NEUROPATHIC PAIN IN CANCER SURVIVORS, PREVALENCE AND ASSESSMENT

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Both acute and chronic pain has been well documented as one of the most frequent and distressing symptoms in cancer, and have been shown to adversely affect quality of life [1][2]. In a recent systematic review of 52 studies, 2 pooled prevalence rates for cancer pain were reported for four subgroups of patients: (1) in studies that included patients after curative treatment 33% (95% CI 21% to 46%); (2) in studies that included patients on cancer treatment 59% (CI 44% to 73%); (3) in studies in patients with advanced or metastatic disease, 64% (CI 58% to 69%); and (4) studies in patients at all stages of the disease, 53% (CI 43% to 63%). Across all of the studies evaluated, approximately 33% of the patients reported moderate to severe pain [3].

Cancer pain is a complex multifactorial phenomenon. The overall concept of cancer pain does not suffice to classify or describe the different pain characteristics that are due to different tumour related, etiologic, pathophysiologic, anatomic, treatment-related and temporal factors. Psychological and patient-related factors strongly influence the individual pain experience. Up-to-date there is no clear standardized approach or taxonomy used for assessing neuropathic pain in patients with cancer, and little consensus exist concerning definitions, framework, format and content related to two related yet distinct concepts; pain assessment and pain classification in relation to cancer.

It is recommended that pain intensity should be assessed by a simple 11-point NRS, whereas well validated instruments such as the Brief Pain Inventory (BPI) or the McGill Short Form questionnaire are recommended for a more comprehensive, multidimensional pain assessment. Despite recommendations, pain is still not routinely measured in cancer clinical practice. This may reflect the fact that most tools are too long and cumbersome for patients and clinicians to use [4]. And yet there is a continuous flow of new instruments, and only a minority is developed according to standardized development procedures [5].

Neuropathic pain (NP), is pain arising as a direct consequence of a lesion or disease affecting the somatosensory system [6]. NP pain in cancer (NCP) is commonly presented in cancer patients and is considered a well-established entity for more than 20 years [7]; can occur if the nervous system itself is damaged, by tumour infiltration of nerves, tumour-associated toxins, therapy-related toxins, or surgical damage. It is characterized by spontaneous and provoked pain, by positive symptoms such as paresthesias and dysesthesias, and by negative signs (sensory deficits) reflecting the neural damage [8]. Despite the fact that the exact prevalence of NCP remains unknown, available data demonstrate that a neuropathic component is present in approximately, 1/3 of cancer patients, usually mixed with nociceptive components, or, occasionally, as a single autonomous entity. Thus although as much as 9% of cancer patients have solely NP, many have a mixed pain syndrome [9],[10].
Diagnostic criteria to identify NP are proposed by the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain. A detailed history and clinical examination are fundamental to a correct diagnosis. A grading system of definite, probable, and possible NP pain has been proposed by a group of experts for clinical and research purposes, in recognition that there is no gold standard and is based on pain distribution, causality, clinical examination and diagnostic tests [6].

Screening tools and questionnaires are useful in indicating probable NP. Several scales have been developed to evaluate various symptoms associated with NP pain, including the Leeds Assessment of Neuropathic Pain, Neuropathic pain questionnaire, the Pain Neurotoxicity Questionnaire, and Pain Detect. They include patient self-reported data, as well as various components of a physical examination. The common denominators across these questionnaires are set of descriptors (sensations of pins and needles, heat or burning, impaired temperature sensitivity, numbness, and electric shock-like sensations; whether or not the pain becomes worse with touch, and whether the joints are painful) [11], [12]. Electrophysiological techniques, quantitative sensory testing, skin and nerve biopsies, and magnetic resonance imaging can be useful to detect lesions of the central or peripheral nervous system.

The main advantage of screening tools is to identify potential patients with NP, particularly by non-specialists (grade A). However, these tools fail to identify 10-20% of patients with clinician diagnosed NP, showing that they cannot replace careful clinical judgment. DN4 reports only about half the cancer NP cases diagnosed by clinicians. There are a few reports validating the questionnaires in various groups of patients with cancer [13].

In a recent systematic review, by M. I. Bennett et al, on the Prevalence and aetiology of NP pain in cancer patients including 19 studies in 11,063 patients, they found that 6569 (59.4%) had nociceptive pain, 2102 (19%) had neuropathic pain, 2227 (20.1%) had mixed-mechanism pain, and 165 (1.5%) were classified as having pain due to unknown or other causes. Therefore the prevalence of NP ranged from a conservative estimate of 19% (9.4% to 28.4%, CI 95%) to a liberal estimate of 39.1% (28.9% to 49.5%) of all patients with cancer pain. It must be stressed though that only 14 studies (64%) clearly stated the use of confirmatory testing as part of the diagnostic criteria consistent with the current grading system for NP pain, and only 8 fully met the NeuPSIG diagnostic criteria. A standardised approach to clinical assessment is essential if neuropathic mechanisms are to be identified with certainty, for appropriate treatment to be initiated, and for data to be comparable across studies [14].

Cancer survival is significantly increased all over Europe [15]. In the US, 10.5 million subjects are cancer survivors. Sixty-four percent of adult cancer patients diagnosed during 1995-2001 reached their 5-year survival [16], [17]. Once an explosive disease that lead to a quick demise, cancer has now become a chronic disease, characterized by a high prevalence of disturbing and persistent physical symptoms and multitude of psychosocial and economic issues that diminish their quality of life, with pain being one of the most disturbing and devastating one [18].

According to the definition of the National Cancer Institute Office of Cancer Survivorship, an individual is considered a cancer survivor from the time of cancer diagnosis, through the
In an editorial in Annals of Oncology [20], it is stated that there is a need to strictly define the population to be studied and distinguish the patients with active disease (persons living with cancer) from the disease and treatment-free patients from at least 5 years (cancer survivors), as cancer survivorship has 3 distinct phases: acute, extended, and permanent. The acute phase starts at the time of diagnosis and lasts until initial treatment is completed; the extended phase begins with completion of initial treatment resulting in partial or complete remission and is characterized by regular follow-up with or without maintenance or intermittent therapy; the permanent survival phase follows the extended phase during which patients have a very low likelihood of recurrence of their primary cancer but might be at some risk of developing associated cancers or cancers secondary to their initial anticancer therapy [19].

On the light of the quite broad definition and the heterogeneity of the cancer survivors population it is inevitable that research is not focused yet, although a few reports exist on the quality of life and other parameters of the cancer survivors life, but not many on pain and especially on neuropathic pain as an aspect of quality of life.

Chronic pain in cancer survivors is caused by residual tissue damage from the cancer, and/or the cancer therapy: surgery, chemotherapy, steroids, hormones, and radiation. Cancer survivors may also have chronic pain from cancer related conditions such as postherpetic neuralgia and non-associated chronic conditions such as collagen vascular diseases, degenerative arthritis, and diabetic neuropathy.

Studies on the prevalence of pain in cancer survivors are scarce. Cancer survivors experiencing chronic pain constitute about 40% of all patients' visits to Pain and Palliative Care Program at a NCI-designated, Comprehensive Cancer Center [21].

The research on pain and neuropathy conducted among cancer survivors is of varying quality. A vast amount of literature addresses cancer pain symptoms, but long-term pain and neuropathy among disease-free survivors has received far less attention, despite evidence that pain can be severe compromising recovery and the quality of life [22]. Few cross-sectional or prospective longitudinal studies document the incidence, time course, and problems associated with the long-term effects of pain and neurologic impairment [23]. Data from surveillance studies are limited, making it difficult to estimate the prevalence and incidence of long-term pain and neuropathies among cancer survivors, as well as their susceptibility to developing these conditions [24], [25]. Most of the research has been conducted among survivors of breast [26], lung [27], head and neck [28], [29], and colorectal cancers [30], [31].

Neuropathic Pain in Breast Cancer Survivors

Chronic pain after surgical treatment, mastectomy or lumpectomy with axillary node dissection chemotherapy, and radiation, mostly referred to as postmastectomy pain syndrome (PMPS), is a common finding in breast cancer survivors. It can develop shortly after surgery or up to several months after surgery, and can persist for years [32], [33]. It is localized in the axilla, medial upper arm, breast and/or chest wall, and its timing is consistent
with the IASP definition of chronic pain [34]. An alternative term, intercostobrachial neuralgia, has been proposed [35].

The characteristics of this pain are described diversely as lancinating pain, paresthesia, dysesthesia, hyperalgesia or allodynia, edema, muscle weakness, and skin irritations, indicating that the symptoms are related to nerve injury or dysfunction. Additionally sensitization processes may occur in the peripheral and central nociceptive system, leading to primary and secondary hyperalgesia. Using the grading proposed by Treede et al, we may consider PMPS as possible neuropathic pain [36].

The prevalence of PMPS is variable on basis of definition, treatment, and anatomical localization of the pain measure. Studies measuring PMPS report prevalence around 25%, whereas studies with a wider definition report prevalence around 50%. A substantial variation in prevalence of the phantom breast, ranging from about 10% to 66%, was also reported. Risk factors for PMPS are unclear, but recent data suggest that it may be more common among younger women (ages 30 to 49 years) and women who are overweight [37], [38].

A large nationwide study showed a prevalence of chronic pain of 25% for patients treated with mastectomy without adjuvant therapy, and 60% for patients treated with breast conserving therapy, axillary lymphnode dissection (ALND), and radiation field including the periclavicular lymphnodes, demonstrating the importance of the type of treatment which patients receive [39].

Furthermore, pain intensity has not been well examined and varies according to treatment, measurement method, whether measurement was taken at rest or during movement, and anatomical location [40]. In a prospective study 174 women were examined. Six months after the operation the incidence of pain syndrome was 52%. Younger women (< 40 years) and those who were submitted to axillary lymph node dissection (with more than 15 lymph nodes excised) have shown a significantly increased risk of pain syndrome after surgery, defined by the presence of one of the following complications: intercostobrachial pain (hyperaesthesia perception related to tactile stimulus at the internal area of the arm or axillary homolateral to treatment); neuroma (report of pain in the surgical scar when submitting to local percussion test); and phantom breast pain (reported by a patient who underwent mastectomy describing an unpleasant sensation of breast presence as pin-prick, burning or torsion), (relative risk (RR) = 5.23 95% (CI): 1.11-24.64) and (RR = 2.01 95% CI: 1.08-3.75) [41].

The validity of ID Pain as a screening tool for NP in 240 breast cancer survivors was evaluated using the Self-Report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) and a reported diagnosis of NP as criterion measures. Receiver Operating Curve analysis demonstrated that ID Pain has a predictive validity of 0.72 and 0.70 for diagnosis of NP as made by clinicians and the S-LANSS, respectively. 45% of the sample reported pain in the past week. Of those reporting pain, 33% reported that they had been diagnosed by their health care provider for NP, 39% had a positive ID Pain (≥ 2) score and 19% had a positive S-LANSS score. The most commonly endorsed ID Pain item was “hot/burning” (n = 48), followed by feeling “numb” (n = 47) and “pins and needles” (n = 45). Total ID Pain score was
significantly associated with a clinical diagnosis of NP ($r = 0.41; P < 0.001$) and the S-LANSS total score ($r = 0.54; P < 0.001$). An ID Pain score of $\geq 2$ corresponded with the likelihood of NP in this sample, consistent with the original ID Pain development study. This study provides evidence for ID Pain as a valid screening measure of NP for breast cancer survivors [42].

**Post-Thoracotomy Pain**

Chronic pain is a common complication after thoracic surgery. Little is known about the underlying cause of chronic post-thoracotomy pain, often suggested to be intercostals nerve damage during surgery leading to neuropathic pain [43]. Previous studies have shown chronic pain in 40% to 80% of patients after thoracotomy [44] and in 20% to 40% after video-assisted thoracic surgery (VATS) [45].

Symptoms of NP pain are present in 35% to 83% of the patients with chronic pain after thoracic surgery.

A questionnaire designed specifically for the study, including questions on neuropathic symptoms was sent to 1152 patients who had undergone thoracic surgery between 7 months and 7 years ago. 948 people were included in the study, 600 responded (63%). Prevalence of chronic pain was 57% at 7-12 months, 36% at 4-5 years and 21% at 6-7 years. The prevalence of each neuropathic symptom was between 35 and 83%. The presence of a neuropathic symptom was associated with significantly more severe pain, more analgesia use and pain more likely to limit daily activity [46]. Patients undergoing thoracotomy with bilobectomy or pneumonectomy had a significantly greater risk of developing chronic pain than patients undergoing a thoracotomy with lobectomy or wedge excision, suggesting a significant role of visceral nociceptive components [47].

The prevalence of the neuropathic component in chronic pain after thoracic surgery was investigated in 243 patients who underwent a video-assisted thoracoscopy (VATS) or thoracotomy by mail. Mean time since surgery was 23 months. Patients retrospectively received a questionnaire with the validated Dutch version of the Pain DETECT Questionnaire. The prevalence of chronic pain was 40% after thoracotomy and 47% after VATS. Definite chronic neuropathic pain was present in 23%. Thus, chronic pain after thoracic surgery has both neuropathic and non-neuropathic components and is only half neuropathic [48].

**Chronic Pain Syndromes that result from the Treatment of Cancer**

After Radiation therapy delayed painful brachial and lumbosacral plexopathies have been described, with the overall prevalence ranging from 2% to 5% [49]. Brachial plexopathies occur most commonly in those patients with breast cancer, followed by lung cancer and lymphoma [50]. The onset is typically delayed from 6 months to as long as 30 years after radiotherapy, with peak onset from 2 to 4 years. In a case series of 33 women who developed brachial plexopathy after treatment with radiotherapy for breast cancer, symptoms began from 6 months to 20 years after therapy [51]. Particularly devastating symptoms are paresthesias (100%), hypoesthesia (74%), weakness (58%), and pain (47%) [52].
In patients treated by contemporary radiation techniques for head-and-neck cancer (HNC), the brachial plexus frequently receives doses in excess of historically recommend limits. Clinically significant peripheral neuropathies believed to be associated with radiation-induced injury of the brachial plexus. In a prospective study, 330 patients who had previously completed radiation therapy for HNC (median time from completion of radiation therapy 56 months), disease-free at the time of screening were prospectively screened using a standardized instrument for symptoms of neuropathy. Forty patients (12%) reported neuropathic symptoms, with the most common being ipsilateral pain (50%), numbness/tingling (40%), motor weakness, and/or muscle atrophy (25%) [53].

In a prospective study, investigators identified pain in 56% of patients with HNC at diagnosis, and found mixed nociceptive and neuropathic pain in 93% of those with pain. The LANSS scale is a simple and suitable screening test for neuropathic pain in patients with HNC pain, (sensitivity 79%; specificity 100%), although some modifications might improve it [54].

Chemotherapy-induced painful peripheral neuropathies (CIPN) are increasing in frequency as more neurotoxic agents are introduced to treat cancer. Patients describe symmetrical, distal painful neuropathy in a "stocking and glove" distribution, usually in the feet/toes and fingers/hands/. Unfortunately, few studies systematically evaluate CIPN in a prospective manner. Further complicating our ability to clearly define the CIPN experience from existing data is the absence of a universally-accepted valid, reliable instrument, that might be used in both clinical and research settings [55]. Although clinically some of the symptoms much the NP pain criteria, these syndromes have not been investigated accordingly.

Well-designed cross-sectional and longitudinal studies would elucidate much about the incidence and prevalence of treatment-induced pain and neuropathies

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