



HAL
open science

Spinal metastases from thyroid cancer : Some prognostic factors

Alexia Planty-Bonjour, Arnaud Dubory, Louis-Marie Terrier, Thiziri Taïbi, Ann-Rose Cook, Joseph Cristini, Kévin Buffenoir, Hugues Pascal-Mouscellard, Alexandre Carpentier, Louis-Romée Le Nail, et al.

► To cite this version:

Alexia Planty-Bonjour, Arnaud Dubory, Louis-Marie Terrier, Thiziri Taïbi, Ann-Rose Cook, et al.. Spinal metastases from thyroid cancer : Some prognostic factors. *EJSO - European Journal of Surgical Oncology*, 2022, 48 (1), pp.292-298. 10.1016/j.ejso.2021.09.001 . hal-04541814

HAL Id: hal-04541814

<https://hal.sorbonne-universite.fr/hal-04541814>

Submitted on 11 Apr 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Spinal metastases from thyroid cancer: some prognostic factors

Alexia Planty-Bonjour¹, MD; Arnaud Dubory² MD-PhD; Louis-Marie Terrier¹, MD; Thiziri Taïbi¹, MD; Ann-Rose Cook¹, MD; Joseph Cristini³, MD; Kévin Buffenoir³, MD-PhD; Hugues Pascal-Moussellard⁴, MD-PhD; Alexandre Carpentier⁵, MD-PhD; Louis-Romée Le Nail⁶, MD; Bertrand Mathon⁵, MD, Aymeric Amelot^{1,7}, MD-PhD

Affiliations:

1. Department of Neurosurgery, Bretonneau Hospital, Tours, France
2. Department of Orthopaedic surgery, Henri-Mondor Hospital, Créteil, France
3. Department of Neurosurgery/Neurotraumatology, Hotel-Dieu Hospital, Nantes, France
4. Department of Orthopaedic Surgery, Pitié-Salpêtrière Hospital, Paris, France
5. Department of Neurosurgery, La Pitié Salpêtrière Hospital, Paris, France
6. Department of Orthopaedic surgery, Trousseau Hospital, Tours, France
7. iBrain, Inserm 1253, Université de Tours, Tours, France

Disclosures

The authors declare that they have no personal conflicts of interest and no institutional financial interest in any drugs, materials, or devices described in this manuscript. The authors have no financial disclosures to report. In addition, all patients gave their informed consent for any medical and scientific investigations. This paper has not been published previously, is not under consideration for publication elsewhere. All authors are responsible for reported research.

Funding statement: None

Corresponding author:

Dr. Amelot Aymeric, MD, Ph.D,
Department of Neurosurgery, Bretonneau Hospital
2 boulevard de Tonnelle, 37 000 Paris
Tel: 00-33- 2-47 47 47 47, Fax: 00-33-1-42 16 34 16, Email: aymmed@hotmail.fr

38 **Authorship**

39 Alexia Planty-Bonjour, Aymeric Amelot, Louis-Marie Terrier, Joseph Cristini, Bertrand
40 Mathon, Thiziri Taibi and Ann-Rose Cook participated in the conception and design of the study,
41 acquisition of data, analysis and interpretation of data, drafted the article, revised it critically
42 for important intellectual content, and gave final approval of the version to be submitted. Kévin
43 Buffenoir, Hugues Pascal-Moussellard, Louis-Romée Le Nail participated to the interpretation
44 of data, drafted the article and revised it; they gave a final approval of the version to be
45 submitted. Alexandre Carpentier participated in the analysis and interpretation of data, revised
46 the manuscript and gave final approval of the version to be submitted.

47

48

49

50 **Short-Title:** Survival in spine metastases from thyroid cancer

51

52 **Abbreviations:**

53 Thyroid Cancer

TC

54 Bone Metastases

BM

55 Overall Survival

OS

56 Metastasis-free survival

MFS

57 Spine metastases

SpM

58

59 **Abstract**

60

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

64

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

68

69 **Results:** Mean overall survival (OS) time for all patients from the diagnosis of a thyroid SpM
70 event was 9.1 years (SD 8.7 months). The 1-year, 5-year and 10-year survival estimates were
71 94 % (SD 3.3), 83.8.0% (SD 5.2), and 74.5% (SD 9.9). The median period of time between
72 primary thyroid tumor diagnosis and the SpM event was 31.4 months (SD 71.6). In univariate
73 analysis, good ECOG-PS (status 0 and 1) ($p < 0.0001$), ambulatory status (Frankel score) ($p <$
74 0.0001) and no epidural involvement ($p = 0.01$), were associated with longer survival, whereas
75 cancer subtype ($p = 0.436$) and spine surgery showed no association ($p = 0.937$). Cox multivariate
76 proportional hazard model only identified good ECOG-PS: 0 [HR: 0.3, 95 % CI 0.1-0.941; p
77 < 0.0001], 1 [HR: 0.8, 95 % CI 0.04-2.124; $p = 0.001$] and ambulatory neurological status:
78 Frankel E [HR: 0.262, 95 % CI 0.048-1.443; $p = 0.02$] to be independent predictors of better
79 survival.

80

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

85

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

88

89 **INTRODUCTION**

90 The standardized incidence rate of thyroid cancer (TC) is 17,4 per 100 000 (world-
91 population) [1], and is more significant in Europe with a standardized incidence rate of 24 per
92 100 000. In France, the incidence of TC is 10 605 per year with a standardize incidence of 5,6
93 for men and 18,4 for women [2]. The incidence rate of thyroid cancer amongst all cancers is in
94 fifth position for women and in nineteenth for men and has increased over the past years,
95 especially for women. It is expected to take the position of colon cancer as fourth leading cancer
96 by 2030 [3]. More than 90% of thyroid carcinoma cases are classified as papillary or follicular
97 carcinomas, both referred to as differentiated thyroid carcinomas (DTCs) and are associated
98 with a 10-year survival rate of 97% to 98% [4].

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

107 However, OS can decrease from 21% to 14% when patients present bone metastases
108 [8]. The most common site for bone metastases is the spine (34.6%), followed by the pelvis
109 (25.5%), thorax (18.3%), appendicular skeleton (15,6%) (the pelvis being included in the
110 appendicular skeleton), craniomaxillofacial (5.4%), and “other” sites (0.6%). Half of the
111 patients present a solitary bone metastasis [10,11]. Spinal metastases (SpM) are a frequent
112 complication especially for follicular TC and are associated with a severely reduced quality of
113 life by causing pain, vertebral fractures, and spinal cord compression. Like for other cancer
114 metastases, pain, fractures, and spinal cord compression were the most common clinical
115 presentations of osseous metastases caused predominantly osteolytic and blow-out lesions.

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

120
121 An analysis was performed on patients diagnosed with TC, presenting SpM, stratified
122 according to survival. First, we sought to identify reliable subtype and clinical prognostic
123 factors associated with improved survival; then we discussed surgical recommendations.

124

125 **MATERIALS AND METHODS**

126

127 Ethics Statement

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

132

133 Inclusion Criteria

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

138

139 Study population

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

147

148 Excluded patients

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

152

153 Statistical analysis

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

167

168

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

179 **3. RESULTS**

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

182

183 **Overall Survival (table 1)**

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

188 In contrast, the mean survival time for all patients from the thyroid SpM event was
189 109.445 months (9.1 years) (SD 8.7 months). The 1-year, 5-year and 10-year survival estimates
190 were 94 % (SD 3.3), 83.8.0% (SD 5.2), and 74.5% (SD 9.9). The median period of time between
191 the primary thyroid tumor diagnosis and SpM was 31.4 months (SD 71.6).

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

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

200

201

202 **Univariate survival analysis (Figure 1 and table 2)**

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

211 Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) was
212 significantly associated with longer OS; 10.9 years (SD 0.5) for the 29 patients with a ECOG-
213 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
214 patients with ECOG-PS 2; and 0.9 years for patient with ECOG-PS 3 ($p< 0.0001$) (Figure 1A).
215 Preserved neurological function at SpM diagnosis was significantly associated with longer OS:
216 9.3 years (SD 0.7) for the 48 patients Frankel E; 4.25 years (SD 2.1) for the 3 patients Frankel
217 D-C ($p< 0.0001$) (Figure 1B) [15].

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

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

228

229 **TC and SpM treatment**

230 Primary TC treatments consisted of: a thyroidectomy (47/51, 92%) and radioactive iodine
231 treatment (31/51, 60.7%). In addition, 8 patients (15.7%) received chemotherapy and 5 (9.8%)
232 external beam radiation therapy. Molecular targeted therapy is an emerging treatment option
233 for patients with metastatic thyroid cancer, especially for those presenting SpM. In our series,
234 we identified that at SpM diagnosis, 21 patients received spine radiotherapy, 12 received
235 complementary radioactive iodine (I131) administration and 26 systemic chemotherapies (4
236 cisplatin-based chemotherapy, 4 Doxorubicin, 6 received tyrosine kinase inhibitors (TKIs) and
237 12 unidentified chemotherapies). Whatever the treatment at SpM diagnosis, none could be
238 identified as a factor of better prognosis, probably because we lacked data on the nature of
239 chemotherapy ($p=0.234$).

240 As described in table 1, 5 patients (9.8%) presented the medullary subtype, 22 (43.1%)
241 the papillary subtype, and 24 (47.1%) the follicular subtype of thyroid cancer. Whatever the
242 subtype of cancer, neither the medullary (mean 3.8 years, SD 1.1), nor the papillary (mean 3.9
243 years, SD 2.5), nor the follicular (mean 4.0, SD 2.4) subtype had a significantly better OS ($p=$
244 0.300).

245

246 **SpM surgery**

247 Ten patients were operated, (19.6%) received a posterior decompressive laminectomy
248 associated with posterior fixation. The procedure did not improve their OS ($p=0.937$). No “en
249 bloc SpM” resection was achieved, only vertebral body debulking. One patient had a post-
250 operative complication (wound infection) with a non-compressive epidural hematoma, which
251 required a surgical revision. In our series, 2 of 3 Frankel C-D patients were operated on: 1
252 recovered a Frankel E after surgery and the second following surgery and radiotherapy. Four
253 patients received surgery for due to a threat in neurological functional caused by spinal cord
254 compression and 7 for major instability due to a fracture or a pathological lysis (SINS > 13)
255 [16].

256

257 **Multivariate survival analysis (table 2)**

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

262 Favorable ECOG-PS (i.e. status 0 and 1 of the scale) 0 [HR: 0.3, 95 % CI 0.1-0.941; p
263 <0.0001], 1 [HR: 0.8, 95 % CI 0.04-2.124; $p =0.001$] and ambulatory neurological status:
264 Frankel E [HR: 0.262, 95 % CI 0.048-1.443; $p =0.02$] were independent predictors of better

265 survival. Whereas the other factors including epidural involvement and cancer subtype were
266 not identified to represent independent prognostic factors of survival.
267
268

269 **DISCUSSION**

270

271 *Prognosis factors*

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

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

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

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

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

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

308

309 *Survival and Spine Metastases*

310 Only few studies have analyzed SpM separately from others bone metastases (BM).
311 In a previous retrospective analysis of 146 non-operative cases of TC BM, Pittas at al. reported
312 5-year and 10-year OS rates at 53% and 35%, respectively, from the time of diagnosis of BMs.

313 Vertebrae localization was not identified as a prognosis factor [20]. Bernier et al. were more
314 pessimistic with OS rates with 41% and 15%, respectively [21]. Moreover, the corresponding
315 5-and 10-year rates among 93 Korean patients evaluated by Choi et al. were at 77.1% and 46.6%
316 [22]. More recently, median survival times after the diagnosis of BM were evaluated at 83%
317 (95% CI: 72-90) at 1-year and 59% (95% CI: 43, 71) at 3-years [12]. Similarly, Slook et al.
318 found an OS rate of 45.3% approximately 10 years after BM detection and concluded that SpM
319 were associated with increased mortality. [23]. In all these studies, the OS were poorer than in
320 our study. However, the distinction between SpM and BM was not always studied, and the
321 majority of these series were non-surgical.

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

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

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

339

340

341

342 ***Surgery discussion for TC' SpM***

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

346 In our series, no “en bloc spondylectomy” (EBS) was performed. Only simple
347 decompression and stabilization surgery with or without vertebral body debulking was
348 performed and did not significantly improve the OS in comparison to cases who did not receive
349 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
350 of spinal metastases, single or multiple. Ohashi et al., included 4 patients with isolated thyroid
351 SpM in their (EBS) series. On the one hand the rate of perioperative complications was high,
352 around 75%, and on the other, 100% of patients experienced newly formed distant metastases
353 and a relapse event with a median of 18 months. OS was not determined. They concluded that
354 margin-free EBS was effective in controlling SpM locally but not in preventing further
355 dissemination, nor in improving OS nor in controlling the disease [27].

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

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

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

366 A first element of response would be the study of the anatomical distribution of SpM
367 across vertebrae levels. Indeed, in the series described by Ohashi et al., SpM all tend to be
368 distant from the thyroid (T12 and lumbar vertebrae) described as “real distance metastases”. In
369 our series, for isolated metastases, 27% were present within the cervical spine. These cervical
370 spine localizations were represented distant SpM for they did not share a direct anatomical
371 environment with the primary TC. In contrast, we presume that sometimes, the spinal
372 localization does not necessarily represent a “metastatic” spreading but rather a local
373 progression of the cancer through direct invasion by continuity, similar to that found in lung
374 cancer and the Pancoast-Tobias syndrom. Therefore we find ourselves at an earlier stage in the
375 natural course of the disease than the metastatic stage, even though a direct extension of a TC
376 into the cervical spine represents an early aggressive and locally advanced disease [29].
377 Furthermore, it was demonstrated that in TC, some of the cancer cells that disseminate at an
378 early stage, remain dormant for a long period of time in their new location. These metastatic
379 cancer cells become active only when their new microenvironment favors their growth [30,31].
380 In our series, unfortunately univariate analysis of surgical modalities (surgery p=0.937,
381 postoperative radiotherapy p=0.436) did not show a significant effect on survival. Like many
382 series, this is undoubtedly due to 2 factors, which are: the good prognosis of the long survival
383 of thyroid cancers, which requires large series (national series) and long follow-ups (close to
384 10 years). These elements therefore make it difficult to clearly establish the impact of
385 therapeutic elements in the survival of TC’SpM.

386 387 *Limitations of the Study*

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

395
396
397
398
399

400 **CONCLUSION**

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

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

407

408

409

410

411

412

413 **REFERENCES**

414

- 415 [1] Leenhardt L, Grosclaude P. [Epidemiology of thyroid carcinoma over the world]. *Ann*
 416 *Endocrinol* 2011;72:136–48. <https://doi.org/10.1016/j.ando.2011.03.025>.
- 417 [2] Santé publique France. Estimations nationales de l'incidence et de la mortalité par
 418 cancer en France métropolitaine entre 1990 et 2018 - Tumeurs solides : Étude à partir des
 419 registres des cancers du réseau Francim 2018. /import/estimations-nationales-de-l-incidence-
 420 et-de-la-mortalite-par-cancer-en-france-metropolitaine-entre-1990-et-2018-tumeurs-solides-
 421 etude-a-partir (accessed January 9, 2021).
- 422 [3] Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM.
 423 Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and
 424 pancreas cancers in the United States. *Cancer Res* 2014;74:2913–21.
 425 <https://doi.org/10.1158/0008-5472.CAN-14-0155>.
- 426 [4] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al.
 427 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid
 428 Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines
 429 Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid Off J Am Thyroid*
 430 *Assoc* 2016;26:1–133. <https://doi.org/10.1089/thy.2015.0020>.
- 431 [5] Carling T, Udelsman R. Thyroid cancer. *Annu Rev Med* 2014;65:125–37.
 432 <https://doi.org/10.1146/annurev-med-061512-105739>.
- 433 [6] Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on
 434 papillary and follicular thyroid cancer. *Am J Med* 1994;97:418–28.
 435 [https://doi.org/10.1016/0002-9343\(94\)90321-2](https://doi.org/10.1016/0002-9343(94)90321-2).
- 436 [7] Lopez-Penabad L, Chiu AC, Hoff AO, Schultz P, Gaztambide S, Ordoñez NG, et al.
 437 Prognostic factors in patients with Hürthle cell neoplasms of the thyroid. *Cancer* 2003;97:1186–
 438 94. <https://doi.org/10.1002/cncr.11176>.
- 439 [8] Muresan MM, Olivier P, Leclère J, Sirveaux F, Brunaud L, Klein M, et al. Bone
 440 metastases from differentiated thyroid carcinoma. *Endocr Relat Cancer* 2008;15:37–49.
 441 <https://doi.org/10.1677/ERC-07-0229>.
- 442 [9] Mazzaferri E. Thyroid Cancer: Impact of Therapeutic Modalities on Prognosis. *Thyroid*
 443 *Cancer* 1998:255–84. https://doi.org/10.1007/978-1-4615-4945-1_11.
- 444 [10] Osorio M, Moubayed SP, Su H, Urken ML. Systematic review of site distribution of
 445 bone metastases in differentiated thyroid cancer. *Head Neck* 2017;39:812–8.
 446 <https://doi.org/10.1002/hed.24655>.
- 447 [11] Nakayama R, Horiuchi K, Susa M, Watanabe I, Watanabe K, Tsuji T, et al. Clinical
 448 outcome after bone metastasis (BM) surgery in patients with differentiated thyroid carcinoma
 449 (DTC): a retrospective study of 40 cases. *Jpn J Clin Oncol* 2014;44:918–25.
 450 <https://doi.org/10.1093/jjco/hyu099>.
- 451 [12] Kondraciuk JD, Rice SL, Zhou X, Gharzeddine K, Knezevic A, Spratt DE, et al. Thyroid
 452 Cancer Bone Metastasis: Survival and Genomic Characteristics of a Large Tertiary Care
 453 Cohort. *Clin Nucl Med* 2019;44:e465–71. <https://doi.org/10.1097/RLU.0000000000002626>.
- 454 [13] Zhang D, Gong H, Shen M, Wang D, Jiao J, Yang X, et al. Surgical Management and
 455 Factors Affecting the Prognosis for Patients with Thyroid Cancer Spinal Metastases: A
 456 Retrospective Analysis of 52 Consecutive Patients from a Single Center. *World Neurosurg*
 457 2019;129:e330–6. <https://doi.org/10.1016/j.wneu.2019.05.143>.
- 458 [14] Krewski D, Rao J. Inference from stratified samples: properties of the linearization,
 459 jackknife and balanced repeated replication methods. *Ann Stat* 1981;9:1010–9.
- 460 [15] Frankel HL, Hancock DO, Hyslop G, Melzak J, Michaelis LS, Ungar GH, et al. The
 461 value of postural reduction in the initial management of closed injuries of the spine with
 462 paraplegia and tetraplegia. I. Paraplegia 1969;7:179–92. <https://doi.org/10.1038/sc.1969.30>.

- 463 [16] Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, et al. A novel
464 classification system for spinal instability in neoplastic disease: an evidence-based approach
465 and expert consensus from the Spine Oncology Study Group. *Spine* 2010;35:E1221-1229.
466 <https://doi.org/10.1097/BRS.0b013e3181e16ae2>.
- 467 [17] Xu JY, Murphy WA, Milton DR, Jimenez C, Rao SN, Habra MA, et al. Bone Metastases
468 and Skeletal-Related Events in Medullary Thyroid Carcinoma. *J Clin Endocrinol Metab*
469 2016;101:4871–7. <https://doi.org/10.1210/jc.2016-2815>.
- 470 [18] Bernstein MB, Chang EL, Amini B, Pan H, Cabanillas M, Wang XA, et al. Spine
471 Stereotactic Radiosurgery for Patients with Metastatic Thyroid Cancer: Secondary Analysis of
472 Phase I/II Trials. *Thyroid Off J Am Thyroid Assoc* 2016;26:1269–75.
473 <https://doi.org/10.1089/thy.2016.0046>.
- 474 [19] Choi D, Fox Z, Albert T, Arts M, Balabaud L, Bungler C, et al. Prediction of Quality of
475 Life and Survival After Surgery for Symptomatic Spinal Metastases: A Multicenter Cohort
476 Study to Determine Suitability for Surgical Treatment. *Neurosurgery* 2015;77:698–708;
477 discussion 708. <https://doi.org/10.1227/NEU.0000000000000907>.
- 478 [20] Pittas AG, Adler M, Fazzari M, Tickoo S, Rosai J, Larson SM, et al. Bone metastases
479 from thyroid carcinoma: clinical characteristics and prognostic variables in one hundred forty-
480 six patients. *Thyroid Off J Am Thyroid Assoc* 2000;10:261–8.
481 <https://doi.org/10.1089/thy.2000.10.261>.
- 482 [21] Bernier MO, Leenhardt L, Hoang C, Aurengo A, Mary JY, Menegaux F, et al. Survival
483 and therapeutic modalities in patients with bone metastases of differentiated thyroid
484 carcinomas. *J Clin Endocrinol Metab* 2001;86:1568–73.
485 <https://doi.org/10.1210/jcem.86.4.7390>.
- 486 [22] Choi YM, Kim WG, Kwon H, Jeon MJ, Lee JJ, Ryu J-S, et al. Early prognostic factors
487 at the time of diagnosis of bone metastasis in patients with bone metastases of differentiated
488 thyroid carcinoma. *Eur J Endocrinol* 2016;175:165–72. <https://doi.org/10.1530/EJE-16-0237>.
- 489 [23] Slook O, Levy S, Slutzky-Shraga I, Tsvetov G, Robenshtok E, Shimon I, et al. LONG-
490 TERM OUTCOMES AND PROGNOSTIC FACTORS IN PATIENTS WITH
491 DIFFERENTIATED THYROID CARCINOMA AND BONE METASTASES. *Endocr Pract*
492 *Off J Am Coll Endocrinol Am Assoc Clin Endocrinol* 2019;25:427–37.
493 <https://doi.org/10.4158/EP-2018-0465>.
- 494 [24] Kushchayeva YS, Kushchayev SV, Carroll NM, Felger EA, Links TP, Teytelboym OM,
495 et al. Spinal metastases due to thyroid carcinoma: an analysis of 202 patients. *Thyroid Off J*
496 *Am Thyroid Assoc* 2014;24:1488–500. <https://doi.org/10.1089/thy.2013.0633>.
- 497 [25] Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, et al. Direct
498 decompressive surgical resection in the treatment of spinal cord compression caused by
499 metastatic cancer: a randomised trial. *Lancet* 2005;366:643–8. [https://doi.org/10.1016/S0140-6736\(05\)66954-1](https://doi.org/10.1016/S0140-6736(05)66954-1).
- 501 [26] Kushchayeva YS, Kushchayev SV, Wexler JA, Carroll NM, Preul MC, Teytelboym
502 OM, et al. Current treatment modalities for spinal metastases secondary to thyroid carcinoma.
503 *Thyroid Off J Am Thyroid Assoc* 2014;24:1443–55. <https://doi.org/10.1089/thy.2013.0634>.
- 504 [27] Ohashi M, Hirano T, Watanabe K, Hasegawa K, Ito T, Katsumi K, et al. *En Bloc*
505 Spondylectomy for Spinal Metastases: Detailed Oncological Outcomes at a Minimum of 2
506 Years after Surgery. *Asian Spine J* 2018;13:296–304. <https://doi.org/10.31616/asj.2018.0145>.
- 507 [28] Kato S, Murakami H, Demura S, Fujimaki Y, Yoshioka K, Yokogawa N, et al. The
508 impact of complete surgical resection of spinal metastases on the survival of patients with
509 thyroid cancer. *Cancer Med* 2016;5:2343–9. <https://doi.org/10.1002/cam4.823>.
- 510 [29] Amelot A, Terrier L-M, Mazon J-J, Valery C-A, Cornu P, Carpentier A, et al.
511 Timeline metastatic progression: in the wake of the « seed and soil » theory. *Med Oncol*
512 *Northwood Lond Engl* 2017;34:185. <https://doi.org/10.1007/s12032-017-1045-8>.

513 [30] Ringel MD. Metastatic dormancy and progression in thyroid cancer: targeting cells in
514 the metastatic frontier. *Thyroid Off J Am Thyroid Assoc* 2011;21:487–92.
515 <https://doi.org/10.1089/thy.2011.2121>.

516 [31] Feller L, Kramer B, Lemmer J. A short account of metastatic bone disease. *Cancer Cell*
517 *Int* 2011;11:24. <https://doi.org/10.1186/1475-2867-11-24>.

518

519

520 **LEGENDS**

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

522

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

526

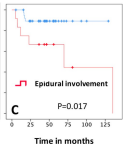
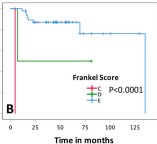
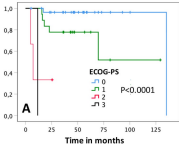
527 **Figure 1: Overall Survival in univariate analyses**

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

531

532

Overall Survival (probability)



	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

	<i>Univariate</i>		<i>Multivariate</i>		
	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)