Factors affecting survival in 43 consecutive patients after surgery for spinal metastases from thyroid carcinoma

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OBJECT Spinal metastases account for the majority of bone metastases from thyroid cancer. The objective of the current study was to analyze a series of consecutive patients undergoing spinal surgery for thyroid cancer metastases in order to identify factors that influence overall survival.

METHODS The authors retrospectively reviewed the records of all patients who underwent surgery for spinal metastases from thyroid cancer between 1993 and 2010 at the University of Texas MD Anderson Cancer Center.

RESULTS Forty-three patients met the study criteria. Median overall survival was 15.4 months (95% CI 2.8–27.9 months) based on the Kaplan-Meier method. The median follow-up duration for the 4 patients who were alive at the end of the study was 39.4 months (range 1.7–62.6 months). On the multivariate Cox analysis, progressive systemic disease at spine surgery and postoperative complications were associated with worse overall survival (HR 8.98 [95% CI 3.46–23.30], $p < 0.001$; and HR 2.86 [95% CI 1.30–6.31], $p = 0.009$, respectively). Additionally, preoperative neurological deficit was significantly associated with worse overall survival on the multivariate analysis (HR 3.01 [95% CI 1.34–6.79], $p = 0.008$). Conversely, preoperative embolization was significantly associated with improved overall survival on the multivariate analysis (HR 0.43 [95% CI 0.20–0.94], $p = 0.04$). Preoperative embolization and longer posterior construct length were significantly associated with fewer and greater complications, respectively, on the univariate analysis (OR 0.24 [95% CI 0.06–0.93], $p = 0.04$; and OR 1.24 [95% CI 1.02–1.52], $p = 0.03$), but not the multivariate analysis.

CONCLUSIONS Progressive systemic disease, postoperative complications, and preoperative neurological deficits were significantly associated with worse overall survival, while preoperative spinal embolization was associated with improved overall survival. These factors should be taken into consideration when considering such patients for surgery. Preoperative embolization and posterior construct length significantly influenced the incidence of postoperative complications only on the univariate analysis.

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KEY WORDS thyroid carcinoma; spinal metastasis; postsurgical survival; oncology

IN general, thyroid carcinoma is associated with excellent prognosis, and the 10-year survival rate is 90%. The presence of distant metastases, however, significantly lowers this life expectancy.^{23,24} The lungs and bones are the most common sites of metastatic disease, accounting for 53% and 20% of the cases of metastasis, respectively, with multiorgan involvement occurring in 16% of patients.³ Metastases to the spine are found in up to 68% of

patients with thyroid cancer and are associated with a poor clinical outcome.^{1,6,8,9,29}

Only 1%–3% of patients with thyroid cancer have distant metastases at the time of initial diagnosis, but 7%–23% of patients will develop distant metastases over time.^{2–4, 13,17,31,34,35} The presence of vertebral metastases from thyroid carcinoma, in particular, causes significant morbidity and mortality. A median survival period of 4.1 years has

ABBREVIATIONS EBRT = external beam radiotherapy; KPS = Karnofsky Performance Scale; NPS = numeric pain scale; PMMA = polymethylmethacrylate; SSRS = spinal stereotactic radiosurgery.

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been reported for patients with thyroid carcinoma that metastasizes to the vertebrae.³ Furthermore, vertebral metastases from thyroid carcinoma are 3–4 times more likely to result in spinal cord compression than metastatic tumors from breast or prostate cancers.⁶ Additionally, up to 13% of patients with thyroid cancer may experience pathological fractures following vertebral metastasis.³ Although radioactive iodine therapy is generally effective for isolated thyroid carcinoma, prior studies have demonstrated that this treatment is relatively ineffective for bone metastases.³⁴ Surgery with or without radiotherapy remains the primary treatment modality for vertebral metastases in patients with uncontrolled back pain, progressive neurological deficit, or spinal instability.^{15,24,26}

Prior studies have assessed the prognostic factors associated with systemic metastasis from thyroid carcinoma; however, none have specifically investigated the factors that affect survival in patients undergoing surgery for spinal metastases.^{3,5,13,16,18,21,25,32,36,39,40} Therefore, the objective of this study was to analyze a series of consecutive patients who underwent surgery for spinal metastasis from thyroid cancer in order to identify factors associated with postoperative survival and complications. This prognostic information may aid in clinical decision making, as patients with a more favorable prognosis may warrant more aggressive intervention and patients with poor life expectancy may be spared from aggressive surgery.

Methods

Patient Population and Selection Criteria

We reviewed the records of all patients who had undergone surgery for spinal metastases from thyroid cancer between June 1993 and June 2010 at the University of Texas MD Anderson Cancer Center. The study was conducted under the auspices of an institutional review board–approved protocol. Patients who had undergone surgery exhibited at least 1 of the following signs or symptoms: spinal deformity with intractable mechanical back pain, spinal cord compression, or medically intractable radiculopathy.

Data Collection and Preoperative Evaluation

Prospectively collected data in the Brain and Spine Database at the University of Texas MD Anderson Cancer Center were used for the study. A supplemental retrospective review of the hospital records and radiographic studies of these patients was performed. Data on patient age, sex, date of initial diagnosis of thyroid cancer, histology of thyroid cancer, history of prior thyroidectomy, date of diagnosis of first metastasis, date of diagnosis of first spinal metastasis, location of the spinal metastasis, previous treatments (including radioactive iodine, chemotherapy, radiation therapy, and vertebral body cement augmentation), preoperative Frankel grade and Karnofsky Performance Scale (KPS) score, preoperative pain as assessed by the numeric pain scale (NPS) (when available), status of systemic and spinal disease burden immediately before surgery, and operative data (surgical approach, presence and type of vertebral body reconstruction, length of anterior or posterior construct, and use of preoperative embolization) were gathered.¹¹

Preoperative evaluation included plain radiography; bone scans; contrast-enhanced axial CT scanning of the chest, abdomen, and pelvis; and contrast-enhanced MRI of the brain and spine. In addition to spine metastases, the location of metastatic disease was classified as involving the lungs, liver, brain, extraspinal bone, or other locations.

Classification of Systemic Disease Status

The location and time of occurrence of extraspinal metastatic lesions were determined through a review of the preoperative radiographic reports. When extraspinal metastatic disease was found to be present, it was further classified as follows: concurrent (first evidence of metastatic disease on the most recent preoperative radiographic evaluation prior to spinal surgery), progressing (evidence of enlargement and/or increase in the number of lesions when comparing 2 consecutive preoperative radiographic studies), or stable (no change in size or number when comparing 2 consecutive preoperative radiographic studies). Spinal disease burden, which considered the status of remote spinal metastases not associated with the index level, was classified as follows: concurrent (first evidence of other spinal metastasis on the most recent preoperative radiographic evaluation), progressing (evidence of enlargement and/or increase in number of other spinal metastases when comparing 2 consecutive preoperative radiographic studies), stable (no change in size or number when comparing 2 consecutive preoperative radiographic studies), or nonexistent.

Surgical Approach

The surgical approach was selected based on the location of the lesion within the spine and the extent of the spinal and paraspinal disease burden. The purpose of operative intervention was 4-fold: 1) completely decompress the involved neural elements; 2) remove as much tumor as possible; 3) correct any spinal deformity; and 4) provide spinal stability. It is our institution's philosophy to direct the surgical approach based on the location of the disease.¹⁰

Standard posterior instrumentation techniques were used depending on the location of the disease within the spine. In the cervical spine, lateral mass screw-rod constructs were used. In the thoracic and lumbar spine, pedicle screws or pedicle hook constructs were used. Anterior stabilization of the cervical and upper thoracic spine was achieved using the polymethylmethacrylate (PMMA) technique along with anterior plating, as previously described.²² Anterior stabilization of the mid- and lower thoracic spine or the lumbar spine was achieved using PMMA or expandable titanium cages along with anterolateral plating.

Postoperative Data

As part of standard of care, routine evaluations were planned for all patients at the time of discharge, 1 month, 3 months, and 6 months postoperation, and every 6 months thereafter. Local control, Frankel grade, ambulatory status, radiographic integrity of the construct, development of further deformities, need for further surgery, and date

of the last follow-up examination or death were gathered. The development of complications, if any, was noted, including the development of pain or any other new neurological symptom.

Statistical Analysis

Frequencies and descriptive statistics of the demographic and clinical variables were calculated. Data were analyzed using SPSS software (version 19.0, IBM). The Kaplan-Meier method was used to estimate postoperative survival, and survival curves were compared using the log-rank test. Factors associated with survival after spine surgery were assessed using univariate and multivariate Cox proportional hazards analyses. Hazard ratios and their corresponding 95% confidence intervals were computed. Factors associated with the incidence of postoperative complications were assessed using univariate and multivariate logistic regression analyses. Odds ratios and their 95% CIs were also computed. All tests were 2-tailed. Here, $p \leq 0.05$ was considered statistically significant.

Results

During the study period, 43 consecutive patients with thyroid cancer metastatic to the spine underwent initial surgical treatment. The characteristics of the 43 patients (26 men [60%] and 17 women [40%]) are presented in Table 1. The median patient age at the time of the diagnosis of the primary thyroid cancer was 51 years (range 26–78 years). The median patient age at the time of diagnosis of the spinal metastasis was 59 years (range 36–79 years). All patients underwent surgical treatment that consisted of intralesional resection of the gross tumor with circumferential decompression of the spinal cord, followed by reconstruction of the affected vertebral bodies and stabilization of the spine (as detailed in *Methods*). The median follow-up period for the 4 patients who were alive at the end of the study was 39.4 months (range 1.8–62.6 months). The median length of the postoperative hospital stay was 9 days (range 4–69 days). One admission ended in death after 69 days.

Thyroidectomy Prior to Spine Surgery and Tumor Histopathology

Of the 41 patients with data, 36 patients (88%) underwent thyroidectomy and 5 patients (12%) did not undergo thyroidectomy. The most common histological subtype in our series was follicular thyroid cancer, which was found in 18 patients (42%). Nine patients (21%) had papillary thyroid cancer, while 6 patients (14%) had medullary thyroid cancer. Six patients (14%) had Hürthle cell histology, and 2 patients (5%) demonstrated poorly differentiated histology. One patient (2%) had mixed follicular-papillary histology, while another patient (2%) had mixed follicular-columnar cell histology.

Treatment Prior to Spine Surgery

Thirty-one patients (72%) received radioactive iodine prior to surgical intervention. Twenty patients (47%) received external beam radiotherapy (EBRT) to their spinal

TABLE 1. Patient and tumor characteristics of 43 patients with thyroid metastasis to the spine

Variable	No. of Patients	%
Sex		
Male	26	60
Female	17	40
Preoperative KPS score		
<70	10	23
≥70	33	77
Thyroidectomy		
No	5	12
Yes	36	88
Histology of thyroid cancer		
Follicular	18	42
Follicular-papillary, mixed	1	2
Follicular, columnar cell	1	2
Papillary	9	21
Medullary	6	14
Hürthle cell	6	14
Poorly differentiated	2	5
Latency of 1st metastasis		
<1 yr	27	63
≥1 yr	16	37
Surgical location of the spine metastasis*		
Cervical	9	21
Thoracic	30	70
Lumbosacral	8	19
Total spine burden (no. of spinal levels w/ metastases)		
1	13	30
2	13	30
≥3	17	40
Treatments prior to spine surgery		
None	20	47
EBRT	20	47
SSRS	3	7
Vertebral augmentation	3	7
Iodine therapy prior to 1st surgery		
No	12	28
Yes	31	72
Frankel grade before spine surgery		
C	3	7
D	9	21
E	31	72
Metastases at other locations*		
Any location	39	91
Lung	27	63
Visceral	9	21
Other bone	32	74
Soft tissue	22	51

(continued)

TABLE 1. Patient and tumor characteristics of 43 patients with thyroid metastasis to the spine (continued)

Variable	No. of Patients	%
Progressive spine disease at spine surgery		
No	18	42
Yes	25	58
Progressive systemic disease at spine surgery		
No	16	37
Yes	27	63

* Some patients had more than 1 metastasis location.

metastasis prior to spine surgery. Three patients (7%) received spinal stereotactic radiosurgery (SSRS). Three patients (7%) underwent vertebral augmentation procedures prior to surgery. For 20 patients (47%), surgery was the initial treatment for spinal metastasis.

Tumor Histology

The 20 patients (47%) who had follicular cell or mixed follicular-dominant cell histology demonstrated a median overall survival of 22.8 months (95% CI 0.0–72.1 months). The 9 patients (21%) who had papillary thyroid cancer demonstrated a median overall survival period of 10.8 months (95% CI 3.6–18.0 months). Patients with medullary or Hürthle cell carcinoma demonstrated median overall survival periods of 15.4 months (95% CI 0.0–36.1 months) and 8.6 months (95% CI 5.9–11.2 months), respectively. Finally, the 2 patients with poorly differentiated carcinoma demonstrated a median overall survival of 7.5 months (95% CI not defined). Tumor histology was not found to significantly influence overall survival on either the univariate or multivariate Cox analyses, though patients with a favorable primary histology (follicular, follicular-papillary, or follicular-columnar) demonstrated a trend toward improved overall survival on the univariate analysis (HR 0.52 [95% CI 0.27–1.04], $p = 0.06$).

Location of Spinal Metastasis

The most common location for spine metastasis in our patient series was the thoracic spine, which was involved in 30 patients (70%). The lumbosacral spine was involved in 8 patients (19%) and the cervical spine in 9 patients (21%). More than 1 region was involved in 4 patients (9%).

Number of Spinal Metastases

Thirteen (30%) patients had a single metastasis that involved only 1 vertebral level. An additional 13 patients (30%) were classified as having metastatic disease involving 2 spinal levels, which consisted of either a single contiguous lesion or 2 remote lesions. Seventeen patients (40%) had metastatic disease involving 3 or more vertebral levels, which consisted of either as a distinct and contiguous lesion or multiple remote lesions. The maximum disease burden was seen in 1 patient who had spinal metastases involving 8 levels.

Systemic Metastases

Twenty-seven patients (63%) had a systemic metastasis

diagnosed within 1 year of their initial diagnosis of thyroid cancer. The remaining 16 patients (37%) had a latency period of at least 1 year between their initial diagnosis and the discovery of metastatic disease. Twenty-seven patients (63%) had lung metastases at the time of spine surgery. Nine patients (21%) had visceral metastases. Twenty-two patients (51%) had soft-tissue metastases. Thirty-two (74%) patients had other bone metastases.

Neurological Status Prior to Surgical Treatment

Preoperatively, 31 patients (72%) had normal neurological function, or Frankel Grade E. Nine patients (21%) were in Frankel Grade D and 3 patients (7%) were in Frankel Grade C. Therefore, 12 patients (28%) had a preoperative neurological deficit.

Postoperative Neurological Function

Twenty-eight of the patients who had normal preoperative neurological function continued to have normal neurological function postoperatively. Three patients developed worse neurological function after surgery: 1 patient declined to a Frankel Grade C, and 2 patients declined to a Frankel Grade D. Of the 9 Frankel Grade D patients, however, 2 improved to normal neurological function and 7 remained at Frankel Grade D. Of the 3 Frankel Grade C patients, their statuses all remained the same postoperatively.

Pre- and Postoperative Pain

Unfortunately, quantitative assessment of pre- and postoperative pain using NPS scoring was only sporadically available on retrospective review. The mean preoperative NPS score was 5.5 (range 0–10, $n = 19$). Postoperative NPS scores were inconsistently collected at 1, 3, and 6 months postoperation. Taking the worst NPS score available for each patient from any of the 3 time points, the mean postoperative NPS was 4.23 (range 0–8, $n = 21$).

Operative Data

Eleven patients (26%) underwent anterior approaches to the spine, 28 patients (65%) underwent posterior surgical approaches, and 4 patients (9%) underwent combined anterior-posterior procedures (Table 2). Of the 43 patients in our cohort, 13 patients (30%) did not undergo vertebral body reconstructions, while 24 patients (56%) underwent PMMA reconstructions and 6 patients (14%) received vertebral body reconstruction using expandable titanium cages. Thirteen patients did not require anterior vertebral column constructs; of those who did, the median length of the construct was 3 vertebral levels (range 3–5 levels). The levels above and below the vertebrectomy site were counted as parts of the anterior column construct when plating, Steinmann pins, or chest tube insertion were involved. Fourteen patients did not require posterolateral stabilization; of those who did, the median length of the construct was 6 vertebral levels (range 3–14). Two patients underwent lumbopelvic or lumbosacropelvic fixation; in these instances, the sacrum or pelvis was treated as 1 level.

Twenty-two patients (51%) did not undergo preoperative tumor embolization, whereas 21 (49%) patients did under-

go embolization. Common reasons for forgoing embolization were concern for spinal ischemia and the absence of dominant tumor blush (Table 2).

Postoperative Complications

Fifteen patients (35%) had complications within 30 days of the procedure. Wound-related complications occurred in 4 patients: 3 of whom developed wound infection and 1 of whom developed a sterile dehiscence. Other complications observed on an individual basis included pseudomeningocele, Ogilvie syndrome, pneumonia and pleural effusion, pulmonary embolus, embolic cerebrovascular accident, subdural hematoma, myocardial infarction, complicated urinary tract infection, persistent dysphagia, deep venous thrombosis, and uncomplicated urinary tract infection (Table 3).

Preoperative embolization was significantly associated with fewer complications on the univariate analysis (OR 0.24 [95% CI 0.06–0.93], $p = 0.04$), but not on the multivariate analysis. Longer posterior construct length was associated with a higher incidence of postoperative complications (OR 1.24 [95% CI 1.02–1.52], $p = 0.03$) and was the only variable left in the model following backward selection. None of the other investigated operative factors were significantly associated with postoperative complications (Table 4).

Overall, the occurrence of complications was significantly associated with poor survival outcomes (Tables 5 and 6).

Reoperation and Hardware Failure

Five patients (12%) underwent further surgical procedures at the index level (Table 7). One of these 5 patients underwent further surgery as a result of an early complication, which required multiple washouts for a persistent wound infection after conservative measures had failed. The remaining 4 patients underwent further surgery as a result of late complications more than 30 days after their initial procedure: 2 patients for wound revisions and 2 patients for hardware failure.

Of the 2 patients (5%) who underwent reoperation for hardware failure, one developed posterolateral screw loosening associated with displacement of the intervertebral cage, while the other developed intervertebral cage subsidence with the loosening of cervical lateral mass screws and an associated lateral mass fracture. One patient who did not undergo reoperation was found to have an extrapedicular T-6 pedicle screw on postoperative imaging. Another patient, who was also managed conservatively, had Steinmann pin migration on serial postoperative imaging.

Routine follow-up imaging was generally confined to MRI of the spine, which precluded a meaningful analysis of the postoperative fusion rate. Bone morphogenetic protein is not used to supplement spinal instrumentation and fusion at our institution.

Postoperative Deformity

One patient (2%) who developed local failure at the operative level developed a compression fracture at the operative site. Another patient (2%), also suffering from

TABLE 2. Surgical methods*

Variable	No. of Patients	%
Approach		
Anterior	11	26
Posterior	28	65
Both	4	9
Anterior approach		
No	28	65
Yes	15	35
Posterior approach		
No	11	26
Yes	32	74
Vertebral reconstruction		
None	13	30
Yes	30	70
Vertebral reconstruction		
None	13	30
PMMA	24	56
Cage	6	14
Preoperative embolization		
No	22	51
Yes	21	49

* Percentages may not add up to 100% due to rounding.

local failure, developed both a compression fracture and kyphosis at the operative site, along with hardware failure.

Local Control

Thirty-three patients (77%) achieved local control at the index level, while 10 patients (23%) developed local failures at their operative site (Table 7).

Postoperative Treatment

Eleven patients (26%) underwent postoperative EBRT at the operative level, only 3 of whom had evidence of local failure. Five patients (12%) underwent postoperative SSRS at the operative level, none of whom had evidence of local failure. One patient with local failure and aggressive recurrent disease underwent both EBRT and SSRS at the operative level after surgery. Postoperative radiotherapy in

TABLE 3. Postoperative complications

Complication	No. of Patients	%	% Overall
Total	15	100	35
Wound infection/dehiscence	4	27	9
Pseudomeningocele	1	7	2
Cardioembolic/thromboembolism	3	20	7
Urinary tract infection	2	13	5
GI complication (ileus, dysphagia)	2	13	5
Other (subdural hematoma, MI, PNA/effusion)	3	20	7

GI = gastrointestinal; MI = myocardial infarction; PNA = pneumonia.

TABLE 4. Surgical factors associated with postoperative complications

Variable	Univariate Analysis		
	OR	95% CI	p Value
Surgical approach			
Anterior	1.00		
Posterior	3.38	0.61–18.57	0.16
Both	1.50	0.10–23.07	0.77
Anterior approach			
No	1.00		
Yes	0.33	0.08–1.45	0.14
Posterior approach			
No	1.00		
Yes	3.08	0.57–16.63	0.19
Approach construct length, no. of levels	1.12	0.77–1.63	0.56
Posterior construct length, no. of levels	1.24	1.02–1.52	0.03
Vertebral reconstruction			
None	1.00		
PMMA	1.35	0.32–5.69	0.68
Cage	1.12	0.14–8.88	0.91
Vertebral reconstruction			
None	1.00		
Yes	1.30	0.32–5.24	0.71
Preoperative embolization			
No	1.00		
Yes	0.24	0.06–0.93	0.04

the absence of local failure was used to treat presumed microscopic or confirmed macroscopic residual disease.

Overall Survival

The median overall survival following surgery for spine metastasis from thyroid cancer in the 43 enrolled patients was 15.4 months (95% CI 2.8–27.9 months).

Univariate Analysis

On the univariate Cox survival analysis, several factors significantly influenced overall survival (Table 5). Previous iodine therapy was associated with worse overall survival (HR 2.1 [95% CI 1.01–4.35], $p = 0.05$). Postoperative complications were associated with worse overall survival (HR 3.45 [95% CI 1.68–7.07], $p = 0.001$). The presence of lung metastasis or soft-tissue metastasis at the time of spine surgery was associated with worse overall survival (HR 3.01 [95% CI 1.44–6.29], $p = 0.003$; and HR 2.86 [95% CI 1.41–5.83], $p = 0.004$, respectively). The presence of progressive systemic disease or progressive spine disease (at levels discrete from the surgical site) at spine surgery was associated with worse overall survival (HR 5.5 [95% CI 2.43–12.43], $p < 0.001$; and HR 5.67 [95% CI 2.65–12.14], $p < 0.001$, respectively). Conversely, preoperative spinal embolization was associated with improved overall survival (HR 0.40 [95% CI 0.20–0.79], $p = 0.009$) (Table 5).

Furthermore, several factors demonstrated trends to-

TABLE 5. Significant factors influencing overall survival on the univariate Cox model analysis

Variable	Univariate Analysis		
	HR	95% CI	p Value
Iodine therapy prior to spine surgery			
No	1.00		
Yes	2.10	1.01–4.35	0.05
Lung metastasis at spine surgery			
No	1.00		
Yes	3.01	1.44–6.29	0.003
Soft-tissue metastasis at spine surgery			
No	1.00		
Yes	2.86	1.41–5.83	0.004
Progressive systemic disease at spine surgery			
No	1.00		
Yes	5.50	2.43–12.43	<0.001
Progressive spine disease at spine surgery			
No	1.00		
Yes	5.67	2.65–12.14	<0.001
Preoperative embolization			
No	1.00		
Yes	0.40	0.20–0.79	0.009
Postoperative complications			
No	1.00		
Yes	3.45	1.68–7.07	0.001

ward improved overall survival. Patients with a KPS score greater than or equal to 70 or preoperative Frankel Grade E demonstrated trends toward improved overall survival (HR 0.51 [95% CI 0.24–1.07], $p = 0.07$; and HR 0.34 [95% CI 0.10–1.19], $p = 0.09$, respectively). Patients with a favorable primary histology (follicular, follicular-papillary, or follicular-columnar) also demonstrated trends toward improved overall survival (HR 0.52 [95% CI 0.27–1.04], $p = 0.06$). These trends did not, however, reach statistical significance.

Age, sex, prior thyroidectomy, surgical spinal metastasis level, latency to first systemic metastasis, number of spinal levels involved, initial spine metastasis treatment, only spine metastasis at the time of surgery, surgery, only bone metastasis at surgery, visceral metastasis at surgery, and other bone metastasis at surgery did not significantly affect overall survival.

Multivariate Analysis

On the multivariate Cox analysis, progressive systemic disease at the time of spine surgery (Fig. 1) and postoperative complications (Fig. 2) remained associated with worse overall survival (HR 8.98 [95% CI 3.46–23.30], $p < 0.001$; and HR 2.86 [95% CI 1.30–6.31], $p = 0.009$, respectively). Additionally, preoperative neurological deficits were significantly associated with worse overall survival on the multivariate analysis (HR 3.01 [95% CI 1.34–6.79], $p =$

TABLE 6. Multivariate Cox survival analysis of overall survival

Variable	Multivariate Model		
	HR	95% CI	p Value
Neurological deficits prior to spine surgery			
No	1.00		
Yes	3.01	1.34–6.79	0.008
Progressive systemic disease at the moment of spine surgery			
No	1.00		
Yes	8.98	3.46–23.30	<0.001
Postoperative complications			
No	1.00		
Yes	2.86	1.30–6.31	0.009
Preoperative embolization			
No	1.00		
Yes	0.43	0.20–0.94	0.04

0.008) (Fig. 3). Preoperative embolization remained significantly associated with improved overall survival on the multivariate analysis (HR 0.43 [95% CI 0.20–0.94], $p = 0.04$) (Fig. 4 and Table 6).

Discussion

This study examined a series of 43 patients who underwent surgical treatment for thyroid cancer metastatic to the spine at The University of Texas MD Anderson Cancer Center. These data, to the best of our knowledge, represent the largest surgical series in the English-language literature to report the surgical outcomes of thyroid cancer metastases to the spine. A retrospective study examining 41 years of clinical data by Bernier et al. reported on 109 patients with bony metastasis, 74 of whom had vertebral metastases.³ However, these patients were not exclusively treated with surgery, and the surgical data were not reported according to the site of bony metastasis (i.e., spine surgery vs surgery for extraspinal bony metastasis). Hosono et al. reported on factors that influenced survival in 165 patients who underwent surgery for spinal metastasis, 15 of which were from the thyroid, and found that favorable histology, absence of paresis, and absence of pain were all associated with improved overall survival.¹⁴ Matsumoto et al. reported on 8 patients who underwent total en bloc spondylectomy for thyroid metastases, all of whom improved at least one Frankel grade at the 1-year follow-up examination.¹⁹

The finding that progressive systemic disease is associated with worse overall survival is not surprising. The presence of progressive systemic disease burden suggests an aggressive tumor biology that would adversely affect postoperative survival.

It is interesting to compare our results to those of a recent retrospective review of 267 patients who underwent resection for renal cell carcinoma spinal metastasis at the same institution (The University of Texas MD Anderson Cancer Center), which also examined the factors that influence

TABLE 7. Postsurgical treatments and outcomes*

Variable	No. of Patients	%
Vital status		
Alive	4	9
Dead	39	91
Complications		
No	28	65
Yes	15	35
Further treatment after spine surgery		
No	21	49
Yes	22	51
Type of treatment		
Reoperation	5	11
EBRT alone	11	26
SSRS alone	5	12
EBRT+SSRS	1	2
Frankel grade after spine surgery		
C	4	9
D	9	21
E	30	70
Local control		
No	10	23
Yes	33	77

* Percentages may not add up to 100% due to rounding.

overall survival.³⁸ Multivariate analysis demonstrated that Fuhrman Grade 4 renal cell carcinoma, the presence of a preoperative neurological deficit, and progressive systemic disease were associated with worse overall survival. The median overall survival was 11.3 months, which is shorter than the median observed in our series (15.4 months). Similarly, in our series, on the multivariate analysis, preoperative neurological deficit and progressive systemic disease were significantly associated with worse overall survival.

The association with improved survival in patients with good preoperative KPS scores or neurological function is intuitive, as healthy patients with more indolent disease

FIG. 1. Kaplan-Meier curve illustrating the impact of progressive systemic disease on overall survival. Circles and diamonds represent patients who were censored.

FIG. 2. Kaplan-Meier curve illustrating the impact of postoperative complications on overall survival. Circles and diamonds represent patients who were censored.

would be expected to live longer than more impaired patients or patients with fixed neurological deficits. Furthermore, it is well established that neurological deficits from spinal metastases result in poorer prognosis.^{14,30,37,38}

The negative association between the occurrence of postoperative complications and postoperative survival is also not surprising. Both the association observed between preoperative embolization and fewer postoperative complications, and the association between longer posterior constructs and greater postoperative complications, are intuitive. Preoperative embolization is likely to decrease intraoperative bleeding and thus intra- and postoperative complications. Conversely, longer posterior constructs require more periosteal dissection, muscle denervation, blood loss, and instrumentation, all of which might increase the risk of postoperative complications and prolong the hospital stay (which is a risk for complications itself). The finding that preoperative embolization is associated with improved overall survival is in line with this thinking.

Interestingly, we found a trend toward an increased incidence of postoperative complications in patients with lung metastasis. It was reported that, in the absence of visceral metastasis, the extent of disease affecting extraspinal bone

FIG. 3. Kaplan-Meier curve illustrating the impact of preoperative neurological deficit on overall survival. Circles and diamonds represent patients who were censored. Neuro = neurological.

FIG. 4. Kaplan-Meier curve illustrating the impact of preoperative embolization on overall survival. Circles and diamonds represent patients who were censored.

is useful for predicting the prognosis of patients with spinal metastases.^{28,37} Similarly, a study by Pittas et al. found the absence of nonosseous systemic metastases was a significant positive predictor of survival in a series of 146 patients, which supports our own findings that demonstrate a negative association between the presence of pulmonary and soft-tissue (i.e., nonosseous) metastases and survival.²⁹

There are mixed reports in the literature regarding the effectiveness of preoperative radioactive iodine therapy. For instance, several studies indicate the beneficial effects of radioiodine therapy for patients with systemic thyroid carcinoma metastases, while several other studies demonstrate no benefit.^{3,7,13,27,30,33} In this study, prior radioactive iodine therapy was found to negatively impact overall survival only on the univariate analysis. Although authors of many of the aforementioned studies pooled bone metastases with other systemic metastases, Bernier et al. found that radioiodine therapy significantly increased the survival of patients with metastatic osseous lesions, which contrasts our results.³ It is possible that the patients in our cohort who previously underwent iodine therapy and still progressed to develop symptomatic spinal metastases represent a subset of clinically aggressive disease.

Previous reports have suggested that total thyroidectomy is generally associated with decreased local recurrence rates and improved long-term survival.²⁰ However, in our series, the surgical treatment of primary thyroid cancer did not affect overall survival when metastatic spinal disease was present. Given the relative indolent nature of the thyroid cancer, it remains that most of our patients had the primary tumor removed before the development of spinal metastasis.¹² We do not view thyroidectomy as a necessary precursor to the surgical management of spinal metastasis, unless the primary tumor has a direct extension to the cervical vertebrae. In this case, thyroidectomy has to be performed to allow access to the spine and decrease local recurrence.

Limitations

The major limitation of this study is its retrospective nature and the small sample size of our cohort (43 patients),

as these may have limited the inherent statistical power of the study. However, these limitations result from the relative rarity of spinal metastases from thyroid carcinoma, as outlined by Bernier et al. who found only 74 of 1977 patients (3.7%) with vertebral metastases.³ Therefore, in the future, multiinstitutional studies should be considered in order to enhance the statistical power and more clearly elucidate the potential prognostic factors.

Conclusions

As indicated by the multivariate analysis, progressive systemic metastatic disease, postoperative complications, preoperative neurological deficit, and preoperative embolization were significantly associated with overall survival. Given the indolent nature of most cases of thyroid cancer, when patients develop spinal metastasis they have usually been subjected to multiple prior treatments, including chemotherapy, radiation, and/or prior surgeries, which most likely makes their general health status more tenuous and the consequences of the postoperative complications more severe. In these cases, aggressive surgical treatment should be approached with caution and these factors should be considered. Shorter construct length and preoperative embolization may mitigate the risks of such complications.

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