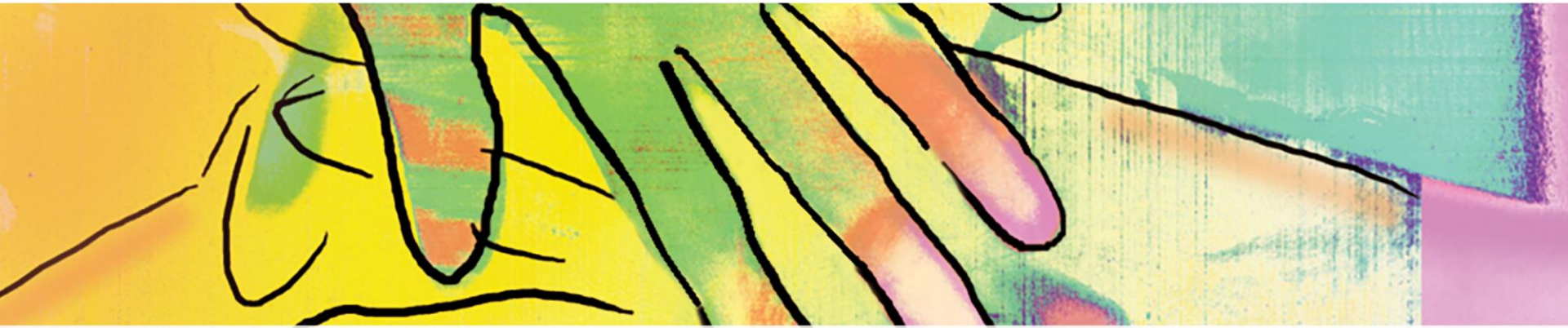
AGSMO

Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie der Deutschen Krebsgesellschaft e.V.



AGSMO JAHRESKONGRESS 2019

Supportive Therapie bei Krebs

Susanne Koeppen
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Berlin, 15.–16. März 2019

Neuropathie als anhaltende Störung bei Tumortherapie

Susanne Koeppen
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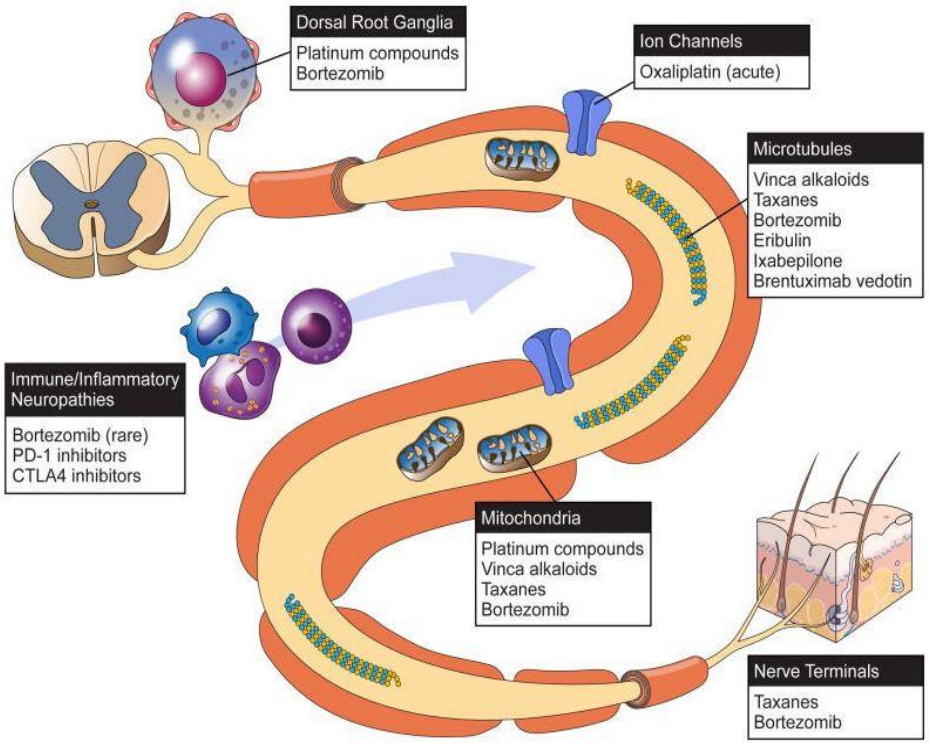
Samstag 16.3.2019

Chemotherapy-induced peripheral neuropathy: A current review

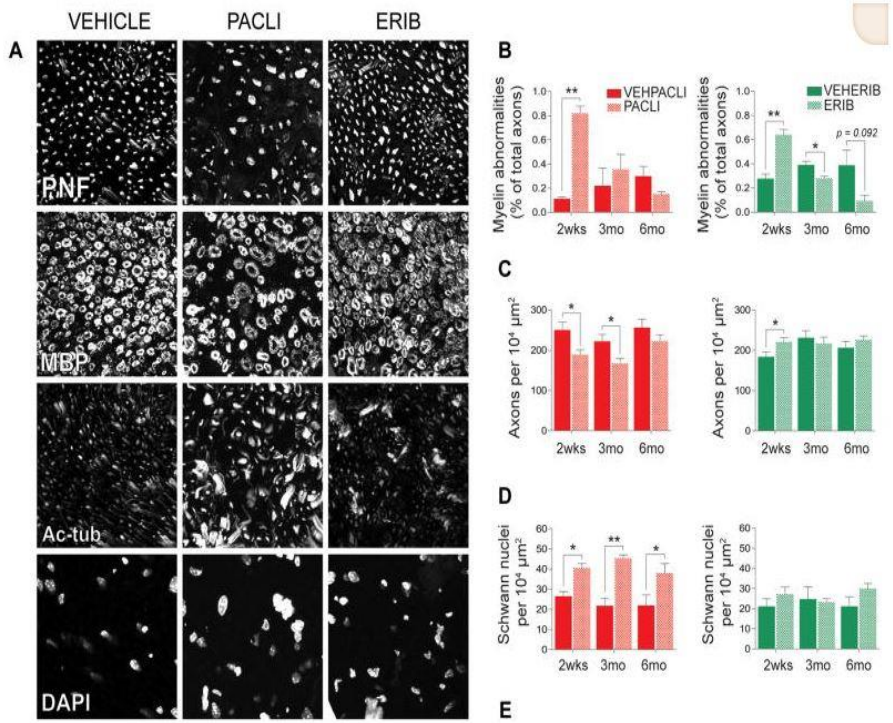
- Approximately 30 to 40% of patients treated with neurotoxic chemotherapy will develop CIPN, and there is considerable variability in its severity between patients.
- The prevalence and burden of CIPN late effects will likely increase as cancer survival rates continue to improve.



Staff NP et al. Ann Neurol 2017

Peripheral Neuropathy Induced by Microtubule-Targeted Chemotherapies: Insights into Acute Injury and Long-term Recovery

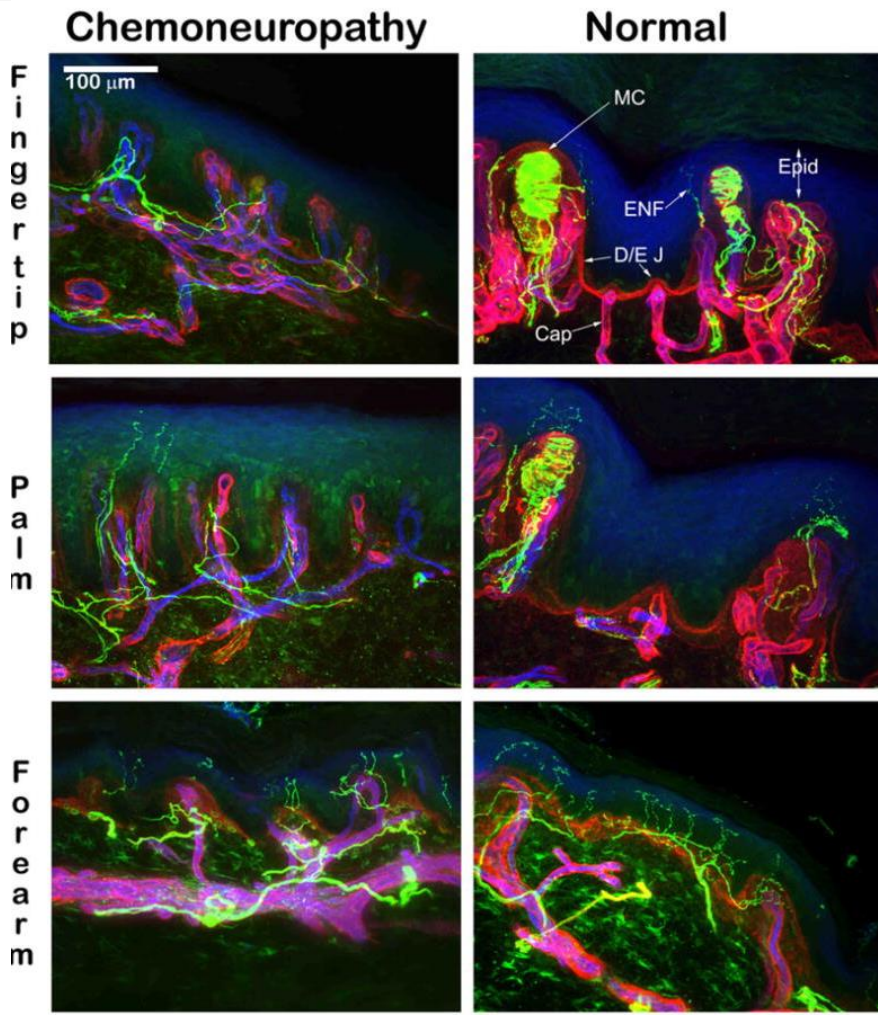
- Axonopathy, with a secondary disruption in myelin structure within 2 weeks of drug administration.
- Reduced sensory NCV and amplitude, with greater deficits after paclitaxel.
- These effects correlated with degeneration in dorsal root ganglia (DRG) and sciatic nerve and abundance of Schwann cells.
- Most injuries were fully reversible after 3-6 months after administration of eribulin, vinorelbine, and ixabepilone.
- Delayed recovery after paclitaxel.



Wozniak KM et al. Cancer Res 2018

Follow-Up Psychophysical Studies in Bortezomib-Related Chemoneuropathy Patients

- The patient´s epidermal nerve fiber (ENF) density is reduced as compared to skin biopsies obtained from a healthy control subject
- Persistent impairment of Aβ, Aδ, and C fibers



Boyette-Davis JA et al. The Journal of Pain 2011

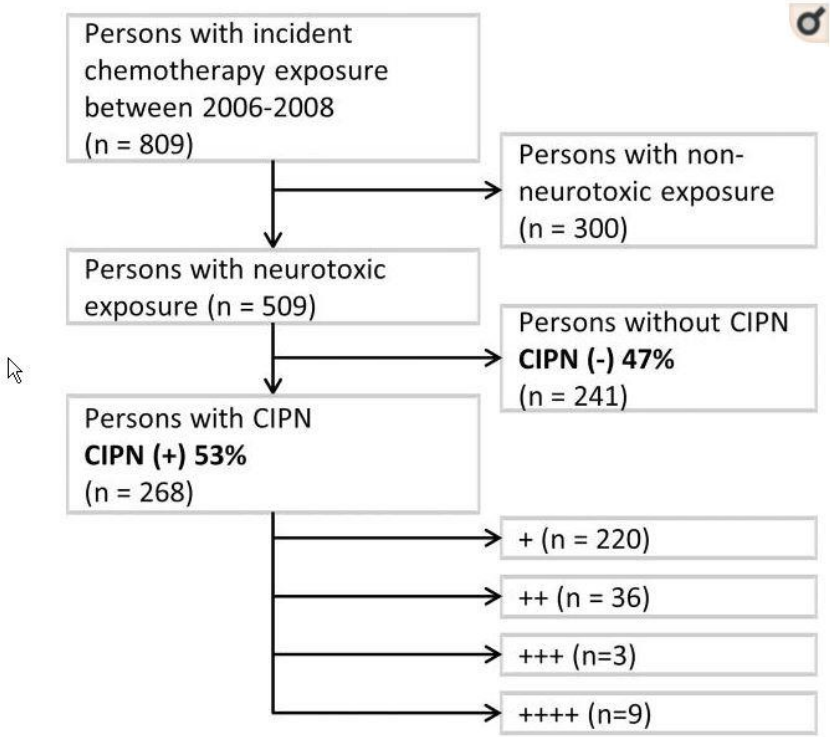
Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis

- 31 studies with data from 4179 patients were included in the analysis.
- CIPN prevalence was 68.1% (57.7-78.4) when measured in the first month after chemotherapy, 60.0% (36.4-81.6) at 3months and 30.0% (6.4-53.5) at 6months or more.
- Different chemotherapy drugs were associated with differences in CIPN prevalence,
- Clinical risk factors, identified in 4 of 31 studies, included neuropathy at baseline, smoking, abnormal creatinine clearance, and specific sensory changes during chemotherapy.
- Although CIPN prevalence decreases with time, at 6months 30% of patients continue to suffer from CIPN.
- Routine CIPN surveillance during post-chemotherapy follow-up is needed.

Seretny M et al. Pain 2014

Incidence and disease burden of chemotherapy-induced peripheral neuropathy in a population-based cohort.

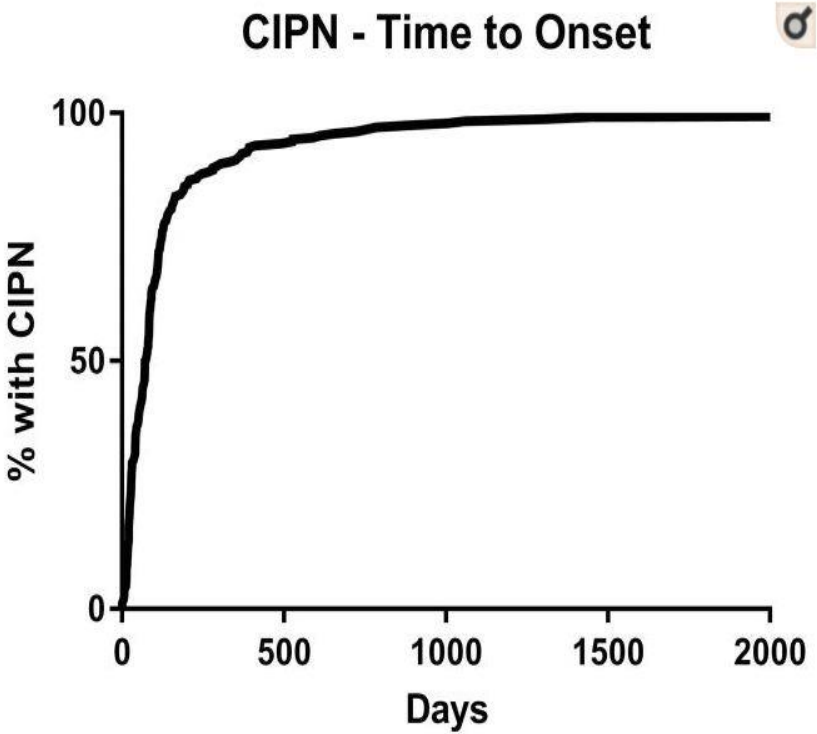
- Olmsted County, Minnesota residents receiving neurotoxic chemotherapy were identified and CIPN was ascertained via text searches of polyneuropathy symptoms in the medical record.
- Patients with CIPN received a neuropathy ICD-9 diagnosis in only 37 instances (13.8%).



Shah A et al. J Neurol Neurosurg Psychiatry 2018

Incidence and disease burden of chemotherapy-induced peripheral neuropathy in a population-based cohort.

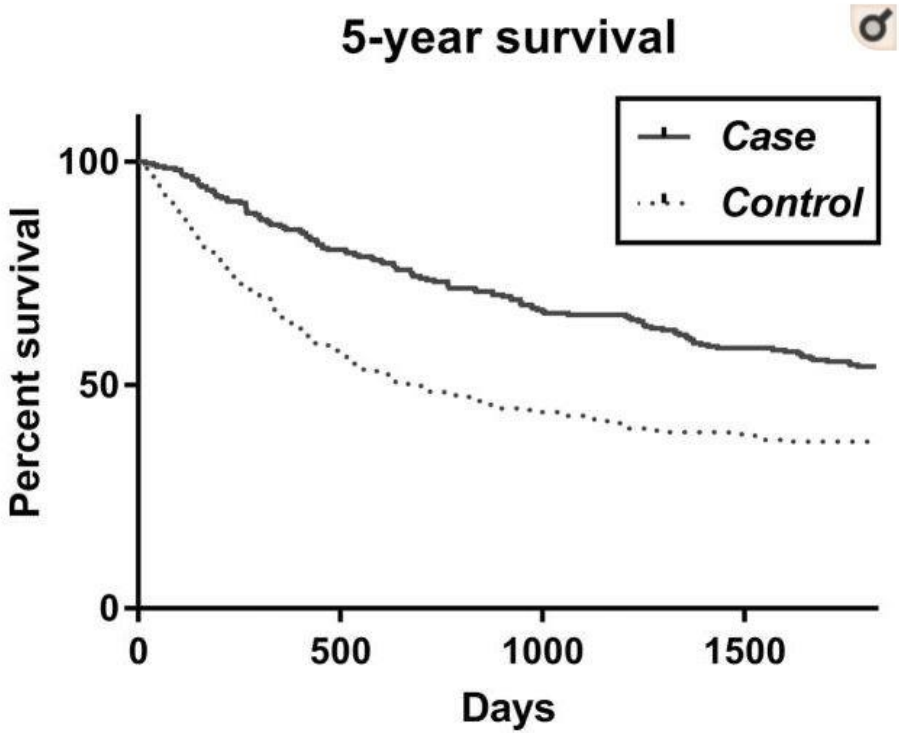
- The median time from incident exposure to first documented symptoms was 71 days.
- Pain symptoms and use of pain medications were observed more often in patients with CIPN.



Shah A et al. J Neurol Neurosurg Psychiatry 2018

Incidence and disease burden of chemotherapy-induced peripheral neuropathy in a population-based cohort.

- Five-year survival was greater in those with CIPN (55.2%) versus those without (36.1%).
- Those with CIPN surviving greater than 5 years (n=145) continued to have substantial impairments and were more likely to be prescribed opioids than those without CIPN (OR 2.0, 1.06-3.69).



Shah A et al. J Neurol Neurosurg Psychiatry 2018

Chemotherapie- induzierte Polyneuropathie

Konsensbasiertes Statement

Zu den individuellen Risikofaktoren, die die Inzidenz und Ausprägung der Chemotherapie induzierten Polyneuropathie erhöhen können, zählen:

- Diabetes mellitus
- Nutritiv toxische Substanzen insbesondere Alkohol
- Niereninsuffizienz
- Hypothyreose
- Kollagenosen/Vaskulitiden
- Vitaminmangel (z.B. B1, B6, B12)
- HIV- Infektion
- CMT- Genmutation

Impact of diabetes comorbidity on the efficacy and safety of FOLFOX first-line chemotherapy among patients with metastatic colorectal cancer: a pooled analysis of two phase-III studies

- A total of 756 patients were enrolled in the current analysis; of which 64 patients have pre-existing DM while 692 patients were non-diabetic.
- Comparing diabetic to non-diabetic patients, there were no differences between the two groups in terms of acute oxaliplatin-induced neurological symptoms including cold-induced dysthesia (P = 0.600), laryngeal dysthesia (P = 0.707), jaw pain (P = 0.743) or muscle pain (P = 0.506).
- Moreover, no difference was seen between the two groups in terms of the incidence of long-term oxaliplatin-induced paresthesia (P = 0.107), highest grade of paresthesia (P = 0.498) or rates of recovery from paresthesia (P = 0.268).
- Diabetic patients have, however, a shorter time to develop oxaliplatin-induced paresthesia (P = 0.024).

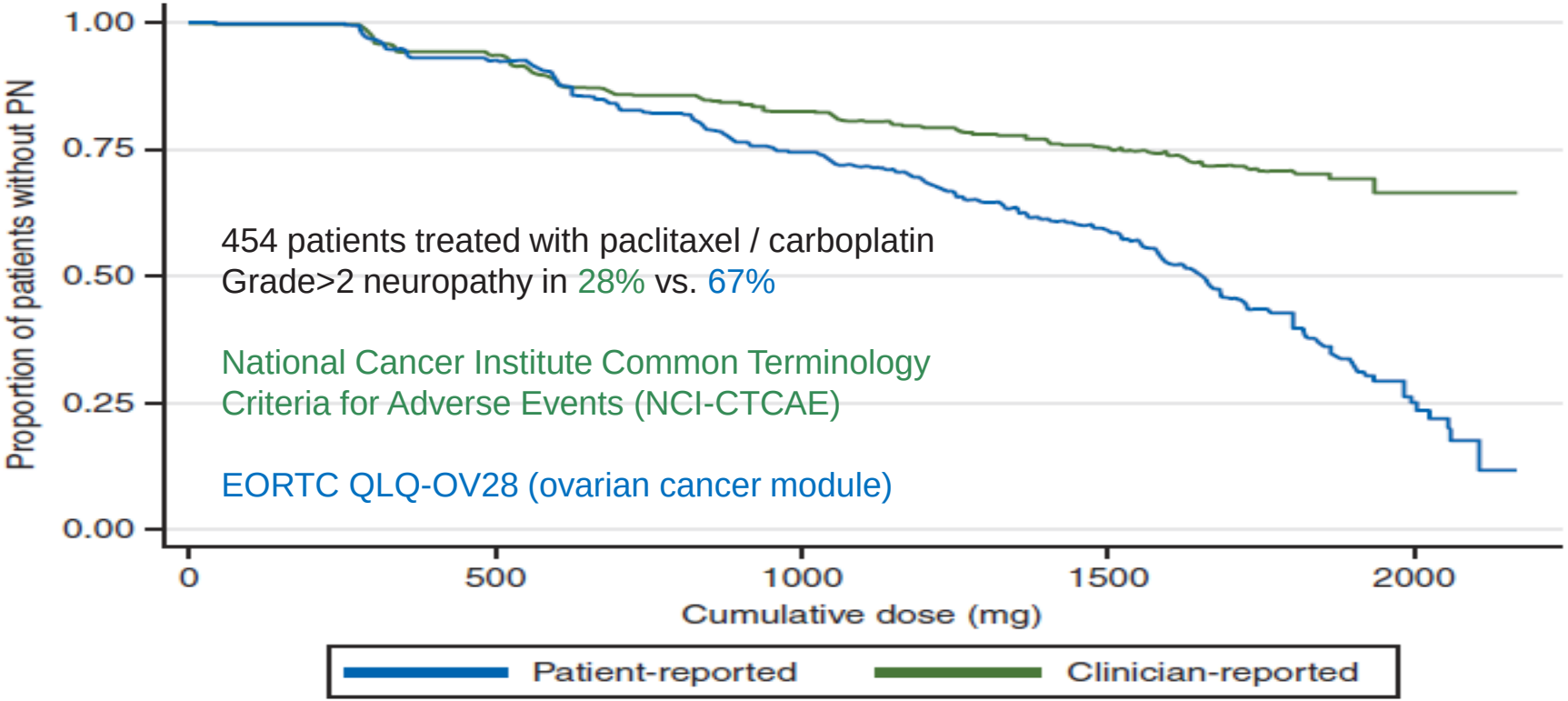
Abdel-Rahman O. Clin Transl Oncol 2018

Chemotherapy-Induced Peripheral Neuropathy Assessment Tools: A Systematic Review

- Electronic searches using keywords were conducted in Medline, PubMed, CINAHL®, and Cochrane Library for articles published from 1980-2015.
- A total of 19 studies describing 20 tools were reviewed.
- The quality of studies varied from strong to weak. The validity ranged from low to high, and the reliability with internal consistency ranged from 0.56-0.96.
- Poor inter-rater agreement was found.
- Not all of the tools were deemed practical.
- Considering the psychometric properties and practicality, two tools (Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity [FACT/GOG-Ntx] and Total Neuropathy Score [TNS]) are recommended for assessing CIPN.

Haryani H et al. Oncol Nurse Forum 2017

Clinical and genetic predictors of paclitaxel neurotoxicity based on patient- versus clinician-reported incidence and severity of neurotoxicity in the ICON7 trial



Park SB et al. Ann Oncol 2017

Chemotherapie- induzierte Polyneuropathie

Erhöhtes Risiko für Neurotoxizität

- **Cisplatin:** **> 300 mg/m² kumulativ**
- **Oxaliplatin:** **> 550mg/m² kumulativ**
- **Docetaxel:** **> 100mg/m² kumulativ**
- **Paclitaxel:** **> 250mg/m² kumulativ**
- **Vincristin:** **Einzeldosis > 2 mg, 4-10mg/m² kumulativ**
- **Thalidomid:** **> 20g/m² kumulativ**
- **Bortezomib:** **>26mg/m² kumulativ**

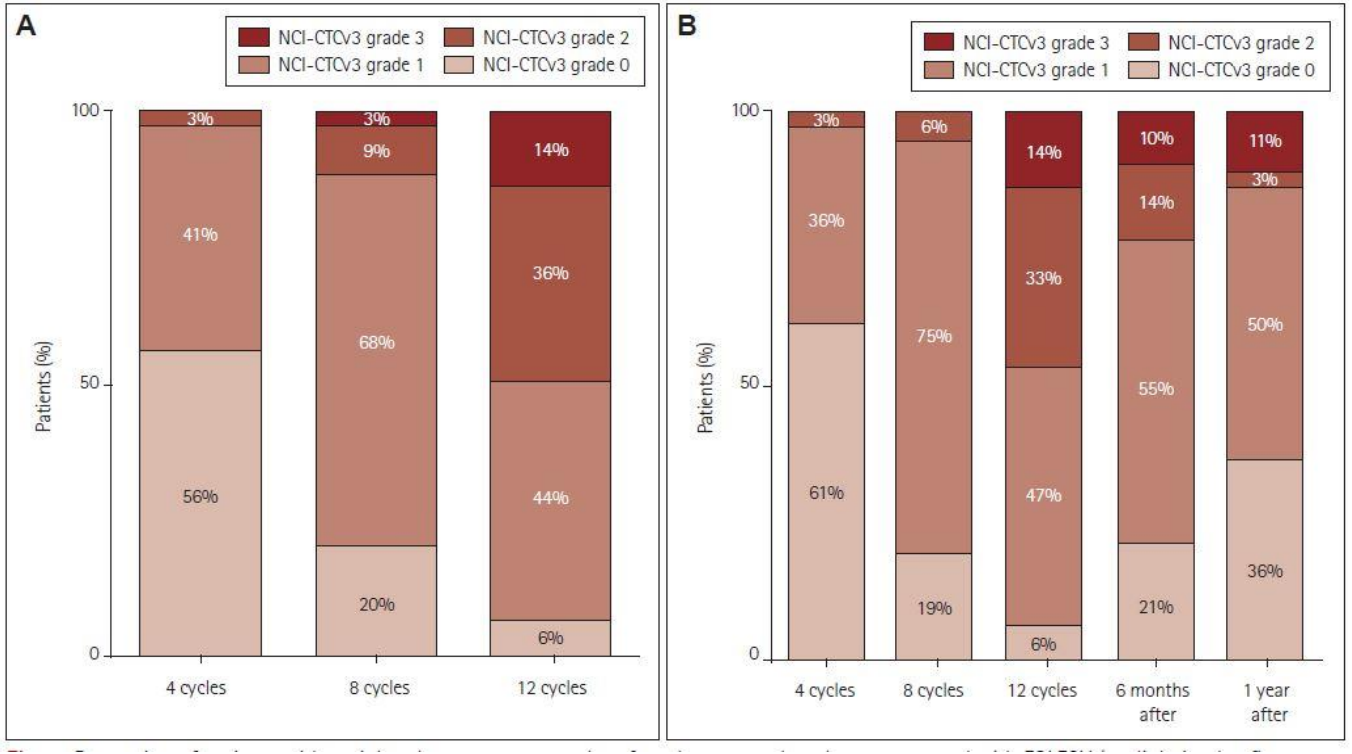
Peripheral neuropathy in colorectal cancer survivors: the influence of oxaliplatin administration. Results from the population-based PROFILES registry

- In total 207 patients, diagnosed with CRC between 2000 and 2009 who underwent adjuvant treatment with oxaliplatin, were included. They completed the EORTC QLQ-CIPN20 2-11 years after diagnosis.
- Patients who received cumulative oxaliplatin dose of ≥ 842 mg/m(2) had a significantly worse EORTC QLQ-CIPN20 sensory score compared to those who received a low cumulative dose of < 421 mg/m(2) (mean 19 vs. 8; p = 0.02). They more often reported tingling toes/feet (13% vs. 2%, respectively; p = 0.01).
- Dose intensity and time delay did not influence the occurrence of CIPN.
- Cumulative dose of oxaliplatin is associated with long-term CIPN.

Beijers AJ et al. Acta Oncol 2015

A Prospective Study of Chronic Oxaliplatin-Induced Neuropathy in Patients with Colon Cancer: Long-Term Outcomes and Predictors of Severe Oxaliplatin-Induced Neuropathy

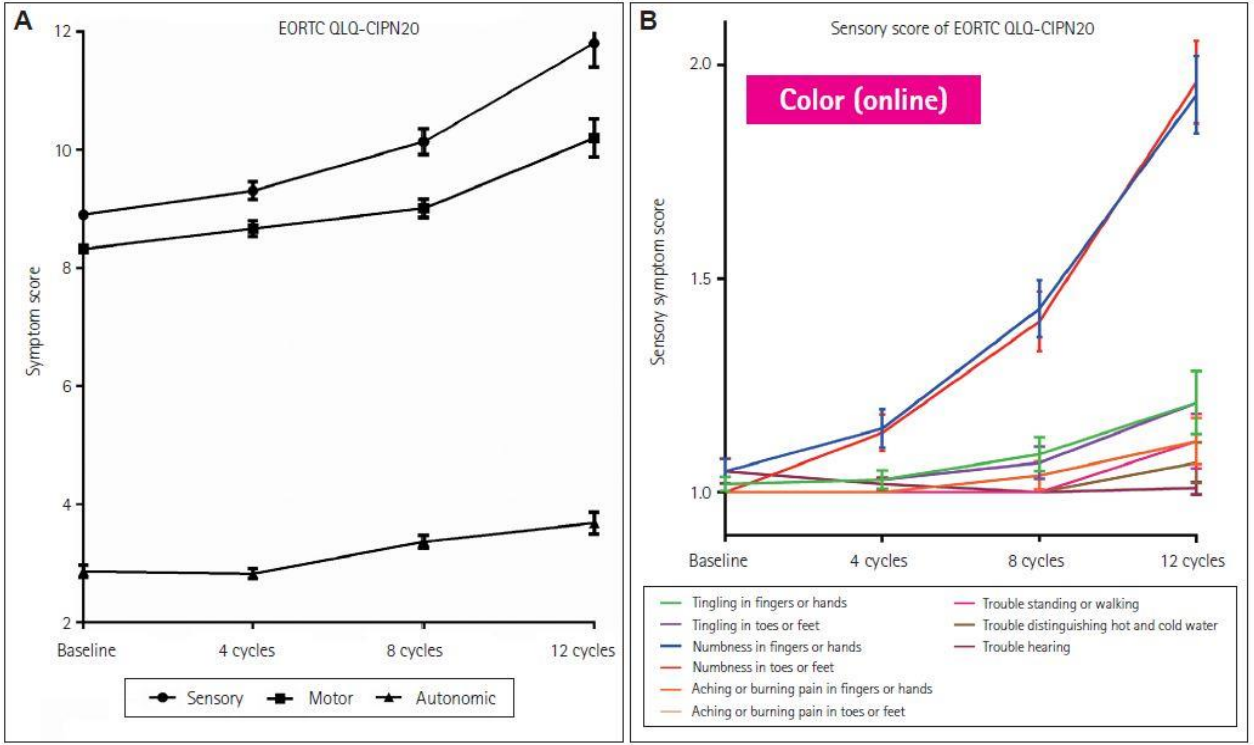
- Sixty-nine patients were prospectively followed prior to starting chemotherapy and after 4, 8, and 12 cycles of chemotherapy.
- Thirty-six patients completed the follow-up at 1 year after the end of chemotherapy.



Kim SH et al. J Clin Neurol 2018

A Prospective Study of Chronic Oxaliplatin-Induced Neuropathy in Patients with Colon Cancer: Long-Term Outcomes and Predictors of Severe Oxaliplatin-Induced Neuropathy

- While the severity of OIPN can improve after oxaliplatin discontinuation, more than half of the patients in this study still had OIPN at 1 year after discontinuation.
- Early changes in the NCS results for sensory nerves can predict the development of severe OIPN during treatment.



Kim SH et al. J Clin Neurol 2018

Long-term neuropathy and quality of life in colorectal cancer patients treated with oxaliplatin containing adjuvant chemotherapy

- One hundred forty-four adjuvant CRC patients (all 72 CAPOX cases and 72 matched FOLFOX controls) were analyzed regarding oxaliplatin induced sensory neuropathy, which was graded according to NCI-CTCAEv3.0.
- Ninety-two long-term survivors responded to the QOL (EORTC QLQ-C30) and Chemotherapy-Induced Peripheral Neuropathy (EORTC CIPN20) questionnaires and were interviewed regarding long-term neuropathy.
- Acute neurotoxicity was present in 94% (136/144) during adjuvant therapy and there was a significant association between acute neurotoxicity and long-term neuropathy ($p < .001$).
- Long-term neuropathy was present in 69% (grade 1/2/3/4 in 36/24/8/1%) at median 4.2 years.
- There were no differences in acute neurotoxicity, long-term neuropathy, or in QOL between CAPOX and FOLFOX treated.

Soveri LM et al. Acta Oncol 2019

Chemotherapie- induzierte Polyneuropathie

Konsensbasierte Empfehlung

Eine Untersuchung des neurologischen Status soll vor Einleitung einer potentiell neurotoxischen Tumortherapie zur Erhebung des Ausgangsbefundes und Identifizierung von Risikopatienten erfolgen.

Vor jedem Zyklus soll eine genaue Anamnese unter besonderer Berücksichtigung möglicher Neurotoxizitäten, ggf. auch eine Wiederholung des Neuro-Status, erfolgen.

Konsensbasiertes Statement

Durch die Erfassung der Patient-related Outcomes in Ergänzung zur Anamnese und klinischen Untersuchung kann die Rate der frühzeitig diagnostizierten Chemotherapie induzierten Polyneuropathie erhöht werden.

Chemotherapy-Induced Peripheral Neuropathy in Long-term Survivors of Childhood Cancer: Clinical, Neurophysiological, Functional, and Patient-Reported Outcomes

- 121 childhood cancer survivors were included in this cross-sectional observational study.
- The cohort underwent neurotoxicity assessments at a median (range) age of 16 (7-47) years, a median (range) 8.5 (1.5-29) years after treatment completion.
- Vinca alkaloids and platinum compounds were the main neurotoxic agents.
- Clinical abnormalities consistent with peripheral neuropathy were common, seen in 53%.
- Functional deficits were seen in manual dexterity, distal sensation, and balance.
- Patient-reported outcomes demonstrating reduction in global quality of life and physical functioning were associated with the Total Neuropathy Score.
- Cisplatin produced long-term neurotoxicity more frequently than vinca alkaloids.

Kandula T et al. JAMA 2018

The prevalence and pattern of chemotherapy-induced peripheral neuropathy among women with breast cancer receiving care in a large community oncology practice

- 126 women with mean age 56.7 years (SD 11.8) previously treated with taxane-based chemotherapy for early-stage breast cancer.
- The mean time since last taxane chemotherapy cycle was 144.9 weeks.
- 73.0% reported having CIPN.
- CIPN symptom severity was negatively correlated with global health status/QOL and physical functioning. It was not associated with age, body mass index, diabetes, or cumulative taxane dosage, but was greater for Black or African American women (e.g., sensory, $p < 0.002$).
- CIPN sensory impairment was marginally greater for patients treated with paclitaxel compared to docetaxel ($p < 0.064$).

Simon NB et al. Qual Life Res 2017

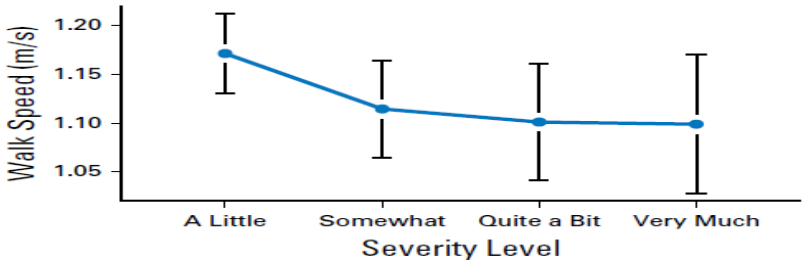
Falls, Functioning, and Disability Among Women With Persistent Symptoms of Chemotherapy-Induced Peripheral Neuropathy

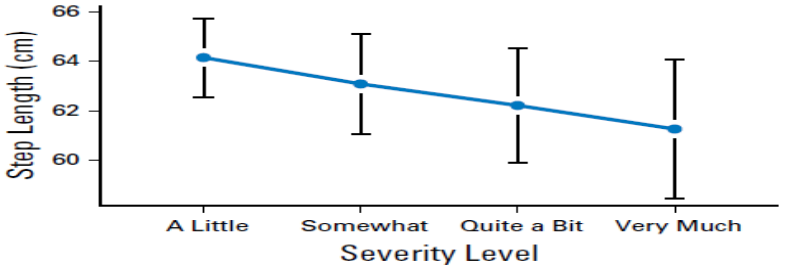
- A secondary data analysis of 512 women cancer survivors (age, 62 ± 6 years; time since diagnosis, 5.8 ± 4.1 years) categorized and compared women self-reporting symptoms of CIPN (CIPN+) with asymptomatic women (CIPN-).
- After an average of 6 years after treatment, 47% of women still reported symptoms of CIPN.
- CIPN+ had significantly worse self-report and objectively measured function than did CIPN-.
- CIPN+ reported significantly more disability and 1.8 times the risk of falls compared with CIPN- ($P < .0001$).
- Increasing symptom severity was linearly associated with worsening function, increasing disability, and higher fall risk (all $P < .05$).

Winters-Stone KM et al. J Clin Oncol 2017

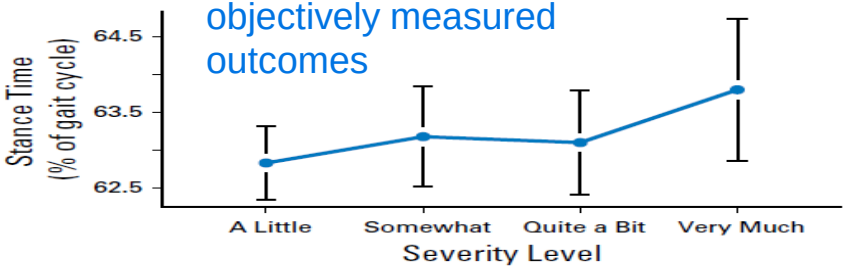
Falls, Functioning, and Disability Among Women With Persistent Symptoms of Chemotherapy-Induced Peripheral Neuropathy

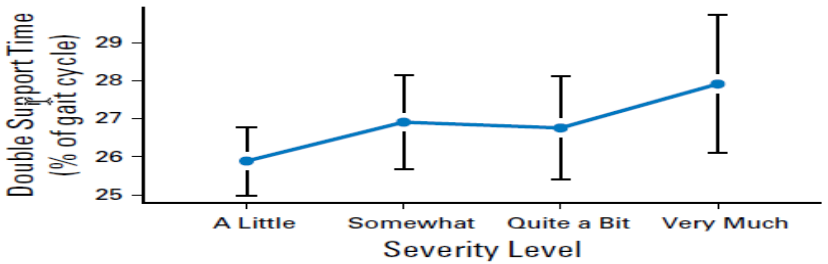
Winters-Stone KM et al. J Clin Oncol 2017

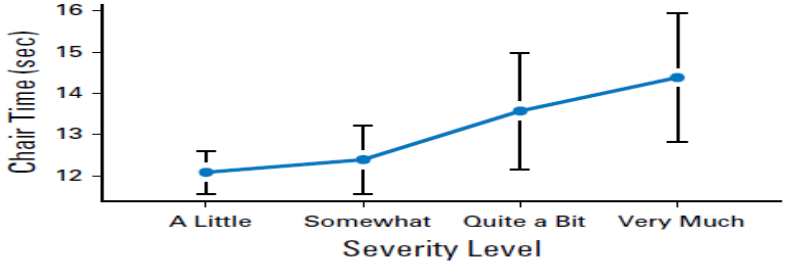


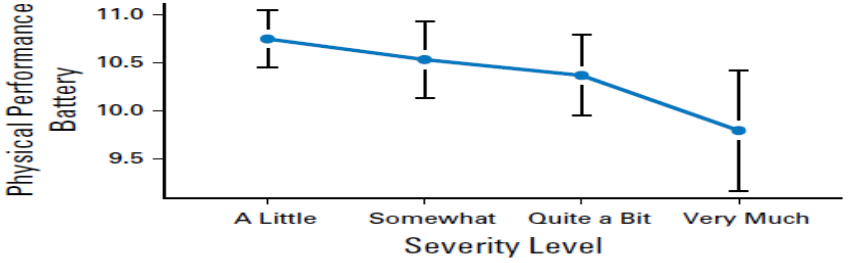


objectively measured outcomes



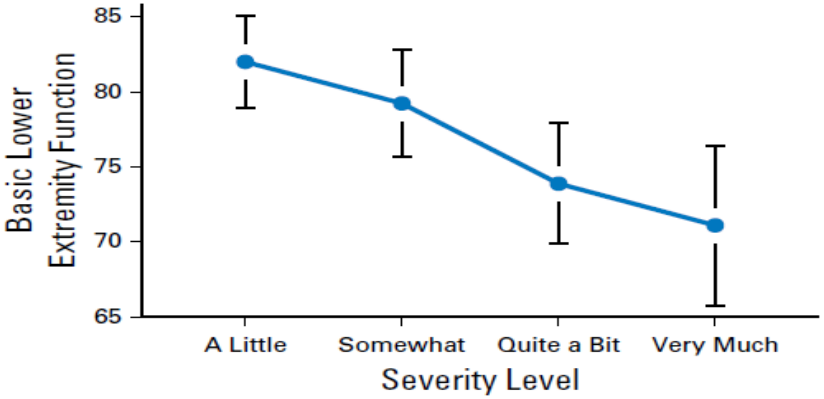


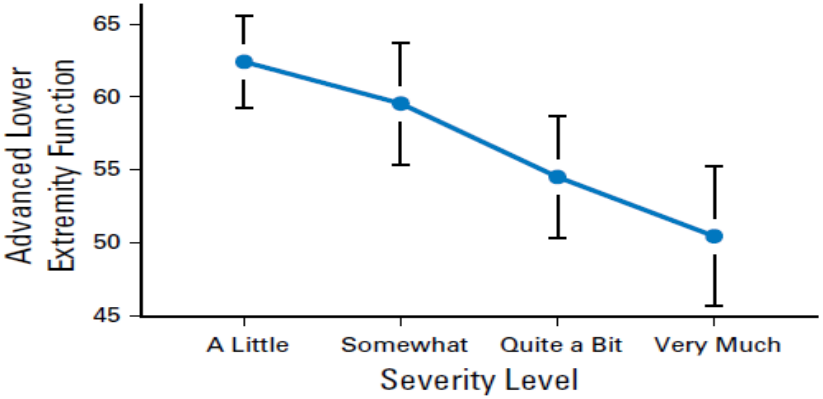




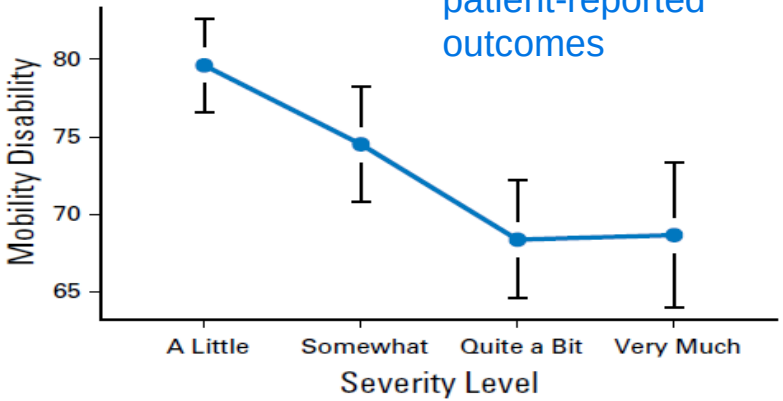
Falls, Functioning, and Disability Among Women With Persistent Symptoms of Chemotherapy-Induced Peripheral Neuropathy

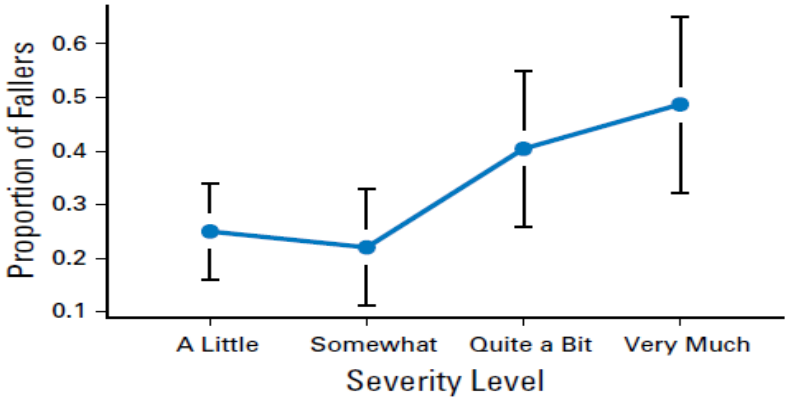
Winters-Stone KM et al. J Clin Oncol 2017



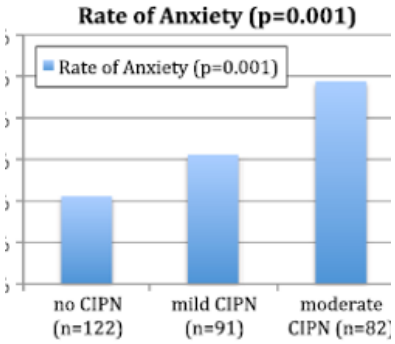


patient-reported outcomes

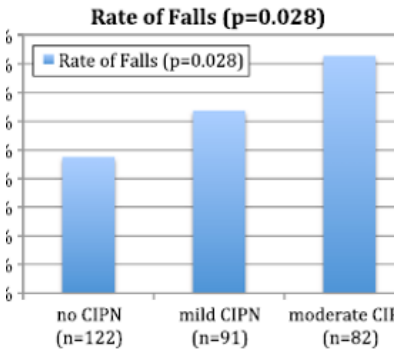




Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk

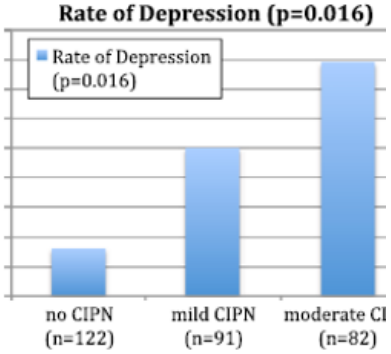


- Postmenopausal women with a history of stage I-III breast cancer who received taxane-based chemotherapy.

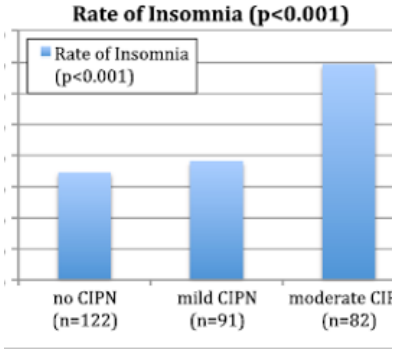


- Among 296 participants, 173 (58.4 %) reported CIPN symptoms, 91 (30.7 %) rated their symptoms as mild, and 82 (27.7 %) rated them moderate to severe.

- Patients with CIPN reported greater insomnia severity, anxiety, and depression than those without (all $p < 0.05$).



- Severity of CIPN was associated with higher rates of falls.
- Obesity was associated with increased risk of CIPN.



Bao T et al. Breast Cancer Res Treat 2016

A longitudinal examination of associations between age and chemotherapy-induced peripheral neuropathy in patients with gynecologic cancer

- Gynecologic cancer patients (n = 90) treated with cytoxic chemotherapy reported their CIPN symptoms via the EORTC-CIPN20 three times during active treatment and at 6 and 12 months post-treatment.
- Older and younger patients reported similar increases in CIPN during the active treatment phase. However, older patients did not recover from CIPN after treatment completion, whereas younger patients exhibited significant declines in CIPN symptoms post-treatment.
- No age differences were observed in the presence of sensory neuropathy and pain; neuropathy-related treatment delays, changes in chemotherapy dose, regimen, or discontinuations; or falls (all p-values > 0.05).
- Older adults are at higher risk for chronic CIPN.

Bulls HW et al. Gynecol Oncol 2018

The Long-Term Impact of Neurofeedback on Symptom Burden and Interference in Patients With Chronic Chemotherapy-Induced Neuropathy: Analysis of a Randomized Controlled Trial

- Seventy-one cancer survivors (mean age 62.5; 87% females) with CIPN were randomized to NFB or to a waitlist control (WLC) group.
- The NFB group underwent 20 sessions of NFB where rewards were given for voluntary changes in electroencephalography.
- At the end of treatment, 30 in the NFB group and 32 in the WLC group completed assessments; at four months, 23 in the NFB group and 28 in the WLC completed assessments.
- The NFB group had greater improvements in worst pain (primary outcome) and other symptoms such as numbness, cancer-related symptom severity, symptom interference, physical functioning, general health, and fatigue compared with the WLC group at the end of treatment and four months (all $P < 0.05$).
- NFB appears to result in long-term reduction in multiple CIPN symptoms and improved postchemotherapy QOL and fatigue.

Prinsloo S et al. J Pain Symptom Manage 2018

Neuropathy as persistent disorder following tumor treatment

- THE "bench-side" (Pharmacogenomics) might benefit from and should cooperate with THE "bed-side" (Clinimetrics), in order to make genetic profiling effective if applied to CIPN.
  Alberti P, Cavaletti G. Methods Mol Biol 2014
- Recent identification of individual genetic variations has advanced understanding of pathomechanisms and may direct future treatment approaches.
  Kandula T et al. Cancer Treat Rev 2016
- Clinical decision-making should be based on a detailed understanding of individual impairments and associated gait abnormalities.
  Wright MJ et al. Gait Posture 2017
- The consensus 'gold standard' clinical assessment remains to be established.
  McCrary JM et al. Support Care Cancer 2017
- The long-term reversibility of these CIPNs remains questionable, notably in the case of platinum-based anticancer drugs and taxanes.
  Kerckhove N et al. Frontiers in Pharmacology 2017

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Neuropathy as persistent disorder following tumor treatment

- A total of 36 papers published from 2010 to 2018 were reviewed.
- Most of these studies describe chronic neurotoxicity due to oxaliplatin or taxane treatment.
- The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), the Total Neuropathy Score, clinical version (TNSc) and the European Organisation for Research and Treatment of Cancer (EORTC) CIPN-related QOL Questionnaire (QLQ-CIPN20) were preferentially used.
- In patients with colorectal cancer, oxaliplatin-induced neuropathy was found in 84% at a median follow-up of 25 months and in 69% at a median follow-up of 4.2 years after oxaliplatin discontinuation.
- Diabetic patients had a shorter time to develop oxaliplatin-induced paresthesia compared to non-diabetic patients.
- Among patients with breast cancer, CIPN was prevalent in 73% after a mean time of 144.9 weeks since last taxane treatment cycle, and in 47% after an average of 6 years following chemotherapy.
- There is a correlation between CIPN severity and rate of falls.

Susanne Koeppen

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Neuropathie als anhaltende Störung bei Tumortherapie Management

- Prävention durch Identifikation von CIPN-Risikofaktoren
- Individuelle Modifikation der Chemotherapie-Regime
- CIPN-Risiko-Management basierend auf pharmakogenomischen Daten
- Frühdiagnose der CIPN durch neurologisches Monitoring
- Dosismodifikation zur Vermeidung einer höhergradigen CIPN
- Differentialdiagnostische Abklärung persistierender neuropathischer Beschwerden
- Nicht-medikamentöse Behandlung der CIPN bereits unter Chemotherapie
- Symptomatische medikamentöse Therapie der CIPN
- Konsequente Behandlung der Begleiterkrankungen
- Supportive Therapiemaßnahmen

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Danke für Ihre Aufmerksamkeit! Ich freue mich auf Ihre Fragen und Kommentare

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