Here, we present four patients with MND and a coexistent neoplasm.

OBJECTIVES
1) To do a retrospective analysis of all patients with MND in our cohort who had an associated tumour.
2) Verify if there is any correlation between treatment of the underlying tumour and improvement of MND in those patients.

METHODS
We analysed through a 4-year retrospective study, from January 2013 to December 2016, the files of patients with an active MND (of every subtype) in our Hospital (N= 35). The hospital total referral population is 315 000 inhabitants. There was no need of approval of ethic committee due to being a retrospective study and no intervention was made. Clinical and electrophysiological examination (EMG) was performed in all patients. Awaji criteria were applied for Clinical and Electrophysiological diagnosis of MND. An active search for a primitive tumour was made as part of the investigation for treatable causes of MND, according to EFNS 2012 Guidelines.

CASES REPORT/RESULTS
A neoplastic process was found in four (11,4%) of our MND patients (table 1).

Case 1 is a 55-year-old female, refered for breast tumorectomy and radiotherapy in 2005 due to invasive ductal breast cancer (IDBC), which was BRCA2 mutation-related. The IDBC was a well-known syndrome presented by the patient or if there is a specific anti-neuronal antibody such as anti-Yo or anti-PNMA2, in serum or cerebrospinal fluid.

INTRODUCTION
Paraneoplastic Neurological Disorders (PNDs) are remote effects of systemic malignancies that affect the nervous system. PNDs are relatively rare compared to metastatic and iatrogenic complications of cancer, and overall affect fewer than 1% of patients with cancer. The most common neoplasms associated with paraneoplastic neurological disorders are small cell lung cancer, breast and gynaecological cancers, and lymphomas.

Association between Motor Neuron Disease (MND) and neoplastic processes is rarely described. Cases of paraneoplastic MND are rarely observed and, as a result, no exhaustive data are available on the exact clinical and neurophysiological phenotype associated with this condition. It is currently unclear whether MND even occurs as a paraneoplastic syndrome. Many authors have questioned whether the association of cancer and MND is simply a coincidence of two relatively common diseases, or if there is a true etiologic relationship. Some small studies have reported a co-occurrence of cancer and MND that appears to be higher than the incidence expected in the general population and few reports addressed the possibility of MND reversal after treatment of a coexistent neoplasm.

In patients with an acute to subacute onset of neuromuscular symptoms without a known tumour, the etiology may be paraneoplastic when there is a well-known syndrome presented by the patient or if there is a specific anti-neuronal antibody such as anti-Yo or anti-PNMA2, in serum or cerebrospinal fluid.

Here, we present four patients with MND and a coexistent neoplasm.

OBJECTIVES
1) To do a retrospective analysis of all patients with MND in our cohort who had an associated tumour.
2) Verify if there is any correlation between treatment of the underlying tumour and improvement of MND in those patients.

METHODS
We analysed through a 4-year retrospective study, from January 2013 to December 2016, the files of patients with an active MND (of every subtype) in our Hospital (N= 35). The hospital total referral population is 315 000 inhabitants. There was no need of approval of ethic committee due to being a retrospective study and no intervention was made. Clinical and electrophysiological examination (EMG) was performed in all patients. Awaji criteria were applied for Clinical and Electrophysiological diagnosis of MND.

An active search for a primitive tumour was made as part of the investigation for treatable causes of MND, according to EFNS 2012 Guidelines.

CASES REPORT/RESULTS
A neoplastic process was found in four (11,4%) of our MND patients (table 1).

Case 1 is a 55-year-old female, refered for breast tumorectomy and radiotherapy in 2005 due to invasive ductal breast cancer (IDBC), which was BRCA2 mutation-related. The IDBC...
Table 1. Summary of the 4 patients of MND with an associated neoplastic process.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Age</td>
<td>55</td>
<td>48</td>
<td>74</td>
</tr>
<tr>
<td>Neoplasm type</td>
<td>Invasive ductal breast Ca (BRCA2 mutation-related)</td>
<td>Imaging: 8mm thyroid nodule Histology: Hürthle cell follicular thyroid tumour</td>
<td>Invasive ductal breast Ca</td>
</tr>
<tr>
<td>Onconeural antibodies</td>
<td>Anti-PNMA2 weakly positive</td>
<td>Anti-Yo positive (in two separated samples)</td>
<td>Not performed</td>
</tr>
<tr>
<td>Topography of MND involvement</td>
<td>U+L MND, B+C+D+LS segments</td>
<td>L MND, B+C+D+LS segments</td>
<td>U+L MND, B+C+D+LS segments</td>
</tr>
<tr>
<td>Neoplasm treatment</td>
<td>Sx, HT</td>
<td>Sx – Hemithyroidectomy</td>
<td>Sx, RT, HT</td>
</tr>
<tr>
<td>IT</td>
<td>--</td>
<td>IVIg – 2 cycles</td>
<td>--</td>
</tr>
<tr>
<td>Evolution and Follow-up</td>
<td>Aggressive with severe bulbar impairment Follow-up in palliative care</td>
<td>Aggressive evolution, patient refused total thyroidectomy</td>
<td>Aggressive evolution. Death in 2017</td>
</tr>
</tbody>
</table>

U – Upper; L – Lower; B – Bulbar, C – Cervical, D – Dorsal; LS – Lumbosacral; Ca – cancer; Sx – surgery; HT – hormonotherapy; RT – radiotherapy; CT – chemotherapy; IT – immunotherapy; dx – diagnosis

relapsed in December 2015 leading to bilateral mastectomy and hormone therapy (the patient refused chemotherapy). After one month, the patient developed symptoms of upper and lower (U+L) MND affecting bulbar, cervical, dorsal and lumbosacral (B+C+D+LS) segments. Onconeural antibodies were weakly positive for anti-PNMA2 detected by immunoblotting. The course was very aggressive and in one year she developed severe functional impairment and died.

Case 2 is a 48-year-old male developing lower MND signs affecting B+C+D+LS segments starting in September 2015 and progressing very rapidly. Onconeural antibodies were positive in two different samples for anti-Yo by immunoblotting. He had one 8 mm thyroid nodule, and a Hürthle cell follicular thyroid tumour was diagnosed in October 2016. The patient was submitted to hemithyroidectomy in November 2016 followed by two cycles of IVIg. He didn’t significantly progress in the subsequent 8 months of these treatments but recently, after a period of stable plateau, the MND aggressively worsened again and anti-Yo remained positive. He was referred for total thyroidectomy but refused another surgical procedure.

Case 3 is a 74-year-old female diagnosed with IDBC in 2014, submitted to mastectomy, radiotherapy and hormone therapy. In January of 2016, the patient developed symptoms of U+L MND affecting B+C+D+LS segments, progressing rapidly. Onconeural antibody analysis wasn’t performed. She died in February 2017.

Case 4 is a 77-year-old male who presented with U+L MND affecting B+C+D+LS, in 2010. He was diagnosed with lung adenocarcinoma in 2011 and prescribed chemotherapy and radiotherapy. He died in January 2016. Onconeural antibody analysis wasn’t performed.

**DISCUSSION**

In our cohort of only 35 MND patients, we identified four that had a coexistent neoplasm. This frequency of co-occurrence is higher than the relatively few previous reports. In one of the four patients (case 2), the initially aggressive MND process became relatively stable, with a plateau phase through 8 months, after hemithyroidectomy followed by therapy with two cycles of IVIg, but progressed aggressively thereafter, and patient refused total thyroidectomy. However this suggests a physiological connection between the MND and neoplasm in this case. The other three patients died, two of them very rapidly due to the aggressiveness of the disease. This ferocious course of the disease, and the relative frequency, strongly supports a recommendation for physicians to for an underlying neoplasm as standard.

MND as a paraneoplastic process is a difficult diagnosis to establish with certainty. The coexistence may be circumstantial. Reports of patients with typical MND who had improvement following treatment of their malignancy suggest that MND could occur as a paraneoplastic phenomenon. Unfortunately, most paraneoplastic motor disorders are unresponsive to treatment of the underlying tumour. To complicate matters, MND may evolve aggressively and death can occur before the identification of an underlying causal neoplasm. In all the literature there are rather too few such cases with disparate antibodies, clinical courses, and underlying tumours to make further generalizations.

**CONCLUSIONS**
Even though paraneoplastic MND is rare, its recognition is essential, because early management with immunotherapy and cancer treatment can lead to neurological improvement or stabilization. This report is relevant to raise awareness of the importance of appropriate and thorough investigation for treatable causes of MND.

**BIBLIOGRAPHY**