

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

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PRESENTATION OUTLINE

- **Provide an overview of chemotherapy-induced peripheral neuropathy (CIPN)**
- **Discuss assessments for CIPN**
- **Briefly review treatments for the management of CIPN**
- **Present results from a prospective observational study on CIPN natural history**
- **Highlight practice and research gaps**

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DEFINITION OF CIPN

- A derangement in structure and function of peripheral motor, sensory and autonomic neurons, causing peripheral neuropathic signs and symptoms.
- Depending on the substance used, a pure sensory and painful neuropathy (with platinum analogues i.e. cisplatin, oxaliplatin, carboplatin) or a mixed sensory-motor neuropathy with or without involvement of the autonomic nervous system (with vinca alkaloids i.e. vincristine, or taxanes i.e. paclitaxel) can ensue

BACKGROUND

- **The overall incidence of CIPN is not clear, but it is estimated to occur in 10-20% of patients during treatment and it may be as high as 100%, depending on the chemotherapy drug, dose-intensity, cumulative dose and other as yet unidentified risk factors. 28.7% in a large prospective study (Pereira 2015)**
- **The implications of CIPN on the quality of life of cancer patients are significant, including dysfunction in daily activities, social well-being, work reintegration and physical impairments including pain.**
- **There is a considerable impact on health care resource utilisation too, with those experiencing CIPN having more often outpatient visits and medication use, estimated to be at US\$17,000 more in patients with CIPN than non-CIPN cancer patients.**
- **The mechanisms by which these drugs cause neuropathy are not well characterised and the long term functional deficits resulting from these treatments have not been systematically monitored**

WHAT IS KNOWN

- **neuropathic symptoms tend to progress during chemotherapy and generally regress once treatment stops**
- **sometimes symptoms can transiently develop or worsen after the end of treatment, a phenomenon known as “coasting”**
- **The pain that is associated with this toxicity can be prolonged, severe, very long lasting and the treatment is usually difficult (Postma et al., 2005)**

SYMPTOMS

- **Symptoms can consist of a mixture of motor, sensory, and autonomic signs.**
- **Motor signs include muscle weakness and atrophy, which tends to begin on the distal limbs, proceeding proximally as it progresses.**
- **Sensory symptoms include paresthesias and feelings of warmth, cold, numbness or tingling**
- **Autonomic neuropathy is less common and can include hypotension, cardiac conduction irregularities, and bowel and bladder dysfunction**

RISK FACTORS

- **Nerves previously damaged by diabetes mellitus, alcohol or inherited neuropathy (Quasthoff & Hartung, 2002)**
- **Thyroid dysfunction, metabolic and infectious diseases (i.e. Hepatitis B or C, Polio, HIV), vitamin deficiencies (i.e. B12, B1, B6), and monoclonal gammopathy (Kaley & DeAngelis, 2009; Armstrong et al., 2005)**
- **Many common medications including, metronidazole, misonidazole, sulfasalazine, phenytoin etc, have all been reported to produce peripheral neurotoxicity (Hausheer et al., 2006)**
- **Age**

ASSESSMENT

- **The NCI-Common Toxicity Criteria (CTCAE v4) for Adverse Events. This grading scale comprises a sensory and motor assessment and utilises a 5-point scale ranging from grade 1 to grade 5.**
- **The WHO grading system for examining CIPN, and includes paresthesias, reflex decrease and extend of motor loss as parameters**
- **10-g monofilament to lightly touch the patient's hands and feet. Abnormal responses including hyperesthesia, anesthesia or hypoesthesia**

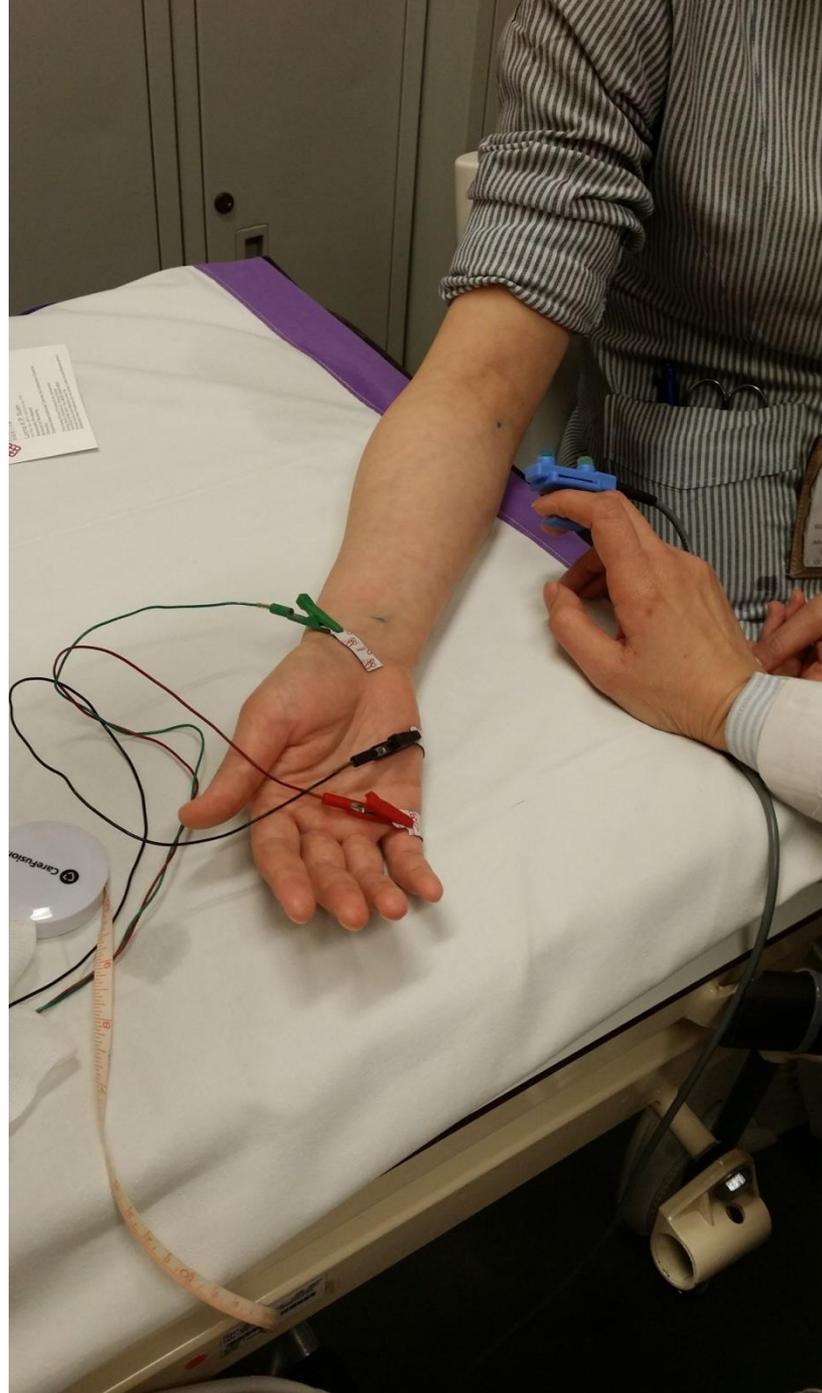
TOTAL NEUROPATHY SCORE SCALE

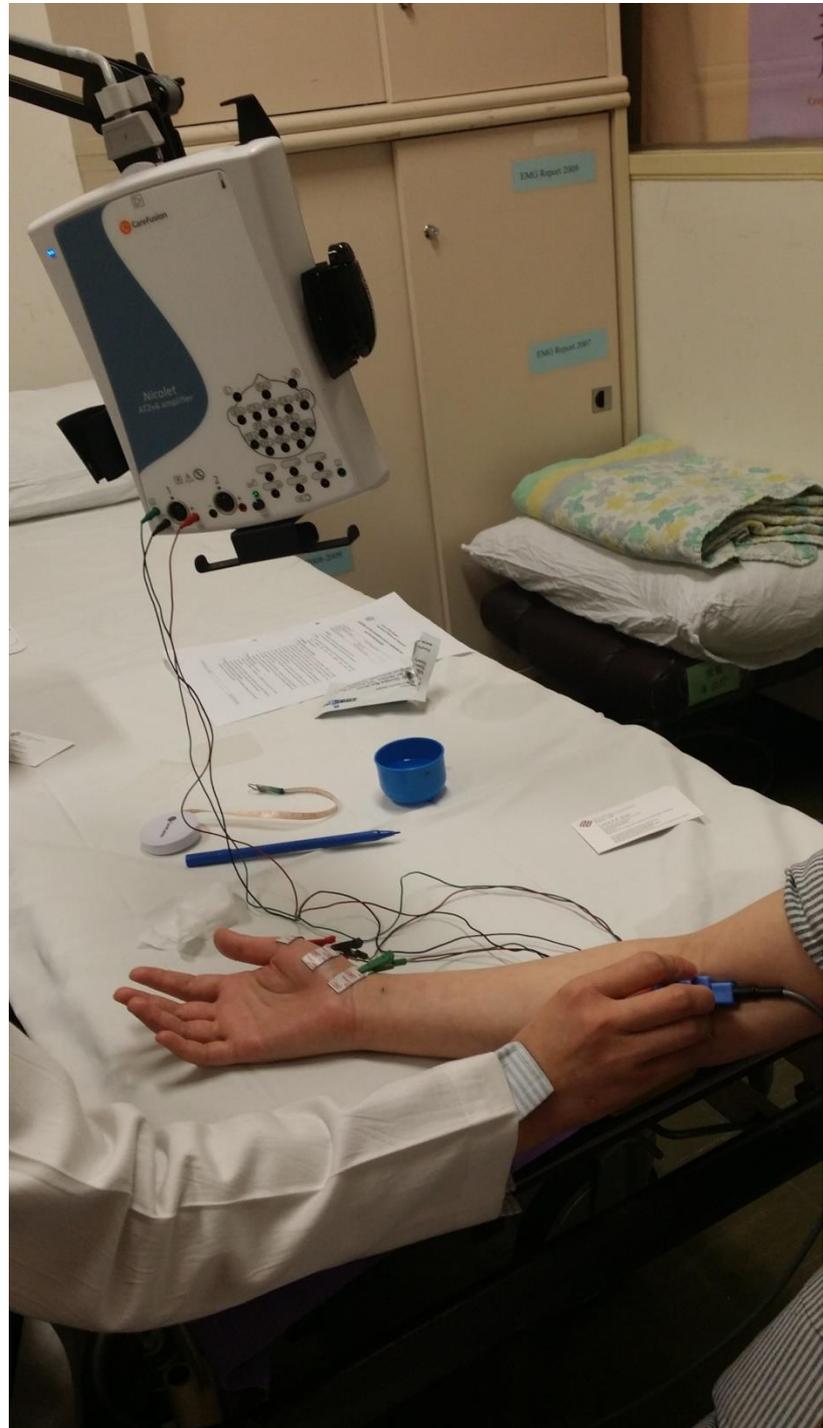
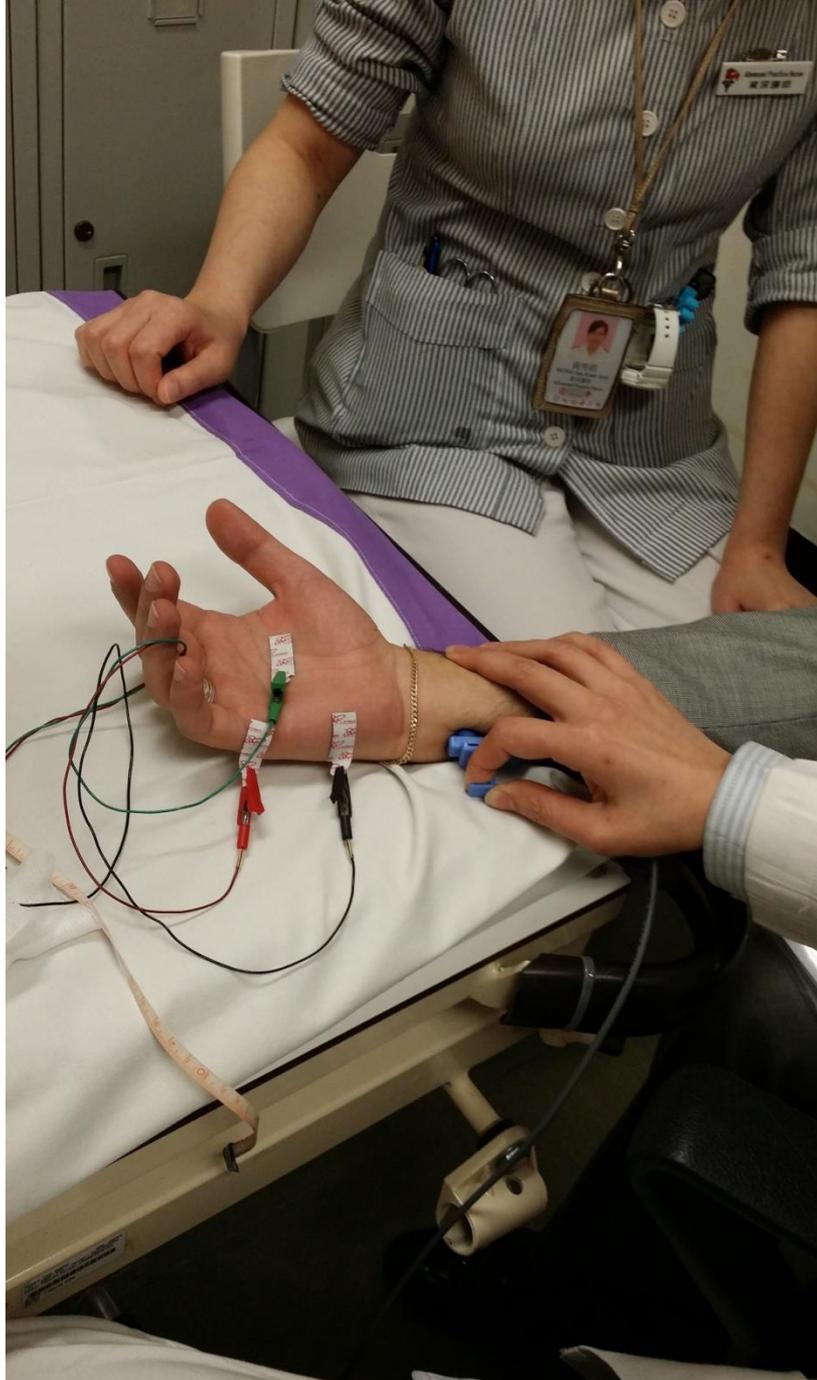
The Total Neuropathy Score clinical version (TNSc). The TNS combines information obtained from grading of symptoms, signs, nerve conduction studies, and quantitative sensory tests, and provides a single measure to quantify neuropathy.

NEUROPHYSIOLOGICAL TESTING: NERVE CONDUCTION STUDY (NCS)

Motor nerves: median nerve (bilateral) and ulnar nerve (bilateral). It registers axonopathy or demyelination. Distal latencies, amplitudes F-waves and conduction velocities are measured.

Sensory nerve: median nerve (bilateral) and ulnar nerve (bilateral).





QUALITY OF LIFE ASSESSMENT SCALES

- **Functional assessment of cancer therapy (FACT/GOG-Ntx) is a 38-item self reported the first one is a 27-item general quality of life sub-scale and a 11-item neurotoxicity sub-scale.**
- **The EORTC QLQ-C30: The EORTC CIPN questionnaire is intended to supplement the core quality of life questionnaire, and is a 20-item patient reported questionnaire. It includes three sub-scales assessing sensory (9-items), motor (8-items) and autonomic (3-items) symptoms and functioning.**

CIPN TREATMENTS

- Largely unsuccessful attempts
- The data are insufficient to conclude that any of the purported chemoprotective agents (acetylcysteine, amifostine, calcium and magnesium, diethyldithiocarbamate, glutathione, Org 2766, oxcarbazepine, retinoic acid, or vitamin E) prevent or limit the neurotoxicity of platin drugs (Albers 2014)
- Antiepileptic or antidepressants used to treat other neuropathies have been generally negative
- Duloxetine(SNRI) for 5 weeks had positive results (Smith, 2013)
- A topical gel treatment containing baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20 mg) (Barton 2011)
- Some evidence for acupuncture from diabetic neuropathy
- 18 pts were treated with a course of six weekly acupuncture sessions. 82% (n=14) of patients reported an improvement in symptoms following their course of acupuncture. Some patients derived additional benefits from the treatment including a reduction in analgesic use and improved sleeping patterns (Donald 2011).

AIMS/OBJECTIVES OF STUDY

The aim of the study is to identify the natural history and characteristics of CIPN within different chemotherapy drugs for up to 12 months after the patient's first chemotherapy treatment

The objectives of the study are to

- (a) identify changes to patients' physical function and quality of life due to CIPN,**
- (b) assess the relative contribution of risk factors in the development of CIPN,**
- (c) to identify the proportion of patients who have a complete resolution of symptoms,**
- (d) to examine the timing to resolution of symptoms, and**
- (e) to compare the sensitivity and specificity of the assessment scales used in order to recommend administering a reliable CIPN instrument in practice.**

METHODS

Design

A prospective observational design over 12 months from the patient's first chemotherapy treatment.

Sample and settings:

A heterogeneous sample of 355 patients receiving chemotherapy in 1 hospital in Hong Kong (=215), 1 in Singapore (=100) & 1 in the UK (=40)

Inclusion Criteria

- Patients must have a diagnosis of breast, ovarian cancer, lung cancer, head & neck cancer with or without metastasis.**
- Expected prognosis of at least 12 months (as judged by the clinicians)**
- Be aged 18+ years**
- Chemotherapy naïve or receiving paclitaxel/ Carboplatin/ Vinorelbine/ cisplatin or carboplatin/Taxotere+Cisplatin for the first time**
- Be able to give informed consent**

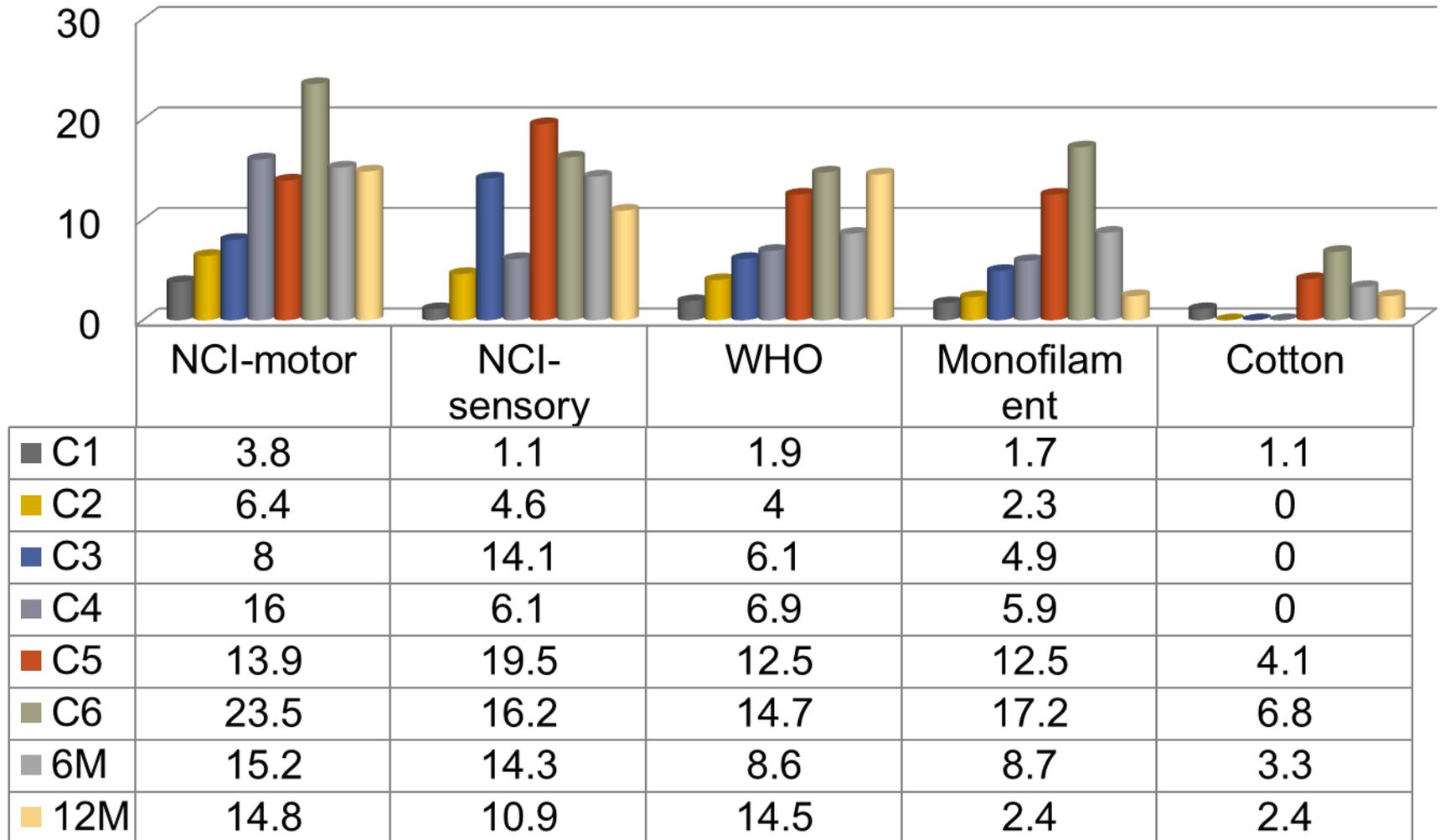
WARNING!

**Preliminary results from about N=215,
final results may be different**

PRELIMINARY DATA

Age	Mean=53, range=34-72
	%
Gender	
Male	21%
Female	79%
Diagnosis	
Lung cancer	15%
Breast cancer	63%
Ovarian cancer	10%
Nasopharyngeal cancer	12%
Stage	
I	29%
II	38%
III	24%
IV	9%
Chemotherapy	
Taxanes	62%
Cisplatin	20%
Carboplatin	16%
Other	2%

INCIDENCE OF CIPN



CORRELATIONS BETWEEN SCALES

NCI motor neuropathy & NCI sensory neuropathy scale:

$r=0.72$ ($p<0.001$)

NCI motor neuropathy & WHO neuropathy:

$r=0.30$ ($p=0.015$)

NCI sensory neuropathy & WHO neuropathy:

$r=0.31$ ($p=0.011$)

[$r=0.44$ & 0.55 respectively at 6M FU]

**NCI & monofilament: $r=0.38$ (motor); $r=0.49$ (sensory) BUT
 $r=0.80$ with WHO scale at 6MFU**

DEMOGRAPHIC & CLINICAL DATA

Increased incidence of CIPN and:

- Cumulative dose**
- Age ($r=0.31$, $p=0.011$)**

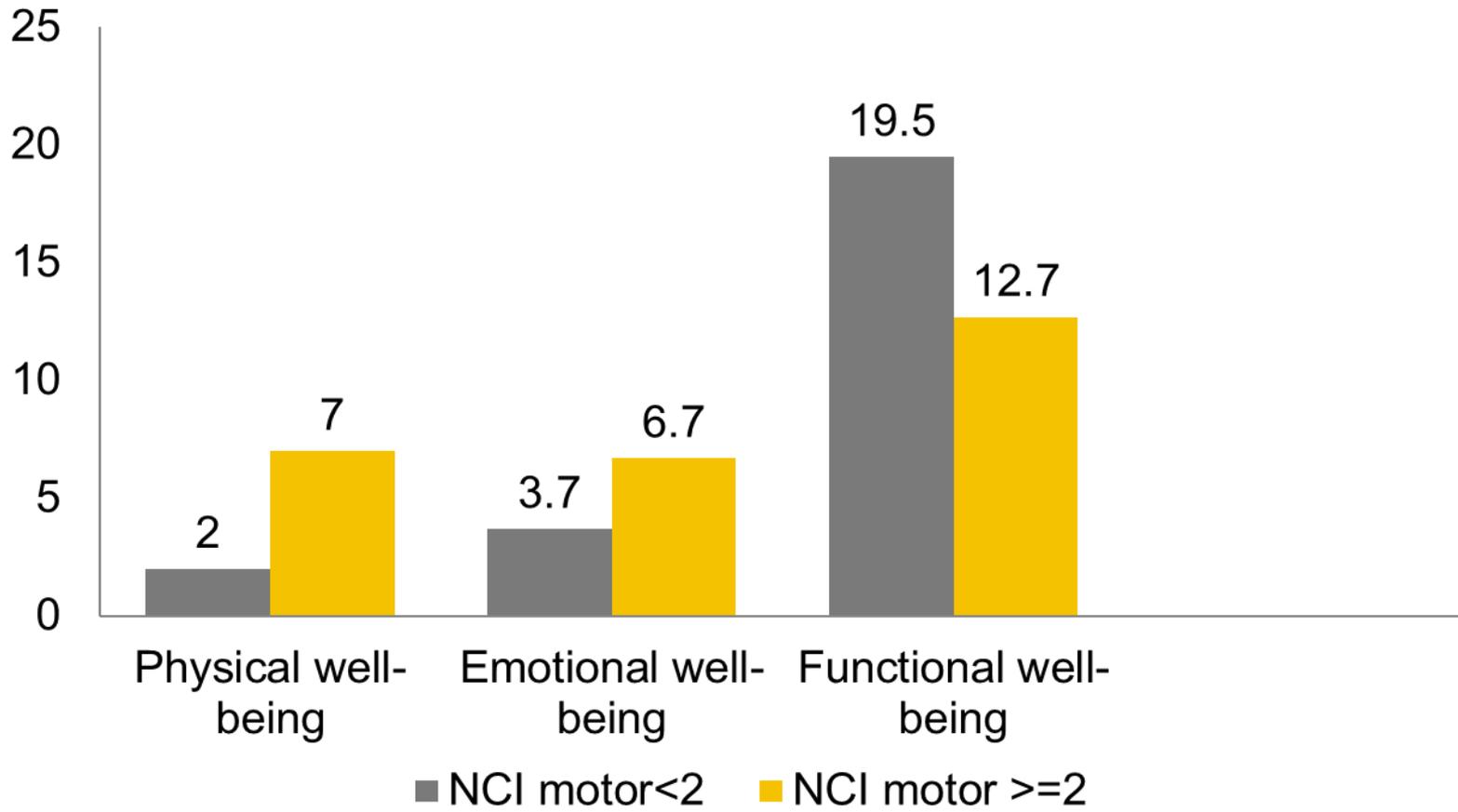
Average time to CIPN development:

- Docetaxel-Cyclophosphamide: 63 days (41-82)**
- TAC: 143 days (39-360)**
- Docetaxel-Carboplatin-Herceptin: 88 days (42-118)**

NEUROPATHY SYMPTOMS AT C6 (FACT-G-NTX)

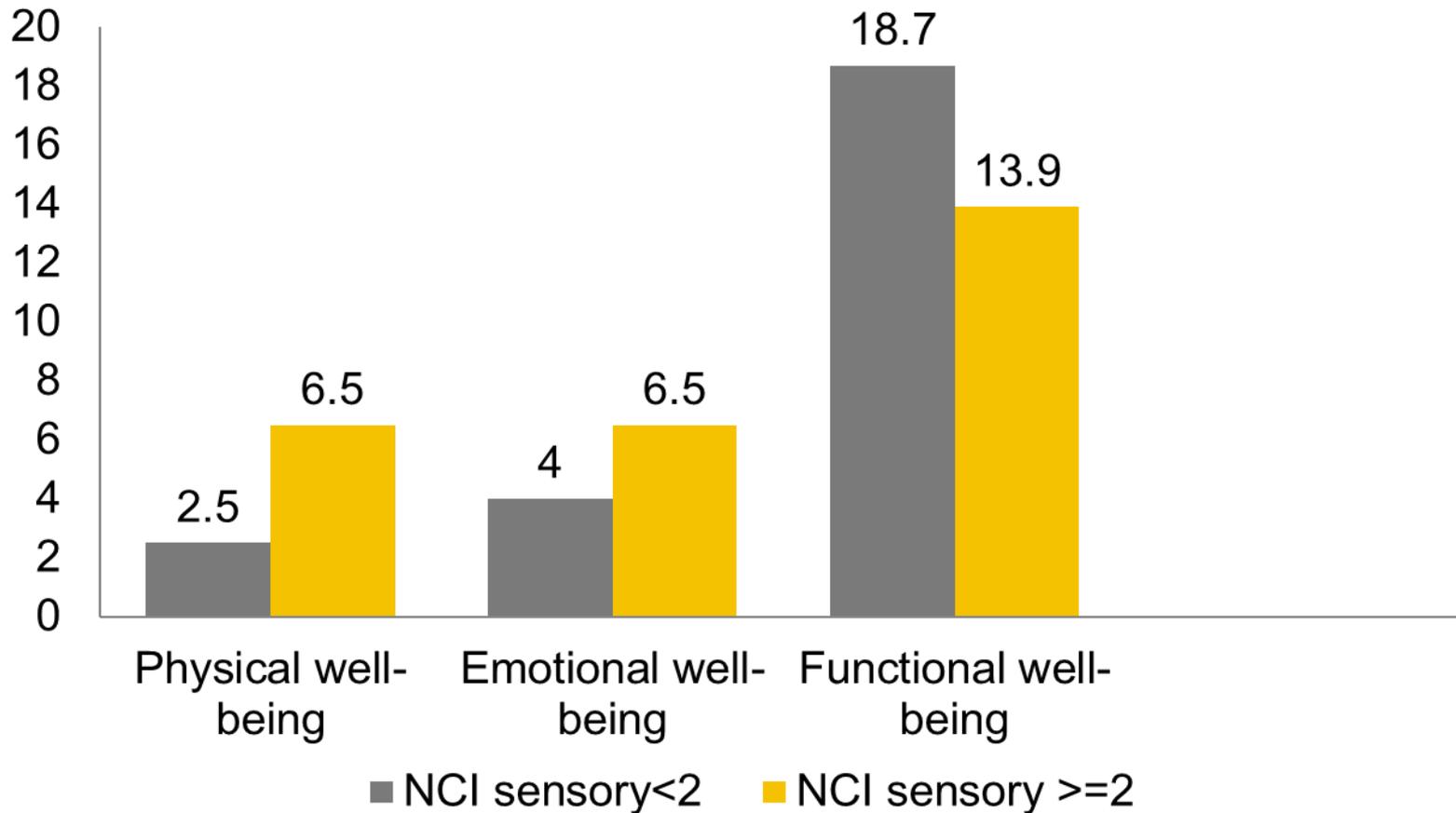
	%	% quite a bit/very much
Numbness/tingling in hands	53	15
Numbness/tingling in feet	41	10
Discomfort in hands	43	12
Discomfort in feet	43	12
Joint pain/muscle cramps	23	4
Feeling weak all over	26	7
Have trouble hearing	13	1.5
Buzzing/ringing in ears	12	3
Having trouble buttoning buttons	6	-
Having trouble feeling shape of small objects	4.5	1.5
Having trouble walking	21	3

NCI-CTC SCORE VS FACT-G-NTX @C6 (ALL P>0.000)



NCI-CTC SCORE VS FACT-G-NTX @C6

P=0.01; P=0.03; P=0.015 RESPECTIVELY



DISCUSSION

- **Complex and difficult to manage symptom**
- **Variable incidence from study to study based on scales/methods used**
- **10-15% of patients with long-lasting CIPN- chronic CIPN**
- **There are factors placing patients at higher risk for CIPN, these need to be used as baseline variables in future trials**
- **More focus in future on the development of higher quality therapeutic trials, including those showing borderline findings**
- **Need for regular assessment – agree on appropriate assessment**
- **Collaboration between oncology and neurology**

*****Collaboration among nurse researchers**