Loss of local tumor control after index surgery for spinal metastases: a prospective cohort study.

Abstract

Background

As survival following treatment for symptomatic spinal metastases increases, the incidence of local tumor recurrence may also increase. However, data regarding incidence and timing of recurrence, or duration of survival after second surgeries are not readily available, and may help to inform clinicians when to perform second surgeries.

Objective

To identify features associated with loss of local control (LLC) at a previously treated or new spinal level.

Methods

Clinical and surgical data were collected from a prospective cohort of 1421 patients who had surgery for symptomatic spinal metastases. Patients undergoing repeat spinal surgery for symptomatic LLC at the same or a different level were identified and analyzed.

Results

3.0% patients underwent repeat surgery for symptomatic LLC after a median interval of 184 days from the first surgery, median survival was 6.1 months after second surgery. Factors associated with second surgery for LLC were the primary tumor type, number of spinal levels, Tomita staging, Tokuhashi and Karnofsky scores, anterior surgical approach, more aggressive surgical resection and postoperative radiotherapy. 1.5% patients were admitted for surgery to a different spinal level than the index operation after median 338 days from the first operation.

Conclusion

The likelihood for repeat surgery due to LLC cannot be accurately predicted at the time of initial presentation. Factors associated with second surgery for LLC relate to less aggressive tumor biology and better survival. Most patients had a reasonable duration of survival after second surgery.

Running title

Repeat surgery for spinal metastases

Keywords

Metastases, Recurrence, Repeat surgery, Spine, Surgery, Tumor

Introduction

Surgery for spinal metastases is effective in the management of patients with cancer when their quality of life is threatened by pathological vertebral fracture or spinal cord compression.[1-5] Evolution of spinal surgery techniques over the past two decades have enabled direct spinal cord or nerve root decompression and tumor resection in combination with tailored spine reconstruction. Hence, the goal of surgery is to reduce pain and to restore or safeguard neurological function. The incidence of spinal metastases has been increasing since treatment for oncologic disorders has improved over recent years resulting in longer patient survival.[6,7] Improved survival has also led to the possibility of patients living long enough to experience loss of local tumor control after surgery and radiotherapy for symptomatic spinal metastases. Although, Patchell and colleagues in their landmark paper demonstrated that surgery is advantageous when a patient first presents with symptoms,[1] little is known about the outcome after revision surgery for local tumor recurrence. To inform the complex decision-making process when a patient presents with symptomatic spinal metastasis, scoring systems have been developed to predict patient survival.[8-11] Moreover, more detailed decision algorithms have been suggested to decide whether more aggressive surgical resection is appropriate.[12,13] Therefore, recurrent spinal cord compression from loss of local control could be considered a shortcoming of the initial choice of surgical technique or approach. While it is thought that radical en bloc resections may reduce the incidence of loss of local control,[9] such interventions are associated with higher surgical risks.[14] The reported incidence of loss of local control after piecemeal intralesional debulking varies between 1.4 and 32% depending on the definition used for loss of local control: 32% for radiological loss of local control,[15] 20-22% for symptomatic loss of local control[16,17] and 1.4-8.4% for patients effectively undergoing revision surgery.[18,19] Laufer et al reported a median survival of 9 months after repeat surgery for recurrent spinal metastasis, and a 65% rate of preserved ambulation.[20] Therefore, the consideration of repeat surgery can be relevant in terms of safeguarding quality of life in patients with spinal metastasis with sufficiently long survival.

The aim of the current study was to identify possible predictors of recurrent spinal symptoms resulting from loss of local tumor control at a previously treated level and to document preoperative status and survival after repeat surgery. We also reviewed data for patients who underwent a second operation for new spinal metastases at a different level to the index operation. The study uses data from the Global Spine Tumour Study Group (GSTSG) database. This database is the largest prospective surgical series of patients with symptomatic spinal metastases. Other GSTSG publications have looked at subsets of patients from the same database, to study aspects of metastatic spine disease.[21-23]

Methods

Patients and GSTSG database

For this study, data from consecutive patients who were admitted for surgery for symptomatic spinal metastases at 23 orthopedic spinal or neurosurgical centers in Belgium, Canada, China, Denmark, France, Germany, Japan, The Netherlands, South Korea, Spain, the United Kingdom and the United States of America were longitudinally followed up in a research database. Indications for surgery were spinal pain, instability or neurological symptoms. Patients were analyzed if recruited between March 2001 and September 2016. Patients were excluded if they were unable to consent or if they had a primary bone tumor of the spine.

A secure Internet database was developed by the GSTSG and hosted on computer servers with secure socket layer Thawte-certificated encryption. Anonymized validated data was prospectively entered by surgeons at the spine centers. Case record forms were locked four weeks after initial data entry so that data could not be altered or amended. Local institutional ethical approvals were granted in all centers.

Variables

Preoperative data at the time of initial surgery included: age, gender, primary tumor type, spinal level(s) affected by tumor, Tomita classification of tumor extent,[24] type and number of visceral metastases, extraspinal bone metastases, Tomita prognostic score,[9] Tokuhashi prognostic score,[10] preoperative radiation therapy, ambulatory status, Frankel score, sphincter control, Visual Analogue Scale (VAS) for axial/radicular pain, Karnofsky performance index, American Society of Anesthesiology (ASA) score, and the EQ-5D questionnaire. Surgical data included: type of surgery,[25] number of spinal levels of tumor resection and fixation, and intraoperative and postoperative complications and ambulatory status. Follow up data included: radiotherapy and other oncological treatments, staging data, ambulatory status, Frankel score, bladder control at or close to 3, 6, 12, 24, 36, 48 months intervals after surgery or to date of death.

Definition of loss of local control

Loss of local control (LLC) was defined as repeat surgery at a previously surgically treated level for recurrent tumor affecting the same level or same level with extension to neighboring levels. Also shifts in levels were included with a maximum of 2 level shifts. Patients whose follow-up was < 1 year and who did not have a date of death documented were deleted from all comparisons in order to avoid bias in reporting LLC resulting from loss of follow up. Other reasons for repeat surgery, such as infection or instrumentation failure, were excluded.

Definition of new tumor occurrence

The incidence of patients presenting with and undergoing repeat surgery for further metastatic tumor at a new level, which was discrete and non-contiguous with the original site of surgery, was documented.

Analysis

The analysis included descriptive and comparative results from 1421 patients. The following variables were documented in the descriptive analysis: proportion of patients, time interval to LLC, primary tumor type, spinal level, initial Tomita classification of tumor extent (figure 1), initial surgery type, symptoms at LLC, metastatic load at LLC and survival after repeat surgery. There was incomplete follow-up data for neurological status and quality of life after second surgery to enable statistical analysis following repeat surgery. In the comparative analysis, variables associated with initial presentation and treatment were compared between the patient groups that underwent repeat surgery for LLC or only had one surgery: age, gender, primary tumor type, number of affected spinal levels, Tomita classification of tumor extent, type and number of visceral metastases, presence of extraspinal bone metastases, Tomita score, Tokuhashi score, Frankel score, sphincter control, Karnofsky performance index, ASA-score and EQ-5D index at initial presentation as well as surgical approach and surgery type, pre/postoperative radiation therapy, and postoperative chemotherapy were considered and their association with the fore-mentioned grouping compared by univariate and multivariate analyses.

Figure 1.

Data were analyzed by encrypted download. Data handling and statistical tests were performed with Stata 13.1 software (StataCorp LP, TX, USA). Data distributions were reviewed for skew deviation before descriptive analysis and means or medians were presented accordingly. Kaplan-Meier plots were produced to assess survival rates. Comparative analyses were performed in a univariate fashion, using t-tests and Pearson's chi-square tests according to the nature of the variables, and logistic regression was used for multivariate analyses. P-values of less than .05 were considered significant. The STROBE checklist for cohort studies has been implemented in this study.

Results

There were 42/1421 (3.0%) patients who underwent repeat surgery for LLC. The median time from the first surgery to the repeat surgery was 184 days (IQR: 87 - 343 days). Primary tumor types are presented in table 1. In the patients that developed LLC, renal and prostate tumors were most frequent (both 23.8%), followed by colorectal tumors (14.3%). Levels where LLC developed were distributed between C5 and the sacrum with a predilection for the thoracic spine (22 out of 34 with documented level information). Tomita classification of tumor extent at initial presentation varied between 1 and 7 with a median of 5, and the large majority (33/42) being extra-compartmental. The majority of patients (28/42) underwent a palliative procedure at initial presentation, while more extensive tumor removal had been performed in 14 patients, 3 of those having undergone an extralesional en bloc resection and 4 an intralesional complete resection.

Table 1.

Table 2.

Symptoms at the time of LLC are shown in table 2. In comparison with the overall initial presentation, there were more patients with no pain or with both axial and radicular pain at presentation of LLC, and pain intensity seemed to be slightly lower. Fewer patients were neurologically intact and a higher proportion had a Frankel D score. At the time of LLC, 6 of 42 patients had brain metastases, 5 had liver metastases, 9 had lung metastases and 26 had other metastases. At the time of initial surgery none of these patients had brain metastases, but 6 had liver metastases, 9 had lung metastases and 34 had other metastases. Therefore, one patient had a good response to treatment for liver metastasis, and 8 patients responded to systemic treatment for other metastases. Survival data were available in 41 patients: the median survival post second surgery was 6.1 months (IQR 4.3 – 15.4 months, figure 2).

Intraoperative complication rates were higher in the revision surgery group, compared to initial surgery. Of 42 patients who received revision surgery, 5 (11.9%) had neurological complications of inadvertent dural tear at the time of surgery, but none of these patients had vascular or visceral complications. At the time of the index surgery, 17 of 1421 (1.2%) patients had neurological complications, of whom 5 (0.4%) had a dural tear.

Figure 2.

When comparing the initial presenting features of patients that did not develop LLC with the 42 patients who eventually developed LLC (table 3), primary tumor type had a significantly different distribution in both groups (P=.003). Later LLC was associated with an initially higher number of affected spinal levels (P=.04). Also, patients that later developed LLC initially had better Tokuhashi scores (P=.02), lower Tomita scores for tumor extent (P=.02) and higher Karnofsky scores (P=.02). In the LLC group, more patients had undergone anterior only surgery (P<.01) and more patients had undergone more aggressive surgery types at initial surgery (P<.01). Finally, in the LLC group, more patients had undergone postoperative radiotherapy (P<.01). The multivariate analysis however did not yield any particular variable that was strongly and independently predictive for later LLC, but this was likely to be due to small sample size of the group undergoing surgery for LLC.

Table 3.

Of 1421 patients, 21 required surgery for tumor occurrence at a different level to the original operation, after a median interval of 338 days (interquartile range 84 to 534 days). Three of these patients (14.3%) had a primary diagnosis of renal carcinoma, 3 patients (14.3%) had myeloma, and 2 patients (9.5%) presented with breast carcinoma, 2 with colorectal cancer and 2 with lung carcinomas. Multiple regression analysis did not reveal any pre-operative factors which were associated with new tumor occurrence at a different level to the first operation, although the number of patients requiring surgery at a new spinal level was small, probably leading to under-powered statistical analysis.

Discussion

In this analysis of the characteristics of patients with LLC after initial surgery for spinal metastases we found that the incidence of LLC, defined as patients requiring repeat surgery at the same level as the first operation, was as low as 3.0%. Hence, this means that in the large majority of this patient cohort, for whom spinal surgery was part of the initial management, local control of the spinal metastasis was maintained until death or for at least one year, or LLC did not result in a decision for repeat surgery. Patients with metastases from renal cell carcinoma more commonly presented with LLC (23.8%) perhaps due to the relative radio-resistance of these tumors. Good post-operative quality of life is achievable and maintained in patients with a preoperative Karnofsky score > 60,[21] and it is likely that symptomatic LLC with reasonable functional status would have been referred for surgery. This supports the idea that initial surgery for spinal metastasis should not be denied based on a fatalistic attitude that spinal cord compression will inevitably recur. In previously published retrospective series the incidence of repeat surgery for LLC was reported to vary between 5/289 (1.7%)[18] and 9/107 (8.4%).[19] When LLC occurred in our cohort, it was relatively early in the postoperative course, with a median interval of just over half a year. We found that the clinical presentation at LLC was slightly different to that before initial surgery, with somewhat lower pain scores and a higher proportion of motor impairment. This is likely to be due to the fixation of the first surgery maintaining mechanical stability, and therefore clinical deterioration is more likely to be neurological as the tumor recurs a second time. The overall metastatic load did not seem to be higher at the time of LLC than at initial presentation. The median survival after the repeat surgery was half a year. In other words, median survival after the initial surgery was approximately one year, and those patients had undergone two spinal surgeries in the meantime. Twenty-one patients (1.5%) presented with new metastases at a different level to the initial operated level, suggesting that surgery was effective at maintaining local tumor control in these patients.

It remains a matter of debate whether repeat surgery is beneficial to patients with symptomatic LLC. Laufer et al justified re-operation by reporting 65% of preserved ambulation after repeat surgery in 39 patients, with an overall complication rate of 5%.[20] Lau et al, in a report of 32 recurrences defined by imaging, found that the 14 patients who underwent repeat surgery were more likely to remain ambulatory than those who did not receive further surgery (100.0% vs. 66.7%, P=.024), and maintained a higher mean Karnofsky score (72.7 vs. 56.9, P=.065).[26] The median survival time after re-operation was 12.4 months in the Laufer series. However, Laufer et al emphasized a strong influence from selection bias, in that repeat surgery was more likely to be offered to patients with adequate systemic cancer control.[20] Figures on survival after repeat surgery vary significantly in the literature, with Chataigner et al. reporting a mean survival of 4.45 months in 17 patients[19] and Jansson et al. a mean survival of 6 months.[16] Given this heterogeneity, decisions in clinical practice should be individualized and take all relevant variables into account, including oncological, neurological, mechanical and patient factors, when faced with recurrent metastatic disease.

The main aim of the present study was to identify predictors for LLC. This may inform surgical decision-making and in particular the extent of proposed operation. In a series by Yoshioka et al on 22 patients that underwent a 3 or more level spondylectomy, amongst 14 metastasis cases, no recurrences were observed for at least one year.[27] In another study from the group of Tomita, 10 patients with spinal metastases for which en bloc spondylectomy was performed, had no recurrences after 10 years of follow up.[28] Complication rates for en bloc spondylectomy vary widely[14,24,29,30] and partially depends on surgeons' caseload and expertise. Whether more radical surgical removal of metastatic spinal lesions affects survival is unclear; a different question is whether en bloc resection might lower the rate of LLC. However, from our analysis, it was not possible to clearly identify predictors of LLC, due to the low rate of LCC (3%) in our and other series. The main variables associated with the likelihood of LLC were the primary tumor type, greater number of affected spinal levels, better Tokuhashi score, anterior only surgery and more aggressive surgery at the initial presentation, and postoperative radiotherapy. In their retrospective analysis of factors associated with recurrence in 32 patients, Lau et al found an association with primary tumor type, postoperative radiotherapy, number of spinal levels and length of survival.[15] Primary tumors associated with a higher proportion of LLC in our series were renal, prostate and colorectal carcinomas. A relation between renal carcinoma and likelihood of recurrence has also been seen in the series of Lau,[15] Chataigner[19] and Weigel[17] and may be associated with their high vascularity.[31] Similar to the current analysis, Lau et al found that rates of postoperative radiotherapy were higher in the LLC group, and they explained this finding by a possible relation between radiotherapy and longer survival, which in their series was a variable associated with a higher proportion of recurrences. In our series, apart from tumor biology and number of affected spinal levels, all other variables associated with surgery for LLC are factors that can potentially be related to longer survival: higher Karnofsky and Tokuhashi scores, and postoperative radiotherapy. It is surprising, therefore, that the median interval to repeat surgery for LLC was as short as 6 months. Aizenberg et al, in a series of 51 spinal surgeries for unknown primaries, could find no relation between the completeness of resection and local recurrence rate.[32] Other authors have reported low recurrence rates after total en bloc excisions.[9,27,28] In our study, we were unable to confirm a relationship between more aggressive tumor removal and decreased local recurrence.

A methodological limitation of the current study is that LLC is defined by those patients who require surgery for LLC, rather than radiological LLC. In our prospective surgical database, follow-up information was based on clinical outcome measures and radiological data was not routinely collected. Nevertheless, asymptomatic or small radiological recurrences may not require treatment and therefore the critical threshold for recurrence is when patients require further treatment. Secondly, missing data might potentially introduce bias, although this effect was minimized by excluding patients who did not have a date of death documented and whose follow-up was < 1 year. There is inevitable bias in a surgical database, in that patients that are considered not fit for surgery were excluded. Hence, the data on LLC in this database cannot be generalized to non-surgical series. Since our data was collected over many years, we do not have sufficient data to analyse the influence of newer techniques such as stereotactic radiotherapy, proton beam therapy, or newer medical treatments which are more recently available. Future analyses of new data will be able correct for these confounding variables, and assess their impact on tumor recurrence and overall survival.

Conclusion

In patients who have had surgery for symptomatic spinal metastases, we found that the likelihood of repeat surgery for local tumor recurrence was not predicted accurately by pre-operative presenting features. However, the incidence of symptomatic local recurrence warranting surgery was low (3.0%). Although it is difficult to predict, at first presentation, which patients may require a second operation for tumor recurrence, factors associated with local recurrence were longer overall survival and favorable tumor biology. These patients were more likely to require repeat surgery. In clinical practice, the decision to operate again for recurrent tumor is a personalized decision, based on oncological, neurological, mechanical and patient factors at the time of re-presentation. However surgery should not be withheld due to a fatalistic attitude: the median survival after second surgery was 6.1 months, and therefore repeat surgery is justifiable for selected patients.

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Figure legends

Figure 1. Tomita classification of tumor extent.[24]

Figure 2. Kaplan-Meier curve expressing survival after repeat surgery in the patients with loss of local control (n=41).

Figure 1

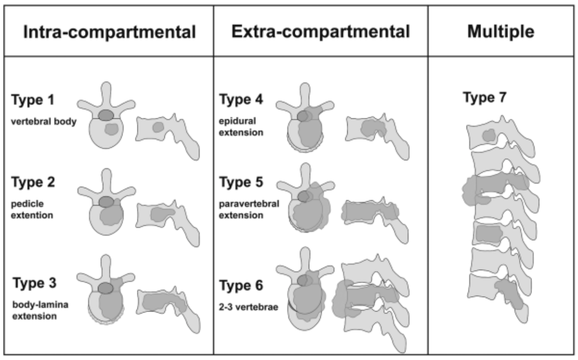

Figure 2

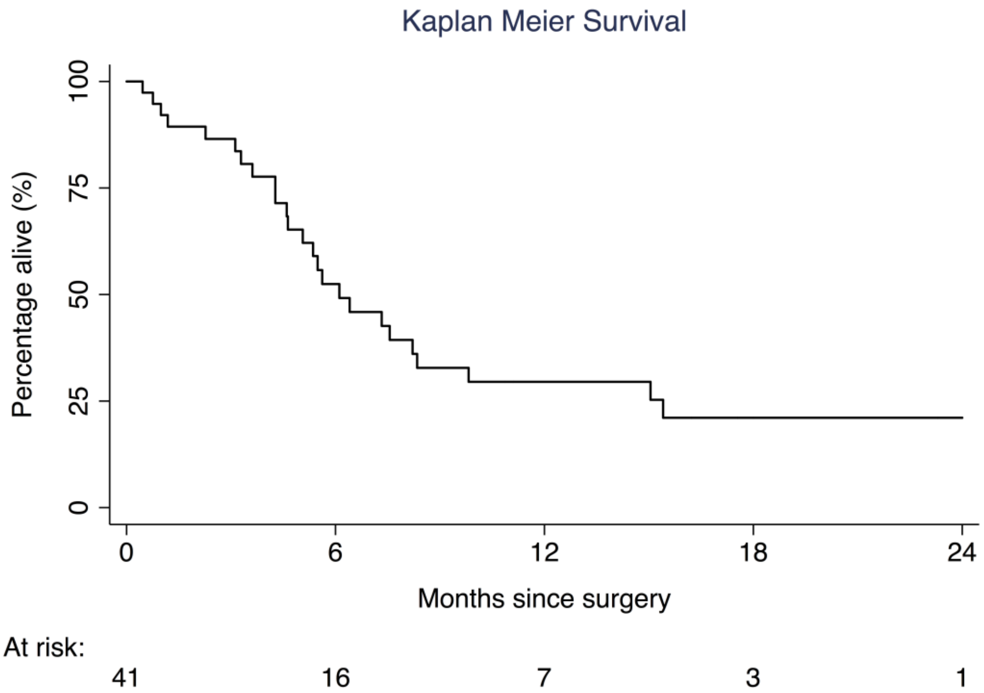

Table 1.

Primary tumor types of the overall cohort (n=1421) and of the patients with loss of local control (n=42), with the proportion of patients in each primary tumor type.

Tumor type	N with tumor at initial surgery	N (%) with repeat surgery for recurrent tumor
Breast	242	3 (7.14%)
Colorectal	70	6 (14.29%)
Renal	156	10 (23.81%)
Lung	202	3 (7.14%)
Prostate	237	10 (23.81%)
Myeloma	65	0
Gastrointestinal	26	0
Liver	32	2 (4.76%)
Bladder	22	0
Lymphoma	19	0
Melanoma	19	1 (2.38%)
Sarcoma	33	3 (7.14%)
Thyroid	24	1 (2.38%)
Other specified	125	2 (4.76%)
Other/unknown	149	1 (2.38%)

Table 2.

Symptoms at initial presentation for the entire group (left column), and at the time of presentation with loss of local control (right column). *Note that detailed information on symptoms at presentation with loss of local control was only available in 36/42 patients.

	Symptoms prior to initial surgery N=1065	Symptoms prior to repeat surgery for loss of local control N=36*
Pain; n (%)		
Back	432 (40.6%)	13 (36.1%)
None	74 (7.0%)	6 (16.7%)

Radicular	222 (20.9%)	3 (8.3%)
Radicular and back pain	337 (31.6%)	14 (38.96%)
Pain intensity; median (IQR)	7 (4, 8)	4 (2, 6)
Frankel Score; n (%)		
A	21 (1.5%)	1 (2.8%)
B	53 (3.8%)	1 (2.8%)
C	317 (22.6%)	5 (13.9%)
D	472 (33.7%)	17 (47.2%)
E	538 (38.4%)	12 (33.3%)
Sphincter Score; n (%)		
No problems	803 (76.0%)	27 (75.0%)
Impaired	174 (16.5%)	6 (16.7%)
Incontinent	80 (7.6%)	3 (8.3%)

Table 3.

Comparison of patient, oncological and treatment variables at initial presentation and for patients with only one surgery (n=1360) and patients that underwent repeat surgery for loss of local control (n=42).

	Initial variables of only one surgery patients (N=1360)	**Initial variables of patients with later repeat surgery for loss of local control (N=42)**	**P-Value**
Age at surgery; mean (SD)	61.1 (12.3) years	63.5 (11.8) years	.23
Gender; n male (%)	798 (58.7%)	28 (66.7%)	.30
First surgery type; n (%)			.24
Emergency	167 (19.2%)	5 (11.9%)	
Scheduled/Urgent	705 (80.1%)	37 (88.1%)	
Tumor Excision; n (%)			.00

Palliative	678 (54.55%)	10 (23.81%)	
Piecemeal debulking	343 (27.59%)	18 (42.86%)	
Piecemeal vertebrectomy	57 (4.59%)	7 (16.67%)	
En bloc intralesional	69 (5.55%)	4 (9.52%)	
En bloc extralesional	96 (7.72%)	3 (7.14%)	
Number of levels affected; median (IQR)	1 (0 to 3)	2 (1 to 3)	.04
Karnofsky score; mean (SD)	61.6 (20.3)	69.3 (19.4)	.02
EQ index; median (IQR)	0.37 (0.13 to 0.69)	0.49 (0.26 to 0.78)	.11
Frankel category; n (%)			.06
A	21 (1.55%)	0 (0.00%)	
B	54 (3.97%)	0 (0.00%)	
C	310 (22.81%)	7 (16.67%)	
D	461 (33.92%)	10 (23.81%)	
E	513 (37.75%)	25 (59.52%)	
ASA; n (%)			.38
1	80 (8.58%)	6 (14.29%)	
2	393 (42.17%)	14 (33.33%)	
3	413 (44.31%)	21 (50.00%)	
>3	46 (4.94%)	1 (2.38%)	
Metastatic tumor diagnosis; n (%)			.003
Breast	239 (17.33%)	3 (7.14%)	
Colorectal	64 (4.64%)	6 (14.29%)	
Renal	146 (10.59%)	10 (23.81%)	
Lung	199 (14.43%)	3 (7.14%)	
Prostate	227 (16.46%)	10 (23.81%)	
Myeloma	65 (4.71%)	0 (0.00%)	
Gastric	26 (1.89%)	0 (0.00%)	
Liver	30 (2.18%)	2 (4.76%)	
Bladder	22 (1.60%)	0 (0.00%)	
Lymphoma	19 (1.38%)	0 (0.00%)	
Melanoma	18 (1.31%)	1 (2.38%)	
Sarcoma			

Thyroid	30 (2.18%)	3 (7.14%)	
Other specified	23 (1.67%)	1 (2.38%)	
Other unknown	123 (8.92%)	2 (4.76%)	
	148 (10.73%)	1 (2.38%)	
Assessment of clinical status; n (%)			
Clinical examination	792 (91.7%)	40 (95.2%)	.41
CT scan	647 (74.9%)	28 (66.7%)	.23
PET scan	104 (12.0%)	3 (7.1%)	.34
Radioisotope scan	57 (6.6%)	3 (7.4%)	.89
US scan	33 (3.8%)	0 (0.0%)	.20
MRI scan	755 (87.4%)	39 (92.9%)	.29
Tomita Score; n (%)			.55
2-3	314 (31.34%)	16 (38.10%)	
4-5	192 (19.16%)	8 (19.05%)	
6-7	235 (23.45%)	11 (26.19%)	
8-10	261 (26.05%)	7 (16.67%)	
Tomita classification; n (%)			.02
1	28 (2.80%)	3 (7.14%)	
2	32 (3.20%)	5 (11.90%)	
3	61 (6.11%)	1 (2.38%)	
4	115 (11.51%)	7 (16.67%)	
5	206 (20.62%)	5 (11.90%)	
6	166 (16.62%)	8 (19.05%)	
7	391 (39.14%)	13 (30.95%)	
Tokuhashi Score; n (%)			.02
0-8	408 (48.46%)	12 (28.57%)	
9-11	306 (36.34%)	18 (42.86%)	
12-15	128 (15.20%)	12 (28.57%)	
Pre-Op radiotherapy; n yes (%)	213 (21.6%)	6 (15.0%)	.32
Post-Op radiotherapy; n yes (%)	367 (27.0%)	24 (57.1%)	.00
Follow-up chemotherapy; n yes (%)	289 (21.3%)	12 (28.6%)	.26
Posterior surgery; n yes (%)	921 (67.7%)	29 (69.1%)	.86

Anterior surgery; n yes (%)	133 (9.8%)	8 (19.1%)	.05
Extraspinal bone mets; n (%)			.54
0	375 (44.3%)	22 (52.4%)	
1-2	259 (30.6%)	12 (28.6%)	
≥3	212 (26.1%)	8 (19.1%)	
Surgical approach			.00
Anterior	43 (4.3%)	7 (17.5%)	
Combined anterior and posterior	109 (11.0%)	3 (7.5%)	
Lateral	2 (0.2%)	1 (2.5%)	
Posterior	840 (84.5%)	29 (72.5%)	