

# Bone Metastases in Well-to-Moderately Differentiated Neuroendocrine Tumors: a Review of Clinical Characteristics, Hormone Levels, and Survival

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## Background

Bone metastases from well-to-moderately differentiated neuroendocrine tumors (NETs) are found in approximately 4-15% of patients, and can lead to significant morbidity and clinical symptoms (1,2). In this study we look at the clinical features associated with bone metastasis in patients with well-to-moderately differentiated NETs, specifically primary tumor characteristics, spinal cord compression, pathologic fractures, elevated hormone levels, and survival.

## Methods

A retrospective study was performed on patients treated for well-to-moderately differentiated NETs diagnosed from 2000 to 2010 who were found to have bone metastases. These patients were compared to patients with NETs without bone mets with regards to demographic data (Table 1) and serum tumor marker levels (Table 2).

The patients with bone metastases were then analyzed with respect to sites of metastases, complications of pathologic fractures and spinal cord compression, treatments given, and imaging modalities used (table 3).

Finally, a survival analysis was performed comparing patients with and without bone metastases (figure 2), as well as several clinical factors.

## Results

Of the 390 patients with well-to-moderately differentiated NETs, 40 were found to have bone metastasis (10.2 %) with characteristics described in Table 1. 11 patients (27.5%) presented with bone metastases on diagnosis, and the median time to diagnosis of bone metastases for patients who did not have bone metastases at presentation was 13 months after diagnosis of NETs.

## Tables and Figures

Table 1. Patient Characteristics

|                                                      | Patients with Bone Metastasis | Patients without Bone Metastasis | P Value |
|------------------------------------------------------|-------------------------------|----------------------------------|---------|
|                                                      | No. (%)                       | No. (%)                          |         |
| Total no. of patients                                | 40 (100)                      | 40 (100)                         |         |
| Gender:                                              |                               |                                  | 0.82    |
| Female                                               | 15 (37)                       | 16 (40)                          |         |
| Male                                                 | 25 (62)                       | 24 (60)                          |         |
| Age at diagnosis (years)                             |                               |                                  | 1       |
| Median                                               | 56                            | 55                               |         |
| Range                                                | 28-85                         | 31-84                            |         |
| Primary Tumor Location                               |                               |                                  | 0.96    |
| Lung                                                 | 2 (5)                         | 1 (2)                            |         |
| Pancreas                                             | 17 (42)                       | 16 (40)                          |         |
| Small Bowel                                          | 8 (20)                        | 11 (27)                          |         |
| Colon                                                | 3 (7)                         | 3 (7)                            |         |
| Other                                                | 3 (7)                         | 1 (2)                            |         |
| Unknown                                              | 7 (17)                        | 8 (20)                           |         |
| Grade of Differentiation of Neuroendocrine carcinoma |                               |                                  | 0.08    |
| Well                                                 | 28 (70)                       | 32 (80)                          |         |
| Moderate                                             | 7 (17)                        | 8 (20)                           |         |
| Well/Moderate                                        | 5 (12)                        | 0 (0)                            |         |
| Sites of Metastasis                                  |                               |                                  | 1       |
| Liver                                                | 37 (92)                       | 38 (95)                          |         |
| Bone                                                 | 40 (100)                      | 0 (0)                            |         |
| Lung                                                 | 5 (12)                        | 0 (0)                            | 0.055   |
| Lymph Node                                           | 14 (35)                       | 4 (10)                           | 0.015   |
| Omental/peritoneal                                   | 0 (0)                         | 10 (25)                          | 0.001   |
| Other                                                | 5 (12)                        | 5 (12)                           | 1       |
| Treatment                                            |                               |                                  | 0.12    |
| Octreotide                                           | 25 (62)                       | 18 (45)                          |         |
| Radiation Therapy                                    | 22 (55)                       | 4 (10)                           | 0.0001  |
| Transarterial Chemoembolization                      | 20 (50)                       | 19 (47)                          | 0.82    |
| Cisplatin/Etoposide                                  | 5 (12)                        | 7 (17)                           | 0.53    |
| Temozolomide                                         | 6 (15)                        | 3 (7)                            | 0.48    |
| Capecitabine                                         | 10 (25)                       | 3 (7)                            | 0.07    |
| Streptozosin                                         | 6 (15)                        | 1 (2)                            | 0.11    |
| Everolimus                                           | 7 (17)                        | 6 (15)                           | 0.76    |
| Bevacizumab                                          | 2 (5)                         | 4 (10)                           | 0.68    |
| 5-fluorouracil                                       | 2 (5)                         | 1 (2)                            | 1       |
| Primary Tumor Size (mm)                              |                               |                                  | 0.024   |
| Median                                               | 47 *                          | 33 **                            |         |
| Range                                                | 10-104*                       | 12-120**                         |         |
| Surgical Resection of Primary                        | 16 (40)                       | 21 (52)                          | 0.26    |
| Surgical Resection of Metastasis                     | 6 (15)                        | 5 (12)                           | 0.75    |
| Carcinoid Syndrome Present                           | 18 (45)                       | 20 (50)                          | 0.65    |

\*29 of 40 patients with bone metastases have tumor size data available

\*\*32 of 40 patients without bone metastases have tumor size data

Figure 1. Spinal Cord Compression on MRI

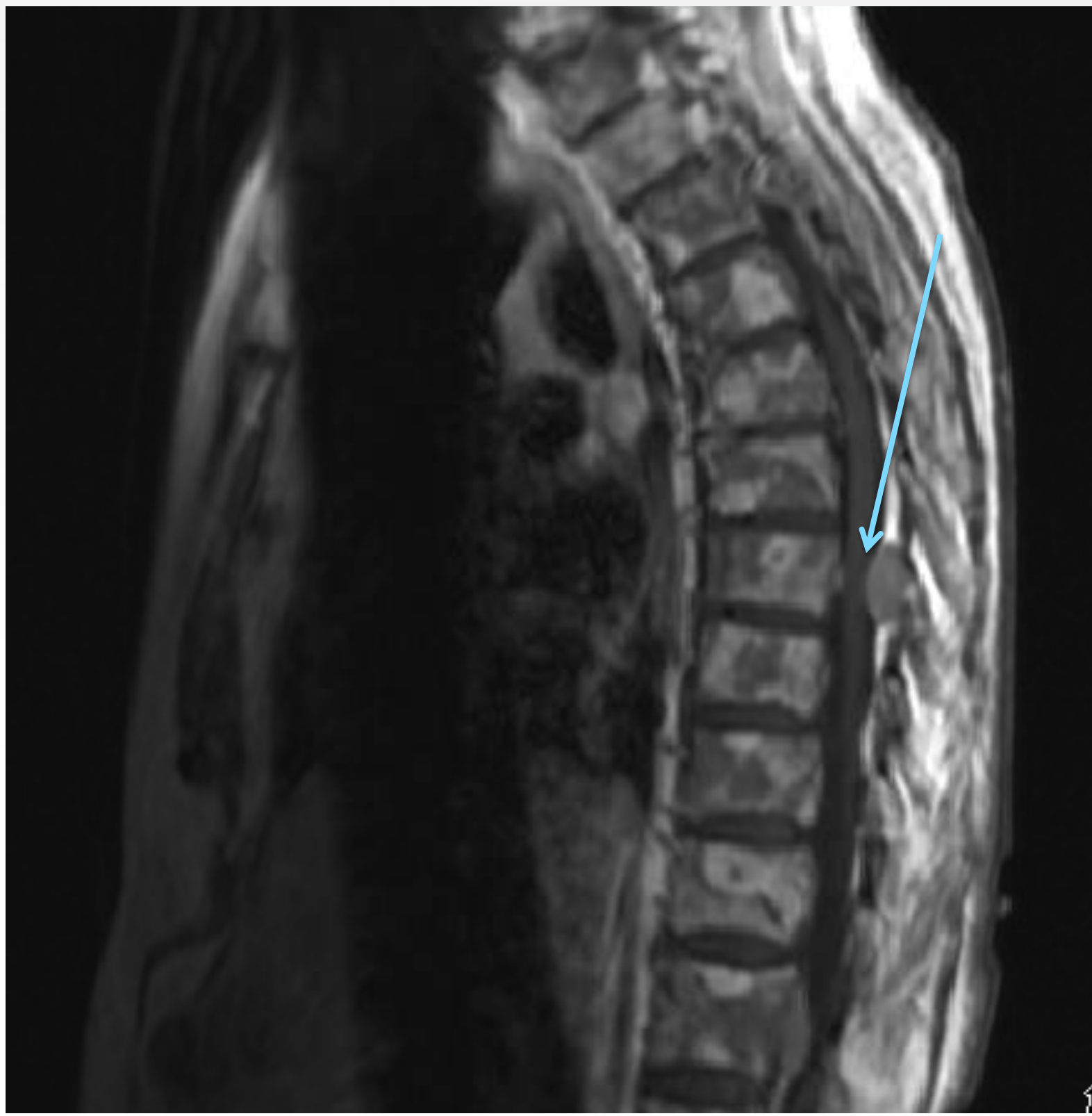


Table 2. Serum Tumor Marker Levels at Diagnosis

| Serum Tumor Marker**                 | Patients with Bone Metastasis | Patients without Bone Metastasis | P value |
|--------------------------------------|-------------------------------|----------------------------------|---------|
| Gastrin                              |                               |                                  |         |
| Number of patients (n)*              | 11 (37)                       | 15 (37)                          | 0.34    |
| Median of levels of gastrin (range)  | 239 (125-915)                 | 293 (126-15353)                  | 0.21    |
| Glucagon                             |                               |                                  |         |
| Number of patients (n)*              | 13 (24)                       | 17 (24)                          | 0.36    |
| Median of levels of glucagon (range) | 527 (253-4575)                | 394 (273-1480)                   | 0.50    |
| Pancreastatin (PAN)                  |                               |                                  |         |
| Number of patients (n)*              | 36 (38)                       | 29 (35)                          | 0.045   |
| Median of levels of PAN (range)      | 1067 (160-107000)             | 984 (150-31000)                  | 0.36    |
| Pancreatic Polypeptide (PP)          |                               |                                  |         |
| Number of patients (n)*              | 14 (37)                       | 10 (34)                          | 0.33    |
| Median of levels of PP(range)        | 1330 (538-14300)              | 1340 (553-14000)                 | 1       |

\*Number of patients with elevated hormone level displayed with total number of patients with level available in parenthesis

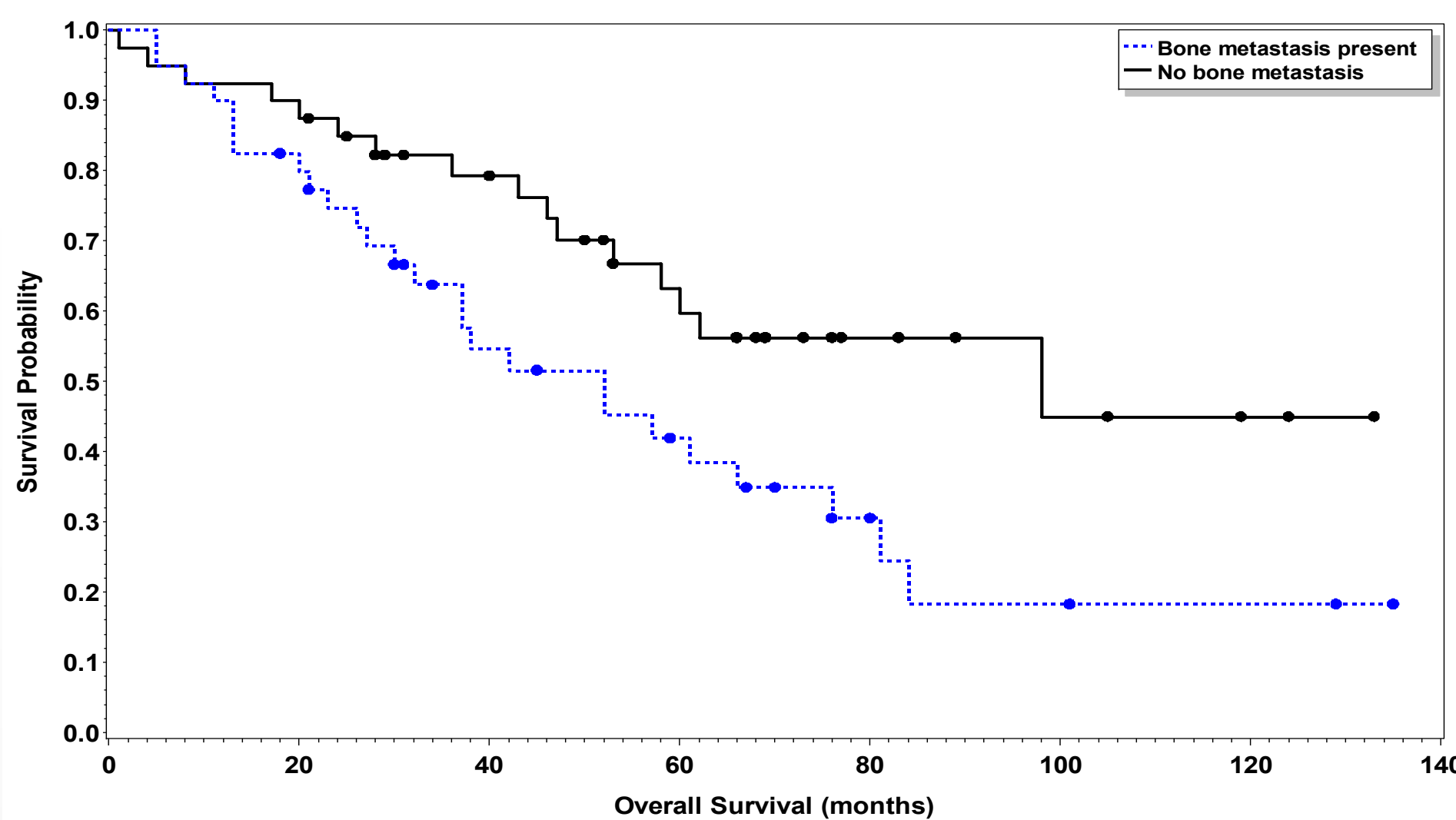
\*\*Normal ranges for serum gastrin, glucagon, pancreastatin and pancreatic polypeptides are <122 pg/ml, 25-250 pg/ml, <135 pg/ml, and <500 pg/ml respectively

Table 3. Characteristics of Patients with Bone Metastases

|                                             | Number of Patients |
|---------------------------------------------|--------------------|
|                                             | No. (%)            |
| Axial Bone Metastases                       |                    |
| <3 lesions                                  | 13 (32)            |
| >3 lesions                                  | 26 (65)            |
| Appendicular Bone Metastases                |                    |
| <3 lesions                                  | 19 (47)            |
| >3 lesions                                  | 6 (15)             |
| Spinal Cord Compression                     | 8 (20)             |
| Pathologic Fracture                         | 6 (15)             |
| Carcinoid Syndrome Present                  | 18 (45)            |
| Radiation Therapy                           | 22 (55)            |
| Bisphosphonate Therapy                      | 12 (30)            |
| Bone Metastasis Present at Diagnosis        | 11 (27)            |
| Patients Undergoing CT scans                | 34 (85)            |
| Patients with Bone Metastases on CT         | 33 (97)            |
| Patients Undergoing MRI                     | 17 (42)            |
| Patients with Bone Metastases on MRI        | 17 (100)*          |
| Patients Undergoing Octreoscan              | 14 (35)            |
| Patients with Bone Metastases on Octreoscan | 10 (71)*           |
| Patients Undergoing X-Ray                   | 7 (17)             |
| Patients with Bone Metastases on X-Ray      | 1 (14)*            |

\* Percentage displayed is out of the number of patients who underwent the study.

Figure 2. Survival Analysis



## Results (Continued)

Axial bone metastases, which were found in 39 patients (97.5%) were much more common than appendicular bone metastases, which were found in 25 patients (62.5%). Patients with bone metastases were found to have an overall shorter survival compared to patients with metastatic disease without bone involvement (median 52 months vs 98 months; p=0.024) as shown in Figure 2. Furthermore, among patients with bone metastases, those with a surgically resected primary lived longer than those without surgery (76 months vs 32 months; p=0.005). There was no significant difference in the survival of patients with spinal cord compression, pathologic fractures, carcinoid syndrome, elevated pancreastatin, treatment with radiation or bisphosphonates, and primary tumor in the pancreas when compared to all other patients with bone metastases.

## Conclusion

The patients with bone metastases were found to have larger primary tumors, and shorter overall survival suggesting more aggressive disease. There was no difference in survival among patients with bone metastases with regards to spinal cord compression, pathologic fractures, carcinoid syndrome, and elevated pancreastatin level. Although these characteristics do not contribute to a patient's prognosis, they may affect the patient's quality of life and may warrant appropriate treatment.

## References

- Janson, E.T., et al., *Carcinoid tumors: analysis of prognostic factors and survival in 301 patients from a referral center*. Ann Oncol, 1997. 8(7): p. 685-90.
- Meijer, W.G., et al., *Bone metastases in carcinoid tumors: clinical features, imaging characteristics, and markers of bone metabolism*. J Nucl Med, 2003. 44 (2): p. 184-91.