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Short-Title: Survival in spine metastases from thyroid cancer

Abbrevations:

Thyroid Cancer	TC
Bone Metastases	BM
Overall Survival	OS
Metastasis-free survival	MFS
Spine metastases	SpM

Abstract

Background: Spinal metastases (SpMs) from thyroid cancers (TC) significantly reduce quality of life by causing pain, neurological deficits in addition to increasing mortality. Moreover, prognosis factors including surgery remain debated.

Methods: Data were stored in a prospective French national multicenter database of patients treated for SpM between January 2014 and 2017. Fifty-one consecutive patients affected by TC with 173 secondary SpM were included.

Results: Mean overall survival (OS) time for all patients from the diagnosis of a thyroid SpM event was 9.1 years (SD 8.7 months). The 1-year, 5-year and 10-year survival estimates were 94 % (SD 3.3), 83.8.0% (SD 5.2), and 74.5% (SD 9.9). The median period of time between primary thyroid tumor diagnosis and the SpM event was 31.4 months (SD 71.6). In univariate analysis, good ECOG-PS (status 0 and 1) ($p < 0.0001$), ambulatory status (Frankel score) ($p < 0.0001$) and no epidural involvement ($p=0.01$), were associated with longer survival, whereas cancer subtype ($p=0.436$) and spine surgery showed no association ($p=0.937$). Cox multivariate proportional hazard model only identified good ECOG-PS: 0 [HR: 0.3, 95 % CI 0.1-0.941; $p < 0.0001$], 1 [HR: 0.8, 95 % CI 0.04-2.124; $p =0.001$] and ambulatory neurological status: Frankel E [HR: 0.262, 95 % CI 0.048-1.443; $p =0.02$] to be independent predictors of better survival.

Conclusion: For cases presenting SpM from TC,, we highlighted that the only prognostic factors were the progression of the cancer (ECOG-PS) and the clinical neurological impact of the SpM (Frankel status). Surgery should be discussed mainly for stabilization and neurological decompression.

Keywords: Thyroid cancer, overall survival, subtype thyroid cancer, personal status, Spine metastases

INTRODUCTION

The standardized incidence rate of thyroid cancer (TC) is 17,4 per 100 000 (world-population) [1], and is more significant in Europe with a standardized incidence rate of 24 per 100 000. In France, the incidence of TC is 10 605 per year with a standardize incidence of 5,6 for men and 18,4 for women [2]. The incidence rate of thyroid cancer amongst all cancers is in fifth position for women and in nineteenth for men and has increased over the past years, especially for women. It is expected to take the position of colon cancer as fourth leading cancer by 2030 [3]. More than 90% of thyroid carcinoma cases are classified as papillary or follicular carcinomas, both referred to as differentiated thyroid carcinomas (DTCs) and are associated with a 10-year survival rate of 97% to 98% [4].

At the diagnosis of TC, it is uncommon to find secondary metastases: only 1% to 2% of patients with papillary carcinoma and 2% to 5% of patients with follicular (or vesicular) carcinoma present concomittant metastases beyond the neck or mediastinum [5,6]. Moreover, throughout the natural course of TC, 10% of papillary carcinomas and 20% of follicular carcinomas will develop distant metastasis (bones, lungs, or liver) [7]. In the timeline of TC, secondary metastases impair survival, by decreasing the OS rate at 10 years to 40%[8]. The targeted organs of metastases are: the lungs (49%), bones (25%), both lungs and bones (15%) and other tissues (10%) [9].

However, OS can decrease from 21% to 14% when patients present bone metastases [8]. The most common site for bone metastases is the spine (34.6%), followed by the pelvis (25.5%), thorax (18.3%), appendicular skeleton (15,6%) (the pelvis being included in the appendicular skeleton), craniomaxillofacial (5.4%), and “other” sites (0.6%). Half of the patients present a solitary bone metastasis [10,11]. Spinal metastases (SpM) are a frequent complication especially for follicular TC and are associated with a severely reduced quality of life by causing pain, vertebral fractures, and spinal cord compression. Like for other cancer metastases, pain, fractures, and spinal cord compression were the most common clinical presentations of osseous metastases caused predominantly osteolytic and blow-out lesions.

Although the spine is the privileged metastastic location, only few studies have assessed the prognosis factors in patients with SpM from TC. Thereby, more recent studies are needed in order to improve predictions of the optimal surgical candidates to therefore adapt specific treatment or palliative care for each patient [12,13].

An analysis was performed on patients diagnosed with TC, presenting SpM, stratified according to survival. First, we sought to identify reliable subtype and clinical prognostic factors associated with improved survival; then we discussed surgical recommendations.

MATERIALS AND METHODS

Ethics Statement

The data collected during the study was stored in a computer file in accordance with the law of the French Data Protection Act of January 6, 1978 amended in 2004. The protocol can be found in the reference methodology MR003 chapter adopted by the CNIL to which conform the different University Hospitals of this project.

Inclusion Criteria

A prospective French national multicenter database of consecutive adult patients treated for SpM between January 2014 and 2017 was generated from the neurosurgery and orthopaedic departments in La Pitié-Salpétrière hospital (Paris), Hotel-Dieu hospital (Nantes), Bretonneau and Trousseau hospitals (Tours).

Study population

The initial number of patients was 794. Thus, we identified 51 consecutive patients treated for SpM from thyroid cancer (TC) and included them in our series. Patient observations began when SpM were detected and all data were collected prospectively and retrospectively since the primitive diagnosis into a database. Clinical patient information including age, gender, date of thyroid tumor diagnosis, thyroid cancer genotype, date of SpM diagnosis, presence of systemic disease at the time of SpM diagnosis as well as the number of metastases, epidural involvement, location, and anatomical position of SpM were collected.

Excluded patients

The patients who did not die, had to have a minimum follow-up (FU) of 6 months as well as imaging and clinical data. Therefore, 21 patients with missing data or lost to follow-up were excluded.

Statistical analysis

All tests were two-sided; p-values < 0.05 were considered statistically significant. Univariate and Multivariate Cox proportional hazard regression models were conducted using SPSS software, version 22.0 (SPSS, Chicago, IL, USA). Establishment and verification of nomograms were implemented using the open-source software R-version 3.2.5 with rms packages (Design, Vienna, Austria). Data are presented as the mean/median ± standard deviation. Gender, metastases localisation and vertebrae, were matched with categorical variables whereas age and follow-up time as continuous variables. The distribution of categorical variables was described with frequencies and percentages, whereas continuous and normally distributed variables with means and standard deviations (SD). To reduce the effects related to a lack of power, we used the 2 following methods: i) decrease the number of criteria in the univariate / multivariate analysis to thus limit the subgroups < 5 (10% of the total) and ii) verify the normality of the series by the test for small samples (> 30 patients) of Shapiro-Wilk. Furthermore, statistical analyses were corrected by the coefficient of Pearson.

In the univariate analysis, categorical variables were assessed using Pearson Chi-square or Fisher's exact test. The multivariate analysis was conducted separately for each diagnosis and the Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). All potential explanatory variables included in the multivariable analyses were subjected to collinearity analysis with a correlation matrix. Variables associated with one another were not included in the model. The goodness-of-fit model was assessed with the determination coefficient (R2). The output was expressed as odds ratios and their bootstrapped 95% confidence intervals. The Kaplan-Meier method was used to estimate the metastases free survival. For descriptive and inferential analyses, boot-strapping with replacement (iterations = 500) was performed to attain variance estimates at the 95% CI [14].

3. RESULTS

In this study, 51 consecutive patients were included, 173 thyroid' SpM were identified, with a mean number of 3.39 and median of 2.0 per patient (range 1-21).

Overall Survival (table 1)

As detailed in table 1, in our series, 27 (52.9%) patients were women and 24 men, with a mean age of 63.9 years (range, 27.1-88.8 years). Mean survival time for all patients from the TC diagnosis was 267.6 months (22.2 years) (SD 32.8 months). The 3-year, 5-year and 10-year survival estimates were 96 % (SD 2.7), 91% (SD 4.1), and 83.5% (SD 6.6) respectively.

In contrast, the mean survival time for all patients from the thyroid SpM event was 109.445 months (9.1 years) (SD 8.7 months). The 1-year, 5-year and 10-year survival estimates were 94 % (SD 3.3), 83.8.0% (SD 5.2), and 74.5% (SD 9.9). The median period of time between the primary thyroid tumor diagnosis and SpM was 31.4 months (SD 71.6).

For 8 patients (15.6%), thyroid cancer and SpM were synchronously diagnosed. Among the 43 patients with previously diagnosed and treated thyroid cancer, 26 (50.9%) had stable disease and 17 had non-controlled cancer. At SpM diagnosis, 25 patients also presented skeletal bone metastases (49%), 17 had lung metastases (33.3%), 8 had liver metastases (15.7%), and 4 presented other metastases. Eighteen patients (35.2%) presented isolated SpM.

Fifteen patients (29.4%) received steroids treatment: 12 for spinal cord compression due to epidural involvement and 3 for spinal cord compression generated by a pathological vertebral fracture.

Univariate survival analysis (Figure 1 and table 2)

We sought to identify prognostic factors associated with OS using a univariate analysis. The results are presented in mean (Table 2). There were successively no differences in median OS for patients younger than 60 years, 60-75 years and patients older at the time of SpM diagnosis (p=0.727), no differences between male and female gender (p=0.355), no differences according to TC control (p=0.204), no differences whether patients had a medical history of other cured cancers (p=0.952), whether they presented a SpM recurrence (p=0.296), whether visceral/peripheral bone metastases were identified (p=0.787) and no differences for the number of SpM (p=0.895), whether they be isolated or not (p=0.976).

Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) was significantly associated with longer OS; 10.9 years (SD 0.5) for the 29 patients with a ECOG-PS 0; 7.4 years (SD 1.3) for the 18 patients with a ECOG-PS 1; 1.2 years (SD 0.4) for the 4 patients with ECOG-PS 2; and 0.9 years for patient with ECOG-PS 3 ($p< 0.0001$) (Figure 1A). Preserved neurological function at SpM diagnosis was significantly associated with longer OS: 9.3 years (SD 0.7) for the 48 patients Frankel E; 4.25 years (SD 2.1) for the 3 patients Frankel D-C ($p< 0.0001$) (Figure 1B) [15].

The median OS did not improve according to the metastasis free survival (MFS) after the initial thyroid cancer diagnosis: 7.6 years (SD 0.4) for the 21 patients with MFS < 2 years; 9.7 years (SD 1.2) for the 12 patients with MFS 2-6 years and 7.5 years (SD 1.2) for the 18 patients with MFS > 6 years (p=0.540).

However, patients presenting an epidural involvement (12, 23.9%) had significantly lower OS than others (6.2 vs 9.3 years, p=0.017) (Figure 1C). Moreover, patients who received spine adjuvant radiotherapy (21, 41.2%) did not have a significantly better OS (p= 0.436). Fourteen patients were treated with spinal radiotherapy without surgery, since they did not present SpM that threatened their spinal stability or neurological prognosis. Thirty patients did not receive spinal radiotherapy including 15 who presented > 3 very sparse SpM.

TC and SpM treatment

Primary TC treatments consisted of: a thyroidectomy (47/51, 92%) and radioactive iodine treatment (31/51, 60.7%). In addition, 8 patients (15.7%) received chemotherapy and 5 (9.8%) external beam radiation therapy. Molecular targeted therapy is an emerging treatment option for patients with metastatic thyroid cancer, especially for those presenting SpM. In our series, we identified that at SpM diagnosis, 21patients received spine radiotherapy, 12 received complementary radioactive iodine (I131) administration and 26 systemic chemotherapies (4 cisplatin-based chemotherapy, 4 Doxorubicin, 6 received tyrosine kinase inhibitors (TKIs) and 12 unidentified chemotherapies). Whatever the treatment at SpM diagnosis, none could be identified as a factor of better prognosis, probably because we lacked data on the nature of chemotherapy (p=0.234).

As described in table 1, 5 patients (9.8%) presented the medullary subtype, 22 (43.1%) the papillary subtype, and 24 (47.1%) the follicular subtype of thyroid cancer. Whatever the subtype of cancer, neither the medullary (mean 3.8 years, SD 1.1), nor the papillary (mean 3.9 years, SD 2.5), nor the follicular (mean 4.0, SD 2.4) subtype had a significantly better OS (p= 0.300).

SpM surgery

Ten patients were operated, (19.6%) received a posterior decompressive laminectomy associated with posterior fixation. The procedure did not improve their OS (p=0.937). No “en bloc SpM” resection was achieved, only vertebral body debulking. One patient had a post-operative complication (wound infection) with a non-compressive epidural hematoma, which required a surgical revision. In our series, 2 of 3 Frankel C-D patients were operated on: 1 recovered a Frankel E after surgery and the second following surgery and radiotherapy. Four patients received surgery for due to a threat in neurological functional caused by spinal cord compression and 7 for major instability due to a fracture or a pathological lysis (SINS > 13) [16].

Multivariate survival analysis (table 2)

All clinical characteristics involved in OS (statistically significant in univariate analyses) were further applied for multiple analyses (Table 2). Cox multivariate proportional hazard model identified the following, as good OS prognosis factors for thyroid cancer patients with SpM:

Favorable ECOG-PS (i.e. status 0 and 1 of the scale) 0 [HR: 0.3, 95 % CI 0.1-0.941; p <0.0001], 1 [HR: 0.8, 95 % CI 0.04-2.124; p =0.001] and ambulatory neurological status: Frankel E [HR: 0.262, 95 % CI 0.048-1.443; p =0.02] were independent predictors of better

survival. Whereas the other factors including epidural involvement and cancer subtype were not identified to represent independent prognostic factors of survival.

DISCUSSION

Prognosis factors

Two previous studies have described SpM from TC. In accordance to these previous series, the mean age of our patients at SpM diagnosis was close 60 years [12,13]. In general, for metastases secondary to TC, other studies have identified old age, follicular cell type and early metastases diagnosis (within 3 years of the primary diagnosis) as poor prognostic factors in TC [2–4]. Like Kondraciuk et al. we did not demonstrate age to be associated with better OS, whereas Zhang et al. identified that patients > 50 years of age had poor OS. This discrepancy might be explained by a low percentage of patients under the age of 50 (26,9%) in our and in Kondraciuk' series.

Similarly, we did not demonstrate the subtype of thyroid cancer to represent a prognosis factor of OS for cases with SpM, in accordance to Kondraciuk et al [12]. Only Zhang et al. found that patients with follicular TC SpM had better survival than the others: these results can be explained by a low percentage of papillar thyroid cancer in their study [13].

Synchrone metastases at the time of TC diagnosis vary between 27 and 43%[12]. In our series this rate was lower, approching 15%, and was not identified as a prognosis factor. In the series of Zhang et al., the median survival time following the diagnosis was slightly less than in our study [12]: survival was at 83% at 1-year, 59% at 3-year and 38.8% at 5-year FU. However our study found OS data comparable to Kondraciuk et al. [13]. A probable explanation for Zhang et al. to have identified synchronous SpM as a poor prognosis factor is that in their series, there were more synchrone SpM. Nevertheless, in our series, the median time between TC and SpM diagnosis (around 30 months) seemed to correspond to the timeline of TC described in other series of BM [12,17].

For TC, as described for other primary tumors, preserved neurological function at SpM diagnosis is significantly associated with longer OS. Therefore, pre-operative Frankel scores C-E represent good prognosis factors, which is confirmed by Zhang for the Frankel scores D and E (C is included in the composite Frankel score A-C without differentiation). Moreover, patients without epidural involvement also had better OS, even if this point remains debated by Bernstein et al. or other stereotaxic radiosurgery specialists [18,19].

Unlike other primary tumors, by summarizing the few studies carried out on SpM secondary to TC, no prognostic factors of survival such as: TC subtype, number of metastases, age, disease status, concomitant metastases, gender, cancer treatment, were clearly identified.

The bone of contention comes from the natural course of TC: currently with the appropriate treatments (thyroid irradiation and surgery), the prognosis is favorable, with a median survival time close to 10 years. Therefore, it is very difficult for studies to determine prognostic factors, except for selected patients with poor survival (< 1year), which remains less frequent. Whilst beeing faced with more favorable OS, the question that arises is the role and benefit of spinal surgery?

Survival and Spine Metastases

Only few studies have analyzed SpM separately from others bone metastases (BM).
In a previous retrospective analysis of 146 non-operative cases of TC BM, Pittas at al. reported 5-year and 10-year OS rates at 53% and 35%, respectively, from the time of diagnosis of BMs.

Vertebrae localization was not identified as a prognosis factor [20]. Bernier et al. were more pessimistic with OS rates with 41% and 15%, respectively [21]. Moreover, the corresponding 5-and 10-year rates among 93 Korean patients evaluated by Choi et al. were at 77.1% and 46.6% [22]. More recently, median survival times after the diagnosis of BM were evaluated at 83% (95% CI: 72-90) at 1-year and 59% (95% CI: 43, 71) at 3-years [12]. Similarly, Slook et al. found an OS rate of 45.3% approximately 10 years after BM detection and concluded that SpM were associated with increased mortality. [23]. In all these studies, the OS were poorer than in our study. However, the distinction between SpM and BM was not always studied, and the majority of these series were non-surgical.

A therefore legitimate question to ask is: Can the general considerations of TC BM be applied SpM secondary to TC?

Like predicted, only few studies detailed BM and SpM separately. In our series, we did not observe OS differences between SpM with BM and SpM alone (p=0.860). In the important series conducted by Kushchayeva et al., 29% of 202 patients had neither BM nor solid organ metastases at the time of presentation [24]. Twenty-nine percent and 54% of patients with single-site SpMs had neither bone nor SpM nor solid organ metastases at the time of presentation. For 35% of patients, SpM represented the initial presentation of TC.

Radiotherapy is indicated when pain, risk of fracture, and/or neurological complications are present or predicted and represents the standard of care when surgery is not indicated. Additionally radiotherapy is best administered postoperatively. In spinal cord compression due to cancer, decompressive surgery plus postoperative radiotherapy appears superior to treatment with radiotherapy alone [25]. In our series, only 21 patients received SpM radiotherapy, but we did not inquire in our data collection if it was external beam radiation or stereotactic body radiotherapy. Furthermore, concerning motor prognosis, 2 patients with neurological impairment improved postoperatively with radiotherapy, contrary to the third. We cannot demonstrate the pain control since this data was not collated in our series.

Surgery discussion for TC' SpM

The American thyroid association guidelines state that complete removal of BMs (peripheral and central) can prolong survival and is appropriate in particular for younger patients [26].

In our series, no "en bloc spondylectomy" (EBS) was performed. Only simple decompression and stabilization surgery with or without vertebral body debulking was preformed and did not significantly improve the OS in comparison to caseswho did not receive surgery: mean OS 9.3 years (SD 1.9y) vs 7.2 y (SD 0.5) p=0.937, with no regards to the number of spinal metastases, single or multiple. Ohashi et al., included 4 patients with isolated thyroid SpM in their (EBS) series. On the one hand the rate of perioperative complications was high, around 75%, and on the other, 100% of patients experienced newly formed distant metastases and a relapse event with a median of 18 months. OS was not determined. They concluded that margin-free EBS was effective in controlling SpM locally but not in preventing further dissemination, nor in improving OS nor in controlling the disease [27].

In the series of Kushchaveva et al., 13% of patients (16) benefited from radical surgeries. The authors concluded that patients with single-level SpM without other distant metastases might be considered for radical treatment without major postoperative risks. Nevertheless, a major problem is that authors did not study the improvement or gain in OS of these patients.

More recently Kato et al., determined that the patients in the complete excision group (EBS) survived significantly longer than those in the incomplete excision group (5-year survival: 84% vs. 50%; and 10-year survival: 52% vs. 8%) [28]. These data are very surprising since 60% of their patients who received radical surgery were multi-metastatic.

Thus, depending on the series, it is difficult to clearly determine whether oncological surgeries offer a benefit on survival for patients with SpM secondary to TC.

A first element of response would be the study of the anatomical distribution of SpM across vertebrae levels. Indeed, in the series described by Ohashi et al., SpM all tend to be distant from the thyroid (T12 and lumbar vertebrae) described as "real distance metastases". In our series, for isolated metastases, 27% were present within the cervical spine. These cervical spine localizations were represented distant SpM for they did not share a direct anatomical environment with the primary TC. In contrast, we presume that sometimes, the spinal localization does not necessarily represent a "metastatic" spreading but rather a local progression of the cancer through direct invasion by continuity, similar to that found in lung cancer and the Pancoast-Tobias syndrom. Therefore we find ourselves at an earlier stage in the natural course of the disease than the metastatic stage, even though a direct extension of a TC into the cervical spine represents an early aggressive and locally advanced disease [29]. Furthermore, it was demonstrated that in TC, some of the cancer cells that disseminate at an early stage, remain dormant for a long period of time in their new location. These metastatic cancer cells become active only when their new microenvironment favors their growth [30,31]. In our series, unfortunately univariate analysis of surgical modalities (surgery p=0.937, postoperative radiotherapy p=0.436) did not show a significant effect on survival. Like many series, this is undoubtedly due to 2 factors, which are: the good prognosis of the long survival of thyroid cancers, which requires large series (national series) and long follow-ups (close to 10 years). These elements therefore make it difficult to clearly establish the impact of therapeutic elements in the survival of TC'SpM.

Limitations of the Study

The main limitation of our study is the small number of patients, which severely limits the strength of any conclusions. It is difficult to draw meaningful conclusions even if our series was prospective. Indeed, only 10 patients in your series were operated, which represent a small subgroup. In addition, given the frequency of spinal metastases for thyroid cancers, it remains difficult to conclude on the relevance of surgery. Further studies with more cases and more control groups with risk adjustments are needed to confirm our findings without these limitations.

CONCLUSION

Given the improvement and the favorable survival of TC, we highlighted that the prognostic factors for SpM are those of the general progression and the natural course of cancer: ECOG-PS and the clinical neurological impact: Frankel status and vertebrae SpM extension.

The position of surgery in curative and oncological management can be discussed for some rare cases (single metastasis) but is not proven. However, surgery remains recommended for stabilization and neurological decompression.

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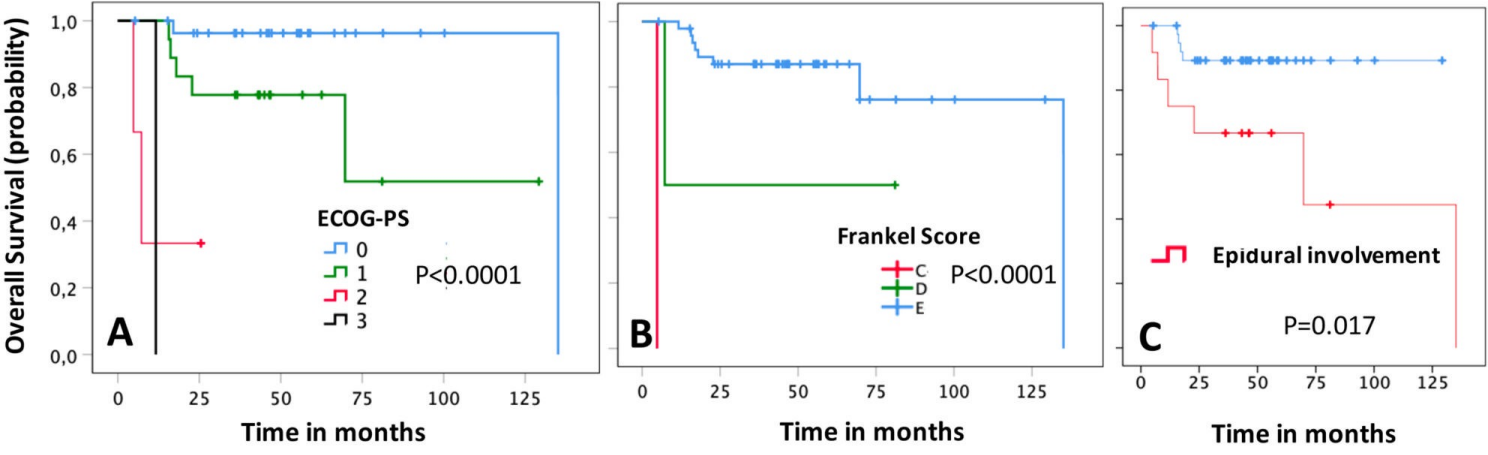
LEGENDS

Table 1: The clinical, cancer and treatment characteristics of the cohort, y: years

Table 2: Univariate and Cox proportional hazards models of overall survival (OS) for thyroid SpM patients. Statistically significant data are in bold. OS is expressed in years with standard deviation (SD)

Figure 1: Overall Survival in univariate analyses

Kaplan-Meier (KM) survival analysis for patients with thyroid cancer and spine metastases according to (A): ECOG-PS at SpM diagnosis [0-> 3], (B): neurological function status (Frankel score), and (C): associated epidural involvement.


Overall Survival (probability)
1,0
0,8
0,6
0,4
0,2
0,0
A
ECOG-PS
0
1
2
3
P<0.0001
0
25
50
75
100
125
Time in months
B
Frankel Score
C
D
E
P<0.0001
0
25
50
75
100
125
Time in months
C
Epidural involvement
P=0.017
0
25
50
75
100
125
Time in months

	Number (range or %)
Gender	
Male	24 (47.1 %)
Female	27 (52.9 %)
Age (years)	
Mean	63.9 (27-89 y)
< 60 y	18 (35.3 %)
60-75 y	23 (45.1 %)
> 75 y	10 (19.6 %)
ECOG-PS	
0	29 (56.9 %)
1	18 (35.3 %)
2	3 (5.9 %)
3	1 (1.9 %)
4	0 (0.0 %)
Frankel score	
C	1 (1.9 %)
D	2 (3.9 %)
E	48 (94.2 %)
Medical History of other cured cancer	8 (15.7 %)
Cancer subtype	
Medullary	5 (9.8 %)
Papillary	22 (43.1 %)
Vesicular	24 (47.1%)
Pathological vertebrae	
1	18 (35.3 %)
2-5	25 (49.0 %)
> 5	8 (15.7 %)
Epidural involvement	12 (23.5%)
Newly formed distant metastases	11 (21.6 %)
Spine surgery	10 (19.6 %)
Spine Radiotherapy	21 (41.2 %)
Synchronous metastasis	8 (15.7 %)
Metastasis free diagnosis	
< 2 y	21 (41.2 %)
2-6 y	12 (23.5 %)
> 6 y	18 (35.3 %)

Table 1: The clinical, cancer and treatment characteristics of the cohort, y : years

	Univariate		*Multivariate*		
	OS years (SD)	p value	Risk ratio	95% CI	p value
Gender		0.355			
Male/Female	6.1/9.5				
Age (y)		0.727			
< 60	8.8 (1.7)				
60-75	6.2 (0.5)				
> 75	7.6 (0.8)				
ECOG-PS		**<0.0001**			
0	10.9 (0.5)		**0.3**	**[0.100-0.941]**	**< 0.0001**
1	7.4 (1.3)		**0.8**	**[0.040-2.124]**	**0.001**
2	1.2 (0.4)		**5.5**	**[2.378-12.975]**	**< 0.0001**
3	0.9 (0.0)				
Frankel score		**<0.0001**			
C	4.8 (0.0)				
D	3.7 (2.1)				
E	9.3 (0.7)		**0.262**	**[0.048-1.443]**	**0.02**
Thyroid cancer controlled		0.204			
Yes/No	9.2/8.4				
Cancer subtype		0.300			
Medullary	3.8 (1.1)				
Papillary	3.9 (2.5)				
Vesicular	4.0 (2.4)				
Pathological vertebrae		0.895			
1	9.1 (0.8)				
2-5	9.0 (1.1)				
> 5	6.1 (0.6)				
Spine surgery		0.937			
Yes/No	9.3/6.4				
Spine Radiotherapy		0.436			
Yes/No	9.8/6.0				
Synchronous metastasis		0.627			
Yes/No	8.9/7.5				
Metastasis free diagnosis		0.540			
< 2 y	7.6 (0.4)				
2-6y	9.7 (1.2)				
> 6 y	7.5 (1.2)				
Newly formed distant metastases					
Yes/No	6.6/9.3	0.296			
Epidural involvement		**0.017**	1.696	[0.323-8.920]	0.533
Yes/No	6.2/9.9				
Visceral metastasis		0.787			
Yes (14)	6.8 (0.8)				
No (37)	9.5 (0.7)				

Table 2: univariate and Cox proportional hazards models of overall survival (OS) for thyroid SpM patients. Statistically significant data are in bold. OS expressed in years with standard deviation (SD)