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A Systematic Review of Metastatic Hepatocellular Carcinoma to the Spine

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Keywords

hepatocellular carcinoma; spine metastasis; liver cancer; tumor; surgery; survival

INTRODUCTION

Hepatocellular carcinoma (HCC) remains the third leading cause of cancer-related death and the fifth most prevalent cancer world-wide¹. The highest incidence of HCC remains in sub-Saharan Africa and East Asia, where Hepatitis B, endemic to these areas, remains the primary cause². Although HCC accounts for less than 2% of all neoplasms in the United States and the Western World³, the incidence of HCC is increasing, doubling in the United States over the past 25 years³. With improved diagnostic tests and treatment modalities long term survival for patients with HCC has improved dramatically over the past three decades^{34–13}. Three decades ago, the mean survival time from diagnosis was 3–4 months, whereas it currently exceeds 2 years¹⁴. With this advancement, the incidence of metastatic HCC has likewise increased, including metastases to the spinal column¹⁴.

The incidence of symptomatic skeletal metastases ranges between 1.5% and 7.3%^{10, 15}, and this number continues to increase along with the longevity of patients with metastatic HCC. Bony lesions are typically osteolytic (approximately 80%)¹⁶. The median occurrence of spinal metastases from the time of diagnosis is 13 months, with the median survival without any intervention from diagnosis of bony skeletal metastases being approximately 7 months in current studies (compared to 3 months in 2006)¹⁶.

With the improved survival of patients with metastatic HCC, surgery for spinal metastases has become more prevalent. We review the literature that describes patients with HCC spinal metastases to gain better insight into the management of metastatic HCC to improve survival and health related quality of life (HRQOL). The overall objective of this manuscript was to answer the following clinical questions: (1) What is the survival rate of patients diagnosed with a HCC spine metastases overall and stratified by treatment type (surgery, chemotherapy, radiation, or observation) (2) Are there clinical, radiographic and histological prognostic variables that may help predict clinical outcomes of patients with HCC who undergo spinal surgical intervention?

METHODS

Electronic Literature Search

A systematic review of the literature was performed using PubMed, Embase, CINAHL, and Web of Science, as well as a review of the bibliographies of eligible articles. The broad search query was designed to include the hepatocellular cancer patient population with spinal metastases reported in the literature since 1950. Additionally, a prognostic variable search specific to metastatic hepatocellular cancer patients was conducted with emphasis on the metastatic-free interval (MFI), which describes the duration between diagnosis of primary disease and first metastasis. Unfortunately given the limited clinical data this analysis could not be performed, and thus a summary of the larger clinical studies was

performed to in order to supplement the limited prognostic variables available. A summary of search strings, as well as inclusion and exclusion criteria are provided in Table 1 and Supplemental Table 1.

Data Extraction

Demographic information extracted from clinical studies included: age, gender, spinal level treated, radiation use, chemotherapy and/or other adjuvant therapy, presentation of symptoms, and type of clinical study performed. (Supplemental Table 2) From the literature detailing spinal surgical outcomes, the following data were extracted: patient population (number of patients with spinal metastases and percent of hepatocellular cancer patients that comprise the entire study population), and survival information (post-op survival time and/or post-op survival rate).

Study Eligibility and Quality Assessment

All potentially eligible studies were determined by two reviewers (AVR and NA). A third reviewer (CRG) resolved instances of disagreement. After finalizing the series of studies to be analyzed, two reviewers (AVR and NA) extracted data in order to answer the inquiries posed in the objectives. A third reviewer independently reviewed and confirmed all results (CRG). We excluded papers that did not originate from a hepatocellular lesion, were not metastatic, had an unknown primary lesion during their entire length of follow-up, focused on leptomeningeal disease and/or included heterogeneous cohorts with no results that were specific to hepatocellular cancer spinal metastases. The PRISMA tool was used as applicable to assess the methodological quality of the included studies.¹⁷

The assessment of individual study quality was performed using the following grading system: high, low, or insufficient similar to previous publications.^{18, 19} 'High' was assigned to studies that were Class of Evidence (CoE) I or II, and the true effect could be confidently assumed to be close to the estimated effect. 'Low' was assigned to studies that were Class III or IV, and the true effect may have been significantly different than the estimated effect. 'Insufficient' was assigned if there was very little confidence in the estimated result, no evidence, or too little evidence to estimate an effect.¹⁹ The quality could be downgraded if the evidence was indirect, results were inconsistent, there were no a priori subgroup analyses or the effect estimates were imprecise. Conversely, overall estimation of quality could be upgraded if the magnitude of effect was large.

Statistical Methods

Survival statistics and Kaplan-Meier curves were calculated using GraphPad Prism 5.0 (GraphPad; La Jolla, CA, USA). All cases from the literature were included as applicable. Cases with unknown follow-up or survival times were excluded from the analysis.

RESULTS

Study Selection

We performed a literature search using PubMed, Embase, CINAHL, and Web of Science, as well as a search through the bibliographies of eligible articles. A total of 476 articles were

identified initially, and after articles were excluded based on our preset inclusion and exclusion criteria, ultimately, 26 studies^{7, 9, 13, 20–42}, with a total of 152 patients, were included in this review based on the eligibility criteria. (Figure 1)

Results Summary

Of the 26 articles included, there were 3 retrospective cohort studies, 17 case reports, 5 case series, and 1 longitudinal observational study. One-hundred and thirty-three (87.5 %) cases were male. The mean age at presentation of spinal metastasis was 53.6 (± 10.52) years. Mean time to spine metastasis from the primary diagnosis was 20.1 (± 10.21) months. The most common locations for metastasis were the thoracic (n = 68, 44.7%) and lumbar (n = 34, 22.4%) spine. (Table 2)

Overall Survival—Overall survival after diagnosis of the primary tumor and survival after diagnosis of spinal metastasis were available for 104 patients and 147 patients, respectively. The mean and median survival after diagnosis of a HCC spinal metastasis was 14.8 (± 13.1) and 10.6 months (IQR: 10 – 26), respectively, and the mean and median overall survival after diagnosis of the primary HCC tumor was 36.9 (± 18.4) months and 39.4 months (IQR: 22.5 – 48), respectively. Of the patients with known overall survival after diagnosis of a spinal metastasis, survival at 3 months, 6 months, 1 year, 2 years, and 5 years was 95.2%, 83.0%, 28.6%, 2.0%, and 1.4% respectively. Additionally, of the patients with known overall survival after diagnosis of the primary tumor, survival at 3 months, 6 months, 1 year, 2 years, and 5 years was 95.2%, 92.3%, 88.5%, 74.0%, and 2.9% respectively. (Figure 2 and Table 2). Of note, when analyzed by highest involved spinal level, patients diagnosed with HCC spinal metastases had a median survival of 2.5 months (IQR: 2.0 – 3.0), 11 months (IQR: 5.3 – 22.5), 6 months (IQR: 2.0 – 10.5), and 6 months (IQR: 5.0 – 8.0) in the cervical, thoracic, lumbar and sacral spinal levels, respectively, that was significant (p = 0.0384). (Figure 3A)

Treatment Result Summaries

The most common treatment for patients with HCC spinal metastasis was surgery alone (n = 48, 31.6%), followed by surgery plus radiation (n = 43, 28.3%) and a combination of surgery, chemotherapy and radiation (n = 36, 23.7%) (Table 2). In the 4 patients with known survival who received no treatment, the mean and median survival after diagnosis of the spinal metastasis was 3.2 ± 5.2 months and 0.7 months (IQR: 0 – 8.5), respectively, whereas the mean survival after the primary diagnosis was 12.7 ± 15.2 months. For patients with known survival who received surgical intervention alone (n=6), the median survival after diagnosis of the spinal metastasis was 7 months (IQR: 4.3 – 11.3), whereas the mean survival after the primary diagnosis was 28.7 ± 21.6 months and the mean survival after spinal metastasis diagnosis was 8.1 ± 5.4 months. For patients with known survival who received the combination of surgery and medical management (chemotherapy and/or radiation) (n=4), the median survival after diagnosis of the spinal metastasis was 13.5 months (IQR: 4.0 – 94.3), whereas the mean survival after the primary diagnosis was 44.8 ± 66.1 months and the mean survival after spinal metastasis diagnosis was 37.4 ± 55.4 months. For patients with known survival who received chemotherapy and/or radiation alone (n=11), the median survival was 6 months (IQR: 5.0 – 24), whereas the mean survival after the primary diagnosis was 25.9 ± 30.0 months and the mean survival after spinal metastasis

diagnosis was 17.5 ± 22.6 months. The differences in survival according to treatment modality only approached statistical significance on Mantel-Cox testing ($p = 0.0971$). These postoperative survivals for surgical and non-surgical studies are trended in Figure 3B.

Study Quality and Overall Strength of Literature

All 26 studies were case reports, case series or observational cohort studies without control groups. Hence, the majority of papers had a baseline CoE of Level IV, with few papers having a CoE of Level III. Based on the CoE and the quality and consistency of data, the overall strength of findings is 'low' to 'insufficient'.

Pre-operative Patient Characteristics and Prognostic Factors

While limited data exists on the natural history of metastatic HCC, one study has recently examined the natural history of bony metastases⁴³. Approximately 60% of bony metastases are found in the spine. The most common presentation is back pain (70%), primarily associated with mechanical instability but in some cases also due to pathological fractures (25%). Weakness due to myelopathy is the presenting feature in approximately 30% of patients but is almost invariably preceded by back pain. Up to 15% of patients present with clinically significant hypercalcemia. The most common site of spinal metastases from the reported literature is the thoracic spine (70%), followed by the lumbosacral spine (20%) and the cervical spine (10%). Several groups have theorized that this may relate to shared arterial and venous supply between the primary hepatocellular carcinoma and these respective spinal levels, including the Batson venous plexus.

The Child-Pugh score has been statistically and clinically validated in patients with HCC in numerous studies as a means for quantifying hepatic function and as a prognostic tool for overall survival⁴⁴. This score combines hematological parameters including serum bilirubin, serum albumin, and INR as markers of hepatic function and ascites and hepatic encephalopathy as clinical markers of hepatic function to partition patients into prognostic groups A–C, which are reviewed in Table 3. These groups correlate directly with expected overall survival in Model for end-stage liver disease (MELD) patients with hepatocellular carcinoma⁴³. Recently, the MELD score has emerged as a more comprehensive alternative to the Child-Pugh score and the MELD score will thus likely supplant the Child-Pugh score in clinical practice in the near future. Existing studies to date in the literature however have largely used the Child-Pugh score.

While numerous scores have been developed to assess systemic disease in patients with spinal metastases, including the Tokunashi score, Tomita score, Bauer score, Linden score, Rades score, and Katagiri score²², most studies involving hepatocellular carcinoma spinal metastases have used the Tomita Score^{45, 46} to determine the severity of the systemic disease. This score weighs the histological grade of the malignancy, the presence of treatable or untreatable visceral metastases and the extent of bony metastases. Overall, this measure gives a score for the extent and severity of systemic disease and is reviewed in Table 3. In terms of neurological function, most studies involving hepatocellular carcinoma spinal metastases have used the Frankel score⁴⁷ for both simplicity and low interobserver variability. This scale classifies motor and sensory function in five grades A–E as shown in

Table 3. In several series, patients diagnosed with spinal metastasis additionally achieved significant improvement in quality of life after surgical intervention^{9, 48–51}. Post-operative ambulatory status was a significant predictor of overall survival in addition to quality of life in these patients, and all studies report an overall mean improvement in ambulatory status in patients who had a compromised ambulatory status pre-operatively^{9, 48–51}. Perhaps most significantly, subsequent loss of ambulatory status from any cause was directly correlated with mortality in one series⁹.

Posterior approaches were generally favored and involved posterior decompression with either *en bloc* resection or debulking of the tumor and instrumentation if deemed necessary by the primary surgeon^{9, 42, 52}. Vertebroplasty was additionally performed in one of the reported series where the primary surgeon deemed it necessary due to loss of height and vertebral body collapse, although the precise indications are not clearly delineated in the existing studies⁹. Anterior approaches were used in all of the series primarily when the lesions were limited to part of the vertebral body and caused ventral spinal cord compression^{9, 42, 52}. Mean blood loss during procedures across series, where they are reported, was 2.0L, with a mean operative time of 4.2 hours^{9, 52}. There is a suggestion in the literature that spinal operations in patients with metastatic HCC may have a higher expected blood loss than patients with other histological tumor types due to the intrinsic coagulopathy associated with HCC. Overall, up to 30% of patients with HCC have coagulopathy with elevated INR > 1.2^{9, 52}. Up to 30% of surgical patients in one series had an INR > 1.2 that was corrected with fresh frozen plasma and vitamin K pre-operatively with replenishment as needed intraoperatively⁹. However, there was no statistically significant correlation between pre-operative INR and intraoperative blood loss⁹. One major study reports pre-operative tumor embolization in selective patients as a means to potentially reduce operative blood loss, although this study did not have any significant difference in operative blood loss compared to other studies where embolization was not performed⁹.

DISCUSSION

HCC metastases are a significant cause of cancer-related morbidity and mortality and the incidence is expected to increase with the improvements in systemic therapies. With the paucity of studies on HCC spinal metastasis, there is limited information available on clinical outcomes for this patient population. In this study, we systematically reviewed the literature for studies that describe the survival and treatment of patients diagnosed with a HCC spinal metastasis. We identified 26 studies meeting the inclusion criteria and a total of 152 patients with spine metastases secondary to a hepatocellular spinal metastasis. Our review demonstrates that the median overall survival for patients diagnosed with a HCC spinal metastasis to the spinal column is 10.6 months after diagnosis of metastasis and 39.4 months after primary tumor diagnosis. Furthermore, we demonstrate that although the survival in comparison to either modality alone approaches statistical significance ($P = 0.0971$), patients treated with surgery plus adjuvant therapy have increased survival compared to either modality alone or observation.

Our systematic review was unable to determine prognostic factors across all studies that were associated with improved survival based on the limited information contained in the

case reports and retrospective studies. Therefore, we summarized the results of the major clinical studies that have been performed to date on HCC spinal metastases and report possible prognostic factors that may help predict clinical outcomes of patients who undergo surgical intervention. Taking the studies by Zhang et al⁴², Kim et al⁹, and Lin et al⁵² together, pre-operative Child Pugh score seemed to correlate with overall post-surgical survival^{9, 42, 52}. Zhang et. al. included primarily Child-Pugh class A patients (34/36) and demonstrated a median overall survival of 12 months, while Kim et al, included 18 class A, 11 class B, and 4 class C patients with a median overall survival of 5 months^{9, 42}. While direct statistical comparison cannot be made, there is a suggestion that perhaps a better pre-operative Child-Pugh class is correlated with a longer survival. Given the demonstrated prognostic strength of the Child-Pugh score in overall survival in HCC, this is highly plausible, suggesting that Child-Pugh A patients may be superior surgical candidates who may maximally benefit from surgical intervention given their overall longevity, although it does not preclude surgical benefit in patients with a pre-operative Child-Pugh B or C classification. Direct assessment of this relationship in future studies will allow surgeons to more carefully select patients who would maximally benefit from surgical intervention.

Although, there is evidence to suggest that the Child-Pugh classification may be able to help predict survival, a similar comparison could not be made with the Tomita score because the Tomita score distribution is more similar among the studies, Zhang et. al. demonstrate in their multivariate analysis that patients with a Tomita score of 8 or more had a mean survival of 8 months, whereas those with a Tomita score of 7 or less had a mean survival of 23.8 months^{9, 42, 52}. Thus, both the Child-Pugh class and the Tomita score may provide substantial pre-operative prognostic information and may prove important guides in patient selection.

Our results demonstrate that patients who underwent surgery plus adjuvant therapy have longer survival compared to either modality alone or observation. However, the difference in survival may be attributable to patient selection when making therapy decisions, rather than the effect that the therapy may have on the survival, with patients with longer expected survival undergoing surgery followed by adjuvant treatment and patients with short expected survival undergoing single-modality therapy. Furthermore, the data regarding the association between survival and therapy was only available for 25 patients, further limiting the conclusions that can be drawn. In the absence of multivariate analysis analyzing the association of survival with intrinsic patient characteristics (i.e. Child-Pugh score) and therapy selection, conclusions about the association of therapy with survival cannot be made. Unfortunately, such analysis could not be performed with the current data.

Despite the increase in quantity of life, a risk-benefit analysis must be performed to determine whether there is significant improvement in the quality of life of these patients (which could not be performed due to lack of data in the reviewed studies). Kim et. al. demonstrate a survival benefit among ambulatory patients and demonstrate that these those patients who achieved ambulatory status had an overall improved survival benefit compared to their non-ambulatory counterparts⁹. Furthermore, Lin et. al. report that 10 out of their 12 patients experienced clinically significant pain relief post-operatively, although they do not quantify pain scales or narcotic usage specifically⁵². Future studies should utilize validated

outcome measures to assess improvements in quality of life for patients diagnosed with HCC spinal metastases. Conversely, although the potential benefits have been demonstrated, the risks of a poor post-surgical outcome have also been shown. For instance, surgical intervention is shown to have up to a 10% peri-operative mortality rate within the first month after surgery and a 15% non-mortality complication rate, as reported by Kim et al. Common complications include wound infection and/or dehiscence, CSF leak, and instrumentation failure. Furthermore, these patients are at high risk of coagulopathy, and careful attention must be paid to the coagulation parameters and qualitative clotting assessment during surgery. Meticulous hemostasis is of paramount importance in patients with HCC in order to prevent post-operative hematoma formation. Additionally, strong consideration should be given to the use of fresh frozen plasma (FFP) prophylactically at the induction of anesthesia both in patients with elevated and normal coagulation parameters. The INR may not accurately predict the ability of the liver to restore vitamin K dependent coagulation enzymes as noted by the fact that patients with normal INR's had equivalent blood loss to those with INR's $> 1.2^9$. Judicious use of FFP early in a surgical case may help prevent intra- and postoperative coagulopathy with associated increased blood loss and other associated complications. As these surgeries become more common, careful documentation of complications and systematic analysis will help reduce the complication rates.

Although this study represents a systematic review of the literature, there are several significant limitations of our study including: publication bias, which is inherent to systematic reviews, the retrospective data collection from studies with small sample sizes, the majority of included studies were case reports, and there was a heterogeneous compilation of treatment modalities that were utilized in this patient population. Also, the majority of clinical studies that met our preset inclusion criteria did not contain sufficient information to adequately analyze the clinical variables and their overall impact on survival. Future multi-center prospective studies analyzing the impact of various treatment modalities are needed to determine the optimal treatment paradigms for patients diagnosed with HCC spinal metastases.

CONCLUSION

The incidence of hepatocellular carcinoma and the overall survival of patients with metastatic HCC have increased multifold over the past several decades. With this increase, the incidence of patients diagnosed with a symptomatic HCC spinal metastases has also escalated. The median overall survival for patients diagnosed with a HCC spinal metastasis is 10.6 months after diagnosis, with patients well enough to undergo surgery plus adjuvant therapy displaying a trend toward longer post-operative survival ($P = 0.0971$) compared to either modality alone or observation. Patients with HCC are at high risk for perioperative coagulopathy, and the risk of postoperative hematoma must be carefully considered. Future studies will be needed to evaluate the benefits and risks of surgical interventions in order to make these treatments safer and more accessible to a broader segment of this patient population and also to determine the appropriate prognostic factors that can predict which patients will benefit maximally from surgical intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CoE	Class of Evidence
HCC	hepatocellular carcinoma
HRQOL	health related quality of life
MELD	Model for end-stage liver disease
MFI	metastatic-free interval

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Figure 1.
CONSORT Diagram detailing article selection per exclusion/inclusion criteria.

Figure 2.

(A) Survival of all patients diagnosed with a hepatocellular carcinoma (HCC) spinal metastasis from primary diagnosis (B) Interval time from primary HCC diagnosis to diagnosis of spinal metastasis [dotted lines indicate standard deviations] (C) Survival from diagnosis of a HCC spinal metastasis.

Figure 3.

(A) Survival of patients diagnosed with a HCC cancer spinal metastasis stratified by highest involved vertebral level. The difference in survival was statistically significant on Mantel-Cox testing ($p = 0.0384$). (B) Survival of patients diagnosed with a HCC cancer spinal metastasis stratified by either no treatment, surgical intervention alone, medical management (chemotherapy and/or radiation), or the combination of surgical intervention and any medical management (chemotherapy and/or radiation). The difference in survival approached statistical significant on Mantel-Cox testing ($p = 0.0971$).

Table 1

Selection Criteria

Search Engine	Number of Results from Key Search String(s)	Inclusion	Exclusion
Pubmed *	184 Results	(a) Publication Date: 1950 or later (b) Language: English or a complete English translation (c) Articles describing operative techniques used to treat spinal metastases in cancer patients (d) Articles describing medical interventions used to treat spinal metastases in cancer patients (e) Fully-published, peer-reviewed, retrospective or prospective studies including randomized controlled trials, nonrandomized trials, cohort studies, case control studies, and case series (f) Must be of hepatocellular carcinoma origin, with known primary (h) Must be study of human patients	a. Articles that did not provide clinical outcomes and statistics specific to hepatocellular cancer spinal metastases patients b. Articles that included hepatocellular cancer spinal metastases cohort outcomes with that of other primary tumor types c. Articles on non-humans
Embase *	134 Results		a. Same as above b. Same as above c. Same as above
CINAHL *	9 Results		a. Same as above b. Same as above c. Same as above
Web of Science *	141 Results		a. Same as above b. Same as above c. Same as above
Cochrane Library *	8 Results: 5 Cochrane Reviews 3 Trials		a. Same as above b. Same as above c. Same as above
			Citation Counts Total Results: 476 Total Duplicates: 140 Total Unique Results: 336

* Search String in Supplemental A)

The Pubmed and Embase searches were limited to humans only. No other limitations were placed on the searches. All searches were run on May 8, 2015.

Table 2

Patient Demographics & Outcomes

Total # of Patients with Spine Metastases	HCC (N=152)
Gender, Male, <i>n</i> (%)	133 (87.5)
Mean Age at Primary, years ($\pm$SD)	53.6 ($\pm$ 10.5)
Mean Time to Spine Metastasis, months ($\pm$SD)[*]	20.1 ($\pm$ 10.2)
Location, <i>n</i> (%)	
Cervical	22 (14.5)
Thoracic	68 (44.7)
Lumbar	34 (22.4)
Sacrum	6 (3.9)
Multi-level	21 (13.8)
Medullary Cone	1 (0.7)
Treatment of Spinal Metastasis, <i>n</i> (%)	
Surgery Only	48 (31.6)
Radiotherapy Only	14 (9.2)
Chemotherapy/Immunotherapy Only	2 (1.3)
Surgery plus radiation	43 (28.3)
Surgery plus chemo/immunotherapy	1 (0.66)
Chemotherapy and Radiation	1 (0.66)
Surgery plus radiation and chemotherapy	36 (23.7)
No treatment/Unknown	67 (4.6)
Survival, <i>n</i> (%)[†]	
Patients with Known Survival	104 (68.4)
Patients with Unknown Survival	48 (31.6)
3 Months Survival	5 (4.8)
4 to 6 Months Survival	3 (2.9)
7 to 12 Months Survival	4 (3.8)
13 to 24 Months Survival	15 (14.4)
25 to 60 Months Survival	74 (71.2)
>60 Months Survival	3 (2.8)
Mean Survival from Spine Metastasis Diagnosis, months ($\pm$ SD) [‡]	14.8 ($\pm$ 13.1)

^{*}Time to spine metastasis provided for 105 patients

[†]Survival from time of primary cancer diagnosis, unless otherwise noted

[‡]Survival from spinal metastasis provided for 147 cases

Abbreviations: hepatocellular carcinoma: HCC; number: n; metastasis: met

All percentages based off of a total # of patients (N), except for survival where percentages are based off of patients with known survival

Table 3

Prognostic Algorithms.

A. Child-Pugh Score			
Parameters	1 Point	2 Points	3 Points
Bilirubin (mg/dL)	<2	2–3	>3
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.3	>2.3
Ascites	None	Mild	Severe
Hepatic Encephalopathy	None	Mild	Severe
B. Tomita Score			
Parameters	1 Point	2 Points	4 Points
Grade of Malignancy	Slow Growth	Moderate Growth	Rapid Growth
Visceral Metastases	N/A	Treatable	Untreatable
Bone Metastases	Solitary	Multiple	
C. Frankel Score			
Score	Definition		
A	Complete motor and sensory dysfunction		
B	Complete motor dysfunction, incomplete sensory		
C	Incomplete motor and sensory dysfunction		
D	Useful motor function with or without assistance		
E	No motor or sensory function disorder		