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Approaching spinal metastases spread profile

Aymeric Amelot[a,*], Louis-Marie Terrier[b], Joseph Cristini[c], Louis-Romée LeNail[d], Kévin Buffenoir[c], Hugues Pascal-Moussellard[e], Raphael Bonaccorsi[e], Bertrand Mathon[a]

[a] Department of Neurosurgery, La Pitié Salpétrière Hospital, Paris, France
[b] Department of Neurosurgery, Bretonneau Hospital, Tours, France
[c] Department of Neurosurgey/Neurotraumatology, Hotel-Dieu Hospital, Nantes, France
[d] Department of Orthopaedic Surgery, Trousseau Hospital, Tours, France
[e] Department of Orthopaedic Surgery, Pitié-Salpêtrière Hospital, Paris, France

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ABSTRACT

Background: Spinal metastases cause significant morbidity. The vertebral column is the most common site of cancer metastasis, however predilection of metastases for the spine is not fully understood.
Objective: The aim of the present investigation was to obtain a better description of the distribution of spinal metastases. The main objective of our study was to figure out how malignant cells disseminate within the spine and determine a potent mapping or profile of the metastatic spread routes.
Study design: A prospective French national multicenter database.
Methods: 740 consecutive patients were treated for spine metastasis (SpM) between January 2014 and 2017. A categorisation of the anatomical distribution of spine lesions was conducted.
Results: One hundred and seventy patients (22.9% of series) presented cervical SpM, 440 (60%) lumbar SpM, and a majority 530 (71.6%) at the thoracic vertebral level. Metastases were more often present in the vertebral body (645 patients, 87.2%) than in a posterior location (278 patients, 37.6%, $p < 0.0001$). 212/740 patients (28.6%) presented circumferential spine involvement (body and posterior elements). An associated epiduritis was presented in 404 patients (54.6%). Primitive neck tumors spread towards the cervical spine: ENT (34.8%, $p = 0.049$), thyroid (33.3%, $p = 0.043$) whereas pelvic tumors targeted the lumbar spine: prostate (72%, $p = 0.011$), bladder (75%, $p = 0.047$). All tumors presented a tropism for thoracic vertebrae. Significant tumor/vertebrae associations were identified: lung ($p = 0.004$) and thyroid ($p = 0.028$) for L_1, bladder for L_5 ($p = 0.0025$), breast for C_6 ($p = 0.006$), Prostate for L_1-L_4 ($p = 0.002$–0.04), multiple myelomas for C_7, $p = 0.03$, T_3-T_7 ($p < 0.0001$–0.025) and L_1-L_4 ($p = 0.004$–0.027). Spine was the latest organ affected by metastases with a median-free survival of 4.2 months (SD 1.8, $p = 0.001$).
Conclusions: Although we determined that some tumors have a significant propensity to localise at certain vertebral level, it remains premature to conclude on a spinal metastases profile. To date, it is too early to provide recommendations in imaging follow-up or in preventive therapeutic based on this mapping of spine metastases.

1. Introduction

Metastatic spinal disease occurs in around 5–30% of cases of primary cancers [1–5], most commonly originating from carcinomas of the breast, lung, prostate, and kidney [6–8]. Bone metastases have a prognostic impact and are significantly related to increased morbidity [9]. The predilection of metastases for the spine is not fully understood, although it may be partially explained by Paget's "seed-and-soil" hypothesis. Several studies have attempted to describe the distribution of metastatic lesions within the vertebral body and postulate a reason for the patterns observed [10–14]. Metastatic spinal disease is considered to be the advanced stage of primary cancers and treatment is generally palliative and not curative [15,16]. Although studies suggested a propensity for metastasis to the posterior vertebral body, they were limited by old imaging modalities and small patient numbers, leaving the anatomic distribution an unanswered question still today [10,12]. As the incidence of spinal metastases continues to increase alongside increasing prevalence of primary tumors; improving comprehension and defining how metastases spread becomes a therapeutic challenge. The establishment of a spinal metastatic profile could allow the adaptation of imaging follow-up, to assess the prognosis and a potential secondary treatment.

* Corresponding author. Department of Neurosurgery, Batiment Babinski Groupe Hospitalier Pitié-Salpêtrière, 47-83 boulevard de l'Hôpital, 75013, Paris.
E-mail address: aymmed@hotmail.fr (A. Amelot).

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The goal of the present investigation was to improve the distribution description of spinal metastases. The main objective of our study was to figure out how malignant cells disseminate within the spine and determine if it is possible to achieve a preferential vertebral metastatic pattern according to the primary tumor.

2. Materials and methods

2.1. Ethics statement

The data collected during the study will be 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.

2.2. Study population

A prospective French national multicenter database of consecutive patients treated for spine metastasis (SpM) between January 2014 and 2017 was generated from the neurosurgery and orthopedic departments in La Pitié-Salpétrière hospital (Paris), Hotel-Dieu hospital (Nantes), Bretonneau and Trousseau hospitals (Tours). The initial number of patients was 794. Fifty-four patients with missing data or lost of follow-up were excluded. Thus, our series reported 740 consecutive patients. These patients were diagnosed with SpM over the course or at the time of diagnosis of their primary cancer: lung, breast, thyroid, hematologic/blood, prostate, kidney, bladder, gastro-intestinal (GI), ears-nose-throat (ENT) and other cancers (gynecological, adrenal, testicle).

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, primary tumor, date of primary tumor diagnosis, date of SpM diagnosis, presence of other organ metastasis at the time of SpM diagnosis, number, location, and anatomical position of SpM (vertebra body, pedicle, posterior arch, epiduritis) were collected. MRI/spine CT were done several times during evolution for all patients.

2.3. MRI/determination of lesion location

At SpM diagnosis and throughout the follow-up, the identification and the evolution of metastases were made by spine CT scan and MRI. To determine the location and extent of metastatic vertebral body/pedicle/posterior arch involvement, each scan and MRI were reviewed independently by at least 3 reviewers (surgeons and radiologists). Axial and sagittal series were used to determine the distribution of lesions.

2.4. Metastasis-free survival (MFS)

Metastasis-free survival (MFS) was defined as the period of time between primary cancer diagnosis and metastasis diagnosis (spine, brain, liver, pleura, peritoneum, bone).

2.5. Statistical analysis

All statistical analyses were performed using SPSS program for Windows V17.0 (SPSS, Chicago, IL, U.S.A). Data are presented as the mean ± standard deviation. For all analyses, p-values < 0.05 was considered statistically significant. Gender, metastases localisation and vertebrae, were used as 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). In the univariate analysis, categorical variables were assessed using Pearson Chi-square or Fisher's exact test. The Kaplan-Meier method was used to estimate the metastases free survival. For descriptive and inferential analyses, boot-strapping with replacement (iterations = 1000) was performed to attain variance estimates at the 95%CI [17].

3. Results

In this study, 740 consecutive patients were included. A total of 3065 SpM were identified at the time of spinal localization diagnosis.

3.1. Overall survival

In our series, 315 (42.6%) patients were women and 425 (57.4%) men, with a mean age of 64.1 years (range, 19.6–97.2 years). As determined by histology, the primary tumor was lung (210, 28.4%), breast (123, 16.6%), blood (81, 10.9%), gastro-intestinal (GI) (79, 10.6%), prostate (72, 9.7%), kidney (55, 7.4%), thyroid (51, 6.9%), ENT (23, 3.1%) melanoma (19, 2.5%), bladder (18, 2.4%), and other cancers (gynecology, adrenal) (7, 0.9%). The median survival time for all patients from spine metastases diagnosis was 17.03 months (SD 1.5). The 2-year, 5-year, and 10-year survival estimates were 42.8% (SD 1.9), 24.9% (2.2), and 10.6% (4.9). For 306 patients (41.5%), SpM were diagnosed synchronously with the primary tumors.

3.2. Vertebral anatomical distribution

The distribution of SpM is given in Fig. 1 and Table 1: thoracic spine, 530 patients (71.6%); lumbar spine, 440 patients (60%); cervical spine, 170 patients (22.9%)"

Metastases were predominantly present in the vertebral body (645, 87.2%), in comparison to the posterior location (posterior arch, pedicles, spinous/tranverse processes or articular facets) concerning 278 patients, 37.6%, ($p < 0.0001$). 212/740 (28.6%) presented circumferential spine involvement (body and posterior elements) (Fig. 2).

Furthermore, 404 patients (54.6%) presented a peri-medullar epidural localisation. The vertebral body alone was affected in 208 (28.1%) patients, 26 (3.5%) presented lesions within the posterior arch/pedicles ($p = 0.324$), and 147 (19.9%) presented body and posterior involvement. Vertebral body involvement with a fracture was presented in 175 (30%) patients, leading to isolated cement bone reinforcement alone or in combination with an osteosynthesis.

3.3. Primary tumor spine metastases distribution (Table 2)

Significant differences were highlighted in disease dissemination among various tumors. Primitive tumors that were anatomically located at neck showed a significant preference to metastasize in the cervical spine region: ENT (34.8%, $p = 0.049$) and thyroid (33.3%, $p = 0.043$), *vs* lung (27.6%) and breast (27.8%) (p value between the different primary tumors = 0.01).

Moreover, in lumbar region we noted similar significant differences in metastases spread routes; some tumors invaded the spine locally and metastasized by direct anatomical proximity: Prostate (72%, $p = 0.011$) and Bladder (75%, $p = 0.047$) whereas others did so by distal dissemination (breast 60%, ENT 40%) $p = 0.01$.

Hematologic cancers (57 multiple myelomas (MM), 22 lymphomas) disseminated in all spine regions but preferentially in lumbar ($p = 0.01$). Moreover, thyroid cancer showed significant afar dissemination in the lombo-sacral region ($p = 0.027$). On the contrary, all primary tumors presented a tropism for the thoracic region, even the most anatomically distant tumors [bladder (60%)-Breast (74.6%)].

All of the different primary tumors metastasized in the vertebral body without significant difference, however we unexpectedly noted that breast ($p = 0.018$) and blood cancers ($p < 0.001$) metastasized significantly in the posterior arch localisation. Futhermoe there existed a significant tendency that the presence of epiduritis was more likely to be observed for lung ($p < 0.001$) and breast cancer ($p = 0.029$) as

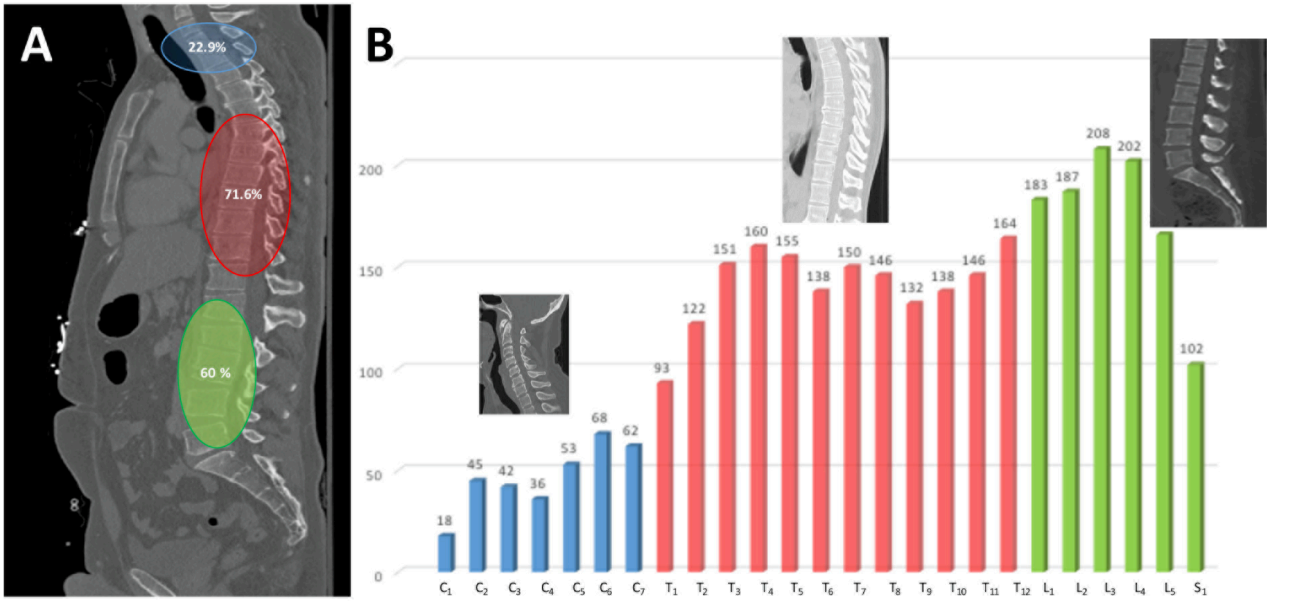

Fig. 1. Spine metastases repartition. (A) Cervical, thoracic and lumbar percentages of spine metastases distribution. (B) Metastases prevalence according to anatomical vertebrae.

opposed to thyroid cancer, which was rarely associated with epiduritis ($p < 0.0001$).

Vertebral or closing plate fractures were highly associated with thyroid (29.4%), GI (24.1%) and blood cancers (22.2%) compared to bladder cancer (0%) ($p < 0.003$).

3.4. Primary tumor vertebral metastases distribution (Table 3)

If some tumors metastasize preferentially in some regions, they do not necessarily target certain vertebrae in particular. However, lung ($p = 0.004$) and thyroid ($p = 0.028$) metastases were predominantly present in vertebra L_1, urology cancer in L_5 ($p = 0.0025$) and breast cancer in C_6 ($p = 0.006$). Prostate cancer was associated with L_1-L_4 vertebrae; ($p = 0.002$–0.04). Multiple myeloma (MM) were significantly associated with multiple vertebrae: C_7, $p = 0.03$, T_3-T_7 ($p < 0.0001$–0.025) and L_1-L_4 ($p = 0.004$–0.027).

3.5. Timeline spine metastases

In our series, when we determined the frequency of metastases in other organs, we only identified a significant high frequency of extra-vertebral osseous metastases in GI cancers ($p = 0.005$). Following spine, lung was the most frequently targeted metastasis organ in GI cancers ($p = 0.005$), prostate cancers ($p = 0.015$), blood cancers ($p < 0.0001$), kidney cancers ($p < 0.0001$) and bladder cancers ($p < 0.0001$). Peritoneum metastases were more frequent in GI cancer ($p = 0.032$) whereas liver metastases were more common in prostate cancer ($p = 0.045$), blood cancers ($p < 0.0001$), melanoma ($p < 0.0001$) and breast cancers ($p = 0.038$). Brain metastasis was more frequent in lung cancer ($p < 0.0001$) and melanoma ($p = 0.008$).

SpM was among the latest events in our series; so the median metastasis-free survival (MFS) determined for each organ was: 0.2 mo (SD 0.05) for lung, 0.6 mo (SD 0.3) for brain, 1.7 mo (SD 0.9) for peritoneum, 1.9 mo (SD 1.1) for pleura, 2.9 mo (SD 1.8) for liver and 4.2 months (SD 1.8) for spine ($p < 0.001$).

4. Discussion

4.1. Spine anatomical distribution

As previously described, we identified that SpM preferentially affected the thoracic (71%), lumbar (60%) then cervical spine (23%). As found in our series, the prevalence of spinal metastasis is highest among individuals between the 4th and 7th decade of life [1,18]. Males are more likely to be afflicted than females; this is thought to reflect the

Table 1
Spine region metastases distribution according to primary cancer. Legends: pa, patients.

	Cervical(170 pa, 22.9%)		Thoracic(530 pa, 71.6%)		Lumbar(440 pa, 60%)		Epiduritis(404 pa, 54.6%)		Vertebral body(645 pa, 87.2%)		Postérior(278 pa, 37.6%)	
Primary Tumor	Nbr; %	p	Nbr; %	p	Nbr; %	p	Nbr; %	p	Nbr; %	p	Nbr; %	p
Lung (206)	56:27.2	0.102	153:74.3	0.363	117; 56.8	0.277	133; 64.5	**0.001**	184; 90.5	0.327	80; 38.8	0.673
Breast (122)	34; 27.6	0.192	92; 74.8	0.444	73; 59.3	0.920	56; 45.5	***0.029***	107; 86.9	0.801	34; 27.8	***0.018***
Hematology (81)	17; 21.0	0.557	58; 71.2	0.792	59; 72.8	***0.010***	44; 55.7	0.905	66; 83.5	0.286	43; 54.4	***0.001***
GI (79)	13; 16.5	0.117	51; 64.6	0.232	45; 57.0	0.494	49; 62.8	0.089	71; 91.0	0.370	28; 35.9	0.805
Prostate (72)	11; 15.3	0.207	49; 68.1	0.493	52; 72.2	***0.011***	33; 45.8	0.135	64; 88.8	0.852	21; 29.2	0.126
Renal (55)	08; 14.9	0.137	41; 74.5	0.751	33; 60.1	0.927	34; 61.8	0.325	50; 90.9	0.529	19; 34.5	0.667
Thyroid (51)	17; 33.3	**0.043**	37; 72.1	0.879	23; 45.1	***0.027***	12; 23.5	***0.0001***	41; 80.4	0.129	21; 41.2	0.654
ENT (23)	08; 34.8	**0.049**	15; 65.2	0.486	09; 39.1	0.70	12; 52.2	0.834	20; 87.0	0.987	09; 39.1	0.911
Bladder (20)	01; 05.0	0.601	12; 60.1	0.313	15; 75.2	**0.047**	09; 45.2	0.496	16; 80.2	0.306	10; 50.0	0.252
Melanoma (19)	02; 10.5	0.271	14; 73.7	0.834	11; 57.9	0.756	12; 63.2	0.435	14; 73.1	0.102	09; 47.4	0.472
		0.01		***0.246***		***0.01***						

Table 2
Metastases vertebrae repartition according to primary cancers (significant p values are in bold italic). Legends: GI (gastro-intestinal), ENT (Ear, Nose, Throat).

	GI (79)	Blood (81)	Melanoma (19)	ENT (23)	Other (7)	Lung (210)	Prostate (72)	Renal (55)	Breast (123)	Thyroid (51)	Bladder (18)	pvalue
C_1	1(1.3)	1(1.2)	0(0.0)	2(8.7)	0(0.0)	9(4.3)	1(1.4)	0(0.0)	4(3.3)	0(0.0)	0(0.0)	0.269
C_2	3(3.8)	7(8.6)	2(10.5)	3(13.0)	0(0.0)	14(6.7)	3(4.2)	1(1.8)	9(7.3)	2(3.9)	1(5.0)	0.645
C_3	6(7.6)	6(7.4)	2(10.5)	1(4.3)	0(0.0)	11(5.2)	3(4.2)	2(3.6)	7(5.7)	3(5.9)	1(5.0)	0.977
C_4	7(8.9)	3(3.7)	1(5.3)	1(4.3)	0(0.0)	10(4.8)	4(5.6)	1(1.8)	6(4.9)	2(3.9)	1(5.0)	0.915
C_5	6(7.6)	4(4.9)	1(5.3)	3(13.0)	1(14.3)	17(8.1)	3(4.2)	1(1.8)	10(8.1)	6(11.8)	1(5.0)	0.628
C_6	6(7.6)	2(2.5)	1(5.3)	3(13.0)	1(14.3)	20(9.5)	2(2.8)	6(10.9)	20(16.3)	6(11.8)	1(5.0)	0.07
C_7	7(8.9)	4(4.9)	0(0.0)	4(17.4)	1(14.3)	19(9.0)	1(1.4)	2(3.6)	15(12.2)	8(15.7)	1(5.0)	0.055
T_1	9(11.4)	13(16.0)	1(5.3)	3(13.0)	0(0.0)	33(16)	6(8.3)	4(7.3)	14(11.4)	8(15.7)	2(10.0)	0.617
T_2	10(12.7)	16(19.8)	3(15.8)	4(17.4)	0(0.0)	39(19)	9(12.5)	7(12.7)	22(17.9)	9(17.6)	3(15.0)	0.878
T_3	12(15.2)	25(30.9)	3(15.8)	5(21.7)	2(28.6)	44(21)	19(26.4)	10(18)	20(16.3)	9(17.6)	2(10.0)	0.285
T_4	10(12.7)	24(29.2)	5(26.3)	3(13.0)	2(28.6)	43(20)	20(27.8)	11(20)	27(22.0)	11(21.6)	4(20.0)	0.427
T_5	14(17.7)	28(34.6)	4(21.1)	2(8.7)	2(28.6)	37(18)	18(25.0)	9(16.4)	30(24.4)	8(15.7)	3(15.0)	0.087
T_6	6(7.6)	37(45.7)	0(0.0)	2(8.7)	0(0.0)	31(15)	17(23.6)	9(16.4)	27(22.0)	6(11.8)	3(15.0)	***0.0001***
T_7	13(16.5)	25(30.9)	1(5.3)	2(8.7)	2(28.6)	38(18)	21(29.2)	10(18)	30(24.4)	5(9.8)	3(15.0)	***0.024***
T_8	10(12.7)	23(28.4)	5(26.3)	0(0.0)	2(28.6)	38(18)	21(29.2)	11(20)	27(22.0)	7(13.7)	2(10.0)	***0.029***
T_9	16(20.3)	18(22.2)	3(15.8)	4(17.4)	1(14.3)	27(13)	16(22.2)	7(12.7)	29(23.6)	7(13.7)	4(20.0)	0.407
T_{10}	16(20.3)	15(18.5)	2(10.5)	4(17.4)	1(14.3)	41(20)	13(18.1)	10(18)	28(22.8)	6(11.8)	2(10.0)	0.881
T_{11}	17(21.5)	18(22.2)	7(36.8)	3(13.0)	2(28.6)	41(20)	15(20.8)	8(14.5)	25(20.3)	6(11.8)	4(20.0)	0.624
T_{12}	11(13.9)	21(25.9)	5(26.3)	4(17.4)	3(42.9)	45(21)	21(29.2)	10(18)	27(22.0)	12(23.5)	5(25.0)	0.554
L_1	14(17.7)	29(35.8)	5(26.3)	5(21.7)	2(28.6)	37(18)	28(38.9)	17(31)	34(27.6)	6(11.8)	6(30.0)	***0.002***
L_2	21(26.6)	31(38.3)	0(0.0)	4(17.4)	2(28.6)	47(22)	25(34.7)	11(20)	31(25.2)	9(17.6)	6(30.0)	***0.018***
L_3	20(25.3)	33(40.7)	3(15.8)	4(17.4)	2(28.6)	54(26)	32(44.4)	10(18)	34(27.6)	9(17.6)	7(35.0)	***0.005***
L_4	19(24.1)	30(37.0)	4(21.1)	6(26.1)	2(28.6)	54(26)	29(40.3)	9(16.4)	32(26.0)	9(17.6)	8(40.0)	***0.047***
L_5	15(19.0)	21(25.9)	2(10.5)	3(13.0)	3(42.9)	40(19)	23(31.9)	9(16.4)	32(26.0)	9(17.6)	9(45.0)	**0.038**
S_1	6(7.6)	14(17.3)	2(10.5)	1(4.3)	1(14.3)	29(14)	15(20.8)	4(7.3)	16(13.0)	10(19.6)	4(20.0)	0.258

higher prevalence of lung cancer in males and the higher prevalence of prostate cancer relative to breast or gynecological cancers [8]. We confirmed that the vertebral body is the commonest site for initial spinal metastasis involvement while the posterior arch is involved in about 37%, which is consistent with the few data evocated in the literature [10,19]. Previous studies suggested a propensity of metastasis for the vertebral body, but they were limited by old imaging modalities and small patient numbers, leaving the anatomic distribution an unanswered question [10–12]. Already in the 90s, Algra et al. were among the first to raise the challenge of spine metastasis spreading preferences [12]. They supposed that the initial anatomic location of metastases within vertebrae was in the posterior portion of the body. They showed that the body was involved before the pedicles [12]. More recently, Guo et al. confirmed that metastases to the spine have a greater propensity for involvement in the vertebral body and in particular the posterior region [13]. In our work design, we have not precisely studied the anatomical topography of lesions within the vertebral body, but we also noted that the majority of vertebral lesions involved posterior region (69%). Tarnoki et al. recently demonstrated that the involvement of the pedicle was more likely to be affected by lung cancer than breast cancer, but we did not confirm this in our series [19]. Contrary to Algra et al. in our series pedicles were invaded without statistical

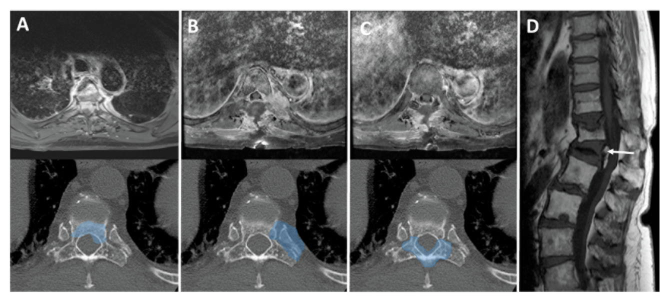

Fig. 2. Spine metastases spreading. MRI (up)/axial CT scan (down) with anterior epiduritis and vertebral body metastases, (B) axial spine CT scan/MRI with pedicular and lateral metastases, (C) axial CT scan/MRI with posterior epiduritis and posterior arch metastases (D) sagittal T1-weighted MRI with L1 vertebral body collapse caused by metastases (white arrow).

combination with the vertebral body (p = 0.3), this suggested that invasion and destruction of the pedicle by the metastatic process occurs by different or separated pathways [12].

However, in agreement with our results and the literature, we can assume distribution differences in spine metastases. (1) The cervical

Table 3
Statistically significant associations between metastases vertebral level and primary cancers.

	Primary tumor: *number of patients, (%), p value*						
Nb	GI	Blood	Lung	Prostate	Breast	Thyroid	Bladder
C_6		2(2.5)p = 0.03			20(16.3)p = 0.006		
C_7							
T_3		25(30.9)p = 0.026					
T_5		28(34.6)p = 0.003					
T_6	6(7.6)p = 0.008	37(45.7)p = 0.0001					
T_7		25(30.9)p = 0.025					
T_8				21(29.2)p = 0.042			
L_1		29(35.8)p = 0.027	37(18)p = 0.004	28(38.9)p = 0.006		6(11.8)p = 0.028	
L_2		31(38.3)p = 0.004					
L_3		33(40.7)p = 0.005		32(44.4)p = 0.002			
L_4		30(37.0)P = 0.032		29(40.3)p = 0.012			
L_5							9(45.0) p = 0.025

and lumbar regions are characterized by an invasion spreading locally by continuity extension; cervical spine for neck tumors, *i.e* thyroid or ENT tumors, and lumbar spine for prostate or bladder tumors. (2) in our series, we identified that the thoracic region represents a metastatic hub for all tumors without statistic differences. All tumors metastasized in the thoracic spine, without anatomical partitioning. The preference for thoracic spine metastatic involvement in comparison to cervical and lumbar spine has been reported previously in general [20,21] and also in lung cancer in particular [22].

4.2. Metastatic spread routes

In a second step, we can assume that spine metastases have different spreads routes; supposedly a majority of malignant cells disseminate via hematogenous/lymphatic pathways or direct extension [23]. The vascular and lymphatic anatomy of the vertebral column is often used to explain the propensity of tumor cells to spread to the spine [10,24]. Indeed, the Batson's vertebral venous plexus draining the thoracic viscera can be one possible explanation of this phenomenon because it is a direct route for metastases towards the axial skeleton through the epidural and perivertebral veins, especially for lung cancer [22,25]. For exemple it was described that breast cancer metastasized through the azygos communicates to the plexus of Batson in the thoracic region [25]. These venous plexus vessels could contribute to multifocal lesion seeding and epiduritis, due especially to their longitudinal and avalvulated anatomy. Thus in our study we identified that epiduritis are mostly associated with the thoracic region ($p < 0.001$). In 1988, Arguello et al. injected cancer cells into the systemic arterial circulation of a murine model, they established that metastatic colonies grew into the vertebral bodies and spread to the epidural and paraspinous tissues along the venous channels [26]. Then, an experimental study showed that cancer cells in the vertebral marrow cavity invade the spinal canal through the foramina of the vertebral veins, towards a posterior location, rather than destroying the cortical bone [27]. Tumor emboli should follow the blood flow until they are trapped and removed from circulation. Furthermore, the position of the metastases in the vertebra correlates with the entrance sites of the vertebral vessels [12]. Indeed, the richly supplied red marrow vasculature which features dilated sinusoids and looped vessels is favourable for the deposition of tumor emboli [26,28]. Furthermore, we can also mention another explanation developed by Ren et al. is the concept of bone metastatic “niche, or hiding” which can explain the maintenance of long-term dormancy of disseminated tumor cells in bone [29].

The mechanisms of dissemination to the posterior elements (arch, spinous/transverse processes, articular facets), even if they are in minority, remain delicate to explain and are probably caused by paraspinous disease or posterior epiduritis. Epiduritis are most often located near the foramina and come from *a priori* vascular origin.

In the study of Moreno et al. spinal vertebrae involvement most often occurred in smaller tumors (4–6 cm), while lung involvement was more likely in large tumors (6–8 cm), with liver involvement usually restricted to the largest tumors (8 cm or larger) [30]. Therefore Moreno et al. suggested that spinal metastases precede lung and liver metastases based on tumor sizes [30]. With our findings, we think otherwise: thereby, the timeline of metastases has already been studied, and a previous work demonstrated that spinal metastasis was one of the latest events in the cancer course [15,31]. To explain why the metastases of some primary tumors target vertebrae at an afar anatomical distance, i.e: prostate/bladder in cervical/thoracic region, or ENT/thyroid in lumbar/thoracic vertebrae, we presume that tumors could also use certain “relay” organs such as the liver, mediastinum, and pleura to employ their lymphatic and vascular network dissemination [32]. Our findings are in favour of this hypothesis, since pulmonary and liver metastases are statistically earlier than spine [33]. Others have observed that prostatic carcinoma cells may pass through the lungs and may thus reach the skeletal system through arterial circulation [34,35].

In prostate and bladder cancers, a backward metastatic pathway, heading from the prostate to the periprostatic and presacral veins as well as the pelvic plexus, was also suggested [24]. Thereby, in our series we determined that these 2 tumors metastasized significantly more in the lumbar region as well as in the pelvic bone ($p = 0.02$) [24].

As expected, in our series the metastatic profile of hematologic cancers was significantly diffused over the entire spine.

Moreover, it seems important to argue that in our study, we did not collect for patients with breast or prostate cancer if they received a bisphosphonate for the prevention or for the treatment of hormone therapy-induced osteoporosis: since this bisphosphonate treatment may have prevent or delay the metastasis process [36].

4.3. Is a metastatic profile possible and what is the therapeutic benefit?

Admittedly, we demonstrated significant local spreading of metastases in the cervical and lumbar spine. Thereby, we determined that some cancers have significant predispositions to vertebrae preferentiality such as: lung, thyroid, prostate and MM in L_1, MM in lumbar or breast in C_6. However, in addition to these particular cases, it is utterly impossible at this point of time to establish a mapping of SpM that could guide imaging follow-up, predict vertebrae metastases according to primary tumors and so improve a complementary preventive treatment *i.e*: enlarging irradiation, for exemple L_1 for spine thoracic lung metastases.

5. Conclusion

Our findings suggest that some tumors such as lung, thyroid, prostate, MM and breast metastasize significantly at certain vertebral level. Furthermore, spine metastases spread according to different pathways: (i) direct invasion, (ii) arterial and venous routes and (iii) relay or step organs. Nevertheless, it remains too premature to establish a spinal metastases mapping according to each primary tumor.

Conflicts of interest

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.

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Abbrevations

Gastro-intestinal GI
Metastasis-free survival MFS
Ear-Nose-Throat ENT
Spine metastases SpM
Multiple Myeloma MM

References

[1] D.M. Sciubba, Z.L. Gokaslan, Diagnosis and management of metastatic spine disease, Surg. Oncol. 15 (2006) 141–151, https://doi.org/10.1016/j.suronc.2006.11.002.

[2] N. Sundaresan, S. Boriani, A. Rothman, R. Holtzman, Tumors of the osseous spine, J. Neuro Oncol. 69 (2004) 273–290.
[3] A.P. White, B.K. Kwon, D.M. Lindskog, G.E. Friedlaender, J.N. Grauer, Metastatic disease of the spine, J. Am. Acad. Orthop. Surg. 14 (2006) 587–598.
[4] R.E. Coleman, Skeletal complications of malignancy, Cancer 80 (1997) 1588–1594.
[5] S. Li, Y. Peng, E.D. Weinhandl, A.H. Blaes, K. Cetin, V.M. Chia, S. Stryker, J.J. Pinzone, J.F. Acquavella, T.J. Arneson, Estimated number of prevalent cases of metastatic bone disease in the US adult population, Clin. Epidemiol. 4 (2012) 87–93, https://doi.org/10.2147/CLEP.S28339.
[6] A. Jemal, R. Siegel, E. Ward, T. Murray, J. Xu, M.J. Thun, Cancer statistics, 2007, CA, Cancer J. Clin. 57 (2007) 43–66.
[7] J. Manabe, N. Kawaguchi, S. Matsumoto, T. Tanizawa, Surgical treatment of bone metastasis: indications and outcomes, Int. J. Clin. Oncol. 10 (2005) 103–111, https://doi.org/10.1007/s10147-005-0478-9.
[8] G. Maccauro, M.S. Spinelli, S. Mauro, C. Perisano, C. Graci, M.A. Rosa, Physiopathology of spine metastasis, Int. J. Surg. Oncol. 2011 (2011) 107969, https://doi.org/10.1155/2011/107969.
[9] B. Depreitere, F. Ricciardi, M. Arts, L. Balabaud, J.M. Buchowski, C. Bunger, C.K. Chung, M.H. Coppes, M.G. Fehlings, N. Kawahara, C.-S. Lee, Y. Leung, J.A. Martin-Benlloch, E.M. Massicotte, C. Mazel, B. Meyer, F.C. Oner, W. Peul, N. Quraishi, Y. Tokuhashi, K. Tomita, C. Ulbricht, J.J. Verlaan, M. Wang, H.A. Crockard, D. Choi, Loss of local tumor control after index surgery for spinal metastases: a prospective cohort study, World Neurosurg 117 (2018) e8–e16, https://doi.org/10.1016/j.wneu.2018.04.170.
[10] W.T. Yuh, J.P. Quets, H.J. Lee, T.M. Simonson, L.S. Michalson, P.T. Nguyen, Y. Sato, N.A. Mayr, K.S. Berbaum, Anatomic distribution of metastases in the vertebral body and modes of hematogenous spread, Spine 21 (1996) 2243–2250.
[11] P.L. Asdourian, M. Weidenbaum, R.L. DeWald, K.W. Hammerberg, R.G. Ramsey, The pattern of vertebral involvement in metastatic vertebral breast cancer, Clin. Orthop. (1990) 164–170.
[12] P.R. Algra, J.J. Heimans, J. Valk, J.J. Nauta, M. Lachniet, B. Van Kooten, Do metastases in vertebrae begin in the body or the pedicles? Imaging study in 45 patients, AJR Am. J. Roentgenol. 158 (1992) 1275–1279, https://doi.org/10.2214/ajr.158.6.1590123.
[13] M. Guo, K.L. Kolberg, E.C. Smith, B.W. Smith, J.E. Yousif, J.L. Kessler, J.R. Linzey, A.-A. Calinescu, G.A. Clines, D.E. Spratt, N.J. Szerlip, Predominance of spinal metastases involving the posterior vertebral body, World Neurosurg 119 (2018) e991–e996, https://doi.org/10.1016/j.wneu.2018.08.029.
[14] S. Paget, The distribution of secondary growths in cancer of the breast, Lancet 1 (1889) 571–573.
[15] D.M. Sciubba, Z.L. Gokaslan, I. Suk, D. Suki, M.V.C. Maldaun, I.E. McCutcheon, R. Nader, R. Theriault, L.D. Rhines, J.A. Shehadi, Positive and negative prognostic variables for patients undergoing spine surgery for metastatic breast disease, Eur. Spine J. Off. Publ. Eur. Spine Soc. Eur. Spinal Deform. Soc. Eur. Sect. Cerv. Spine Res. Soc. 16 (2007) 1659–1667, https://doi.org/10.1007/s00586-007-0380-4.
[16] A. Amelot, L.-M. Terrier, J.-J. Mazeron, C.-A. Valery, P. Cornu, A. Carpentier, M. Leveque, Timeline metastatic progression: in the wake of the « seed and soil » theory, Med. Oncol. Northwood Lond. Engl. 34 (2017) 185, https://doi.org/10.1007/s12032-017-1045-8.
[17] D. Krewski, J. Rao, Inference from stratified samples: properties of the linearization, jacknife and balanced repeated replication methods, Ann. Stat. 9 (1981) 1010–1019.
[18] P. Vineis, C.P. Wild, Global cancer patterns: causes and prevention, Lancet Lond. Engl. 383 (2014) 549–557, https://doi.org/10.1016/S0140-6736(13)62224-2.
[19] D.L. Tarnoki, A.D. Tarnoki, S. Ohlmann-Knafo, D. Pickuth, Pattern of tumour spread of common primary tumours as seen on magnetic resonance imaging, Pathol. Oncol. Res. 22 (2016) 79–85, https://doi.org/10.1007/s12253-015-9975-y.
[20] H. Schirrmeister, A. Guhlmann, K. Elsner, J. Kotzerke, G. Glatting, M. Rentschler, B. Neumaier, H. Träger, K. Nüssle, S.N. Reske, Sensitivity in detecting osseous lesions depends on anatomic localization: planar bone scintigraphy versus 18F PET, J. Nucl. Med. Off. Publ. Soc. Nucl. Med. 40 (1999) 1623–1629.
[21] P. Klimo, M.H. Schmidt, Surgical management of spinal metastases, The Oncologist 9 (2004) 188–196.
[22] U. Aydinli, C. Ozturk, S. Bayram, S. Sarihan, T. Evrensel, H.S. Yilmaz, Evaluation of lung cancer metastases to the spine, Acta Orthop. Belg. 72 (2006) 592–597.
[23] D.F. Quail, J.A. Joyce, Microenvironmental regulation of tumor progression and metastasis, Nat. Med. 19 (2013) 1423–1437, https://doi.org/10.1038/nm.3394.
[24] H. Saitoh, K. Yoshida, Y. Uchijima, N. Kobayashi, J. Suwata, S. Kamata, Two different lymph node metastatic patterns of a prostatic cancer, Cancer 65 (1990) 1843–1846.
[25] O.V. Batson, The function OF the vertebral veins and their role IN the spread OF metastases, Ann. Surg. 112 (1940) 138–149.
[26] F. Arguello, R.B. Baggs, C.N. Frantz, A murine model of experimental metastasis to bone and bone marrow, Cancer Res. 48 (1988) 6876–6881.
[27] F. Arguello, R.B. Baggs, R.E. Duerst, L. Johnstone, K. McQueen, C.N. Frantz, Pathogenesis of vertebral metastasis and epidural spinal cord compression, Cancer 65 (1990) 98–106.
[28] B.A. Berrettoni, J.R. Carter, Mechanisms of cancer metastasis to bone, J. Bone Joint Surg. Am. 68 (1986) 308–312.
[29] G. Ren, M. Esposito, Y. Kang, Bone metastasis and the metastatic niche, J. Mol. Med. Berl. Ger. 93 (2015) 1203–1212, https://doi.org/10.1007/s00109-015-1329-4.
[30] A.J. Conde Moreno, C. Ferrer Albiach, R. Muelas Soria, V. González Vidal, R. García Gómez, M. Albert Antequera, Oligometastases in prostate cancer: restaging stage IV cancers and new radiotherapy options, Radiat. Oncol. Lond. Engl. 9 (2014) 258, https://doi.org/10.1186/s13014-014-0258-7.
[31] A. Amelot, L.-M. Terrier, J.-J. Mazeron, C.-A. Valery, P. Cornu, A. Carpentier, M. Leveque, Timeline metastatic progression: in the wake of the « seed and soil » theory, Med. Oncol. Northwood Lond. Engl. 34 (2017) 185, https://doi.org/10.1007/s12032-017-1045-8.
[32] L. Bubendorf, A. Schöpfer, U. Wagner, G. Sauter, H. Moch, N. Willi, T.C. Gasser, M.J. Mihatsch, Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients, Hum. Pathol. 31 (2000) 578–583.
[33] S.J. Fabozzi, P.F. Schellhammer, A.M. el-Mahdi, Pulmonary metastases from prostate cancer, Cancer 75 (1995) 2706–2709.
[34] S.C. Jacobs, Spread of prostatic cancer to bone, Urology 21 (1983) 337–344.
[35] P.R. Dodds, V.J. Caride, B. Lytton, The role of vertebral veins in the dissemination of prostatic carcinoma, J. Urol. 126 (1981) 753–755.
[36] B. Bouvard, J. Chatelais, P. Soulié, E. Hoppé, P. Saulnier, O. Capitain, M. Mege, N. Mesgouez-Nebout, E. Jadaud, S. Abadie-Lacourtoisie, M. Campone, E. Legrand, Osteoporosis treatment and 10 years' oestrogen receptor + breast cancer outcome in postmenopausal women treated with aromatase inhibitors, Eur. J. Cancer Oxf. Engl. 101 (2018) 87–94, https://doi.org/10.1016/j.ejca.2018.06.028 1990.