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Neuropathic Pain due to antineoplastic therapies

Venice May 26th, 2006 - EAPC Satellite Workshop

Pain in Cancer Patients

- Pure Neuropathic Pain 10%
- Nociceptive Pain 49%
- Mixed Pain 41%

(NI Cherny: Neurology 1994; 44:857)

- Pure Neuropathic Pain 5%
- Nociceptive Pain 64%
- Mixed Pain 31%

(S Grond et al.: Pain 1999; 79:15-20)

Neuropathic Cancer Pain

- Pain secondary to compression, infiltration and deafferentation produced by cancer in the peripheral or central nervous system
- Iatrogenic Pain: diagnostic/surgery procedure-related, radiation-induced (myelopathy, plexopathy, fibrosis, entrapment, ischemia) post-chemotherapy (toxic neuropathy)
- Indirect neurologic complication: paraneoplastic neuropathy, vasculitis, infections

NEUROPATHIC PAIN

Burning [unmyelinated small caliber fibers, cutaneous or visceral]

Pricking [myelinated small caliber fibers, cutaneous]

Paroxysmal, electric shock-like [mixed activation of small and large myelinated afferent fibers, cutaneous]

Deep, aching, cramping [unmyelinated and myelinated small caliber fibers, muscle]

Nerve trunk pain [nociceptive nerve pain due to activation of unmyelinated and myelinated small caliber fibers of the perinevrium]

Sensory examination

Diagnosys

- Complete history of pain
- Detailed neurologic examination
- Mapping of pain and sensory disturbancies

Neurophysiology

- **ENG - EMG**
- **EP**
- **QTT**
- **TTG**

Imaging

- **X-ray**
- **Bone-scan**
- **CT**
- **MRI**
- **P ET**

BRACHIAL PLEXOPATHY

Painful ***brachial plexopathy*** is the most common syndrome due to radiotherapy. The nerve injury may be direct, or indirect, through infarction of the brachial plexus due to thrombosis of the subclavian artery and its branches. High voltage radiation may cause acute painful, but reversible brachial plexopathy. A brachial plexopathy due to radiation fibrosis may develop after months from radiotherapy. This condition is characterised by a non-painful paresthesias and large fibers sensory loss, predominantly into an upper plexus distribution.
About 18 % of the patients complain of a pain that is usually mild.
Brachial plexopathy due to cancer recurrence, on the contrary, is often severely painful.

Marchettini P, Formaglio F, Lacerenza M.
Iatrogenic painful neuropathic complications of surgery in cancer.
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ECTOPIC ACTIVITY IN BRACHIAL PLEXOPATHY

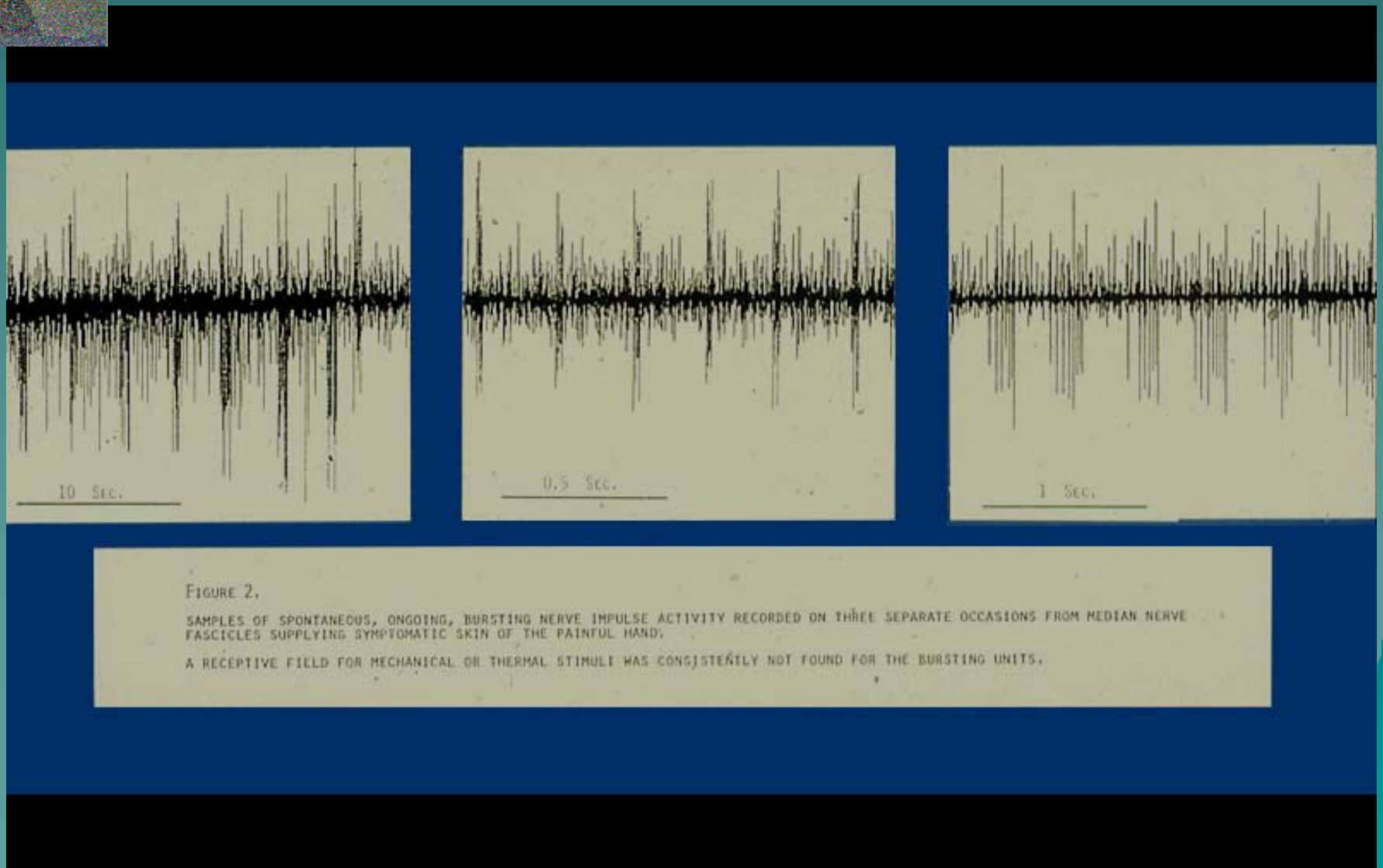


FIGURE 2.

SAMPLES OF SPONTANEOUS, ONGOING, BURSTING NERVE IMPULSE ACTIVITY RECORDED ON THREE SEPARATE OCCASIONS FROM MEDIAN NERVE FASCICLES SUPPLYING SYMPTOMATIC SKIN OF THE PAINFUL HAND.

A RECEPTIVE FIELD FOR MECHANICAL OR THERMAL STIMULI WAS CONSISTENTLY NOT FOUND FOR THE BURSTING UNITS.

Plexus radiation injury

Acute (days-wks) painful brachial plexus palsy in Hodgkin's disease

Early-delayed (4 months) reversible brachial plexus palsy, + symptoms and sometime pain, weakness and atrophy C6-T1 in breast ca RT. Similar lumbar plexopathy after WF pelvic RT

Late-delayed (=> yr), brachial or lumbar, usually painless, *myokymia*!!, slowly progression

Brachial Plexopathies

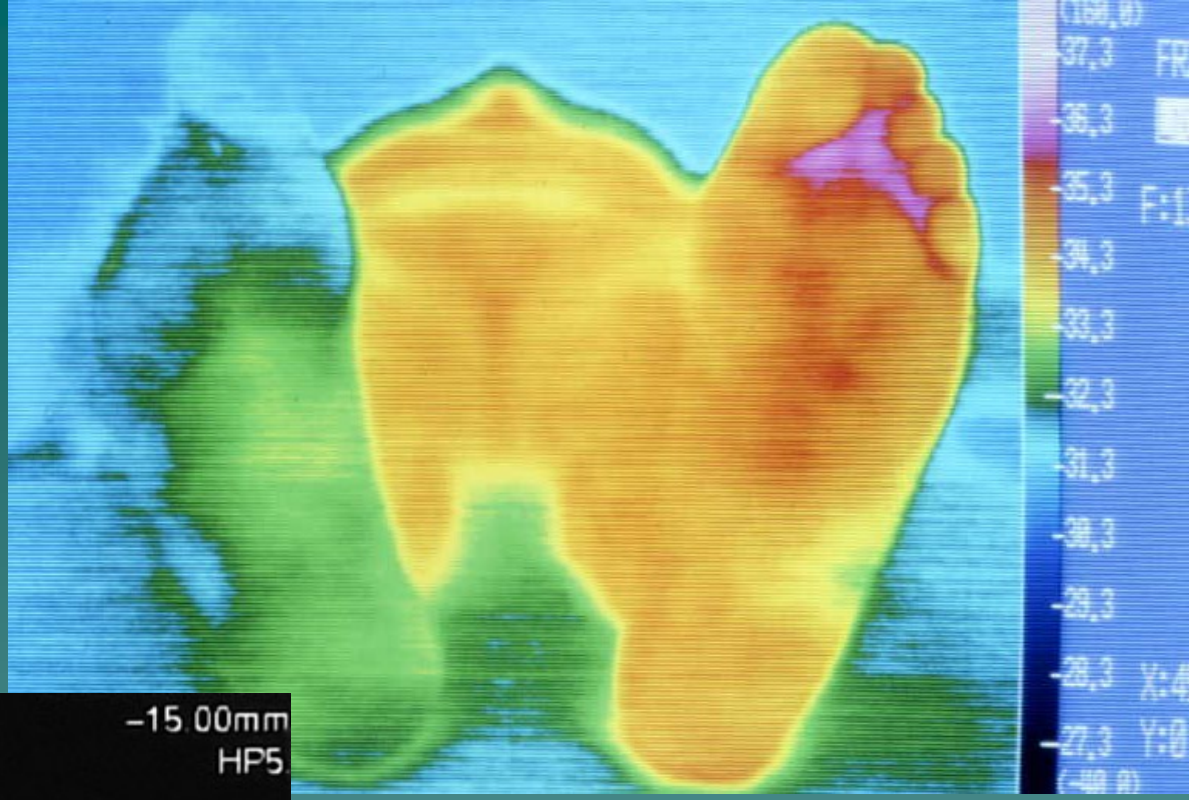
- 15% of neurologic complication of cancer
- Pain in 85%
- Lymph nodes spread from lymphoma and breast cancer upper/panplexopathy
- Direct extension from apex lung carcinomas lower plexus
- Epidural extension from adjacent vertebral disease Horner, panplexopathy, Spurling

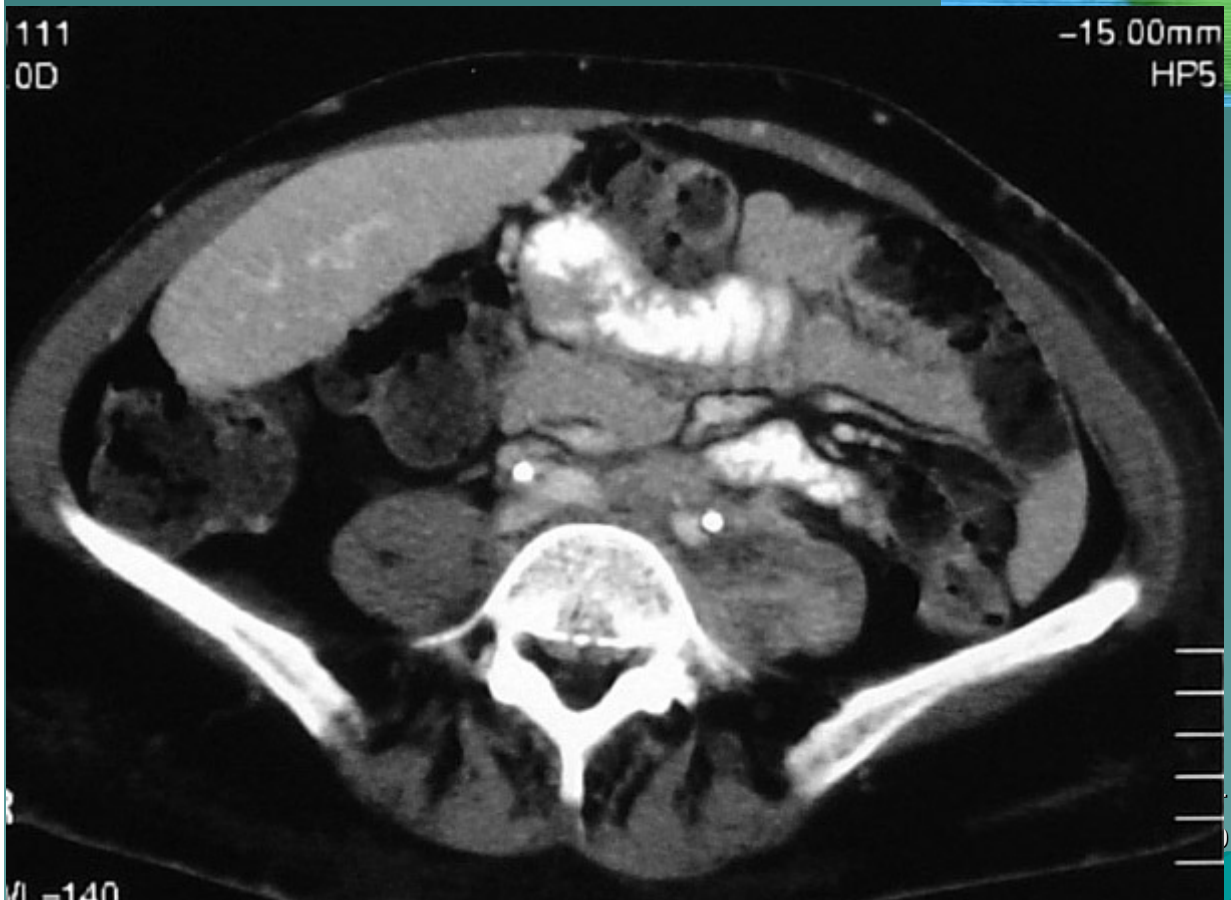
Lumbosacral Plexopathies

- Pain in almost all patients insidious, aching
- Direct extension (3/4) colorectal, sarcoma, genitou., lymphoma
- Metastatic (1/4) breast, melanoma, lung
- Upper L1-L4 (1/3)
- Lower L5-S1 (1/2) leg edema, progressive weakness
- Sacral extension or bony lesion
- Coccygeal : sphyncter loss, perineal sensory loss
- Panplexopathy (1/5) leg edema
- Reverse SLRT + upperL paravertebral and lowerL with pelvic wall extension
- Autonomic: foot thermal alterations, 10% impotence and incontinence
- EMG: (neuropathy, radiation-plexopathy, m.radiculopathy
- DD: meningeal carcinomatosis, epidural and cauda compression, retroperitoneal or iliopsoas hemorrhage or abscess.

50 yo F, Ca uterus, lumboaortic bilateral limph nodes an iliopsoas metastasis > left

6 months of aching progressive pain in the lumbar region radiating in the left groin and
Thigh exacerbated by leg movements





Left lower limb edema
Upper lumbar plexopathy
Weakness L2-L5
Allodynia L groin – thigh
Dry and hot L foot
+L reverse SLRT

Toxic Neuropathy in cancer

TAXOID: (Taxol) dose-limiting side effect, symmetrical distal >sensory PNP affecting myelinated fibers, mild tingling-burning pain, mild weakness

CISPLATIN: same features Taxol + Lhermitte, autonomic symptoms

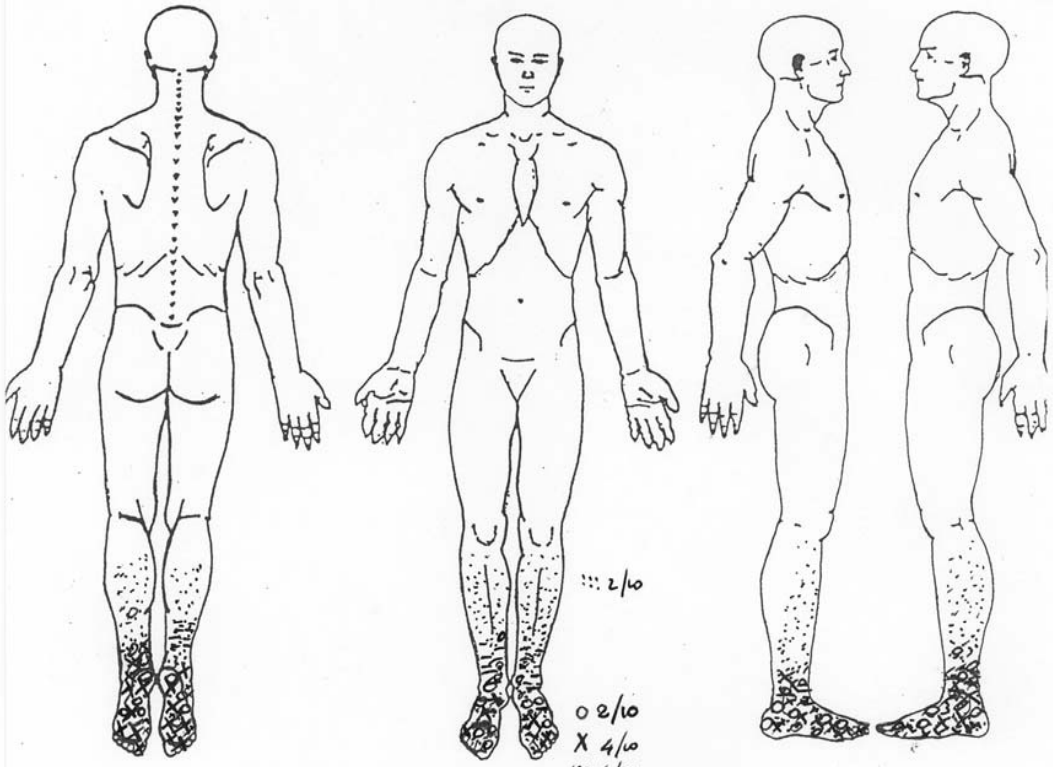
VINCRISTINE: mild S-M axonal pnp in all patients, tingling in the fingers, autonomic symptoms, muscle pain and weakness of extensors of the hand and dorsiflexion of the feet, mononeuropathy reported

SURAMIN: lenght-dependent axonal S-M pnp (30-55%) and GBS-like PRNP (15%)

ETOPOSIDE: after high-dose distal sensory axonal PNP (10%)

Axonal Polineuropathy

AREE DEI DISTURBI DI SENSIBILITA'



Dati anagrafici ♀ 65a 65Kg

Diabete mellito ID (NID) dall'età 58 insorgenza disturbi S 3a M - V -
Compenso metabolico scarso
Patologie associate ipertensione arteriosa calo ponderale

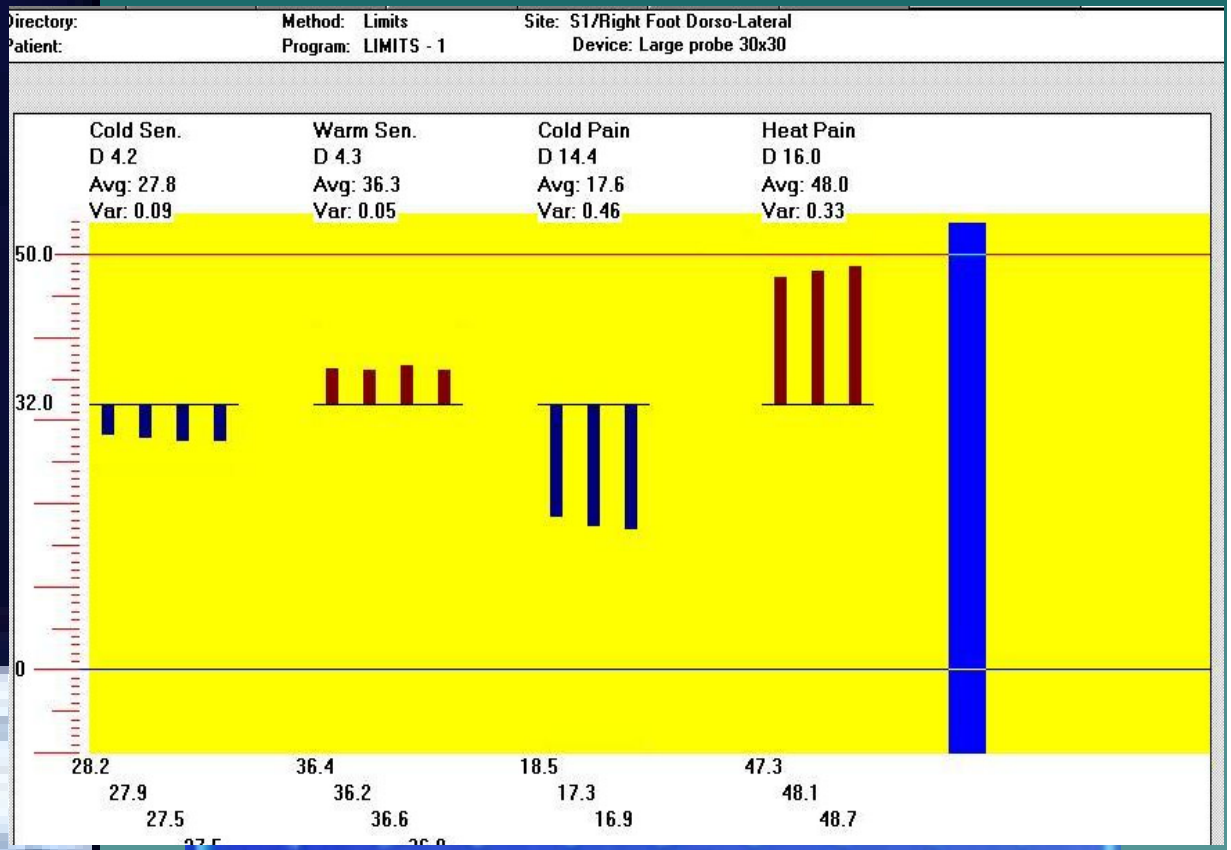
Sintomi sensitivi:	gonfiore, trazione	=	dolore urente profondo	X
	formicolii	::	dolore urente superficiale	xx
VAS globale 4/10	punture di spilli	o	dolore folgorante	
dopo > di notte	corrente elettrica		dolore lancinante	
	sensazioni termiche		dolore gravativo	

Allodinia meccanica statica ☐ dinamica S altro ☐ sede pianta piedi < dorso > dx
Iperalgesia mecc, caldo S sede piedi pianta > dorso > destra
EMG-ENG PNP demielinizzante S>M test SNA ✓
QTT lieve deficit x caldo e freddo TTG Piedi Freddi
Blocco ischemico allodinia ↓/↓

Venice Ma
Sate

Taxol-induced sensory neuropathy

Hypoesthesia to touch and vibration and cold Hyperalgesia



Chemotherapy also at times induces brachial and lumbosacral plexopathy. Subclavian or regional iliac arterial chemotherapy administration may result in an acute painful ***brachial or lumbosacral plexopathy***, sometimes irreversible. This is probably due to small vessels direct damage and thrombosis, leading to plexus infarction.

However, ***peripheral polineuropathy*** is by far the most common complication of chemotherapy. Burning pain and dysesthesia or allodynia with a stock-like distribution often arises after peripheral nerve damage due to chemotherapy.

Vinca alkaloid therapy provokes a sensory motor subacute neuropathy in almost all treated patients. The severity of nerve damage is directly proportionate to the drug dosage. Cisplatinum neuropathy becomes clinically evident with cumulative dosages of the drug and nerve and deterioration may continue for months after drug discontinuation. In addition, the widely used chemoterapic agent paclitaxel is known to provoke painful neuropathies in almost 30 % of patients.

Marchettini P, Formaglio F, Lacerenza M. *Iatrogenic painful neuropathic complications of surgery in cancer.* **Acta Anaesthesiologica Scandinavica 45/9 1090-1094, 2001.**

- **Ganglionopathy Distal sensory-motor neuropaty axonal or demyelinating**
- **Vasculitis**

- **GBS in Hodgkin's lymphoma 5% of cancer pts. have signs of Paraneoplastic NP**

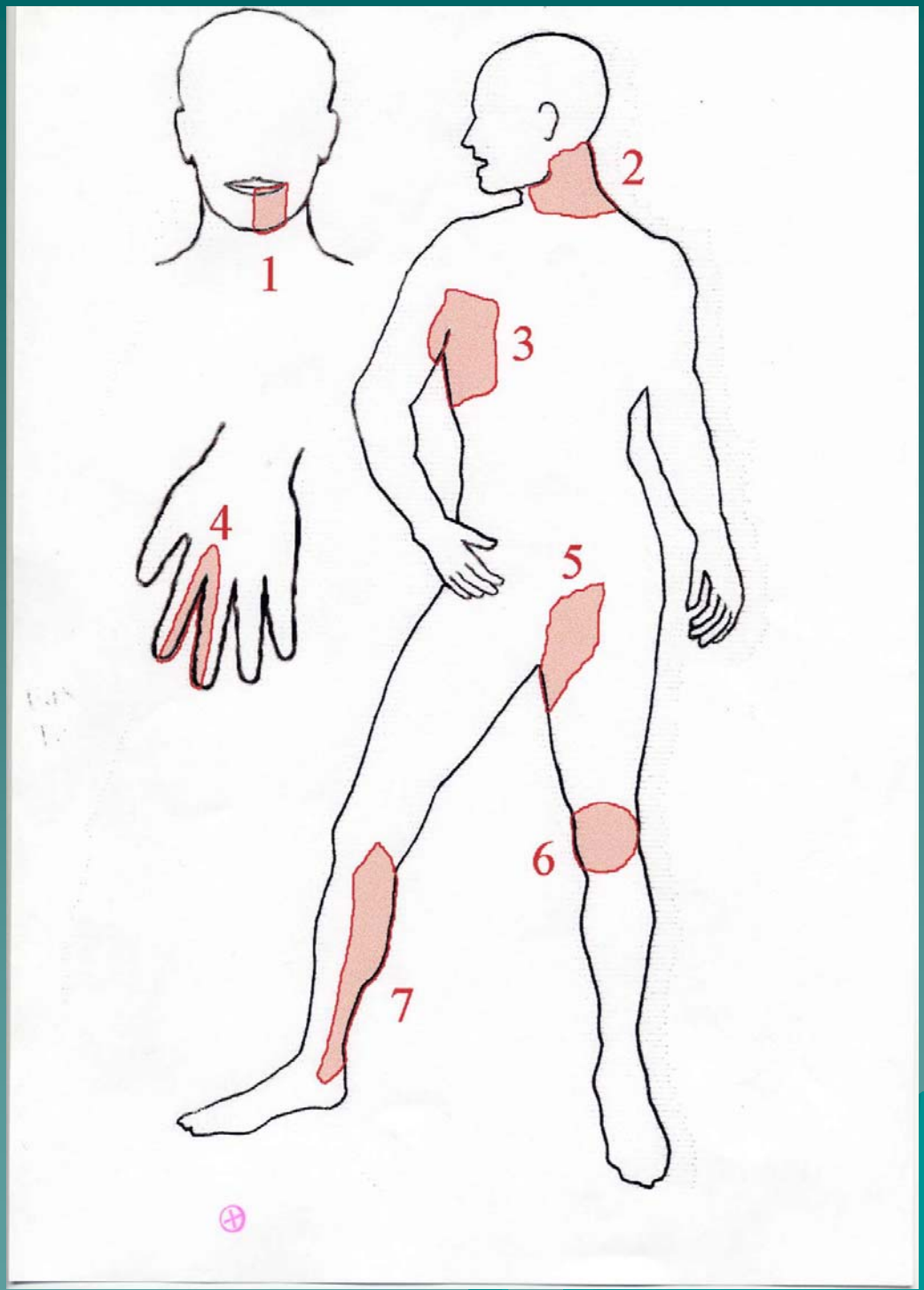
- **5% of cancer pts. have signs of Paraneoplastic NP**
- **30-40% when EMG-ENG and biopsy are performed**

- **1/3 of pts with multiple myeloma have EMG-ENG signs**
- **Causes: metabolic, nutritional, cytokines, autoimmune**

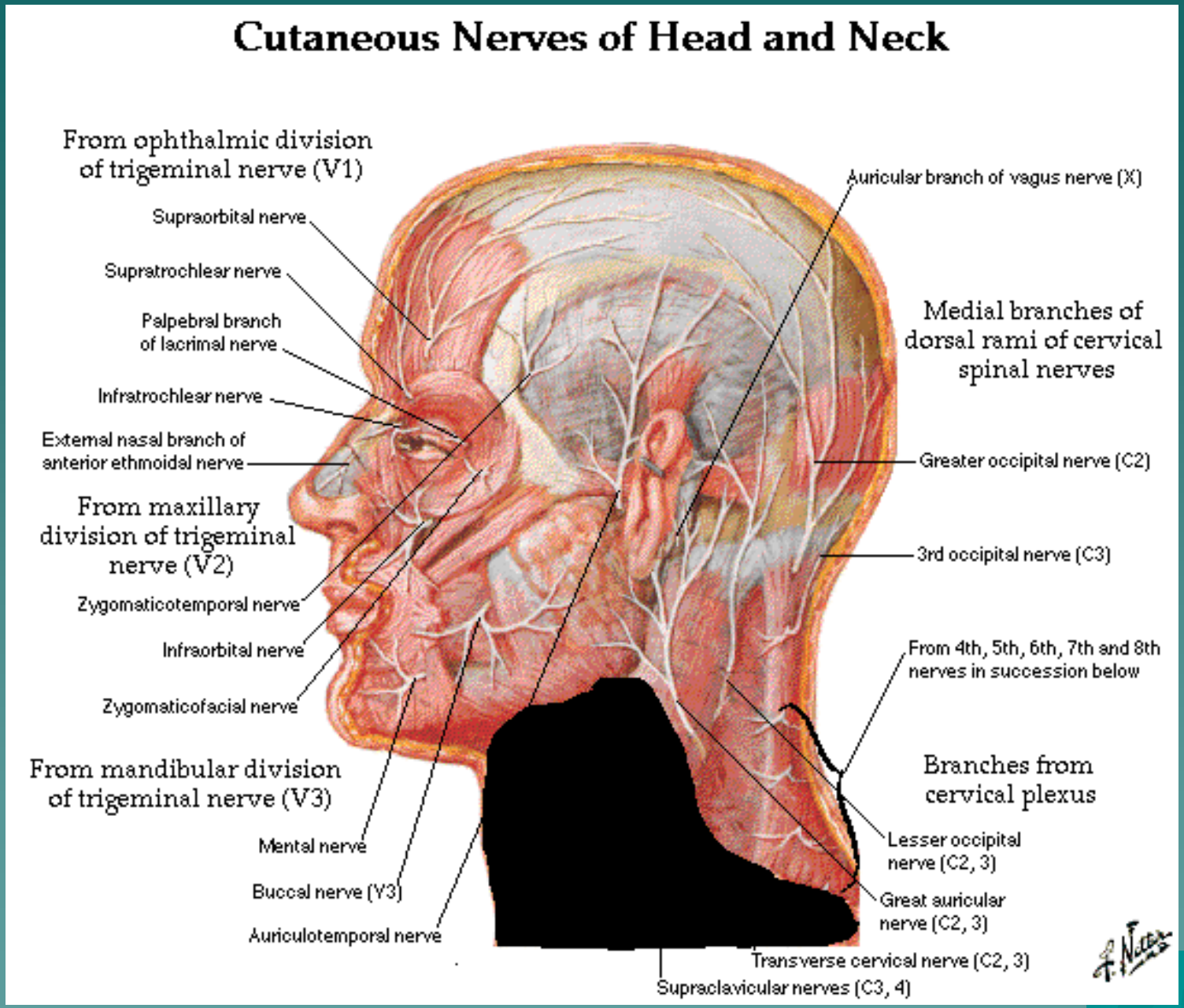
Subacute Sensory Neuropathy

- Neuropathic pain and numbness in the extremities or arms or face in middle aged ♀ or ♂
- Neurologic symptoms develop in ½ to 2/3 of pts before the cancer is apparent
- 70% of pts have small-cell lung cancer
- All sensory modalities are affected, severe ataxia
- Other regions of the nervous system involved in 50% of pts
- CSF: inflammatory!
- SAPS ↓ or absent; MUAPS normal, absent denervation

Post - surgical neuropathies

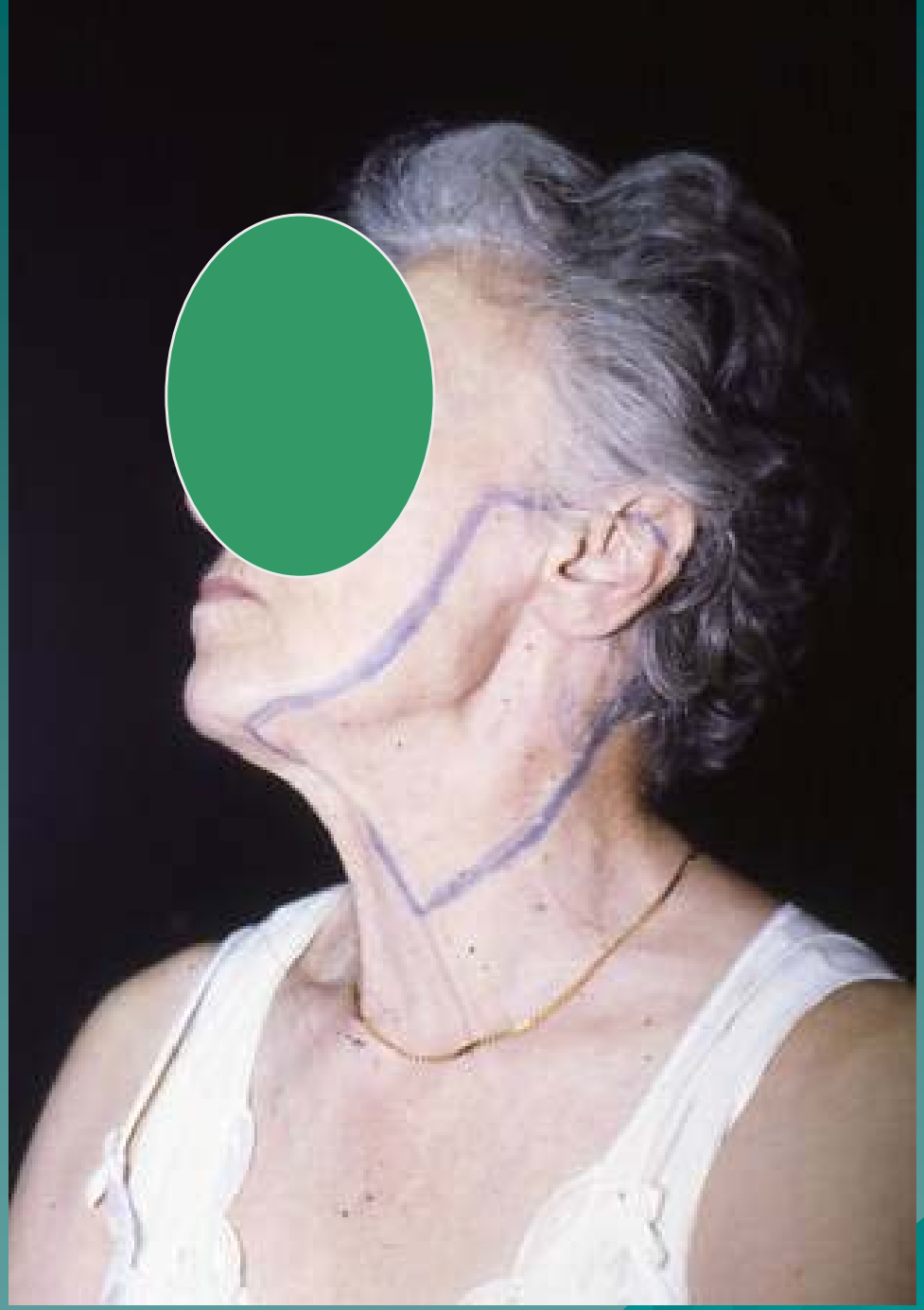


Cervical plexopathy



neuropathic pain in the infraorbitar nerve territory after removal of maxillary sinus carcinoma

neuropathic pain in the great auricular nerve territory after removal of parotid gland carcinoma



Post neck surgery syndrome:

Neck and nuchal pain may arise as a consequence of cutaneous nerve lesions provoked by surgical interventions for othorynolaryngoiatric tumours. Great auricular nerve is usually damaged in near the sternocleidomastoid muscle dissection. Lesser occipital and great occipital nerves, and supraclavicular nerves are frequently involved too. Pain affects almost 50 % of patients, sometimes weeks after neck dissection, 8 % of which rated the pain as "severe".

In half of the patients, pain subsides in a few months, but in the other half, it lasts for years.

Neck surgery frequently damages the spinal accessory nerve, particularly in dissection of the posterior cervical triangle.

However, lymph node biopsy in the neck is by far the most common cause of injury to the accessory nerve. Iatrogenic injury represents 50 % of all causes responsible for lesion of this nerve.

Post mastectomy syndrome

Pain persists after mastectomy in the majority of patients. Pain occurrence significantly correlates with the surgery extension: is infrequent in lumpectomy, but involves up to 72 % of patients submitted to axillary lymph nodes dissection (36). In these cases, pain appearance is positively associated with the number of lymph nodes removed (36). Pain seem also less frequent when careful surgical techniques are used, or when surgeons perform more interventions, as in hospitals experienced in breast surgery (37). In 15 – 20 % of patients post mastectomy pain as the quality of a burning, tight sensation and dysesthesia / allodynia in the armpit and medial part of upper arm.

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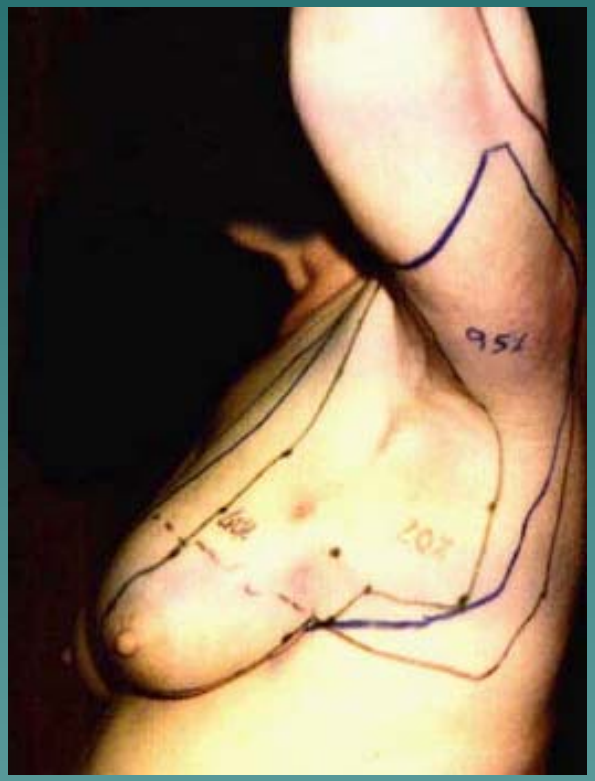
Intercostobrachial nerve syndrome



Post-thoracotomy pain

Post-thoracotomy pain 1 year after surgery is reported by up to 61 % of the patients, 3 – 5 of which complain of severe pain. Chronic pain development is directly related to post operative pain severity.

This pain may be due to intercostal nerve lesion, or to traction on the brachial plexus. Intercostal rib resection is also one of the causes of brachial plexus injury (40). Persistent chest pain may also be due to complete intercostal nerve transection, sometimes followed by painful neuromas. Severe pain is complained by 70 % of the patients after thoracotomy, and subsides in a 2 months period. Worsening of the pain over weeks or months, and a chest pain recurrence following a pain free period, is a significant negative prognostic symptom, suspicious for cancer recurrence (41).

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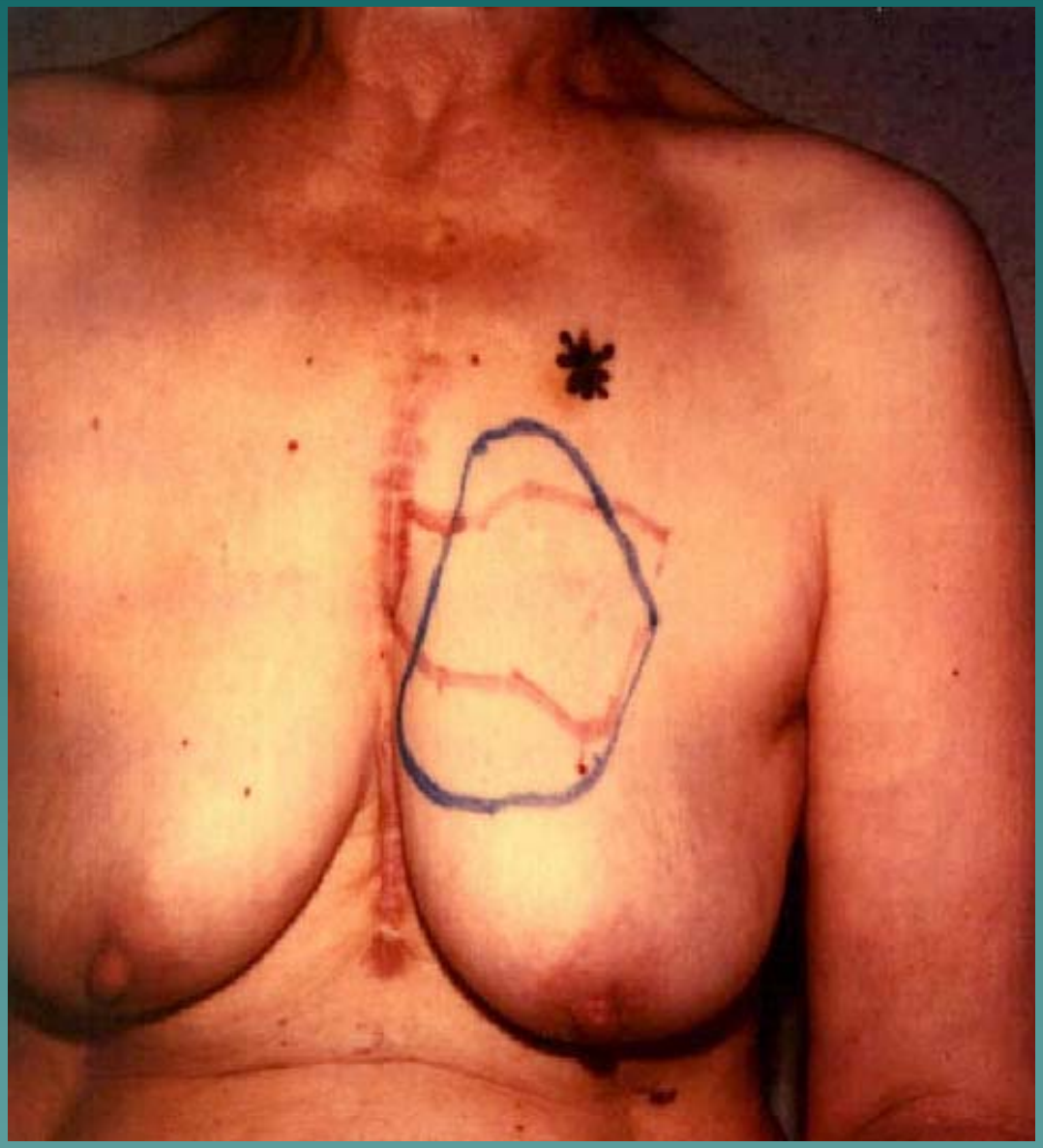
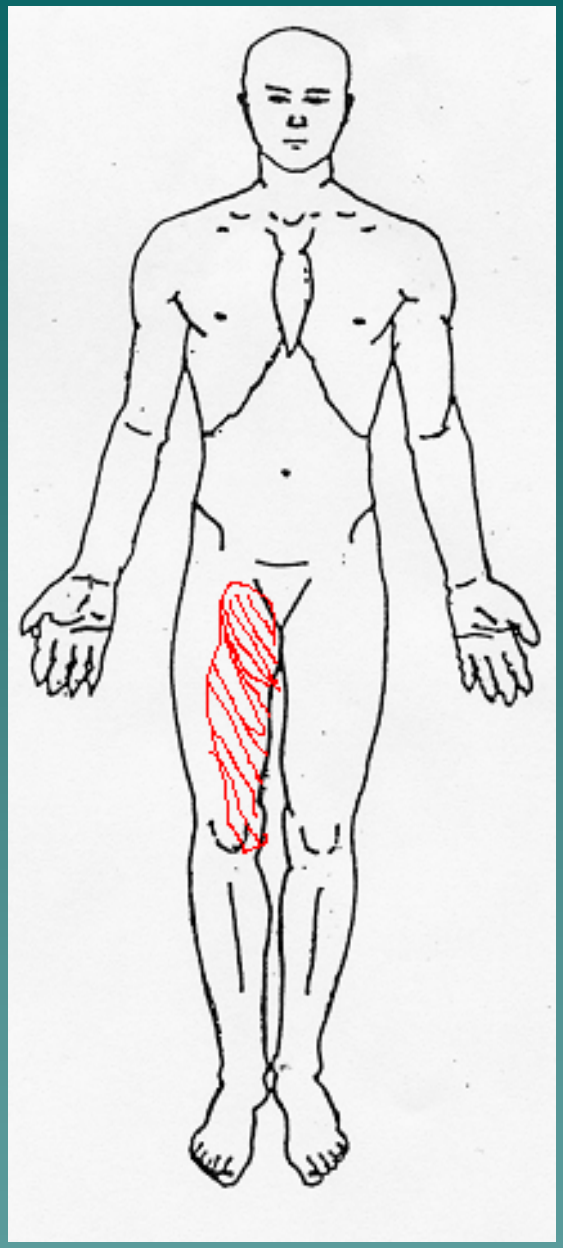
Painful post thoracotomy neuropathy



Painful post thoracotomy neuropathy



Nerve lesions occurring during anaesthesia.

As anticipated, patient positioning under general anaesthesia used to be frequently complicated by brachial plexus injury, while local anaesthesia was a frequent cause of peripheral nerve damage.
With more information and awareness of the problem, the incidence of these complications has decreased.

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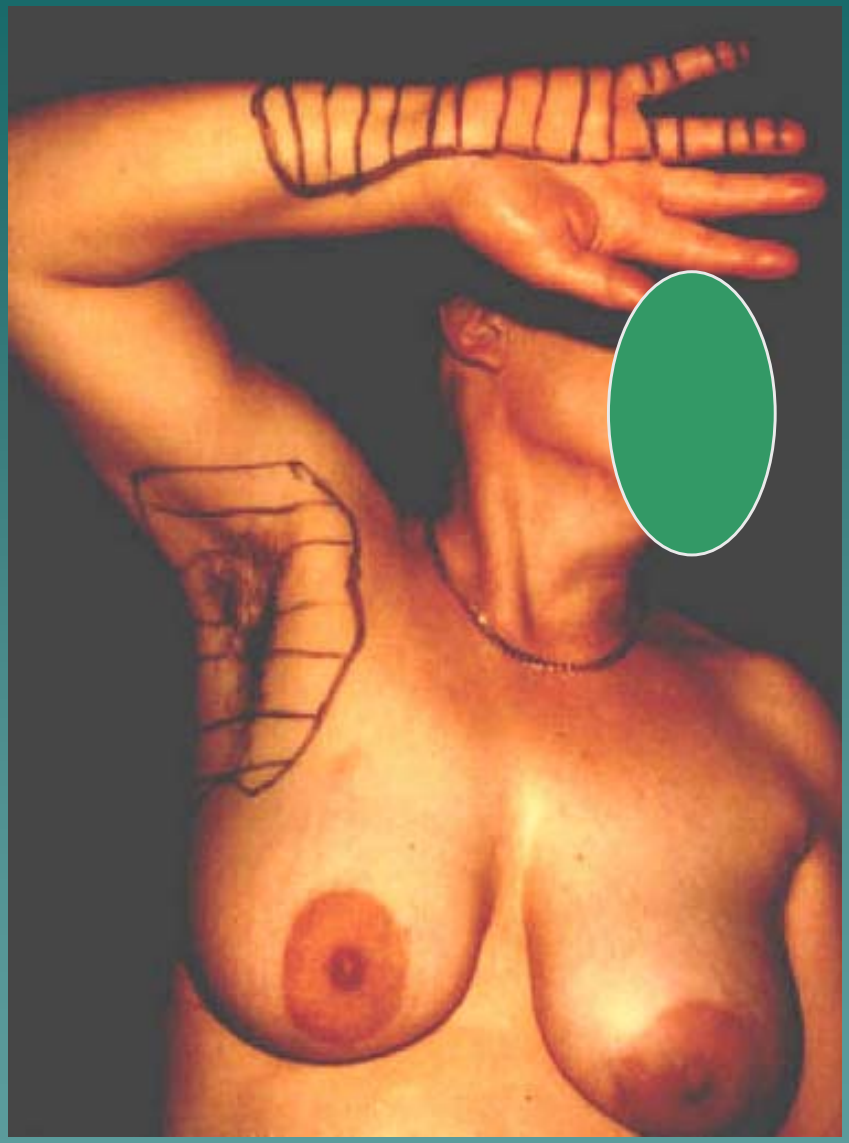
partial brachial plexus lesion



Pain, 61 (1995) 3–10

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Research Papers

Pre-injury lidocaine treatment prevents thermal hyperalgesia and cutaneous thermal abnormalities in a rat model of peripheral neuropathy

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Elsevier

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Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade

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Thank you for listening