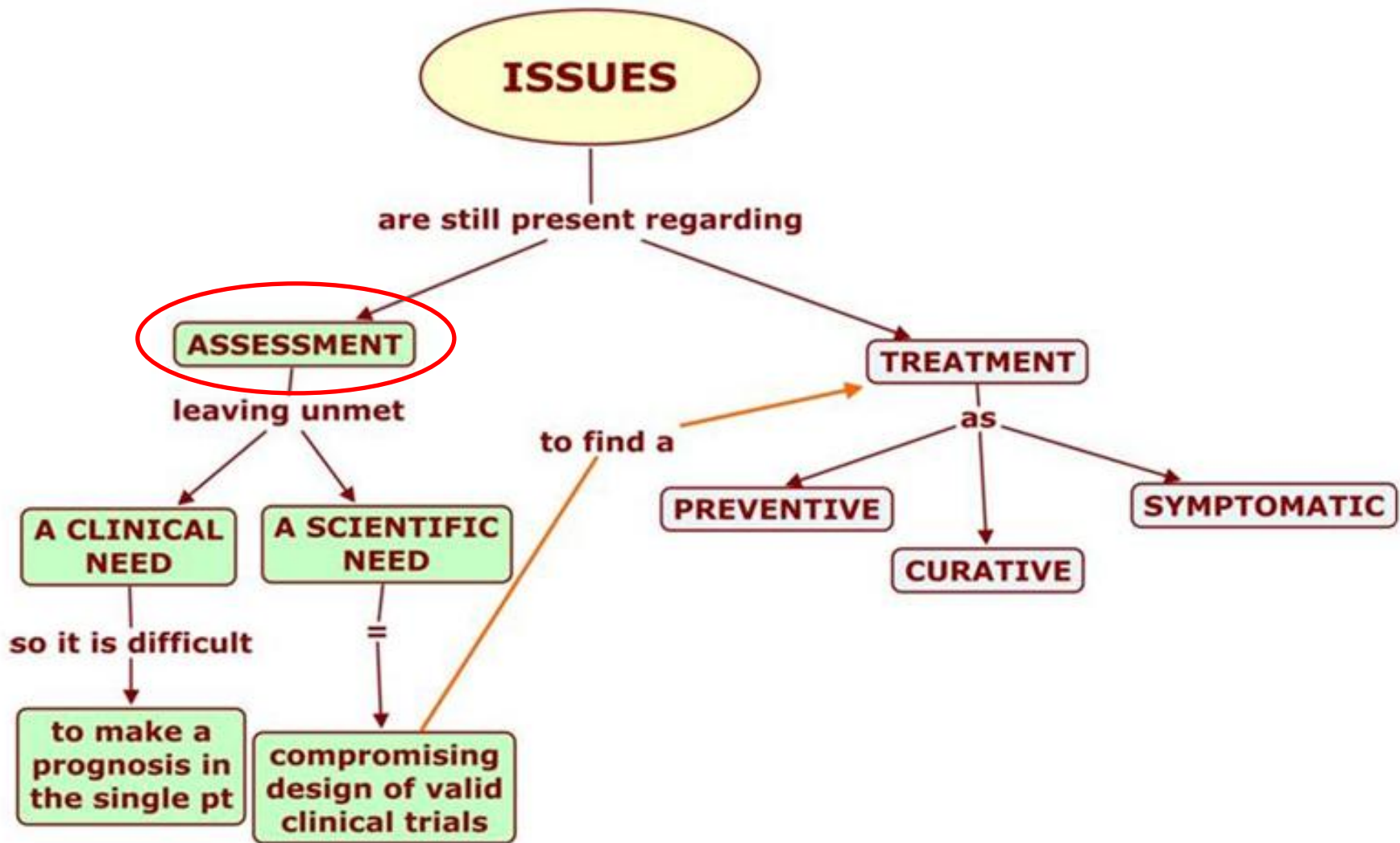


# **La modalità di rilevazione e gradazione della tossicità neurologica**

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# Neurotossicità: problemi irrisolti



# Scale di gradazione della neurotossicità (1)

	0	1	2	3	4	
<b>WHO</b>	Neuropathy – motor	Normal	Subjective weakness	Mild objective weakness	Marked weakness	Paralysis
	Neuropathy – sensor	Normal	Decreased tendon reflexes or paraesthesias	Severe paresthesias	Intolerable paresthesias	-
<b>ECOG</b>	Neuropathy – motor	Normal	Subjective weakness	Mild objective weakness	Severe weakness	Respiratory dysfunction secondary to weakness, paralysis confining patient to bed/wheelchair
	Neuropathy – sensor	Normal	Decreased tendon reflexes or mild paraesthesias	Absent deep tendon reflexes, severe paresthesias	Disabling sensory loss, severe neuropathic pain	-
	Neuropathy – autonomic	Normal	Mild constipation	Severe constipation	Bladder dysfunction, obstipation	Obstipation requiring surgery

# Scale di gradazione della neurotossicità (2)

		0	1	2	3	4	
<b>Ajani</b>	Neuropathy – motor	Normal	Mild or transient muscle weakness	Persistent moderate weakness but ambulatory	Unable to ambulate	Complete paralysis	
	Neuropathy – sensor	Normal	Paresthesias. Decreased deep tendon reflexes	Mild objective abnormality, absence of deep tendon reflexes, mild to moderate functional abnormality	Severe paraesthesias, moderate objective abnormalities, severe functional abnormalities	Complete sensory loss, loss of function	
		0	1	2	3	4	5
<b>NCI-CTCAE 4.0</b>	Neuropathy – motor	Normal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening symptoms; urgent intervention indicated	Death
	Neuropathy – sensor	Normal	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening symptoms; urgent intervention indicated	Death

# Scale di gradazione a confronto

Distribution of grading scores per observer and scale:

Scale	Grade 0	Grade 1	Grade 2	Grade 3
<b>WHO</b>				
Observer 1	1	30	6	0
Observer 2	0	27	8	2
<b>ECOG</b>				
Observer 1	1	14	17	5
Observer 2	0	20	15	2
<b>CTC 2.0</b>				
Observer 1	0	5	20	12
Observer 2	1	16	15	5
<b>Ajani</b>				
Observer 1	1	6	29	1
Observer 2	0	20	16	1

Definitions of G3:

- *WHO*: intolerable paresthesias
- *ECOG*: disabling sensory loss
- *CTC 2.0*: severe objective sensory loss or paresthesias which interfere with functions
- *Ajani*: severe functional abnormality

Inter-observer agreement for all grades (0-4), for the dichotomy 0-2 vs 3 and interclass correlation coefficients:

Scale	Agreement 0-4 (%)	Agreement 0-2 vs 3 (%)	Exact agreement on score 3 (%)	ICC (Score 0-4)
<b>WHO</b>	83.8	94.6	0	0.55
<b>ECOG</b>	75.6	91.9	40	0.75
<b>CTC 2.0</b>	45.9	81.1	42	0.58
<b>Ajani</b>	56.7	94.6	0	0.37

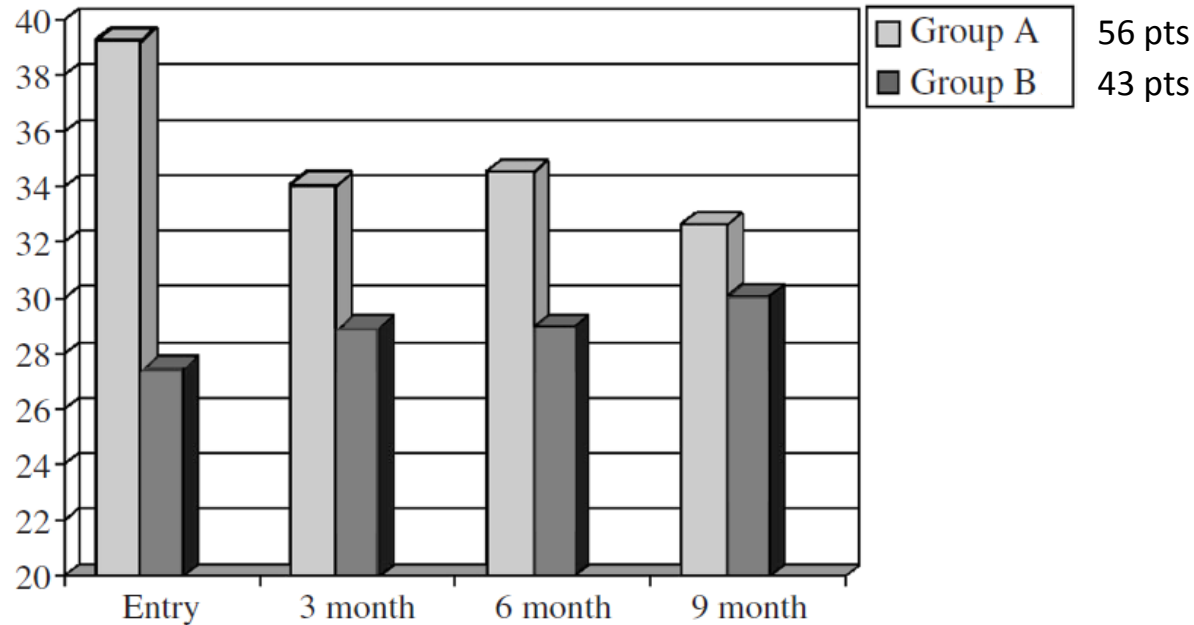
Degree of Agreement:

- *ICC*  $\leq 0.40$ : poor to fair
- *ICC* 0.41-0.60: moderate
- *ICC* 0.61-0.80: substantial
- *ICC* 0.81-1.00 almost perfect

# Questionari: FACT/GOG Ntx

Area	Item	Question
<b>Sensory</b>	Ntx1	I have numbness or tingling in my hands
	Ntx2	I have numbness or tingling in my feet
	Ntx3	I feel discomfort in my hands
	Ntx4	I feel discomfort in my feet
<b>Hearing</b>	Ntx6	I have trouble hearing
	Ntx7	I get ringing or buzzing in my ears
<b>Motor</b>	Ntx5	I have joint pain or muscle cramps
	HI12	I feel weak all over
	AN6	I have trouble walking
<b>Dysfunction</b>	Ntx8	I have trouble buttoning buttons
	Ntx9	I have trouble feeling the shape of small objects when they are in my hand

# Validazione del FACT/GOG Ntx



Time of Assessment

	Baseline	Mid course	End of chemo	3 months after chemo	6 months after chemo	9 months after chemo	12 months after chemo
Pin test	n = 56	n = 46	n = 38	n = 39	n = 19	n = 23	n = 14
Sensory	-0.52 <sup>b</sup>	-0.49 <sup>b</sup>	-0.58 <sup>b</sup>	-0.73 <sup>b</sup>	-0.51 <sup>a</sup>	-0.19	-0.73 <sup>b</sup>
Motor	-0.20	-0.56 <sup>b</sup>	-0.64 <sup>b</sup>	-0.60 <sup>b</sup>	-0.37	-0.59 <sup>b</sup>	-0.41
Autonomic	-0.49 <sup>b</sup>	-0.24	-0.43 <sup>a</sup>	-0.31	-0.15	-0.22	-0.03
Pin sensitivity	-0.57 <sup>b</sup>	-0.27	-0.27	-0.29	-0.37	-0.43 <sup>a</sup>	-0.50
Strength	-0.31 <sup>a</sup>	-0.35 <sup>a</sup>	-0.39 <sup>ab</sup>	-0.57 <sup>a</sup>	-0.63 <sup>b</sup>	-0.41	
Reflexes	-0.39 <sup>a</sup>	-0.24	-0.41 <sup>a</sup>	-0.55 <sup>b</sup>	-0.61 <sup>a</sup>	-0.56 <sup>a</sup>	-0.80 <sup>b</sup>
Case IV							
Finger (vibration)	-0.22	-0.12	-0.41 <sup>a</sup>	-0.25	-0.69 <sup>a</sup>	-0.05	-0.21
Hand (cold)	-0.06	-0.05	-0.34	-0.16	-0.38	-0.36	-0.18
Toe (vibration)	-0.08	-0.16	-0.09	-0.36 <sup>a</sup>	-0.47	-0.46 <sup>a</sup>	-0.26
Foot (cold)	-0.10	-0.10	-0.04	-0.29	-0.32	-0.12	-0.3

<sup>a</sup>*p* < 0.05; <sup>b</sup>*p* < 0.01.

# Questionari: il PNQ

## Patient Neurotoxicity Questionnaire (PNQ)<sup>®</sup>

*Taxanes, Cisplatin and Carboplatin*

Item 1.

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
A	B	C	D*	E*
I have no numbness, pain or tingling in my hands or feet.	I have mild tingling, pain or numbness in my hands or feet. This does not interfere with my activities of daily living.	I have moderate tingling, pain or numbness in my hands or feet. This does not interfere with my activities of daily living.	I have moderate to severe tingling, pain or numbness in my hands or feet. This interferes with my activities of daily living.	I have severe tingling, pain or numbness in my hands or feet. It completely prevents me from doing most activities of daily living.

Item 2.

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
A	B	C	D*	E*
I have no weakness in my arms or legs	I have a mild weakness in my arms or legs. This does not interfere with my activities of daily living.	I have moderate weakness in my arms or legs. This does not interfere with my activities of daily living.	I have moderate to severe weakness in my arms or legs. This interferes with my activities of daily living.	I have severe weakness in my arms or legs. It completely prevents me from doing most activities of daily living.

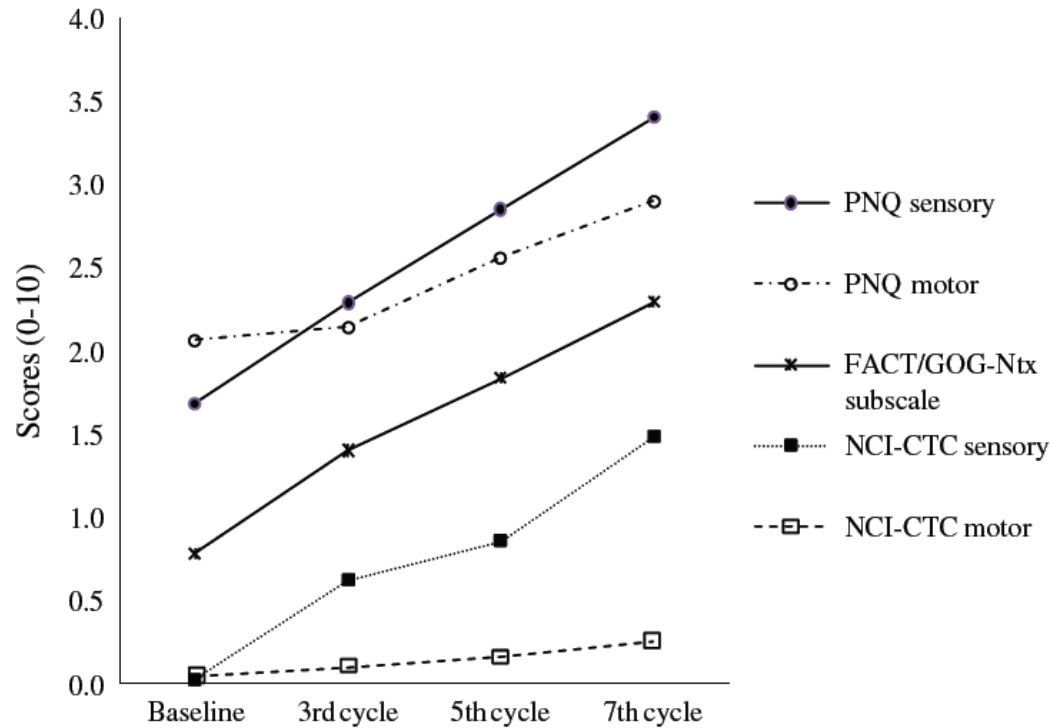
\* Please indicate by placing an X in the box or writing in the space provided which activity or activities have been interfered with as a result of therapy.

My ability to:

<input type="checkbox"/> Button clothes	<input type="checkbox"/> Open doors	<input type="checkbox"/> Fasten buckles	<input type="checkbox"/> Write	<input type="checkbox"/> Sew
<input type="checkbox"/> Use a knife	<input type="checkbox"/> Put in or remove contact lenses	<input type="checkbox"/> Sleep	<input type="checkbox"/> Walk	<input type="checkbox"/> Work
<input type="checkbox"/> Use a fork	<input type="checkbox"/> Dial or use telephone	<input type="checkbox"/> Climb stairs	<input type="checkbox"/> Put on jewelry	<input type="checkbox"/> Tie shoes
<input type="checkbox"/> Use a spoon	<input type="checkbox"/> Operation of remote control	<input type="checkbox"/> Type on a keyboard	<input type="checkbox"/> Knit	<input type="checkbox"/> Drive
	<input type="checkbox"/> Other eating utensils, etc	<input type="checkbox"/> Perform activities of importance to me, specify:		



# Validazione del PNQ



Kappa=0.16	NCI-CTC Sensory					Kappa=0.02	NCI-CTC Motor				
	0	1	2	3	4		0	1	2	3	4
PNQ Sensory <sup>a</sup>						PNQ Motor <sup>a</sup>					
A	489	38	0	0	0	A	492	5	1	0	0
B	432	252	4	0	0	B	701	37	2	0	0
C	113	171	5	0	0	C	231	17	3	0	0
D	44	66	11	3	1	D	62	10	5	1	0
E	9	1	0	0	0	E	9	0	0	0	0

# Questionari: EORTC QLQ-CIPN20

## Contents of the EORTC QLQ-CIPN20

---

### *Sensory scale (9 items)*

Tingling

Numbness

Pain

Instability when walking or standing

Distinguishing temperature

Hearing

### *Motor scale (8 items)*

Cramps

Writing

Manipulating small objects

Weakness

### *Autonomic scale (3 items)*

Vision

Dizziness after changing position

Erection disorder

---

# EORTC QLQ-CIPN20

DURING THE PAST WEEK	Not at all	A little	Quite a bit	Very much
31. Did you have tingling fingers or hands	1	2	3	4
32. Did you have tingling toes or feet?	1	2	3	4
33. Did you have numbness in your fingers or hands?	1	2	3	4
34. Did you have numbness in your toes or feet?	1	2	3	4
35. Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
36. Did you have shooting or burning pain in your toes or feet?	1	2	3	4
37. Did you have cramp in your hands?	1	2	3	4
38. Did you have cramp in your feet?	1	2	3	4
39. Did you have problems standing or walking because of a difficulty in feeling the ground under your feet?	1	2	3	4
40. Did you have difficulty in distinguishing between hot and cold water?	1	2	3	4
41. Did you have a problem holding a pen, which made writing difficult?	1	2	3	4
42. Did you have difficulty in manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4
43. Did you have difficulty in opening a jar or bottle because of weakness in your hand?	1	2	3	4
44. Did you have difficulty because your feet dropped downwards?	1	2	3	4
45. Did you have difficulty in climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4
46. Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
47. Did you have blurred vision?	1	2	3	4
48. Did you have difficulty in hearing?	1	2	3	4
<b>Please, answer the following question, only if you drive a car:</b>	1	2	3	4
49. Did you have difficulty using pedals?	1	2	3	4
<b>Please, answer the following question, only if you are a man:</b>	1	2	3	4
50. Did you have difficulty in having or maintaining an erection?	1	2	3	4

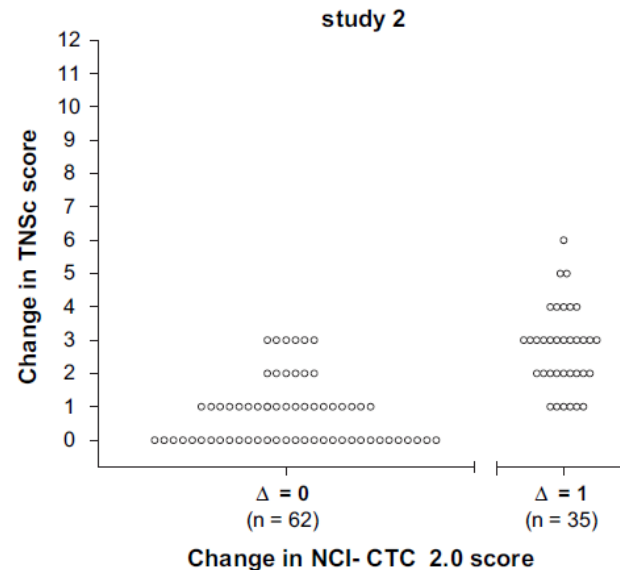
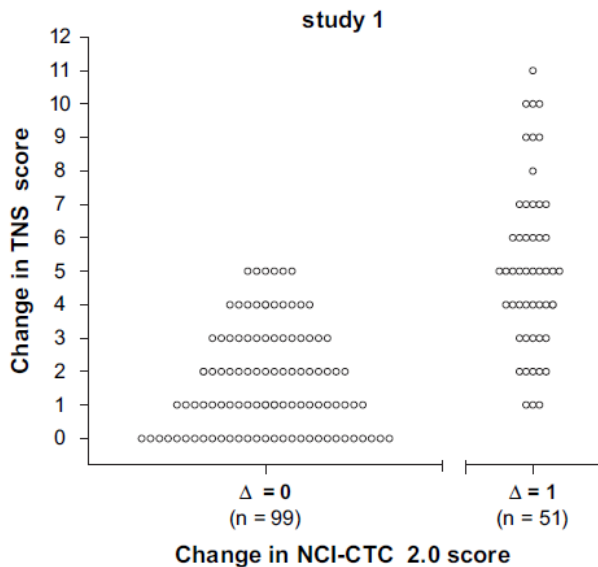
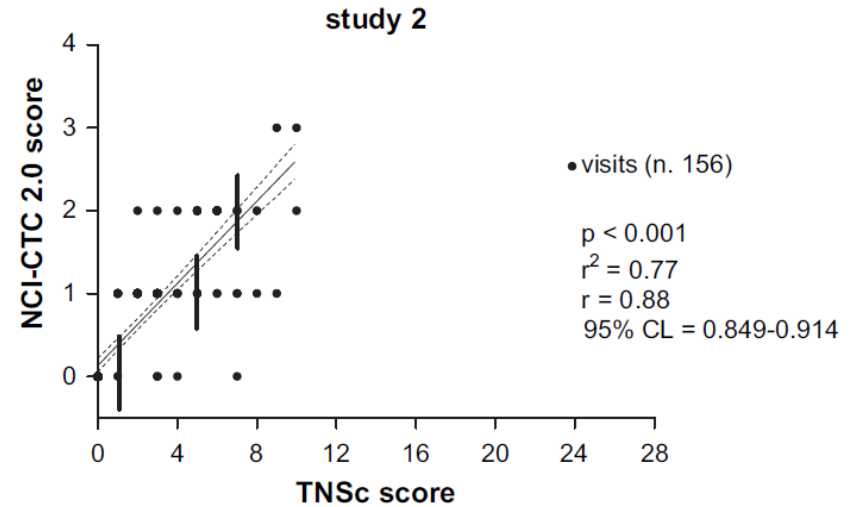
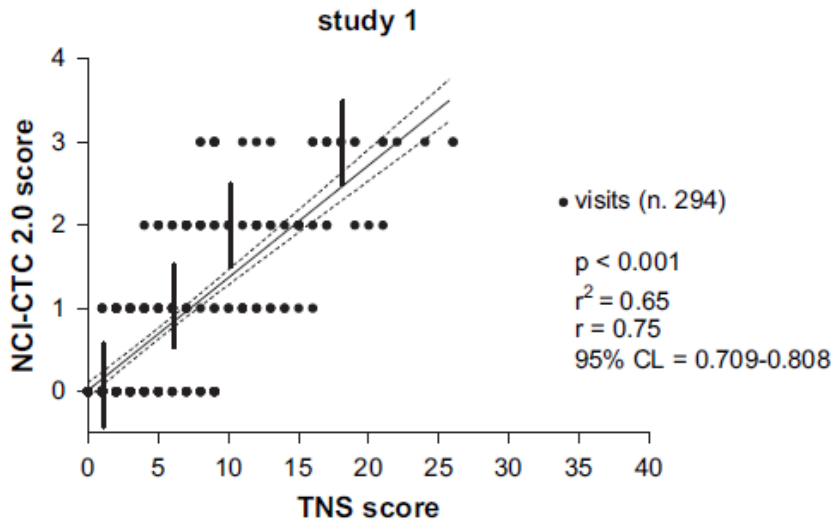
# Valutazioni composite: TNS

Parameter	SCORE				
	0	1	2	3	4
Sensory symptoms	None	Symptoms limited to finger or toes	Symptoms extends to ankle or wrist	Symptoms extends to knee or elbow	Symptoms above knees or elbows, or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis
Autonomics symptoms	0	1	2	3	4 o 5
Pin sensibility	Normal	Reduced in finger/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Vibration sensibility	Normal	Reduced in finger/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflex	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
Vibration sensation (QST vibration)	Normal to 125% of ULN	126–150% of ULN	151–200% of ULN	201–300% of ULN	>300% of ULN
<u>Sural amplitude</u>	Normal/reduced to <5% of LLN	76–95% of LLN	51–75% of LLN	26–50% of LLN	0–25% of LLN
<u>Peroneal amplitude</u>	Normal/reduced to <5% of LLN	76–95% of LLN	51–75% of LLN	26–50% of LLN	0–25% of LLN

QST = Quantitative Sensory Test; ULN = Upper Limit of Normal; LLN = Lower Limit of Normal

Note: In addition to the TNSc, parameters written in italics are used only in full-length TNS, underlined ones in TNSr.

# Validazione del TNS e confronto con NCI-CTC



# Uno studio di fattibilità con biotesiometro



- Esercita una vibrazione di intensità variabile, a pressione tarata
- Viene applicato sulla falange distale del I dito del piede e sul malleolo esterno

# Caratteristiche dei pazienti

	N (%)
<b>Pazienti</b>	37 (100)
<b>Sesso</b>	
Maschi	9 (25)
Femmine	28 (75)
<b>Età</b>	
Mediana in anni	62
<b>Farmaci</b>	
Taxano	21 (57)
Cisplatino	3 (8)
Oxaliplatino	5 (13)
Carboplatino	1 (3)
Platino+Taxano	5 (13)
Taxano+Alcaloide della Vinca	2 (5)

Mesi dall'ultima terapia	Taxano	Platino	Platino + Taxano	Taxano + Vinca-Alc.	Tot.
Terapia in corso	13	2	3	2	20
1-6	4	5	-		9
7-12	1	1	1		3
>12	3	1	1		5

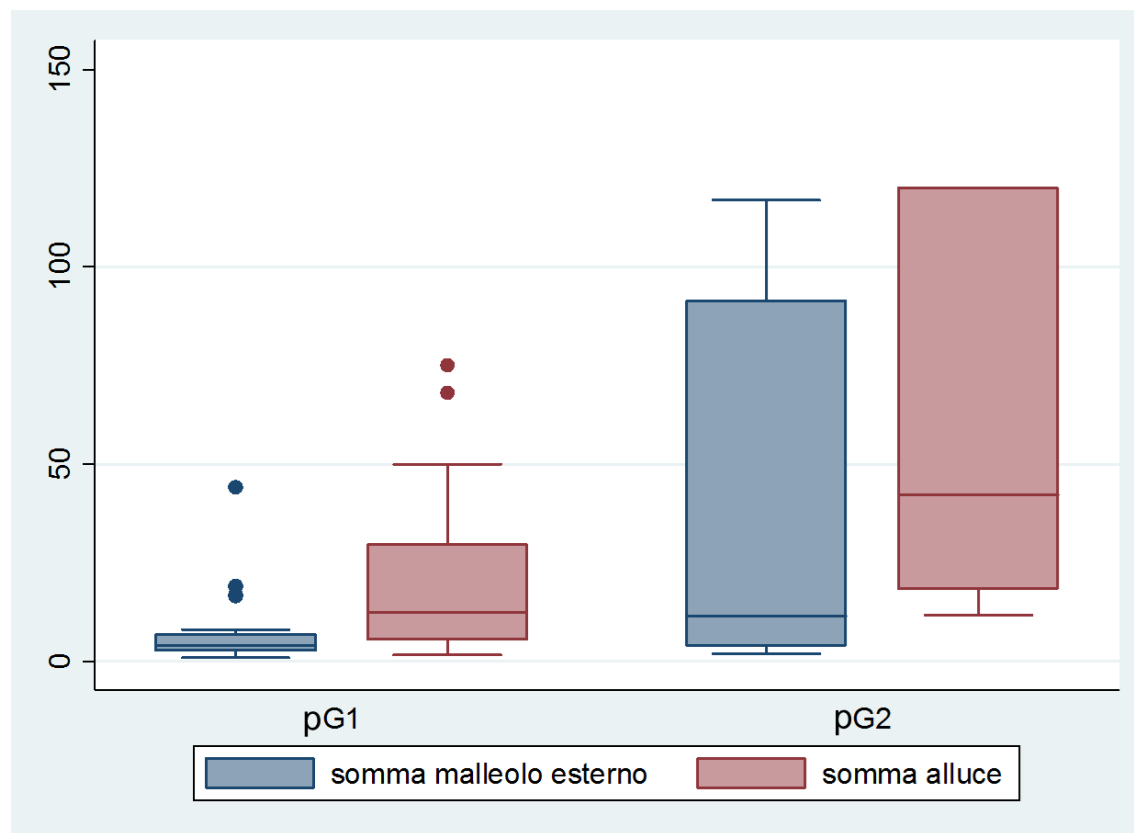
# Questionari

somma pnq	somma ntx																
	3	4	6	7	8	9	10	11	12	14	15	16	17	19	21	25	28
1		1			1												
2			5	2	4	1		1		1							
3	1	1						1	1		1						
4			1		1		1	1	1				3				
5										1			2				
6														1	1	1	
7																	1

somma pnq	gruppo ntx			
	ntx<10	10<ntx<15	ntx>15	
1	2			<b>pG1</b>
2	12	2		
3	2	3		
4	2	3	3	<b>pG2</b>
5		2	2	
6			3	
7			1	

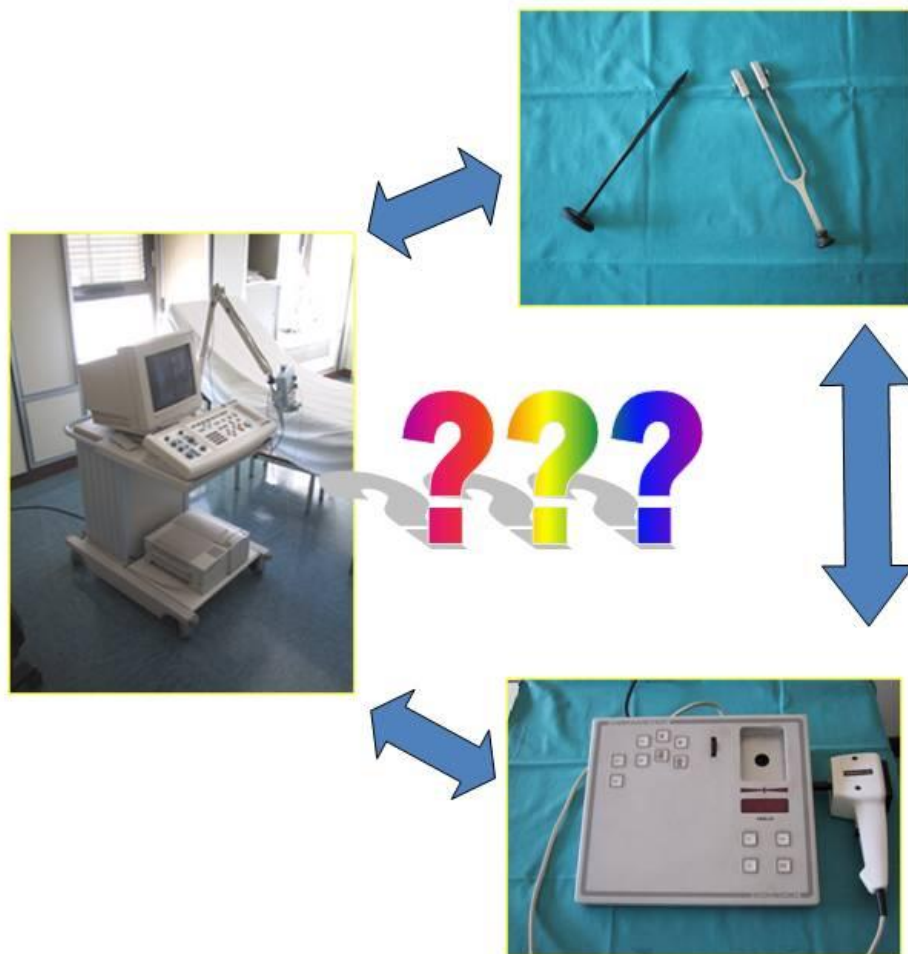


# Correlazione tra biotesiometria e questionari



	Valori biotesiometria malleolo esterno (Volts)			Valori biotesiometria alluce (Volts)		
	Mediana	IQR	$p$	Mediana	IQR	$p$
pG1	4.0	2.7-6.9	0.023	12.4	5.4-29.5	0.003
pG2	11.5	4.0-91.5		42.4	18.3-120.0	

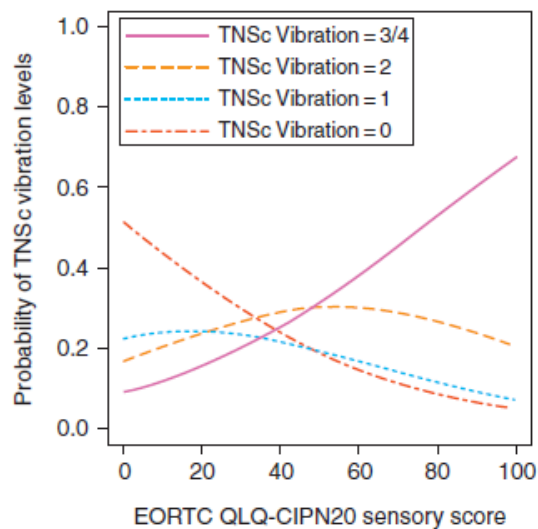
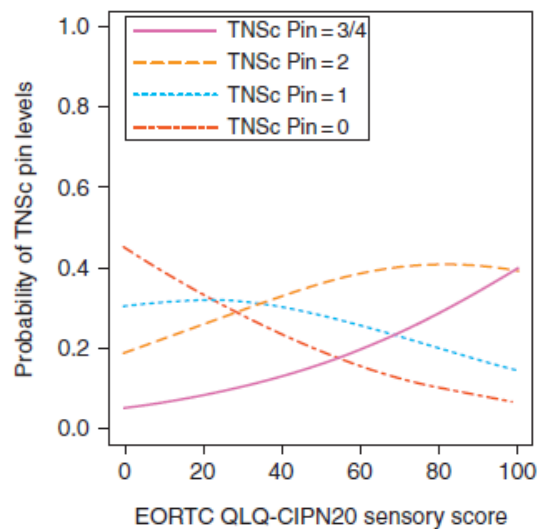
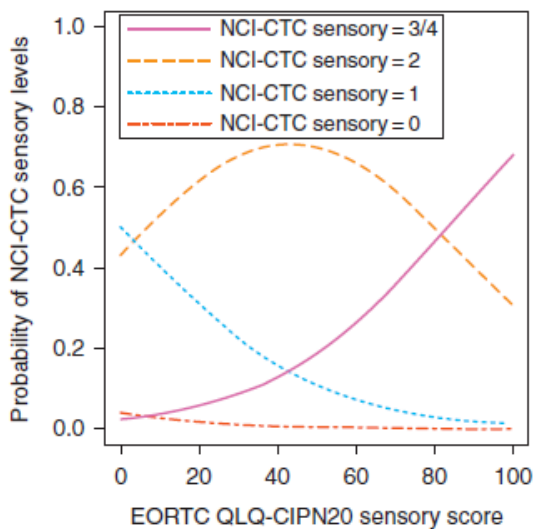
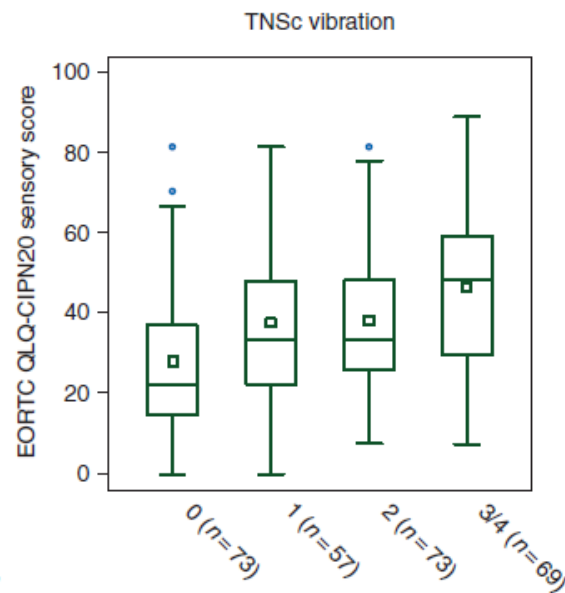
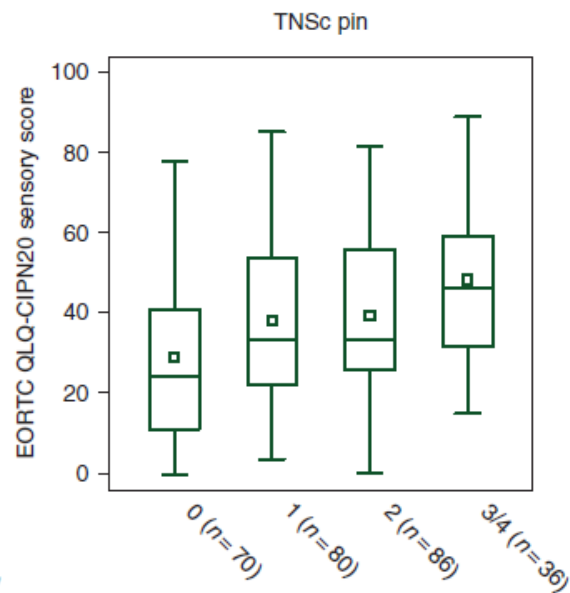
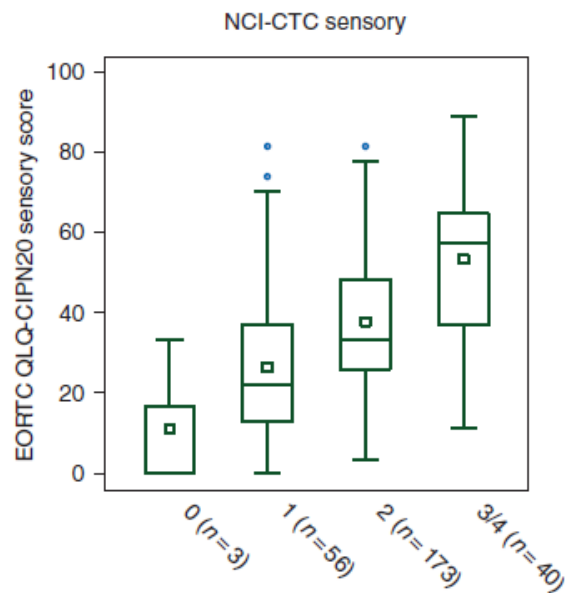
# Quale strumento usare?



## Outcome measures

- Clinical?
- Neurophysiological?
- QST?
- CTC?
- Composite scales?
- PRO?

# Due facce della stessa medaglia



# Rilevazione della neurotossicità

JOURNAL OF CLINICAL ONCOLOGY

A S C O S P E C I A L A R T I C L E

## Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

- The identification of valid and reproducible tools to assess the extent and severity of CIPN is needed to define the best end point for clinical trials
- It is well accepted that PRO measures of sensory CIPN are preferred over clinician-determined assessments
- There are several PRO CIPN measures, which have strong psychometric properties, that have been extensively studied (EORTC CIPN20 scale, FACT/GOG Ntx, TNS)
- Recent work comparing such tools does note that each have strengths and that no clear-cut winner can be declared



Ospedale  
**Sacro Cuore Don Calabria**  
PRESIDIO OSPEDALIERO ACCREDITATO - REGIONE VENETO

# GRAZIE



# PER L'ATTENZIONE