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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ABSTRACT

Study Design: Systematic literature review from 1970 to 2007.

Objective: Laminectomy has not demonstrated a benefit over radiation therapy in treating metastatic spine lesions. This study reports the results of a systematic review, spanning 37 years of literature, comparing surgical decompression and stabilization to radiation therapy alone.

Summary of Background Data: Currently the optimal treatment of metastatic spine lesions is not well defined and 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 English literature from 1970 to 2007 was performed in Medline database using general MeSH terms. Relevant outcome studies for the treatment of metastatic spinal cord compression were selected through defined criteria. The primary outcome was ambulatory capacity. A mixed effect model was built to compare results between treatment groups, based on calculated proportions from each study.

Results: Of 1595 articles screened, 33 studies (2495 patients) were selected based on our inclusion and exclusion criteria. On average, 64% of patients who underwent surgical excision and stabilization had neurological improvement from nonambulatory to ambulatory status. Twenty-nine percent of radiation therapy group made a similar neurologic recovery ($p \leq 0.001$). 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 patients in the surgical studies and in 74% of patients in studies of radiation therapy ($p \leq 0.001$). The overall surgical complication rate was 29%.

Conclusion: This systematic review suggests that surgical excision of tumor and instrumented stabilization may improve clinical outcomes with regard to neurological function and pain. However, these observational data do not adjust for inherent selection bias, compromising our ability to compare the results of both treatments directly.

INTRODUCTION

The vertebral column is the most common osseous site of metastasis. Metastatic spinal cord compression (MSCC) has been reported in as high as 20% of patients with cancer[3,24,34]. Unrecognized or previously untreated vertebral metastasis often present with severe pain, and this bony compromise may eventually progress to the onset of neurological deficits[3,6,12,24,26,34,42]. Previous studies have demonstrated an association between a loss of ambulatory capacity and a shortened life expectancy[18,22,23,25,27,28,32,41]. Thus, neurological function has been commonly utilized as the primary outcome measure for both surgical and nonsurgical management studies addressing vertebral metastasis.

In the 1970's and early 80's, 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 outcome without the added risk of operative complications or iatrogenic spinal instability[5,12,14,27]. 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 spinal cord decompression and stabilization have become possible. Modern surgical approaches and strategies enable direct excision of bone and tumor with immediate restoration of spinal stability. Several studies have reported improved neurological outcomes with modern surgical techniques compared to radiation[13,16,29,31,35].

In 2005, Patchell *et al* published the first randomized controlled trial that demonstrated superior neurological outcomes with surgery ± RT compared to RT alone[31]. The study was terminated early due to significantly improved ambulatory capacity and increased survival time within the surgical cohort. However, due to the nature of the study, patients with radiosensitive tumors were excluded, and the outcomes of radiation were found to be inferior to those of prior stud-

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ies[17,27,31,33,36]. Despite these 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 results of surgical decompression and instrumented stabilization to those of RT alone.

MATERIALS AND METHODS

This systematic review reports publications in English 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 MeSH (Medical Subject Heading) keywords: *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 initial screening tools. The references from these selected articles were also manually reviewed to identify additional studies. We narrowed the final selection of articles by applying strict inclusion and exclusion criteria to all of the articles that assessed the treatment of metastatic spinal column tumors using surgical intervention, RT, or both (Figure 1).

Inclusion criteria required a minimum of 25 patients per study, treatment involving multiple tumor types, use of the 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. A common radiation dose ranged from 20 to 45 Gy given in various fractions (5-20 Fr). Neoadjuvant steroid was inconsistently reported.

Exclusion criteria were: surgical interventions that consisted of decompression without stabilization (*i.e.* laminectomy), incompatible data, and duplicate patient population published in multiple studies. Incompatible data consisted of studies with no information on neurologic function, lack of specification of 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.

Study results were pooled, and a systematic review was performed with each study weighted based on sample size. The parameters of interest were demographic data, tumor type, pre- and post treatment ambulatory capacity, pain relief, and complications. 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 non-ambulatory). All patients who had significant lower extremity weakness rendering them incapable of ambulation (Frankel grade A-C) were categorized as "non-ambulatory." We also included a separate analysis of patients with absent functional motor capacity (Frankel grade A-B), which was classified as "paraplegia."

Baseline characteristics were compared using weighted means, to provide higher weight to larger studies. The main outcome was considered by percent of patients changing their status from "nonambulatory" to "ambulatory." The mixed effect model was built to compare outcome of surgical versus radiation interventions. Statistical significance was determined for p-values ≤ 0.05.

RESULTS

Literature search results. 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, 33 studies were included for the final analysis. Nineteen studies investigated surgical treatment of spine metastasis[1,2,4,9,10,15,16,18,19,21,29,30,35,37-39,41,43,44], and 13 studies evaluated RT only[7,14,17,20,22,23,25,27,28,32,33,36,42]. One study was included for both treatment arms[31] (Fig. 1).

A total of 189 studies were excluded. Sixty-two studies reported on treatments involving a single type of tumor, 34 studies consisted of less than 25 patients, and 18 investigations reported results for stand alone laminectomy procedures. Sixteen articles were rejected because two or more publications by the same author analyzed the patients during the overlapping time period, and thus could not be ruled as a unique population. Fifty-nine articles were missing vital data points that did not permit analysis of demographic information and neurological outcome. In two studies, data for patients treated with RT were included, while surgical patients from the same investigation were excluded because they received laminectomy alone[28,36].

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 these 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 surgical literature included the data on complications; however, similar data addressing complications were not available from the RT studies. Most articles documented on the use of preoperative RT (14 out of 20 studies), but rarely included information about the adjuvant therapy.

Demographics and tumor profile. Eight of the surgical studies and 10 of the RT studies reported the patient median age; these were 57 and 60 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. The *weighted* mean ages of patients in the two groups were 57.5 years for surgery and 59.9 years for radiation, indicating that radiation group was somewhat older. The male-to-female ratio (56:44) was similar regardless of the treatment.

The location of spinal metastases in both groups was most prevalent in the thoracic spine (65%), followed by lumbosacral (25%) and cervical spine (10%). The source of metastases included a wide variety of cancers with breast, lung, prostate and kidney being the common primary sites. The distribution was similar for both surgical and radiation treatment groups. There were certain tumor types which were preferentially treated with one method (Table 1). 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 excision and stabilization generally led to improved functional outcomes (Figure 2, Table 2). Among non-ambulatory patients, approximately 64% were able to ambulate after surgery compared to a 29% ambulatory rate for patients after treatment with RT alone ($p \leq 0.001$). Forty-two percent of paraplegic patients in the surgical group regained ambulatory function whereas only 10% of patients receiving radiation regained ambulatory function ($p \leq 0.001$). Clinical deterioration, with loss of pre-treatment function, was uncommon in both groups. Only 1% of ambulatory patients in the surgical group became non-ambulatory following treatment, as compared with 9% of ambulatory patients in the RT group ($p = 0.003$) (Table 2).

Pain control. A similar proportion of patients in both groups had pain prior to treatment: 88% of those receiving surgery and 84% in the RT group. The treatment successfully relieved pain in both groups. Surgery provided pain relief in 88% of patients, compared to 74% of those treated with RT ($p \leq 0.001$) (Figure 2, Table 2).

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% in the post-operative period of 30-days (range 0 - 22%). 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 patients in the surgical group had 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[31,39]. Forty to sixty-seven percent of patients undergoing preoperative radiation had 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 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; reports ranging from 1 - 8 months[10,15,18,19,23,27,29,41,43]. Tumor of unknown origin had a similarly poor prognosis with survival of 3 - 5 months[23,27]. The median survival of patients when considering all tumors was generally higher for the surgical group (17 vs. 3 mont hs)[10,17,18,23,27,28,32,36,39,41]. Regardless of treatment, the patients who were ambulatory had approximately 5 - 6 fold greater median survival than nonambulatory patients[18,22,23,25,27,32,41]

DISCUSSION

Decompressive laminectomy was once the primary treatment for MSCC. With the advent of RT, however, several comparative studies found surgical decompression to offer no additional benefit[5,12,14,27,45]. 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[8,13]. Additionally, 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[4,12,14,45]. New surgical techniques and improved spinal instrumentation enable surgeons to directly remove bone and tumor in order 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.

In general, all patients included in this study shared similar demographic parameters and primary tumor distribution (Table 1). Furthermore, due to the metastatic nature of the cancer most patients were presumed to be at an advanced stage. The notable differences were those patients with carcinomas of the prostate, genitourinary tract and soft-tissue sarcomas, which were preferentially treated with surgery or RT. We also selected articles that analyzed multiple tumor types to reflect a representative population with MSCC, but at the cost of obtaining more homogenous patients with similar co-morbidities and cancer burden.

Neurological function was the most commonly studied outcome in the literature. While there are many ways to grade ambulatory and neurological status (*i.e.* Tomita, Frankel, Findlay and American Spinal Injury Association), the most important measure of a successful intervention is the recovery of ambulatory ability. Based on the results presented here, surgical resection ± radiation appears to have an advantage over RT in terms of restoring ambulatory function following treatment. Furthermore, patients who were paraplegic had the best chance of regaining ambulatory function with surgical intervention as a part of the treatment.

As pain represents one of the most common symptoms of spine metastasis, pain relief is another vital therapeutic goal. Cancer pain can be intractable and severe, significantly compromising one's quality of life. The severity of pain can cause patients to become sedentary or bed-bound despite normal neurological function[11]. Both surgery and radiation were noted to be successful in reducing pain. Most reports, however, failed to use objective measures (*i.e.* narcotic dose) to quantify pain relief.

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 since most studies did not control for confounding factors such as the stage of cancer and the associated medical co-morbidities. The 30-day mortality in the surgical group was documented in all 20 studies; and ranged from 0 - 22% with a mean of 5%. However, only Patchell RA *et al* and Maranzano E *et al* in the radiation group reported the 30-day mortality, which was 14% and 10% respectively[27,31]. An inherent weakness in attempting to draw conclusions about survival data from the nonrandomized studies is the risk of selection bias, whereby only patients "healthy enough" to tolerate a spinal reconstructive procedure would have been offered surgery.

According to our analysis, surgery carries 29% risk of complications. Infections and pulmonary complications were the most common. A widely cited risk for surgical wound complication is previous exposure to radiation[16]. As such, complication rates were significantly influenced by the burden of systemic disease and neoadjuvant therapies. Radiation therapy, while recognized to be the safer alternative, is also not without risks. The post-radiation clinical course in one study included a 10% incidence of adverse events, including cardiogenic shock and sepsis[27].

There are several limitations to the current study. Most of the studies included in this analysis were retrospective, and only one study was designed specifically to compare outcomes of patients treated surgically to those receiving RT[31]. Furthermore, the decisions regarding treatment in the studies we included were likely determined by the radiation oncologists and surgeons based on individual experience; therefore, substantial selection bias cannot be excluded.

In recent years, modern surgical techniques for spine lesions have consistently demonstrated improved results[13,16,29,31,35,40]. Nonetheless, an early referral to a spinal surgeon to assess the surgical options still remains inconsistent, and often occurs only after an a course of radiation has been initiated[11]. Based on our study, surgery may provide a valuable advantage over radiation in terms of restoration of ambulatory function, and pain reduction. Definitive resolution of this therapeutic question will require more randomized trials.

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