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SYSTEMATIC REVIEW AND META-ANALYSIS

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Comparison of Short-Course Radiotherapy Versus Long-Course Radiotherapy for Treatment of Metastatic Spinal Cord Compression

A Systematic Review and Meta-Analysis

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Abstract: In this study, we evaluate the efficacy of short-course radiotherapy (SCRT) versus long-course radiotherapy (LCRT) in the treatment of metastatic spinal cord compression (MSCC).

PubMed, EMBASE, and Web of Science were searched up to April 2015. Relevant data were extracted based on inclusion and exclusion criteria. Methodological quality of randomized controlled trial (RCT) was evaluated using modified Jadad scale; non-RCT was evaluated using Newcastle-Ottawa Scale. Meta-analysis was performed using RevMan 5.3 software.

Fourteen studies with 2239 patients were included. Results of meta-analysis showed that there were no significant differences between SCRT and long-course radiotherapy LCRT in 6-month overall survival rate (risk ratio [RR] = 0.97, 95% confidence interval [CI] 0.88, 1.07, $P = 0.55$), 1-year overall survival rate (RR = 0.94, 95% CI 0.85, 1.04, $P = 0.22$), motor function improvement (RR = 0.96, 95% CI 0.81, 1.13, $P = 0.63$), no change on motor function (RR = 0.98, 95% CI (0.88, 1.09), $P = 0.74$], and deterioration on motor function (RR = 0.96, 95% CI 0.71, 1.31, $P = 0.78$). Compared with SCRT, LCRT significantly increased 6-month local control rate (RR = 0.87, 95% CI 0.80, 0.95, $P = 0.002$), 1-year local control rate (RR = 0.83, 95% CI 0.71, 0.97, $P = 0.02$), and 2-year local control rate (RR = 0.83, 95% CI 0.79, 0.87, $P < 0.00001$).

Both LCRT and SCRT provided similar survival rates and functional outcome, but LCRT showed better local control rates than SCRT. However, considering low cost and good patient's compliance, SCRT may be a better choice.

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Abbreviations: CI = confidence interval, LCRT = long-course radiotherapy, MSCC = metastatic spinal cord compression, RCT = randomized controlled trials, RR = risk ratio, SCRT = short-course radiotherapy.

INTRODUCTION

Metastatic spinal cord compression (MSCC) is a deadly complication of advanced malignancy, which significantly decreases patients' quality of life and life expectancy.[1] Incident rate of MSCC varies from 7.9% to 0.2% in patients with different kinds of primary tumor.[2] However, most patients will be paraplegic if no treatment is given. Therefore, early diagnosis and treatment are critical for MSCC patient.[1,3]

Radiotherapy (RT) and surgery are 2 major options for MSCC. A meta-analysis[4] showed that surgery was superior to RT with regard to survival rates and motor function outcome. However, surgery is limited to a minority of patients because of strict patient selection.[5] Therefore, RT has been the most common modality for MSCC patients. Yet, the most appropriate RT schedule is still uncertain.[2] All kinds of RT schedule, such as 1×8 Gy/F, 1×10 Gy/F, and 15×2.5 Gy/F, 20×2 Gy/F, have been used in MSCC patients in many countries. Long-course RT (LCRT) (>2 weeks) is the standard regimen in German centers, whereas short-course RT (SCRT) is the standard regimen in United Kingdom, Bosnia, the Netherlands, and Herzegovina.[6] Several studies have been done to compare the efficacy of LCRT and SCRT in MSCC patients. Maranzano et al conducted 2 studies,[7,8] one of which used a split-course schedule of 30 Gy in 8 fractions compared with a short-course schedule of 16 Gy in 2 fractions; the other study used 8 Gy in a single fraction compared with 16 Gy in 2 fractions. But both studies were performed in a poor prognosis population. Rades et al conducted some retrospective studies in a comprehensive population, which indicated that SCRT could be recommended for patients with a poor survival prognosis, whereas LCRT was a better option for patients with a good survival prognosis.[5,6,9–11] However, since retrospective study has limitations, more evaluation in the results of relevant publications is needed. In this

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study, we performed a meta-analysis to evaluate the efficacy of SCRT compared with LCRT in patients with MSCC.

MATERIALS AND METHODS

Study Selection

Inclusion criteria were as follows: study type (control study, including randomized controlled trial [RCT], non-RCT, prospective or retrospective control studies); participants (patients diagnosed with MSCC from any type of primary tumor, patients treated with RT but did not underwent previous surgery and treated with RT in the spinal region, patients with or without administration of steroids during RT, and if overlapping data appeared in several relevant articles, only studies performed in the largest population or published most recently were included); intervention and comparison (SCRT [less than a week] vs LCRT [2 weeks at least]); Outcomes (any form of the efficacy, such as local control rates, survival rates, and motor function outcome). Local control rates as the primary outcome indicators. This study is not a primary trial; thus, ethical approval was not necessary.

Exclusion criteria were as follows: noncontrolled trials, such as single arm study, case series or case report; key information was incomplete to provide the required data; non-original researches, such as review, letter etc; short course was <1 week, and long course >2 weeks[6] (SCRT, 1×8 Gy in 1 day or 5×4 Gy in 1 week; LCRT, 10×3 Gy in 2 weeks, 15×2.5 Gy in 3 weeks, or 20×2 Gy in 4 weeks). Eligibility assessment was performed independently in a nonblinded standardized manner by 2 reviewers. Disagreements between the reviewers were resolved by consensus.

Search Strategy

We searched MEDLINE, EMBASE, Web of Science, CBM, and CKNI from establishment of database to April 2015. Search terms were as follows: ''spinal cord compression,'' ''metastatic spinal cord compression,'' ''malignant spinal cord compression,'' and ''radiotherapy''; more electronic search details were shown in appendix. Bibliographies of relevant articles were also reviewed for additional literatures that met inclusion criteria. Furthermore, we also checked abstracts that were published in major academic conferences (American Society of Clinical Oncology, European Society for Medical Oncology, American Society for Therapeutic Radiology and Oncology, and European Society for Radiotherapy & Oncology). No language restrictions were applied. We also contacted the corresponding author or first author to obtain information if research results were unclear or more information was needed.

Quality Assessment

Based on the detailed data of included studies, 2 reviewers evaluated the quality of eligible trials independently. Any

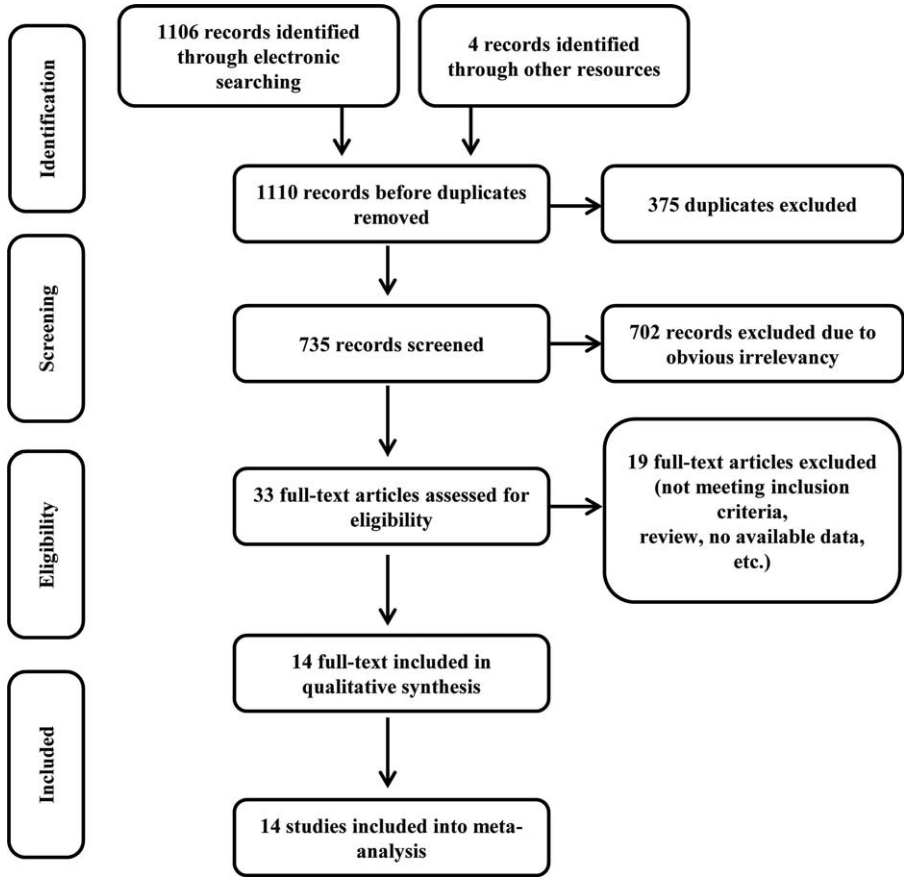

FIGURE 1. The process of the study selection.

TABLE 1. Basic Characteristics of Included Studies

Study	Design Type	Median Age, y	Type of Tumor	No of Patients	Inclusion Period	Country	RT Regimen		With Adjuvant Steriods	Quality
							Short Course RT	Long Course RT		
Rades, 2005A[9]	Retrospective	63	Multiple types	1304	1992.1–2003.12	Germany	8 GY/1F, 20 GY/5F	30 GY/10F, 40 GY/20F, 37.5 GY/15F	16–32 mg/day during the whole RT	7
Rades, 2005B[10]	Retrospective	65	Multiple types	204	1999.1–2003.12	Germany	8 GY/1F	30 GY/10F	Yes, but not given in detail	7
Rades, 2006A[11]	Retrospective	60	Colorectal tumor	81	1991.1–2005.6	Germany	8 GY/1F, 20 GY/5F	30 GY/10F, 40 GY/20F, 37.5 GY/15F	Yes, but not given in detail	7
Rades, 2006B[6]	Retrospective	65	Multiple types	1852	1992.1–2005.12	Germany	8GY/1F, 20 GY/5F	30 GY/10F, 40 GY/20F, 37.5 GY/15F	12–32 mg/day at least for 1 week	7
Rades, 2006C[16]	Retrospective	65	Myeloma	172	1994.1–2004.12	Germany	8 GY/1F, 20 GY/5F	30 GY/10F, 40 GY/20F, 37.5 GY/15F	Yes, but not given in detail	7
Rades, 2006D[17]	Retrospective	60	Breast cancer	335	1992.1–2003.12	Germany	8 GY/1F, 20 GY/5F	30 GY/10F, 40 GY/20F, 37.5 GY/15F	12–32 mg/day at least 1 week	7
Rades, 2006E[5]	Retrospective	70	Prostate cancer	281	1992.1–2003.12	Germany	8 GY/1F, 20 GY/5F	30 GY/10F, 40 GY/20F, 37.5 GY/15F	Yes, but not given in detail	7
Rades, 2006F[18]	Retrospective	65	Renal cell cancer	87	1991.1–2004.6	Germany	8 GY/1F, 20 GY/5F	30 GY/10F, 40 GY/20F, 37.5 GY/15F	16–32 mg/day for at least 2 weeks	7
Rades et al, 2007[19]	Retrospective	75	Multiple types	308	1992.1–2005.12	Germany	8 GY/1F, 20 GY/5F	30 GY/10F, 40 GY/20F, 37.5 GY/15F	12–32 mg/day at least for 1 week	7
Rades et al, 2011[21]	Prospective	67	Multiple types	265	2006.1–2007.12	Germany	8 GY/1F, 20 GY/5F	30G Y/10F, 40 GY/20F, 37.5 GY/15F	Treatment during RT at least 1 week	7
Rades, 2012A[22]	Retrospective	65	Myeloma	214	1992–2010	3 Countries	8 GY/1F, 20 GY/5F	30 GY/10F, 40 GY/20F, 37.5 GY/15F	Yes, but not given in detail	7
Rades, 2012B[21]	Retrospective	70	Prostatic cancer	436	1992–2010	Germany	8 GY/1F, 20 GY/5F	30 GY/10F, 40 GY/20F, 37.5 GY/15F	Treatment during RT at least 1 week	7
Rades, 2012C[15]	Retrospective	64	Lung cancer	365	1992–2010	Germany	8 GY/1F, 20 GY/5F	30 GY/10F, 40 GY/20F, 37.5 GY/15F	Yes, but not given in detail	7
Abu-Hegazy and Wahba, 2011[20]	RCT	60	Multiple types	285	2007.4–2009.12	Egypt	8 GYp/1F	30 GY/10F, 40 GY/20F	Not given	5*

The quality of prospective or retrospective studies was evaluated by the 9-star Newcastle-Ottawa Scale. RCT = randomized controlled trial, RT = radiotherapy.
* RCTs were assessed by the modified JADAD scale.

discrepancy was resolved by consultation. The 9-star Newcastle-Ottawa Scale was used to assess and quantify retrospective or prospective studies .[12] Quality of RCT was assessed by the modified JADAD scale.[13] This 7-point assessment includes the following categories: randomization, concealment of allocation, double blinding, withdrawals, and dropouts.

Data Extraction

Two reviewers extracted data in the same standards from each study independently. Any disagreement about study selection was resolved by a third reviewer. Information retrieved from the studies included the first author, publication year, number of patients (including SCRT and LCRT), the regimen of radiotherapy and the outcomes, such as 6-minute survival rates, 1-year survival rates, 2-year suvival rates, 6-minute local control rates, 1-year local control rates, 2-year local control rates, and motor function.

Statistical Methods

The software RevMan 5.3 (Review Manager) was applied to pool the results in this meta-analysis. Relative risk (RR) with its 95% confidence interval (CI) was used to evaluate the influence strength of SCRT comparing with LCRT on the effectiveness of MSCC; $P < 0.05$ was considered significant. The I^2 statistic was used to tested heterogeneity. I^2 <50% and $P > 0.1$ were considered no or slight heterogeneity, and then fixed-effect model was used; otherwise, random-effect model would be adopted.[14]

RESULTS

Study Selection and Characteristics of Included Studies

After a comprehensive search, 33 full-text articles were assessed for eligibility, and 19 of them were excluded (interventions of 12 studies do not meet the inclusion criteria, 3 were review, 3 were single-arm trials, and from 1 data cannot be extracted); therefore, only 14 eligible studies[5,6,9–11,15–23] were included. The selection process was shown in Figure 1. Only 1 study was RCT, which was published in Egypt,[23] 1 was nonrandomized prospective study,[20] and the rest were all retrospective studies, which were written by the same first author in Germany. Though there are some overlapping data, it was reported in different outcomes. Thus, we ensure that there were no overlapping patients in meta-analyses of each outcome. These meta-analyses included 909 cases in the SCRT group and 1208 cases in the LCRT group. According to the 9-star Newcastle-Ottawa, the quality of every prospective or retrospective study was graded as level 2 (7 point); the quality of this relevant RCT was assessed by the modified JADAD scale. Details were shown in Table 1, including the basic characteristics of included trials.

Analysis of Local Control Rates

Six-Month Local Control Rate

Because of the overlapping publications, only 2 trials met the inclusion criteria, one of them was retrospective analysis[19]

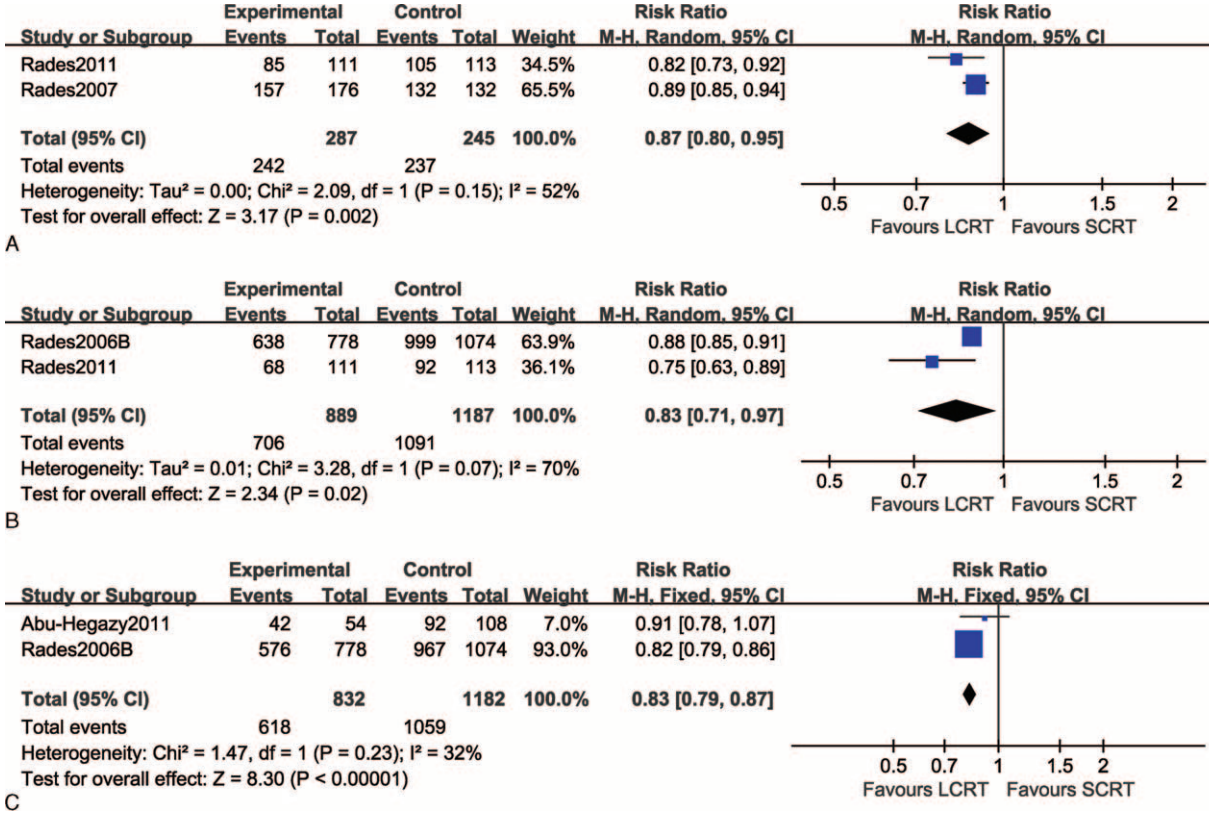

FIGURE 2. Forest plot of the risk ratio of 6-month local control rate (A), 1-year local control rate (B), and 2-year local control rate (C). Experimental: short-course radiotherapy (SCRT). Control: long-course radiotherapy (LCRT).

and the other was a nonrandomized prospective study.[20] Moderate heterogeneity between the trials was found ($I^2 = 52\%$, $P = 0.15$); the random-effects model was performed. There was significant difference in 6-month local control rate (RR = 0.87, 95% CI 0.80, 0.95). The pooled results suggested that LCRT was superior to SCRT in 6-month local control rate (Fig. 2A).

One-Year Local Control Rate

Two studies[6,20] were included in the meta-analysis. Significantly, heterogeneity was detected $I^2 = 70\%$; thus, the random-effects model was adopted. We found that there were significant differences in 1-year local control rates (RR = 0.83, 95% CI 0.71, 0.97, $P = 0.02$), which indicated that LCRT achieved better outcomes in 1-year local control rates than SCRT (Fig. 2B).

Two-Year Local Control Rate

Only 1 RCT[23] and a retrospective trial[6] were included in the meta-analysis to evaluate 2-year local control rate. No apparent heterogeneity was detected ($I^2 = 32\%$, $P = 0.23$), so fixed-effects model was used. The combined results implied that SCRT was inferior to LCRT in 2-year local control rate (RR = 0.83, 95% CI 0.79, 0.87, $P < 0.00001$), (Fig. 2C).

Analysis of Overall Survival Rates

Six-Month Overall Survival Rate

Three studies[16,17,20] were included. Six-month survival rates in SCRT and LCRT were 63.0% (203/322) and 69.1% (311/450), respectively. No heterogeneity was detected ($I^2 = 0\%$), so fixed-effects model was used. The pooled results demonstrated that there were no significant differences between SCRT and LCRT in 6-month survival rate (RR = 0.97, 95% CI 0.88, 1.07, $P = 0.55$), (Fig. 3A). Although some studies[15,19,21] could not be pooled due to overlapping participants, the conclusion was the same.

One-Year Overall Survival Rate

Only 2 trials[6,20] were included in the meta-analysis. No heterogeneity was detected ($I^2 = 4\%$, $P = 0.31$), so fixed-effects model was used. No significant differences were found in the pooled results (RR = 0.94, 95% CI 0.85, 1.04, $P = 0.22$), which indicated that there was no significant difference between the 2 groups in 1-year survival rate, (Fig. 3B).

Two-Year Overall Survival Rate

Three trials[6,17,22] met the inclusion criteria, and due to the overlapping follow-up patients, we could not pool the results; 1[22] of 3 studies showed there was no difference between 2 different radiotherapy regimen, whereas the rest [6,17] showed that LCRT was superior to SCRT in 2-year overall survival rate (Fig. 3C).

Analysis of Motor Function

Improvement on Motor Function

We obtained the data from 6 trials[5,11,16–18,20] and performed the meta-analysis. There was no significant heterogeneity between

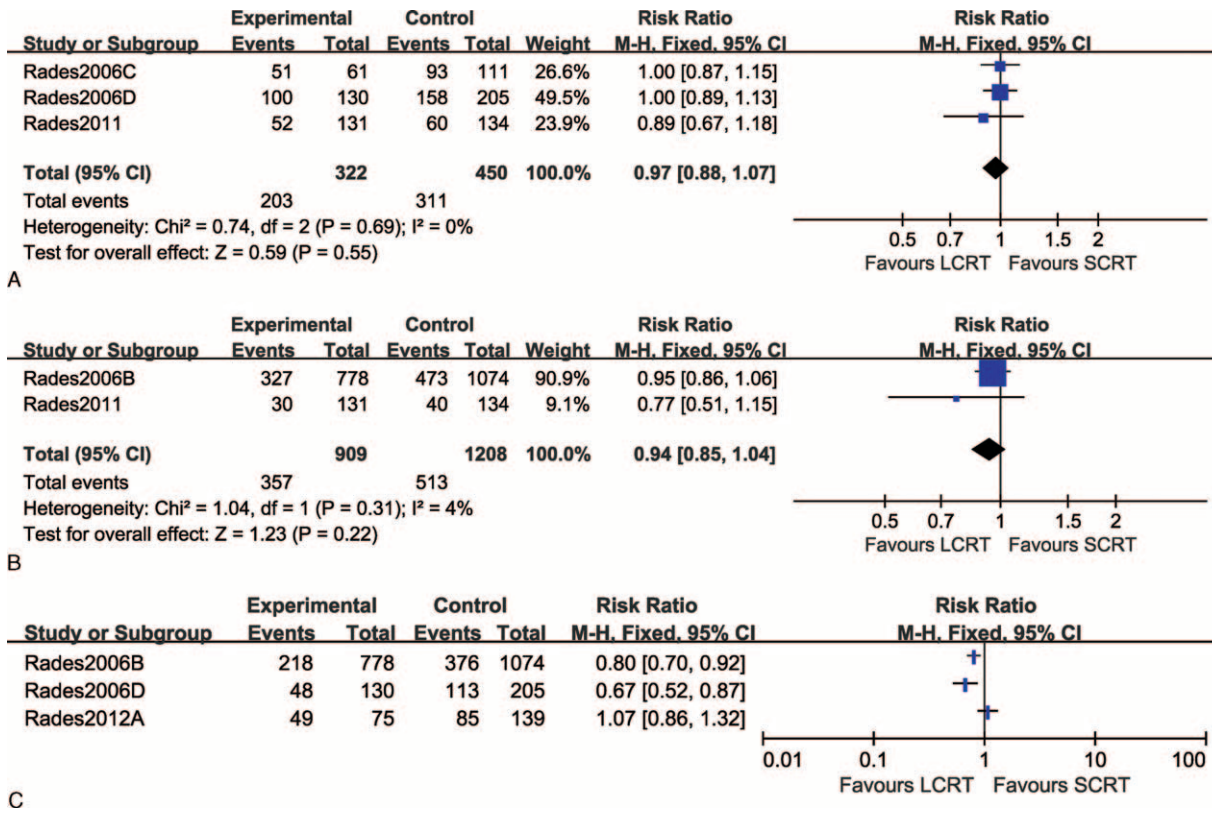

FIGURE 3. Forest plot of the risk ratio of 6-month overall survival rate (A), 1-year overall survival rate (B), and 2-year overall survival rate (C). Experimental: short-course radiotherapy (SCRT). Control: long-course radiotherapy (LCRT).

the trials; thus, fixed-effects model was used ($I^2 = 19\%$, $P = 0.29$). There was no significant differences in the pooled result (RR = 0.96, 95% CI 0.81, 1.13, $P = 0.63$), which showed that LCRT did not provide a better outcome than SCRT in improvement on motor function (Fig. 4A).

No Change on Motor Function

No heterogeneity was detected between the included 5 studies[5,11,17,18,20] ($I^2 = 0\%$, $P = 0.73$); thus, fixed-effects model was used. The pooled result showed there were no significant differences between SCRT and LCRT in terms of no change on motor function (RR = 0.98, 95% CI 0.88, 1.09, $P = 0.74$, Fig. 4B).

Deterioration on Motor Function

We got a same result about deterioration on motor function.[5,11,17,18,20] Neither significant differences between 2 radiotherapy regimens nor significant heterogeneity was detected (RR = 0.96, 95% CI 0.71, 1.31, $I^2 = 0\%$, $P = 0.78$, Fig. 4C).

DISCUSSION

The present meta-analysis was designed to compare the efficacy of SCRT versus LCRT in the treatment of MSCC. Compared with SCRT, LCRT was associated with better local control rates in 6 months, 1 year, and 2 years, but there was no significant difference in 6-months, 1-year overall survival rate, and motor functional outcome.

Spinal cord compression is a deadly complication of metastatic malignancy. Radiotherapy plays a vital role in the management of patients with MSCC.[24] The prognosis of spinal cord compression is usually poor and many MSCC patients are too debilitated to walk[9]; most of them have a limited life with only a few months. Therefore, selecting an optimal treatment for the patient with a limited life was important. According to our results, there was no significant difference between 2 RT regimens in life expanding and motor function outcome. Application of SCRT instead of LCRT means a less overall treatment time, less expenditure, and less steps of treatment sessions. For a debilitated or paralyzed patient, a shorter treatment program is

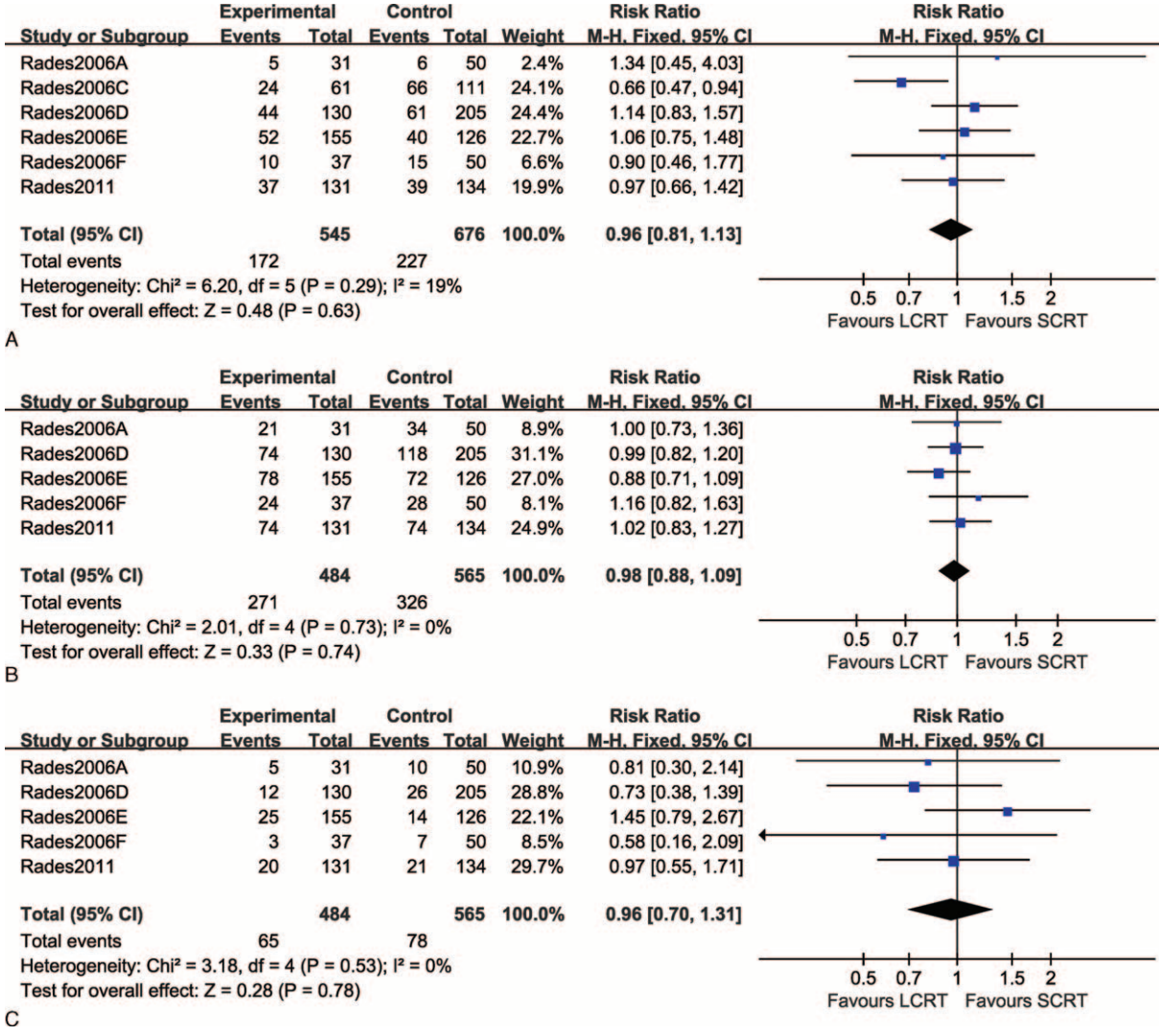

FIGURE 4. Forest plot of the risk ratio of improvement on motor function (A), no change on motor function (B), and deterioration on motor function (C). Experimental: short-course radiotherapy (SCRT). Control: long-course radiotherapy (LCRT).

in need; every single treatment step can cause discomfort and inconvenience. Furthermore, a longer treatment regimen leads to a higher cost. Therefore, for such patients with poor prognosis, SCRT is an ideal option, whereas for patients with a better prognosis and who may live long enough to get a local recurrence, LCRT might be a better choice, which shows better outcome in local control rates. Two reviews[2,25] drew a similar conclusion with our conclusion. Hoskin et al[26]did a comparison about 1 or 2 fractions versus multi-fraction, which demonstrated that there was no difference in function outcome between 2 fractions. However, more well-designed studies were needed to verify our conclusion.

As far as we know, this is the first meta-analysis to compare 2 RT regimens in the treatment of MSCC. However, there are several limitations in this meta-analysis. First, almost all including publications were written by Rades et al. Second, most included studies were retrospective analyses. With its inherent limitations, the risk of bias could not be ignored. For example, in the included prospective study, pooled results showed that local control rates were lower than those from retrospective publications,[20] which implies that some messages were missed in retrospective analysis. Third, in the included trials, the usage of steroids as well its dosage was not considered. In addition, the dose of steroids differed from individuals, and this may introduce some biases. A publication[1] reported that patients with no neurologic deficits do not require steroids, whereas patients with paralysis need a high dose. There was lack of evidence to justify such case.[27] So more head-to-head RCTs were needed to further verify these results.

CONCLUSIONS

This meta-analysis indicated that LCRT, compared with SCRT, shows better local control rates, but with no difference in survival rates and motor function outcome. However, considering the low cost and good patient's compliance, SCRT may be a better regimen. It is noted that more high-quality RCTs are needed to further identify which was the best RT scheme.

APPENDIX

PubMed Search Terms

#14 Search (((((((''spinal cord compression'') OR ''metastatic spinal cord compression'') OR ''malignant spinal cord compression'') OR ''Spinal Cord Compression''[Mesh])) AND (((radiotherapy) OR ''radiation therapy'') OR (''Radiotherapy''[Mesh] OR ''radiotherapy'' [Subheading] OR ''Radiotherapy, Image-Guided''[Mesh] OR ''Radiotherapy, Intensity-Modulated''[Mesh] OR ''Radiotherapy, Conformal''[Mesh]))))) AND ((''short term'' OR ''short course'' OR ''long term'' OR ''long course''))

#13 Search (''short term'' OR ''short course'' OR ''long term'' OR ''long course'')

#12 Search (((((''spinal cord compression'') OR ''metastatic spinal cord compression'') OR ''malignant spinal cord compression'') OR ''Spinal Cord Compression''[Mesh])) AND (((radiotherapy) OR ''radiation therapy'') OR (''Radiotherapy''[Mesh] OR ''radiotherapy'' [Subheading] OR ''Radiotherapy, Image-Guided''[Mesh] OR ''Radiotherapy, Intensity-Modulated''[Mesh] OR ''Radiotherapy, Conformal''[Mesh]))

#11 Search ((radiotherapy) OR ''radiation therapy'') OR (''Radiotherapy''[Mesh] OR ''radiotherapy'' [Subheading] OR ''Radiotherapy, Image-Guided''[Mesh] OR ''Radiotherapy, Intensity-Modulated''[Mesh] OR ''Radiotherapy, Conformal''[Mesh])

#10 Search ''Radiotherapy''[Mesh] OR ''radiotherapy'' [Subheading] OR ''Radiotherapy, Image-Guided''[Mesh] OR ''Radiotherapy, Intensity-Modulated''[Mesh] OR ''Radiotherapy, Conformal''[Mesh]

#8 Search ''radiation therapy''

#7 Search radiotherapy

#6 Search (((''spinal cord compression'') OR ''metastatic spinal cord compression'') OR ''malignant spinal cord compression'') OR ''Spinal Cord Compression''[Mesh]

#5 Search ''Spinal Cord Compression''[Mesh]

#3 Search ''malignant spinal cord compression''

#2 Search ''metastatic spinal cord compression''

#1 Search ''spinal cord compression''

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