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LITERATURE REVIEW

Clinical Outcome of Metastatic Spinal Cord Compression Treated With Surgical Excision ± Radiation *Versus* Radiation Therapy Alone

A Systematic Review of Literature

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Study Design. Systematic literature review from 1970 to 2007.

Objective. This study reports the results of a systematic review comparing surgical decompression ± radiation to radiation therapy alone among patients with metastatic spinal cord compression.

Summary of Background Data. Currently, the optimal treatment of metastatic spine lesions is not well defined and is inconsistent. Radiation and surgical excision are both accepted and effective. There appears to be a favorable trend for improved neurological outcome with surgical excision and stabilization as part of the management.

Methods. A review of the English literature from 1970 to 2007 was performed in the Medline database using general MeSH terms. Relevant outcome studies for the treatment of metastatic spinal cord compression were selected through criteria defined *a priori*. The primary outcome was ambulatory capacity. A random effects model was built to compare results between treatment groups, based on calculated proportions from each study.

Results. Of the 1595 articles screened, 33 studies (2495 patients) were selected based on our inclusion and exclusion criteria. Sixty-four percent of the patients who underwent surgical decompression, tumor excision, and stabilization had neurological improvement from nonambulatory to ambulatory status. Twenty-nine percent of the radiation therapy group regained the ability to ambulate after treatment ($P < 0.001$). Paraplegic patients had a 4-fold greater recovery rate to functional ambulation with surgical intervention than with radiation therapy alone (42% *vs.* 10%, $P < 0.001$). Pain relief was noted in 88% of the patients in the surgical studies and in 74% of the patients in studies of radiation therapy ($P < 0.001$). The overall surgical complication rate was 29%.

Conclusion. This systematic review suggests that surgical excision of tumor and instrumented stabilization may improve clinical outcomes compared with radiation therapy alone, with regard to neurological function and pain. However, most data in the current literature are from observational studies, where variations in patient population and treatments cannot be controlled. This compromised our ability to compare the results of both treatments directly.

Key words: Metastatic spinal cord compression, radiation, surgical decompression. **Spine 2012;37:78–84**

The vertebral column is the most common osseous site of metastasis. Metastatic spinal cord compression (MSCC) has been reported in as many as 20% of patients with cancer.[1–3] Unrecognized or previously untreated vertebral lesions often present with severe pain and bony compromise that may eventually progress to the onset of neurological deficits.[1–7] Previous studies have demonstrated an association between a loss of ambulatory capacity and a shortened life expectancy.[8–15] Thus, neurological function has been commonly utilized as the primary outcome measure for both surgical and nonsurgical treatment studies addressing MSCC.

In the 1970s and early 1980s, stand-alone decompressive laminectomy was considered to be the intervention of choice for MSCC. During this same time period, published reports of radiation therapy documented similar clinical outcomes without the added risk of operative complications or iatrogenic spinal instability.[7,10,16,17] As a result, radiation therapy (RT) supplanted surgical intervention as the preferred treatment for MSCC.

With the development of new surgical techniques and improved spinal instrumentation, more direct approaches to

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spinal cord decompression and stabilization have become possible. Modern surgical approaches and strategies enable direct removal of bone and tumor with immediate restoration of spinal stability. Several studies have reported improved neurological outcomes with modern surgical techniques compared with radiation.[18–22] Despite these more recent contributions to the literature, the optimal approach to the treatment of MSCC has yet to be established. The purpose of this study was to perform a comprehensive systematic review of the literature to compare the ambulatory status of patients treated for MSCC with surgical decompression and instrumented stabilization with those having received RT alone.

MATERIALS AND METHODS

Search

This systematic review reports on all English-language publications from January 1970 to December 2007 that investigated the treatment of spine metastasis using surgery, radiation, or both. The Medline database was searched using the following medical subject heading key words: metastasis, spinal cord compression, surgery, surgical decompression, radiotherapy, and radiation. A combination of these general terms was used to extract a comprehensive list of articles, from which the titles and abstracts were used as the initial screening tool. The references from these selected articles were also manually reviewed to identify additional studies. We narrowed the final selection of articles by applying inclusion and exclusion criteria to all of the articles that assessed the treatment of MSCC using surgical intervention, RT, or both (Figure 1). The literature search was completed on January 27, 2010.

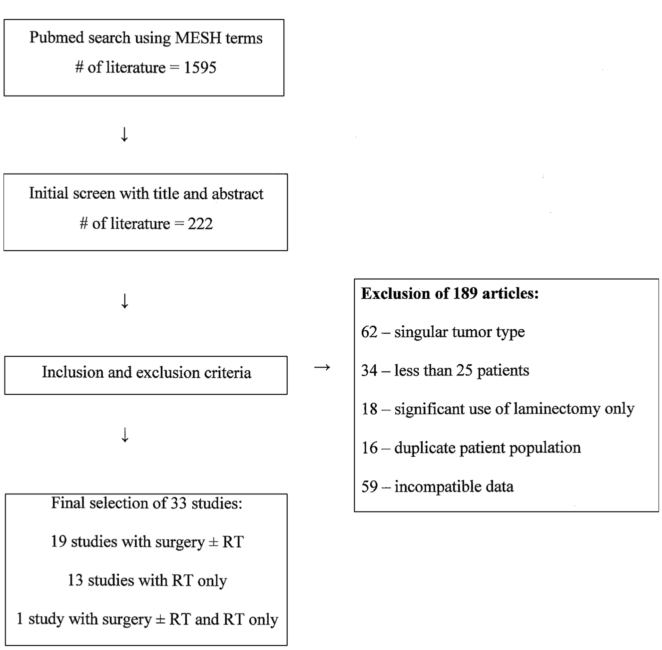

Figure 1. Literature search algorithm.

Study Selection

Inclusion criteria required a minimum of 25 patients per study, treatment involving multiple tumor types, use of ambulatory status as one of the outcome measures, and appropriate outcome data that allowed for pooled data analysis. For papers to be included in the surgical cohort, the surgical procedure (regardless of the anatomic approach) had to have the stated goals of direct neurological decompression and instrumented reconstruction to provide immediate restoration of spinal stability. For the radiation therapy arm, the dose ranged from 20 to 45 Gy given in various fractions (5–20 Fr). Neoadjuvant steroid use was inconsistently reported.

Exclusion criteria included surgical interventions that consisted of decompression without stabilization (*i.e.*, laminectomy), incompatible data, or a duplicate patient population that was published in multiple studies. Incompatible data consisted of studies with no information on neurologic function, lack of specification of pre- or post-treatment ambulatory status, and a single combined outcome of surgery and radiation. Subjects who used steroids, pre- and/or postoperative chemotherapy, or hormonal therapy were not excluded. Implementation of preoperative neoadjuvant therapy and dosage of RT also did not impact the selection process. The accuracy of collected data was verified by 2 orthopedic surgeons (J.M.K., M.B.H.) and 1 statistician (J.E.C.). No exclusions were made based on study design.

Data Items

The parameters of interest were demographic data, tumor characteristics, pre- and post-treatment ambulatory capacity, pain relief, and complications. Tumor characteristics included the primary site of origin and the location within the spine. Common sources of metastatic origin were breast, lung, prostate, renal/genitourinary, gastrointestinal, melanoma, sarcoma, liquid tumors (myeloma/lymphoma), and unknown primaries. Rare spine metastatic tumors such as head and neck, pancreas, germ cell tumors, uterine, adrenal, carcinoid, giant cell carcinoma, vascular, basal cell carcinoma, neurofibroma, or unspecified tumors were grouped under the term “others.” Tumor metastatic locations were divided into cervical, thoracic, and lumbosacral.

Post-treatment complications were categorized as wound-related problems, pulmonary embolism/deep venous thrombosis, instrumentation failure, gastrointestinal bleeding/perforation, cardiac events, pulmonary/pneumonia, excessive bleeding/hematoma, cerebrospinal fluid leak, reoperation, and others. Both mean and median survival rates were recorded for each type of cancer when available (9 out of 34 studies). The more common form of reporting survival data was based on the rate of 1-year survival and 30-day mortality. The detailed summary table with extracted data is available in the electronic appendix (see Appendix, Supplemental Digital Content 1, http://links.lww.com/BRS/A544).

In this body of literature, neurological status was not uniformly classified. For the purposes of this investigation, outcomes were converted to either functional recovery (*i.e.*, non-ambulatory to ambulatory) or deterioration (*i.e.*, ambulatory to nonambulatory). All patients who had significant lower extremity weakness rendering them incapable of ambulation (Frankel grade A–C) were categorized as nonambulatory. We also included a separate analysis of patients with absent functional motor capacity (Frankel grade A–B), which was classified as paraplegia.

Summary Measures

The primary outcome measure was the percent of patients improving their functional status from nonambulatory to ambulatory. Studies were pooled within each intervention, weighted by the inverse variance of the percent of patients becoming ambulatory. Baseline characteristics were compared using weighted means. Random effects models were built to compare outcome measures. All statistical analyses were performed at a 5% level of significance using SAS statistical software version 9.2 (SAS Institute, Cary, NC).

RESULTS

Literature Search

Between 1970 and 2007, 1595 articles were identified from the Medline database using our search criteria. Following title and abstract review, 222 articles were found to be relevant, describing the treatment of spine metastases using surgery, RT, or both. Based on established criteria, 34 studies were included in the final analysis. Nineteen studies investigated surgical treatment of spine metastasis,[8,11,20–36] and 13 studies evaluated RT only.[5,9,10,12–16,37–41] One study was included twice for both treatment arms.[18] The flow chart of study selection is shown in Figure 1.

Only 1 randomized controlled study exists in the current literature. The remainder of the studies included were case series analyzing the outcomes of surgery or radiation. Although not explicitly stated in the studies, surgeons and radiation oncologists used a variety of interventions and patient selection criteria within the same treatment arm. Therefore, the uniformity of the patient population and the treatment could not be assumed.

A total of 2495 patients were compiled from the included studies. The surgical group consisted of 1249 patients, and the RT group contained 1246 patients. All studies documented the neurological status pre- and post-treatment, and the vast majority of articles contained adequate information on demographics (31 out of 33 studies), tumor type (28 out of 33 studies), and pain relief (21 out of 33 studies). All of the studies regarding surgical intervention presented data on complications; however, similar data addressing complications were not available from the investigations involving RT. Most articles documented the use of preoperative RT (14 out of 20 studies) but rarely included information about adjuvant therapy.

Demographics and Tumor Profile

Eight of 20 surgical studies and 11 of 14 RT studies reported the patient median age; these were 57 years and 60 years, respectively. Twelve of the surgical studies and one of the RT studies reported the mean age, which was 57 years in the surgical group and 56 in the RT group. Two studies from the RT group did not report the age of the patients. The weighted mean ages of patients in the 2 groups were 57.5 years for surgery and 59.9 years for radiation, indicating that the radiation group was somewhat older. The male-to-female ratio (56:44) was similar irrespective of treatment.

The location of spinal metastases in both groups was most prevalent in the thoracic spine (65%), followed by lumbosacral (25%) and cervical regions (10%). The source of metastases included a wide variety of cancers; breast, lung, prostate, and kidney were the most common primary loci. The source of metastases was similar for both surgical and RT groups. There were certain tumor types, which were preferentially treated using one method (Table 1). For example, prostate cancer was most often treated with radiation, while genitourinary cancers and sarcoma were more frequently managed with surgical intervention.

Ambulatory Status

Surgical intervention with tumor decompression and spinal stabilization generally led to improved functional outcomes (Figure 2, Table 2). Among pretreatment nonambulatory

TABLE 1. Demographic Information, Tumor Locations, and Types for Each Treatment Group

		Surgery ± RT†	RT Alone†	P
Demographics	Number of patients	1249	1246	
	Median age (yr)	57.5	59.9	0.107
	% male	55.9	56.3	0.895
Tumor location (%)	Cervical	12.8	6.4	0.082
	Thoracic	63.2	68.2	0.283
	Lumbosacral	24.0	25.4	0.751
Tumor type, n (%)	Breast	223 (19)	382 (25)	0.144
	Lung	171 (15)	245 (17)	0.436
	Prostate	80 (7)	260 (19)	<0.001*
	Renal/GU	145 (12)	80 (5)	<0.001*
	GI	60 (5)	50 (4)	0.427
	Melanoma	47 (4)	27 (2)	0.374
	Sarcoma	44 (4)	11 (1)	0.044*
	Myeloma/lymph	119 (11)	150 (10)	0.729
	Unknown	62 (6)	98 (6)	0.964
	Others	235 (19)	167 (12)	0.064

*Statistical significance.

†The number and percentage are derived from aggregated data of all studies reviewed.

GI indicates gastrointestinal; GU, genitourinary; RT, radiation therapy.

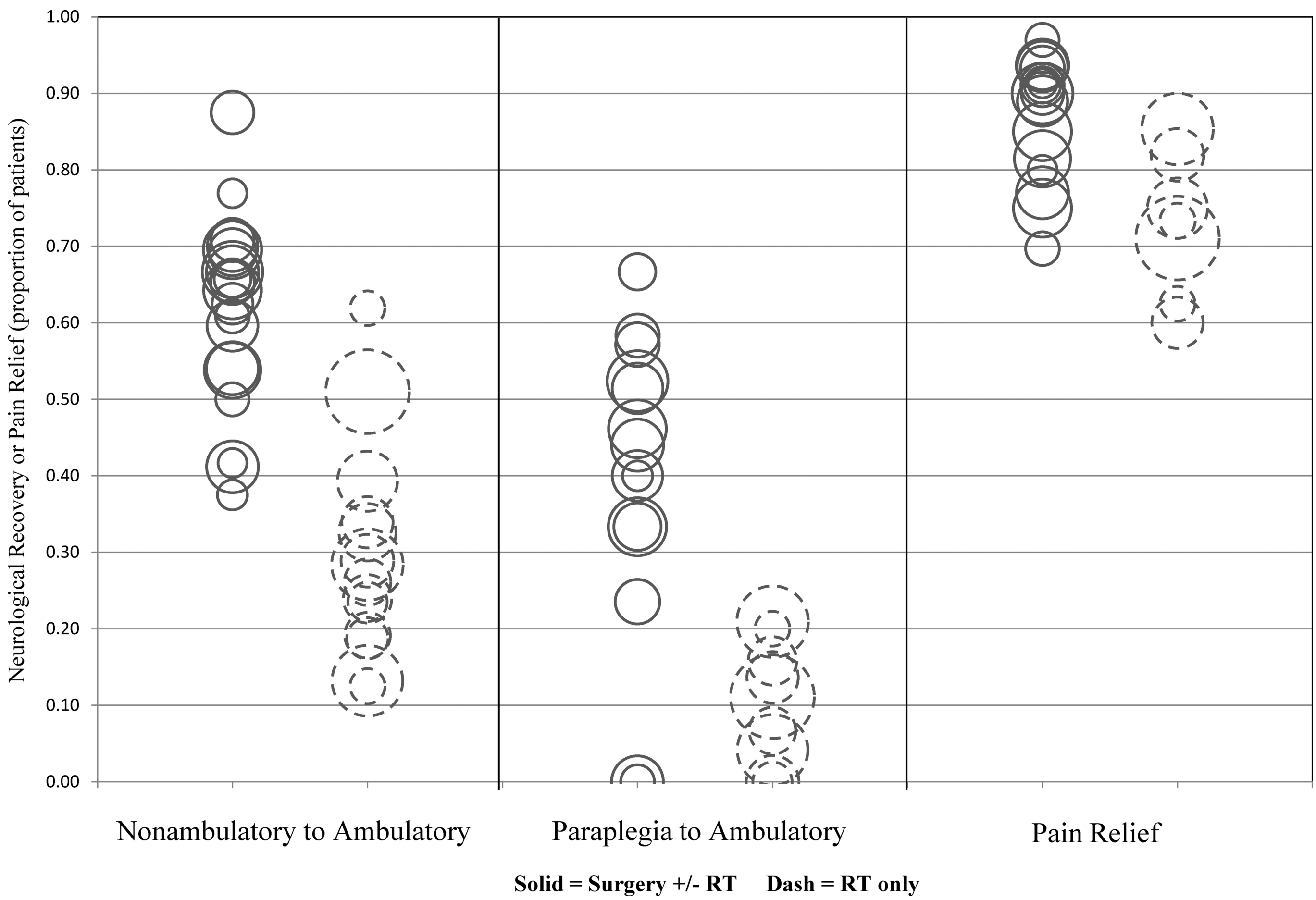

Figure 2. Clinical outcomes of surgery ± RT and RT only. Each circle represents a study. The area of each circle is proportional to the number of patients in the study. Each column contains the outcomes of neurological recovery or pain relief. The solid circles represent the results of surgery ± RT, and the dashed circles represent the results of RT only. The outcome of each treatment is demonstrated by clustering of circles. All studies from 1970 to 2007 are included.

patients, approximately 64% were able to regain ambulatory capacity after surgery compared with 29% of the patients that received RT alone ($P < 0.001$). Forty-two percent of the pretreatment paraplegic patients in the surgical group regained ambulatory function, whereas only 10% of patients who received radiation regained ambulatory function ($P < 0.001$). Clinical deterioration, or loss of pretreatment function, was uncommon in both groups. Less than 1% of ambulatory patients in the surgical group became nonambulatory after treatment, compared with 9% of ambulatory patients in the RT group who subsequently lost their ability to ambulate ($P < 0.001$, Table 2).

Insufficient data were available to assess the neurologic outcome of surgical decompression based on tumor type.

TABLE 2. Functional Status and Pain Relief Pre- and Post-treatment

			Surgery ± RT (N = 1438)				RT Alone (N = 1331)				
			Absolute Number of Patients			Weighted Mean	Absolute Number of Patients			Weighted Mean	*P*
Functional status*			Pre		Post		Pre		Post		
Nonamb	→	Amb	584	→	373	0.641	649	→	196	0.289	<0.001
Paraplegic	→	Amb	173	→	80	0.420	160	→	20	0.100	<0.001
Amb	→	Nonamb	549	→	5	0.01	504	→	40	0.087	<0.001
Pain relief (%)			680/777 (88)				450/606 (74)				<0.001

**Nonamb corresponds to Frankel grade A–C. Amb corresponds to Frankel grade D–E. Paraplegic corresponds to Frankel grade A–B.*

Amb indicates ambulatory; Nonamb, nonambulatory; Pre, pretreatment; Post, post-treatment; RT, radiation therapy.

Among the radiation studies, 5 studies (191 patients) reported functional recovery specific to the primary site of tumor origin.[10,13,14,16,41] Radiosensitive tumors such as breast and lymphoproliferative origin led to recovery of ambulatory status in 55.4% and 70.1% of nonambulatory patients, respectively. Aggressive or radioresistant tumors responded poorly, with recovery of ambulatory function in 19.5% for lung, 37.1% for prostate, and 27.0% for kidney metastases.

Pain Control

Both the radiation and surgical groups presented with significant pain prior to the onset of treatment: 88% in the surgery group and 84% in the RT group. Surgery resulted in pain relief in 88% of the patients compared with 74% of those treated with RT ($P \leq 0.001$; Figure 2, Table 2). The assessment of pain was largely based on self-report, and the perception of patients' progress was subject to reporting bias.

Complications

Complication rates resulting from RT alone were not available, and very few studies documented systemic disease progression during therapy. For surgical intervention, the overall complication rate was 29% (range: 5%–65%), and the rate of mortality was 5% (range: 0%–22%) in the acute postoperative period (within 30 days of surgery). Common surgical complications included wound infection/dehiscence (8%), pneumonia/pleural effusion/respiratory failure (4%), instrument failure (4%), deep vein thrombosis/pulmonary embolism (2%), and CSF leak (2%).

Approximately 50% of the patients in the surgical group received radiation treatment prior to surgery (reported in 14 out of 20 articles). Two studies specifically documented the difference in complication rates among those patients who received preoperative radiation and those who did not.[18, 36] Forty percent to 67% of patients undergoing preoperative radiation developed complications, in contrast to 33% of those who received surgery as the initial intervention. Wound infection and dehiscence were the most common problems encountered in those undergoing surgery after having received RT.

Survival

The overall 30-day mortality rate in the surgical group was 5% (20 out of 20 studies). There was limited reporting of the 30-day mortality rate in the RT alone group (2 out of 14 studies). A diagnosis of lung cancer or melanoma in either treatment group had a poor survival rate, with reports ranging from 1 to 8 months.[8–11,20,24,26,29,32] Tumors of unknown origin had a similarly poor prognosis, with a survival of 3 to 5 months.[9, 10] The median survival of patients when considering all tumors was generally higher for the surgical group relative to RT (17 *vs.* 3 months).[8–12,15,24,36,38,39] Commonly treated spinal metastases in the surgical group such as those from breast, lung, prostate, genitourinary, and lymphoproliferative tumors had a mean survival range of 12 to 21 months, 2 to 9 months, 8 to 32 months, 9 to 25 months, and 26 to 54 months, respectively. In the radiation group, only 2 studies reported survival based on tumor type.[9, 10] The median survival of breast, lung, prostate, genitourinary, and lymphoproliferative tumors were 11 months, 1 to 3 months, 9 months, 3.5 months, and 9 to 14 months, respectively. Regardless of treatment, the patients who were ambulatory had approximately 5- to 6-fold greater median survival than nonambulatory patients.[8–14]

DISCUSSION

Decompressive laminectomy was once the primary treatment for MSCC. With the advent of RT, however, several comparative studies found that surgical decompression offered no additional benefit.[7,10,16,17,42] Although laminectomy allows for a larger posterior space for the spinal cord, most metastatic impingement originates from the vertebral body and leads to primarily ventral pressure.[19,43] In addition, a traditional wide laminectomy will not afford the surgeon the opportunity to safely remove the tumor in its entirety, thus ultimately resulting in both residual cord compression and further structural compromise.[7,16,25,42]

New surgical techniques and improved spinal instrumentation enable surgeons to directly remove bone and tumor to more completely decompress the cord and simultaneously stabilize the spinal column. The clinical results of more extensive surgery identified in this systematic review reflect these improved surgical techniques.[18–22,44] Nonetheless, an early referral to a spine surgeon to assess surgical options still remains inconsistent and frequently occurs only after a course of radiation has been initiated.[45]

In 2005, Patchell *et al*[18] published the first randomized controlled trial that demonstrated superior neurological outcomes with surgery ± RT compared with RT alone. This study was terminated early because of a significantly improved ambulatory capacity and increased survival time for patients in the surgical cohort. However, because of the nature of the study, patients with radiosensitive tumors such as lymphoma, leukemia, and multiple myeloma were excluded, and, subsequently, the outcomes of radiation were found to be inferior to those of prior studies.[10,18,37–39]

The most common and relevant measure of a successful intervention is the recovery of ambulatory function and pain relief. On the basis of our systematic review, surgical decompression and stabilization ± radiation appear to have an advantage over RT alone in terms of restoring ambulatory function. A dramatic difference was noted among the subpopulation of paraplegic patients receiving surgical intervention. No distinction was made between radiosensitive and radioresistant tumors in our study. The overall risk of complications for surgery was noted to be 29% and was likely influenced by the burden of systemic disease. RT alone, while recognized to be the safer alternative, is also not without complication risks. The postradiation clinical course in 1 study included a 10% incidence of adverse events, including cardiogenic shock and sepsis.[10]

The survival and mortality data of this patient cohort were often presented using different methods and were, therefore, not subject to statistical analysis. There was, however, a more favorable trend for those patients who were ambulatory after treatment. This observation must be viewed carefully because most studies did not control for confounders such as stage of cancer and associated medical comorbidities.

There are several limitations to this study. Most of the investigations included in this analysis were retrospective, and only 1 study was specifically designed to compare outcomes between patients treated surgically and those receiving RT alone.[18] Furthermore, the decisions regarding the treatments in the studies were likely determined by the clinicians, based on their individual experiences as well as institutional resources. Subsequently, an inherent weakness in attempting to draw conclusions about patient outcome from the nonrandomized studies is the risk of substantial selection bias and confounding by indication.

Surgery may provide a valuable advantage over radiation alone in terms of restoration of ambulatory function, but the literature is subject to selection bias. Ultimately, further research of a prospective, randomized nature is required before more definitive conclusions can be drawn.

➢ Key Points

- ❑ The results of this systematic review suggest that individuals treated with surgical decompression and instrumented stabilization had a greater chance of decreased pain and improved ambulatory function compared with patients who received radiation alone.
- ❑ The results of this analysis cannot, however, adjust for the possibility of selection bias in the studies under review, limiting the potential to directly compare results of both treatments.
- ❑ More randomized controlled trials are needed in the future.

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