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# Treatment of Metastatic Neuroendocrine Carcinomas Based on WHO Classification

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**Abstract.** *A single institution prospective trial was conducted to evaluate the efficacy of biotherapy or chemotherapy in metastatic neuroendocrine carcinomas (NECs). The choice of therapy was based on the revised histological classification criteria of the WHO in an effort to define a standardized protocol for therapy of these cancers. Patients with well-differentiated NECs (WD-NECs; n=11) received therapy with octreotide long-acting release and interferon-α-2b for a maximum of 1 year; cases with poorly-differentiated NECs (PD-NECs; n=8) were given combination cisplatin, L-leucovorin and 5-fluorouracil chemotherapy for a maximum of 9 cycles. Five patients (4 with WD-NECs) had carcinoid syndrome. Among the patients with WD-NECs (median follow-up 20 months, range 4-40), 4 had partial responses and 7 had stable disease. In patients with PD-NECs (median follow-up 10.5 months, range 3-30), 3 had partial response, 2 stable disease, and the disease progressed in 3 cases. The 2-year survival rate in WD-NECs and PD-NECs was 88% and 66%, respectively. Grade 3-4 side-effects were limited to 9% thrombocytopenia and 12.5% neutropenia. Both these treatment regimens had a good therapeutic index and compared favourably with those previously reported for metastatic WD-NECs and PD-NECs.*

Neuroendocrine tumours (NECs) are a broad group of neoplasms whose clinical behaviour varies from benign to very aggressive depending on the primary tumour site, size, grade of differentiation and proliferative index, which are all taken into consideration in the most recent WHO classification (1). Surgery remains the treatment of choice for patients with resectable disease, although significant uncertainties exist for management of patients with metastatic NECs (2, 3). For this latter group of patients, several loco-regional and systemic treatments have been proposed (2-4). In general, the more aggressive poorly-differentiated cancers (PD-NECs) are treated with chemotherapy, while well-differentiated tumours (WD-NECs) may be treated with a variety of biotherapeutic regimens. However, standardized guidelines for clinical management of metastatic NECs have not been established, due to the limited numbers of published series combined with objective difficulties in interpretation of clinical outcome measures.

For WD-NECs, radiological responses are limited, although therapies with somatostatin analogues, such as octreotide and lanreotide and/or IFN-α-2b, generally result in both biochemical and subjective responses. In particular, the biochemical and objective response rates after IFN-α-2b have been reported in the ranges of 40-60% and 10-12%, respectively (5). Octreotide, at a subcutaneous daily dose of 200-450 μg, is associated with symptomatic, biochemical, and radiological response rates of 60%, 70% and 8%, respectively (6). Slightly higher tumour response rates are obtained with daily doses of octreotide greater than 3 mg or doses of lanreotide greater than 5 mg daily (5, 7). Slow-release formulations of octreotide (20-30 mg *i.m.* monthly) or lanreotide (20 mg *i.m.* every 10-14 days) have also been reported to provide similar tumour and symptomatic response rates with an administration schedule that is more convenient for both patients and care givers (8). More recently, a significant advantage of the combination of octreotide plus IFN-α-2b *vs.* octreotide alone has been demonstrated in terms of risk of tumour progression (9).

Single agent chemotherapy with either fluorouracil, dacarbazine, streptozotocin, or doxorubicin results in

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objective responses lower than 10% (10), while multiple agent chemotherapies with fluorouracil-leucovorin-streptozotocin, doxorubicin-fluorouracil or cisplatin-etoposide result in somewhat higher objective responses ranging from 20% to 67% (11, 12). However, the wide variability in the reported response rates is probably due to the heterogeneity of patient cohorts in terms of previous loco-regional or systemic treatments, extent of disease and definition of clinical parameters used to evaluate patient response.

The latest World Health Organization (WHO) histological classification of endocrine tumours provides more consistent criteria for histopathological interpretation and includes the analysis of histochemical markers for tumour proiliferation such as Ki-67. Numerous studies have documented that a Ki-67 proliferation index <2% is associated with more favourable survival (13, 14).

Moreover, the Ki-67 proliferation index generally correlates with the grade of differentiation, as WD-NECs frequently have a Ki-67 <2% and PD-NECs present with a Ki-67 >15% (1). Accordingly, the Ki-67 proliferative index is often used to predict clinical aggressiveness, although tumours with Ki-67 indices between 2% and 15% have more unpredictable behaviour (15). In fact, therapeutic strategies are more difficult to establish in this group of patients.

To date, no standardized protocols have been established for the management of metastatic NECs. In the present study, we applied a uniform therapeutic protocol based on the grade of differentiation, as determined by the most recent WHO guidelines for histological classification. In particular, patients with WD-NECs were given biotherapy with octreotide and IFN-α-2b, while patients with PD-NECs received more aggressive therapy with a combination of cisplatin, leucovorin and fluorouracil (CDDP/L/LVFU2). The combination of drugs for chemotherapy was chosen on the basis of their documented activity in NECs and the lower number of observed side-effects compared to other combination therapies such as streptozotocin and doxorubicin (16, 17). Tumour response was evaluated by objective, subjective and biochemical parameters in a prospective manner.

## Patients and Methods

*Patients and diagnostic work-up.* Between April 2000 and September 2003, 53 patients with NECs were observed at our Institution. Of these, 19 (36%) had metastatic disease and were included in the study. Eleven patients had WD-NECs (2 gastric, 7 small-bowel, 2 unknown primary); 4 had received previous systemic treatment for advanced disease (2 chemotherapy, 2 octreotide). Eight patients had PD-NECs (5 pancreatic, 3 unknown primary); none of these had received previous systemic treatment.

NECs were diagnosed according to the most recent WHO criteria based on histological and histochemical analyses (1). In particular, WD-NECs and PD-NECs were distinguished on the basis of cellular atypia, proliferation index and the presence of focal necrosis. Neuroendocrine differentiation was assessed by immunohistochemical markers against chromogranin A (clone DAK-A3; Dako A/S, Glostrup, Denmark) and synaptophysin (clone SY-38, Biogenex Labs, San Ramon, CA, USA). Immunohistochemistry with Ki-67 (clone MIB-1, Dako) was used to assess the proliferation index. All WD-NECs had a proliferation index ≤5% (range 1-5), while PD-NECs showed a proliferation index >5% (range 7-90%). Only patients with WD or PD-NECs were considered; other histological classes, such as Merkel cell carcinoma and small cell lung cancer, were excluded from the study.

Diagnostic work-up included physical examination, abdominal and pelvis CT scan, chest X-ray and somatostatin receptor scintigraphy (SRS $^{111}$In-penteotride). Radiological evaluation of target lesions was performed every 3 months. Serum chromogranin A (CgA), serum neuron-specific enolase (NSE) and urinary 5-hydroxy-3-indole acetic acid (5-HIAA) were determined at baseline and at each radiological evaluation.

*Treatment plan.* Patients with WD-NECs were treated with the somatostatin analogue octreotide acetate LAR (long-acting release) 30 mg *i.m.* every 4 weeks in combination with IFN-α-2b ($5x10^6$ IU *s.c.*) 3 times weekly for at least 3 months. In the case of disease response, treatment was continued for a maximum of 1 year. Dose reduction and discontinuation were made according to current pharmaceutical recommendations. In the case of tumour progression, patients with WD-NECs were given treatment with the same chemotherapeutic regimen applied to PD-NECs.

Patients with PD-NECs were treated with L-leucovorin (100 mg/m$^2$ *i.v.* over 2 hours), followed by a bolus injection of 5-fluorouracil (400 mg/m$^2$). Next, infusion of 5-fluorouracil (600 mg/m$^2$) was performed over a 22-hour period on days 1 and 2, plus cisplatin (45 mg/m$^2$) on day 1 every 14 days (CDDP/L/LVFU2 regimen). Patients were subjected to a minimum of 3 cycles and, in the case of tumour response, a maximum of 9 cycles were carried out. A low dose of cisplatin was chosen because our previous experience (data not shown) suggested that it has a good therapeutic index and toxicity profile in NECs. Patients with carcinoid syndrome, who did not experience any symptomatic relief after 3 cycles of chemotherapy, were concomitantly treated with a somatostatin analogue.

Adverse events after biotherapy or chemotherapy were recorded according to the National Cancer Institute's common toxicity grading criteria (18). In the case of grade 3 and 4 toxicities, treatment was delayed for ≥1 week until resolution of symptoms related to toxicity. Upon resumption of therapy, the dose was reduced by 25%.

*Evaluation of response*

*Radiological response.* According to RECIST criteria (19), a partial response (PR) was defined as at least a 30% decrease in the sum of the longitudinal diameter of target lesions. Progressive disease (PD) was defined as at least a 20% increase in the sum of the longitudinal diameter of target lesions or the appearance of one or more new lesions. Stable disease (SD) was defined as neither a sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for progression disease. Complete response (CR) was defined as the absence of radiologically documented lesions.

*Biochemical response.* Biochemical CR and PR were defined as the normalization and ≥50% decrease of at least a tumour marker, respectively. Biochemical progression was defined as a >25% increase in any tumour marker.

*Symptomatic response.* Symptomatic CR was defined as the complete relief of all symptoms, and a PR as a reduction of at least 50% in both the frequency and intensity of flushing and/or diarrhoea.

*Clinical benefit.* Clinical benefit was defined as an objective response or stable disease lasting for at least 6 months.

*Statistical analysis.* The probabilities of 2-year survival, progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier product limit estimate method (20). The rates of OS and PFS were measured from the date of start of treatment to the date of last follow-up or death and the date of progression, respectively. Fisher's exact test was used to determine statistical significance of the association between biochemical and radiological responses in WD- and PD-NECs.

## Results

A total of 19 patients with metastatic NECs were subclassified according to the grade of differentiation based on the most recent WHO criteria (1). Relevant clinicopathological characteristics of the patient cohort are shown in Table I. Eleven patients had WD-NECs, while 8 cases presented with PD-NECs. The WD-NECs had a median Ki-67 proliferation index of 1%, while the PD-NECs had a median Ki-67 index of 30%. Five patients had carcinoid syndrome, including 4 WD-NECs and 1 PD-NEC.

The therapeutic strategy was chosen on the basis of the differentiation state of the primary tumour. Patients with WD-NECs received therapy with octreotide long-acting release and IFN-α-2b for a maximum of 1 year; cases with PD-NECs were given combination cisplatin, L-leucovorin, and 5-fluorouracil chemotherapy for a maximum of 9 cycles. Tumour response was evaluated by radiological imaging, as well as by assessment of biochemical, symptomatic and clinical parameters.

Table I. *Clinical characteristics of patients with NECs.*

| | Grade of differentiation (WHO classification) | | |
|---|---|---|---|
| | All patients | Well-differentiated | Poorly-differentiated |
| Males/Females | 19<br>10/9 | 11<br>6/5 | 8<br>4/4 |
| Median age (range) | 63<br>(29-83) | 68<br>(29-83) | 54<br>(40-77) |
| ECOG status | | | |
| 0 | 11 | 8 | 3 |
| 1 | 8 | 3 | 5 |
| 2 | - | - | - |
| 3 | - | - | - |
| Site of primary tumour | | | |
| Pancreas | 5 | - | 5 |
| Stomach | 2 | 2 | - |
| Bowel | 7 | 7 | - |
| Unknown | 5 | 2 | 3 |
| Median (range) tumour proliferation index as % of Ki-67 positive cells | | 1 (1–5) | 30 (7–90) |
| Carcinoid syndrome | | 5 | 4 1 |
| - Flushing | | 2 | - |
| - Diarrhoea | | 3 | 1 |
| Elevated levels of: | | | |
| serum CgA | 17 | 9 | 8 |
| serum NSE | 8 | 2 | 6 |
| urinary 5-HIAA | nd | 2 | nd |
| Positive whole body somatostatin scintigraphy/patients evaluated | 15/18 | 10/10 | 5/8 |

*Abbreviations:* CgA, chromogranin A; NSE, neurone specific enolase; 5-HIAA, 5-hydroxy indolacetic acid; nd, not determined.

*Radiological response.* Two representative cases of objective tumour response as observed by CT imaging are shown in Figures 1 and 2 for a WD- and PD-NEC, respectively. The median follow-up for patients with WD-NECs and PD-NECs, were 20 (range 4-40) and 10.5 (range 3-30) months, respectively. Tumour responses at the last available follow-up examination, as documented by radiological imaging, are presented in Table II. Of the 11 cases of WD-NECs, 4 patients (36%) achieved a partial response and 7 had SD (64%). Progression of disease was not documented in any WD-NEC at the first evaluation. When disease progression was detected in 2 patients with WD-NECs, they were crossed over to CDDP/L/LVFU2, resulting in 1 SD and 1 PD.

In the group of 8 patients with PD-NECs, 3 cases achieved a PR (37%) and 2 had SD (25%). Progression of disease was observed in 3 cases (37%).

*Biochemical response.* At the start of therapy, 9 of the 11 patients with WD-NECs had abnormal baseline levels of CgA, while 2 cases also had abnormal levels of NSE and 5-HIAA. After 3 months of biotherapy, a biochemical response (reduction in serum CgA) was observed in 6 cases: 3 of these also showed a radiological response and 3 had SD. Three patients did not show a biochemical response and had radiological stabilization of disease. In 2 of these patients, a

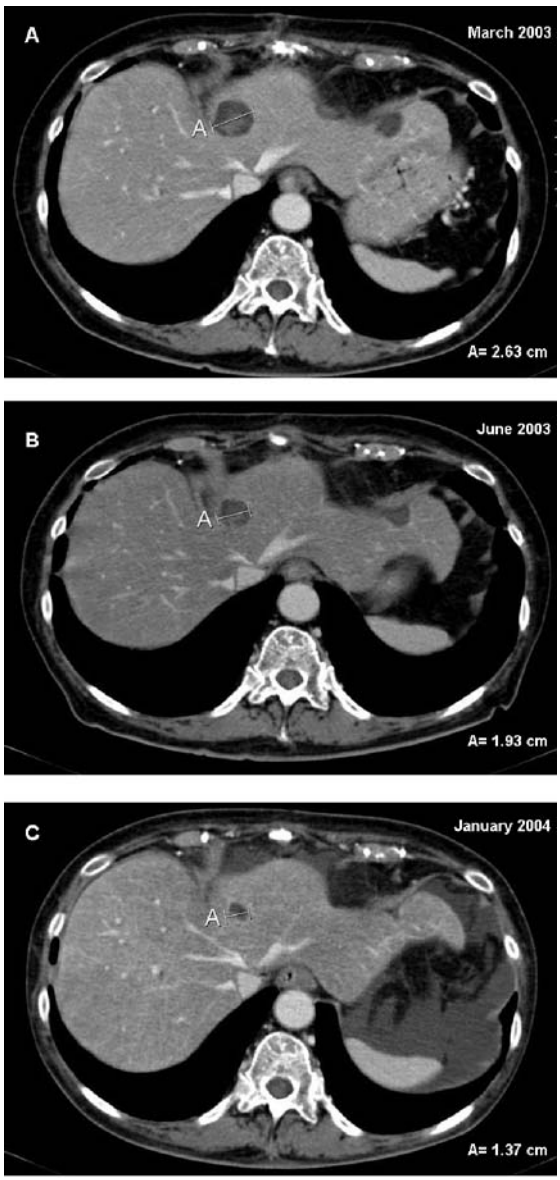


Figure 1. *CT scans of a representative patient with WD-NECs undergoing octreotide LAR plus IFN-α-2b therapy. Panel A shows pre-treatment assessment; panels B and C show tumour regression at 3 and 12 months, respectively.*

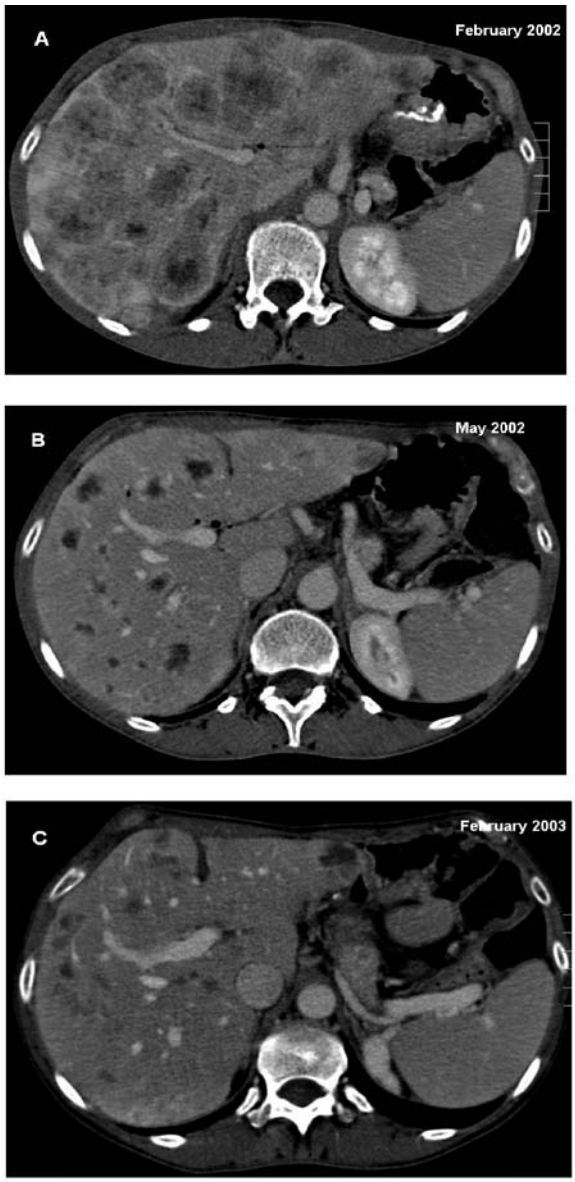


Figure 2. *CT scans of representative patient with PD-NECs undergoing cisplatin and L-leucovorin/fluorouracil combination chemotherapy. Panel A shows pre-treatment assessment; panels B and C show objective response of multiple liver metastases at 3 and 12 months, respectively.*

≤50% reduction in CgA levels was observed, while 1 case had CgA levels that increased by more than 25.

All patients with PD-NECs had elevated baseline levels of CgA, and 6 also had increased levels of NSE. After 3 cycles of therapy, a biochemical response of both CgA and NSE was observed in 3 patients, all of which also showed a radiological response. In contrast, patients who achieved radiological stabilization showed unchanged or increased levels of tumour markers. The remainder of patients with PD-NECs showed increased levels (>50%) of serum markers. In this regard, the biochemical response was significantly associated with a partial response by radiology ($p<0.01$).

*Symptomatic response in patients with carcinoid syndrome.* Five patients, 4 with WD-NECs and 1 with a PD-NEC had carcinoid syndrome (4 cases of diarrhoea and 2 of flushing). After 3 months of combined octreotide and IFN-α-2b

Table II. *Therapeutic responses in patients with NECs.*

**Response to octreotide plus IFN-α-2b in WD-NECs***

| | | Objective treatment responses | | | |
|---|---|---|---|---|---|
| Site of primary tumour | | Partial response | Stable disease | Clinical benefit | Progressive disease |
| Stomach | 2 | 0 | 2 | 1 | 0 |
| Bowel | 7 | 4 | 3 | 4 | 0 |
| Unknown | 2 | 0 | 2 | 2 | 0 |
| Total | 11 | 4 | 7 | 7 | 0 |

*Median follow-up 20 months (range 4-40)

**Response to cisplatin and L-leucovorin/fluorouracil in PD-NECs***

| | | Objective treatment responses | | | |
|---|---|---|---|---|---|
| Site of primary tumour | | Partial response | Stable disease | Clinical benefit | Progressive disease |
| Pancreas | 5 | 2 | 1 | 1 | 2 |
| Unknown | 3 | 1 | 1 | 1 | 1 |
| Total | 8 | 3 | 2 | 2 | 3 |

*Median follow-up 10.5 (range 3-30) months

Table III. *Adverse effects related to biotherapy or chemotherapy.*

**Octreotide plus IFN-α-2b in WD-NECs**

| Adverse effect | Grade 1-2 | Grade 3-4 |
|---|---|---|
| Nausea/vomiting | 18% | 0 |
| Neutropenia | 18% | 0 |
| Thrombocytopenia | 9% | 9% |
| Myalgia | 27% | 0 |
| Fever | 27% | 0 |
| Pruritus | 9% | 0 |
| Headache | 9% | 0 |
| sGOT/sGPT elevation | 9% | 0 |
| Cholelitiasis | 9% | 0 |

**Cisplatin and L-leucovorin/fluorouracil regimen in poorly-differentiated NECs**

| Adverse effect | Grade 1-2 | Grade 3-4 |
|---|---|---|
| Nausea/vomiting | 37.5% | 0 |
| Diarrhoea | 12.5% | 0 |
| Neutropenia | 25% | 12.5% |
| Thrombocytopenia | 0 | 0 |
| Peripheral neuropathy | 37.5% | 0 |
| Nephrotoxicity (creatinine levels) | 12.5% | 0 |
| Alopecia | 0 | 25% |

therapy, 3 patients with WD-NECs experienced a reduction of at least 50% in the frequency and intensity of flushing and diarrhoea, and 1 complete relief of diarrhoea; 2 of these also responded to therapy. In the patient with PD-NEC, symptoms due to excessive hormonal secretion by the tumour persisted after 3 cycles of chemotherapy, while partial symptomatic relief was achieved following administration of octreotide LAR.

*Response duration, overall survival; progression-free survival.* The median duration of response, calculated from the first documented complete or partial response, was 11 months (range 5-22) in patients with WD-NECs and 4 months (range 1-14) in patients with PD-NECs. The probability of progression-free survival at 2 years was 67% (CI: 29-100%) and 0% in WD-NECs and PD-NECs, respectively (Figure 3A). The overall 2-year survival rate was 66% and 88% in patients with PD-NECs and WD-NECs, respectively (Figure 3B).

*Treatment toxicity.* The adverse effects observed in each treatment category are reported in Table III. In patients treated with octreotide LAR/IFN-α-2b, the most frequent side-effects were grade 1 myalgia and fever (27%). In one patient the dose of IFN-a2b was reduced to $3x10^6$ IU due to long-lasting grade 4 thrombocytopenia; 1 patient developed cholelithiasis requiring surgery. One patient treated with CDDP/L/LVFU2 experienced grade 4 neutropenia without documented infection. No patient in either treatment group required discontinuation of therapy due to adverse events.

## Discussion

While treatment of NECs based on histopathological parameters has been suggested (21), the majority of the studies reported to date are extremely heterogeneous in terms of patient selection and type of chemotherapy or biotherapy utilized (21, 22), which accounts for the wide variability of reported results. In the present study, patients with metastatic NECs were subclassified according to the grade of differentiation: WD-NECs were treated with biotherapy (IFN-α-2b plus octreotide LAR), while patients with PD-NECs were subjected to CDDP/L/LVFU2 combination chemotherapy. In the former group of tumours, the biotherapy was well-tolerated and permitted long-lasting tumour control in the majority of patients. In PD-NECs, the combination chemotherapy was associated with an antitumoral response rate of 37%, which is higher than that reported for other combination chemotherapy

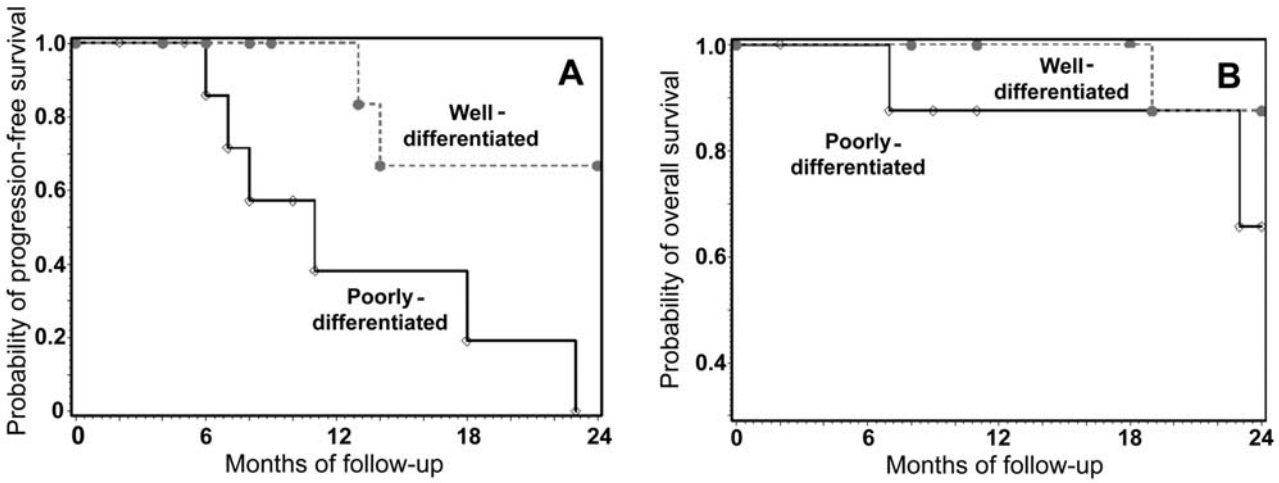


Figure 3. *Two-year probability of progression-free (A) and overall (B) survival of WD- and PD-NECs.*

regimens, although the duration of the responses was similar (23, 24).

It is worth noting that the present chemotherapeutic regimen had an excellent therapeutic index and was associated with only 1 case of grade 4 toxicity with a low incidence of alopecia (25%). The adverse effects of previously reported chemotherapy regimens for NECs are generally more clinically relevant. In particular, the combination of cisplatin/etoposide is associated with severe renal (53%), haematological (64%) and gastro-intestinal toxicity, while treatment with streptozotocin and doxorubicin is limited by the occurrence of severe heart failure and chronic renal insufficiency requiring dialysis in approximately 5% of cases (25-27). Alopecia is universal to both the previous regimens. In our study, no patients treated with either chemotherapy or biotherapy required discontinuation of therapy because of side-effects.

We can also confirm a positive, significant relationship between the biochemical and radiological responses in most patients with NECs receiving either biotherapy or chemotherapy. For long-term follow-up of patients with NECs, biochemical markers and, in particular, serum CgA should be used for routine disease monitoring instead of frequent radiological evaluation.

The results presented herein demonstrate that these therapies have a good therapeutic index and compare favourably with previously published series (12, 23-25, 27). The relative paucity of patients evaluated in the present series of cases managed by a single institution should also be considered in light of the encouraging results during the brief (41 months) recruitment period. Our data are in favour of applying the WHO classification criteria for the therapy of PD-NECs and WD-NECs with chemotherapy or biotherapy, respectively. Moreover, the current classification scheme facilitates multicentre research on treatment outcomes by using standardized histopathological criteria. Lastly, since a higher Ki-67 proliferation index generally correlates with a poorer grade of differentiation, it might be considered as an additional parameter for choosing between chemotherapy or biotherapy; in our series, a Ki-67 index of 5% was found to discriminate between WD- and PD-NECs. Nonetheless, therapy for patients with a Ki-67 proliferation index between 2% and 15% remains highly discretionary.

In conclusion, our study confirmed that management with either biotherapy or chemotherapy can be guided by WHO classification in patients with NECs. Biotherapy with IFN-α-2b plus octreotide LAR is highly effective in WD-NECs. Combination chemotherapy with CDDP/L/LVFU2 represents a valid therapeutic option in PD-NECs, having a good therapeutic index and favourable toxicity profile.

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