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LITERATURE REVIEW

Direct Decompressive Surgery Followed by Radiotherapy *Versus* Radiotherapy Alone for Metastatic Epidural Spinal Cord Compression

A Meta-analysis

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Study Design. A systemic review and meta-analysis.

Objective. To compare the ambulatory status and survival for metastatic epidural spinal cord compression (MESCC) in patients treated with direct decompressive surgical resection (DDSR) followed by radiotherapy (RTx) with those in patients treated with RTx alone.

Summary of Background Data. Surgical techniques have remarkably evolved from decompressive laminectomy without ventral tumor excision to DDSR, which has displayed favorable outcomes since the 2000s. RTx alone has also evolved and is regarded to have accomplished outcome comparable with that of the surgery. The optimal treatment of MESCC has not been clearly defined yet.

Methods. We searched MEDLINE, EMBASE, and the Cochrane library in July 2013. Comparative studies enrolled patients with similar performance, primary cancer, age, and sex at the baseline state were included. Outcome measures included ambulatory status and overall survival rate. We did a fixed-effects meta-analysis of the ambulatory status and survival in patients with MESCC compared with DDSR+RTx and RTx alone.

Results. Five studies were used to obtain data from 238 and 1137 patients treated with DDSR+RTx and RTx alone, respectively. The DDSR+RTx group displayed substantial improvement in ambulatory status after the treatment that was superior to the improvement in the RTx-alone group (relative risk [RR], 1.43; 95% confidence interval [CI], 1.14–1.78) in a fixed-effects model and significantly lower deterioration after treatment than the RTx group (RR, 0.35; 95% CI, 0.19–0.63). The DDSR+RTx group showed significant improvement in the survival rate at 6 months post-treatment (RR, 1.21; 95% CI, 1.09–1.33). Similar findings were observed at 12 months post-treatment (RR, 1.32; 95% CI, 1.12–1.56).

Conclusion. The meta-analysis indicates that DDSR+RTx may produce better clinical improvement of ambulation status and survival than RTx alone in the treatment of MESCC. Additional prospective studies are warranted to better address this question.

Key words: meta-analysis, metastasis, epidural, spinal cord compression, surgery, radiotherapy, comparison.

Level of Evidence: 1

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Metastatic epidural spinal cord compression (MESCC) is defined as compression of the dural sac and its contents (spinal cord and/or cauda equina) by an extradural tumor mass. The clinical features include any or all of the following: pain (local or radicular), weakness, sensory disturbance, and/or evidence of sphincter dysfunction.[1] The goals of treatment for MESCC are pain relief, preservation or recovery of neurological function, and preservation of spinal stability.[2] Clinicians need to consider many factors in the treatment decision for MESCC as follows: the patient's general condition (age and comorbidity), status of disease (histological type of primary tumors and other metastatic sites), clinical status (back pain, neurological deficit, and stability of the spine), and life expectancy.[3] The mainstays of treatment for MESCC are radiotherapy (RTx) and surgery. The optimal treatment of MESCC has not been clearly defined.

In the 1970s and early 1980s, decompressive laminectomy without ventral tumor excision was attempted for the alleviation of neural compression before the availability of spinal instrumentation.[4,5] During this period, some articles reported that RTx accomplished similar clinical outcomes without surgical risks.[5,6] In the 1980s, an advanced type of

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surgical procedure, direct decompressive surgical resection (DDSR), was developed for the treatment of MESCC. This procedure achieves circumferential decompression immediately, and stabilization is added using pedicle screws. In 2005, a prospective randomized controlled study by Patchell *et al*[7] comparing DDSR followed by RTx with RTx alone indicated that patients who underwent the surgery improved, regained ambulation status, and survived longer than patients treated with RTx alone. In turn, other investigators raised objections to the study by Patchell *et al*.[7] They insisted that the functional results after RTx alone of the study by Patchell *et al* were very poor when compared with the literature and that the enrollment of patients was biased to obtain the best outcome by surgery. They revealed that the criteria regarding suitability for surgery in the study by Patchell *et al* are only applicable to 10% to 15% of patients with MESCC and concluded that RTx alone is the most common treatment.[8] Some authors have concluded that functional outcome after surgery or RTx is equivalent,[9] whereas others have found that both surgery alone and surgery combined with RTx improve ambulatory function and health-related quality of life.[7,10]

The purpose of this study is to compare ambulatory status and survival for MESCC after treatment with DDSR+RTx with those outcomes after RTx treatment alone using a meta-analysis.

MATERIALS AND METHODS

Data Source

We performed a computerized search of MEDLINE (PubMed) (2005 to July 2013), EMBASE (2005 to July 2013), and the Cochrane Database of Systematic Reviews (Issue 7 of 12, July 2013). The keywords used for the literature search were as follows: epidural, metastasis or metastases, surgery or surgical resection, and RTx or radiation. Inclusion criteria were all studies involving adults who were diagnosed as having MESCC and comparing direct decompression with tumor removal followed by RTx with RTx alone. We also searched the bibliographies of relevant articles to identify additional studies. The language of publication was not restricted.

Two reviewers independently assessed the eligibility of all studies retrieved from the databases. Any disagreement between reviewers was resolved by discussion. We included human clinical comparative studies of DDSR+RTx *versus* RTx alone for MESCC that reported the change in ambulatory status and the survival rate. From the studies included in the final analysis, we extracted the following data: the study name (along with the name of the first author and the year of publication), the journal name, the affiliation of the first and corresponding authors, the country, the recruitment period and follow-up period (in years), the number of patients, the histology of the primary cancer, the ambulatory status before and after the treatment, and the survival rate at 6 and 12 months after the treatment. Relative risk (RR) with 95% confidence intervals (CIs) was calculated from the numbers of the 4 cells of the 2×2 tables of each of the studies. We assessed the risk of bias by using the Cochrane Collaboration's "risk of bias" tool in the randomized controlled study and a modified form of the Newcastle-Ottawa Scale for nonrandomized studies.[11,12] The risk of bias was assessed by at least 2 researchers independently, with disagreements resolved by discussion.

Statistical Method

Statistical analyses were conducted on the basis of 2×2 tables from individual study results on the basis of an intention-to-treat analysis using the number of patients. If there was no event in 1 of the 2 groups (*i.e.*, a "zero cell" in the 2×2 table), 0.5 was added to each cell of the table so that the estimated RR would not be 0 or infinity and so that the standard error could be calculated. To estimate heterogeneity across studies, we used Higgins I^2, which measures the percentage of total variation across studies due to heterogeneity. We estimated the pooled RR with a 95% CI on the basis of both the fixed and random effects models. Because we observed low heterogeneity ($I^2 < 60\%$) in all analyses and because the between-study variance was difficult to estimate, we reported the pooled RR with a 95% CI on the basis of the fixed-effects models. Publication bias was evaluated using a Begg funnel plot and the Egger test. All statistical tests were performed using R software (version 3.0.1; The R Foundation for statistical Computing, Vienna, Austria).

RESULTS

The method used to select relevant studies is presented as a flow diagram in Figure 1. A total of 248 articles were identified after searching the 3 databases and hand-searching relevant bibliographies. Among 248 studies, 74 studies were not original article or duplication. Patients of 106 articles were diagnosed as not having MESCC, and 42 articles were not comparative studies. Eighteen studies that dealt with novel treatments such as iodine, radiosurgery, and intraoperative brachytherapy or did not describe clear surgical techniques were excluded. We included a randomized controlled study and 4 observational studies in the final analysis.[7,9,10,13–15]

The 5 studies included a total of 1375 patients, with 238 and 1137 patients who underwent DDSR+RTx and RTx alone, respectively. The mean ages of the DDSR+RTx and RTx-alone groups were 63.3 and 66.8 years, respectively. Table 1 lists the general characteristics of the 5 studies included in the analysis. The countries in which the studies were conducted were as follows: the United States (n = 1),[7] Germany (n = 2),[9,14] Norway (n = 1),[13] and Brazil (n = 1).[15] The patients who could move independently (Frankel grade D or E) were 62.2% (range, 56.9%–68.0%) of the study population in the DDSR+RTx group and 74.2% (range, 63.0%–88.8%) of the study population in the RTX-alone group. In the DDSR+RTx group, 76 patients (28.6%) had lung cancer, 33 patients (12.4%) had prostate cancer, 29 patients (10.9%) had breast cancer, 14 patients (5.3%) had renal cell carcinoma, 12 patients (4.5%) had colorectal carcinoma, and 102 patients (38.3%) were diagnosed as having other types of cancer (Figure 2). In the RTx-alone group, 297 patients (24.4%) had lung cancer, 283 patients (23.2%) had prostate

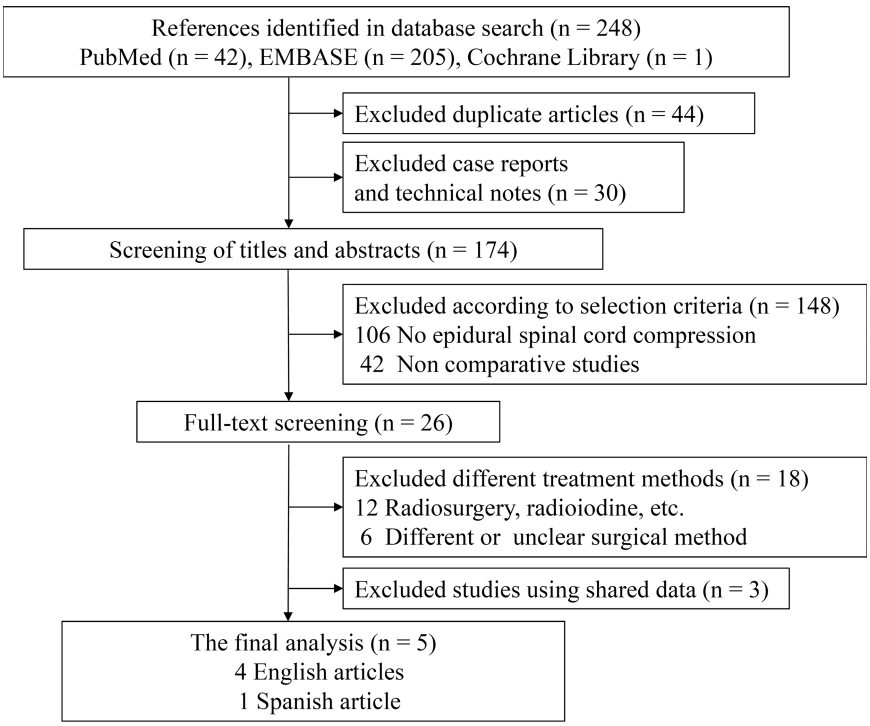

Figure 1. Flowchart of identification of relevant studies.

cancer, 187 patients (15.4%) had breast cancer, 59 patients (4.8%) had renal cell carcinoma, 22 patients (1.8%) had colorectal carcinoma, and 370 patients (30.4%) were diagnosed as having other types of cancer (Figure 2).

In a fixed-effects meta-analysis of 4 studies (1 study[13] did not obtain reliable data about ambulatory status after the treatment), the DDSR+RTx group displayed a significant improvement of ambulatory status after the treatment that was superior to that displayed by the RTx-alone group (RR, 1.43; 95% CI, 1.14–1.78) (z test; $P = 0.002$) with moderate heterogeneity ($I^2 = 57.7\%$) (Figure 3). The DDSR+RTx group displayed significantly lower deterioration after treatment than the RTx group (RR, 0.35; 95% CI, 0.19–0.63) (z test; $P = 0.001$) with low heterogeneity ($I^2 = 7\%$) (Figure 3).

In all 5 studies, the DDSR+RTx group displayed a significant prolongation of the survival rate at 6 months post-treatment (RR, 1.21; 95% CI, 1.09–1.33) (z test; $P < 0.001$) with small heterogeneity ($I^2 = 34.3\%$) (Figure 4). Similar findings were observed in 4 studies at 12 months post-treatment (RR, 1.32; 95% CI, 1.12–1.56) (z test; $P = 0.001$) with moderate heterogeneity ($I^2 = 48.3\%$) (Figure 4).

Publication Bias

The funnel plots for the improvement of ambulatory status and survival rate at 6 months were analyzed, and the Egger test results were calculated as 1.01 ($P = 0.58$) and 0.17 ($P = 0.92$), respectively. This result indicates that there is no evidence of publication bias in the dataset, although the

TABLE 1. Summary of Included Articles

Study	Study Design	Affiliation of Authors	Number		Good Ambulatory State*	
			DDSR+RTx	RTx Alone	DDSR+RTx (%)	RTx Alone (%)
Patchell *et al*[7] (2005)	RCT	NS	50	51	63.0	63.0
Falavigna *et al*[15] (2007)	Observational	NS	17	15	58.8	86.7
Rades *et al*[9] (2010)	Matched cohort	Rad	70	140	64.2	64.2
Rades *et al*[14] (2011)	Matched cohort	Rad	43	86	68.0	68.6
Zaikova *et al*[13] (2011)	Observational	OS	58	845	56.9	88.8
Total (average)			238	1137	(62.2)†	(74.2)†

**Frankel grade D or E at baseline state.*

†There is no significant difference between the 2 groups (P = 0.09).

DDSR indicates direct decompressive surgical resection; RTx, radiotherapy; RCT, randomized controlled trial; NS, neurosurgery; Rad, radiation oncology; OS, orthopedic surgery.

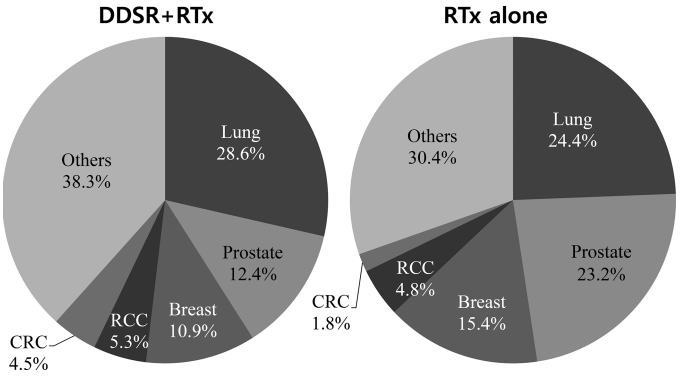

Figure 2. Tumor histology of the primary cancer in each group. Lung cancer shows the most common cancer in both treatments, followed by prostate, breast, kidney, and colorectal cancer. DDSR indicates direct decompressive surgical resection; RTx, *radiotherapy; RCC, renal cell carcinoma*.

published literature is likely to exhibit a publication bias. The funnel plot demonstrated a slight asymmetry, which may indicate an underpowered analysis. The Egger test results of all comparisons were not significant. Therefore, no correction for publication bias was performed.

DISCUSSION

There are 2 milestone studies for MESCC. Patchell (a neurologist/neurosurgeon) *et al*[7] reported that DDSR+RTx treatment is superior in maintaining and regaining ambulatory function to treatment with RTx alone for patients with spinal cord compression caused by metastatic cancer.[7] Rades (a radiation oncologist) *et al*[9] reported that outcomes such as motor function, local control, and overall survival at the end points after DDSR+RTx displayed better results than those after RTx alone; however, the difference was not significant. These authors implied that RTx alone, a less invasive treatment, is superior to the surgical resection, which is an invasive treatment. We found some evidence that DDSR+RTx improved the ambulatory status compared with RTx alone. The deterioration of ambulatory status was more frequent in the RTx-alone group than in the surgery group. The ambulatory status before treatments was better in the RTx-alone group than in the DDSR+RTx group, but there was not a significant difference. The survival rate was also improved in the DDSR+RTx group compared with the RTx-alone group. In the literature review, the Eastern Cooperative Oncology Group scale reflecting ambulatory status is a significant prognostic factor for survival in the treatment of MESCC and the ambulatory status is closely related with infectious diseases and death.[9,16–18] Therefore, DDSR+RTx treatment improves ambulatory status and seems to extend overall survival.

Positive reasons for DDSR are as follows: immediate decompression, decreased tumor burden, high chance of motor improvement, and rare motor deterioration after the treatment. The negatives of DDSR are as follows: spinal cord or root injury, extensive bleeding, infection, dura tear, and complications related to general anesthesia. In this study, the mean complication rate of surgical resection was 12.4% (range, 8.0%-29.4%). Recent advances in surgical and supporting techniques for MESCC have decreased surgical risks and include spinal angiography and embolization of tumor vessels, percutaneous instrumentation, and vertebroplasty. These advances provide more opportunities to treat patients with MESCC with low risks, and surgical resection followed by RTx may achieve a better outcome with a lower surgical risk.

There is a general consensus regardless of author affiliation in the prior studies regarding 4 points. First, DDSR can produce more favorable outcomes than decompressive laminectomy without ventral tumor excision.[7,9,14] Second, patients with MESCC from a relatively radioresistant tumor, such as renal cell carcinoma, colorectal cancer, or non-small cell lung cancer, seemed to display improvement of motor function more often after DDSR+RTx than RTx alone.[7,9,14] Third, RTx alone is recommended for the treatment of MESCC from

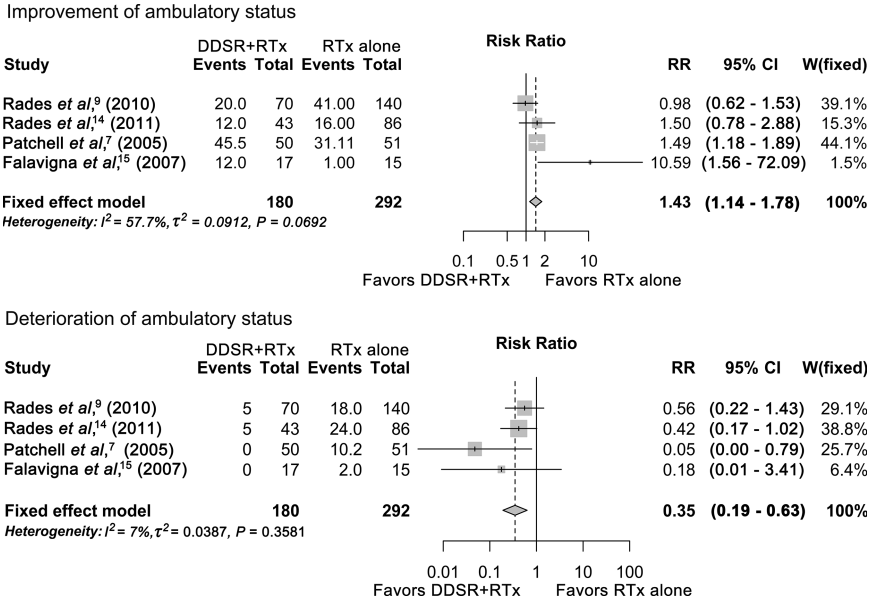

Figure 3. Forest plot of the improvement and deterioration of ambulatory status. Ambulatory status is improved in the DDSR+RTx group and is deteriorated in the RTx-alone group, which shows significant difference. DDSR indicates direct decompressive surgical resection; RTx, *radiotherapy*; RR, relative risk; CI, confidence interval.

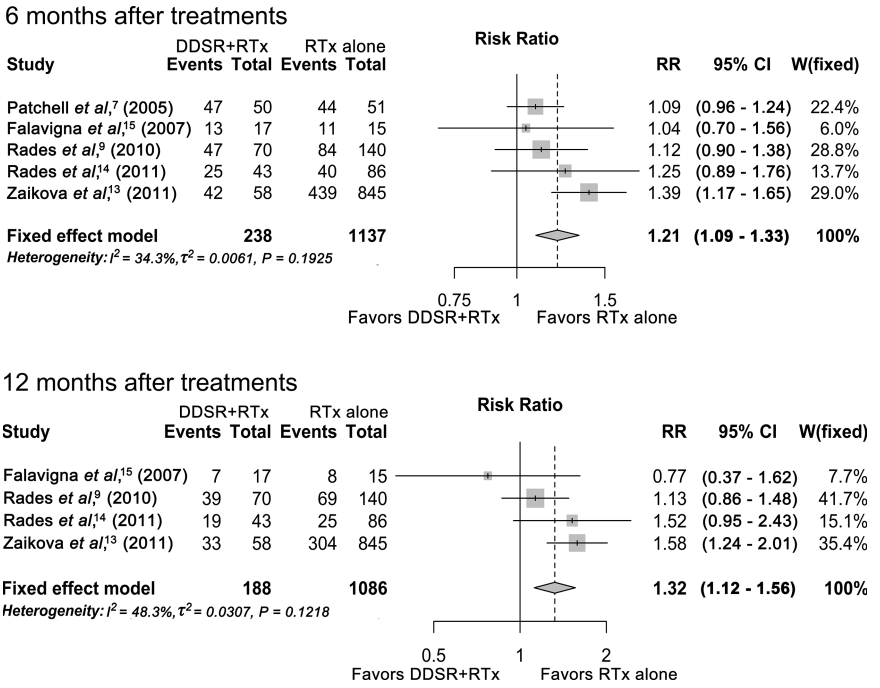

Figure 4. Forest plot of survival rate at 6 and 12 months after the treatments. The survival rate is high in the DDSR+RTx group compared with the RTx-alone group at 2 time points. Significant difference is observed for survival rate at 6 and 12 months after the treatments. DDSR indicates direct decompressive surgical resection; RTx, *radiotherapy*; RR, relative risk; CI, confidence interval.

radiosensitive tumors.[8,13] Fourth, MESCC accompanied with mechanical instability requires surgical stabilization regardless of tumor histology.[8,13]

Patients with myeloma or lymphoma, which are radiosensitive tumors, were enrolled and underwent DDSR in 2 studies.[9,13] The reason why radiosensitive tumors were removed *via* surgical resection could be explained by the high rate of patients with motor impairment in this group and improved survival expectancy. Another explanation might be the osteolytic metastasis of these tumors. Bony metastatic lesions from lymphoma and myeloma are usually osteolytic, which may produce mechanical instability and indication for surgery, especially in the case of pathological fractures and medulla compression by bony fragments. In such cases, RTx is often considered less effective than surgery.[13]

Limitations of Our Study

Our study has some limitations that must be considered when interpreting our results. We included only studies comparing DDSR+RTx and RTx alone since 2005. Patients who underwent decompressive laminectomy without ventral tumor excision were not included in this study. Although decompressive laminectomy without ventral tumor excision has been also performed until today, it was excluded to compare DDSR+RTx with RTx alone. Another limitation is the method we used to classify patients and tumors. The most important factors in deciding treatment methods are patient factors and tumor histology. The general conditions for surgical resection and the radiosensitivity of tumors were not considered in this study. However, the included studies enrolled a matched patients group. Therefore, the heterogeneity of the patients might be low. Actually, preoperative motor function of the RTx-alone group is slightly better than the others. Finally, estimations of patients' satisfaction and quality of life after treatments are important to evaluate the treatments. Unfortunately, enrolled studies did not describe them or evaluated incompatible scoring systems.

CONCLUSION

We found a notable difference for ambulatory status and survival between DDSR+RTx and RTx alone in the treatment of MESCC in our meta-analysis of published studies since 2005. The DDSR+RTx accomplish improvement in the clinical parameters of ambulation status and survival more than RTx alone in the treatment of patients with MESCC. DDSR+RTx is a considerable option for the treatment of MESCC to improve and maintain ambulatory state.

➢ Key Points

- ❑ A total of 5 comparative studies that treated with RTx alone *versus* DDSR+RTx for the patients with MESCC showed similar performance status were included in this meta-analysis.
- ❑ The DDSR+RTx group displayed substantial improvement in ambulatory status after the treatment that was superior to the improvement in the RTx-alone group (RR, 1.43; 95% CI, 1.14–1.78) and lower deterioration after treatment than the RTx group (RR, 0.35; 95% CI, 0.19–0.63).
- ❑ The DDSR+RTx group showed higher survival rate than the RTx-alone group at 6 and 12 months follow-up (6 mo: RR, 1.21; 95% CI, 1.09–1.33; 12 mo: RR, 1.32; 95% CI, 1.12–1.56).
- ❑ DDSR+RTx may produce better clinical improvement of ambulation status and survival than RTx alone in the treatment of MESCC.

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