

# Prevalence of neuropathic pain in patients with cancer

## Prevalência da dor neuropática em pacientes com câncer

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### ABSTRACT

**BACKGROUND AND OBJECTIVES:** To evaluate the prevalence and factors associated with neuropathic pain in cancer patients

**METHODS:** A prospective cross-sectional study conducted from August 2016 to July 2017, with 267 cancer patients above 18 years of age, with pain. Diabetic patients and patients with previous chronic pain unrelated to the current neoplasia were excluded. The demographic and disease information was obtained from the medical records and directly with the patient. The Douleur Neuropathique en 4 questions questionnaire and the numeric pain scale were later applied.

**RESULTS:** The prevalence of neuropathic pain in the study population was 53%. The average age of patients was 55.3 years. Of the 267 patients, 76% were female. There was no significant difference in the occurrence of neuropathic pain among gender, age, histological type of cancer and type of treatment. Of the patients, 35.5% who underwent chemotherapy had neuropathic pain, and there was no statistical difference between the types of chemotherapy performed. Twenty-four patients who reported pain at the radiotherapy site were diagnosed with neuropathic pain. Of the total, 63 patients who reported pain at the surgical site, 36 were classified with neuropathic pain. An increasing trend of neuropathic pain was observed when treatments were associated. The intensity of this pain was reported as moderate to severe by the majority of patients in the various types of treatment: chemotherapy, radiotherapy, and surgery.

**CONCLUSION:** When compared to other studies, a high prevalence of neuropathic pain was observed in more than half of the patients evaluated.

**Keywords:** Chemotherapy, Douleur Neuropathique en 4 questions, Neuropathic pain, Oncologic pain, Pain.

### RESUMO

**JUSTIFICATIVA E OBJETIVOS:** Avaliar a prevalência e os fatores associados à dor neuropática em pacientes oncológicos.

**MÉTODOS:** Estudo transversal prospectivo realizado no período de agosto de 2016 a julho de 2017. Participaram 267 pacientes oncológicos maiores de 18 anos que apresentavam dor, e excluídos os pacientes diabéticos e portadores de dor crônica progressiva sem relação com a neoplasia atual. Foram obtidas informações demográficas e sobre a doença no prontuário e diretamente com o paciente. Posteriormente foi aplicado o questionário *Douleur Neuropathique en 4 questions* e a escala numérica da dor.

**RESULTADOS:** A prevalência da dor neuropática na população de estudo foi de 53%. A idade média dos pacientes foi 55,3 anos. Dos 267 pacientes, 76% eram do sexo feminino. Não houve diferença significativa de ocorrência de dor neuropática entre os sexos, idade, tipo histológico do câncer e o tipo de tratamento. Dos pacientes, 35,5% que realizaram quimioterapia tinham dor neuropática, não havendo diferença estatística entre os tipos de quimioterapia realizada. Vinte e quatro pacientes que referiam dor no local do tratamento radioterápico apresentaram o diagnóstico de dor neuropática. Do total, 63 pacientes que referiam dor na área cirúrgica, 36 foram classificados com dor neuropática. Observou-se tendência crescente de dor neuropática quando os tratamentos foram associados. A intensidade dessa dor foi referida como moderada a intensa pela maioria dos pacientes nos diversos tipos de tratamento: quimioterapia, radioterapia e cirurgia.

**CONCLUSÃO:** Quando comparada a outros estudos, foi observada alta prevalência de dor neuropática, em mais da metade dos pacientes avaliados

**Descritores:** Dor, Dor neuropática, Dor oncológica, *Douleur Neuropathique en 4 questions Questionnaire*, Quimioterapia.

### INTRODUCTION

Pain is one of the symptoms most feared by cancer patients. Pain can be secondary to a tumor, to metastases and courses of treatment carried out<sup>1,2</sup>. From the physiopathological standpoint, it can be considered nociceptive, neuropathic, or mixed<sup>3</sup>. Neuropathic pain (NP) can be defined as any pain that arises as a direct consequence of a lesion, or of other disorders that affect the somatosensory system<sup>4</sup>. Neuropathic pain (NP) occurs in between 7 and 8% of the oncologic population<sup>5,6</sup>. However, the lack of awareness of this theme, and of appropriate methods for the appraisal of NP, among medical professionals are a factor that contributes to the underdiagnosis of this specific ailment<sup>1,4</sup>. In a recent meta-analysis, diagnostic tests were used for identification of cases of NP, and a prevalence rate of 31% was found<sup>7</sup>.

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Turning now to the causes that could bring about the occurrence of NP among patients living with cancer, we can include surgical treatment, due to the lesions to sensitive fibers of the skin, together with local inflammation, thereby bringing about a sensitization of the neurons<sup>8,9</sup>. Chemotherapy may also lead to peripheral neuropathy due to metabolic changes, as also structural and self-immune changes, that cause axonal lesions on the peripheral nerves, especially those in more distal locations<sup>9,10</sup>. With regard to radiotherapy, this intervention promotes neuronal lesions due to inflammatory and fibrogenic processes, together with vascular changes that cause ischaemia<sup>8</sup>. In addition, NP may result from the direct invasion of the nerve fibers by the tumour<sup>7</sup>. The diagnosis of NP is based on the patient's clinical history and a detailed physical examination, together with other methods such as neuroimaging and electroneuromyography<sup>11</sup>. As pain is an individual and subjective entity, with no pathognomonic signs or symptoms for NP, we recommend the association with auxiliary screening instruments, such as the Douleur Neuropathique en 4 questions questionnaire (DN-4), to establish a difference between nociceptive pain and neuropathic pain<sup>11,12</sup>.

The DN-4 questionnaire can indeed identify NP<sup>11-13</sup> through objective questions, related to the characteristics of the pain, associated symptoms, and a simplified physical examination, directing the appropriate treatment for this illness<sup>10</sup>. However, these screening instruments should not be used alone as a criterion for diagnosis, as they are no replacement for a detailed clinical appraisal<sup>12</sup>.

Due to the rising number of people living with cancer, together with the greater survival time of these patients, in addition to the scientific and technological advances<sup>7</sup>, the present study has sought to identify the prevalence of NP and its associated factors in cancer patients.

## METHODS

A cross-sectional prospective observational study was carried out in the Oncology Sector of the Barão de Lucena Hospital and at the 'Professor Fernando Figueira' Institute of Integral Medicine (IMIP), both in the city of Recife, State of Pernambuco, Brazil, between August 2016 and July 2017. All participants signed the Free and Informed Consent Form (FICT).

Considering the lack of agreement in information regarding the occurrence of NP among the oncologic population, the size of the sample was calculated making use of a conservative formula corresponding to a 95% level of confidence ( $n=1.96^2 \times 0.25/E^2$ , where E refers to the margin of error as adopted). In this study, a margin of 6% was adopted. This means that the sample size was 267 patients. The study included patients with cancer, aged over 18, who showed signs of pain; on the other hand, diabetic patients and people living with previous chronic pain without any connection to the current neoplasm were excluded from the study.

Based on the information obtained in the medical records and that supplied directly by the patient, first, a questionnaire was completed, for appraisal of the demographical data and to get information about the histological type of cancer and its treatment. Next, we observed to see if the pain as alleged by the patient was or was not related to the site of the medical interventions as performed, including surgical procedures and radiotherapy, or if the pain was in limbs associated to the effects of chemotherapy. Next, for each positive

response regarding pain, the DN-4 questionnaire was then applied to identify the presence of NP. Finally, the study used the numeric pain scale, to assess the intensity of pain in each region where the patient mentioned the symptom. The patient was asked to make a numeric assessment of the intensity of pain, using the Numeric Rating Scale (NRS), on a scale from zero to 10. For the purpose of statistical analysis, the pain was then considered either mild (1 to 3), moderate (4 to 7) or severe (8 to 10).

The DN-4 questionnaire is an auxiliary instrument to distinguish NP from other types of pain. It is validated for the Portuguese language and shows high sensitivity, specificity, and positive predictive precision. This questionnaire has 10 items regarding the characteristics of non-nociceptive pain: 7 questions about the symptoms and the characteristics of the pain, and 3 related to the physical examination. A score of 4 points or more backs up the diagnosis of NP.

With regard to the symptoms, the subjects were asked about the presence of burning, a sensation of painful cold, thermal shock, numbness, 'pins and needles', tingling, and itching. In the physical examination, touch sensitivity was assessed with the use of cotton pads, while sensitivity to pain was evaluated with a sharp instrument. The presence of pain was also assessed by brushing the painful area. One point was given for each positive response, while no points were assigned for a negative response.

This study had the approval of the Research Ethics Committee of the School of Health of Pernambuco (CAEE: 57436116.2.0000.5569).

## Statistical analysis

Frequency distribution tables were compiled for the different variables, which were duly categorised and coded. The categorical data were summarised using absolute and relative frequencies; numerical data such as age were defined using the arithmetic mean and the standard deviation. Proportions were compared between groups using Pearson's Chi-square test ( $\chi^2$ ), or the Chi-square test for trends. The comparison of the mean ages between the groups of patients with and without NP was carried out using Student's t-test for independent samples. In all tests, a level of significance of 0.05 was used. The statistical analysis was carried out using the Stata software, version 12.1 SE.

## RESULTS

The occurrence of NP within the population studied was 53.3% (CI95%: 46.6% to 59.65%). The sample here considered had a mean age of 55.3±12.6 years. When analyzing those patients identified as having symptoms of NP, there was no statistical association between this pain and gender, age, or the histological type of cancer (Table 1). Considering the courses of treatment as implemented, we see that, out of the 238 patients in the sample, 228 had chemotherapy, 77 radiotherapies, and 145 surgeries. It is also important to mention that many patients had more than one treatment for their oncological disease. Studying NP and its association with the treatments carried out, we see no association between the type of treatment (chemotherapy, radiotherapy or surgery) and the presence and intensity of NP (Table 2).

Out of the 228 patients who underwent chemotherapy, 121 (53.7%) reported pain in the extremities. This pain was identified as NP in 81 of the patients with pain in the extremities, of whom 50.62% had NP in upper and lower limbs at the same time. Here it is important

**Table 1.** Relationship between the type of cancer, gender, and age with the presence of neuropathic pain

Types of cancer	Neuropathic pain		p-value	
	Yes n (%)	No n (%)		
Breast	60 (61.9)	37 (38.1)	0.158	
Prostate	5 (38.5)	8 (61.5)		
Gastrointestinal tract	32 (50.8)	31 (49.2)		
Ovary	6 (42.9)	8 (57.1)		
Uterus	8 (53.3)	7 (46.7)		
Haematological neoplasm	8 (61.5)	5 (38.5)		
Lung	3 (23.1)	10 (76.9)		
Others	4 (40.0)	6 (60.0)		
Gender			0.560	
Male	28 (49.1)	29 (50.9)		
Female	98 (54.1)	83 (45.9)		
Age	NP	n	Mean (SD)	0.91
	Yes	44	53.3 (12.0)	
	No	50	55.4 (12.3)	

**Table 2.** Association between treatments as performed and the presence and intensity of neuropathic pain

Treatment	Reported pain		NP		p-value	Pain intensity			p-value
	n	n (%)	Yes n (%)	No n (%)		Mild n (%)	Moderate n (%)	Severe n (%)	
Radiotherapy	77	40(52)	24(31.1)	16(20.7)	0.389	NP at site of radiation	5 (20.8)	13(54.2)	6 (25,0)
Surgery	145	63(43)	36(24.8)	27(18.6)		NP at site of surgery	10 (27.8)	18(50.0)	8 (22,2)
Chemotherapy	228	121(53.07)	81(35.5)	40(17.5)		NP in limbs	15 (18.5)	48(59.3)	18 (22,2)
						Upper limbs only	0(-)	12(75.0)	4 (25,0)
						Lower limbs only	9 (37.5)	9(37.5)	6 (25,0)
						Both	6 (14.6)	27(65.9)	8 (19,5)

NP = Neuropathic pain.

to stress that 29.73% (24) of the patients identified as living with NP only had pain in the upper limbs, while 19.75% (16) only had pain in the lower limbs. The intensity of NP in the extremities was reported as being mild by 18.5% of the participants; as moderate by 59.3%; and as severe by the remaining 22.2% (Table 2). There was no statistical difference in relation to the association between the type of chemotherapy used and the presence of peripheral pain (Table 3).

**Table 3.** Association between the type of chemotherapy and the occurrence of neuropathic pain

Type of chemotherapy	Neuropathic pain		p-value
	Yes n (%)	No n (%)	
Neoadjuvant	11(25)	33(75)	0.174
Adjuvant	38(41.3)	54(58.7)	
Palliative	32(34.8)	60(65.2)	

Out of the 77 patients who mentioned pain at the site of the radiotherapy treatment, 24 (31.1%) of the total showed symptoms of NP. This pain was considered moderate or severe by more than two-thirds

of the patients (Table 2). It is also worth pointing out that 13 of the patients also had surgery in the same region.

Regarding surgical procedure, out of the 145 patients who had surgery, we see that that 63 (43%) complained of pain. On applying the DN-4 questionnaire to these patients, the pain was considered neuropathic in 36 of the participants, corresponding to 24.8% of the total number of patients who underwent surgery. Analysing the intensity of the pain considered as neuropathic, we see that most patients reported this symptom as being moderate to severe, in the region as appraised (Table 2).

When we considered the patients who had only one course of treatment for the basic illness, we saw that, out of the two patients who received only the radiotherapy, only one was identified as being a bearer of NP at the location of radiation. With regard to surgery, four participants were subjected only to this type of treatment, and three showed symptoms of NP when the DN-4 was applied. Out of all patients studied, a mere 68 were subjected only to chemotherapy, and 20 obtained a point score of over four on the application of the DN-4, thus identifying the presence of pain with neuropathic characteristics.

With the association of the different treatments for cancer (chemotherapy, radiotherapy, and surgery), there was a significant improvement in the percentage of patients showing symptoms of NP (Table 4).

**Table 4.** Association between the number of treatments carried out and the presence of neuropathic pain

Number of treatments received	Neuropathic pain		p-value
	Yes	No	
	n (%)	n (%)	
1	24 (32.4)	50 (67.6)	
2	64 (55.7)	51 (44.3)	<0.001
3	38 (77.6)	11 (22.4)	
Total	126 (52.9)	112 (47.1)	

## DISCUSSION

In this study, the occurrence of NP in adults with the oncologic disease was 53%. This result was higher than that found in a recent meta-analysis that observed a prevalence of NP in 31.45% of cases<sup>7</sup>, and in the study by Oosterling, Boveldt and Verhagen<sup>15</sup> which, on using the DN-4 questionnaire, identified a prevalence of 19% for NP. This difference found in the present study can be explained by the fact that only DN-4 was used as a method of screening.

An additional fact that would justify the high occurrence of NP is difficulty, of the population studied, to gain access to diagnostic services and therapeutic interventions within a reasonable period, as mentioned by another author<sup>7</sup> who found, among patients undergoing palliative care, a rate of occurrence of NP higher than that for patients in outpatient wards. It is also reported that the tardy commencement of treatment for cancer may increase this prevalence<sup>16</sup>, as the occurrence of NP is related to more advanced stages of oncologic disease<sup>6,8</sup>.

Another result is that approximately two-thirds of the included patients were females and this data is in agreement with the high percentage of cancer of the breast of the sample<sup>8</sup>.

However, the current results have not found a significant statistical association between the presence of this symptom and gender, and neither between the presence of the symptom and different age brackets. This study did not see any association between NP and the types of treatments performed, different from other studies that suggested a greater association of neuropathic harm for those people subjected to chemotherapy<sup>8,15</sup>. However, there was no appraisal of the chemotherapy schemes that knowingly affect the risk of dysfunction of the central nervous system<sup>6,8,10</sup>. One important datum found was that those patients who had a greater number of interventions (chemotherapy, radiotherapy, and surgery) had a significantly larger proportion of symptoms characteristic of NP. This result shows that the combination of interventions could indeed increase the risk of development of NP<sup>8,16-18</sup>.

It is well known that the appearance of peripheral neuropathy, induced by chemotherapy, is affected by the dose, the cumulative effect, and by the class of chemotherapeutic agent used, especially when the chemical used in chemotherapy is an alkaloid, a taxane, or a platinum complex<sup>8,10,15-17</sup>. In the present study, these variables were

not assessed, and this could explain the lack of a significant difference in researching the association between NP and chemotherapy. Out of the patients who had chemotherapy, more than a third showed symptoms compatible with a diagnosis of NP. The results were similar to those reported by other authors<sup>8,10</sup>. The presence of NP on both extremities took place in more than half those subjected to chemotherapy. Regarding the intensity of NP, over 70% considered the pain moderate or severe. It is well known that chemotherapy can lead to neuronal dysfunction, due to mitochondrial toxicity, with the increase in TRPV1, changes to the n-methyl d-aspartate receptor, among other signs. These changes are part of the very genesis of peripheral NP<sup>18</sup>.

With regard to the occurrence of NP at the site of radiotherapy, 31.1% of patients who underwent this treatment were identified as having these symptoms. This result was higher than that described in another study, where the prevalence was between 10 and 15%<sup>8</sup>. This pain was considered moderate or severe by the large majority of the patients. Once again, it is worth remembering that there was the overlap of different treatments performed (54.1% of these patients also had surgery), explaining the occurrence of NP and even the pain intensity as reported by the patients. Hence, the overlap of these two treatments made it impossible to distinguish whether the NP was a result of the radiotherapy or the surgery. The most likely hypothesis was that it resulted from both courses of treatment.

Regarding the surgery, the frequency of NP at the site of surgery was 24.8%, which agrees with the results found in other studies<sup>5,6,8</sup>. NP was considered severe by over half the patients. This can be explained by the fact that most patients who had surgery also had other treatment for the oncological disease, especially radiotherapy, as in the case of breast and prostate tumors.

Concerning the DN-4 questionnaire in its recent French revision, the Portuguese version was the most satisfactory among all the versions in languages other than French<sup>11</sup>. It is a questionnaire for the screening of NP<sup>10</sup>, easy and quick to use, this being the reason for its use in this study<sup>13</sup>.

Despite the important results about the prevalence of NP among cancer patients, this study has some limitations. The first is that NP was assessed using only one instrument, the DN-4 questionnaire. The second is that the patients excluded, namely those with diabetes mellitus (DM) and bearers of chronic pain, could have pain secondary to the cancer pain and/or to the treatments used. Finally, the most important limitation is that it did not study the class of chemotherapy substances, quantifying the number of cycles to which the patients were subjected, and the time that elapsed between the start of treatment and the appearance of pain symptoms.

## CONCLUSION

In this academic paper, we observed a high occurrence of NP, which was reported as moderate or severe by the majority of those interviewed.

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