>Median<br/>follow<br/>up</b> | <b>Adjuvant<br/>therapies</b> |
| Yamaguchi<br>2012         | IV                           | 2000-2011                               | GTR:<br>60<br>STR:<br>69<br>Bx: 31          | MRI<br>GTR = no<br>residual<br>enhancement                     | 21 mos                          | ACNU, Cis, T                  |
| Zinn 2013                 | IV                           | 1973-2007                               | GTR:<br>4981<br>STR:<br>8753<br>Bx:<br>3197 | Surgical code<br>according to<br>SEER<br>handbook              | NS                              | RT, Ch                        |

eTable 1. Demographic characteristics of all studies that were included in at least one comparison. Key: GTR, Gross total resection as defined in the individual studies STR, subtotal resection Bx, biopsy, NS, Not stated ND, Not Defined RT, Radiation therapy PCV, procarbazine, cisplatin, vincristine, T, temozolomide, Ch, chemotherapy not otherwise specified, Br, brachytherapy, BCNU, carmustine, H, hydroxyurea, At, Alkylating therapy, not otherwise stated, G, gliadel wafer, ACNU, nimustine, IFNB, interferon-beta, Cis, cisplatin MeCCNU, semustine

**eTable 2. Subgroup Meta-analysis Results**

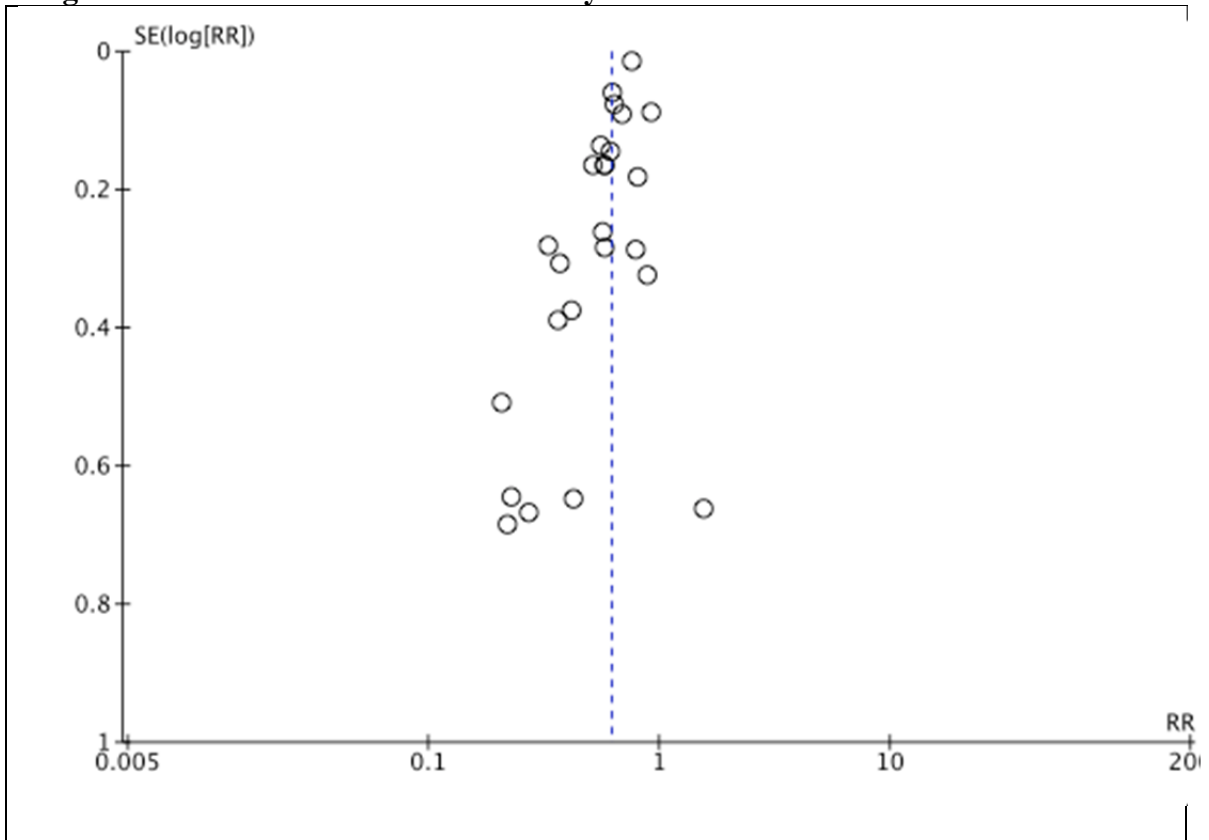
| <b>Comparison</b>            | <b>RR overall</b>              | <b>RR without SEER</b>         | <b>RR without SEER and RTOG</b> | <b>RR only Class II studies</b> | <b>RR only studies since 2005</b> | <b>RR only studies since 2000</b> |
|------------------------------|--------------------------------|--------------------------------|---------------------------------|---------------------------------|-----------------------------------|-----------------------------------|
| 1 yr RR mortality GTR vs STR | 0.62<br>[0.56-0.69]<br>p<0.001 | 0.60<br>[0.53-0.67]<br>p<0.001 | 0.59<br>[0.53-0.65]<br>p<0.001  | 0.62<br>[0.55-0.69]<br>p<0.001* | NA                                | 0.53<br>[0.43-0.67]<br>p<0.001    |
| 2 yr RR mortality GTR vs STR | 0.84<br>[0.79-0.89]<br>p<0.001 | 0.83<br>[0.77-0.89]<br>p<0.001 | 0.82<br>[0.76-0.89]<br>p<0.001  | 0.72<br>[0.49-1.07]<br>p=0.11*  | NA                                | 0.84<br>[0.79-0.91]<br>p<0.001    |
| 1 yr RR mortality STR vs Bx  | 0.85<br>[0.80-0.91]<br>p<0.001 | 0.85<br>[0.78-0.92]<br>p<0.001 | 0.86<br>[0.79-0.93]<br>p<0.001  | 0.89<br>[0.78-1.01]<br>p=0.06** | 0.85<br>[0.68-1.07]<br>p=0.17     | 0.84<br>[0.71-1.00]<br>p=0.05     |
| 2 yr RR mortality STR vs Bx  | 0.99<br>[0.97-1.00]<br>p=0.07  | 0.99<br>[0.96-1.01]<br>p=0.2   | 1.00<br>[0.98-1.01]<br>p=0.72   | 0.92<br>[0.65-1.30]<br>p=0.63** | 0.92<br>[0.73-1.18]<br>p=0.53     | 1.00<br>[0.96-1.03]<br>p=0.77     |
| 1 yr RR mortality Any vs Bx  | 0.77<br>[0.71-0.84]<br>p<0.001 | 0.76<br>[0.69-0.84]<br>p<0.001 | 0.76<br>[0.68-0.85]<br>p<0.001  | 0.89<br>[0.78-1.01]<br>p=0.06** | 0.91<br>[0.75-1.10]<br>p=0.32     | 0.69<br>[0.58-0.82]<br>p<0.001    |
| 2 yr RR mortality Any vs Bx  | 0.94<br>[0.89-1.00]<br>p=0.04  | 0.96<br>[0.92-0.99]<br>p=0.02  | 0.97<br>[0.93-1.00]<br>p=0.05   | 0.92<br>[0.65-1.30]<br>p=0.63** | 0.92<br>[0.73-1.18]<br>p=0.53     | 0.95<br>[0.89-1.01]<br>p=0.12     |

eTable 2. Results of meta-analysis when further analyzed. Studies since 2000 includes only studies which included patients after 2000. Studies since 2005 only includes studies that analyzed patients accrued after 2005. The SEER studies included Zinn 2013 and Noorbakhsh 2014. RTOG data was published in Simpson 1993

\*Only two class II studies were included in this analysis, Li 2015 and Pichlmeier 2008.

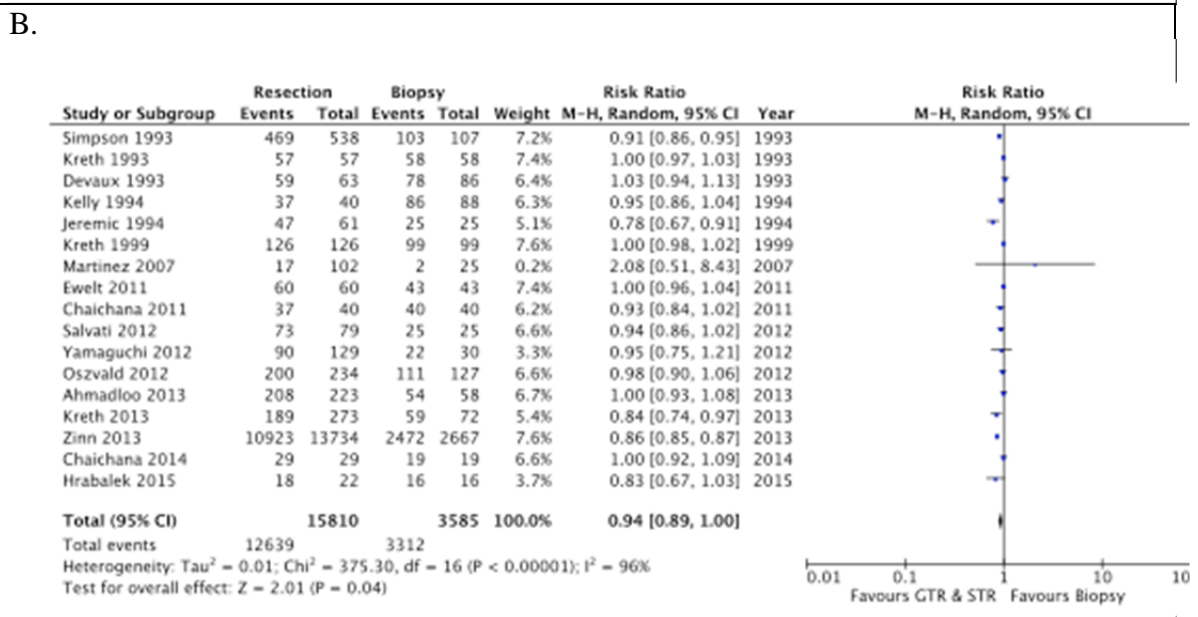
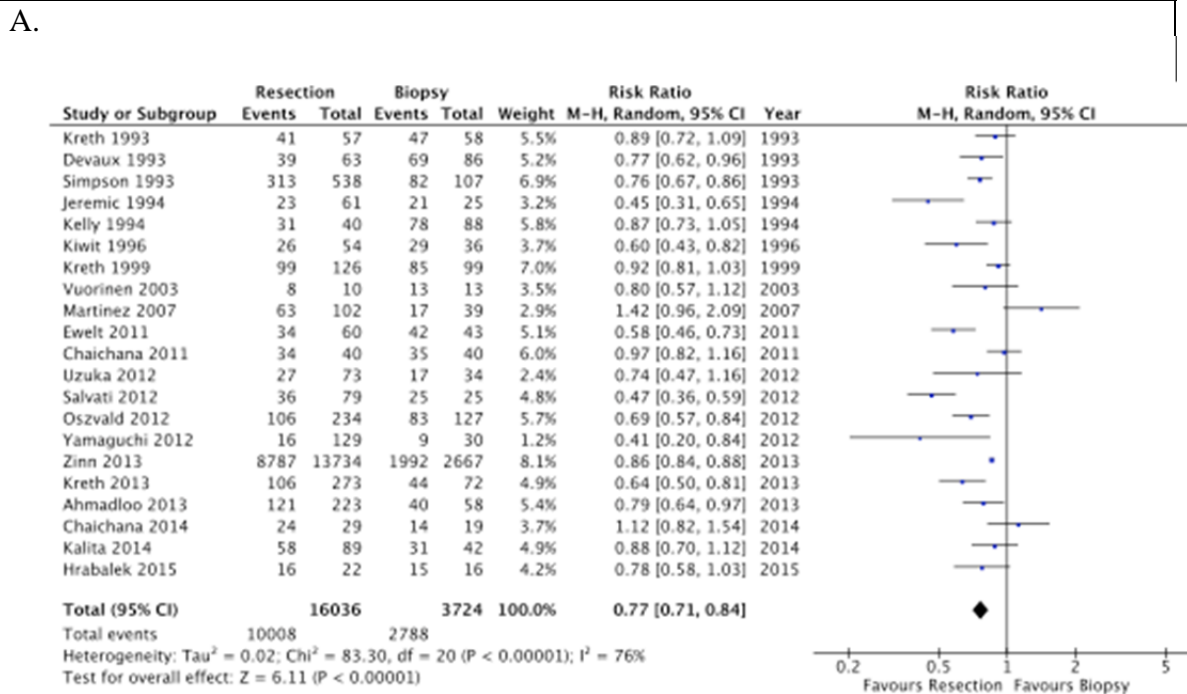
\*\*Only two class II studies were included in this analysis, Kreth 1999 and Hrabalek 2015. The same data were used in both comparisons at the respective timepoints.

**eFigure 1. Funnel Plot of 1-Year Mortality for GTR vs STR**



Funnel plot for the one-year mortality for GTR vs STR meta-analysis. The midline of the studies indicates a slight publication bias of studies showing benefit with GTR over STR.

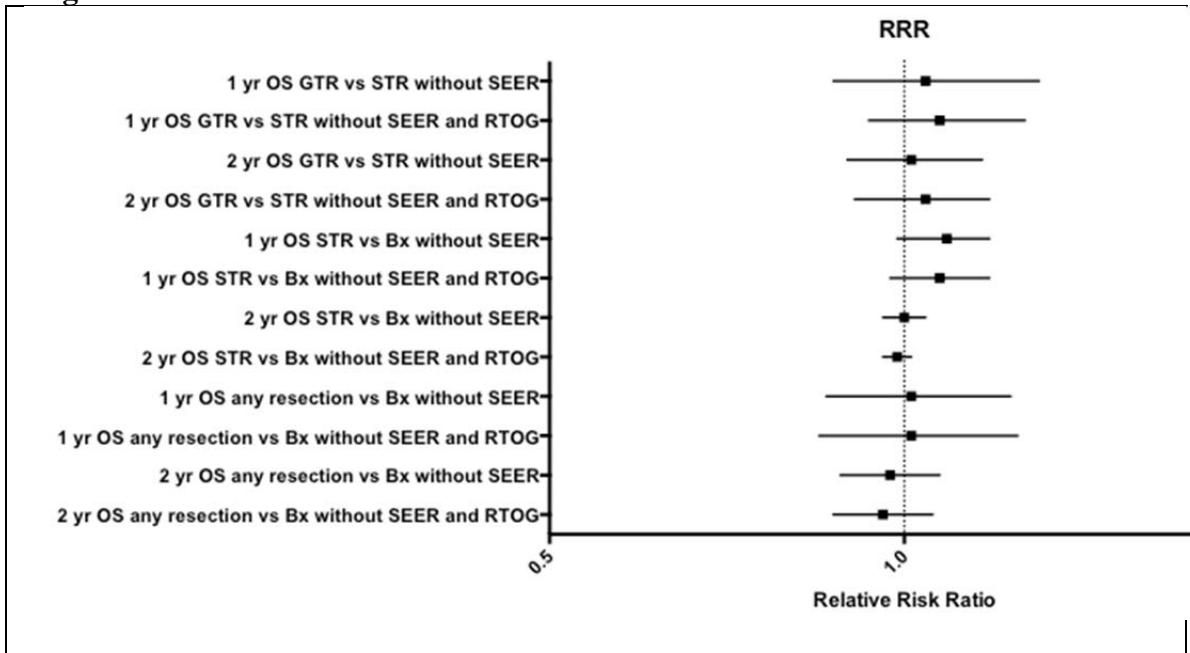
**eFigure 2. RR of Mortality at 1 and 2 Years for Any Resection vs Biopsy**



(A) One year RR mortality comparing any resection to biopsy. Twenty-one studies were included in this analysis of a total of 19 760 patients. The RR of mortality at one year is 0.77 (0.71-0.84),  $p < 0.001$  comparing any resection to biopsy. Removing SEER data, the RR of mortality at one year is 0.76 (0.69-0.84),  $p < 0.001$  with any resection compared to biopsy. (B) Two-year RR mortality comparing any resection to biopsy. This analysis of seventeen studies covers a total of 2994 patients. The RR of mortality at two years is 0.94 (0.89-1.00),  $p = 0.04$  comparing any resection to biopsy. Removing SEER data, the RR of mortality at two years is 0.96 (0.92-0.99),  $p = 0.02$  significantly favoring any resection over biopsy.

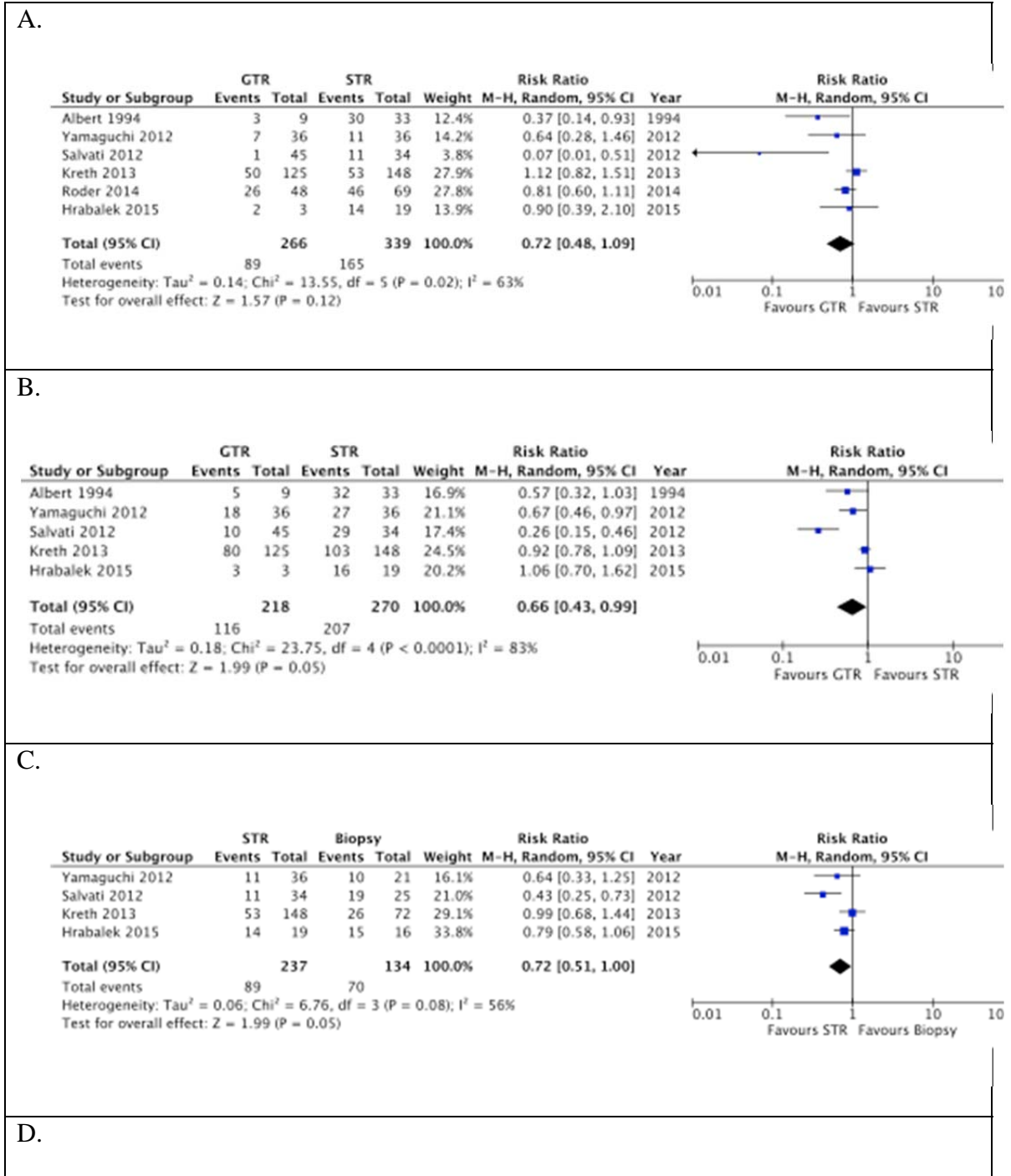


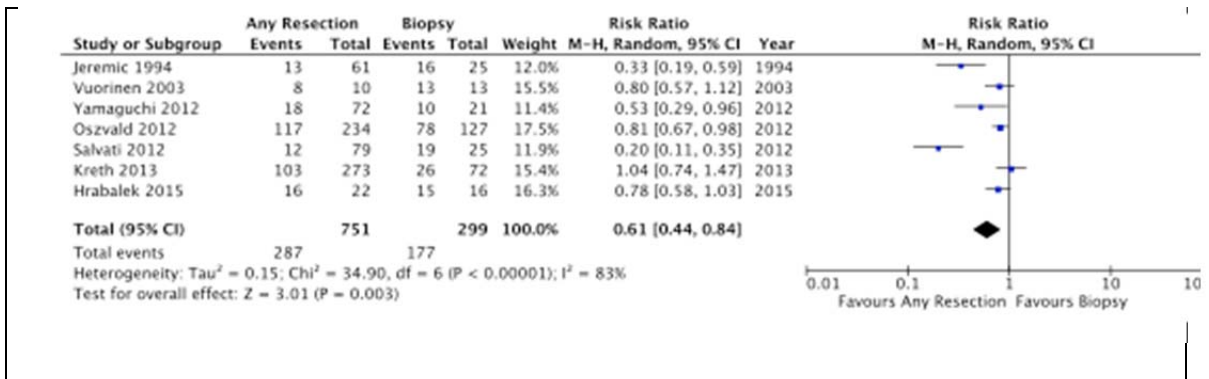
**eFigure 3. Relative Risk Ratios**



Relative risk ratios comparing relative risks of death at specific time points in the original meta-analysis and the repeated meta-analysis without SEER data (Zinn 2013, Noorbakhsh 2104) and without SEER and RTOG (Simpson 1993) data. This demonstrates inclusion of SEER and RTOG data insignificantly affects the overall meta-analysis and can be considered representative of the population and the body of literature.

eFigure 4. Analysis of RR of Progression-Free Survival





(A) RR of progression at six months, GTR vs. STR, not significantly favoring GTR. (B) RR of progression at one year, GTR vs STR. (C) RR of progression at six months, STR vs Bx. (D) RR of progression at 6 months for any resection vs Bx. All four of these analyses trended toward favoring more extensive resection, with all except the STR vs Bx comparison reaching significance. However, it is important to note that this topic is not as extensively studied as the relationship between overall survival and EOR. PFS was defined in the primary literature.