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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

# Longitudinal assessment of cognitive decline in breast and prostate cancer survivors

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TESE DE DOUTORAMENTO EM SAÚDE PÚBLICA

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I. **Interchangeability of two versions of the Montreal Cognitive Assessment for the longitudinal evaluation of patients with breast cancer.** Araujo N, Lopes-Conceição L, Morais S, Fontes F, Dias T, Tedim Cruz V, Ruano L, Pereira S, Lunet N. [*Submitted*].

**II.** **Neuropathic pain, chemotherapy-induced peripheral neuropathy and cognitive decline in a 5-year prospective study of breast cancer patients– NEON-BC.**
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IV. **Cognitive decline in patients with prostate cancer: study protocol of a prospective cohort, NEON-PC.** Araújo N, Morais S, Costa AR, Braga R, Carneiro F, Tedim Cruz V, Ruano L, Oliveira J, Pacheco-Figueiredo L, Pereira S, Lunet N. BMJ Open, 2021. 11(2): p. e043844.

**V.** **Prevalence of cognitive impairment before prostate cancer treatment.**
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**VI.** **Androgen deprivation therapy and cognitive decline in the NEON-PC study: the impact of COVID-19 pandemic.**
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Em cumprimento com o disposto no referido Decreto-Lei, declaro que participei ativamente na definição dos objetivos de todos os trabalhos que constituem esta tese, bem como na análise dos dados e interpretação dos resultados que estes reportam (manuscritos I-III e V e VI). Fui responsável pela redação da versão inicial de todos os manuscritos, tendo colaborado ativamente na preparação das versões finais dos mesmos.

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# TABLE OF CONTENT

**LIST OF ABBREVIATIONS AND ACRONYMS**

ADT - Androgen deprivation therapy
AJCC - American Joint Committee on Cancer
aOR - adjusted odds ratio
ASCO - American Society of Clinical Oncology
AUC - Area Under the Receiver Operating Characteristic Curve
CCI - Coeficiente de correlação de intraclasses
COVID-19 - Coronavirus disease of 2019
CPG - Cambridge Prognostic Group
CRCI - Cancer-related cognitive impairment
DP - Desvio-padrão
EAU - European Association of Urology
EBRT - External beam radiation therapy
ESMO - European Society of Medical Oncology
HDI - Human Development Index
HER2 - Human epidermal growth factor 2
HR - Hormone receptor
IC a 95% - Intervalo de confiança a 95%
ICC - Intraclass Correlation Coefficients
IGRT - Image-guided radiotherapy
IMRT - Intensity-modulated radiotherapy
IPO-Porto - Instituto Português de Oncologia do Porto
LHRH - Luteinizing hormone-releasing hormone
mCSPC - metastatic castration sensitive prostate cancer
MoCA - Montreal Cognitive Assessment
NCCN - National Comprehensive Cancer Network
OR - Odds Ratio
PROMs - Patient reported outcomes
PSA - Prostate-specific antigen
SBRT - Stereotactic body radiation therapy
SD - Standard deviation
SERM - Selective oestrogen receptor modulators
TNM - Tumor Node Metastases
TPA - Terapia de privação de androgéneos

## ABSTRACT

Breast and prostate cancers are the most common cancers in women and in men, respectively. Their high survival rates emphasize the importance of controlling the adverse effects of these cancers and of their treatments throughout the survivorship continuum. Cognitive impairment is a common cancer-related symptom that may have a sizable impact on the patients' quality of life as well as on the family and at the professional level. Cognitive deficits related to memory, attention, concentration and other aspects of cognitive function, commonly referred to as *chemo brain*, have been frequently reported among patients with cancer treated with chemotherapy. Cognitive impairment appears to be frequent even before chemotherapy, and other treatments, namely endocrine therapy, commonly used in breast and prostate cancers, and radiotherapy, immunotherapy and surgery, have also been shown to be associated with cognitive deterioration. However, results on the frequency of cognitive impairment and the potential contribution of cancer treatments for its occurrence, have been inconsistent, namely due to methodological heterogeneity: many studies were cross-sectional, retrospective or prospective studies with small sample size; different types of control groups were used, as well as a diversity of cognitive tests and cognitive outcomes.

Therefore, this thesis aims to contribute for a better understanding of the burden of cognitive deterioration in patients with breast and prostate cancers, namely its frequency, course over time and determinants, through the longitudinal assessment of cognitive performance over five years in a cohort of patients with breast cancer – the NEON-BC study – and over one year in a cohort of patients with prostate cancer – the NEON-PC study.

The NEON-BC study aimed to investigate the neuro-oncological complications of breast cancer treatments and included 506 women with a recent diagnosis of breast cancer, proposed

for surgery at the Portuguese Institute of Oncology of Porto (IPO-Porto), recruited in 2012. The Montreal Cognitive Assessment (MoCA) was used to evaluate participants' cognitive performance before treatments, and after one (n=503), three (n=475) and five years (n=466).

The NEON-PC study aimed to investigate cognitive decline in patients with prostate cancer over ten years of follow-up (study protocol described in Paper 4). Recruitment took place at IPO-Porto from February 2018 to June 2021, with an interruption of four months due to the COVID-19 pandemic. Patients with a recent prostate cancer diagnosis, proposed for different treatments, and patients with a recurrence of the disease, proposed for androgen deprivation therapy (ADT), were evaluated with the MoCA before treatment (n=609) and after one year (n=366). The baseline and one-year evaluations were completed before the COVID-19 pandemic onset for 449 and 147 participants, respectively, and after the first case reported in Portugal, in March 2nd 2020, for 160 and 219 participants, respectively.

The following paragraphs describe the specific objectives defined for the current thesis, along with the corresponding methods and results.

1. To evaluate the interchangeability of two versions of the MoCA for the longitudinal assessment of the cognitive performance of patients with breast cancer (Paper 1).

At the three-year evaluation of the NEON-BC cohort, 422 participants were evaluated with version 7.1 of the MoCA, previously administered at baseline and at one year, as well as version 7.3. Versions 7.1 and 7.3 were administered at the beginning and at the end of the evaluation, respectively, with an interval of approximately 60 minutes. Bland-Altman plots and Intraclass Correlation Coefficients (ICC), estimated in two-way mixed-effects models for

absolute agreement, were used to assess agreement between versions regarding the total, sub-domain and task scores.

Overall, there were no statistically significant differences in the distribution of total scores between versions and the ICC was 0.890 [95% confidence interval (CI): 0.868, 0.908]. The Bland-Altman limits of agreement were -3.70 to 3.88. Among women with mid-range scores, scores in version 7.1 were statistically higher than in version 7.3, and there were differences in seven of the 12 tasks and in three cognitive domains: the language and memory domains presented higher scores in version 7.1, while the opposite was observed for visuospatial ability.

2. To describe the prevalence of cognitive impairment among patients with breast cancer followed during five years after cancer diagnosis, and to quantify the relation between patients' characteristics and clinical information with the incidence of cognitive decline (Paper 2).

This study analyzed data from 462 women with non-metastatic breast cancer of the NEON-BC cohort with a complete follow-up during the first five years since breast cancer diagnosis. Cognitive impairment was defined as a MoCA score below age- and education-specific normative values [below 2 standard deviations (SD)]. Multivariate linear regression was used to identify the determinants of cognitive changes in participants with normal cognitive performance at baseline.

Cognitive impairment was observed in 17.7% of the women in at least one of the four evaluations performed during the five years of follow-up. Among women without cognitive impairment before breast cancer treatments, baseline anxiety, depression and poor sleep quality were associated with worse cognitive changes from baseline to follow-up evaluations (β coefficients ranging from -1.60 to -0.63, $p<0.050$).

3. To describe the five-year cognitive trajectories of patients with breast cancer (Paper 3).

In the NEON-BC cohort, 464 participants completed the MoCA in all evaluations of the five-year follow-up. Mixed-effects models were used to fit MoCA scores over time and cluster-based analysis was used to group participants with similar cognitive trajectories. The Areas Under the Receiver Operating Characteristic Curves (AUC) were computed to evaluate the accuracy of models to predict the five-year cognitive trajectory.

Two cognitive trajectories were identified: most women had higher scores and an increase in cognitive scores over time, whereas 25.9% had a trajectory characterized by a continuous decrease. Within each trajectory, participants were grouped based on their baseline MoCA being above or below the median value of the trajectory-based group. Four groups were obtained: 1) highest baseline scores, stable over time; 2) lowest baseline scores; 3) mid-range scores at baseline, increasing over time; 4) mid-range scores at baseline, decreasing over time. The model based on the baseline predictors age, education and MoCA score had an AUC of 0.732 to predict the cognitive trajectory, which significantly ($p<0.001$) increased to 0.841 when the variation in cognitive scores from baseline to the one-year evaluation was added to the model.

4. To estimate the prevalence of cognitive impairment among patients with prostate cancer (Paper 5).

In the NEON-PC cohort, cognitive impairment before prostate cancer was identified in a two-step evaluation: first, all men with incident prostate cancer (n=609) completed the MoCA to identify probable cognitive impairment, defined as a score below age- and education-specific normative values (below 1.5 SD), and second, the confirmation of probable cognitive impairment with the administration of a battery of neuropsychological tests. The population-based cohort EPIPorto (n=351) was used as a comparison group. Multivariate logistic regression

was used to obtain the age and education adjusted odds ratio (aOR) of the association between prostate cancer/prostate cancer treatments and cognitive impairment.

The prevalence of probable cognitive impairment was similar in men of the general population and in men with a recent diagnosis of prostate cancer before cancer treatment (17.1% and 15.9%, respectively; aOR: 1.02, 95% CI: 0.70, 1.50). Patients who were proposed for ADT as a single treatment or in combination with chemotherapy were more likely to present probable cognitive impairment than patients with other proposed treatments (aOR: 1.92, 95%CI: 0.95, 3.86). Following the neuropsychological evaluation, half of the probable cognitive impairment cases had confirmed cognitive impairment.

5. To quantify the association between prostate cancer treatments and cognitive deterioration during the first year of prostate cancer treatments (Paper 6).

In the NEON-PC cohort, 366 participants were evaluated with the MoCA before treatment and after one year (186 who received ADT and 180 who underwent other treatments). Cognitive decline was defined as a change in cognitive scores (score at one year minus score at baseline) below 1.5 SD of the distribution of cognitive changes in the whole cohort. Incident cognitive impairment was defined as a MoCA score below age-and education-specific normative values (below 1.5 SD), among participants without cognitive impairment at baseline. Logistic regression was used to compute age- and education aOR of the association between ADT and cognitive decline/cognitive impairment.

Mean MoCA scores increased from baseline to the one-year evaluation (22.3 *vs.* 22.8, p<0.001). Cognitive decline was more frequent in the ADT group, and even more after the onset of the COVID-19 pandemic (aOR 6.91 *vs.* 1.93, p for interaction=0.233). The one-year cumulative incidence of cognitive impairment was 6.9% (9.1% before and 3.7%% after the pandemic onset),

which was higher among patients receiving ADT, but only after the pandemic (aOR 5.53 *vs.* 0.49, p for interaction=0.044).

**Conclusion**

With the present thesis, we were able to provide new epidemiological data on the occurrence of cognitive impairment over five years since cancer diagnosis, in patients with breast cancer, and over the first year, in patients with prostate cancer. Nearly a quarter of the patients with breast cancer had a declining cognitive trajectory and 17.7% had cognitive impairment in at least one of the four evaluations. In patients with prostate cancer, the prevalence of cognitive impairment at baseline was similar to that of the general population, and the incidence of cognitive impairment at one-year was nearly 7%.

We also identified determinants of worse cognitive changes over time in patients with breast and prostate cancers: anxiety, depression and poor sleep quality at baseline were associated with incident cognitive decline at five-years in patients with breast cancer, and ADT was associated with cognitive decline and incident cognitive impairment at one year in patients with prostate cancer.

On average, cognitive performance improved in the first year since the pre-treatment evaluation, both in patients with breast cancer and with prostate cancer, and half the patients with prostate cancer who had cognitive impairment at baseline had normal scores at one-year. The variation in MoCA scores during the first year after breast cancer diagnosis was identified as an essential marker to add to baseline predictors to predict long-term cognitive decline. An association between ADT and cognitive deterioration after one year since initiation of ADT was observed among patients with prostate cancer.

These results highlight the importance of assessing cognitive performance in patients with breast and prostate cancers, especially during the first year after cancer diagnosis to

identify patients more likely to present cognitive decline. Interventions focusing on controlling anxiety, depression, sleep problems and pain should be investigated for their potential to decrease the likelihood of cognitive decline in patients with breast cancer. Future research is needed to identify possible mediators of the effect of ADT on cognitive performance and its persistence after treatment discontinuation in patients with prostate cancer.

# RESUMO

Os cancros da mama e da próstata são os cancros mais frequentes nas mulheres e nos homens, respectivamente. As elevadas sobrevivências observadas nos últimos anos enfatizam a importância de controlar os efeitos adversos destes cancros e dos seus tratamentos a curto e a longo prazo. O défice cognitivo relacionado com o cancro poderá ter um impacto importante na qualidade de vida dos doentes, afetando também a sua situação profissional e os seus familiares. As manifestações relacionados com a memória, a atenção, a concentração e outros aspetos da função cognitiva, habitualmente denominados *chemo brain*, são frequentes durante a quimioterapia. O défice cognitivo parece ser frequente até antes da quimioterapia e outros tratamentos têm também sido associados à deterioração cognitiva, nomeadamente a terapia endócrina, muitas vezes usada nos cancros da mama e da próstata, a radioterapia, a imunoterapia e a cirurgia. Contudo, os resultados acerca da frequência do défice cognitivo e do potencial contributo dos tratamentos para a sua ocorrência têm sidos inconsistentes, o que pode ser justificado pela heterogeneidade metodológica; muitos estudos eram transversais, retrospetivos ou prospetivos com reduzido tamanho amostral, tendo também sido utilizados diferentes tipos de controlos, assim como uma diversidade de testes e de *outcomes* cognitivos.

Esta tese pretende contribuir para um melhor conhecimento sobre a carga da deterioração cognitiva nos doentes com cancro da mama ou com cancro da próstata, nomeadamente a sua frequência, a sua trajetória ao longo do tempo e os seus principais determinantes, através da avaliação longitudinal do desempenho cognitivo ao longo de cinco anos numa coorte de doentes com cancro da mama – o estudo NEON-BC – e durante um ano numa coorte de doentes com cancro da próstata – o estudo NEON-PC.

O projeto de investigação NEON-BC teve por objetivo avaliar as complicações neuro-oncológicas dos tratamentos para o cancro da mama e incluiu 506 mulheres com um diagnóstico recente de cancro da mama, propostas para cirurgia no Instituto Português de Oncologia do Porto (IPO-Porto), recrutadas em 2012. O *Montreal Cognitive Assessment* (MoCA) foi utilizado para avaliar o desempenho cognitivo das participantes antes dos tratamentos e após um (n=503), três (n=475) e cinco anos (n=466).

O projeto de investigação NEON-PC pretende investigar o declínio cognitivo nos doentes com cancro da próstata ao longo de 10 anos de seguimento (o protocolo de estudo encontra-se descrito no artigo 4). O recrutamento foi realizado no IPO-Porto, entre fevereiro de 2018 e junho de 2021, com uma interrupção de quatro meses devido à pandemia de COVID-19. Os doentes com um diagnóstico recente de cancro da próstata, propostos para diferentes tipos de tratamentos, e os doentes com uma recidiva do cancro da próstata propostos para a terapia de privação de androgéneos (TPA), foram avaliados com o MoCA antes dos tratamentos (n=609) e após um ano (n=366). As avaliações pré-tratamentos e ao fim de um ano decorreram antes do início da pandemia de COVID-19 em 449 e 147 participantes, respectivamente, e após o primeiro caso reportado de COVID-19 em Portugal, a 2 de março de 2020, em 160 e 219 participantes, respetivamente.

Nos parágrafos seguintes saõ descritos os objetivos específicos definidos para esta tese, assim como os respetivos métodos e resultados.

1. Avaliar a intermutabilidade de duas versões do MoCA para a avaliação longitudinal do desempenho cognitivo nos doentes com cancro da mama (Artigo 1).

Na avaliação dos três anos da coorte NEON-BC, foram avaliadas 422 participantes com a versão 7.1 do MoCA, previamente utilizada nas avaliações pré-tratamentos e do primeiro ano, bem como com a versão 7.3 do teste. As versões 7.1 e 7.3 foram administradas no início e no

fim da avaliação, respetivamente, com um intervalo de aproximadamente 60 minutos. O gráfico de *Bland-Altman* e os coeficientes de correlação de intraclasses (CCI), estimados em modelos de dois níveis de efeitos mistos para a concordância absoluta, foram utilizados para avaliar a concordância entre as duas versões, relativamente às pontuações totais e nos domínios e tarefas cognitivas.

No geral, não houve diferença estatisticamente significativa na distribuição das pontuações totais entre as duas versões e o CCI foi de 0,890 [intervalo de confiança a 95% (IC a 95%): 0,868 – 0,908]. Os limites da concordância de *Bland-Altman* foram de -3,70 a 3,88. Nas mulheres com pontuações médias, os resultados obtidos na versão 7.1 foram estatisticamente superiores do que na versão 7.3. Verificaram-se diferenças estatisticamente significativas em sete das 12 tarefas, assim como em três domínios cognitivos: os domínios da linguagem e da memória apresentaram valores mais altos na versão 7.1, observando-se o oposto no domínio referente à capacidade visuo-espacial.

2. Descrever a prevalência do défice cognitivo nas doentes com cancro da mama seguidas durante cinco anos após o diagnóstico de cancro, e quantificar a relação entre as características das doentes e a informação clínica com a incidência do declínio cognitivo (Artigo 2).

Este estudo incluiu 462 doentes da coorte NEON-BC, com cancro da mama não metastático, com seguimento completo ao longo de cinco anos após o diagnóstico de cancro. O défice cognitivo foi definido baseado numa pontuação no MoCA inferior ao valor normativo específico para a idade e para a escolaridade (abaixo de dois desvios-padrão (DP)). Os determinantes das variações nas pontuações cognitivas, nas participantes sem défice cognitivo na avaliação pré-tratamentos, foram identificados através da regressão linear multivariada.

O défice cognitivo foi observado em 17,7% das mulheres em pelo menos uma das quatro avaliações realizadas ao longo dos cinco anos de seguimento. Nas mulheres sem défice cognitivo na primeira avaliação, verificaram-se associações negativas e estatisticamente significativas entre a ansiedade, a depressão e a má qualidade de sono pré-tratamentos, com a variação nas pontuações do teste cognitivo (os coeficientes β variaram entre -1,60 e -0,63, $p<0,050$).

3. Descrever as trajetórias de desempenho cognitivo ao longo de cinco anos de seguimento de doentes com cancro da mama (Artigo 3).

Esta análise incluiu 464 participantes da coorte NEON-BC avaliadas com o MoCA em todos os momentos de avaliação. Utilizaram-se modelos de efeitos mistos para ajustar as pontuações no MoCA ao longo do tempo e a análise por *clusters*, para agrupar participantes com trajetórias semelhantes. Calcularam-se as áreas sob a curva (AUC) ROC (*Receiver Operating Characteristic Curves)* para avaliar a exatidão dos modelos preditivos das trajetórias cognitivas aos cinco anos.

Foram identificadas duas trajetórias: a maioria das mulheres tiveram pontuações altas, verificando-se um aumento ao longo do tempo, enquanto que 25,9% tiveram uma trajetória caracterizada por uma descida contínua das pontuações. Em cada trajetória, agruparam-se as participantes conforme a pontuação no MoCA na avaliação pré-tratamentos fosse superior ou inferior ao valor mediano do grupo. Obtiveram-se quatro grupos: 1) pontuações mais altas, estáveis ao longo do tempo; 2) pontuações mais baixas, estáveis ao longo do tempo; 3) pontuações médias com um aumento ao longo do tempo; 4) pontuações médias com uma diminuição ao longo do tempo. O modelo baseado nos fatores preditivos pré-tratamentos, nomeamente a idade, a escolaridade e a pontuação no MoCA, previu as trajetórias cognitivas com uma AUC de 0,732, que aumentou significativamente ($p<0,001$) para 0,841, quando se

acrescentou ao modelo a variação nas pontuações no MoCA entre as avaliações pré-tratamentos e do primeiro ano.

4. Estimar a prevalência do défice cognitivo nos doentes com cancro da próstata, antes de efetuarem tratamento para o cancro (Artigo 5).

Na coorte NEON-PC, o défice cognitivo foi identificado em duas etapas: primeiro, todos os participantes (n=609) realizaram a avaliação com o MoCA para detetar défice cognitivo provável, definido pela obtenção de uma pontuação inferior ao valor normativo específico para a idade e para a escolaridade (abaixo de 1,5 DP); e segundo, nos casos detetados pelo MoCA, a confirmação do provável défice cognitivo com a administração de uma bateria de testes neuropsicológicos. A coorte de base populacional EPIPorto (n=351) foi utilizada como grupo de comparação. Para estimar a associação entre o cancro da próstata/tratamentos para o cancro da próstata e o défice cognitivo, calcularam-se *odds ratios* ajustados para a idade e para a escolaridade (aOR), por regressão logística multivariável.

A prevalência de défice cognitivo provável foi semelhante nos homens da população geral e nos homens com diagnóstico recente de cancro da próstata (17,1% e 15,9%, respetivamente; aOR: 1,02, IC a 95%: 0,70 – 1,50). Os doentes propostos para a TPA como único tratamento ou em combinação com quimioterapia tinham mais frequentemente défice cognitivo do que os doentes propostos para outros tratamentos (aOR: 1,92, IC a 95%: 0,95 – 3,86). Metade dos casos com défice cognitivo provável foram confirmados como sendo défice cognitivo, através da avaliação neuropsicológica.

5. Quantificar a associação entre a ADT para o cancro da próstata e a deterioração cognitiva durante o primeiro ano de seguimento (Artigo 6).

Na coorte NEON-PC, foram avaliados 366 participantes com o MoCA antes dos tratamentos e ao fim de um ano (186 receberam a TPA e 180 fizeram outros tratmentos). Todas as avaliações pré-tratamento foram realizadas antes do início da pandemia de COVID-19 e 69,7% das avaliações do primeiro ano ocorreram após o ínicio da pandemia. O declínio cognitivo foi definido como uma variação nas pontuações (pontuação após um ano de seguimento menos a pontuação obtida na avaliação pré-tratamentos) inferior a 1,5 DP da distribuição das variações na coorte. O défice cognitivo incidente foi definido como uma pontuação no MoCA inferior ao valor normativo específico para a idade e para a escolaridade (abaixo de 1,5 SD), nos homens sem défice cognitivo pré-tratamentos. Os OR ajustados para a idade e para escolaridade (aOR) relativos à associação entre a TPA e o declínio cognitivo/défice cognitivo foram calculados através de modelos de regressão logística.

As pontuações médias no MoCA aumentarm ao fim de um ano (22,3 *vs.* 22,8, p<0,001). Os doentes tratados com TPA apresentaram declínio cognitivo mais frequentemente sobretudo após o início da pandemia (aOR de 6,91 antes e 1,93 após a pandemia; p=0,233 para a interação). A incidência cumulativa do défice cognitivo após um ano de seguimento foi de 6,9% (9,1% antes e 3,7%, após a pandemia), sendo superior nos homens tratados com TPA, um efeito que só foi observado após o início da pandemia de COVID-19 (aOR 5,53 *vs.* 0,49, p =0.044 para a interação).

**Conclusão**

A presente tese permitiu a obtenção de novos dados epidemiológicos da ocorrência do défice cognitivo nas doentes com cancro da mama, ao longo de cinco anos após o diagnóstico do cancro, e nos homens com cancro da próstata, durante um ano de seguimento.

Cerca de um quarto das doentes com cancro da mama tiveram uma trajetória de declínio cognitivo e 17,7% tiveram défice cognitivo em pelo menos uma das quatro avaliações.

Nos doentes com cancro da próstata, a prevalência do défice cognitivo pré-tratamentos foi semelhante ao da população geral e a sua incidência cumulativa a um ano foi de quase 7%.

Foram também identificados os determinantes de piores variações cognitivas ao longo do tempo nas doentes com cancro da mama e nos doentes com cancro da próstata: a ansiedade, a depressão e a má qualidade de vida pré-tratamentos estavam associadas ao declínio cognitivo incidente ao fim de cinco anos nas mulheres com cancro da mama, e a TPA estava associada ao declínio cognitivo a um ano, e ao défice cognitivo incidente, no período após o início da pandemia de COVID-19.

A variação nas pontuações no MoCA durante o primeiro ano foi identificada como sendo um marcador essencial para prever o declínio cognitivo a longo-prazo.

Estes resultados salientam a importância de avaliar o desempenho cognitivo nos doentes com cancro da mama ou com cancro da próstata, especialmente durante o primeiro ano após o diagnóstico, de forma a identificar os doentes com maior probabilidade de desenvolver declínio cognitivo. Além disso, as intervenções que focam o controlo da ansiedade, da depressão e dos problemas de sono, deverão ser investigadas devido ao seu potencial para reduzir o risco de declínio cognitivo nas mulheres com cancro da mama. É necessário investigar em investigações futuras, os possíveis mediadores do efeito da TPA no desempenho cognitivo e a sua persistência depois de terminado o tratamento.

# INTRODUCTION

## 1. BREAST AND PROSTATE CANCERS

### 1. Breast and prostate cancers – two large populations of patients

Worldwide, breast and prostate cancers were the most common in women and men, respectively, in 2020, accounting for nearly 7.8 million women and 5.0 million men surviving cancer five years following diagnosis [1]. Countries with high and very high Human Development Index (HDI) concentrate 87.4% and 95.5% of five-year prevalent cases of breast and prostate cancers, respectively, reflecting the high incidence of both cancers in these countries and their high survival rates: estimated crude incidence was 128.7 and 57.2 per 100 000 women for breast cancer, and 116.0 and 26.2 per 100 000 men for prostate cancer in very high and high HDI, respectively [2], whereas five-year net survival rates among individuals diagnosed between 2010-2014, were above 85% for breast cancer and above 90% for prostate cancer in most of these countries [3].

Figure 1 depicts the prevalence of breast and prostate cancers in the world. The highest prevalence of five-year survivors of breast and prostate cancers were observed in Australia, Canada, some European countries, New Zealand and the United States.

In Portugal, in 2020, an estimated 27 051 women and 25 602 men were living five years after a diagnosis of breast or prostate cancer, respectively [1]. Age-standardized (World) incidence [1] and five-year net survival [3] were 70.8 per 100 000 women and 87.6% for breast cancer, and 50.6 per 100 000 men and 90.9% for prostate cancer, respectively.

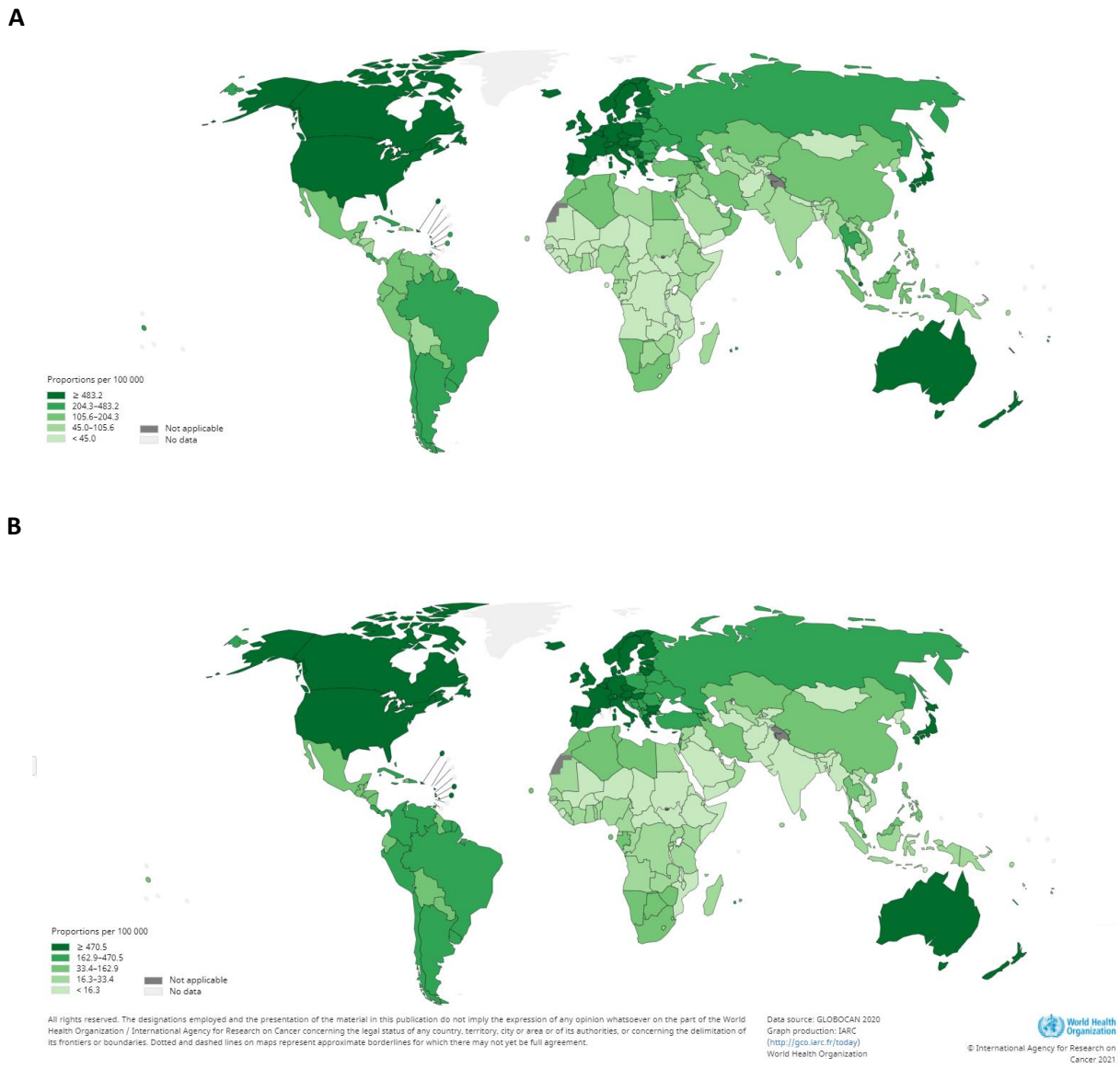


**Figure 1.** Prevalence of breast cancer among women (A) and prostate cancer among men (B) in the world.

In very high HDI countries, the number of new diagnoses of both cancers is not expected to decrease in the next years, namely due to the ageing of the population [4-7]. Older age is an important risk factor for prostate cancer. Also, the prevalence of protective factors for breast cancer, childbearing with early first birth and a large number of births, are not expected to change substantially, unless there are migratory populations with different patterns of reproductive behaviours. Early menarche and late menopause are among the non-modifiable risk factors for breast cancer. Women with a family history of breast cancer and men with a

family history of prostate cancer have a higher risk for these cancers. A genetic component, such as the mutation in *BRAC1* or *BRAC2* genes, and common lifestyles and a similar pattern of exposure to environmental carcinogens among members of a family may explain the higher incidence of these cancers in certain families. Ethnicity has also been described to be associated with prostate cancer. African-American men have the highest incidence rate of prostate cancer among ethnic groups in the United States. Genetic factors, such as chromosome *8q24* variants, are more prevalent among African-American men, and a higher rate of variations in genes that suppress tumours, such as *EphB2*, or that regulate cell apoptosis, such as *BCL2*, may explain the higher incidence of prostate cancer among this specific population. However, there are also actionable risk factors: obesity for breast cancer in post-menopausal women and for aggressive prostate cancer, alcohol consumption for breast cancer and smoking for prostate cancer. Physical activity should also be considered as it is a protective factor for both cancers [8-10].

Mammography screening programmes for the early detection of breast cancer was shown to reduce in 33% breast cancer mortality among women who attended screening [11] and the World Health Organization recommends organized population-based mammography screening programs for women aged 50-69 years, every two years, in well-resourced settings [12]. For prostate cancer, screening is currently not recommended in most countries worldwide and it remains a highly controversial issue [13, 14]. The population-based European Randomised Study of Screening for Prostate Cancer showed a reduction of 21% in prostate cancer mortality in the screening arm after a median follow-up of 13 years [15], but over diagnosis was higher than 50% in several scenarios that considered different age-ranges and frequencies of screening [16].

Improvements in breast cancer treatment over the last decades have contributed significantly for the reduction of breast cancer mortality. An increase from 46.7% to 71.5% in 10-year overall survival was reported by the Danish Breast Cancer Cooperative Group, comparing patients with early breast cancer treated in 1978-1987 to those treated in 2008-2012 [17]. However, further

investigation is needed regarding the de-escalation of treatments without compromising their effectiveness and the optimization of the duration of adjuvant therapy, and survivorship and quality of life among women with breast cancer [10].

Overtreatment is an important concern in the control of cancer and a better identification of the tumour biology could help avoiding unnecessary treatments. This is particularly true for prostate cancer, which has a very heterogeneous biology: there are cases that may progress slowly, without causing harm if left undiagnosed, others may be identified before metastasis onset and may be cured by radical treatments, such as radical prostatectomy or radiotherapy, and others may develop early metastases, not identified clinically, that may progress slowly for years after diagnosis. However, there are no recommended markers to identify prostate cancer biology subtypes. Although active surveillance is more often used in prostate cancer than in breast cancer, multimodal treatments are not as well established for high-risk prostate cancer as they are for high risk breast cancer [18].

### 1.1. Treatments for non-metastatic breast cancer

Breast cancer stage and subtype guide therapeutic options, along with patients' age, menopausal status, overall health and preferences. In developed countries, 90% of breast cancers are localized to the breast and regional lymph nodes, and the intent of treatments is to eradicate the tumour by surgery (sometimes preceded by neoadjuvant therapy) and prevent its recurrence with adjuvant treatments. The choice of systemic treatment depends on breast cancer subtype. Three major invasive breast cancer subtypes may be defined based on the presence or absence of tumour expression for oestrogen and progesterone receptors and human epidermal growth factor 2 (HER2): hormone receptor (HR) positive/HER2 negative, representing nearly 70% of patients in Western countries; HER2 positive (15% to 20% of

patients), and triple-negative (tumours lacking all three standard biomarkers; 15% of patients) [19].

**Breast cancer surgery**

In non-metastatic breast cancer (stages I to III), surgery is performed with the complete surgical removal of the breast – total mastectomy – or with the resection of the tumour, in a breast-conserving surgery or lumpectomy, usually followed by radiotherapy. Both approaches are equivalent regarding relapse-free and overall survival [20], and women with non-metastatic breast cancer may choose between the two surgical approaches, except in particular cases, in which breast-conserving surgery and/or subsequent radiotherapy are not recommended. This may occur in the presence of diffuse suspicious micro calcifications in breast imaging; positive pathologic margins after breast-conserving surgery; large or multi-centric tumours; certain collagen-vascular diseases, such as scleroderma; and prior radiotherapy to the involved breast [19]. Breast reconstruction can also be performed immediately or in a subsequent surgery [21]. Axillary lymph node dissection is used in clinically confirmed involvement of lymph nodes. In the remaining cases, sentinel lymph node biopsy is preferred and may prevent axillary lymph node dissection being performed if up to two nodes are positive [22, 23]. Sentinel lymph node biopsy has been associated with a lower risk of lymphedema and sensory loss, and better quality of life and arm functioning than axillary lymph node dissection [24], while having similar overall survival, disease-free survival and regional control [25].

**Radiotherapy**

Radiotherapy to the whole breast after breast-conserving surgery reduces by approximately half the risk of recurrence at 10 years, and by one-sixth the risk of death at 15

years [23], but older women with low-risk HR+/HER2- may benefit little from radiotherapy [26, 27]. Hypo fractionated radiotherapy is as effective as traditional dose and scheduled radiotherapy treatments but with significantly less common breast shrinkage, telangiectasia and breast oedema [28]. Following total mastectomy, radiotherapy to the chest wall may also be recommended if axillary lymph nodes were positive and/or for large primary tumours [29]. Among women with node-positive or high-risk node-negative breast cancer (tumour size greater than five cm or smaller than two cm with fewer than 10 axillary nodes removed, and at least one of the following: grade three histologic categorization, oestrogen-receptor negativity or lymphovascular invasion), the addition of regional nodal irradiation to whole-breast irradiation reduces the rate of breast cancer recurrence [30, 31].

**Systemic therapy for non-metastatic breast cancer**

Endocrine therapy is the main systemic treatment for patients with HR+ tumours (with some patients requiring chemotherapy as well), whereas, anti-HER2 therapy (usually including trastuzumab) plus chemotherapy is recommended for most patients with HER2+ tumours (plus endocrine therapy if the tumour is also HR+), and chemotherapy alone for those with triple-negative breast cancer [19].

*Endocrine therapy*

In tumours sensitive to oestrogen, that is those which are HR+, endocrine therapy is the main systemic therapy and includes two pharmacological classes of drugs: selective oestrogen receptor modulators (SERMs), which compete with oestrogen for oestrogen receptors, reducing oestrogen activity, and aromatase inhibitors that inhibit the conversion of androgens in oestrogen and therefore, reduce oestrogen activity. In the former, tamoxifen is used for

adjuvant treatment of breast cancer in pre- and post-menopausal women, whereas the latter includes letrozole and anastrozole (non-steroidal drugs) and exemestane (steroidal drug) used in post-menopausal women or, combined with ovarian suppression, in pre-menopausal women.

Based on a meta-analysis of trials of five years of tamoxifen use in early breast cancer, the Early Breast Cancer Trialists' Collaborative Group reported a substantial reduction of breast cancer recurrence throughout the first 10 years of follow-up (nearly 50% in the first five years and 30% in the subsequent years) and of breast cancer mortality by about a third throughout the first 15 years after tamoxifen initiation [32].

A meta-analysis of randomised trials compared the effectiveness of five years of endocrine therapy among post-menopausal women between three groups of treatment: tamoxifen, aromatase inhibitors and two to three years of tamoxifen followed by aromatase inhibitors. The results of this meta-analysis showed that aromatase inhibitors reduced recurrence rates by about 30% compared with tamoxifen, while treatments differ but not thereafter, and that five years of an aromatase inhibitor reduced 10-year breast cancer mortality rates by about 15% compared with five years of tamoxifen, and by about 40% compared with no endocrine treatment [33].

Two randomised trials, the Suppression of Ovarian Function Trial and the Tamoxifen and Exemestane Trial were conducted to test the potential benefit of adding ovarian suppression to treatments with tamoxifen and aromatase inhibitors, among pre-menopausal women with breast cancer. The treatments including ovarian suppression resulted in significantly higher eight-year disease-free and overall survival than those with tamoxifen alone, and the use of exemestane and ovarian suppression resulted in even lower rates of recurrence. However, the frequency of adverse events was higher in the two groups that received ovarian suppression than in the group receiving tamoxifen only [34].

As breast cancer recurrence may occur decades after therapy with curative intent [35], the effectiveness of extending endocrine therapy for ten years has also been tested in many clinical trials. It has been shown that continuing tamoxifen to ten years rather than stopping at five years further reduces recurrence and mortality [36, 37]. There was also a reduction in the risk of recurrence but not overall survival tor ten- *vs.* five-year treatments with letrozole [38]. However, adverse effects were also more frequent, namely higher rates of endometrial cancer and thromboembolic events with tamoxifen [36, 37], and new-onset osteoporosis and fractures with letrozole [38].

*Chemotherapy*

Some women with HR+/HER2- tumours may benefit from chemotherapy. Cancer stage and grade are used to decide whether these women should receive chemotherapy, and genomic risk scores can also help with that decision. Several trials have been conducted to assess the clinical utility of genomic risk scores [19]. In the MINDACT trial (Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy study), among women who were at high clinical risk and low genomic risk for recurrence based on the 70-gene signature Mammaprint, the five-year survival without distant metastasis was 1.5 percentage points lower among patients treated without chemotherapy compared to those who received chemotherapy. Additionally, the trial estimated that approximately 46% of women with breast cancer who were at high clinical risk might not require chemotherapy [39].

The risk of local and distant recurrence is higher among patients with HER2+ tumours than among those with HR+/ HER2- cancer, thus chemotherapy is usually recommended to the former. Among patients with non-metastatic triple negative tumours, chemotherapy is still the main systemic treatment available and its use is recommended when tumours are larger than five mm, even with negative axillary nodes [19].

In low-risk disease, the regimens docetaxel with cyclophosphamide, doxorubicin with cyclophosphamide, and cyclophosphamide with methotrexate and 5-fluorouracil are possible options, and in high-risk breast cancers, chemotherapy regimens containing both anthracycline and a taxane, such as doxorubicin and cyclophosphamide followed by a taxane, are associated with the greatest recurrence risk reduction. The use of anthracyclines appears to be more beneficial among patients with higher burden of lymph node involvement and/or with triple-negative disease [19].

Neoadjuvant systemic therapy may be useful for reducing tumour size until it becomes resectable, for down-staging cancer in patients desiring breast-conserving surgery, and for reducing axillary lymph node positivity to avoid axillary node dissection. Moreover, pathologic response to neoadjuvant chemotherapy is informative regarding prognosis; in the case of incomplete pathological response, adjuvant treatment with capecitabin in triple negative breast cancer, and trastuzumab emtansine in HER2+/HR- disease are recommended [19]. Platinum-based neoadjuvant chemotherapy may be considered an option in patients with triple negative tumours [40].

*Targeted therapy*

The addition of one year of treatment with trastuzumab to chemotherapy regimens has been shown to halve recurrence and mortality risk, compared with chemotherapy alone, translating into a 10% absolute improvement in long-term disease-free survival and a 9% increase in 10-year overall survival among women with HER2+ breast cancer [41-43]. The single use of paclitaxel with trastuzumab in women with small HER2+, node-negative tumours also appears to be effective to reduce the risk of loco-regional recurrence [44].

### 1.2. Prostate cancer treatments

Risk stratification of prostate cancer is used to determine therapeutic options. Usually, Tumor Node Metastases (TNM) classification, Gleason score and prostate-specific antigen (PSA) levels are used to classify the risk of disease progression, occurrence of metastases and prostate cancer-specific death. Imaging exams and genomic tests may also provide more individualized information for patient-tailored treatment [45].

The American Joint Committee on Cancer staging system classifies prostate cancer into nine prognostic stage groups based on the TNM classification, Gleason grade and PSA. This staging of prostate cancer has been shown to predict biochemical recurrence-free, metastasis-free and cancer-specific survival [46, 47]. Also, the National Comprehensive Cancer Network (NCCN) uses TNM classification, Gleason grade and PSA to classify the risk of recurrence of prostate cancer in low, intermediate and high. Furthermore, a PSA density below 15ng/mL/g, fewer than three positive biopsy cores and less than 50% of cancer in each core, complement the classification to further discriminate very low risk, whereas the criterion of more than four positive biopsy cores with a Gleason grade group 4 or 5 is part of the very high risk group [45]. The European Association of Urology (EAU) classifies prostate cancer risk regarding biochemical recurrence in low, intermediate, and high risk [14]. The Cambridge Prognostic Group (CPG) classification further divides the intermediate risk group of the EAU classification into CPG2, with favourable features, and CPG3, with unfavourable features, and the high risk group into CPG4 and CPG5, to predict the risk of prostate cancer-specific mortality [48]. The European Multicenter Prostate Cancer Clinical and Translational Research Group further discriminates high risk after retro pubic radical prostatectomy with pelvic lymphadenectomy, into good, intermediate and poor prognoses groups [49].

These and other risk classifications [50, 51], and the differences among them may explain the variation between guidelines regarding the use of treatments, especially active

surveillance, brachytherapy and radiotherapy, whereas for radical prostatectomy and androgen deprivation therapy (ADT), the recommendations for clinical practice are more consistent internationally [50].

**Observation or watchful-waiting**

Observation consists in clinical follow-up with regular PSA testing and physical exams (not more often than every six months) but no repetition of biopsy nor radiographic imaging until symptoms develop or are imminent (PSA above 100 ng/ml or changes observed during the physical exam), and then patients begin palliative ADT. The goal of observation is to maintain the quality of life of the patient who has a prostate cancer that is unlikely to cause morbidity or death. Older patients or those with high frailty, for whom other health conditions compete with prostate cancer for death, are eligible for observation [45].

**Active surveillance**

The high accessibility and use of PSA testing has contributed to an earlier detection of prostate cancer. Active surveillance is a recommended option of treatment for very low risk cancer in the NCCN guidelines [45] and for low risk disease in the EAU guidelines [14]. It consists in regular PSA testing (not more often than every six months), multiparametric magnetic resonance imaging and repetition of prostate biopsy (both, not more often than once a year). The revised Epstein criteria [52] are used to identify prostate cancer with a low tumor load that benefits from active surveillance. These include PSA density below 0.15 ng/mL, a Gleason score equal or below 6, less than three biopsy cores containing prostate carcinoma and 50% involvement or lower of any core with prostate carcinoma [53].

Patients on active surveillance may need to repeat prostate cancer biopsy if there is suspicion of disease progression. The Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) score was developed, based on the changes of the tumour in the multiparametric magnetic resonance imaging, to provide a criterion for disease progression on imaging and contributes to reduce unnecessary biopsies [54].

The ten-year results of the ProtecT Randomised Controlled Trial of men with localized prostate cancer allocated to active surveillance, radical prostatectomy or radiotherapy with androgen deprivation therapy, demonstrated that the occurrence of deaths was low overall but it was higher among patients on active surveillance (1.85% *vs.* 0.67% for surgery and 0.73% for radiotherapy). Also, disease progression (active surveillance 20.35%, surgery 5.87%, radiotherapy 6.62%) and metastases (active surveillance 5.6%, surgery 2.4%, radiotherapy 2.7%) were more frequent in patients under active surveillance but sexual dysfunction (95% at six months) and urinary incontinence (55% at six months) were more common in patients treated with radical prostatectomy, and sexual (88% at six months) and bowel dysfunctions (5% at six months) in patients treated with radiotherapy. The active surveillance arm, as the other arms of the trial, included patients with intermediate and high risk prostate cancer (most international guidelines do not recommend active surveillance in these groups). Radical treatments were performed in 45% of men after at least 12 months under active surveillance [55]. This trial provided important information on the benefits and disadvantages of deferring treatments.

**Radiotherapy**

Radiotherapy is effective as a standalone treatment for low risk prostate cancer [56] or with ADT for intermediate and high risk disease [57], as salvage treatment after radical prostatectomy [58] and in low-volume metastatic disease (bone metastases) [59].

Modern techniques of radiotherapy in prostate cancer include external beam radiation therapy (EBRT), proton radiation and brachytherapy. Within EBRT, intensity-modulated radiotherapy (IMRT) and stereotactic body radiation therapy (SBRT) are used with the guidance of imaging information on the target position and movements (image-guided radiotherapy − IGRT), and increases the safety procedures and treatment accuracy within smaller margins. SBRT involves delivering high daily doses using unique beam arrangements. Only five fractions are delivered, reducing the duration of radiotherapy from the usual 45 to four or five days. In a pooled analysis from a multi-institutional consortium of prospective phase II trials, the five-year relapse-free survival was 95%, 84% and 81% for low-, intermediate- and high-risk patients treated with SBRT, respectively [60]. In another study, the seven-year cumulative rates of biochemical recurrence were 4.5% [95% confidence interval (CI), 3.2%-5.8%] among patients with low-risk disease, 8.6% (95%CI, 6.2%-11.0%) for favourable intermediate-risk disease and 14.9% (95%CI, 9.5%-20.2%) for unfavourable intermediate-risk disease. Moreover, SBRT was associated with low rates of severe adverse events [61]. These results support that SBRT should be considered in the therapeutic options to treat low and intermediate risk patients.

Proton radiotherapy has been used for decades to treat prostate cancer and to date, there is no robust evidence on better clinical outcomes with this technique compared to IMRT, with both being recommended by the NCCN [45].

Brachytherapy differs from EBRT and proton therapy because it requires the hospitalization of patients for surgery. It has the advantage of being performed in a single treatment and not in several daily sessions. Radioactive sources are placed into the prostate tissue, either as low-dose-rate permanent seeds or as high-dose-rate temporary sources.

Seven years after brachytherapy, biochemical recurrence of prostate cancer (PSA higher than 0.4 ng/mL) occurred in 6.9%, 0.0% and 4.8% of patients aged 62 years or younger, and with low, intermediate and high-risk disease, respectively [62]. The NCCN recommends

brachytherapy as a single treatment for very low, low and favourable intermediate risk prostate cancer, or as a boost after EBRT [45].

**Radical prostatectomy**

Most guidelines recommend radical prostatectomy as a suitable option to treat any prostate cancer that has not spread to lymph nodes nor metastasized in patients with more than ten years of life expectancy [50]. Three trials [55, 63, 64] have reported on the effectiveness of radical prostatectomy, for the outcomes of disease recurrence and prostate cancer-specific mortality. The Scandinavian Prostate Cancer Group Study Number 4 included men with clinically localized prostate cancer who were randomly allocated to radical prostatectomy or watchful-waiting. After ten years of follow-up, prostate cancer mortality was lower among patients assigned to radical prostatectomy (8.6% *vs.* 14.4%). The relative risks (95%CI) were 0.60 (0.42, 0.86) for metastases and 0.33 (0.25, 0.44) for local progression [65]. At 23 years, a mean of 2.9 extra years of life were gained with radical prostatectomy, and after 29 years of follow-up, the number needed to treat to avert one death from any cause was 8.4 [66].The Prostate Intervention Versus Observation Trial randomly assigned prostate cancer patients to watchful-waiting or to radical prostatectomy. Surgery did not significantly reduce all-cause or prostate-cancer mortality, as compared with observation, through at least 12 years of follow-up, but prostate-cancer mortality was lower in the radical prostatectomy group than in the observation group, among men with a PSA value of more than 10 ng/ml (5.6% *vs.* 12.8%, P=0.02) and among men with high-risk prostate cancer (9.1% *vs.* 17.5%, P=0.04) [64]. The most recent randomized clinical trial is the ProtecT Randomised Controlled Trial, which included men with prostate cancer assigned to radical prostatectomy, radiotherapy with ADT or active surveillance. After 10 years of follow-up, deaths occurred in 0.67%, biochemical progression in 5.87% and metastases in 2.4% of patients of the radical prostatectomy arm, which were less frequent than in the active

surveillance group. However, sexual dysfunction and urinary incontinence were more frequent in the surgery arm: 95% and 55%, respectively, after six months. Together, these trials suggest a benefit of performing radical prostatectomy to reduce prostate cancer recurrence and cancer-specific mortality in high-risk patients.

**Androgen deprivation therapy**

Prostate cancer is an endocrine-responsive disease [67] and ADT aims to achieve a testosterone castration level by bilateral orchiectomy, or by the administration of an agonist or an antagonist of the luteinizing hormone-releasing hormone (LHRH) [68]. Antiandrogens may also be used prior to or at initiation of ADT with an agonist of the LHRH (aLHRH) to reduce the initial surge in testosterone in the first week of ADT, and the related potential risk of bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression and cardiovascular death due to hyper coagulation status [69]. Complete androgen blockade is achieved with the concomitant administration of aLHRH and an antiandrogen [68]. The effectiveness of orchiectomy, different aLHRH drugs (leuprolide, triptorelin, goserelin) and the antagonist of the LHRH (degarelix) are considered equivalent, although orchiectomy and degarelix achieve castration within 12 hours and 72 hours, respectively, whereas aLHRH takes a longer time (two to four weeks) [70].

ADT induces tumour regression, allows for the reduction of symptoms and prolongs survival. ADT is recommended as a primary treatment in T3/T4 tumours and/or with positive lymph nodes and/or metastases [50], as neoadjuvant treatment to radiotherapy in localized or regional (N1 M0) disease, as adjuvant treatment in patients with positive lymph node after radical prostatectomy and in high-risk patients after radical prostatectomy (biochemical recurrence within the first three months after surgery, and PSA doubling time lower than nine months, or Gleason score equal to or higher than 8) [45, 68, 71]. In asymptomatic oligo

metastatic prostate cancer (without visceral metastases), ADT may be deferred and metastasis-directed therapy (stereotactic body radiation therapy, surgery or focal thermal ablation) is an option [68].

ADT in combination with standard radiotherapy to treat localized prostate cancer is recommended only in patients with intermediate- or high-risk disease, during six months and 24-36 months, respectively [45, 50, 72]. The benefits of short ADT duration in intermediate-risk disease treated with dose escalation radiotherapy is currently under investigation in several trials [72]. The duration of ADT associated with salvage radiotherapy has not been established in clinical trials but is recommended to be six to 12 months [68].

Patients who begin ADT are said to have castration sensitive or castration naïve prostate cancer, that is, ADT achieves a castration level of serum testosterone and the cancer is under control, until there is evidence from biochemical data, imaging exams or symptoms that the tumour is progressing despite the castration level of testosterone. At this stage, prostate cancer is said to be castration resistant, independently of metastases being present or not [73].

Despite specific indications for ADT as a neoadjuvant treatment of radiotherapy in incident prostate cancer, its duration when combined with salvage radiotherapy has not been defined, and for advanced prostate cancer, ADT is used indefinitely. Controlling the adverse effects of ADT is therefore highly relevant, namely bone fragility, and associated skeletal events, cardiovascular disease, diabetes, neurocognitive effects and hot flashes [68].

**Abiraterone acetate, enzalutamide and apalutamide, and docetaxel**

Two randomized clinical trials, Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) [74] and Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) demonstrated the benefits of adding docetaxel to ADT in metastatic castration sensitive

prostate cancer (mCSPC): a longer time for the development of castration resistance, a lower number of prostate-cancer deaths [74] and substantially longer overall survival [74, 75].

The randomized clinical trial LATITUDE reported a higher overall survival with ADT combined with abiraterone compared with ADT alone in men with newly diagnosed mCSPC [76].

Therefore, in high volume mCSPC (four or more bone metastases, including at least one outside of axial skeleton, or visceral, i.e. lung, liver metastases), ADT with abiraterone and ADT with docetaxel are recommended instead of ADT alone, and in low volume disease, ADT with abiraterone is preferred to ADT alone [68].

In castration resistant prostate cancer, ADT should be continued and complemented with abiraterone or enzalutamide, if there are metastases, or with enzalutamide or apalutamide in non-metastatic castration resistant prostate cancer [45, 70].

### 1.3. Cancer- and cancer treatment-related complications

Breast and prostate cancers rank first and second, respectively among cancers associated with the highest number of years of life lost because of disability, in Europe [77] and generally in high-income countries [78]. Among a common core of 13 cancer- and cancer-related symptoms, the three most frequent in patients with breast and prostate cancer were the same and with similar prevalences (in patients with breast cancer, in patients with prostate cancer): fatigue or tiredness (31.3%, 35.5%), disturbed sleep (27.5%, 25.6%) and pain (18.5%, 17.5%). Distress ranked fifth (18.9%) in patients with breast cancer and eighth (13.5%) in patients with prostate cancer. Patients with these cancers presented similar prevalence of none, more than three, more than five and more than seven moderate or severe symptoms: 47.0%, 30.1%, 17.0% and 8.5% in women with breast cancer, and 43.1%, 27.8% , 15.3% and 7.2% in men with prostate cancer [79]. Besides these symptoms, patients with breast and prostate cancers share other

cancer- and cancer treatment-related complications: gonadal failure and hot flashes, sexual dysfunction, bone loss and osteoporotic fractures, and depression and anxiety. Patients with breast cancer also frequently present lymphedema, infertility, neuropathic pain and chemotherapy induced peripheral neuropathy, whereas urinary and bowel dysfunctions, anaemia, and cardiovascular and metabolic effect, are frequent in patients with prostate cancer [4, 80, 81].

In an online survey conducted in 2006 and in 2010 aiming to evaluate the concerns of patients with cancer (32% breast cancer and 7.0% prostate cancer) diagnosed within the previous five years, fatigue and cognitive problems were the most frequently reported physical concerns [82]. The 2010 survey described that nearly half and one-fifth of patients with breast and prostate cancers, respectively had perceived cognitive dysfunction.

The documents *Patient Guide on Survivorship* [83] and *Cancer Survivorship* [84], targeting survivors of cancer, and produced by the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO), respectively, present cognitive complaints as a possible problem that may affect patients with cancer and recommend patients to report their complaints to doctors. These documents refer the term *chemo brain* but highlight that patients not treated with chemotherapy may also present cognitive complaints. ESMO's *Patient Guide Survivorship* describes cognitive problems as "memory impairment (trouble remembering things); inability to concentrate; changes in executive function (lower ability to process information, make decisions), problems with multi-tasking; difficulty learning new material/reading comprehension; troubling working with numbers (calculating)".

Cognitive dysfunction is referred in international clinical practice guidelines as a potential complication of systemic cancer treatments: the American Society of Oncology includes a specific recommendation on cognitive impairment in the Breast Cancer Survivorship Care Guideline, regarding pro-actively asking if the patient has cognitive problems, assessment

of reversible contributing factors, and referral to neuropsychological assessment and rehabilitation [80]; the NCCN guidelines on survivorship includes a specific section *Cognitive Function*, where the NCCN panel acknowledges that, despite the limited evidence on how to manage cognitive dysfunction, patients benefit from the validation of their symptom experience and that patients should be screened for potentially reversible factors that may contribute to cognitive impairment [85]; ESMO also describes the potential problem of cognitive dysfunction in young women with breast cancer but did not issue any recommendation regarding the detection and management of this problem [86]; and the EAU refers cognitive impairment as a possible effect of ADT, but did not issue any recommendation to detect and manage cognitive impairment [70].

The different positions of international cancer societies regarding the assessment and management of cognitive impairment in patients with breast and prostate cancers, reflect the lack of strong evidence to support recommendations.

## 2. COGNITIVE IMPAIRMENT IN PATIENTS WITH BREAST AND PROSTATE CANCERS

### *Chemo brain and cancer-related cognitive impairment*

Most research on cognitive impairment in cancer patients began with the observation that breast cancer patients frequently reported cognitive complaints during chemotherapy [87]. This perception by cancer patients, also expressed under the designation of c*hemo brain* was further analysed in longitudinal studies with a pre-chemotherapy assessment of cognitive performance and with cancer controls not treated with chemotherapy, showing that cognitive impairment was also present in the controls and before cancer treatments [88, 89]. A new term, cancer-related cognitive impairment (CRCI) was introduced to describe cognitive impairment in

a more comprehensive population of patients with cancer, exposed to potential causes of cognitive impairment other than chemotherapy. The International Cognition and Cancer Task Force published a set of recommendations to harmonize studies on CRCI, however, without the intent to define diagnostic criteria. Learning and memory, information processing speed, and executive function were considered as the essential cognitive domains to be assessed with neuropsychological tests, as these cognitive domains were described as being affected by chemotherapy [90]. The absence of a definitive definition of CRCI and of a specific test to diagnose this condition led to the proposal of another term, "cancer-related cognitive dysfunction" [91].

**Proposed mechanisms for cancer-related cognitive impairment**

Imaging studies have reported changes in brain structure and function of patients treated with chemotherapy, and animal studies have contributed to understand the mechanisms involved in *chemo brain* [92, 93]. Although most antineoplastic drugs do not cross the blood brain barrier, smaller concentrations than the ones needed to kill cancer cells, have been shown to be neurotoxic in animal studies. Moreover, individual variability in the permeability of the blood brain barrier may exist [92], and brain vascular disease, ageing [94] and increased serum cytokines observed in cancer [95] may interfere with the permeability of the blood brain barrier. Most neurons are not dividing cells and they lack DNA repair mechanisms, which make them susceptible to antineoplastic drugs that induce DNA damage [92, 93], such as cyclophosphamide in breast cancer treatment [96]. Also, neurons rely on an extensive microtubule-based network for proper functions and communication, which makes them vulnerable to microtubule-targeting agents, such as paclitaxel and docetaxel, used in breast and prostate cancer treatments. Chemotherapy may also reduce neurogenesis and glycogenesis, which are crucial processes for maintaining the health and plasticity of the central

nervous system [93]. Neurotoxic effects of inflammation and cytokine deregulation observed in patients undergoing chemotherapy may also take part in the mechanisms for CRCI [92]. Variants of catechol-O-methyltransferase (COMT), which regulates dopamine, epinephrine and norepinephrine metabolism, may also explain a higher individual susceptibility to CRCI [92, 93].

Regarding treatments other than chemotherapy, the serum level of IL-6 was described as a mediator of the detrimental effect of radiotherapy on cognitive performance [97], and research suggests that oestrogen and testosterone have protective effects on the brain and that a reduction in these hormones through endocrine therapy for breast cancer and ADT in prostate cancer may contribute for cognitive impairment [92]. Testosterone seems to be involved in the expression of the apoE allele [98] and in the regulation of the clearance of β-amyloid protein [99], both markers of Alzheimer's disease.

**Epidemiological studies on the cognitive performance of patients with breast and prostate cancers**

A review from 2012 reported on 53 studies aiming to examine the cognitive effects of chemotherapy on patients with breast cancer: 26 were longitudinal, of which 23 assessed cognitive function after surgery and before chemotherapy, and then up to one year after chemotherapy (only two studies had a follow-up of two years); the sample size ranged from 16 to 136, and patients were generally in their 40s; there were women with cognitive dysfunction at baseline in eight out of the 17 studies reporting cognitive function before chemotherapy; in 16 out of the 23 studies, there was evidence of a negative effect of chemotherapy on cognitive performance consistent with a frontal subcortical profile including deficits in learning and memory, information processing speed, and executive function. The incidence of cognitive decline varied between 19% and 78% across studies. Seven studies assessed cognitive

performance in multiple time points, and one study reported a progressive and new emerging cognitive decline after completion of chemotherapy [100].

Older women (above 60 years), that constitute half of the women with breast cancer, were under-represented in these studies. Late and long-term effects of chemotherapy could not be evaluated, except in cross-sectional studies. The large range in the incidence of cognitive decline was attributed in part to methodological issues, namely the variability in the neuropsychological tests used and the criteria used to define cognitive impairment [90].

Seven meta-analyses [101] aimed to overcome the limitations of small sample size and variability in cognitive measures, by using mean scores of the cognitive tests used in each study and computing effects sizes for the comparison between patients who received chemotherapy and controls. The results of these studies demonstrated that the detection of a negative effect of chemotherapy in cognitive performance of patients with breast cancer varied with the cross-sectional or longitudinal analysis of the data, the control group and the cognitive domain: cross-sectional data indicated worse performance in patients treated with chemotherapy in several cognitive domains [101-107], whereas in longitudinal analyses, only visual memory was consistently worse in the chemotherapy group regardless of the control group (normative data, healthy controls or breast cancer controls) [104], and memory recall and executive function were associated with worse performance in the chemotherapy group compared to healthy controls [101]. Longitudinal studies also showed that cognitive performance improved over time [102], an effect that was stronger in patients than in controls [107].

Regarding the effects of endocrine therapy in cognitive performance of patients with breast cancer, the most recent meta-analysis included 14 studies: eight cross-sectional studies with cognitive assessment occurring 26 to 40 months after endocrine therapy initiation, and six longitudinal studies with only five to 12 months of endocrine therapy. A total of 1822 subjects (911 patients with breast cancer treated with endocrine therapy, 249 controls with breast

cancer, and 662 non-cancer controls) were included in the analysis and the main results were as follows: there were significantly worse performances in verbal learning/memory, visual learning/memory, frontal executive function and information processing speed among patients receiving endocrine treatments than in controls, in cross-sectional studies. Longitudinal analyses showed no differences between patients and controls in any cognitive domain. Overall, patients treated with tamoxifen did not differ from patients treated with aromatase inhibitors; however, subgroup analyses indicated that patients treated with tamoxifen performed better than those treated with non-steroidal aromatase inhibitors (*e.g.* letrozole and anastrozole) in several domains, but showed few performance differences relative to patients treated with steroidal aromatase inhibitors (*e.g.* exemestane) [108].

Nevertheless, the longitudinal studies included in the meta-analysis mentioned above, had a relatively short duration of follow-up (up to two years) that did not allow for the detection of cumulative or late effects of hormonal treatment, which are particularly important because endocrine therapy is prescribed for five to ten years.

A recent systematic review (2021) analysed 17 longitudinal studies conducted in patients with breast cancer treated with chemotherapy, radiotherapy and endocrine therapy, and reported that the prevalence of cognitive impairment was 25% before treatment, 24% after chemotherapy and 21% at the maximum follow-up of one year (10%, 10% and 7% in healthy controls at the corresponding evaluations). Compared to their pre-treatment cognitive functioning, 24% of patients declined after treatment and 24% at the one-year follow-up. Some studies also reported a cognitive improvement showing that 15% and 31% of patients improved, after treatment and at one-year, respectively. In general, patients undergoing chemotherapy had a higher odds of cognitive impairment and decline than no-chemotherapy patients and healthy controls [109]. None of the studies included had a follow-up longer than one year.

Research on CRCI in patients with prostate cancer addressed mostly the effects of ADT. A meta-analysis included 14 studies: three cross-sectional (23 to 31 months after ADT initiation) and 11 longitudinal (pre-ADT and 6 to 9 months after ADT initiation). A total of 417 patients were included. The main results of the meta-analysis were that patients treated with ADT performed worse than controls or their own baseline on visuomotor tasks ($g = -0.67$, $p = .008$; $n = 193$), whereas there were no statistically significant differences regarding the other six cognitive domains (attention/working memory, executive function, language, verbal memory, visual memory and visuospatial ability) [110]. The maximum duration of ADT in the longitudinal studies of this meta-analysis was nine months. Longer follow-up is needed to understand the course of cognitive impairment in patients treated with ADT.

Only one prospective study reported the effect of ADT after a longer follow-up, 36 months; compared to prostate cancer controls not treated with ADT and to non-cancer individuals, the variation in cognitive performance in the ADT group was worst in only one task of the battery of 14 neuropsychological tests. When considering a global measure of cognitive performance computed from the z-score of each test, the prostate cancer control group improved compared to the ADT and non-cancer groups, which had similar global measures [111].

Information on the effects of new-generation hormonal therapies (NGHT: abiraterone acetate, enzalutamide, apalutamide and darolutamide) on cognitive performance comes from the randomized controlled trials conducted to assess the effectiveness of these drugs in prostate cancer treatment. A systematic review analysed 19 of those randomized clinical trials and observed that investigator-based evaluation of cognitive impairment was available in only seven. The enzalutamide arm appeared to have more negative cognitive outcomes than the abiraterone or the placebo arms, although no confidence intervals or p values were reported [112].

In the last decade, many retrospective studies, based on large databases of electronic medical records and administrative databases, reported conflicting results on the association of ADT with dementia and Alzheimer's disease. A recent meta-analysis of 14 of these studies showed that ADT, compared to no ADT, was associated with increased risk of dementia [all causes; hazard ratio (HR): 1.21, 95%CI: 1.11, 1.33] and Alzheimer disease (HR 1.16, 95%CI: 1.09, 1.24). This effect was not significant if ADT duration was shorter than 12 months [113].

Retrospective studies are limited by the quality of the database, that include data not collected for research purpose and may miss important confounders, by the possibility of exposure misclassification, and immortal time bias [114]. Misclassification of dementia may also have occurred in some studies, because the diagnosis of dementia may not have been recorded in primary care settings [115]. Prospective studies with long follow-up times are needed to better inform on the association of ADT with dementia.

## 2. THE ASSESSMENT OF COGNITIVE PERFORMANCE OVER TIME

Longitudinal study designs allow for the study of cognitive trajectories over time. This is particularly important for understanding the course of CRCI. It has been proposed that chemotherapy could induce an acute injury to the brain, similar to what happens in traumatic brain injury, but milder, and that a partial recovery could occur due to the adaptive mechanisms

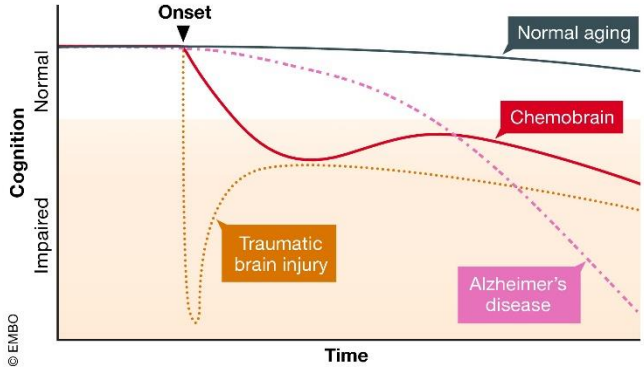


**Figure 2** Proposed trajectory of *chemo brain* in comparison with normal aging, Alzheimer's disease, and traumatic brain injury.

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of the brain. Then, because of the progressive depletion of these mechanisms, a progressive decline in cognitive performance could take place, at a rate between what is expected from normal ageing and a neurodegenerative disease, such as Alzheimer's. A representation of this model is presented in Figure 2 [93]. Patient characteristics, namely emotional state, co-morbities, lifestyle, cognitive reserve, genetics, as well as pathological alterations due to the tumour and cancer treatments, could influence the baseline cognitive performance and the inflection of the trajectory towards recovery.

Longitudinal analyses could also strengthen the efforts for identifying the determinants of cognitive decline and causal inference. The small sample size of previous studies limited the power to identify those determinants [100]. However, extensive evaluations that include the administration of a battery of neuropsychological tests as well as questionnaires to assess emotional state and socio-demographic data of patients and their lifestyle may limit the feasibility of large studies and the acceptance of patients to participate over time, both in patients with cancer and non-cancer controls. Moreover, neuropsychological assessment may not be available in all clinical settings, at least for an initial approach of a suspected cognitive dysfunction, which limits the translation to clinical practice of the results obtained from research with neuropsychological tests.

The Montreal Cognitive Assessment (MoCA) is a screening test designed to detect mild cognitive impairment. Its validity has been established to detect mild cognitive impairment and Alzheimer's disease. The positive and negative predictive values were 89% and 91%, respectively, for mild cognitive impairment, and 89% and 100%, respectively, for Alzheimer's disease. The MoCA has a higher sensitivity for the identification of mild cognitive impairment and Alzheimer's disease (90% and 100%, respectively) than the Mini Mental State Examination (18% and 78%, respectively) [116]. It is translated into 56 languages and dialects. MoCA assesses

memory, language, executive functions, visuospatial skills, calculation, abstraction, attention, concentration and orientation [117]. These characteristics of the MoCA make this tool an attractive instrument to assess cognitive performance in large research studies as well as in clinical practice.

In the repeated assessment of patients' cognitive performance over time to detect a decline or an improvement due to cognitive rehabilitation or to drug administration, practice effects should be considered as a source of measurement error. The practice effect can be defined as "the changes in test performance attributed to practice with the test material(s) and/or prior exposure to test instruments, paradigms, or settings", and they include deliberate rehearsal, incidental learning, procedural learning, changes in an examinee's conceptualization of a task, shift in strategy, or increased familiarity with the test-taking environment and/or paradigm (*i.e.*, "test-wiseness") [118]. The magnitude of this effect varies among neuropsychological tests. In a battery of neuropsychological tests administered weekly for six weeks to healthy young volunteers, there was no practice effect for the Trail Making Test Part A, while the Stroop test had the greatest practice effect, albeit for all tests, six alternative forms had been used to prevent participants from repeating the same version of the test [119]. The use of alternate forms of a test aims to reduce the practice effect but it is essential that both versions are equivalent in their ability to measure cognitive performance, so as to not introduce another measurement error in longitudinal assessment.

## AIMS

Many women with breast cancer and men with prostate cancer may expect to live many years after their cancer diagnosis. Cognitive decline is frequently reported among patients with cancer but there is a lack of knowledge on the real dimension of this problem, namely its course over time and its determinants.

Therefore, this thesis aims to contribute for a better understanding of the occurrence of cognitive decline in patients with breast cancer and with prostate cancer, filling gaps in research regarding the possible long lasting effects of breast cancer and its treatments on patients' cognitive performance, and by quantifying the effects of ADT in the cognitive performance of patients with prostate cancer. The data of two cohorts, NEON-BC, 466 women with breast cancer followed for five years, and NEON-PC, 366 men with prostate cancer followed for one year (study protocol presented in Paper 4), will be used in this thesis.

The specific objectives are as follows:

I. To study the interchangeability of two versions of the MoCA for the longitudinal assessment of the cognitive performance of patients with breast cancer (Paper 1).
II. To describe the prevalence of cognitive impairment among patients with breast cancer over five years after cancer diagnosis and to quantify the relations between patients' characteristics and clinical variables with incident cognitive decline in patients with breast cancer (Paper 2).
III. To describe the trajectories of cognitive performance of patients with breast cancer, over five years (Paper 3).
IV. To estimate the prevalence of cognitive impairment before prostate cancer treatment (Paper 5).
V. To quantify the relation between ADT and cognitive deterioration during the first year of follow-up of patients with prostate cancer (Paper 6).

## RESEARCH METHODS

The objectives of the thesis were accomplished using data from two cohorts: the NEON-BC cohort of patients with breast cancer and the NEON-PC cohort of patients with prostate cancer.

### NEON-BC

The NEON-BC cohort was assembled with the main objective of studying the neuro-oncological complications of breast cancer treatments, and the relations between cancer and treatments with patient reported outcomes (PROMs) [120]. Adult women with a recent diagnosis of breast cancer, proposed for surgery and expected to be followed at the Portuguese Institute of Oncology of Porto (IPO-Porto) were considered eligible. Those with a history of breast surgery for benign reasons, radiotherapy or chemotherapy for another cancer were excluded. Patients with a MoCA score below 17, or 16 in patients aged 65 or older, were considered to be less likely to reliably answer self-questionnaires assessing PROMs, and were excluded. A total of 506 women were evaluated before surgery or neoadjuvant treatment, and 503, 475 and 466 patients after one, three and five years, respectively.

### NEON-PC

The NEON-PC cohort was planned and implemented during this thesis, to study cognitive decline over ten years in patients with prostate cancer, and the possible association of ADT with cognitive deterioration. The study protocol is described in Paper 4.

Briefly, the cohort included all patients with a recent diagnosis of prostate cancer and patients with recurrent disease who were proposed for ADT, expected to be followed at IPO-Porto. Patients with a history of radiotherapy, chemotherapy, ADT, and psychiatric or neurologic

conditions impairing cognitive function, were excluded. Cognitive performance was assessed with the MoCA before treatments and after one year. Patients with a MoCA score below age- and education-specific normative values were referred for a comprehensive neuropsychological assessment to confirm cognitive impairment.

The recruitment of participants started in February 2018 and ended in June 2021. Field activities were suspended during four months from March to June 2020 due to the COVID-19 pandemic. Since July 2020, procedures for the evaluation of participants were adapted to reduce the risk of coronavirus contagion: only the cognitive assessment was performed in person, the structured interview of participants was done through a phone call, and self-administered questionnaires were completed at home by patients and returned by mail. The one-year evaluation was postponed in several cases because, when possible, patients had consultations by phone call and did not visit IPO-Porto in person. The baseline and one-year evaluations were completed before the COVID-19 pandemic onset for 449 and 147 participants, respectively, and after the first case reported in Portugal, in March 2$^{nd}$ 2020, for 160 and 219 participants, respectively.

**PAPER 1**

# Interchangeability of two versions of the Montreal Cognitive Assessment for the longitudinal evaluation of patients with breast cancer

## Paper 1

# Interchangeability of two versions of the Montreal Cognitive Assessment for the longitudinal evaluation of patients with breast cancer.

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**Keywords:** Mental Status and Dementia Tests, Data Accuracy, Psychometric, Alternate Forms, Montreal Cognitive Assessment

**Abstract**

**Purpose**: The cognitive performance of patients with breast cancer (BCa) may be affected by cancer and its treatments. The Montreal Cognitive Assessment (MoCA) is a widely used cognitive impairment screening tool, but practice effects must be considered for longitudinal assessments. Since learning effects could be overcome through the alternate use of two versions of the MoCA, we aimed to explore their interchangeability by comparing their overall, and domain- and task-specific scores, among patients with BCa.

**Methods**: Patients with BCa from the NEON-BC cohort were evaluated with the MoCA, version 7.1, after diagnosis and after one year. At the three-year follow-up (n=422), the 7.1 and 7.3 versions of the MoCA were applied at the beginning and at the end (approximately one hour later) of this evaluation, respectively. Agreement between versions regarding the total, sub-domain and task scores were assessed using Bland-Altman plots and Intraclass Correlation Coefficients (ICC) estimated in two-way mixed-effects models for absolute agreement of individual scores.

**Results**: The means of total scores were not statistically different between versions and the ICC was 0.890 (95%confidence intervals:0.868,0.908). The Bland-Altman limits of agreement were -3.70 to 3.88. For women with mid-range scores, total scores were significantly higher in version 7.1. Seven of the 12 tasks presented a significantly different percentage of correct answers: the language and memory domains presented higher scores in version 7.1, while the opposite was observed for visuospatial ability.

**Conclusion**: Despite similar overall scores being obtained with the two versions of the MoCA, there were item-specific differences that may compromise their interchangeable use.

**Introduction**

Cancer is often accompanied by cognitive complaints, with cognitive impairment being present at the time of cancer diagnosis in up to one-third of the patients, or occurring during treatments, in up to three-quarters of cancer survivors, and potentially persisting thereafter [1, 2]. Monitoring cognitive status throughout the course of the disease is important to understand the potential impact of cancer and its treatments on the occurrence of cognitive impairment and to shape clinical care to meet the specific needs of patients with cancer.

The Montreal Cognitive Assessment (MoCA) is a brief screening instrument developed to detect mild cognitive impairment [3] and is one of the most used cognitive test in patients with cancer [4]. However, the possibility of practice effects is suggested by anecdotal reports of patients who train for visuospatial ability tasks or create mnemonics to improve delayed recall (personal communication), and has been supported by studies that used this instrument for serial testing [5, 6].

Different versions of the MoCA have been developed to be used alternately to minimize this limitation [7, 8]. Previous studies conducted in the general population or in geriatric outpatient clinics compared alternate forms with the original version of the MoCA, and showed similar total scores [9-11], though analyses at the task level found systematic differences [9, 11].

To the best of our knowledge there are no previous reports on the use of the MoCA - original and alternate versions - for the longitudinal assessment of cognitive performance in patients with breast cancer. Therefore, this study aims to explore the interchangeability of two Portuguese versions of the MoCA, the original version 7.1 and its alternate, version 7.3, regarding the overall scores, and the domain- and task-specific scores, when applied to patients with breast cancer.

**Methods**

The Montreal Cognitive Assessment (MoCA)

The MoCA is a screening test that assesses eight cognitive domains (executive function; visuospatial ability; short-term memory; language; attention; concentration; working memory; and temporal and spatial orientation), through 12 tasks: the *adapted trail-making B* and the *verbal abstraction* tasks (executive function); the *phonemic fluency* task (executive function and language); the *clock-drawing* and the *three-dimensional geometric figure copy* tasks (visuospatial abilities); the *short-term memory recall* task (short-term memory); *target detection using tapping*, *serial subtraction,* and *digits forwards and backwards* tasks (attention, concentration and working memory); the *repetition of two syntactically complex sentences* and the *three-item confrontation naming task with low-familiarity animals* (language); and answering questions related to time and place (orientation). The overall score ranges from 0 to 30, with higher scores corresponding to better cognitive performance [12].

The original version 7.1 and its alternate form 7.3 were translated and culturally adapted to the Portuguese population [13, 14], but the validation study and normative data for the general Portuguese population were published for version 7.1 only [15].

Evaluation of the participants

The present study is based on the three-year follow-up evaluation of the NEON-BC cohort of patients with breast cancer, which was assembled to estimate the incidence of neurological complications of the disease or its treatments during the first years after diagnosis, as previously described in detail [16]. Adult women admitted to the Breast Clinic of the Portuguese Institute of Oncology of Porto (IPO-Porto) with newly diagnosed breast cancer and proposed for surgery were consecutively recruited in 2012; only those scoring at least 17 in the MoCA, or 16 for those

aged 65 years or older, were included, under the assumption that lower scores correspond to a high probability of cognitive impairment [15]. A total of 506, 503 and 475 patients were evaluated at baseline (before any treatment), and after one and three years, respectively, with the original version of the MoCA (version 7.1). Participants lost to follow-up were older [mean (standard deviation (sd)) in years: 60.1 (15.2) *vs.* 54.9 (10.8), p=0.013] and had a lower baseline MoCA score [mean (sd): 21.4 (2.9) *vs.* 23.2 (3.6), p=0.006].

At the three-year follow-up both the 7.1 and 7.3 versions of MoCA were applied at the beginning and at the end (approximately one hour later) of this evaluation, respectively, by the same researcher. The MoCA was administered in a quiet room at IPO-Porto, in a day the participant had an appointment or an exam to perform at the hospital, to minimize inconvenience due to travel and to increase participant adherence to the study. A total of 39 participants did not perform the second test due to lack of time and, therefore, were not included in this study. Also, participants with metastatic disease (n=14) were not considered for data analysis. Therefore, the present study included data from 422 participants who were not statistically different from those excluded, regarding age [mean (sd) in years: 54.9 (10.5) *vs.* 54.7 (13.0), p=0.883], education (median, percentiles 25 and 75, in years: 4, 6 and 11 *vs.* 4, 6 and 12, p=0.854) and MoCA scores with version 7.1 at the three-year evaluation [mean (sd): 23.5 (4.1) *vs.* 23.5 (4.5), p=0.997]. Probable cognitive impairment (PCI) at baseline and at the one-year follow-up was considered present if the MoCA score was lower than two standard deviations below the mean of age- and education- specific distributions from normative data [15].

Statistical analysis

Single-item task scores, scored with 0 or 1, were compared between versions, using McNemar's test [17]. Multiple-item task scores, cognitive domains scores and MoCA total scores were

compared with Student´s t-test for paired data. Pearson's correlation coefficient (r) for paired data was calculated between total scores of the two MoCA versions.

Agreement between MoCA versions regarding the total scores and scores in each cognitive domain were evaluated with the Bland-Altman plot and respective limits of agreement [18] and Intraclass Correlation Coefficients (ICCs) and 95% confidence intervals (95%CI) estimated in two-way mixed-effects models considering absolute agreement between individual scores.

Participants were grouped according to their classification as having PCI at baseline or at the one-year evaluation in: never had PCI; had PCI at baseline or at one-year; and had PCI at baseline and at one-year.

Tests of hypothesis were performed considering a level of significance of 5%, two-sided.

All analyses were performed using Stata version 11.2 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).

**Results**

The distributions of the total scores were similar for versions 7.1 and 7.3 of the MoCA (Figure 1); the median, percentiles 25 and 75 were the same for both versions (24, 21 and 27, respectively), and Pearson's correlation coefficient was 0.889, p<0.001.

Table 1 presents the percentage of correct answers in single-item tasks, the mean of scores in multiple-item tasks and in each cognitive domain, for the two MoCA versions. A total of seven out of the 12 tasks presented significant differences between the two versions: *Phonemic fluency, Repetition of two syntactically complex sentences*, *Three-item confrontation naming task with low-familiarity animals*, *Short-term memory recall* and *Three-dimensional geometric figure copy, resulting* in significantly higher mean scores in the language and short-term memory cognitive domains and a lower mean score in visuospatial ability when using version 7.1; *Adapted trail-making B*, and *Digits forwards and backwards* also had significantly different mean scores between the MoCA versions, but not in their corresponding cognitive domains.

Figure 2 presents the Bland-Altman plot of the total scores of the MoCA. The limits of agreement of the MoCA scores ranged from -3.70 to 3.88. Among women aged 65 or older, those with up to four years of education and those with the lowest average MoCA scores (first quartile), the limits of agreement corresponded to a wider interval. The total scores were systematically higher with version 7.1 (mean difference: 0.317) among participants with mid-range average MoCA scores (second and third quartiles), while no differences were observed for the lowest and highest average scores.

The limits of agreement for language (maximum possible score: 6) and short-term memory (maximum possible score: 5) were the highest observed among all cognitive domains: -1.74 to 2.34 and -1.96 to 2.41, respectively (Figure 3).

Table 2 presents the ICCs of the total agreement between the MoCA scores in each version, for the groups based on the presence of PCI at baseline and at the one-year evaluation, and

according to age and education categories. The ICC was 0.890 (95%CI: 0.868, 0.908) in the whole sample and above 0.800 irrespective of a history of PCI in previous evaluations. Among women with the highest educational level, the ICC was 0.636 (95%CI: 0.055, 0.895) for those with PCI at baseline or at one-year.

**Discussion**

No systematic difference between total scores attained with the original version of the MoCA and its alternative version was found, and the ICC was above 0.800, which may be considered as good agreement [19]. However, the limits of agreement of the Bland-Altman plot were -3.70 to 3.88 and for mid-range average scores the scores with version 7.1 were significantly higher than with version 7.3. Additionally, there were systematic differences in the language, short-term memory and visuospatial ability sub-scores.

The large variance in participants' scores may have contributed to a high ICC [20], even if the differences larger than two points observed in the Bland Altman limits of agreement may be considered clinically unacceptable. Indeed, in a previous study conducted in a general population aged 57-78 years, participants who developed mild cognitive impairment after 3.5 years of follow-up had a significant mean decrease in MoCA scores of 1.73 points while scores were stable in participants who remained cognitively healthy, suggesting 1.73 points as a clinically significant decline [21]. A two point decrease in MoCA scores was also used to define cognitive decline in another study on the cognitive deterioration of patients with symptomatic and asymptomatic cerebrovascular disease [22].

Practice effects have been suggested to contribute for improvements in MoCA scores in yearly assessments of healthy older adults [5], and in the present study, language and short-term memory scores attained with version 7.1, which was applied at baseline and at the one- and three-year evaluations, were higher than with version 7.3, which had not been used before. However, in other studies [9, 11], the original and its alternate version were both applied for the first time, and higher language scores were also observed with version 7.1, though no systematic differences in the short-term memory domain were reported. In our study, version 7.3 was applied approximately 60 minutes after version 7.1, and this short period of time may have also contributed to confusion regarding which words the participant had to recall, and a lower

performance with version 7.3 may have occurred due to contamination of the test performed an hour earlier. However, this task was scored based only on the number of correct answers, that is, no penalization was attributed for incorrect recalled words, and participants had no time limit to answer. Moreover, between the administration of the two versions, participants were evaluated with self-administered questionnaires and in a structured interview, which may have contributed to minimize practice effects or interference between the MoCA evaluations. Therefore, it is plausible that learning effects contributed for higher scores with version 7.1 than with version 7.3 for the short-term memory domain.

In three previous studies [9, 11, 23], abstraction scores were lower with version 7.1 than with version 7.3, however, no such difference was observed in the present study. Learning effects may have improved scores at the three-year evaluation with version 7.1 and reduced the difference between versions. Indeed, increases in the number of correct answers were observed from baseline to both the one- and three-year evaluation, for the pair of words train and bike but not for watch and ruler.

We found differences between the cube copy task (version 7.1) and the cylinder copy task (version 7.3), suggesting a higher difficulty in performing the former. A similar result was obtained in the study of parallelism between the original Italian version and its two alternate versions [11], as well as in a study using a Rasch analysis [23].

The strengths of our study are the assessment of a large sample with a wide range of age, education and MoCA scores, and the fact that participants were evaluated with the MoCA two and three years earlier, allowing us to study agreement between versions according to different cognitive ability and cognitive impairment status overtime. The higher mean scores in version 7.1 that were observed among participants with mid-range scores (between 21 and 27) may be due to a higher difficulty level of version 7.3 and/or learning effects from previous assessments with version 7.1. For participants with low and high cognitive performance, floor and ceiling

effects, respectively, may explain the absence of systematic differences. Moreover, in stratified analyses of agreement between versions according to status of PCI in previous years, ICCs were as high as in the whole sample, suggesting that agreement between total MoCA scores in each version was similar in healthy and cognitively impaired participants. For participants with a higher educational level, a smaller variance in scores was noticed, which may explain the lower ICC, while a similar level of agreement may exist.

One limitation of our study is the potential practice effect from the first test (version 7.1) to the second test (version 7.3), which was applied one hour later. This possible interference could have been better evaluated if the two versions of the test were applied in a different order in half of the participants. However, the original version was applied first to avoid compromising the longitudinal evaluation of the participants with a version of the instrument that was not yet shown to be equivalent to the original.

Additionally, the generalizability of our results is limited to women with non-metastatic, mostly early-stage breast cancer and due to the fact that this is a single centre-study, although IPO-Porto is the largest hospital delivering cancer care in Northern Portugal and receives patients from the entire country.

**Conclusions**

Our results suggest that using alternate versions of the MoCA for clinical monitoring of patients and for epidemiological studies of cognitive decline may not be a suitable approach, due to item-specific differences between the two versions.

## Declarations


### Funding

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### Conflicts of interest/Competing interests

None to declare.

### Availability of data and material

The datasets generated and analysed in this study will not be publicly available given that the included patients do not specifically provide their consent for public sharing of their data and that anonymization is unlikely to be feasible, since the identification of patients treated in only

one institution within a relatively short period may be possible when taking sociodemographic and clinical characteristics into account.

**Code availability**

Not applicable.

**Authors' contributions**

**Natália Araújo**: Formal analysis, Writing original draft, Writing - Review & Editing; **Luísa Lopes-Conceição**: Investigation, Writing - Review & Editing; **Samantha Morais**: Writing - Review & Editing; **Filipa Fontes**: Funding acquisition, Investigation, Data curation, Writing - Review & Editing; **Teresa Dias**: Resources, Writing - Review & Editing; **Vítor Tedim Cruz**: Conceptualization, Funding acquisition, Writing - Review & Editing; **Luís Ruano**: Conceptualization, Funding, Writing - Review & Editing; **Susana Pereira**: Conceptualization, Funding acquisition, Investigation, Supervision, Project administration, Writing - Review & Editing; **Nuno Lunet**: Conceptualization, Funding acquisition, Supervision, Project administration, Writing - Review & Editing.

**Ethics approval**

The NEON-BC study was approved by the Portuguese National Authority for Data Protection (nº 3478/2017) and by the Ethics Committee of IPO-Porto (Ref. CES 406/011 and CES 99/014). All participants gave their written informed consent.

**Consent for publication**

Not applicable.

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**Table 1**. Comparison of results in single-item tasks, multiple-item tasks and cognitive domains between versions 7.1 and 7.3 of the Montreal Cognitive Assessment (MoCA).

| | **Version 7.1** | **Version 7.3** | |
|---|---|---|---|
| | % of correct answers in each item (except if otherwise specified) | | P |
| **EXECUTIVE FUNCTION** (maximum score=4; three tasks; four items scored 0 or 1) | | | |
| Task 1, one item: Adapted trail-making B | 62.8 | 74.4 | <0.001 |
| Task 2, one item: Phonemic fluency* - words beginning with the letter: P (v.7.1); M ( v.7.3) | 44.8 | 35.1 | <0.001 |
| Verbal abstraction task scores (2 items), mean (sd) | 1.4 (0.7) | 1.4 (0.6) | 0.138 |
| *Executive function scores, mean (sd)* | *2.5(1.3)* | *2.5(1.2)* | *0.564* |
| **VISUOSPATIAL ABILITY** (maximum score=4; two tasks; four items scored 0 or 1) | | | |
| Task 1, one item: Three-dimensional geometric figure copy: cube (v.7.1); cylinder (v.7.3) | 35.1 | 77.7 | <0.001 |
| Task 2, item 1: Clock-drawing - clock circle | 99.5 | 99.1 | 0.317 |
| Task 2, item 2: Clock-drawing - clock numbers | 87.0 | 90.0 | 0.033 |
| Task 2, item 3: Clock-drawing - time: "ten past eleven" (v.7.1); "ten past nine" (v.7.3) | 59.2 | 56.9 | 0.307 |
| *Visuospatial ability total scores, mean (sd)* | *2.8(0.9)* | *3.2(0.9)* | *<0.001* |
| **ATTENTION, CONCENTRATION AND WORKING MEMORY** | | | |
| (maximum score=6; three tasks; two items scored 0 or 1; one item scored 0, 1, 2 or 3) | | | |
| Task 1, item 1: Digits forwards | 79.6 | 84.1 | 0.046 |
| Task 1, item 1: Digits backwards | 71.1 | 62.6 | 0.011 |
| Task 2, one item: Target detection using tapping | 93.1 | 93.4 | 0.655 |
| Task 3: Serial subtraction of 7, beginning with 100 (v.7.1) or 80 (v.7.3) | | | |
| no correct results | 6.9 | 7.3 | 0.480 |
| one correct result | 17.3 | 18.5 | 0.275 |
| two or three correct results | 31.5 | 28.9 | 0.131 |
| four or five correct results | 44.3 | 45.3 | 0.547 |
| Total scores in the task "Serial subtraction", mean (sd) | 2.1 (0.9) | 2.1 (1.0) | 0.593 |
| *Attention, concentration and working memory scores, mean (sd)* | *4.6 (1.3)* | *4.5 (1.3)* | *0.300* |
| **LANGUAGE** (maximum score=6; three tasks; six items scored 0 or 1) | | | |
| Repetition of two syntactically complex sentences (2 items) - task scores, mean (sd) | 1.5 (0.7) | 1.5 (0.6) | 0.038 |
| Three-item confrontation naming task with low-familiarity animals - task scores, mean (sd) | 2.6 (0.7) | 2.4 (0.7) | <0.001 |
| Phonemic fluency* - words beginning with the letter: P (v.7.1); M ( v.7.3) | 44.8 | 35.1 | <0.001 |
| *Language total scores, mean (sd)* | *4.5(1.3)* | *4.2(1.4)* | *<0.001* |
| **SHORT-TERM MEMORY** (maximum score=5; one task; five items scored 0 or 1) | | | |
| *Short-term memory scores, mean (sd)* | *3.6 (1.2)* | *3.4 (1.3)* | *<0.001* |
| **ORIENTATION** (maximum score=6; one task; six items scored 0 or 1) | | | |
| Item 1: date | 96.7 | 96.9 | 0.317 |
| Item 2: month | 99.8 | 99.8 | 1.000 |
| Item 3: year | 95.3 | 96.0 | 0.083 |
| Item 4: day of the week | 98.8 | 99.3 | 0.157 |
| Item 5: place | 99.8 | 99.8 | 1.000 |
| Item 6: city | 99.8 | 99.8 | 1.000 |
| *Orientation total scores, mean (sd)* | *5.9 (0.3)* | *5.9 (0.3)* | *0.014* |

* The phonemic fluency task is performed and accounted for in the total MoCA score only once but it is part of the executive function and of the language cognitive domains.

† Each of the four possible scores (no correct answers scored with 0, one correct answer scored with 1, two or three correct answers scored with 2 and four or five correct answers scored with 3) were coded as 1 or 0, whether the participant received this sc

**Table 2.** Agreement between scores in each version of the Montreal Cognitive Assessment (MoCA), among participants who never had probable cognitive impairment (PCI), those who had PCI at baseline or at one-year, and those who had PCI at baseline and at one-year. Intraclass Correlation Coefficients and 95% confidence intervals [ICC (95% CI)] of two-way mixed-effects models, expressing absolute agreement between individual measurements.

| | | Age (years) | | | Education (years) | | |
|---|---|---|---|---|---|---|---|
| | All | 25-49 | 50-64 | ≥65 | 1-4 | 5-9 | 10-20 |
| All | n=422 | n=100 | n=202 | n=120 | n=177 | n=123 | n=122 |
| Version 7.1, MoCA , mean (sd) | 23.5 (4.1) | 25.5 (3.6) | 23.8 (3.7) | 21.4 (4.2) | 20.8 (3.9) | 24.3 (3.0) | 26.7 (2.4) |
| Version 7.3, MoCA , mean (sd) | 23.4 (4.1) | 25.5 (3.6) | 23.7 (3.8) | 21.3 (4.1) | 20.8 (3.9) | 24.2 (3.3) | 25.6 (2.4) |
| ICC (95% CI) | 0.890 (0.868,0.908) | 0.855 (0.792, 0.900) | 0.882 (0.848, 0.909) | 0.870 (0.818, 0.907) | 0.841 (0.792, 0.880) | 0.825 (0.760, 0.874) | 0.772 (0.689, 0.835) |
| Participants who never had PCI | n=371 | n=80 | n=177 | n=114 | n=171 | n=97 | n=103 |
| Version 7.1, MoCA , mean (sd) | 23.7 (4.1) | 26.1 (3.3) | 24.1 (3.7) | 21.6 (4.1) | 20.9 (3.8) | 25.2 (2.4) | 27.0 (2.2) |
| Version 7.3, MoCA , mean (sd) | 23.6 (4.1) | 26.0 (3.2) | 24.0 (3.7) | 21.4 (4.1) | 20.9 (3.7) | 25.1 (2.7) | 26.8 (2.2) |
| ICC (95% CI) | 0.884 (0.860, 0.905) | 0.811 (0.720, 0.874) | 0.876 (0.837, 0.907) | 0.866 (0.811, 0.905) | 0.831 (0.778, 0.872) | 0.716 (0.603, 0.801) | 0.753 (0.655, 0.826) |
| Participants who had PCI at baseline or at one-year | n=32 | n=11 | n=15 | n=6 | n=6 | n=16 | n=10 |
| Version 7.1, MoCA , mean (sd) | 22.0 (4.2) | 23.0 (4.5) | 22.8 (3.4) | 18.0 (3.9) | 16.7 (4.6) | 21.7 (2.7) | 25.6 (2.0) |
| Version 7.3, MoCA , mean (sd) | 21.8 (4.7) | 23.4 (5.6) | 22.1 (3.6) | 18.2 (4.4) | 16.2 (5.2) | 21.2 (2.9) | 26.1 (2.4) |
| ICC (95% CI) | 0.926 (0.854, 0.963) | 0.960 (0.859, 0.989) | 0.886 (0.695, 0.960) | 0.858 (0.293, 0.979) | 0.903 (0.466, 0.986) | 0.875 (0.679, 0.954) | 0.636 (0.055, 0.895) |
| Participants who had PCI at baseline and at one-year | n=19 | n=9 | n=10 | n=0 | n=0 | n=10 | n=9 |
| Version 7.1, MoCA , mean (sd) | 22.1 (3.9) | 23.7 (4.2) | 20.6 (3.1) | na | Na | 19.8 (2.8) | 24.6 (3.5) |
| Version 7.3, MoCA , mean (sd) | 22.1 (3.4) | 23.7 (2.9) | 20.7 (3.3) | na | Na | 20.5 (2.4) | 23.9 (2.5) |
| ICC (95% CI) | 0.869 (0.693, 0.948) | 0.800 (0.340, 0.951) | 0.888 (0.614, 0.971) | na. | na. | 0.840 (0.483, 0.958) | 0.821 (0.393, 0.957) |

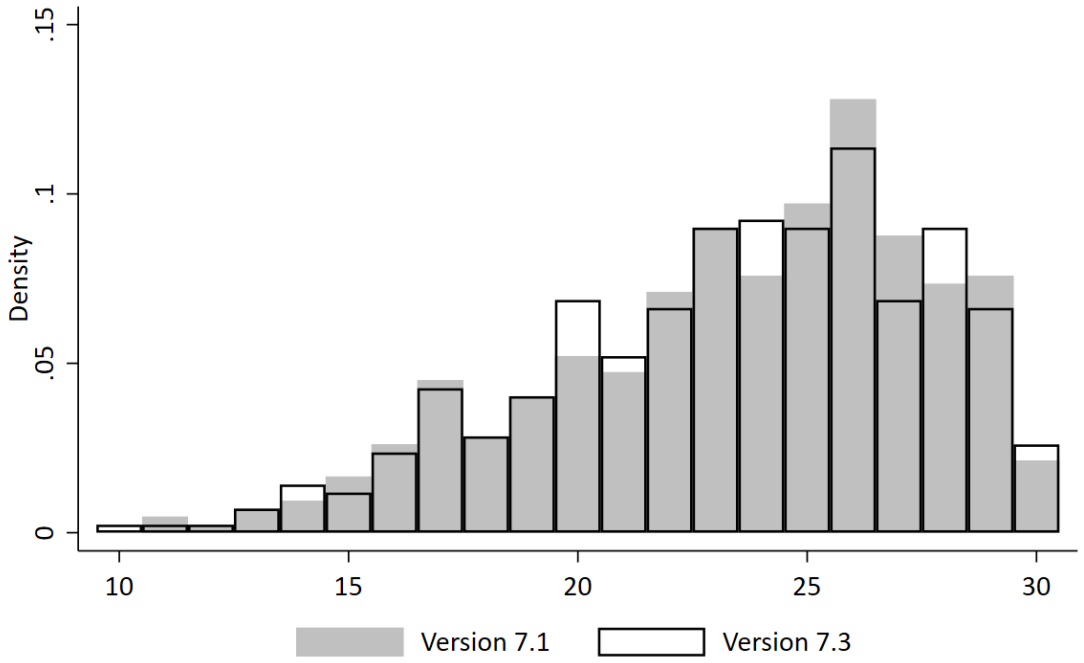



Figure 1. Distribution of the total scores of the Montreal Cognitive Assessment (MoCA) for each of the tests performed using the original version (version 7.1) or the alternate (version 7.3).

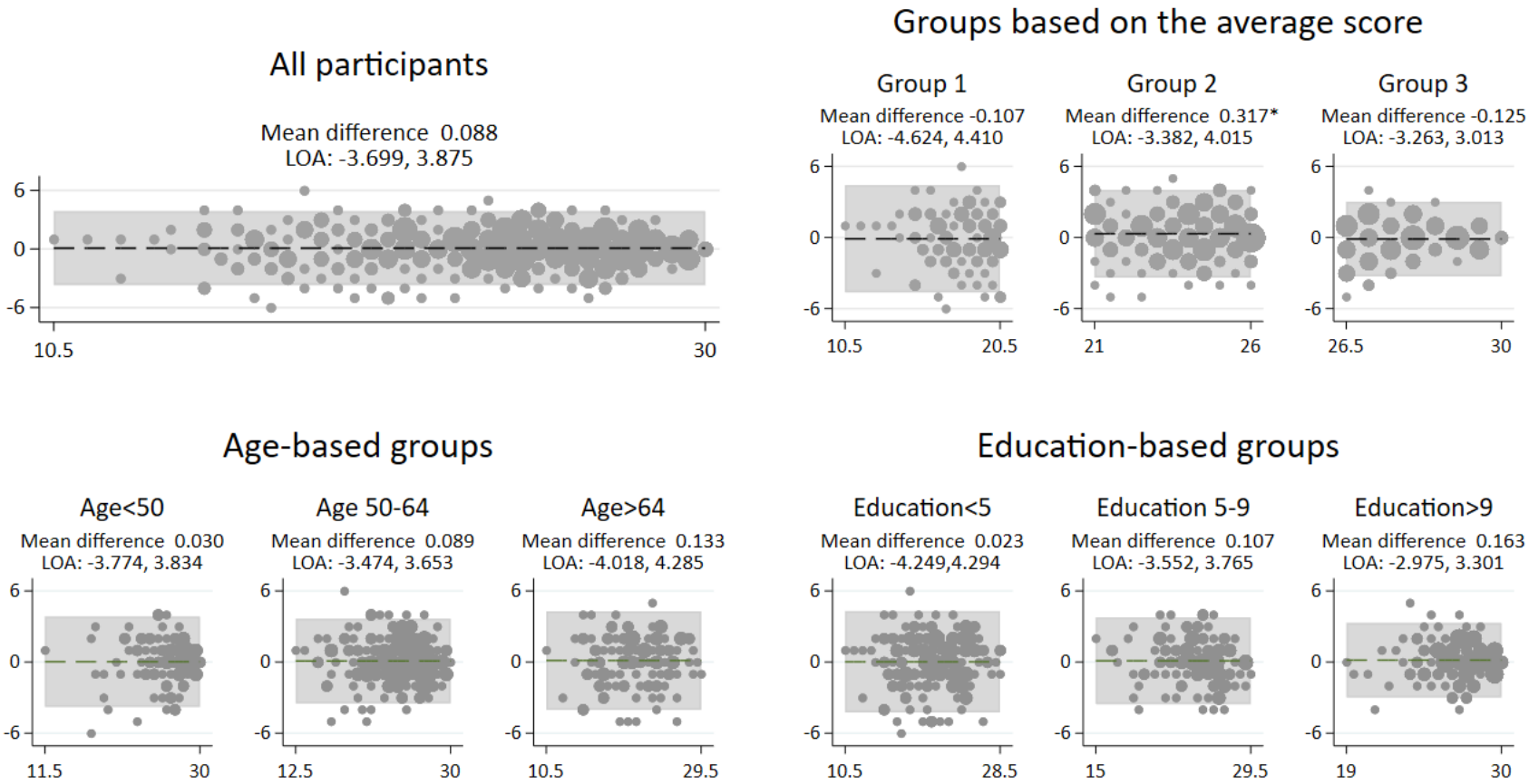
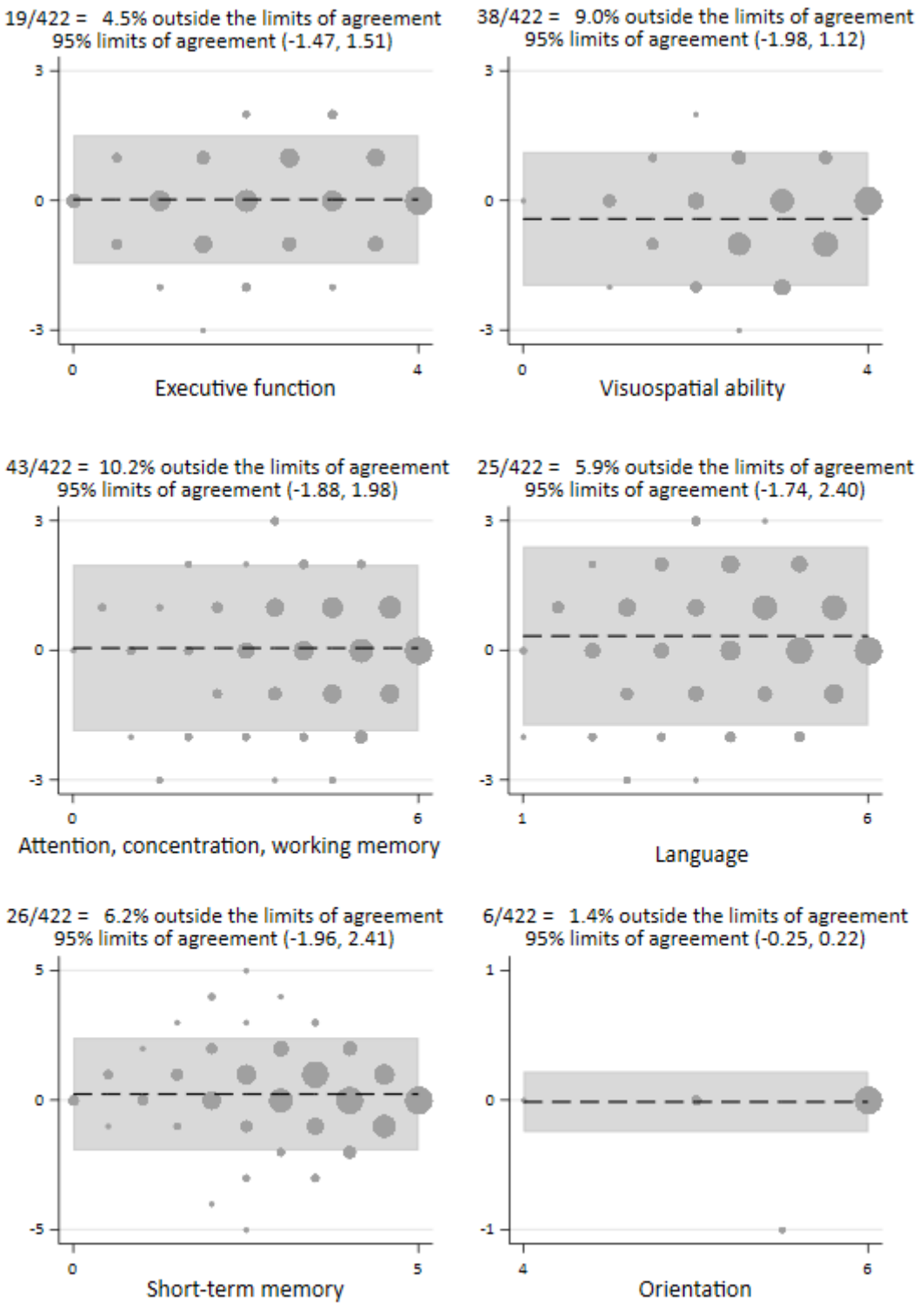



Figure 2. Bland Altman plots comparing total scores attained in versions 7.1 (v.7.1) and 7.3 (v.7.3) of the Montreal Cognitive Assessment (MoCA), considering all participants and groups of participants based on the average score (group 1- first quartile of the average scores; group2- second and third quartiles of the average scores; group3- fourth quartile of the average scores), and on age and education.
*p<0.05




Y axis: difference of scores between versions (v.7.1-v.7.3)
X axis: average of scores of the two tests [(v.7.1 + v.7.3)/2]

Figure 3. Bland Altman plots comparing cognitive domains sub scores attained in versions 7.1 (v.7.1) and 7.3 (v.7.3) of the Montreal Cognitive Assessment (MoCA).

**PAPER 2**

# Neuropathic pain, chemotherapy-induced peripheral neuropathy and cognitive decline in a 5-year prospective study of breast cancer patients– NEON-BC.

## Paper 2

# Neuropathic pain, chemotherapy-induced peripheral neuropathy and cognitive decline in a 5-year prospective study of breast cancer patients–NEON-BC.

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**Keywords:** Breast Neoplasms; Neuropathic Pain; Peripheral Nervous System Diseases / chemically induced; Cognition disorders

**Abstract**

**Purpose:** To describe the occurrence of neurological complications among breast cancer patients up to five years after diagnosis, and to assess determinants of neuropathic pain (NP), chemotherapy-induced peripheral neuropathy (CIPN) and cognitive decline.

**Methods:** Women with an incident breast cancer (n=462) were recruited at the Portuguese Institute of Oncology-Porto in 2012, and underwent systematic neurological examinations and evaluations with the Montreal Cognitive Assessment (MoCA) before treatment and after one, three and five years. Multivariate logistic regression was used to assess determinants of NP and CIPN, and multivariate linear regression for variation in MoCA scores.

**Results:** Prevalence of NP and CIPN decreased from the first to the fifth year after diagnosis (NP: from 21.1% to 16.2%, p=0.018; CIPN: from 22.0% to 16.0% among those undergoing chemotherapy, p=0.007). Statistically significant associations were observed between: cancer stage III and both NP and CIPN; triple negative breast cancer and NP; chemotherapy and NP; taxanes and CIPN. Cognitive impairment was observed in 17.7% of the women at least once. The mean MoCA scores were 23.3, 24.0, 23.6 and 23.7 at baseline and after one, three and five years, respectively. Anxiety, depression and poor sleep quality at baseline were associated with decreases in MoCA values from pre- to post-treatment (β coefficients ranging -1.60 to -0.63, $p<0.050$).

**Conclusion:** Neurological complications are frequent after breast cancer treatment. Follow-up protocols should consider the persistence of these conditions for several years following diagnosis.

**Introduction**

In developed countries, breast cancer is the most prevalent in women, reflecting its high incidence and survival. Breast cancer ranks first in incidence among women worldwide [1] and the five-year net survival is over 80% in most of the more developed countries [2]. This justifies the concern about the burden associated with the long-term effects of cancer and its treatment, including neurological complications, among survivors.

Breast cancer-related neurological complications may result from direct nervous system invasion, namely by metastatic disease [3], as well as from indirect nervous system effects, including treatment-related neurological complications. The latter are a growing concern due to their potential to decrease the quality of life or even limit breast cancer treatments among the growing population of cancer survivors [4, 5]. Neuropathic pain (NP), chemotherapy-induced peripheral neuropathy (CIPN) and cognitive impairment are potential breast cancer treatment-related complications [6-8]. Regarding NP due to breast cancer, data are available mostly from studies using only screening questionnaires to assess the outcome, and evidence regarding long-terms effects is scarce and mostly from cross-sectional study designs [8, 9]. Acute and short-term effects have been described for CIPN, but few studies have reported a follow-up longer than six months following chemotherapy [6]. Likewise, longitudinal studies allowing for the assessment of cognitive decline over several years since breast cancer diagnosis are scarce and presenting conflicting results. There are reports of no evidence of an association between chemotherapy [10, 11] or hormone therapy [12] and cognitive decline, as well as studies suggesting a positive association of antineoplastic drugs [13, 14] and anastrazole with cognitive deterioration [15].

We have previously presented results from a cohort of women with incident breast cancer [16], and showed that cancer-related neurological complications were frequent, even three years after cancer diagnosis [17]. Here we update the previous report by quantifying the prevalence

of neurological complications up to five years after diagnosis of breast cancer, including NP, CIPN, cognitive impairment, phantom breast syndrome, brain metastases and cerebrovascular disease, as well as the determinants of NP, CIPN and cognitive decline.

**Methods**

*Patients and setting*

NEON-BC is a prospective cohort study designed to evaluate the neurological complications of breast cancer; the study protocol has been described elsewhere [18]. Briefly, between January and December 2012 all women admitted to the Breast Clinic of the Portuguese Institute of Oncology – Porto (IPO) with a histological diagnosis of breast cancer in the previous three months, proposed for surgery and expected to be followed at IPO were eligible. Those who had been submitted to breast surgery for benign conditions, or to chemotherapy or radiotherapy to the chest for another primary cancer were excluded. Breast cancer patients who were illiterate or scored less than 17 (or 16 for those aged 65 years or older) in the Portuguese version of the Montreal Cognitive Assessment (MoCA) [19, 20] were also excluded.

A total of 506 women were evaluated at baseline, before any treatment for breast cancer, and at one (n=503), three (n=475) and five years (n=466) since breast cancer diagnosis; a total of 464 participants were evaluated in all moments. Reasons for losses to follow-up were: 18 died (the cause of death was neurological in six: meningeal carcinomatosis in two, systemic and cerebral metastases in two, limbic encephalitis and cerebral metastasis in one each), 12 abandoned the study, four transferred to another hospital, two were considered unable to participate by the neurologist and four could not be contacted.

The 42 participants lost to follow-up were not significantly different from included participants regarding age (mean 57.4 years *vs.* 54.5 years, p=0.103), and education (mean 6.9 years *vs.* 7.7 years, p=0.227), though presented less often with early stage (0, I, II, IIIA) breast cancer (87.8 % *vs.* 95.7%, p=0.026).

*Data collection*

Face-to-face interviews of the participants were conducted by trained interviewers who collected socio-demographic and lifestyles data using a structured questionnaire. Clinical data on the tumor and treatments were retrieved from medical records. Participants completed the Hospital Anxiety and Depression Scale (HADS) [21, 22] at baseline to measure the levels of anxiety and depression, in the previous week; anxiety and depression sub-scores equal to or higher than 11 out of a possible 21 were considered indicative of clinically significant anxiety or depression, respectively. They also answered the Pittsburgh Sleep Quality Index [23, 24] to assess sleep quality in the previous month; those with scores equal to or higher than five were classified as having poor quality of sleep.

Breast cancer subtypes were based on information from medical files regarding immunohistochemistry and in situ hybridization-based biomarkers, namely hormone receptors (HR; estrogen and progesterone receptors, considered positive if present in ≥1% of cells) and human epidermal growth factor receptor (HER2), and were classified into HR-positive/HER2-negative; HER2-positive; and triple-negative breast cancer (HR-negative/HER2-negative).

*Assessment of neurological complications*

Patients were observed by a neurologist and a neurological exam was performed at all evaluations.

CIPN was defined as peripheral neuropathy diagnosed after chemotherapy or worsening of a preexisting neuropathy after chemotherapy. The Total Neuropathy Score, clinical version (TNSc) [25] and the Common Terminology Criteria for Adverse Events, V.4.0 (CTCAE) [26] were used for CIPN classification.

Probable NP was diagnosed according to the Neuropathic Pain Special Interest Group (NeuPSIG) criteria [26], which incorporate information from a neurological exam and clinical history. The Brief Pain Inventory Short Form [27] was used to rate pain, which consists of a mean score of

four questions measuring the worst, least, average and current pain in the past 24 hours (range: 0 to 10, with 0 = “no pain” and 10 = “pain as bad as you can imagine”).

Among patients submitted to mastectomy, phantom breast syndrome was considered present when women reported the sensation that the removed breast was still present [28].

Cognitive performance was assessed with MoCA before cancer treatment, and after one, three and five years. Cognitive impairment was considered present if the participant scored at least two standard deviations below the mean of age- and education-specific distributions from normative data [29].

*Statistical analysis*

Since only two participants had stage IV breast cancer, they were excluded from the present analysis, and a total of 462 participants who underwent the four evaluations – baseline, one, three and five years – were considered.

Characteristics of the patients and their lifestyle, of the tumor, and of the treatments received were presented as counts and proportions.

For each neurological complication, point prevalences at the follow-up evaluations and period prevalences over the five years were computed; for cognitive impairment, prevalence at baseline was also estimated. Comparisons between different moments of evaluation were performed using the McNemar test.

Adjusted odds ratios (OR) were computed using logistic regression, to quantify the association between participants’ characteristics, clinical data of the tumor and treatments received, with the presence of NP and CIPN over the five-year follow-up. Multiple linear regression analysis was used to estimate β coefficients of the relation between participants’ characteristics, clinical data of the tumor and treatments performed, with the variation in the MoCA score between

baseline assessment and each follow-up evaluation. Variables introduced in the logistic regression or linear regression models are described in the footnotes of the tables.

Statistical analyses were performed using Stata, version 15.1 (StataCorp, College Station, Texas, USA) and a significance level of 0.05 was considered.

*Ethics*

The study was approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES 406/011, CES 99/014, CES 290/014). All participants provided written informed consent.

**Results**

At baseline, nearly half of the women were 55 years or older, 42.0% had up to four years of education and 29.2% had more than 10 years. Cancer stage was 0 or I for 55.0% of the women, while 30.3% and 14.7% of the patients presented with stages II and III, respectively. More than three quarters of the participants had HR+/HER2- breast cancer subtype, 14.8%, HER2+, and 8.3%, triple negative (supplementary table 1).

Table 1 describes the oncological treatments received over the five years of follow-up. Most women (94.6%) received cancer treatment only during the first year following diagnosis. Just over half of the women underwent breast-conserving surgery, and nearly one third lymph node dissection. Chemotherapy was used in 60.3% of the patients, mostly as an adjuvant treatment (88.9%), radiotherapy in 73.8%, hormone therapy in 84.0% and targeted therapy in 13.2%.

A total of 29 patients received additional treatment between the first and the fifth year of follow-up, due to recurrence of breast cancer (n=11) or an incident second primary cancer (n=19). Breast surgery, with the intent of breast reconstruction, occurred after the first-year evaluation and was performed in 23.8% of the participants submitted to mastectomy.

At least one neurological complication was observed during the five-year follow-up in 60.0% (95% confidence interval [95%CI]: 55.3%,64.5%) of the participants, including NP, CIPN, phantom breast syndrome, cognitive impairment, brain metastases or cerebrovascular disease.

*Neuropathic pain*

The prevalence of NP was 21.0% (95%CI: 17.4%,25.0%) at the one-year evaluation, 24.0% (95%CI: 20.2%,28.2%) after three years and 16.2% (95%CI: 13.0%,19.9%) after five years (Figure 1). A total of 35.1% (95%CI: 30.7%,39.6%) of the participants presented NP at least once over

the five years of follow-up, 7.8% in all evaluations and 16.7% in only one (supplementary material, figure 1). Among those presenting NP at the three evaluations, the median pain severity score increased significantly from the one- to the three-year evaluation (2.5 *vs.* 3.6, p=0.006) and there was no significant change between the third and the fifth year after breast cancer diagnosis (3.6 *vs*. 3.5, p=0.640). Similarly, the mean of the maximum pain felt in the past 24 hours increased significantly from the one- to the three-year evaluation (4.6 *vs.* 6.2, p<0.001) and no significant change was observed between the third and the fifth year after breast cancer diagnosis (6.2 *vs.* 6.3, p=0.836). Women who presented NP only once had a median pain severity score lower than women with NP more than once (1.0 *vs.* 2.4, p<0.001 at one-year, 2.5 *vs.* 3.3, p=0.002 at three-years, and 2.4 *vs.* 3.5, p=0.050, at five-years). Similarly, the mean of the maximum pain felt in the last 24 hours was lower for women with NP once (3.4 *vs.* 4.3, p=0.021 at one-year, 4.8 *vs.* 6.0, p=0.006, at three-years and 4.6 *vs.* 6.2, p=0.012, at five-years).

*Chemotherapy-induced peripheral neuropathy*

Among women who underwent chemotherapy in the five years, the prevalence of CIPN was 22.1% (95%CI: 17.4%,27.4%), 19.2% (95%CI: 14.8%,24.3%) and 16.0% (95%CI: 11.9%,20.8%) after one, three and five years of follow up, respectively (Figure 1). A total of 26.3% (95%CI: 21.3%-31.9%) of participants had CIPN at least once during the follow-up period, 11.7% in all evaluations and 7.1% in only one evaluation (supplementary material, figure 1). Among those presenting CIPN in the three evaluations, the median TNSc scores decreased non-significantly from the one- to the three-year evaluation (5.0 *vs.* 4.0, p=0.075) and decreased significantly between the third and the fifth year after breast cancer diagnosis (4.0 *vs.* 3.0, p<0.001). Women who presented CIPN only once had a lower median TNSc score than women with CIPN more than once, (1.5 *vs.* 5.0 at the one-year evaluation, p<0.001), but no significant differences were observed at the three and five-year evaluations (10.0 [n=1] *vs*. 4.0, p=0.109, after three years,

and 4.0 *vs.* 4.0, p=0.089, after five years). Among women presenting CIPN in the three evaluations, peripheral sensory neuropathy grades one or two of the CTCAE classification were observed for 100%, 97.0% and 97.0% of the cases after one, three and five years of follow-up, respectively. Peripheral motor neuropathy was less frequent, with grades one or two present in 9.1%, 15.2% and 15.2% of the women, at the one-, three- and five-year evaluations, respectively.

*Cognitive performance assessed using MoCA*

Cognitive impairment affected 7.8% (95%CI: 5.5%,10.6%) of women with breast cancer before any treatment and its prevalence remained stable over the five years: 6.7% (95%CI: 4.6%,9.4%), 7.8% (95%CI: 5.5%,10.6%) and 7.6% (95%CI: 5.3%,10.4%) at years one, three and five, respectively (Figure 1). A total of 17.7% (95%CI: 14.4%,21.5%) of the women presented cognitive impairment at least once during the five years (supplementary material, figure 2). The mean MoCA scores increased from 23.3 at baseline to 24.0 at one year (p<0.001), followed by a decrease to 23.6 at three years (p<0.001) and was 23.7 at the end of follow-up (p=0.144).

*Other neurological complications*

Among women undergoing mastectomy, the prevalence of phantom breast syndrome was 33.9% (95%CI: 27.8%,40.5%), 21.6% (95%CI: 16.4%,27.5%) and 14.1% (95%CI: 9.8%,19.3%) at one, three and five years, respectively; a total of 44.1% (95%CI: 37.5%,50.8%) reported phantom breast syndrome at least once over the study period.

Cerebrovascular disease related to breast cancer during the five years of follow-up, were ischemic strokes: one large-artery atherosclerosis (partial anterior circulation infarct) at the one-year evaluation and 11 small vessels occlusions (two at one year, three new cases at three years and six new cases at five years, of which three were asymptomatic and cerebrovascular disease was diagnosed during the clinical investigation of headache).

At the five-year evaluation, three women presented metastases in the central nervous system: one patient with a cerebral metastasis and secondary epilepsy who was clinically stable, after radiotherapy carried out before the three years of follow-up; one patient with sequel brain lesions on magnetic resonance imaging after surgery and radiotherapy for brain metastases, but without any relapse; and one case of spinal cord epidural metastasis treated with radiotherapy.

*Factors associated with NP, CIPN and variation in cognitive performance*

Cancer stage III, triple negative breast cancer and chemotherapy were significantly associated with NP, either at least once during the five years of follow-up, at five years or in all evaluations (adjusted OR [aOR] ranged from 2.02 to 4.04). Anxiety, depression and poor sleep quality were also positively associated with NP (aOR between 2.24 and 6.13). Associations between patients aged 55 or older (OR= 0.61, 95%CI: 0.42,0.90), those with at least ten years of education (aOR= 0.59, 95%CI: 0.35,0.99) and axillary node dissection (aOR= 2.11, 95%CI: 1.13,3.03) with NP was significant only for NP at least once over the follow-up period (Table 2).

Cancer stage III and treatment with taxanes were associated with CIPN (aOR ranging between 3.63 and 12.69; Table 3).

Table 4 describes MoCA changes from baseline to one, three and five years later in participants without probable cognitive impairment at baseline. Being 65 years or older was negatively associated with variations in the MoCA score between the baseline and the one-year evaluation, and the baseline and the five-year assessment (β=-0.74 and β=-0.87, respectively, $p<0.050$), while higher education was positively associated with changes in cognitive performance from baseline to the follow-up evaluations (adjusted β coefficients ranging from 0.91 to 2.38, $p<0.010$). Significant negative associations were observed between anxiety, depression and

poor sleep quality with the variation in MoCA score (adjusted β coefficients between -1.60 and -0.63).

**Discussion**

Our results show that neurological complications are frequent in the first five years after breast cancer diagnosis, and long-lasting effects of NP and CIPN were observed over the five years. Nearly one in every five participants had cognitive impairment at least once during the follow-up. Clinical characteristics of the breast cancer and its treatment were associated with CIPN and NP, but not with cognitive decline, while patients' characteristics at baseline, namely, anxiety, depression and poor sleep quality, were associated with NP and cognitive decline, but not with CIPN.

NP was the most frequent treatment-related neurological complication throughout the follow-up. Despite the median pain severity scores at the fifth year being only 3.5, the mean of the maximum pain felt in the previous 24 hours was 6.3, reflecting the paroxysmal character of neuropathic pain. A recent systematic review and meta-analysis reported the prevalence of neuropathic pain after breast cancer treatment [8]. Among the studies identified, two [30, 31] had a follow-up time similar to our study but in one[31], only women submitted to axillary lymph node dissection were included and this surgery is associated with higher odds of NP; in the other study, the estimated prevalence was 9.0% [30], but NP was assessed with questionnaires, which may explain the lower prevalence compared to our results.

We found associations between younger age, axillary node dissection, cancer stage III, triple negative breast cancer, and chemotherapy, with NP at least once over the follow-up period. The same predictors have been described in studies that analyzed pain in general, that did not distinguish between NP or nociceptive pain [32, 33].

In line with previous studies, taxane-based chemotherapy was strongly associated with CIPN [5, 34], but alcohol consumption and diabetes at baseline were not. The latter could be related to limited statistical power due to the low levels of alcohol intake, as well as the fact that diabetes was only controlled with oral medicines in most of the patients (93.5%). However, a positive

association between diabetes and CIPN due to cancer has been previously described in colorectal cancer patients [35-37].

The prevalence of cognitive impairment ranged between 6.9% and 7.8% over the five years, but this disorder affected 17.7% of participants at least once during the five-year follow-up period. Indeed, for most women, cognitive impairment was not consistently observed in all evaluations (supplementary material, figure 2). This may have several possible explanations: 1) in repeated evaluations, practice effects may mask cognitive decline [38], and a score that remains stable or improves may not correspond to a real improvement in cognitive function; 2) different treatments for breast cancer may affect cognitive performance in different moments, namely, an acute effect at the end of chemotherapy, with a recovery after six months has been reported [39], as well as a short-term effect of radiotherapy over seven months following treatment and a recovery after three years [40], and short- and long-term effects of hormone therapy [41]; 3) factors, such as anxiety and depression, associated with the experience of a cancer diagnosis and treatment may also have an impact on cognitive assessment, being present to a different extent in different moments of the follow-up; 4) some of these cases of cognitive impairment may also be completely independent of cancer, namely in older women. Our results on the prevalence of cognitive impairment at each evaluation are lower than previously reported, namely 28.0% of women with breast cancer before surgery or any other treatment [42], 35.0% of women before adjuvant treatment for breast cancer [43], 16.0% of patients six months after chemotherapy [44], and 19.0% of patients treated with chemotherapy or not, after a median of 17 months since diagnosis [45]. Methodological differences may account for the heterogeneous results; in a previous study [45] the prevalence of cognitive impairment varied between 19.0% and 35.5%, depending on the criterion used to define the outcome. Global scores of cognitive performance, such as the MoCA score, are less sensitive to cognitive impairment affecting specific domains. The International Cognition Cancer Task Force recommends the assessment of verbal learning and memory, information processing speed and executive functions as they

are cognitive domains that could be most affected by chemotherapy [46]. However, the cognitive domains affected among patients with breast cancer in general and which tests should be used to assess them remain unclear. Another possible explanation is that 80 patients were excluded from the NEON-BC study, because the MoCA test score suggested cognitive impairment [29] before starting breast cancer treatments. We used this criterion to ensure the reliability of data provided by patients in *self*-rating scales (such as HADS or the Brief Pain Inventory Short Form) and to exclude primary dementia, not related to cancer; however, this might be a population particularity susceptible to cognitive decline. As other previous studies have described cognitive impairment before treatment, we may have excluded some cases of cognitive impairment in the context of paraneoplasic neurological syndrome. If these 80 women had been included, the prevalence of cognitive impairment at baseline would have been 21.0%.

To assess factors associated with cognitive performance overtime, we used the variation in the MoCA score from baseline to subsequent assessments as the cognitive outcome, under the assumption that even when not translating into incident cognitive impairment, less favorable changes in performance may be associated with progressive cognitive deterioration. We identified a negative association between anxiety, depression and poor quality of sleep at baseline and changes in the MoCA score, namely from baseline to the five-year evaluation, which is in accordance with previous studies on cognitive decline conducted in the general population [47-49]. We did not identify previous studies analyzing the possible associations of anxiety, depression or sleep quality at baseline with long-term cognitive decline in breast cancer patients. Our results show that anxiety, depression and poor sleep quality before treatments may be considered important factors to identify groups of women more likely to develop a less favorable change in cognitive performance, even up to five years later.

Finally, three participants followed over the five years developed brain metastasis, and there were other three cases among women who died during follow-up, which corresponds to a frequency similar to the reported in a previous study [50].

To the best of our knowledge, this is the first study providing a prospective and comprehensive assessment of long-term neurological effects of breast cancer management, including NP, CIPN and cognitive impairment over five years following a breast cancer diagnosis. The occurrence of these neurological complications was based on a clinical examination by a neurologist, not only self-report of symptoms by patients, and standardized instruments were used to assess cognitive function, CIPN and NP. Moreover, the baseline evaluation before cancer treatments, allowed us to exclude neurological conditions not related to cancer. Despite the single-center study design, IPO-Porto is the largest breast cancer oncological center in Portugal, receiving patients from any part of the country. Finally, we only included patients proposed for breast surgery, which limits the generalizability of our results to advanced breast cancer.

**Conclusion**

NP and CIPN are frequent adverse effects of breast cancer treatments and they are often long-lasting. Cognitive impairment was often present before treatments and affected nearly 18% of the women over the five years. These results suggest that follow-up protocols should take into account the persistence of these conditions for several years following diagnosis. Special attention is recommended for women presenting cancer stage III and those with triple negative breast cancer, those treated with chemotherapy, and particularly with taxanes. Also, anxiety, depression and poor sleep quality before treatment should be valued as they are associated with both NP and less favorable cognitive changes after treatments.

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**Declaration of Interest statement**

None declared.

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Table 1. Cancer treatments received during the five years after diagnosis of breast cancer.

| | Cancer treatments received | | |
|---|---|---|---|
| | During the 1st year after diagnosis n (%) | Between the 1st and the 3rd year after diagnosis n (%) | Between the 3rd and the 5th year after diagnosis n (%) |
| **Breast surgery** | | | |
| Mastectomy | 212 (45.9) | - | - |
| Mastectomy + breast-reconstruction | 15 (3.2) | - | - |
| Breast-conserving | 235 (50.9) | - | - |
| Breast reconstruction | - | 26 (5.6) | 33 (7.1) |
| Breast-conserving surgery for a contra-lateral breast cancer | - | 1 (0.2) | 3 (0.6) |
| Total mastectomy for a contra-lateral breast cancer | - | - | 1 (0.2) |
| **Axillary surgery**[a] | | | |
| Sentinel lymph node biopsy | 295 (65.9) | - | - |
| Axillary lymph node dissection | 153 (34.1) | 1 (0.2) | 1 (0.2) |
| **Metasectomy** | | | |
| Hepatic metastasectomy | - | 1 (0.2) | 1 (0.2) |
| Cerebral metastasectomy | - | 1 (0.2) | - |
| **Chemotherapy** | | | |
| Timing | | | |
| Neo-adjuvant | 30 (10.8) | - | - |
| Adjuvant | 249 (89.2) | - | - |
| For a recurrence or another primary cancer | - | 5 (1.1) | 10 (2.2) |
| Drugs | | | |
| Doxorubicin + cyclophosphamide | 56 (20.1) | - | - |
| Doxorubicin + cyclophosphamide + docetaxel | 29 (10.4) | - | - |
| Doxorubicin + cyclophosphamide + paclitaxel | 1 (0.4) | - | - |
| Cyclophosphamide + docetaxel | 2 (0.7) | - | - |
| Carboplatin + docetaxel | 1 (0.4) | - | - |
| 5-FU + epirubicin + cyclophosphamide | 23 (8.3) | - | - |
| 5-FU + epirubicin + cyclophosphamide + docetaxel | 165 (59.4) | - | 1 (0.1) |
| 5-FU + cyclophosphamide + methotrexate | 1 (0.4) | - | - |
| Capecitabine | - | 2 (0.9) | 3 (0.3) |
| Docetaxel | - | - | 1 (0.1) |
| Paclitaxel | - | 3 (0.8) | 5 (0.5) |
| Vinorelbine | - | - | 2 (0.2) |
| Carboplatin | - | - | 1 (0.1) |
| Gemcitabine | - | - | 2 (0.2) |
| Epirubicin | - | - | 1 (0.1) |
| Rituximab + cyclophosphamide + doxorubicin + vincristine | - | 1 (0.5) | - |
| **Radiotherapy** (chest, axillary and/or supraclavicular) | 341 (73.8) | 3 (0.7) | 4 (0.9) |
| **Endocrine therapy** | 388 (84.0) | 385 (83.3) | 379 (82.0) |
| **Other systemic treatments** | | | |
| Trastuzumab | 61 (13.2) | - | 2 (0.4) |
| Pertuzumab | - | - | 1 (0.2) |
| Lapatinib | - | 1 (0.2) | - |

[a] Patients who had both axillary lymph node dissection and sentinel lymph node biopsy are reported as axillary lymph node dissection; N<462, because 14 patients only performed breast surgery.

Table 2. Association between socio-demographic and clinical characteristics of the patients and neuropathic pain (NP).

| | Patients who never n | Patients with NP at least once n (%) | Patients who never had *vs.* those with NP at least once Adjusted OR | Patients with NP at five-years (N=75) n (%) | Patients who never had *vs.* those with NP at five-years Adjusted OR | Patients with NP in all evaluation n (%) | Patients who never had *vs.* those with NP in all evaluations Adjusted OR |
|---|---|---|---|---|---|---|---|
| Age (years) | | | | | | | |
| <55 | 138 | 94 | ref. | 44 | ref. | 18 (7.8) | ref. |
| ≥55 | 162 | 68 | 0.62* | 31 | 0.60 | 18 (7.8) | 0.85 [0.43,1.70] |
| Education | | | | | | | |
| ≤4 | 122 | 72 | ref. | 33 | ref. | 19 (9.8) | ref. |
| 5-9 | 87 | 46 | 0.66 | 24 | 0.77 | 9 (6.8) | 0.56 |
| ≥10 | 91 | 44 | 0.59* | 18 | 0.54 | 8 (5.9) | 0.47 |
| Cancer stage | | | | | | | |
| 0/I | 179 | 75 | ref. | 32 | ref. | 16 (6.3) | ref. |
| II | 91 | 49 | 1.29 | 26 | 1.56 | 10 (7.1) | 1.29 |
| III | 30 | 38 | 2.95*** | 17 | 3.04** | 10 | 3.82** |
| Breast | | | | | | | |
| HR+/HER | 219 | 114 | ref. | 51 | ref. | 22 (6.6) | ref. |
| HER2+ | 45 | 19 | 0.82 | 7 (10.9) | 0.68 | 4 (6.3) | 0.95 |
| Triple | 17 | 19 | 2.02* | 11 | 2.60* | 7 (19.4) | 4.04** |
| Breast | | | | | | | |
| Breast- | 161 | 74 | ref. | 34 | ref. | 17 (7.2) | ref. |
| Mastecto | 139 | 88 | 1.19 | 41 | 1.13 | 19 (8.4) | 0.73 |
| Axillary | | | | | | | |
| SLNB | 212 | 83 | ref. | 39 | ref. | 18 (6.1) | ref. |
| ALND | 79 | 74 | 2.11* | 34 | 1.80 | 18 | 2.67 |
| Chemothera | | | | | | | |
| No | 135 | 46 | ref. | 19 | ref. | 9 (5.0) | ref. |
| Yes | 165 | 116 | 2.05* | 56 | 2.69* | 27 (9.6) | 3.40* |
| Radiotherap | | | | | | | |
| No | 84 | 35 | ref. | 19 | ref. | 8 (6.7) | ref. |
| Yes | 216 | 127 | 1.16 | 56 | 0.67 | 28 (8.2) | 0.61 |
| Anxiety[c] | | | | | | | |
| No | 208 | 75 | ref. | 28 (9.9) | ref. | 11 (3.9) | ref. |
| Yes | 91 | 87 | 2.72*** | 47 | 3.95*** | 25 | 6.02*** |
| Depression[c] | | | | | | | |
| No | 287 | 137 | ref. | 59 | ref. | 27 (6.4) | ref. |
| Yes | 13 | 25 | 3.91*** | 16 | 6.13*** | 9 (23.7) | 10.95*** |
| Poor sleep | | | | | | | |
| No | 112 | 36 | ref. | 11 (7.4) | ref. | 5 (3.4) | ref. |
| Yes | 187 | 126 | 2.24**[1.42,3.5 | 64 | 4.13*** | 31 (9.9) | 4.19** |

ALND, Axillary lymph node dissection; CI, Confidence interval; NP, Neuropathic pain; OR, Odds ratio; SLNB, Sentinel lymph node biopsy. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

[a] This information is missing for 29 participants.

[b] Patients who had both ALND and SLNB are reported as ALND; N<462, because 14 patients only performed breast surgery.

[c] Baseline depression and anxiety were defined as presenting the respective sub-score equal to or higher than 11 in the Hospital Anxiety and Depression Scale.

[d] Poor quality of sleep at baseline was defined as presenting a total score equal to or higher than five in the Pittsburg Sleep Quality Index.

[e] Adjusted for age.

[f] Adjusted for age and education.

[g] Adjusted for age, education, cancer stage and breast cancer subtypes.

[h] Adjusted for age, education, cancer stage, breast cancer subtypes, breast and axillary surgeries.

[i] Adjusted for age, education and cancer stage.

Table 3. Association between socio-demographic, lifestyle, clinical and treatment characteristics of the patients among those who were submitted to chemotherapy, and chemotherapy-induced peripheral neuropathy (CIPN).

| | Patients who never had CIPN (N=207) n (%) | Patients with CIPN at least once (N=74) n (%) | Patients who never had *vs.* those with CIPN at least once Adjusted OR [95%CI] | Patients with CIPN at five-years (N=45) n (%) | Patients who never had *vs.* those with CIPN at five-years Adjusted OR [95%CI] | Patients with CIPN at all evaluations (N=33) n (%) | Patients who never had *vs.* those with CIPN at all evaluations Adjusted OR [95%CI] |
|---|---|---|---|---|---|---|---|
| Age (years) | | | | | | | |
| ≤55 | 123 (74.5) | 42 (25.5) | ref. | 22 (13.3) | ref. | 15 (9.1) | ref. |
| >55 | 84 (72.4) | 32 (27.6) | 1.12 [0.65,1.91] | 23 (19.8) | 1.53 [0.80,2.92] | 18 (15.5) | 1.76 [0.84,3.68] |
| Education (years) | | | | | | | |
| ≤4 | 72 (73.5) | 26 (26.5) | ref. | 14 (14.3) | ref. | 10 (10.2) | ref. |
| 5-9 | 77 (77.0) | 23 (23.0) | 0.87 [0.44,1.73][c] | 15 (15.0) | 1.26 [0.54,2.96][c] | 11 (11.0) | 1.39 [0.52,3.67][c] |
| ≥10 | 58 (69.9) | 25 (30.1) | 1.25 [0.63,2.50][c] | 16 (19.3) | 1.75 [0.75,4.08][c] | 12 (14.5) | 1.95 [0.75,5.10][c] |
| Diabetes at baseline | | | | | | | |
| No | 190 (72.8) | 71 (27.2) | ref. | 43 (16.5) | ref. | 31 (11.9) | ref. |
| Yes | 17 (85.0) | 3 (15.0) | 0.41 [0.11,1.49][d] | 2 (10.0) | 0.43 [0.09,2.03][d] | 2 (10.0) | 0.59 [0.12,2.83][d] |
| Alcohol consumption at baseline | | | | | | | |
| <10g/day | 166 (73.5) | 60 (26.5) | ref. | 35 (15.5) | ref. | 24 (10.6) | ref. |
| ≥10 g/day | 41 (74.5) | 14 (25.5) | 0.99 [0.49,1.97][d] | 10 (18.2) | 1.26 [0.56,2.84][d] | 9 (16.4) | 1.71 [0.71,4.12][d] |
| Cancer stage | | | | | | | |
| 0/I | 76 (80.9) | 18 (19.1) | ref. | 9 (9.6) | ref. | 4 (4.3) | ref. |
| II | 95 (77.9) | 27 (22.1) | 1.24 [0.63,2.44][d] | 17 (13.9) | 1.63 [0.68,3.92][d] | 15 (12.3) | 3.32* [1.04,10.61][d] |
| III/IV | 36 (55.4) | 29 (44.6) | 3.63*** [1.76,7.47][d] | 19 (29.2) | 5.07*** [2.04,12.63][d] | 14 (21.5) | 8.75*** [2.60,29.41][d] |
| Breast cancer subtypes | | | | | | | |
| HR+/HER2 | 145 (77.5) | 42 (22.5) | ref. | 25 (13.4) | ref. | 18 (9.6) | ref. |
| HER2+ | 41 (65.1) | 22 (34.9) | 1.84 [0.99,3.44][d] | 12 (19.0) | 1.63 [0.75,3.56][d] | 11 (17.5) | 2.10 [0.91,4.86][d] |
| Triple negative | 21 (67.7) | 10 (32.3) | 1.72 [0.75,3.96][d] | 8 (25.8) | 2.46 [0.97,6.27][d] | 4 (12.9) | 1.70 [0.52,5.61][d] |
| Taxanes-based chemotherapy | | | | | | | |
| No taxanes | 74 (96.1) | 3 (3.9) | ref. | 2 (2.6) | ref. | 1 (1.3) | ref. |
| Taxanes | 133 (65.2) | 71 (34.8) | 12.69*** [3.45,46.74][e] | 43 (21.1) | 8.79** [1.80,42.97][e] | 32 (15.7) | 8.77* [1.04,73.60][e] |
| 5-FU-based chemotherapy | | | | | | | |
| No 5-FU | 71 (78.0) | 20 (22.0) | ref. | 14 (15.4) | ref. | 8 (8.8) | ref. |
| 5-FU | 136 (71.6) | 54 (28.4) | 1.45 [0.75,2.80][e] | 31 (16.3) | 1.05 [0.48,2.30][e] | 25 (13.2) | 1.31 [0.51,3.38][e] |
| Anxiety[a] | | | | | | | |
| No | 128 (74.9) | 43 (25.1) | ref. | 31 (18.1) | ref. | 22 (12.9) | ref. |
| Yes | 78 (71.6) | 31 (28.4) | 1.28 [0.73,2.25][f] | 14 (12.8) | 0.79 [0.38,1.62][f] | 11 (10.1) | 0.84 [0.37,1.89][f] |
| Depression[a] | | | | | | | |
| No | 193 (74.2) | 67 (25.8) | ref. | 40 (15.4) | ref. | 30 (11.5) | ref. |
| Yes | 14 (66.7) | 7 (33.3) | 1.27 [0.47,3.42][f] | 5 (23.8) | 1.40 [0.44,4.39][f] | 3 (14.3) | 0.90 [0.22,3.63][f] |
| Poor quality of sleep[b] | | | | | | | |
| No | 78 (80.4) | 19 (19.6) | ref. | 15 (15.5) | ref. | 11 (11.3) | ref. |
| Yes | 129 (70.1) | 55 (29.9) | 1.72 [0.94,3.17][f] | 30 (16.3) | 1.16 [0.57,2.34][f] | 22 (12.0) | 1.09 [0.48,2.45][f] |

5-FU, 5- Fluorouracil; CI, confidence interval; CIPN, chemotherapy induced preipheral neuropathy; OR, Odds ratio. * p < 0.05, ** p < 0.01, *** p < 0.001.
[a] Baseline depression and anxiety were defined as presenting the respective sub-score equal to or higher than 11 in the Hospital Anxiety and Depression Scale; [b] Poor quality of sleep at baseline was defined as presenting a total score equal to or higher than five in the Pittsburg Sleep Quality Index; [c] Adjusted for age; [d] Adjusted for age and education; [e] Adjusted for age, education, cancer stage and breast cancer subtypes; [f] Adjusted for age, education and cancer stage.

Table 4. Association of socio-demographic and clinical characteristics of patients without cognitive impairment before treatment, with the variation in the MoCA score between the follow-up and the baseline evaluations.

| | MoCA value after one year minus baseline value | | MoCA value after three years minus baseline value | | MoCA value after five years minus baseline value | |
|---|---|---|---|---|---|---|
| | mean (sd) | Adjusted Beta coefficient [95%CI] | mean (sd) | Adjusted Beta coefficient [95%CI] | mean (sd) | Adjusted Beta coefficient [95%CI] |
| All participants | 0.6 (2.4) | | 0.1 (2.8) | | 0.3 (2.9) | |
| MoCA score at baseline | | -0.20***[-0.26,-0.14] | | -0.36***[-0.46,-0.26] | | -0.38***[-0.48,-0.28] |
| Age (years)[a] | | | | | | |
| <50 | 0.5 (2.2) | ref. | 0.2 (2.7) | ref. | 0.5 (2.3) | ref. |
| 50-64 | 0.6 (2.5) | -0.29 [-0.80,0.23][e] | 0.0 (2.8) | -0.17 [-0.79,0.44][e] | 0.4 (2.9) | -0.15 [-0.78,0.47][e] |
| ≥ 65 | 0.6 (2.6) | -0.74* [-1.42,-0.06][e] | -0.0 (3.1) | -0.19 [-0.96,0.57][e] | -0.3 (3.5) | -0.87* [-1.65,-0.09][e] |
| Education (years)[a] | | | | | | |
| ≤4 | 0.7 (2.6) | ref. | -0.2 (3.3) | ref. | 0.1 (3.4) | ref. |
| 5-9 | 0.5 (2.3) | 0.91** [0.28,1.53][f] | 0.2 (2.5) | 1.65*** [0.91,2.39][f] | 0.3 (2.7) | 1.25** [0.50,2.01][f] |
| 10-12 | 0.4 (2.4) | 1.33*** [0.56,2.10][f] | 0.1 (2.5) | 2.06*** [1.15,2.97][f] | 0.4 (2.2) | 1.94*** [1.02,2.87][f] |
| >12 | 0.4 (1.9) | 1.73*** [0.85,2.61][f] | 0.6 (2.1) | 2.87*** [1.82,3.91][f] | 0.5 (2.1) | 2.38*** [1.32,3.44][f] |
| Cancer-stage | | | | | | |
| 0/I | 0.6 (2.6) | ref. | 0.1 (2.9) | ref. | 0.1 (3.0) | ref. |
| II | 0.5 (2.2) | -0.02 [-0.52,0.49][g] | 0.0 (2.5) | -0.21 [-0.80,0.38][g] | 0.5 (2.7) | 0.28 [-0.32,0.88][g] |
| III | 0.6 (2.4) | 0.08 [-0.58,0.73][g] | -0.2 (3.2) | -0.44 [-1.21,0.33][g] | 0.5 (2.9) | 0.29 [-0.49,1.08][g] |
| Subtypes[b] | | | | | | |
| ER+/HER2 | 0.5 (2.5) | ref. | 0.0 (2.9) | ref. | 0.2 (3.0) | ref. |
| HER2+ | 0.5 (2.1) | 0.03 [-0.62,0.68][g] | 0.0 (2.6) | -0.02 [-0.79,0.75][g] | 0.6 (2.4) | 0.44 [-0.34,1.22][g] |
| Triple negative | 0.2 (2.3) | -0.39 [-1.23,0.45][g] | -0.5 (2.9) | -0.60 [-1.59,0.39][g] | 0.0 (2.6) | -0.36 [-1.37,0.65][g] |
| Chemotherapy | | | | | | |
| No | 0.8 (2.6) | ref. | 0.2 (2.9) | ref. | 0.2 (3.1) | ref. |
| Yes | 0.4 (2.3) | -0.32 [-0.78,0.15][g] | -0.0 (2.8) | -0.32 [-0.87,0.23][g] | 0.3 (2.8) | 0.02 [-0.54,0.58][g] |
| Radiotherapy | | | | | | |
| No | 0.9 (2.3) | ref. | 0.4 (2.7) | ref. | 0.4 (3.1) | ref. |
| Yes | 0.4 (2.5) | -0.19 [-0.69,0.31][g] | -0.1 (2.9) | -0.28 [-0.87,0.31][g] | 0.3 (2.8) | 0.01 [-0.59,0.62][g] |
| Hormone therapy | | | | | | |
| No | 0.6 (2.0) | ref. | 0.2 (2.7) | ref. | 0.3 (2.6) | ref. |
| Yes | 0.5 (2.5) | 0.09 [-0.51,0.68][g] | 0.0 (2.9) | -0.02 [-0.73,0.69][g] | 0.3 (3.0) | 0.17 [-0.55,0.89][g] |
| Anxiety[c] | | | | | | |
| No | 1.0 (2.4) | ref. | 0.5 (2.8) | ref. | 0.7 (2.9) | ref. |
| Yes | 0.3 (2.5) | -0.63** [-1.07,-0.19][g] | -0.1 (2.9) | -0.48 [-1.01,0.05][g] | 0.0 (2.9) | -0.71** [-1.25,-0.18][g] |
| Depression[c] | | | | | | |
| No | 0.7 (2.5) | ref. | 0.3 (2.8) | ref. | 0.5 (2.9) | ref. |
| Yes | 0.5 (2.5) | -0.47 [-1.28,0.34][g] | -0.4 (3.5) | -1.13* [-2.08,-0.18][g] | -0.5 (3.2) | -1.60** [-2.55,-0.64][g] |
| Poor quality of sleep[d] | | | | | | |
| No | 1.0 (2.2) | ref. | 0.6 (2.8) | ref. | 1.0 (2.6) | ref. |
| Yes | 0.6 (2.6) | -0.23 [-0.70,0.23][g] | 0.1 (2.9) | -0.49 [-1.04,0.06][g] | 0.2 (3.1) | -0.68* [-1.23,-0.12][g] |

CI, confidence interval; MoCA, Montreal Cognitive Assessment; SD, Standard deviation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

[a] Categories of age and education as they are used in the classification for cognitive impairment based on normative data; [b] This information is missing for 24 participants; [c] Baseline depression and anxiety were defined as presenting the respective sub-score equal to or higher than 11 in the Hospital Anxiety and Depression Scale; [d] Poor quality of sleep at baseline was defined as presenting a total score equal to or higher than five in the Pittsburg Sleep Quality Index; [e] Adjusted for MoCA score at baseline; [f] Adjusted for MoCA score at baseline and for age; [g] Adjusted for MoCA score at baseline, age and education.

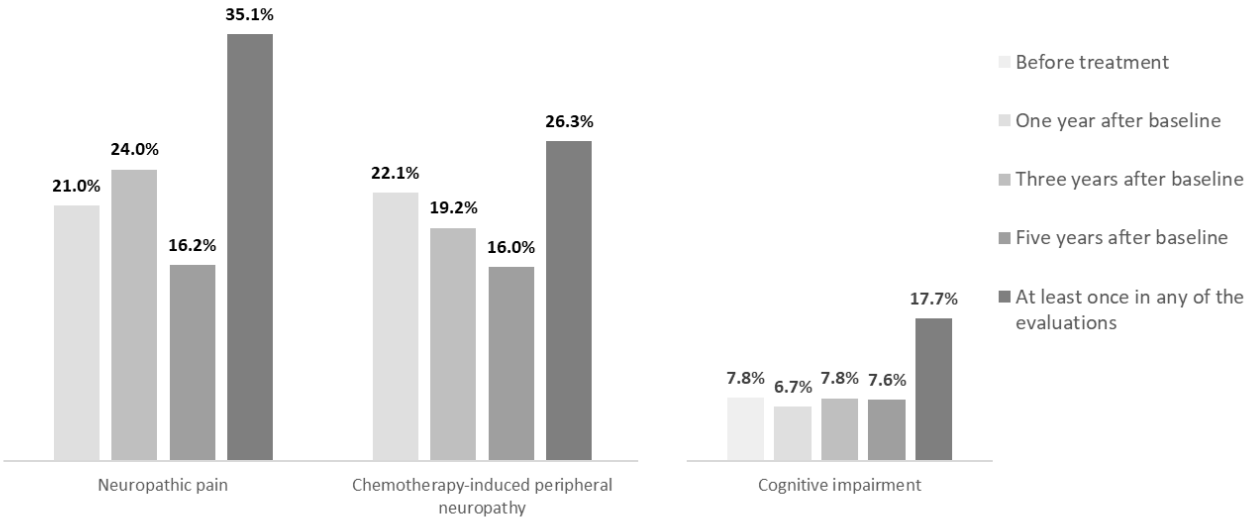


**Figure 1.** Prevalence of neuropatic pain, chemotherapy-induced peripheral neuropathy and cognitive impairment, during the five-years of follow-up.
For chemotherapy-induced peripheral neuropathy, only participants who underwent chemotherapy were considered (N=281).

## PAPER 3

# Trajectories of cognitive performance over five years in a prospective cohort of breast cancer patients (NEON-BC)

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# Trajectories of cognitive performance over five years in a prospective cohort of patients with breast cancer (NEON-BC)

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ABSTRACT

*Purpose:* To identify trajectories of cognitive performance up to five years since diagnosis and their predictors, in a cohort of patients with breast cancer (BCa).
*Methods:* A total of 464 women with BCa admitted to the Portuguese Institute of Oncology, Porto, during 2012, were evaluated with the Montreal Cognitive Assessment (MoCA) before any treatment, and after one, three and five years. Probable cognitive impairment (PCI) at baseline was defined based on normative age- and education-specific reference values. Mclust was used to define MoCA trajectories. Receiver Operating Characteristic curves were used to assess the predictive accuracy for cognitive trajectories.
*Results:* Two trajectories were identified, one with higher scores and increasing overtime, and the other, including 25.9% of the participants, showing a continuous decline. To further characterize each trajectory, participants were also classified as scoring above or below the median baseline MoCA scores. This resulted in four groups: 1) highest baseline scores, stable overtime (0.0% with PCI); 2) lowest baseline scores (29.5% with PCI); 3) mid-range scores at baseline, increasing overtime (10.5% with PCI); 4) mid-range scores at baseline, decreasing overtime (0.0% with PCI). Adding the change in MoCA during the first year to baseline variables significantly increased the accuracy to predict the downward trajectory (area under the curve [AUC] = 0.732 *vs.* AUC = 0.841, $P < 0.001$).
*Conclusion:* Four groups of patients with BCa with different cognitive performance trends were identified. The assessment of cognitive performance before treatments and after one year allows for the identification of patients more likely to have cognitive decline in the long term.


## 1. Introduction

Different cancer treatments, including chemotherapy [1,2], hormone therapy [3–5], radiotherapy [6], immunotherapy [7] and surgery [8], as well as cancer itself [9], have been described as possible causes of cognitive changes. Cognitive impairment has been estimated to affect up to 30% of patients before chemotherapy, up to 75% during treatment and up to 35% several years after the completion of treatment [10]. Although cancer-related cognitive impairment may be milder compared to cognitive impairment due to stroke, traumatic brain injury or dementia, it was shown to have a sizable impact on the daily life of oncologic patients, namely patients with breast cancer [11,12]. However, studies on the frequency of cognitive impairment among patients with cancer have yielded heterogenous results, which largely reflect methodological

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differences [13,40], namely regarding the validity of the instruments used and their coverage of cognitive domains, the criteria used to define cognitive impairment, and the type of comparison groups included.

Most of the studies have a post-treatment evaluation only or pre- and post-treatment assessments within a short period of time, which do not inform about the reversibility or persistence of cognitive impairment. The definition of trajectories over long periods and the early identification of their determinants are particularly important in cancers with an increasing number of long-term survivors, such as breast cancer [15–17]. Cancer treatments may affect cognitive performance during the first year after breast cancer diagnosis, with deficits persisting for longer periods, or being reversed following the end of treatment, due to compensatory or adaptative mechanisms. Cognitive decline may also occur in the longer term, due to a delayed effect of the initial treatments, as well as due to longer treatments, such as hormone therapy.

Therefore, this study aimed to identify trajectories of cognitive performance up to five years since diagnosis and their predictors, in a cohort of patients with breast cancer submitted to surgery, and to local and systemic adjuvant treatments.

## 2. Methods

### 2.1. The NEON-BC cohort

This study is based on the NEON-BC cohort, which was designed to investigate the neurological complications of breast cancer, and is previously described in detail [18]. Briefly, this is a prospective cohort assembled in 2012. Women recently diagnosed with breast cancer and admitted to the Breast Clinic of the Portuguese Institute of Oncology of Porto, Portugal, were consecutively invited to participate if they did not have a history of chemotherapy or radiotherapy treatment for another primary cancer, had no previous breast surgery, and were able to understand the purpose of the study. Those who presented a Montreal Cognitive Assessment (MoCA) score lower than 17 or 16, if they were aged 65 years or more, were excluded because they were considered less likely to understand the study and to complete the questionnaire evaluations [19]. A total of 506 participants were assessed at baseline, before any cancer treatment; 503, 475 and 466 were evaluated at one, three and five years after diagnosis, respectively.

### 2.2. Evaluation of the participants

Socio-demographic characteristics and lifestyles were assessed in face-to-face interviews using a structured questionnaire. Clinical characteristics and treatment details were abstracted from clinical files. Staging was defined by the AJCC TNM 7th edition classification [21]. Breast cancer subtypes were based on the information from medical files regarding immunohistochemistry and in situ hybridization-based biomarkers, namely hormone receptors (HR) (estrogen receptors and progesterone receptors present in more or less than 1% of the cells) and human epidermal growth factor receptor (HER2), and were classified in HR-positive/HER2-negative (HR+/HER2-), HER2-positive (HER2+), and triple negative (HR-negative/HER2-negative). Validated questionnaires were used to assess patient-reported outcomes, namely anxiety and depression (Hospital Anxiety and Depression Scale [HADS] [20,21]), and sleep quality (Pittsburg Sleep Quality Index [PSQI] [22]). At each wave, cognitive performance was evaluated with MoCA (Portuguese version 7.1), by trained researchers; all participants except two were evaluated with MoCA in all follow-up assessments [18]. This cognitive test was designed as a screening tool to detect mild cognitive impairment by assessing eight cognitive domains: executive function; visuospatial ability; short-term memory; language; attention; concentration; working memory; and temporal and spatial orientation. Its score ranges from 0 to 30. It has good reliability, sensitivity and specificity to detect mild cognitive impairment [23,24]. Participants with a MoCA score below two standard deviations of age- and education-specific distributions from normative data [19] were classified as having probable cognitive impairment (PCI).

### 2.3. Statistical analysis

A total of 464 participants with a MoCA score in the four evaluations were included in the present analysis; these were not significantly different from those excluded (n = 42), regarding age (mean, 54.5 *vs.* 57.4, P = 0.103), education (mean, 7.7 *vs.* 6.9, P = 0.227) and cancer stage (stage 0/I, 54.7% *vs.* 39.0%; stage II, 30.2% *vs.* 39.0%; stages III/IV, 15.1% *vs.* 22.0%, P = 0.147).

The nlme package of the R Statistic Software [25] was used to fit a linear mixed-effects model with the fixed-effect of age and education as continuous variables (plus education as a quadratic term), and time as a random variable. An adjusted MoCA score (aMoCA) was computed as follows: aMoCA = raw MoCA − (coefficient$_{age}$ x age + coefficient$_{education}$ x education + coefficient$^2_{education}$ x education$^2$). Mclust [26] was used to obtain model-based clusters of the trends in the aMoCA score over the five years and the decision regarding the number of clusters was based on the Bayesian Information Criteria (Supplementary material, Fig. 1).

Data are presented as counts and proportions. Proportions were compared using the Chi-square test. The association between variables measured at baseline or within the first year of follow-up and the five-year cognitive trajectories was estimated with Odds Ratios (ORs) and their respective 95% confidence intervals (CI), computed using multivariable logistic regression; the variables included in the models are described in the footnotes of Fig. 2. The predictive accuracy of the variables significantly associated with the trajectories was further assessed using Receiver Operating Characteristic curves (ROC) and the corresponding areas under the curve (AUC) were compared [27].

Statistical analysis was conducted using R, version 3.3.1 (R Core Team, Vienna, Austria) and Stata, version 15.1 (StataCorp, College Station, Texas, USA).

## 3. Results

### 3.1. Characterization of the cohort overtime

At baseline, median age was 54 years, a total of 42% of the women had less than five years of education and 29.4% had more than 10 years. Most tumours were classified as stage 0/I (54.7%), and stages II, III and IV represented 30.2%, 14.7% and 0.4% of the cases, respectively. The most frequent breast cancer subtype was HR+/HER2- (77.0%), followed by HER2+ (14.7%) and triple negative (8.3%) (Supplementary material, Table 1).

Only 15 (3.2%) women were treated with surgery as the single treatment. Regarding the treatments performed during the first year after diagnosis, 36.2% of the women received a combination of chemotherapy, radiotherapy and hormone therapy, and 21.9% were treated with radiotherapy and hormone therapy (Supplementary material, Table 2).

### 3.2. Identification of the cognitive trajectories

Two trajectories of cognitive performance were identified based on the aMoCA score: 1) the *upward trajectory*, with higher scores and increasing overtime, and 2) the *downward trajectory*, which

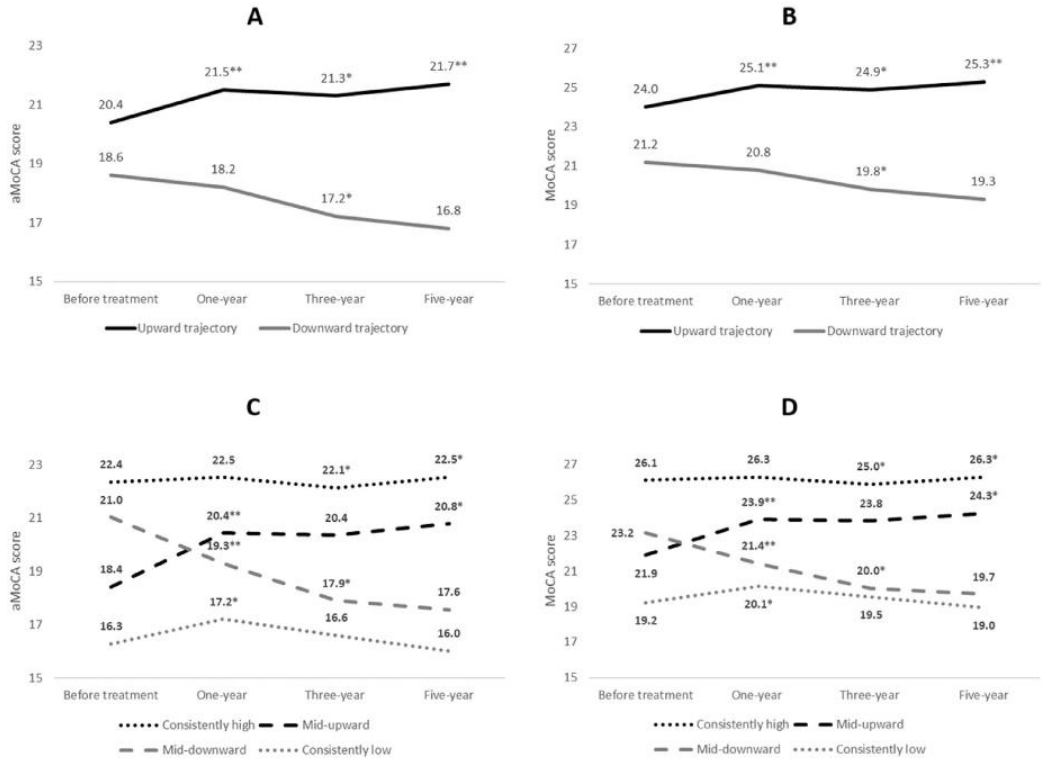


**Fig. 1.** Cognitive trajectories since before treatment to five years after diagnosis, represented with the raw score of the Montreal Cognitive Assessment (MoCA) and with its age- and education-adjusted value (aMoCA score). Graphs A and B: the two model-based trajectories, Upward and Downward; Graphs C and D: patterns of cognitive performance in the groups Consistently high - women of the Upward trajectory with a baseline MoCA score > median; Mid-upward - women of the Upward trajectory with a baseline MoCA score ≤ median; Mid-downward - women of the Downward trajectory with a baseline MoCA score > median; Consistently low - women of the Downward trajectory with a baseline MoCA score ≤ median. *P < 0.01 and **P < 0.001, for the change between consecutive evaluations, within each trajectory.

included 25.9% of the participants, and showed a continuous decline (Fig. 1A and B). To further characterize each trajectory, participants were also classified in each trajectory as scoring above or below the median of the baseline MoCA scores within each trajectory. The trajectories in each of the four groups obtained are depicted in Fig. 1C and D, and may be described as follows: 1) the *consistently high* group (n = 172) had the highest baseline scores, stable overtime (0.0% with PCI); 2) the *consistently low* group (n = 61) had the lowest scores overtime (29.5% with PCI); 3) the *mid-upward* group (n = 172) had mid-range scores at baseline, increasing overtime (10.5% with PCI); 4) the *mid-downward* group (n = 59) had mid-range scores at baseline, decreasing overtime (0.0% with PCI). All groups presented an increase in cognitive performance beween the baseline and the one-year evaluation (not statistically significant for the *consistently high* trajectory), except the *mid-downward* group that presented the highest decrease in the first year after diagnosis. The age, education, MoCA scores over the five years, and changes in MoCA scores in each of these groups are presented in supplementary table 3. In the *mid-downward* group, the mean changes (95%CI) in the MoCA score from baseline to the one-, three- and five-year evaluations were −1.7 (−2.5, −1.0), −3.1 (−3.9, −2.3) and −3.5 (−4.4, −2.6), respectively.

Fig. 2 depicts the ORs for the association between variables measured at baseline and during the first year, and the five-year *downward trajectory*. Significant associations were observed for age (≥65 *vs.* <50 years: OR = 2.34, 95%CI, 1.32–4.18), education (>12 *vs.* ≤4 years: OR = 0.31, 95%CI, 0.14–0.70), baseline MoCA score (per one point increase: OR = 0.77, 95%CI, 0.70–0.84), change in MoCA score during the first year (per one point increase: OR = 0.58, 95%CI, 0.51–0.66), consumption of psycholeptic drugs (OR = 1.67, 95%CI, 1.07–2.59), and depression but only at the one-year evaluation (OR = 2.64, 95%CI, 1.48–4.66).

Fig. 3 depicts the ROC curves for age, education, baseline and one-year MoCA scores, variation in the MoCA score during the first year of follow-up, and combinations of these variables to classify participants as pertaining to the *downward* or the *upward* trajectory. When considering all baseline predictors, the AUC was 0.732, and increased significantly when adding the one-year MoCA score (AUC = 0.841) or the change in MoCA during the first year (AUC = 0.841) to the model. The AUC for the consumption of psycholeptic drugs at baseline was 0.651 (95%CI: 0.597, 0.705), and it did not increase the accuracy of the remaining models. PCI at baseline was a predictor of cognitive trajectories with a low AUC of 0.549, and did not significantly improve the models based on age, education, and MoCA scores at baseline and at the one-year evaluation.

Fig. 4 depicts the distribution of the probability of belonging to the *downward* trajectory, as predicted by the model including only baseline variables (A) or baseline variables and variation in the MoCA score during the first year (B), with the latter showing a much smaller overlap between individuals in the *upward* and *downward* trajetories. This translates into an increased ability of the model including the variation in the MoCA score during the first year to identify women in the *downward* trajectory; the positive

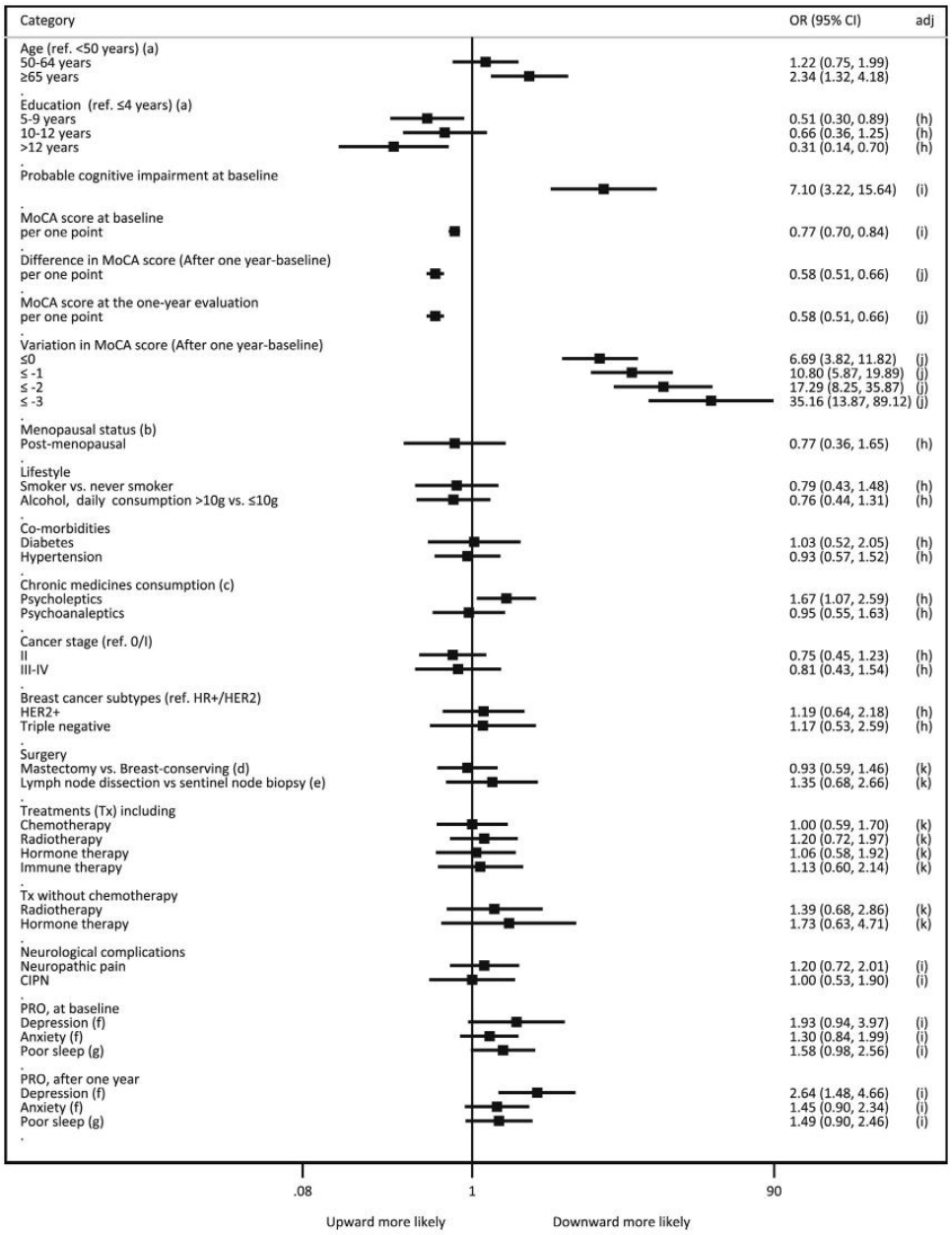


**Fig. 2.** Association of cognitive performance at baseline and its variation after one year, socio-demographic characteristics of the patients, lifestyle, co-morbidities, clinical characteristics of the tumor, treatments, neurological complications and patient-reported outcomes (PRO) with cognitive trajectories - *Downward vs.Upward*. CIPN, chemotherapy-induced peripheral neuropathy; PRO, patient-reported outcomes; Tx, treatments (a) Categories of age and education as they are used in the classification for cognitive impairment based on normative data. (b) When menopausal status was not specified, all women with at least 60 years of age, women who underwent a bilateral oophorectomy and those with an intact uterus and being amenorrheic for 12 or more consecutive months prior to the diagnosis in the absence of alternative pathological or physiological cause and follicle stimulating hormone and serum estradiol levels within the laboratory's reference ranges were classified as postmenopausal, or otherwise as premenopausal. (c) According to drug classification of the WHO Collaborating Centre for Drug Statistics Methodology (https://www.whocc.no/atc_ddd_index). (d) One patient only performed axillary surgery. (e) Patients who had both lymph node dissection and sentinel lymph node biopsy are reported as lymph node dissection. https://www.whocc.no/atc_ddd_index (f) Depression and anxiety were defined as presenting the respective sub-score equal to or higher than 11 in the Hospital Anxiety and Depression Scale. (g) Poor quality of sleep was defined as presenting a total score equal to or higher than five in the Pittsburg Sleep Quality Index. (h) Adjusted for age. (i) Adjusted for age, education. (j) Adjusted for age, education and baseline MoCA score. (k) Adjusted for age, education and cancer stage.

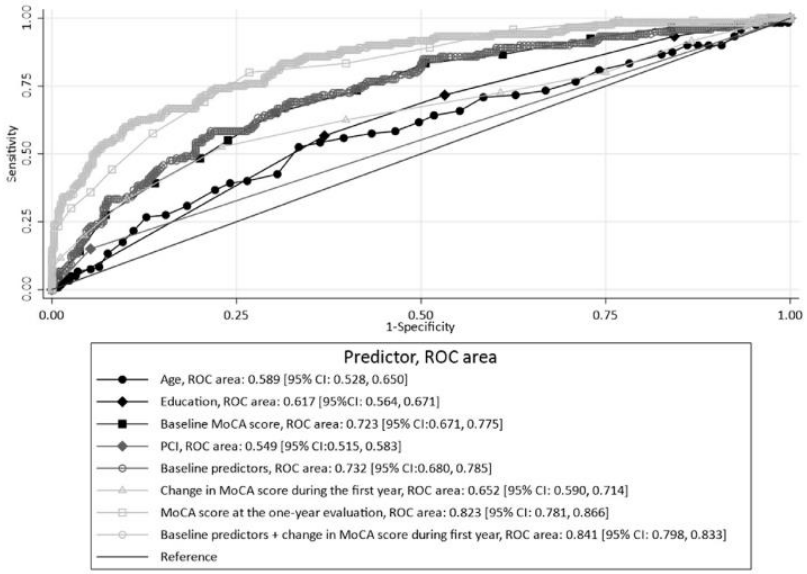


**Fig. 3.** Receiver operating characteristic curves of predictive models of the downward trajectory in women with breast cancer. AUC, Area Under the Curve; MoCA, Montreal Cognitive assessment; PCI, Probable cognitive impairment at the baseline evaluation defined as scoring below two standard deviations of the age- and education-specific distribution from normative data; ROC, Receiver Operating Characteristic. Age in years, education in four categories (≤4, 5–9, 10–12, >12 years); Baseline predictors: age, education and baseline MoCA score. AUC(model with age)≠AUC(model with education), P = 0.378. AUC(model with age)≠AUC(model with PCI), P = 0.319. AUC(model with education) ≠ AUC(model with baseline MoCA score), P < 0.001. AUC (model with baseline MoCA score)≠ AUC(model with baseline predictors), P = 0.295. AUC (model with baseline predictors) ≠ AUC(model with baseline predictors + change in MoCA score during the first year), P < 0.001. AUC(model with MoCA score at the one-year evaluation)≠AUC(model with baseline predictors + change in MoCA score during the first year), P = 0.102.

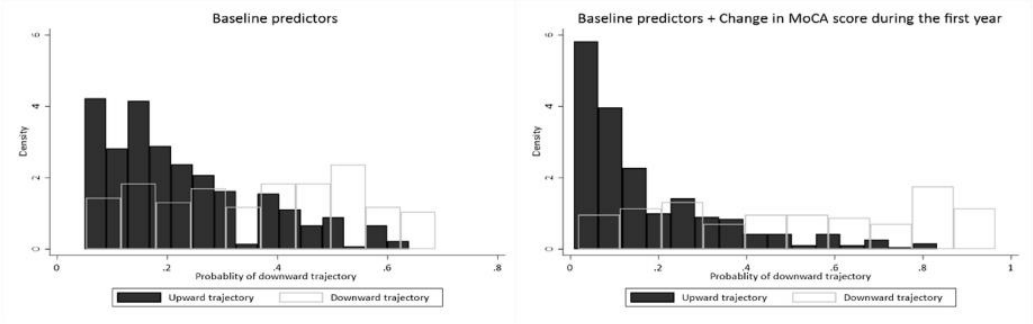


**Fig. 4.** Distribution of the probabilities of belonging to the *downward* trajectory estimated by the model based on the baseline predictors age, education (≤4, 5–9, 10–12, >12 years) and Montreal Cognitive Assessment (MoCA) score, and by the same model plus the variation in the MoCA score during the first year (score at the one-year evaluation - baseline score).

likelihood ratios ranged between 5.6 and 80.5 when the cut-off was set at estimated probabilities between 40% and 80% (Table 1).

## 4. Discussion

D*ownward* and *upward* cognitive trajectories were identified among women with breast cancer followed for five years. Just over one-quarter of the participants were in the *downward* trajectory, which included women with consistently low cognitive tests, as well as those who had a worsening performance overtime. The *upward* trajetory included both patients with consistently high scores and those who improved their performance. A model including age, education and baseline MoCA had a moderate accuracy to predict the five-year trajectory, which was significantly improved when further considering the variation in MoCA during the first year.

Our results show that cognitive impairment before breast cancer treatments detected using MoCA does not necessarily predict a *downward* cognitive trajectory as approximately half of these women recovered at follow-up evaluations. Cognitive performance also increased from baseline to the one-year evaluation in most of the women. Distress due to cancer diagnosis may have negatively affected cognitive performance at the baseline evaluation [28], and has been shown to be lower one year after breast cancer diagnosis [29]. Accordingly, in our cohort, we observed that the proportion of women with anxiety decreased significantly from baseline to the one-year evaluation. On the other hand, an increase in the MoCA score after one year was previously described in an elderly general

**Table 1**
Predictive models of the *downward* trajectory: sensitivity, specificity and likelihood ratios.

| Model A: Baseline predictors | | | | | | | Model B: Baseline predictors + change in the MoCA score during the first year | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pr % | Women predicted to be in the *downward* trajectory in the | | Sensitivity % | Specificity % | LR+ | LR- | Pr % | Women predicted to be in the *downward* trajectory in the | | Sensitivity % | Specificity % | LR+ | LR- |
| | *upward* trajectoy (n = 344) | *downward* trajectory (n = 120) | | | | | | *upward* trajectoy (n = 344) | *downward* trajectory (n = 120) | | | | |
| 1 | 344 | 120 | 100.0 | 0 | 1.0 | – | 1 | 340 | 120 | 100.0 | 1.2 | 1.0 | – |
| 5 | 343 | 120 | 100.0 | 0.3 | 1.0 | 0.0 | 5 | 257 | 117 | 97.5 | 25.3 | 1.3 | 10.1 |
| 10 | 287 | 114 | 95.0 | 16.6 | 1.1 | 0.3 | 10 | 188 | 112 | 93.3 | 45.4 | 1.7 | 6.8 |
| 20 | 167 | 95 | 79.2 | 51.5 | 1.6 | 0.4 | 20 | 105 | 97 | 80.8 | 69.5 | 2.7 | 3.6 |
| 30 | 94 | 72 | 60.0 | 72.6 | 2.2 | 0.6 | 30 | 67 | 81 | 67.5 | 80.5 | 3.5 | 2.5 |
| 40 | 49 | 53 | 44.2 | 85.8 | 3.1 | 0.7 | 40 | 37 | 72 | 60.0 | 89.2 | 5.6 | 2.2 |
| 50 | 24 | 35 | 29.2 | 93.0 | 4.2 | 0.8 | 50 | 21 | 61 | 50.8 | 93.9 | 8.3 | 1.9 |
| 60 | 3 | 8 | 6.7 | 99.1 | 7.7 | 0.9 | 60 | 13 | 47 | 39.2 | 96.2 | 10.4 | 1.6 |
| 70 | 0 | 0 | 0.0 | 100.0 | – | 1.0 | 70 | 5 | 41 | 34.2 | 98.6 | 23.6 | 1.5 |
| 80 | 0 | 0 | 0.0 | 100.0 | – | 1.0 | 80 | 1 | 28 | 23.3 | 99.7 | 80.5 | 1.3 |
| 90 | 0 | 0 | 0.0 | 100.0 | – | 1.0 | 90 | 0 | 9 | 7.5 | 100.0 | – | 1.1 |
| 95 | 0 | 0 | 0.0 | 100.0 | – | 1.0 | 95 | 0 | 2 | 1.7 | 100.0 | – | 1.0 |
| 99 | 0 | 0 | 0.0 | 100.0 | – | 1.0 | 99 | 0 | 0 | 0.0 | 100.0 | – | 1.0 |

MoCA, Montreal Cognitive Assessment; Pr, probability; LR+, positive likelihood ratio; LR-, negative likelihood ratio.
Model A, based on the baseline predictors age, education (≤4, 5–9, 10–12, >12 years) and MoCA score, and model B, based on the same baseline predictors plus the variation in the MoCA score during the first year (score at the one year evaluation - baseline score).

population and may be explained by a practice effect [30], which may be defined as a change or improvement that results from practice or repetition of task items or activities [31]. Practice effect may be due to deliberate rehearsal, incidental learning, procedural learning, changes in an examinee's conceptualization of a task, shift in strategy, or increased familiarity with the test-taking environment and/or paradigm (i.e., "test-wiseness") [32], and it represents a source of measurement error. However, it may also be informative, since practice effect is largely absent in patients with Alzheimer's disease and it may predict cognitive outcomes in amnestic mild cognitive impairment [33].

Among women in the *mid-downward* group, a decrease of at least two points in the MoCA score, which could be considered a clinically significant difference [34], was observed in more than half of the women after one year and in all except one after five years of follow-up. These women were older and less educated, in accordance with older age and lower education being associated with a pathologic progressive deterioration of cognition, such as mild cognitive impairment and dementia [35,36]. Several other sociodemographic characteristics of the participants, lifestyle data and clinical characteristics at baseline were tested but none except age, education and consumption of psycholeptics drugs were associated with the trajectories. Psycholeptics drugs, namely benzodiazepines may increase the risk of cognitive decline [37]. Although chemotherapy was not associated with the *downward* trajectory, we have previously reported a statistical association between chemotherapy and incident cognitive impairment after one year of follow-up in the NEON-BC cohort, which was only observed among women with no anxiety at baseline [38]. The potential negative effect of antineoplasic drugs in cognitive function may be milder and transient in some patients, and chronic in others. Therefore, patients who received chemotherapy and had mild or transient cognitive decline may not be included in the worse cognitive trajectories, which could explain the absence of an association between chemotherapy and long-term cognitive decline. Also, the overall toxicity level of chemotherapy treatments may have decreased in the last two decades, due to the use of different drugs and doses, as well as a better mangement of toxic effects, and women of the NEON-BC cohort may have not been exposed to toxicity levels that would have an impact on cognitive function. The chemo brain hypothesis may not hold considering the current use of chemotherapy in early-stage breast cancer.

The baseline MoCA score alone or with age and education predicted the *downward* trajectory better than age or education, and a significant increase in accuracy was obtained when the change in the MoCA score at one year was added to the predictive model, which corresponds to a predictive model with age, education, and the MoCA score at baseline and after one year. Despite the overlap in age, education, MoCA scores and MoCA variation in the first year between the two trajectories, these results show that the five-year trajectory can be accurately predicted considering only variables available within one year of the cancer diagnosis. Similar results were obtained when considering only the one-year MoCA score, which could be of interest in clinical practice. However, cognitive performance one year following the baseline evaluation may have not been the same as if MoCA had been administered for the first time one-year after diagnosis. Indeed, the practice effect needs to be considered in the test result as part of the cognitive performance on a second test.

### 4.1. Strengths and limitations of our study

Our study is based on the NEON-BC cohort that initially included a large number of women with breast cancer (n = 506) and suffered a low attrition over the five years (7.9%). The complete follow-up consisted of four different moments, including a baseline assessment, after diagnosis and prior to any cancer treatment. This allowed us to describe cognitive trajectories occuring during the continuum of breast cancer care, from diagnosis, to shortly after the completion of treatment, and to long-term care, and to show that some women recover from a pre-treatment cognitive impairment, while others have a declining cognitive trajectory.

We used MoCA to assess cognitive performance overtime, which is one of the most commonly used cognitive screening tests in cancer settings [39] and a comprehensive neuropsychological evaluation may not be available during the clinical care of patients with cancer.

The external validity of our study is limited by the fact that patients with more advanced disease corresponded to a very small part of the cohort and because only one hospital was involved. However, the Portuguese Institute of Oncology of Porto is the largest hospital providing cancer care in Northern Portugal and is the reference hospital of a large geographical area. Additionally, our results can not be generalized to women with breast cancer with

very low cognitive performance at diagnosis, because patients with baseline MoCA scores lower than 17 or 16, if they were older than 65 years, were excluded from the cohort, considering that they were less likely to be able to understand the study and to answer to questionnaires assessing important health outcomes over the five years.

## 5. Conclusion

This study shows that cognitive decline occurs during the first five years of breast cancer care, with these long-term trajectories being largely influenced by the baseline cognitive performance and its variation in the first year following diagnosis. In this study, the variation in cognitive performance during the first year was essential to more accurately predict worse trajectories, and may allow for the identification of women with a decreased performance who are more likely to develop cognitive decline in the future.

## Declaration of competing interest

None declared.

## Acknowledgement

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.05.006.

## Ethical approval

All procedures performed in the present study were approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (ref. CES 406/011, CES 99/014 and CES 290/014) and by the Portuguese Data Protection Authority (ref. 9469/2012 and 8601/2014), and are in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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**Table 1.** Socio-demographic characteristics of the participants (N=464), lifestyles, co-morbidities and clinical characteristics of the oncologic disease, at the baseline evaluation, before any treatment.

| | n | % |
|---|---|---|
| **Socio-demographic** | | |
| Age (years) | | |
| <50 | 162 | 34.9 |
| 50-64 | 216 | 46.6 |
| ≥65 | 86 | 18.5 |
| Education (years) | | |
| ≤4 | 195 | 42.0 |
| 5-9 | 133 | 28.7 |
| 10-12 | 74 | 16.0 |
| >12 | 62 | 13.4 |
| Living in the Greater Porto Area[a] | 209 | 45.0 |
| Marital status | | |
| Married/living together | 324 | 69.8 |
| Single | 50 | 10.8 |
| Widower/divorced | 90 | 19.4 |
| Professionally active (n=462) | 243 | 52.6 |
| Monthly income above 500€ (n=456)[b] | 206 | 45.2 |
| **Lifestyles** | | |
| Alcohol consumption, more than 10g/day (n=463) | 92 | 19.9 |
| Past or current smoker | 96 | 20.7 |
| Daily consumption of fruits and vegetables of at least 5 portions (n=461) | 101 | 21.9 |
| Practicing physical activity | 80 | 17.2 |
| **Comorbidities** | | |
| Hypertension | 146 | 31.5 |
| Diabetes | 46 | 9.9 |
| Chronic medicines consumption (n=462) | | |
| None | 166 | 35.8 |
| One | 78 | 16.8 |
| Two to five | 149 | 32.1 |
| More than five | 69 | 14.9 |
| **Clinical characteristics of the oncological disease** | | |
| Cancer stage | | |
| 0/I | 254 | 54.7 |
| II | 140 | 30.2 |
| III/IV | 70 | 15.1 |
| Breast cancer subtype (n=435) | | |
| HR+/HER2 | 335 | 77.0 |
| HER2+ | 64 | 14.7 |
| Triple negative | 36 | 8.3 |

[a] Greater Porto Area covers 560 km$^2$ and has about 1.1 million inhabitants. It includes the counties Espinho, Gondomar, Maia, Matosinhos, Porto, Póvoa de Varzim, Santo Tirso, Trofa, Valongo, Vila do Conde e Vila Nova de Gaia. Women not living in this area were mostly from other areas of the Northern Region of Portugal, South of Douro and North of Aveiro, the area covered by the Portuguese Institute of Oncology of Porto.

[b] 500€ is the median value of monthly income in the sample.

HR+/HER2 stands for tumor expressing Hormone Receptor but not overexpressing Human Epidermal growth factor Receptor 2; HER2+ stands for tumor overexpressing HER2; Triple negative stands for tumor not expressing estrogen receptors, nor progesterone receptors, nor overexpressing HER2.

**Table 2.** Cancer treatments performed during the five years after diagnosis of breast cancer.

| | Cancer treatments performed | | |
|---|---|---|---|
| | **During the 1st year after diagnosis** | **Between the 1st and the 3rd year after diagnosis** | **Between the 3rd and the 5th year after diagnosis** |
| | n (%) | n (%) | n (%) |
| **Breast surgery** | | | |
| Mastectomy | 213 (46.0) | - | - |
| Mastectomy + breast-reconstruction | 15 (3.2) | - | - |
| Breast-conserving | 235 (50.8) | - | - |
| Breast reconstruction | - | 26 (5.6) | 34 (7.3) |
| Breast-conserving surgery for a contra-lateral breast cancer | - | 1 (0.2) | 3 (0.6) |
| Total mastectomy for a contra-lateral breast cancer | - | - | 1 (0.2) |
| **Axillary surgery** | | | |
| Sentinel lymph node biopsy | 295 (65.6) | 1 (0.2) | 1 (0.2) |
| Lymph node dissection | 155 (34.4) | - | - |
| **Metastasectomy** | | | |
| Hepatic metastasectomy | - | 1 (0.2) | 1 (0.2) |
| Cerebral metastasectomy | - | 1 (0.2) | - |
| **Chemotherapy** | | | |
| Timing | | | |
| Neo-adjuvant | 31 (11.1) | - | - |
| Adjuvant | 249 (88.9) | - | - |
| For a recurrence or another primary cancer | - | 4 (0.2) | 10 (2.2) |
| Drugs | | | |
| Doxorubicin + cyclophosphamide | 57 (20.4) | - | - |
| Doxorubicin + cyclophosphamide + docetaxel | 29 (10.4) | - | - |
| Doxorubicin + cyclophosphamide + paclitaxel | 1 (0.4) | - | - |
| Cyclophosphamide + docetaxel | 2 (0.7) | - | - |
| Carboplatin + docetaxel | 1 (0.4) | - | - |
| 5-FU + epirubicin + cyclophosphamide | 23 (8.2) | - | - |
| 5-FU + epirubicin + cyclophosphamide + docetaxel | 165 (59.1) | - | - |
| 5-FU + epirubicin + cyclophosphamide + methotrexate | 1 (0.4) | - | - |
| Capecitabine | - | 2 (0.9) | 3 (0.3) |
| Docetaxel | - | - | 1 (0.1) |
| Paclitaxel | - | 3 (0.8) | 5 (0.5) |
| Vinorelbine | - | - | 2 (0.2) |
| Carboplatin | - | - | 1 (0.1) |
| Gemcitabine | - | - | 2 (0.2) |
| Epirubicin | - | - | 1 (0.1) |
| Rituximab + cyclophosphamide + doxorubicin + vincristine | - | 1 (0.5) | - |
| **Radiotherapy** (chest, axillary and/or supraclavicular) | 340 (73.3) | 3 (0.7) | 4 (0.9) |
| **Endocrine therapy** | 390 (84.1) | 387 (83.4) | 381 (82.1) |
| **Other systemic treatments** | | | |
| Trastuzumab | 61 (13.2) | - | 1 (0.2) |
| Pertuzumab | - | - | 1 (0.2) |
| Lapatinib | - | 1 (0.2) | - |

**Table 3**. Age and education at baseline, mean scores on the Montreal Cognitive Assessment (MoCA), cognitive changes and occurrence of probable cognitive impairment (PCI), over five years of follow-up.

| | **Groups based on cognitive trajectory and baseline performance** | | | | |
|---|---|---|---|---|---|
| | *Consistently high* (N=172) | *Mid-upward* (N=172) | *Mid-downward* (N=59) | *Consistently low* (N=61) | P* |
| Age (years), n (%) | | | | | 0.014 |
| <50 | 67 (39.0) | 61 (35.5) | 12 (20.3) | 22 (36.1) | |
| 50-64 | 80 (46.5) | 83 (48.3) | 26 (44.1) | 27 (44.3) | |
| ≥65 | 25 (14.5) | 28 (16.3) | 21 (35.6) | 12 (19.7) | |
| Education (years), n (%) | | | | | 0.005 |
| ≤4 | 62 (36.0) | 65 (37.8) | 37 (62.7) | 31 (50.8) | |
| 5-9 | 49 (28.5) | 58 (33.7) | 12 (20.3) | 14 (23.0) | |
| 10-12 | 33 (19.2) | 23 (13.4) | 5 (8.5) | 13 (21.3) | |
| >12 | 28 (16.3) | 26 (15.1) | 5 (8.5) | 3 (4.9) | |
| MoCA scores, mean [95% CI] | | | | | |
| At baseline | 26.1 [25.8, 26.5] | 21.9 [21.4, 22.3] | 23.2 [22.4, 24.0] | 19.2 [18.5, 21.8] | 0.018 |
| After one year | 26.3 [25.9, 26.6] | 23.9 [23.4, 24.4] | 21.4 [20.6, 22.3] | 20.1 [19.3, 21.0] | <0.001 |
| After three years | 25.9 [25.5, 26.3] | 23.8 [23.3, 24.3] | 20.0 [18.9, 21.1] | 19.5 [18.5, 20.6] | <0.001 |
| After five years | 26.3 [25.9, 26.7] | 24.3 [23.8, 24.7] | 19.7 [18.6, 20.8] | 19.0 [18.1, 19.8] | <0.001 |
| aMoCA scores, mean [95% CI] | | | | | |
| At baseline | 22.4 [22.1, 22.6] | 18.4 [18.2, 18.6] | 21.0 [20.5, 21.6] | 16.3 [15.9, 16.7] | <0.001 |
| After one year | 22.5 [22.2, 22.8] | 20.4 [20.1, 20.7] | 19.3 [18.6, 20.1] | 17.2 [16.6, 17.8] | 0.002 |
| After three years | 22.1 [21.8, 22.5] | 20.4 [20.1, 20.7] | 17.9 [17.0, 18.8] | 16.6 [15.8, 17.4] | <0.001 |
| After five years | 22.5 [22.3, 22.8] | 20.8 [20.5, 21.1] | 17.6 [16.6, 18.5] | 16.0 [15.4, 16.6] | <0.001 |
| Difference in MoCA/aMoCA scores, mean [95% CI] | | | | | |
| Score after one year – score at baseline | 0.1 [-0.1, 0.5] | 2.0 [1.7, 2.3] | -1.7 [-2.5, -1.0] | 0.9 [0.3, 1.5] | <0.001 |
| Score after three years – score at baseline | -0.2 [-0.5, 0.1] | 1.9 [1.7, 2.2] | -3.1 [-3.9, -2.3] | 0.3 [-0.6, 1.2] | <0.001 |
| Score after five years – score at baseline | 0.2 [-0.1, 0.5] | 2.4 [2.1, 2.7] | -3.5 [-4.4, -2.6] | -0.3 [-1, 0.4] | <0.001 |
| Proportion of women with a difference in the MoCA score after one year (score after one year – score at baseline), n (%) | | | | | |
| ≤0 | 101 (58.7) | 36 (20.9) | 47 (79.7) | 28 (45.9) | <0.001 |
| ≤ -1 | 63 (36.6) | 16 (9.3) | 41 (69.5) | 22 (36.1) | <0.001 |
| ≤ -2 | 30 (17.4) | 5 (2.9) | 34 (57.6) | 6 (9.8) | <0.001 |
| ≤ -3 | 15 (8.7) | 0 (0) | 23 (39.0) | 1 (1.64) | <0.001 |
| Prevalence of PCI, n (%) | | | | | |
| At baseline | 0 (0) | 18 (10.5) | 0 (0) | 18 (29.5) | <0.001 |
| After one year | 0 (0) | 6 (3.5) | 8 (13.6) | 18 (29.5) | <0.001 |
| After three years | 0 (0) | 1 (0.6) | 13 (22.0) | 22 (36.1) | <0.001 |
| After five years | 0 (0) | 2 (1.2) | 11 (18.6) | 22 (36.1) | <0.001 |

aMoCA: age- and education adjusted score on Montreal Cognitive Assessment; PCI: Probable cognitive impairment detected with the Montreal Cognitive Assessment, and defined as scoring below two standard deviations of age- and education-specific distribution from normative data.
*P-value for comparisons between groups, using $\chi^2$ test or one-way Anova.

**Table 4**. Socio-demographic characteristics of the patients, lifestyle and co-morbidities before treatments, clinical characteristics of the tumor, oncological treatments, neurological complications and patient-reported outcomes (PRO) according to the four cognitive groups - *Consistently high*, *Mid-upward*, *Mid-downward*, and *Consistently low*.

| | *Consistently high* (N=172) n (%) | *Mid-upward* (N=172) n (%) | *Mid-downward* (N=59) n (%) | *Consistently low* (N=61) n (%) | P[g] |
|---|---|---|---|---|---|
| Menopausal status[a] | | | | | |
| Post-menopausal | 90 (52.3) | 97 (56.4) | 41 (69.5) | 35 (57.4) | 0.152 |
| Lifestyle | | | | | |
| Never smoker | 126 (73.3) | 139 (80.8) | 52 (88.1) | 51 (83.6) | |
| Smoker | 22 (12.8) | 9 (5.2) | 4 (6.8) | 2 (3.3) | |
| Former smoker | 24 (14.0) | 24 (14.0) | 3 (5.1) | 8 (13.1) | 0.042 |
| Daily alcohol consumption ≤10g | 134 (78.4) | 139 (80.8) | 49 (83.1) | 49 (80.3) | 0.872 |
| Co-morbidities | | | | | |
| Diabetes | 11 (6.4) | 20 (11.6) | 10 (16.9) | 5 (8.2) | 0.093 |
| Hypertension | 52 (30.2) | 51 (29.7) | 19 (32.2) | 24 (39.3) | 0.541 |
| Chronic medicines consumption[b] | | | | | |
| Psycholeptics | 55 (32.0) | 46 (26.7) | 23 (39.0) | 27 (44.3) | 0.055 |
| Psychoanaleptics | 43 (25.0) | 29 (16.9) | 8 (13.6) | 15 (24.6) | 0.116 |
| Cancer stage | | | | | |
| 0/I | 88 (51.2) | 92 (53.5) | 36 (61.0) | 38 (62.3) | |
| II | 54 (31.4) | 56 (32.6) | 18 (30.5) | 12 (19.7) | |
| III/IV | 30 (17.4) | 24 (14.0) | 5 (8.5) | 11 (18.0) | 0.322 |
| Breast surgery | | | | | |
| Breast-conserving | 92 (53.5) | 79 (46.2) | 31 (52.5) | 33 (54.1) | |
| Mastectomy[c] | 80 (46.5) | 92 (53.8) | 28 (47.5) | 28 (45.9) | 0.516 |
| Axillary surgery | | | | | |
| Lymph node dissection [d] | 103 (62.4) | 112 (66.7) | 40 (70.2) | 40 (66.7) | |
| Sentinel lymph node biopsy | 62 (37.6) | 56 (33.3) | 17 (29.8) | 20 (33.3) | 0.710 |
| Combination of treatments including | | | | | |
| Chemotherapy | 110 (64.0) | 106 (61.6) | 33 (55.9) | 33 (54.1) | 0.475 |
| Radiotherapy | 140 (81.4) | 116 (67.4) | 41 (69.5) | 47 (77.0) | 0.021 |
| Hormone therapy | 148 (86.0) | 140 (81.4) | 49 (83.1) | 53 (86.9) | 0.609 |
| Trastuzumab | 21 (12.2) | 24 (14.0) | 8 (13.6) | 8 (13.1) | 0.971 |
| Combination of treatments without chemotherapy | | | | | |
| Radiotherapy | 44 (71.0) | 31 (47.0) | 17 (65.4) | 18 (64.3) | 0.040 |
| Hormone therapy | 54 (87.1) | 53 (80.3) | 22 (84.6) | 26 (92.9) | 0.434 |
| Neurological complications, at least once during the five years | | | | | |
| Neuropathic pain | 63 (36.6) | 52 (30.2) | 24 (40.7) | 24 (39.3) | 0.354 |
| Chemotherapy-induced peripheral neuropathy | 26 (15.1) | 30 (17.4) | 8 (13.6) | 10 (16.4) | 0.888 |
| PRO, before treatment | | | | | |
| Depression[e] | 10 (5.8) | 14 (8.1) | 6 (10.2) | 8 (13.1) | 0.312 |
| Anxiety[e] | 63 (36.6) | 64 (37.4) | 28 (47.5) | 24 (39.3) | 0.504 |
| Poor quality of sleep[f] | 114 (66.7) | 111 (64.5) | 45 (76.3) | 45 (73.8) | 0.275 |
| PRO, one year after diagnosis | | | | | |
| Depression[e] | 18 (10.5) | 17 (9.9) | 12 (20.3) | 14 (23.0) | 0.015 |
| Anxiety[e] | 45 (26.2) | 38 (22.1) | 21 (35.6) | 16 (26.2) | 0.241 |
| Poor quality of sleep[f] | 118 (68.6) | 121 (70.3) | 45 (76.3) | 49 (80.3) | 0.282 |
| PRO, three years after diagnosis | | | | | |
| Depression[e] | 10 (5.8) | 10 (5.8) | 8 (13.6) | 14 (23.0) | <0.001 |
| Anxiety[e] | 31 (18.0) | 32 (18.6) | 15 (25.4) | 22 (36.1) | 0.016 |
| Poor quality of sleep[f] | 118 (68.6) | 108 (63.2) | 47 (79.7) | 47 (77.0) | 0.052 |
| PRO, five years after diagnosis | | | | | |
| Depression[e] | 10 (5.8) | 14 (8.1) | 12 (20.3) | 12 (19.7) | 0.001 |
| Anxiety[e] | 42 (24.6) | 35 (20.5) | 19 (32.2) | 22 (36.1) | 0.062 |
| Poor quality of sleep[f] | 122 (73.1) | 124 (73.4) | 44 (80.0) | 45 (78.9) | 0.624 |

[a] When menopausal status was not specified, all women with at least 60 years of age, women who underwent a bilateral oophorectomy and those with an intact uterus and being amenorrheic for 12 or more consecutive months prior to the diagnosis in the absence of alternative pathological or physiological cause and follicle stimulating hormone and serum estradiol levels within the laboratory's reference ranges were classified as postmenopausal, or otherwise as premenopausal.

[b] Classification of medicines in accordance with WHO Collaborating Centre for Drug Statistics Methodology

[c] Patients who had both mastectomy and breast-conserving surgery are reported as mastectomy; N<464, because one patient only performed axillary surgery.

[d] Patients who had both lymph node dissection and sentinel lymph node biopsy are reported as lymph node dissection.

[e] Depression and anxiety were defined as presenting the respective sub-score equal to or higher than 11 in the Hospital Anxiety and Depression Scale.

[f] Poor quality of sleep was defined as presenting a total score equal to or higher than five in the Pittsburg Sleep Quality Index.

[g] P-value for any differences between groups, obtained with the $\chi 2$ test.

## PAPER 4

# Cognitive decline in patients with prostate cancer: study protocol of a prospective cohort, NEON-PC

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# Cognitive decline in patients with prostate cancer: study protocol of a prospective cohort, NEON-PC

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## ABSTRACT

**Introduction** Prostate cancer is the most prevalent oncological disease among men in industrialised countries. Despite the high survival rates, treatments are often associated with adverse effects, including metabolic and cardiovascular complications, sexual dysfunction and, to a lesser extent, cognitive decline. This study was primarily designed to evaluate the trajectories of cognitive performance in patients with prostate cancer, and to quantify the impact of the disease and its treatments on the occurrence of cognitive decline.

**Methods** Participants will be recruited from two main hospitals providing care to approximately half of the patients with prostate cancer in Northern Portugal (Portuguese Institute of Oncology of Porto and São João Hospital Centre), and will comprise a cohort of recently diagnosed patients with prostate cancer proposed for different treatment plans, including: (1) radical prostatectomy; (2) brachytherapy and/or radiotherapy; (3) radiotherapy in combination with androgen deprivation therapy and (4) androgen deprivation therapy (with or without chemotherapy). Recruitment began in February 2018 and is expected to continue until the first semester of 2021. Follow-up evaluations will be conducted at 1, 3, 5, 7 and 10 years. Sociodemographic, behavioural and clinical characteristics, anxiety and depression, health literacy, health status, quality of life, and sleep quality will be assessed. Blood pressure and anthropometrics will be measured, and a fasting blood sample will be collected. Participants' cognitive performance will be evaluated before treatments and throughout follow-up (Montreal Cognitive Assessment and Cube Test as well as Brain on Track for remote monitoring). All participants suspected of cognitive impairment will undergo neuropsychological tests and clinical observation by a neurologist.

**Ethics and dissemination** The study was approved by the Ethics Committee of the hospitals involved. All participants will provide written informed consent, and study procedures will be developed to ensure data protection and confidentiality. Results will be disseminated through publication in peer-reviewed journals and presentation in scientific meetings.

## Strengths and limitations of this study

- This protocol describes a prospective cohort study of patients with prostate cancer, expected to reflect the contemporary patterns of diagnosis and treatment in developed countries.
- Cognitive impairment will be characterised regarding its severity and possible aetiologies through neuropsychological and clinical evaluations.
- Short-term and long-term effects as well as mediators of the effect of androgen deprivation therapy on cognitive performance will be analysed.
- A longitudinal remote monitoring tool of cognitive function will be used, in addition to state-of-the-art methods, which allows for more frequent standardised evaluations, while reducing learning effects of repeated measurements.
- Only a measure of overall cognitive function will be obtained from all participants and multiple cognitive domains will only be evaluated in patients with probable cognitive impairment.

## INTRODUCTION

Prostate cancer is the second most common neoplasm and the fifth-leading cause of death from cancer among men, with nearly 1.3 million new cases and 359 thousand deaths estimated in 2018 worldwide.[1] In recent decades, prostate cancer incidence has been heavily influenced by diagnoses following prostate-specific antigen testing of asymptomatic individuals and by the detection of latent cancer in tissue removed during prostatectomy or autopsy.[1] At the same time, prostate cancer mortality has been decreasing in many countries, which has been linked to earlier diagnosis because of extensive use of prostate-specific antigen screening, and improved treatment including radical prostatectomy, hormonal therapy and radiation therapy.[2 3] Increases in prostate cancer survival[4] require a comprehensive assessment of the burden of cancer, due to the disease, treatment and sequelae.[5 6]

Androgen deprivation therapy is used in the treatment of approximately half of all patients with prostate cancer,[7 8] and it may

last from 6 to 36 months, on an intermittent basis or continue indefinitely.[9] The use of androgen deprivation therapy and its impact on cognitive function has been assessed, both in prospective studies evaluating cognitive performance using neuropsychological tests and in large retrospective studies reporting the risk of dementia or of Alzheimer's disease in patients with prostate cancer according to androgen deprivation therapy exposure.[10–12] However, methodological heterogeneity does not allow for the direct comparison of results, and shortcomings of the study designs, including small sample sizes, short follow-up periods or limited quality of information on cognitive status, as well as residual confounding, preclude more robust conclusions on this topic.[10] Also, in addition to the possible direct effect of androgen deprivation therapy on cognitive function due to the drop in serum testosterone and its biological activity in certain areas of the brain,[13] hormonal changes may also cause metabolic alterations,[14] with an increase in cardiovascular risk factors, such as an increase in insulin resistance, serum cholesterol and triglycerides or anaemia,[15] which in turn are associated to cognitive decline.[16–19] This possible indirect effect may take longer to manifest in the brain than the direct decrease in testosterone serum levels, and it may be related to the development of dementia. The potential mediator effect of these biochemical and haematological parameters has not been studied. Prospective investigations including an accurate characterisation of the cognitive performance of patients with prostate cancer proposed for different types of treatment, and analyses accounting for distinct causal pathways may contribute to a better understanding of the effects of prostate cancer and its treatments on cognitive decline.

Therefore, this project primarily aims to understand the impact of androgen deprivation therapy on the cognitive performance of patients with prostate cancer in Northern Portugal. The main specific objectives are as follows:

1. To describe the trajectories of cognitive performance over time (up to 10 years) in patients with prostate cancer under different treatments and, in comparison to the general population, by using the Montreal Cognitive Assessment tool, the Cube Test and Brain on Track. The relation between patients' characteristics, cancer treatments and different cognitive trajectories will also be assessed.
2. To quantify the association between androgen deprivation therapy and cognitive decline, in the short term and in the long term.
3. To assess the role of metabolic syndrome and anaemia as possible mediators of the androgen deprivation therapy effect on cognitive performance.

## METHODS AND ANALYSIS

We describe a prospective cohort study that will evaluate patients with prostate cancer selected among those being treated at the two largest hospitals providing cancer care in the North of Portugal, which attend half of the patients with prostate cancer in this region. Recruitment started in February 2018 and is ongoing. We expect to complete it in the first semester of 2021.

### Eligibility criteria

Eligible participants are those with a recent diagnosis of prostate cancer and being initially proposed for radical prostatectomy (group 1), brachytherapy or radiotherapy (group 2), radiotherapy in combination with androgen deprivation therapy (group 3), or androgen deprivation therapy with or without chemotherapy (group 4), and prostate cancer survivors never treated with androgen deprivation therapy before, who present with a recurrence of the disease to be treated with androgen deprivation therapy, with or without chemotherapy (group 5).

Participants who had a previous chemotherapy or radiotherapy treatment for another primary cancer, or a diagnosis of a psychiatric or a neurological condition impairing cognitive function before the prostate cancer diagnosis, or being unable to understand the purpose of the study or to collaborate will be excluded, as well as those expected to receive cancer treatments outside the Portuguese Institute of Oncology of Porto or the São João Hospital Centre.

### Participants' recruitment and follow-up

Patients with prostate cancer will be consecutively recruited at the Portuguese Institute of Oncology of Porto and the São João Hospital Centre, from February 2018 to the first semester of 2021. Participants will be evaluated at baseline (before any treatment for recently diagnosed patients or before androgen deprivation therapy for patients with a recurrence of the disease), and at 1, 3, 5, 7 and 10 years after enrolment, as depicted in figure 1.

### Data collected from medical records

Clinical characteristics, including comorbidities, medication and cancer treatment (including all drugs used for systemic treatment of prostate cancer, either at initial or follow-up treatments and duration), as well as prognostic and treatment response biomarkers will be systematically collected by medical doctors from the patients' medical records. Prostate cancer staging based on tumor (T), nodes (N) and metastases (M) (TNM stages) will be in accordance with the American Joint Committee on Cancer TNM system classification[20] and risk stratification according to the National Comprehensive Cancer Network (www.nccn.org).

### Questionnaire evaluation

Data on sociodemographic (birth date, address, marital status, education, occupation), lifestyle and dietary characteristics (smoking and alcohol consumption, and intake of fruits and vegetables, physical activity and sedentary behaviours) will be collected through questionnaires applied by a trained interviewer. Anxiety and depression,[21 22] sleep quality,[23 24] quality of life and health status,[25–28] and health literacy[29 30] will be evaluated through self-administered questionnaires validated for


**Figure 1** Study design, and timing of baseline and follow-up evaluations in the main cohort and the subcohort of participants with suspected cognitive impairment. *Subsequent follow-up evaluations will be at 3, 5, 7 and 10 years after the baseline evaluation. †The Brain on Track evaluation will be conducted every 3 months. ‡Only participants who score below 1.5 SD of age-adjusted and education-adjusted cut-offs on the Montreal Cognitive Assessment during each evaluation (baseline, and 1, 3, 5, 7 and 10 years of follow-up) and a random sample of 30 participants will be invited for a neuropsychological evaluation where a battery of cognitive tests will be applied. The type of cognitive impairment will be classified through a clinical evaluation performed by a neurologist.

the Portuguese population, and are described in detail in table 1.

### Blood pressure

Blood pressure will be measured with a digital blood pressure monitor (Omron M6). Participants will be asked to remain seated, with the right arm and back supported and feet firmly on the floor, and to abstain from speaking during the entire procedure. The cuff will be placed on the right arm so the bottom margin is approximately 2–3 cm above the antecubital fossa. A larger or a smaller cuff will be used as necessary to fit the arm of the participant. Three measurements with 1 min intervals will be registered.

### Anthropometrics

Weight and height will be measured with participants in light clothes and no shoes, and registered to the nearest kilogram and centimeter, respectively, using a digital column scale (Seca 799). Waist and hip perimeters will be measured using a non-elastic measuring tape (Seca 211) with participants standing, with feet slightly apart and the arms relaxed along the body; waist perimeter will be measured at half the distance between the last rib and the iliac crest. Hip perimeter will be measured with participants in the same position, with the measuring tape placed at the widest part of the hip below the iliac crest. Both waist and hip circumferences will be registered to the nearest millimeter. Most measurements are expected to be performed in the morning.

### Blood sample

A fasting blood sample (at least 12 hours) will be collected by the hospitals' nurses using venous puncture, and blood samples will be centrifuged at 3000 rpm for 10 min to obtain plasma and serum, within 30–60 min. Total cholesterol, high density lipoprotein cholesterol, triglycerides, glycaemia, glycated haemoglobin and haemoglobin will be analysed. Plasma and serum samples will be stored in small aliquots at −80°C until the end of the study (10 years).

### Cognitive function evaluation

Cognitive function will be evaluated using the Montreal Cognitive Assessment[31 32] and the Cube Test,[33] at baseline and at each of the subsequent follow-up evaluations, and with a web-based tool for remote longitudinal assessment (Brain on Track),[34] every 3 months for a period of up to 10 years.

Participants suspected of cognitive impairment will undergo a comprehensive neuropsychological assessment that will allow specific domains of cognitive function to be analysed; the battery of tests is described in table 2. Additionally, those with confirmed cognitive impairment will undergo a clinical evaluation by a neurologist.

#### The Montreal Cognitive Assessment

The Montreal Cognitive Assessment is a pen-and-paper screening test, developed to detect mild cognitive impairment. It assesses eight cognitive domains (visuospatial ability, executive function, attention, concentration, working memory, language, verbal memory and orientation), generating a total score ranging from 0 to 30.[31] The translated, culturally adapted and validated version of the Montreal Cognitive Assessment for the Portuguese population[35] will be used, and the performance of participants will be classified as probable cognitive impairment when the score is 1.5 SD below the mean of age-based and education-based group distribution from published normative data.[32]

#### The Cube Test

The Cube Test will be used as a rapid cognitive screening tool, which can be applied to illiterate participants, or those with low educational levels, language or hearing deficits.[33] The Cube Test is easy to apply, and the simple instructions and scoring procedures contribute for standardised use. The test is based on the time spent in

**Table 1** Description of the instruments used for the evaluation of all patients

| Instrument | Description | Domains/subscales | Score |
|---|---|---|---|
| MoCA[31 35] | Test for the rapid screening of mild cognitive impairment—an intermediate clinical state between normal cognitive ageing and dementia. | Attention and concentration; executive functions; memory; language; visuoconstructional skills; calculations; orientation. | Range: 0–30<br>Higher scores represent better cognitive performance. |
| Cube Test[33] | A two-task cognitive screening tool that consists in completing a 3D cube from six pieces (task 1) and remembering the position of the six pieces on a grid with 25 squares measuring eight by eight centimeters from a previously shown scheme (task 2). | Visuoconstructional skills; executive function; processing speed; delayed memory. | Time to construct the first vertex and to complete cube and the number of pieces correctly assembled in up to 6 min (task 1); number of pieces correctly positioned on the grid (task 2). |
| Brain on Track[34] | A self-administered computerised test intended for longitudinal cognitive testing that includes eight subtests. | Attention; memory; executive functions; language; calculation; constructive ability; visuospatial processing. | Range: virtually unlimited (maximum number of correct answers in a fixed time)<br>Higher scores represent better cognitive performance.<br>Scores falling below an expected performance threshold for each age/education group; a pattern of decline in individual performance. |
| HADS[21 22] | Scale with 14 questions assessing anxiety and emotional distress among patients during the previous week. | Depression; anxiety. | Range (for each subscale): 0 to 21<br>Scores greater than or equal to 11 represent a case of anxiety or depression, as applicable. |
| PSQI[23 24] | Index with 18 questions assessing sleep quality and disturbances during the previous month. | Subjective sleep quality; sleep latency; duration of sleep; habitual sleep efficiency; sleep disorders; use of medications for sleep; daytime dysfunction. | Range: 0–21<br>Scores greater than five indicate poor sleep quality. |
| QLQ-C30[25 26] | Scale with 30 questions assessing quality of life in patients with cancer during the previous week. | Global health status.<br>Functional scales: physical functioning; role functioning; emotional functioning; cognitive functioning; social functioning.<br>Symptom scales/items: fatigue; nausea and vomiting; pain; dyspnoea; insomnia; appetite loss; constipation; diarrhoea; financial difficulties. | Range (scales and single-item): 0–100<br>Higher scores for the global health status and for a functional scale represent a healthy level of quality of life and functioning, respectively.<br>Higher scores for a symptom scale/item represents a higher level of symptomatology/ problems. |
| QLQ-PR25[27] | Specific Prostate Cancer Scale with 25 questions assessing quality of life in patients with prostate cancer during the previous week and the last 4 weeks. | Functional scales: sexual activity; sexual functioning.<br>Symptom scales: urinary symptoms; bowel symptoms; hormonal treatment-related symptoms; incontinence aid. | Range (scales and single-item): 0 to 100<br>Higher scores for a function scale/item reflect a healthy level of functioning.<br>Higher scores for a symptom scale/item reflect a higher level of symptomatology/problems. |
| EQ-5D-5L[28] | A measure of health-related quality of life with five questions and a Visual Analogue Scale. | Mobility, self-care, usual activities, pain/discomfort; anxiety/depression and a visual analogue scale. | A total of 3125 possible health states are defined to describe the patient's health state. Each state is referred to in terms of a 5-digit code.<br>Vertical Visual Analogue Scale<br>Range: 0–100<br>Higher scores reflect 'The best health you can imagine' and lower scores reflect 'The worst health you can imagine'. |
| METER[29 30] | A measure of health literary including 40 words and 30 non-words. | 40 words and 30 non-words. | Range: 0–40 and 0–30<br>Adequate health literacy is defined as scoring at least 35/40 in words and 18/30 in non-words. |

3D, three dimensions; EQ-5D-5L, Measure of health-related quality of life of the EuroQol Group; HADS, Hospital Anxiety and Depression Scale; METER, Medical Term Recognition Test; MoCA, Montreal Cognitive Assessment; PSQI, Pittsburgh Sleep Quality Index; QLQ-C30, Quality of Life Questionnaire of the European Organisation for Research and Treatment of Cancer; QLQ-PR25, Prostate cancer-specific module of the Quality of Life Questionnaire of the European Organisation for Research and Treatment of Cancer.

assembling the six faces of a 3D cube and then, the correct placement of the six faces of the 3D cube on a grid with 25 squares measuring eight by eight centimeters. The Cube Test assesses visuoconstructive, visuospatial and executive functions, visuospatial working memory, information processing speed, incidental learning, motor processing speed and manual dexterity.

### Brain on Track

The Brain on Track test will be used for the remote evaluation of changes in cognitive function. This is a computerised cognitive monitoring test, which was developed and validated in the Portuguese population, showing good internal consistency, discriminative ability and reliability.[34 36] Brain on Track evaluates different cognitive

**Table 2** Description of the battery of instruments used for the comprehensive neuropsychological assessment*

| Instrument | Description | Cognitive domains/ function | Score |
|---|---|---|---|
| SMC[45 46] | A 10-item scale regarding subjective memory complaints. | Subjective memory. | Range: 0–21<br>Higher scores reflect maximal memory complaints. |
| Phonemic Verbal Fluency[47 48] | A test consisting of three trials of 1 min each where participants are asked to produce orally as many words as possible beginning with a specific letter. | Executive function; language; semantic memory. | The total trial score corresponds to the no of words correctly produced within 1 min. The total test score corresponds to the sum of the three trials.<br>Higher scores correspond to better performance. |
| 18-point CDT[49–51] | An 18-point clock-drawing scoring system where participants are asked to draw a big circle and put the numbers of the clock, and then they were asked to indicate the time as '10 past 11'. | Visuospatial; executive function. | Range: 0–18<br>Scoring system with three main components: (1) assessment of circle integrity (two points); (2) number placement and sequencing (six points) and (3) placement and size of the hands (six points). Additionally, there are two points for representation of the clock's centre and two points for general gestalt. |
| TMT[52 53] | Part A: participants are asked to draw lines to connect 25 randomly positioned numbered circles in numeric order as quickly as possible. | Part A: attention; visual scanning and speed of eye-hand coordination and information processing. | Direct measures of performance: time (seconds) to complete part A and part B, and performance errors during part A and part B. |
| | Part B: participants are asked to draw lines to connect circles in numeric and alphabetic order as quickly as possible, alternating between numbers and letters (progressively up to number 13). | Part B: working memory and executive functions; particularly, the ability to switch between sets of stimuli. | Derived scores: difference score (B–A), ratio score (B/A), proportion score (B–A/A), sum score (A+B), and multiplication score (A×B/100).<br>Lower raw scores and higher adjusted scores correspond to better performance. |
| WMS-III[54 55] | Evaluates memory and attention functions using both auditory and visual stimuli.<br>A test composed of 17 subtests designed to measure different memory functions in a person with the aim of detecting and discriminating between subcortical vascular dementia and Alzheimer's disease.<br>Subtests used: Logical Memory I, II; Visual Reproduction I, II; Digit Span. | Verbal and visual memories; working memory. | Range:<br>► Immediate recall: 0–50<br>► Delayed recall: 0–50<br>► Auditory recognition: 0–30<br>► Visual reproduction: 0–104<br>► Digit span: 0–30<br>Higher scores correspond to better performance. |
| WAIS-III[56 57] | Measures intelligence and cognitive ability in adults and older adolescents.<br>Subtests used: Digit-Symbol-Coding, which consists of digit-symbol pairs followed by a list of digits and under each digit participants write down the corresponding symbol as fast as possible; and Symbol Search, in which, participants are asked to look at two groups of symbols and to indicate if any of the symbols of the first group are present in the other group. | Attention/concentration; executive function (sequencing); motor function; processing speed. | The number of correct symbols within the allowed time (120 s) is measured. |
| Stroop Test[58 59] | Assesses the ability to inhibit cognitive interference, which occurs when the processing of a stimulus feature affects the simultaneous processing of another attribute of the same stimulus.<br>This test has three trials: (1) the participant is required to read the colour names printed in black ink as quickly as possible; (2) the participant is required to name the colour of coloured dots as quickly as possible; (3) the participant is required to name the colour of the ink of the colour name words (the colour name does not match the colour of the ink). | Executive functions (inhibitory control); selective attention. | Scores for each trial indicate the number of correct responses. An interference score can be generated that quantifies the participant's ability to inhibit the inappropriate response of reading the colour name as opposed to the colour of the ink used to print the colour name in the third trial. |

Continued

Table 2 Continued

| Instrument | Description | Cognitive domains/ function | Score |
|---|---|---|---|
| Token Test-short form[60] | A test designed to assess the comprehension of commands that vary in degree of linguistic difficulty but which are relatively independent of defects in other aspects of intellectual capacity such as memory and vocabulary.<br>The test consists of six subsections that represent different levels of linguistic difficulty. The participant is presented with tokens of different shapes (ie, circles, squares, triangles), sizes, and colours, and is required to perform certain acts with the tokens, such as point to selected tokens, touch them, pick them up and place one token on top of another. | Attention and vigilance; verbal functions. | Range: 0–36<br>Higher scores correspond to better performance. |
| SDMT[61] | A quick screening test for organic cerebral dysfunction.<br>The test involves a simple substitution task that can be easily performed: using a reference key, the participant has 90s to pair specific numbers with given geometric figures. | Organic cerebral dysfunction. | Individuals with cerebral dysfunction perform poorly. |
| TeLPI[62] | A Portuguese irregular word reading test using 46 irregular, infrequent Portuguese words designed to assess premorbid intelligence. | Premorbid IQ: full scale IQ; Verbal IQ; Performance IQ | Range: number of errors (maximum of 46) and years of education are inserted in three linear equations to calculate the three types of IQ |
| BDI-II[63 64] | A 21 question measure assessing the presence of depressive symptoms experienced by the participant within the past week. | Emotional functioning. | Range: 0–63<br>A cut-off score indicative of mild depressive symptoms is greater than 10 and for severe depressive symptoms is greater than 30. |
| Barthel ADL Index[65 66] | An index to measure functional disability, focused on bodily oriented personal care. | Functional domains: feeding; incontinence; transferring; toileting; dressing; bathing. | Range: 0–100<br>Lower scores reflect increased disability. |
| IADL[67 68] | An eight item scale used to assess independent living skills which include more complex activities (ie, 'instrumental activities of daily living') necessary for functioning in community settings. | Functional domains: using the telephone; shopping; food preparation; housekeeping; laundry; transport; medication; finances. | Range: 0–8<br>Higher scores reflect high function, independence. |

*Only patients who score below 1.5 SD of age-adjusted and education-adjusted cut-offs at the Montreal Cognitive Assessment during each evaluation (baseline, and 1, 3, 5, 7 and 10 years of follow-up) and a random sample of 30 participants will be invited for a neuropsychological evaluation.
Barthel ADL Index, Barthel Activities of Daily Living Index; BDI-II, Beck Depression Inventory-Second Edition; CDT, Clock Drawing Test; IADL, Lawton and Brody Instrumental Activities of Daily Living; SDMT, Symbol and Digit Modalities Test; SMC, Subjective Memory Complains scale; TeLPI, Irregular Word Reading Test; TMT, Trail Making Test; WAIS-III, Wechsler Adult Intelligence Scale-Third Edition; WMS-III, Wechsler Memory Scale-Third Edition.

domains, including attention, memory, executive functions, language, calculation, constructive capacity and visuospatial processing, through 11 exercises designed to include random elements and alternate sequences to lower the learning effect of repeating cognitive tests. It is to be performed using a home computer to access a web platform where different cognitive tests are uploaded. Each patient's results are stored and can be monitored by the research team.

Patients will be eligible to participate if they have completed at least 3years of schooling, have no severe motor, visual or language impairments that prevent cognitive assessment, have easy access to a computer with an internet connection, and are able to use a computer without help. At the end of the baseline evaluation, participants will undergo a training session, and will be instructed to remotely log into the web platform and proceed to the first evaluation after 1week, and then every 3months. A Short Message Service reminder will be sent to participants 1day before each remote evaluation. The research team will be automatically notified when participants fail to perform the test in order to reschedule the evaluation.

### Comprehensive neuropsychological assessment and clinical evaluation by a neurologist

All participants who score below 1.5 SD of age-adjusted and education-adjusted cut-offs on the Montreal Cognitive Assessment[31 32] in each evaluation (baseline, and 1, 3, 5, 7 and 10 years of follow-up) will undergo a

neuropsychological evaluation, expectedly within 1 month, comprising a battery of cognitive tests (table 2). The type and progressive nature of cognitive impairment, and its functional impact will be determined through a clinical evaluation performed by a neurologist, with a close surrogate present. Additionally, participants with a first neuropsychological evaluation will be reassessed with the same battery of tests, independently of their Montreal Cognitive Assessment score in the subsequent follow-up evaluations. A random sample of 30 patients with normal scores on the Montreal Cognitive Assessment will also perform a neuropsychological evaluation at 1, 3, 5, 7 and 10 years of follow-up, as a control group.

Participants will be classified as having mild cognitive impairment when presenting cognitive complaints over a period of at least 6 months, as reported by the patient or family members, modest cognitive decline from a previous level of performance reported by the patient or family members, and neuropsychological evaluation scores at least 2.0 SD below the age-corrected norms in at least one cognitive domain or at least 1.5 SD below the age-corrected norms in at least two cognitive domains, while also presenting no clinical depression or interference of cognitive function with independence in daily activities.[37 38]

Dementia will be defined according to the criteria used for defining major neurocognitive disorder of the Diagnostic and Statistical Manual of Mental Disorders (fifth edition), that is, significant cognitive impairment in at least one cognitive domain representing a significant decline from a previous level of functioning that interferes with independence in daily activities.[38] The severity of dementia will be classified using the clinical dementia rating scale.[39] The initial clinical classification will be confirmed after at least 6 months of clinical follow-up by a neurologist, and a complete diagnostic workup to identify other potential causes of cognitive impairment not related to oncological disease, including blood analyses for treatable causes of dementia and imaging studies.

### Data analyses and sample size

The frequency of cognitive decline and impairment will be described in the different categories of sociodemographic (age, education, employment, marital status) and lifestyle (alcohol intake, tobacco smoking, physical activity, and fruit and vegetables consumption) variables, as well as patient reported outcomes (anxiety, depression, quality of sleep), and according to the clinical characteristics of prostate cancer (cancer stage, risk strata) as well as treatments.

Trajectories of cognitive decline will be described through indicators of cognitive performance at different moments of evaluation using the appropriate format according to the nature of the variables and their distribution. Fixed-effects and mixed-effects models will be computed to compare cognitive performance trajectories (considering age and education) over time, according to other sociodemographic and clinical characteristics, for each of the treatment groups.

Prevalence at baseline and incidence measures (incidence rates and cumulative incidences) and the corresponding 95% CIs will be estimated to quantify the frequency of cognitive impairment, and the association between treatments and incident cognitive impairment. Cumulative incidence will be estimated considering death as a competing event, according to the Kalbfleisch and Prentice method.[40] Crude and adjusted relative risks will be calculated.

The sample size was calculated considering the objective to quantify the association between the use of androgen deprivation therapy and cognitive decline between the baseline and the 1-year evaluation, defined as a variation in the score from baseline to the 1-year evaluation below 1.5 SD of the distribution in the cohort, of the changes in cognitive scores over the same time period. For this, assuming a statistical power of 80%, a level of significance of 5% and a 1:1 ratio between androgen deprivation therapy-exposed (groups 3 and 4) and unexposed (groups 1 and 2), 600 prostate cancer patients will be necessary to detect a twofold higher proportion of participants (14%) with cognitive decline in the androgen deprivation therapy group. Secondary analyses will be conducted considering the exposure to each specific hormonal treatment.

For the description of cognitive performance trajectories, and the calculation of the prevalence of cognitive impairment at baseline and incidence measures (incidence rates and cumulative incidences), the sample size will influence the precision of the estimates at each moment but will not be a limiting factor for the essentially descriptive accomplishment of these objectives. Nevertheless, considering the prevalence of cognitive impairment in the general population of Northern Portugal of 9.6%,[41] a precision of 2.4%, and a 95% confidence level, a sample of 579 individuals will be needed. As such, the estimated sample size calculated above will also be sufficient for estimating the prevalence of cognitive impairment in the population of patients with prostate cancer.

Considering the high potential for confounding by indication, propensity scores calculated based on several disease characteristics, including prognostic biomarkers and predictors of response to treatment, will be used in data analysis. Causal diagrams will be used to support the decisions regarding the potential role of the different sociodemographic, lifestyle, clinical and treatment variables in the causal pathways.

Training of interviewers and the use of standardised procedures for data collection are expected to contribute to a low proportion of missing data, and no imputation is being planned.

Considering our experience in another cancer cohort,[42] we estimate that approximately a third of the total sample will participate in the Brain on Track evaluation. Using as criteria for referral of participants to the comprehensive neuropsychological assessment, the Montreal Cognitive

Assessment cut-off score, 1.5 SD below the mean of age and education-based group distribution from published normative data,[32] we expect at least 42 patients to undergo a neuropsychological assessment at baseline and at each subsequent evaluation.

Taking into account the survival of patients with prostate cancer in the North of Portugal,[43] and the high participation obtained in a previous prospective cohort study of patients with breast cancer;[42 44] we estimate at least 90% and 80% of patients will participate in the 1-year and 5-year follow-up evaluations, respectively. In order to minimise refusals and losses to follow-up, all evaluations will be scheduled to take place on the same day as routine appointments in the respective hospital and participants will be invited again when they miss scheduled appointments.

### Contingency plan

Due to the COVID-19 pandemic, recruitment and evaluation of participants were interrupted from March to June 2020. Beginning in July, procedures were adapted to minimise the risk of infection for participants and members of the research team. Only the Montreal Cognitive Assessment and the neuropsychological evaluation will be performed face-to-face at the hospital. Participants will answer the questionnaire on sociodemographic, and lifestyle and dietary characteristics during a telephone interview. Self-administered questionnaires will be completed at home and sent mailed back with a prepaid envelope.

Anthropometrics measurements, blood sample collection and the Cube Test evaluation will not be performed. Weight, height, blood pressure and blood sample parameters will be retrieved from medical records when available or asked to the participants. The initial training session for the Brain on Track evaluation will be conducted through videoconference.

The impact of the pandemic on the course of this investigation, namely regarding participation and retention rates, completeness of information and potential losses of validity and precision will be addressed specifically. Additional mitigation measures may have to be adopted, namely an extension of the recruitment period or an increase in the sample size.

### Patient and public involvement

Patients and public were not involved in the conception, design and dissemination of this study.

## ETHICS AND DISSEMINATION

Ethics approval was obtained from the Ethics Committees of the Portuguese Institute of Oncology of Porto (Ref. CES 89/017) and the São João Hospital Centre (Ref. 76/17), and by the Portuguese Data Protection Authority (Authorisation 3478/2017). Written informed consent will be obtained from all participants after the project's aims and procedures are fully explained by a member of the research team.

This is an observational study in which patients with prostate cancer will be followed according to usual clinical practice, as such the occurrence of harmful effects related to participation in the study are not expected. Participants will receive detailed information about the research purpose and objectives, name and institution of the researchers, expected duration of the interview, voluntary nature of participation, clearly stating that there will be no penalty for those who refuse to participate, and ensuring confidentiality and anonymity of all the information provided. Participants will be asked to give authorisation for collection of data from their personal clinical records. After clarification of any doubts, an informed consent will be signed in duplicate and a copy will be given to each participant. All participants will be informed that they can leave the study at any time, and this decision does not affect their medical care. There is no expected risk or discomfort other than those arising from interviewing, collecting venous blood samples and physical measurements (height, weight, blood pressure). Only participants able to understand the study and provide informed consent will be included. To minimise possible discomfort due to the required trips to the hospital for face-to-face evaluations or the duration of interviews, and to avoid unnecessary burden and travel expenses, data collection procedures were designed to last no more than 60 min, and will be scheduled to take place on the same day as other appointments in the respective hospitals as part of regular clinical care, preferably in the morning due to the fasting requirement. Starting in July 2020, only the Montreal Cognitive Assessment will be performed face-to-face at the hospital, to reduce the risk of infection by SARS-CoV-2.

This study requires the collection and processing of sensitive personal data including health and clinical data from questionnaires and the clinical files of patients. Therefore, additional measures will be taken to protect the anonymity and the confidentiality of all participants. All data regarding clinical aspects will be collected by clinical members of the research team and privacy is assured. All participants will have a study-specific identification number, which will be used in all questionnaires and stored blood samples. The correspondence between this identification number and the personal identifiable information will be stored in a file, to which only the principal investigator will have access. Only the research team will have access to the database with anonymised data, saved on a password-protected secure computer. No personal identifiers will be used in data analyses. The same procedures will be adopted for each of the evaluations.

The expected results may contribute to elucidate the magnitude of the androgen deprivation therapy effect on the cognitive function of patients with prostate cancer, and the possible mediator effect of metabolic syndrome and anaemia in this process. This may help clinical decisions regarding the pharmacological class to be used in patients more vulnerable to cognitive impairment. This study may also contribute to the refinement and

validation of the longitudinal monitoring tool Brain on Track. Considering the 10-year temporal horizon of this project, the follow-up of the cohort assembled will contribute to a better understanding of the long-term trajectories of cognitive performance and the iatrogenic effects of prostate cancer treatments.

The findings of this project will be submitted for publication in international peer-reviewed journals, and proposed for presentation in relevant national and international conferences, which will allow for the dissemination of the main findings across the medical community. Press releases through mass media will also be issued to promote the dissemination of information relevant to the general population and policy-makers. Furthermore, the project will contribute to the training of researchers through the production of masters' theses and doctoral dissertations.

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**PAPER 5**

## Prevalence of cognitive impairment before prostate cancer treatment.

## PAPER 5

# Prevalence of cognitive impairment before prostate cancer treatment.

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**Key words:** prostate cancer, prevalence, cognitive impairment, treatments

**Abstract**

**Background/objective:** Up to one-third of patients with cancer may present cognitive impairment before treatment, but data regarding prostate cancer (PCa) are scarce. This study aimed to estimate the prevalence of cognitive impairment in patients with incident PCa, before cancer treatment.

**Methods:** Between February 2018 and April 2021, the NEON-PC cohort included 609 patients with a recent PCa diagnosis proposed for treatment at the Portuguese Institute of Oncology of Porto. The Montreal Cognitive Assessment (MoCA) was used to assess cognitive performance. Participants with a MoCA <1.5 standard deviations (SD) of age- and education-specific normative values were considered to have probable cognitive impairment (PCI) and were reffered for a comprehensive neuropsychological assessment; patients were classified as having cognitive impairment when at least one cognitive domain was impaired. Data from the population-based cohort EPIPorto (n=351 men aged ≥40 years, evaluated in 2013-2015) were used for comparison.

**Results/Discussion:** The prevalence of PCI was 17.4% in EPIPorto and 15.1% in NEON-PC (age- and education-adjusted odds ratio (aOR):1.02, 95% confidence interval (CI):0.70,1.50). Among patients with PCa, PCI was more frequent in those proposed for androgen deprivation therapy, with or without chemotherapy (aOR: 1.92, 95%CI:0.95,3.86). A neuropsychological assessment was performed in 65 patients with PCa: 38.5% had normal cognitive function, 7.7% had a mild deficit (one or more cognitive scores <1.0 SD of age-corrected normative values but without fullfilling the criterion for cognitive impairment) and 53.9% had cognitive impairment. Executive functions were the most affected cognitive domain.

**Conclusions:** PCI was similar among patients recently diagnosed with PCa and in the general population. Prevalence of cognitive impairment was lower than in previous reports among patients with other cancers, which may be explained by differences in the assessment and definition of cognitive impairment, and of the specificities of each cancer type.

**Introduction**

Pathophysiological processes induced by cancer, the experience of a cancer diagnosis or cancer treatment may negatively impact cognitive performance, and cognitive impairment has been often reported among these patients [1, 2]. However, cancer is not a single disease and even among tumours with the same tipology, there is a large heterogeneity regarding cancer-related symptoms, including those related with the impairment of the patients' cognitive status [3, 4].

In some longitudinal studies aiming to assess the impact of chemotherapy on cognitive performance, cognitive impairment was reported to be frequent even before treatment initiation: in 11% [5] to 35% [6] of patients with breast cancer, in 46% of patients with testicular cancer [7], and in 45% of patients with colorectal cancer [8]. In patients with small cell lung cancer, 70% had impairment in verbal memory, up to 30% in frontal lobe executive functions, and one-third in motor coordination, which was attributed to paraneoplastic syndrome by the authors; the latter is rare in most cancers, but may affect 10% of patients with small cell lung cancer [9]. Alterations in cytokine serum levels observed in patients with acute myelogenous leukemia or myelodysplastic syndrome [10], and in women with breast cancer [11] have also been associated to impairment in certain cognitive domains. The post-traumatic stress syndrome related to cancer diagnosis observed in women with breast cancer may also explain impaired performance in cognitive tests [12].

Prostate cancer is the most prevalent neoplasm among men [13], due to its high incidence rates and overall good prognosis, which highlights the importance of understanding and managing cognitive impairment among patients with prostate cancer throughout the cancer care continuum. The occurrence of cognitive impairment among newly diagnosed cases as well as among long-term survivors is expected to reflect the characteristics of the patients, namely regarding male sex and older average age at diagnosis [14], as well as the patterns of early diagnosis and treatments available [3]. The cognitive performance of patients with this cancer

has been studied in the context of the association of androgen deprivation therapy (ADT) with cognitive decline [15] and dementia [16]. Although the prevalence of cognitive impairment was reported to vary between 10% and 69%, these values refer to the percentage of men who presented cognitive decline, that is a measure of cognitive variation from before ADT to months after the baseline evaluation, and not to the impairment of cognitive function with regard to what would be expected to be normal cognitive functionning according to age and education [17]. Indeed, only one study reported the prevalence of cognitive impairment before ADT based on scores below specific normative cut-off values on cognitive tests [18], but patients proposed for non-hormonal treatment were not included in the study. Another study reported the percentage of cognitive impairment before ADT but patients performing low in a cognitive screening instrument were not included [19].

Therefore, this study aims to estimate the prevalence of cognitive impairment in patients recently diagnosed with prostate cancer before cancer treatment. A global measure of cognitive performance will be compared between patients with prostate cancer and men of the general population. Among patients with prostate cancer, the prevalence of impairment in each cognitive domain and in the overall cognitive performance will be described.

**Methods**

This study is based on cross-sectional evaluations of the NEON-PC cohort of patients with prostate cancer and the EPIPorto cohort of the general population.

*NEON-PC cohort*

This prospective cohort study took place at the Portuguese Institute of Oncology of Porto (IPO-Porto), which is one of the largest cancer hospital in Portugal, providing care mainly to patients of the Northern region, after a referal from the family doctor or according to public hospital collaboration protocols.

The study protocol was previously described in detail [20]. Briefly, between March 2018 and April 2021, patients recently diagnosed with prostate cancer and expected to be treated at IPO-Porto were considered elegible. Patients without at least one year of education, not being Portuguese native-speakers, those with a history of chemotherapy, radiotherapy or androgen deprivation therapy treatments, or with previously diagnosed neurologic or psychiatric conditions impairing cognitive performance were excluded. Due to the COVID-19 pandemic, field activities at IPO-Porto were suspended from March 9$^{th}$ to June 30$^{th}$ 2020. A total of 609 patients accepted to participate, 98 refused and in 32 cases the evaluation could not be performed before treatments due to the COVID-19 pandemic.

*Evaluation of participants' cognitive performance*

The Montreal Cognitive Assessment (MoCA) is a cognitive test designed to detect mild cognitive impairment, showing good sensitivity and specificty [21]. Version 7.1, which is validated in the Portuguese population, was used in the current study [22]. MoCA assesses executive functions, visuospatial ability, short-term memory, language, attention, concentration, working memory, and temporal and spatial orientation, through 12 tasks. The overall score ranges from 0 to 30,

with higher scores corresponding to better cognitive performance. Participants scoring below 1.5 standard deviations (SD) of age- and education-specific normative values [23] were considered to present probable cognitive impairment (PCI).

In the NEON-PC cohort, participants with PCI were invited to perform a comprehensive neuropsychological assessment, with a trained neuropsychologist. The battery of tests assessed verbal and visual memory, working memory, information processing, executive functions and language, using tests validated in the Portuguese population: Wechsler Memory Scale – Third Edition [24], Wechsler Adult Intelligence Scale – Third Edition [25], Trail Making Test [26], Stroop Test [27], Phonemic Verbal Fluency [28], Clock Drawing Test [29] and the Token Test – short-form [30]. For each cognitive domain, the criterion used for the classification of cognitive impairment was based on the number of tests used to assess the cognitive domain and the number of scores below age-corrected norm cut-off values (below 1, 1.5 or 2 SD), as described in detail in Table 1 [31]; patients were classified as having cognitive impairment when at least one cognitive domain was impaired.

A total of 10 participants refused to perform this evaluation, four abandoned the study, and the evaluation could not been performed in 13 participants, as such, 65 patients completed the neurospsychological assessment. Those who underwent the neuropsychological assessment were not statistically different than those who did not, regarding age (p=0.553), education (p=0.164), and the treatment proposed to treat PCa, either ADT +/- chemotherapy or other treatments (p=0.745).

*Assessment of anxiety and depression, and clinical information in the NEON-PC cohort*

Patients with prostate cancer answered the Hospital Anxiety and Depression Scale [32, 33]. Anxiety and depression sub-scores equal to or higher than 11 out of a possible 21 were considered indicative of clinically significant anxiety or depression, respectively. Information on

tumor size (T), invasion of lymph node (N) and metastases (M), Gleason score and prostate specific antigen (PSA) were retrieved from medical files, and used to classify each patient according to the American Joint Committee on Cancer TNM staging system, eight edition [34]. Gleason scores were grouped into Gleason grades according to the International Society of Urological Pathology [35].

*EPIPorto cohort*

EPIPorto is a population-based closed cohort assembled between 1999 and 2003 in the city of Porto (≈400 000 inhabitants), representative of dwellers aged 18 years or older (n=2485). Random digit dialing of landline telephones was used to select households and a permanent resident aged at least 18 years was selected within each household, by simple random sampling, with a participation rate of 70% [36]. A total of 354 male participants aged 40 or older were tested with MoCA in the 2013-15 reevaluation of the cohort [37]. In accordance with the exclusion criteria used in the NEON-PC cohort, three participants who presented with Parkinson's or Alzheimer's diseases were excluded.

*Data analysis*

A total of 609 patients with prostate cancer (NEON-PC) and 351 men from the general population (EPIPorto) were considered for analysis.

Sample characteristics are presented as counts and proportions for categorical variables, and median, $25^{th}$ and $75^{th}$ percentiles for quantitative variables. Multivariate logistic regression was used to estimate the age- and education-adjusted odds ratio (aOR) of the association between belonging to the NEON-PC cohort *vs.* to the EPIPorto cohort with the presence of PCI, and the association between socio-demographic and clinical variables with PCI among patients with prostate cancer.

The prevalence of cognitive impairment and the respective 95% confidence interval (95% CI) were computed.

All analyses were performed using STATA v.15 (StataCorp). All tests were two sided and a $p<0.05$ was considered significant.

*Ethics*

Ethics approval was obtained from the Ethics Committee of the IPO-Porto for the NEON-PC cohort, and from the Ethics Committee of the Hospital de São João, for the EPIPorto cohort. The study was carried out according to the Helsinki Declaration and all participants completed the informed written consent form.

**Results**

Table 2 presents the characteristics of participants with prostate cancer and those from the general population. The former were older and had lower educational levels (p<0.001). Most patients with prostate cancer were classified as stage II (59.0%) and 13.3% as stage IV.

In the NEON-PC cohort, 92 participants (15.1%) presented PCI whereas in the EPIPorto cohort, they were 61 (17.4%), corresponding to an age- and education-adjusted odds ratio of 1.02 (95%CI: 0.70,1.50). Figure 1 presents the distribution of PCI among patients with prostate cancer proposed for different treatments. PCI was more frequent (23.1%) among those proposed for ADT alone or with chemotherapy, and less frequent (12.1%) among those proposed for radiotherapy (external beam radiation with no hormonal treatment).

Figure 2 presents the associations between sociodemographic and clinical variables with PCI among patients with prostate cancer. A higher educational level was associated with higher odds of PCI (age-adjusted OR: 1.77, 95%CI: 1.11, 2.80). Depression was associated with PCI, although this was a non-statistically significant result (age-and education-adjusted OR: 2.51, 95%CI: 0.93, 6.69). Although the association after adjustment for age and education did not reach a statistically significance (age-and education-adjusted OR: 1.92, 95%CI: 0.95, 3.86), participants proposed for ADT alone or with chemotherapy were more likely to present PCI.

Considering patients with prostate cancer and PCI who performed the neuropsychological assessment, 38.5% had normal cognitive function, 7.7% had mild deficits (one or more cognitive scores below 1.0 SD of age-corrected norms but without fullfilling the criterion for cognitive impairment) and 53.9% had cognitive impairment.

Table 3 presents the number of participants with impairment in each cognitive domain. Executive function was the most affected domain, being impaired in 47.7% of the participants who performed the neuropsychological assessment. One participant had impairment in executive functions, while in the other cognitive domains his scores were within the normal

range. All of the remaining participants had at least one additional cognitive domain with a score below the normal range, either showing disfunction or impairment.

**Discussion**

The prevalence of PCI was similar in patients with prostate cancer and in the general population. Patients proposed for ADT alone or with chemotherapy presented PCI more frequently than patients proposed for other treatments. Cognitive impairment was confirmed by neuropsychological testing in just over half the patients with PCI, and executive function was the most frequently impaired domain.

The prevalence of cognitive impairment in the present study, detected with MoCA and with a neuropsychological test battery, was much lower than in previous studies performed in patients with other cancers [5-9, 38]. Prostate cancer, which is an indolent and localized disease in many men, may not induce the same pattern of systemic pathophysiologic alterations as other cancers, that might be a cause of cognitive impairment. Moreover, there is no gold standard for measuring cognitive function, and the different methods used to evaluate cognitive performance and define cognitive impairment may also explain the heterogenous results. Indeed, the cognitive tests and the cognitive domains they assess, the number of tests, and the criterion used to classify cognitive impairment vary substantially across studies [39]. Using the criterion for the classification for cognitive impairment based on presenting at least one score below the cut-off of 2 SD of the norms is associated with a 5% probability of misclassification due to chance only, if one out of two administered tests are below the cut-off. This probability increases with the number of tests administered and if one out of nine tests is below the cut-off, then the probability of misclassification is more than 20%. Likewise, using the criterion of presenting at least two scores below 1.5 SD of the norm is associated with a 5% probability of misclassification if two out of six scores are below the cut-off and more than 20% if two out of twelve scores are below the cut-off [31]. Therefore, misclassification due to chance could explain the high values for cognitive impairment reported in patients with cancer in other studies. We classified cognitive impairment in each cognitive domain, considering three factors: the number

of tests administered, the cut-off based on age-corrected norms (1, 1.5 or 2 SD), and depending on the two others, the number of tests with a score below the cut-off, to not exceed by 5% the probability of misclassification [31].

Among men with prostate cancer, there is only one previous study reporting the prevalence of cognitive impairment before ADT [18]. In addition to the critera used to define cognitive impairment, the particular characteristics of the sample could explain the high value of 45%. Indeed, 15% of the patients had asymptomatic metastatic disease and 85% of the patients had biochemical relapse [18], that is, most of the patients were previously treated for prostate cancer and frequent sequelae of previous treatment, such as anemia [40] and depression [41], may have contributed to an increased prevalence of cognitive impairment [42, 43], compared to patients recently diagnosed with prostate cancer. In this study, participants were classified with cognitive impairment when presenting two low scores and these were most frequently observed in tasks assessing memory and executive functions, which is in accordance with our findings.

Older age is considered to increase the likelihood for cognitive impairment while higher education is associated with decreased risk [44]. However, in the NEON-PC cohort, PCI was more frequent in participants with more than four years of school attainment than in less educated individuals. Unmeasured confounders related to socioeconomic level may explain the observed association. Further in-depth analyses of sociodemographic, lifestyle and clinical characteristics of the patients are needed to understand this result.

Depression may impair performance in cogntive tests, particularly in an ederly population [43, 45]. Among patients with prostate cancer, the association between depression and PCI was not statistically significant. However, the prevalence of depression was low, which contributes for limited statistical power. Previous studies conducted among patients with prostate cancer before ADT did not report on the effect of depression on cognitive impairment [18, 19].

Our results show PCI may be more frequent in patients with advanced disease proposed for ADT. This may contribute to explain the conflicting results regarding cognitive decline from studies that included only patients who would receive radiotherapy with ADT and showed no effect of ADT on cognitive performance over time [46], and others that did not include these patients but only those to be treated with androgen ablation and reported a negative effect of ADT on cognitive tests [47].

*Strengths and limitations*

This is the first study to report the prevalence of cognitive impairment in a large cohort of patients with prostate cancer including patients proposed for several different treatments.

We used data from the EPIPorto population based-cohort for comparison, which allowed us to consider the prevalence of cognitive impairment in patients with prostate cancer as similar to that observed in the general population. The control group is of increased importance when the definition of the outcome differs from study to study, difficulting the apreciation of the findings. Indeed, two studies reported similar values of prevalence of cognitive impairment in patients with prostate cancer, 45% and 41%, which may be considered worrying values, but in the latter, the age- and education-matched control group also presented a prevalence of 44% for cognitive impairment.

EPIPorto was a representative sample of the population of the city of Porto in 1999-2003, and suffered from attrition since its assembling to the third evaluation in 2013-2015. It is more likely that the participants who abandoned the study had higher odds of cognitive impairment [48]. On the other hand, IPO-Porto admits patients mostly from the Northern region and Portuguese urban areas have a lower prevalence of cognitive impairment than rural areas [49]. Thus, the prevalence of PCI in the EPIPorto cohort may be lower than it would be in a newly assembled

cohort representative of the Portuguese Northern region and it is not likely that PCI would be more frequent in patients with prostate cancer than in the general population.

**Conclusions**

Patients with advanced prostate cancer proposed for androgen deprivation therapy may present cognitive impairment more frequently than men with prostate-localized cancer. PCI was similar among patients recently diagnosed with prostate cancer than in the general population. The prevalence of cognitive impairment among prostata cancer patients was lower than in previous reports, which may be explained by differences in the assessment and definition of cognitive impairment and of the type of cancer.

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**Table 1.** Criteria used for the classification of cognitive impairment, considering the number of tests administered to assess each cognitive domain.

| Cognitive domain | Test | Criteria for impairment |
|---|---|---|
| **Verbal memory** | WMS III – Logical memory I and II | 2 scores<1.5SD<br>or 1 score<2SD |
| **Visual memory** | WMS III – Visual reproduction I and II | 2 scores<1.5SD<br>or 1 score<2SD |
| **Working memory** | WMS III– Digit span | score <2SD |
| **Processing speed** | WAIS III – Digit – Symbol – Coding and<br>Symbol search<br>Trail Making Test, part A<br>Stroop test – word reading | at least 3 scores<1SD<br>or 2 scores<1.5SD |
| **Executive functions** | Stroop test (color naming and word<br>color naming)<br>Trail Making Test, part B and B-A<br>Phonemic Fluency – letters M, R and P<br>Phonemic Fluency – categories of<br>animals<br>18-points Clock drawing test | at least 3 scores<1SD<br>or 2 scores<1.5SD |
| **Language** | Token Test – short-form | score <2SD |

SD, standard deviation; WAIS III, Wechsler Adult Intelligence Scale Third Edition; WMS III, Wechsler Memory Scale Third Edition.

**Table 2.** Sociodemographic and clinical characteristics of the participants.

| | **Patients with prostate cancer (NEON-PC)** | **Men from the general population (EPIPorto)** | **P** |
|---|---|---|---|
| Age (years) – median, P25-P75 | 68, 63-74 | 64, 56-71 | <0.001 |
| Education (years) – median, P25-P75 | 4, 4-9 | 9, 5-15 | <0.001 |
| Cancer stage* – n (%) | | | |
| Stage I | 46 (7.6) | _ | _ |
| Stage II | 359 (58.9) | _ | _ |
| Stage III | 116 (19.1) | _ | _ |
| Stage IV | 81 (13.3) | _ | _ |

* 7 participants had undefined cancer stage (II/III)
P25 – percentile 25; P75 – percentile 75

**Table 3**. Participants with prostate cancer who performed the neuropsychological assessment and presenting impairment in each cognitive domain.

| Cognitive domain | Participants with normal functioning [a] n (%) | Participants with dysfunction [b] n (%) | Participants with impairment [c] n (%) |
|---|---|---|---|
| Verbal memory | 45 (69.2) | 13 (20.0) | 7 (10.8) |
| Visual memory | 39 (60.0) | 22 (33.8) | 4 (6.2) |
| Working memory | 55 (84.6) | 10 (15.4) | 0 |
| Processing speed | 41 (63.1) | 19 (29.2) | 5 (7.7) |
| Executive functions | 25 (38.5) | 9 (13.8) | 31 (47.7) |
| Language | 59 (90.8) | 4 (6.2) | 2 (3.1) |

[a] Normal functioning in each cognitive domain was considered when all scores were within the normal range [≥ 1 standard deviation (SD) below mean].
[b] Dysfunction in each cognitive domain was considered when one or more scores were below the normal range (<1SD) but the criteria for cognitive impairment were not fulfilled.
[c] Cognitive impairment in each cognitive domain was considered according to the following criteria: 1 score<2SD, for working memory and language; at least 2 scores<1.5SD or 1 score<2SD, for verbal and visual memories; at least 3 scores<1SD or 2 scores<1.5SD, for processing speed and executive functions.

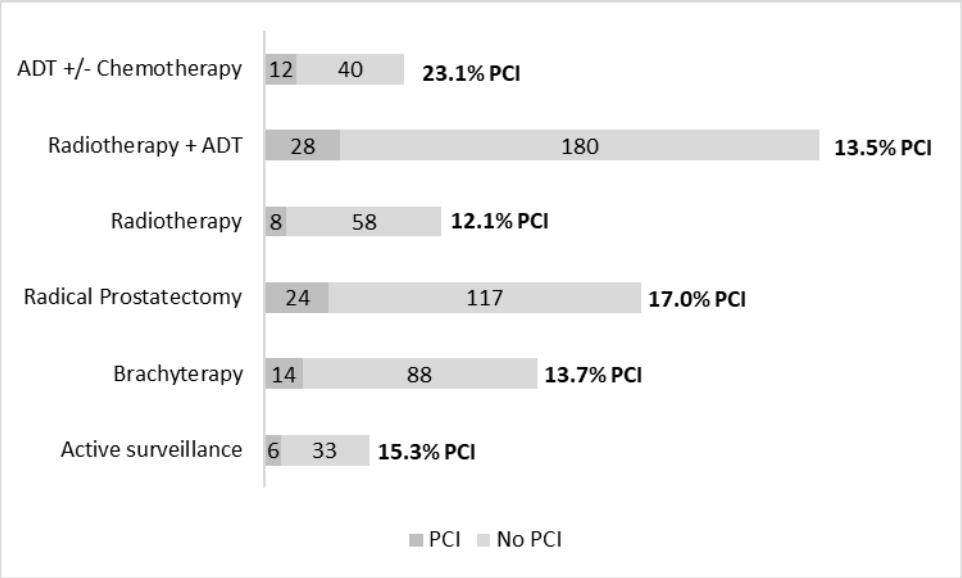


**Figure 1.** Participants with probable cognitive impairment (PCI) according to the proposal of treatment.
ADT, androgen deprivation therapy.

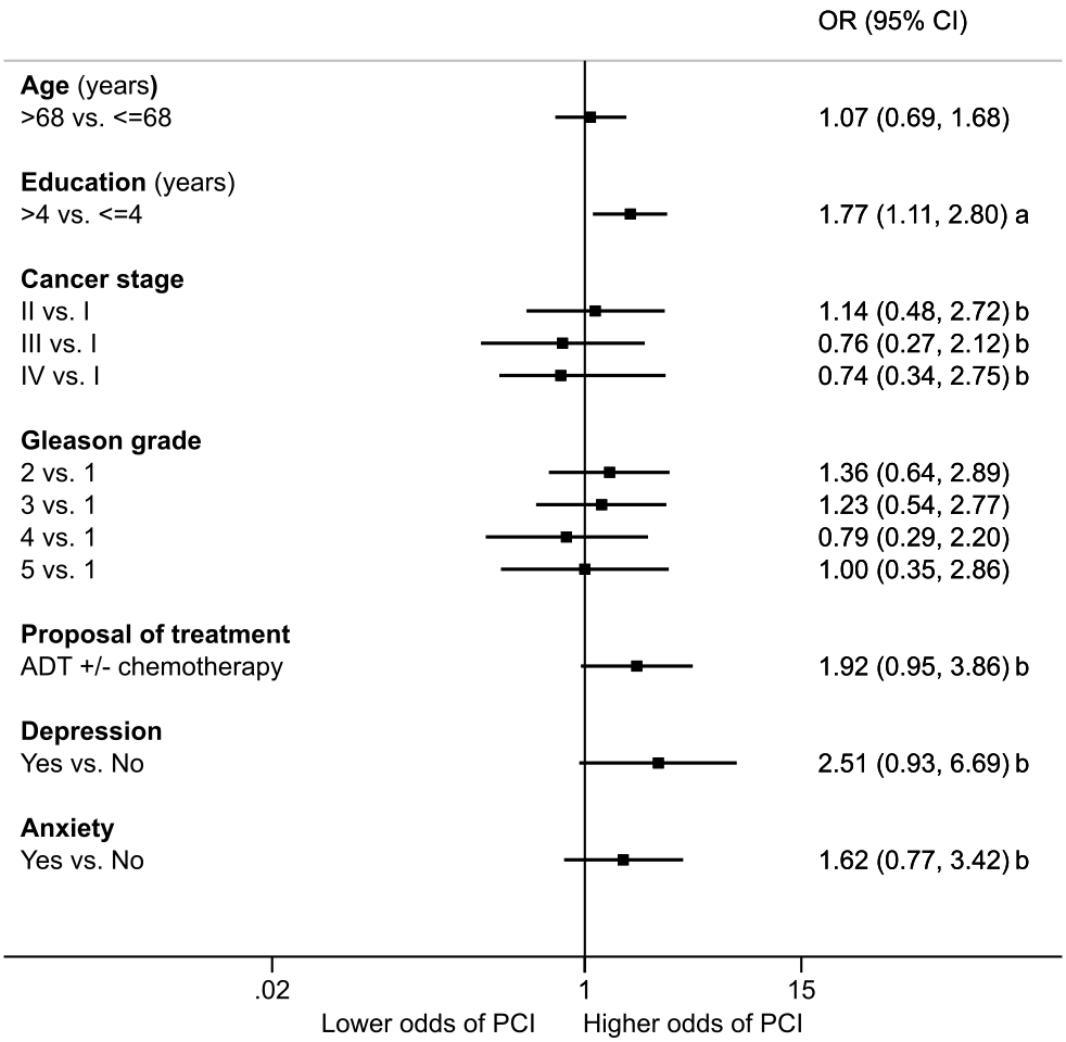


**Figure 2**. Association of sociodemographic characteristics of the patients, clinical characteristics of the tumour and patient-reported outcomes- anxiety and depression- with PCI (probable cognitive impairment) among patients with prostate cancer.
OR, odds ratio
a, OR adjusted for age
b, OR adjusted for age and education
Age- and education-based categories according to the respective median value.

**PAPER 6**

# Androgen deprivation therapy and cognitive decline in the NEON-PC prospective cohort: the impact of the COVID-19 pandemic

## PAPER 6

# Androgen deprivation therapy and cognitive decline in the NEON-PC prospective cohort: the impact of the COVID-19 pandemic

**Running title:** Androgen deprivation therapy and cognitive decline

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**Abstract**

**Background:** Androgen deprivation therapy (ADT) has been associated with cognitive decline, but results are conflicting. This study describes changes in cognitive performance in patients with prostate cancer, according to ADT, during the first year after prostate cancer diagnosis.

**Methods:** Patients with prostate cancer treated at the Portuguese Institute of Oncology of Porto (n=366) were evaluated with the Montreal Cognitive Assessment (MoCA), before treatment and after one year. All baseline evaluations were performed before the COVID-19 pandemic and 69.7% of the one-year assessments were completed after the first lockdown. Cognitive decline was defined as the decrease in MoCA from baseline to the one-year evaluation below 1.5 standard deviations of the distribution of changes in the whole cohort. Participants scoring below age- and education-based normative reference values in the MoCA were considered to have cognitive impairment. Age- and education-adjusted odds ratios (aOR) were computed to estimate the association between ADT and cognitive decline/incident cognitive impairment.

**Results:** Mean MoCA scores increased from baseline to the one-year evaluation (22.3 *vs.* 22.8, p<0.001). Cognitive decline was more frequent in the ADT group, and even more after the onset of the COVID-19 pandemic (aOR 6.91 *vs.* 1.93, p for interaction=0.233). The one-year cumulative incidence of cognitive impairment was 6.9% (9.1% before and 3.7%% after the pandemic onset), which was higher among patients receiving ADT, but only after the pandemic (aOR 5.53 *vs.* 0.49, p for interaction=0.044).

**Conclusions:** The COVID-19 pandemic may have worsened the effect of ADT on the cognitive performance of patients with prostate cancer.

**Key words:** cancer, prostate; neurocognitive disorders; longitudinal studies; hormones, hormone substitutes, and hormone antagonists/analogs and derivatives; covid-19/complications

**Introduction**

With nearly five million five-year prevalent cases estimated in 2020, patients with prostate cancer represent the largest population of male cancer survivors worldwide (1). Nearly half of these patients may have been submitted to androgen deprivation therapy (ADT) during the course of the disease (2). ADT is used in clinically localized prostate cancer to complement radical radiotherapy, in regional disease (lymph nodes affected), alone or associated with radiotherapy, in metastatic disease, and in persistent or recurrent disease after radical prostatectomy or radiotherapy (3). However, ADT has been associated with several adverse effects, including cognitive decline and dementia. Most studies on cognitive decline were small and yielded heterogeneous results, and have been summarized in a meta-analysis that showed an association between ADT and a decline in visuomotor tasks (4). More recently, retrospective studies based on large health records, claims and other administrative electronic databases, found conflicting results on the association between ADT and dementia (5-7). In the available prospective studies, an accurate assessment of the potential effect of ADT on cognitive performance was limited by instrument variability, small sample sizes and short follow-up duration (8). Moreover, cognitive outcomes were essentially based on the variation in cognitive performance from a baseline to a follow-up evaluation, and there is no study reporting the incidence of cognitive impairment, defined as a performance below the expected, accounting for age and education (9).

Therefore, in a cohort evaluated before treatments for prostate cancer and after one year, this study aimed to compare the variation in cognitive performance scores and the incidence of cognitive impairment between patients treated with ADT and those who received treatments without ADT.

**Methods**

The NEON-PC prospective cohort study was developed at the Portuguese Institute of Oncology of Porto (IPO-Porto), and has been described in detail elsewhere (10). Briefly, between February 2018 and March 2020, patients recently diagnosed with prostate cancer and proposed for any treatment, including active surveillance, and those with a disease recurrence to be treated with ADT, were considered eligible. Illiterate patients and non-Portuguese native-speakers were excluded, as well as those with a previous history of chemotherapy, radiotherapy, ADT and neurologic or psychiatric conditions impairing cognitive performance diagnosed before prostate cancer. Patients were recruited at the end of the multidisciplinary tumour board meeting when the different available options to treat their cancer were proposed.

A total of 486 participants were evaluated at baseline and 366 (75.3%) at the one-year evaluation. All baseline evaluations were concluded before the COVID-19 pandemic and 69.7% of the one-year assessments were performed after the first lockdown due to the pandemic. A total of 120 participants were not evaluated at one-year because their evaluation was postponed due to the pandemic (n=66), or were lost to follow-up, due to refusal to participate (n=36), follow-up at another hospital (n=5), severe hypoacusia precluding the one-year evaluation (n=1), ADT refusal (n=1), brachytherapy not performed because of diagnosis and treatment with chemotherapy for another primary tumour (n=2) or death (n=7). Those who did not perform the one-year evaluation had a lower educational level [education in years, median, percentile 25-percentile 75 (P25-P75): 4, 4-8 *vs.* 5, 4-10; p=0.013] and had a lower baseline MoCA score [mean, standard deviation (SD): 20.6, 4.12 *vs*. 22.4, 3.69; p<0.001]. Participants evaluated at one-year received treatments including ADT more frequently and underwent brachytherapy less frequently (p=0.006; Table 1).

At baseline and at the one-year evaluation, the cognitive performance of participants was evaluated with the Montreal Cognitive Assessment (MoCA). This cognitive test was developed to detect mild cognitive impairment, and demonstrated good sensitivity and specificity. It assesses eight cognitive

domains with 12 tasks and its score ranges from 0 to 30, with lower scores indicating worse cognitive performance (11). Participants completed the Hospital Anxiety and Depression Scale (HADS), and anxiety and depression sub scores equal to or higher than 11 out of 21 were considered indicative of anxiety and depression symptoms, respectively (12,13).

Clinical information regarding cancer stage and treatments performed were retrieved from medical files. Cancer stage, based on tumour (T), nodes (N), metastases (M), Gleason grade and prostate specific antigen (PSA), was defined according to the AJCC (American Joint Committee on Cancer) TNM system, eighth edition (14). Gleason scores were grouped into Gleason grades according to the International Society of Urological Pathology (15). This is an observational study and participants were treated according to usual practice at IPO-Porto. First line drugs used in ADT included goserelin with or without bicalutamide or, in a few cases, degarelix; second line treatment included abiraterone acetate and enzalutamide. Most patients admitted to IPO-Porto with symptomatic metastatic prostate cancer were prescribed 150 mg bicalutamide per day at the first consultation until the administration of goserelin. In these cases, the baseline evaluation was performed approximately three weeks after initiating antiandrogen but before the first goserelin administration. Docetaxel was used for chemotherapy.

*Statistical analysis*

Patients' characteristics are described using counts and percentages, means and SD or medians and P25 and P75.

Variation in cognitive performance was computed as the difference between MoCA at one-year and at baseline. Participants with a variation below 1.5 SD of the distribution of changes in the cohort were considered to have cognitive decline.

Participants were considered to have cognitive impairment when scoring below age- and education-normative reference values (1.5 SD below the mean (16,17)). Among participants with no cognitive

impairment at baseline, those presenting cognitive impairment at the one-year evaluation were considered to have incident cognitive impairment.

The incidence of cognitive impairment and cognitive decline was compared between the ADT group and the non-ADT group using multivariate logistic regression to estimate odds ratios (OR) and the corresponding 95% confidence intervals (95%CI). The ADT group included patients treated with ADT only, those treated with radiotherapy (with or without brachytherapy) and ADT, those treated with ADT and chemotherapy, and those with persistent disease after radical prostatectomy and/or radiotherapy treated with ADT. Stratified analyses were conducted according to the moment of the one-year follow-up, and interaction terms computed: before *vs.* after the onset of the pandemic.

**Results**

Mean MoCA scores increased from baseline to the one-year evaluation (mean, SD: 22.3, 3.7 *vs.* 22.8, 3.8, respectively; p<0.001). The variation after the pandemic was not statistically significant.

Table 2 presents the mean difference in t-scores from baseline to the one-year evaluation according to prostate cancer treatment. Only the group treated with ADT and chemotherapy, and those who underwent radical prostatectomy (without adjuvant radiotherapy) had a statistically significant increase in mean t-scores over time [mean difference of MoCA at one-year minus MoCA at baseline (95%CI): 7.59 (0.52, 14.67) and 3.73 (1.10, 6.37), respectively]. Participants treated with ADT only had a non-statistically significant decrease and the remaining treatment groups had non-statistically significant increases. The increase in scores was less pronounced after the COVID-19 pandemic.

At baseline, 47 participants had cognitive impairment and of these, 51.6% scored within the normal MoCA range at the one-year evaluation. Patients with cognitive decline presented a variation in MoCA scores that ranged from -9 to -4 points.

Table 3 presents the percentage of participants with cognitive decline and with incident cognitive impairment at the one-year evaluation according to treatments received. None of the patients treated with prostatectomy or with radiotherapy only had cognitive decline. Patients with ADT as part of their treatments presented cognitive decline more often (range: 7.8% - 16.0%). There were 22 incident cases of cognitive impairment corresponding to a one-year cumulative incidence of cognitive impairment of 6.9% (95%CI: 4.3%, 10.2%), which was higher after the COVID-19 pandemic (9.1% *vs.* 3.7%, p=0.057). Patients who received radiotherapy as an adjuvant treatment after radical prostatectomy had the highest one-year cumulative incidence of cognitive impairment (15.4%), followed by those treated with radiotherapy combined with long duration ADT (13.1%), and those treated with ADT for incident prostate cancer only (10.0%). None of the patients who received ADT and chemotherapy had incident cognitive impairment at one-year.

A higher educational level (more than 12 years) was associated with cognitive decline [age-adjusted OR (95%CI): 2.89 (1.12, 7.46)]. Patients who underwent treatments including ADT had higher odds of cognitive decline compared with patients who were not treated with ADT [age- and education-adjusted OR (aOR; 95%CI): 3.71 (1.31, 10.59)]. The moment of the one-year assessment (pre-/post-COVID-19) was not significantly associated with cognitive decline [aOR (95%CI): 0.95 (1.41, 32.87)] and the interaction with ADT-based treatments was not statistically significant (p=0.233), but the association between the COVID-19 pandemic and incident cognitive impairment was nearly statistically significant [aOR (95%CI): 2.65 (0.95, 7.23)] and its interaction with ADT-based treatments was significant (p=0.044). The association between ADT and incident cognitive impairment was only statistically significant after the pandemic [aOR (95%CI): 5.53 (1.46, 20.95)]. Anxiety and depression symptoms were not associated with cognitive decline or incident cognitive impairment (Figure 1).

**Discussion**

Overall, cognitive performance increased from baseline to the one-year evaluation. Patients treated with ADT were more likely to have cognitive decline after one year of follow-up. The incidence of cognitive impairment was almost 7% and it was higher in patients treated with ADT, alone or with other treatments, but this effect was only observed when the one-year assessment was conducted after the COVID-19 pandemic.

In the current study, mean MoCA scores increased over time, which was also observed in women with breast cancer during the first year after cancer diagnosis (18). This increase may reflect a practice effect, that is an improvement due to becoming familiar with the testing procedures and the cognitive tasks but also due to a lower performance at baseline because of the overwhelming experience of a cancer diagnosis, and fear of treatments and prognosis, that may have dissipated after one year (19). Indeed, in the present study, borderline anxiety (a score equal to or above eight in the anxiety sub score of the HADS) was associated with MoCA scores at baseline, and patients proposed for radical prostatectomy had the lowest mean MoCA scores and the highest prevalence of borderline anxiety. However, this may not explain the low baseline MoCA scores in patients proposed for ADT and chemotherapy, as the prevalence of borderline anxiety was low in this group. It is unlikely that pain associated with bone metastases could explain lower cognitive performance at baseline, because this assessment was usually performed after three weeks of antiandrogens for pain management and flare prevention. Pathological alterations due to cancer and the control of the disease after one year may explain low cognitive performance at baseline and improvement thereafter, respectively.

Cognitive decline, defined as having a variation in MoCA scores over time below 1.5 SD of the variation in the cohort, was consistently more frequent in participants treated with ADT, regardless of the duration of ADT or associated treatments, and the incident or recurrent nature of the disease. This result supports the evidence from previous studies reporting an association of ADT with cognitive decline (4).

A higher educational level is associated with a decreased risk for cognitive impairment (20) but in the present study, the association was in the opposite direction regarding cognitive decline. Unmeasured confounders related to socio-economic level may explain the observed association. Further in-depth analyses of socio-economic, lifestyle and clinical characteristics are needed to understand this result.

The incidence of cognitive impairment at one year was similar to the observed among women with breast cancer one-year after cancer diagnosis and using the MoCA (8.1%) (21). These are two different populations of patients with cancer, regarding not only sex but also age and treatments. To our knowledge, there are no studies reporting the incidence of cognitive impairment in prostate cancer patients (9). Patients treated with ADT were more likely to develop cognitive impairment, a consistent observation considering ADT alone or with radiotherapy, although none of the participants treated with ADT and chemotherapy had incident cognitive impairment. Patients proposed for chemotherapy were younger than those with ADT, which could explain this difference in the cognitive impairment incidence, as well as unmeasured factors related to overall health and lifestyle. Additionally, docetaxel may not have deleterious effects in cognitive function as other drugs or combinations of drugs used in other cancers.

The first COVID-19 case in Portugal was reported on March 2$^{nd}$ 2020, and the NEON-PC cohort evaluations were suspended from March 9$^{th}$ to July 1$^{st}$ 2020. The first general lockdown occurred from March 22$^{nd}$ to April 30$^{th}$ 2020 and the second between January 16$^{th}$ to March 15$^{th}$ 2021, during which the general population was forbidden from using public spaces, and compulsory confinement was legally imposed, except for basic shopping necessities, health consultations and treatments, and going to work when working from home was not possible (22). Total confinement and restrictions to normal daily activities since March 2020 have caused many alterations in everyone's life, with a decrease in physical activity and an increase in sedentary behaviours (23), and changes in eating patterns (24). Moreover, the reduction in contact with nature was associated with worse mental health (25), and sleep problems were frequent during the COVID-19 pandemic (26). ADT has been associated with a

higher risk for weight gain and metabolic syndrome (27), depression (28) and sleep disturbances (29). These adverse effects of ADT are associated with cognitive dysfunction (30-34), acting as potential mediators of the effect of ADT on cognitive performance. We observed a negative effect of ADT on the incidence of cognitive impairment, but only after the COVID-19 pandemic, which may be explained by a worsening effect of the pandemic in the prevalence of metabolic syndrome, depression and sleep problems among patients who received ADT.

*Strengths and limitations*

This is the largest prospective study comparing cognitive decline in patients with prostate cancer treated with or without ADT, and the first to report cognitive impairment cumulative incidence in these patients. Although neuropsychological tests are considered the gold standard to assess cognitive performance (35), which and how many tests to include to assess which cognitive domains, and the criteria to define cognitive impairment have not yet been standardized. Moreover, neuropsychological assessment may not be feasible both in clinical practice and in research. Indeed, due to the long duration for the administration of the battery of tests (at least one hour), the availability of neuropsychologists to administer and score the tests, and the willingness of participants to perform such long sessions may compromise the execution of comprehensive neuropsychological evaluations. Even using a cognitive test that may not detect subtle changes in cognitive performance, our results show that ADT is associated with the deterioration of overall cognitive function.

Although this study was conducted in only one hospital, IPO-Porto receives patients from all over the country, though mostly from the North, and it is the largest cancer dedicated public hospital in Portugal.

*Conclusion*

Patients with prostate cancer treated with ADT are more likely to have a deterioration in cognitive performance one year after initiating treatment. Therefore, cognitive assessment should be

considered in the clinical follow-up protocols of these patients. Socio-economic, lifestyle and clinical characteristics should also be considered in-depth to identify the moderators of the association of ADT with cognitive performance, and studies with longer follow-up are needed to understand if the negative effect of ADT is reversible after treatment termination. The COVID-19 pandemic may have worsened the effect of ADT in the cognitive performance of patients with prostate cancer.

**Additional information**

**Conflicts of interest:** The authors have no relevant financial or non-financial interests to disclose.

**Ethics approval and consent to participate:** Ethics approval was obtained from the Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES 89/017) and by the Portuguese Data Protection Authority (Authorisation 3478/2017). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants after the project's aims and procedures had been fully explained by a member of the research team.

**Consent for publication:** Not applicable.

**Availability of data and materials:** The datasets generated and analysed in this study will not be publicly available given that the included patients do not specifically provide their consent for public sharing of their data and that anonymization is unlikely to be feasible, since the identification of patients treated in only one institution within a relatively short period may be possible when taking socio-demographic and clinical characteristics into account.

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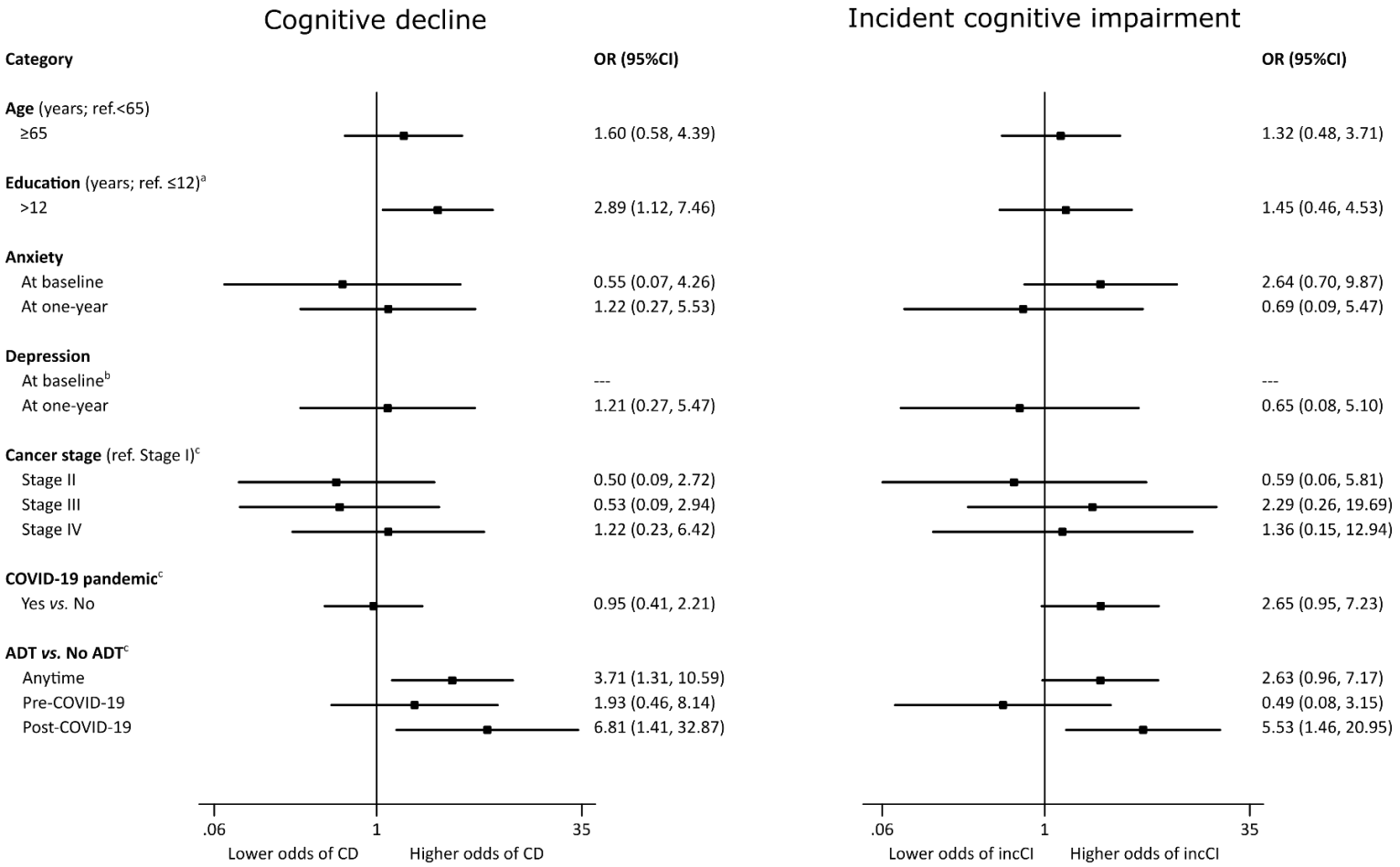
**Figure 1.** Association between age, education anxiety and depression, and treatments with cognitive decline and with incident cognitive impairment.




ADT, androgen deprivation therapy; CD, cognitive decline defined as a variation in cognitive performance (MoCA at one-year minus MoCA at baseline) below 1.5 standard deviations of the variation in the whole cohort; incCI, incident cognitive impairment defined as a score below age- and education-specific values from normative data at the one-year evaluation in participants without cognitive impairment at baseline.

[a] Adjusted for age.

[b] None of the participants had the outcome (cognitive decline/incident cognitive impairment)

[c] Adjusted for age and education.

**Table 1.** Characteristics of the participants evaluated at one-year.

| | **Participation at one-year** | | |
|---|---|---|---|
| | **No** | **Yes** | |
| | N=120 | N=366 | **p-value** |
| **Age** (years), mean (SD) | 68.1 (6.95) | 67.8 (7.27) | 0.736 |
| **Education** (years), median (P25;P75) | 4 (4;8) | 5 (4;10) | 0.013 |
| **MoCA, mean (SD)** | 20.6 (4.13) | 22.4 (3.69) | <0.001 |
| **Cancer stage**, N (%) | | | 0.001 |
| I | 14 (11.7) | 20 (5.5) | |
| II | 63 (52.5) | 150 (41.0) | |
| II/III | 3 (2.5) | 3 (0.8) | |
| III | 28 (23.3) | 116 (31.7) | |
| IV | 12 (10.0) | 77 (21.0) | |
| **Treatments**, n (%) | | | 0.006 |
| Active surveillance | 8 (6.7) | 18 (4.9) | |
| Brachytherapy | 37 (31.1) | 52 (14.2) | |
| RT | 13 (10.9) | 38 (10.4) | |
| RP | 22 (18.5) | 59 (16.1) | |
| RT + ADT (6 months) | 15 (12.6) | 35 (9.6) | |
| RT + ADT (24 months)[a] | 16 (13.8) | 90 (24.6) | |
| ADT (incident disease) | 4 (3.4) | 22 (6.0) | |
| ADT + chemotherapy | 1 (0.8) | 12 (3.3) | |
| ADT (recurrent disease) | 6 (5.0) | 25 (6.8) | |
| RT + palliative ADT | 0 | 1 (0.3) | |
| RP + RT | 2 (1.7) | 13 (3.6) | |
| RP + ADT | 0 | 1 (0.3) | |

ADT, androgen deprivation therapy; MoCA, Montreal Cognitive Assessment; P25, percentile 25; P75, percentile 75; RP, radical prostatectomy; RT, radiotherapy; SD, standard deviation.

[a] Participants were proposed for 24 months of ADT and were still on ADT at the one-year evaluation.

**Table 2**. Mean difference in the Montreal Cognitive Assessment (MoCA) t-scores, according to cancer treatments (t-score at one year minus t-score at baseline).

| | All | | Moment of the one-year evaluation | | | |
|---|---|---|---|---|---|---|
| | | | Pre-COVID-19 | | Post-COVID-19 | |
| **Treatments** | **N** | **Difference in MoCA t-scores**[b] mean (95%CI) | **N** | **Difference in MoCA t-scores**[b] mean (95%CI) | **N** | **Difference in MoCA t-scores**[b] mean (95%CI) |
| Active surveillance | 18 | 0.601 (-3.760, 4.962) | 1 | -17.778 | 17 | 1.682 (-2.279, 5.643) |
| Brachytherapy | 52 | 1.333 (-1.639, 4.305) | 22 | 2.359 (-1.623, 6.341) | 30 | 0.581 (-3.847, 5.008) |
| RT | 38 | 1.739 (-1.426, 4.904) | 12 | 3.996 (-2.705, 10.698) | 26 | 0.698 (-3.020, 4.415) |
| RP | 59 | **3.731 (1.097, 6.366)** | **25** | **4.211 (0.507, 7.915)** | 34 | 3.379 (-0.454, 7.212) |
| RT + ADT 6 months | 35 | 1.649 (-2.578, 5.555) | 8 | 4.319 (-6.816, 15.454) | 27 | 0.857 (-3.449, 5.164) |
| RT + ADT 24 months[a] | 90 | 1.233 (-0.775, 3.241) | 42 | 2.866 (-0.004, 5.736) | 48 | -0.195 (-3.034, 2.643) |
| ADT, incident PCa | 22 | -0.033 (-4.344, 4.278,) | 12 | 1.582 (-2.920, 6.084) | 10 | -1.971 (-10.778, 6.836) |
| ADT + chemotherapy | 12 | **7.591 (0.516, 14.667)** | 5 | 7.651 (-0.685, 15.986) | 7 | 7.549 (-5.442, 20.540) |
| ADT, recurrent PCa | 25 | 0.249 (-4.939, 5.436) | 13 | 0.814 (-7.453, 9.081) | 12 | -0.364 (-7.873, 7.145) |
| RT + palliative ADT | 1 | 10.490 | 0 | -- | 1 | 10.490 |
| RP + RT | 13 | 0.877 (-4.823, 6.576,) | 6 | -1.159 (-10.443, 8.124) | 7 | 2.622 (-6.854, 12.099) |
| RP + ADT | 1 | -1.748 | 1 | -1.748 | 0 | - |
| *Total* | ***366*** | ***1.738 (0.687, 2.794)*** | ***147*** | ***2.623 (1.019, 4.227)*** | *219* | *1.143 (-0.260, 2.547)* |

ADT, androgen deprivation therapy; CI, confidence interval; PCa, prostate cancer; RP, radical prostatectomy; RT, radiotherapy.

[a] Participants were proposed for 24 months of ADT and were still on ADT at the one-year evaluation.

[b] Based on the mean and SD of age- and education-specific norms (17), MoCA z-scores and t-scores were computed based on the formula (z-score*10)+50, to obtain a more intelligible score, so that most values are positive and vary from 0 to 100.

Results in bold correspond to statistically significant variations.

**Table 3.** Cognitive outcomes at one year, according to prostate cancer treatment, before and after the COVID-19 pandemic.

| | Cognitive decline | | | | | | Incident cognitive impairment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All | | Moment of the one-year evaluation | | | | All | | Moment of the one-year evaluation | | | |
| | | | Pre-COVID-19 | | Post-COVID-19 | | | | Pre-COVID-19 | | Post-COVID-19 | |
| **Treatments** | N | n(%) | N | n(%) | N | n(%) | N at risk | n(%) | N at risk | n(%) | N at risk | n(%) |
| Active surveillance | 18 | 1 (5.6) | 1 | 1 (100.0) | 17 | 0 (0.0) | 15 | 0 (0.0) | 1 | 0 (0.0) | 14 | 0 (0.0) |
| Brachytherapy | 52 | 3 (5.8) | 22 | 1 (4.5) | 30 | 2 (6.7) | 45 | 1 (2.2) | 20 | 0 (0.0) | 25 | 1 (4.0) |
| RT | 38 | 0 (0.0) | 12 | 0 (0.0) | 26 | 0 (0.0) | 34 | 0 (0.0) | 11 | 0 (0.0) | 23 | 0 (0.0) |
| RP | 59 | 0 (0.0) | 25 | 0 (0.0) | 34 | 0 (0.0) | 48 | 3 (6.3) | 23 | 1 (4.3) | 25 | 2 (8.0) |
| RT + ADT 6 months | 35 | 3 (8.6) | 8 | 1 (12.5) | 27 | 2 (7.4) | 28 | 2 (7.1) | 6 | 0 (0.0) | 22 | 2 (9.1) |
| RT + ADT 24 months[a] | 90 | 7 (7.8) | 42 | 1 (2.4) | 48 | 6 (12.5) | 84 | 11 (13.1) | 40 | 1 (2.5) | 44 | 10 (22.7) |
| ADT, incident PCa | 22 | 3 (13.6) | 12 | 1 (8.3) | 10 | 2 (20.0) | 20 | 2 (10.0) | 11 | 1 (9.1) | 9 | 1 (11.1) |
| ADT + chemotherapy | 12 | 1 (8.3) | 5 | 0 (0.0) | 7 | 1 (14.3) | 10 | 0 (0.0) | 5 | 0 (0.0) | 5 | 0 (0.0) |
| ADT, recurrent PCa | 25 | 4 (16.0) | 13 | 3 (23.1) | 12 | 1 (8.3) | 22 | 1 (4.5) | 11 | 0 (0.0) | 11 | 1 (9.1) |
| RT + palliative ADT | 1 | 0 (0.0) | 0 | 0 (0) | 1 | 0 (0.0) | 1 | 0 (0.0) | 0 | 0 (0) | 1 | 0 (0.0) |
| RP + RT | 13 | 1 (7.7) | 6 | 1 (16.7) | 7 | 0 (0.0) | 13 | 2 (15.4) | 6 | 2 (33.3) | 7 | 0 (0.0) |
| RP + ADT | 1 | 1 (100.0) | 1 | 1 (100.0) | 0 | 0 (0) | 1 | 0 (0.0) | 1 | 0 (0.0) | 0 | 0 (0.0) |
| *Total* | *366* | 24 (6.6) | 147 | 10 (6.8) | 219 | 14 (6.4) | *321* | 22 (6.9) | 135 | 5 (3.7) | 186 | 17 (9.1) |

Differences between treatments: age (p<0.001), education (p=0.094), cognitive decline (p=0.004), incident cognitive impairment (p=0.285).

ADT, androgen deprivation therapy; PCa, prostate cancer; RP, radical prostatectomy; RT, radiotherapy.

[a] Participants were proposed for 24 months of ADT and were still on ADT at the one-year evaluation.

# DISCUSSION AND CONCLUSIONS

This thesis contributed with new insights on the cognitive performance of patients with breast cancer over a period of five years after cancer diagnosis, and of patients with prostate cancer during the first year after cancer diagnosis or ADT initiation for recurrent disease.

The objectives of the present thesis were accomplished through the analysis of data from two cohorts: NEON-BC and NEON-PC. The former followed 466 women during five years and had a high retention rate (92.1% of participants at baseline were evaluated at five years). The large sample size, the baseline evaluation before treatments and the few losses to follow-up are methodological features that contribute to the validity of the results. Most previous studies have been cross-sectional or longitudinal with a short follow-up of only two assessments [109, 121], which does not allow for the observation of the late and long-term effects of treatments, or for a more precise and informative description of the trajectories of cognitive performance. NEON-BC had a follow-up of five years since breast cancer diagnosis and a total of four evaluations were carried out. The NEON-PC cohort included 609 men with a recent diagnosis of prostate cancer and the one-year evaluation is ongoing. Most prospective studies on cognitive performance among patients with prostate cancer have been very small and most have not had a follow-up longer than nine months [110]. A longitudinal study followed patients with prostate cancer during 36 months, but included only men with at least eight years of education, a pre-treatment score on the Mini Mental State Examination of at least 24 and, more importantly, patients with non-metastatic cancer [111], which represents only a part of the patients treated with ADT. The large sample size of the NEON-PC cohort, the baseline evaluation before treatments, the inclusion of patients with any cancer stage and proposed for any type of treatment, the detection of cognitive impairment in a two-step evaluation − the MoCA administered to all participants and the neuropsychological assessment performed in those with

a suspicion of cognitive impairment – and the strict criteria to define cognitive impairment, contributed for more robust findings regarding the prevalence of cognitive impairment before prostate cancer treatment, reported in Paper 5.

Due to the COVID-19 pandemic, field activities in the NEON-PC cohort were suspended during a period of four months and after the first lockdown, study procedures were adapted to reduce the risk of infection. Although 70% of the one-year evaluations were performed after the onset of the COVID-19 pandemic, the cognitive assessment with the MoCA and the neuropsychological evaluation were performed in person as usual. The results in Paper 6 showed the negative effect of ADT on the likelihood of having cognitive decline and incident cognitive impairment. The latter was observed only after the onset of the COVID-19 pandemic. It seems that all the restrictions on activities and relationships in everyday life imposed by the pandemic may have potentiated the effect of ADT on cognitive performance. This result highlights the importance of potential contributing factors to cognitive deterioration in addition to cancer treatments.

Both cohorts had no exclusion criteria regarding age, menopausal status, education level (only having at least one year of formal education) or cancer treatments. This contributed to more generalizable and more relevant results on the burden of cognitive dysfunction among patients with breast and prostate cancers, which are particularly important for the healthcare planning.

In Paper 1 of the present thesis, we observed differences in scores in cognitive tasks and cognitive domains between two versions of the MoCA, suggesting that the alternating use of the two versions to assess one's cognitive performance over time, could introduce error in the longitudinal analysis of scores. Therefore, we only used version 7.1 of the MoCA for the assessment of cognitive performance in both the NEON-BC and NEON-PC cohorts.

In Paper 2, the identification of baseline anxiety, depression and poor quality of sleep as determinants of worse cognitive changes at five years was an important finding as these are actionable risk factors that could be used in the design of interventions to reduce cognitive deterioration in patients with breast cancer. These results also highlighted the importance of assessing these factors in other studies. Therefore, the NEON-PC cohort also evaluated anxiety and depression as described in Paper 4, although these factors were not associated with cognitive outcomes (Paper 6). Anxiety was more frequent in the NEON-BC than in the NEON-PC cohort. Other potentially contributing factors for cognitive dysfunction, namely lifestyle and co-morbidities, should be investigated in patients with prostate cancer treated with ADT, as well as the potential mediator effects of metabolic syndrome, anaemia, and hot flashes and sleep quality.

We described the cognitive trajectories of patients with breast cancer followed for five years in Paper 3. Two cognitive trajectories were identified, and women were grouped based on their MoCA score at baseline being above or below the median MoCA value within each trajectory. On the one hand, two groups with relatively stable scores over time were observed, one with the highest scores, and the other with the lowest scores and, on the other hand, two groups with mid-range scores with opposite trajectories were also found: one, with an increase in scores, particularly after one year, and the other, with a decreasing cognitive trajectory. Most women had an improvement in cognitive performance at one-year except for those with mid-range scores who had a continuous declining trajectory. This allowed us to identify the first year after breast cancer diagnosis as a very important period during which, the variation in cognitive scores was essential to accurately predict long-term cognitive decline. This result highlighted the importance of assessing cognitive performance before treatments and after one year. This information may also be used for the development of a tool to identify patients diagnosed with cancer who may need specific care from the neurology department.

The first year after cancer diagnosis was the period with the highest rate in cognitive changes in the NEON-BC cohort (Papers 2 and 3). Therefore, assuming a similar pattern among patients with prostate cancer, a follow-up of one year since cancer diagnosis was considered as an adequate period of time to observe cognitive decline in patients with prostate cancer. Prostate cancer treatment often does not include multimodal therapies as in breast cancer. Indeed, during the first year after cancer diagnosis, most patients perform only one treatment – active surveillance, brachytherapy, radiotherapy, prostatectomy or ADT – or a combination of two treatments – radiotherapy with ADT or ADT with chemotherapy – and monotherapy with docetaxel is usually used for chemotherapy. The fact that each of these modalities of treatments included a relatively large number of participants, and that patients treated with ADT are usually of old age, may have contributed for the detection of the effects of ADT on cognitive performance, and the COVID-19 pandemic appears to have worsened these effects.

The three-year evaluation of the NEON-PC cohort is ongoing and should allow for the study of the effect of ADT on cognitive performance after termination of treatment, in patients who were treated with radiotherapy and ADT for 24 months, as well as the effects of long ADT duration.

The main conclusions of the present thesis are as follows:

- The alternating use of different versions of the MoCA may introduce an error in the longitudinal assessment of cognitive performance.
- Cognitive deterioration is frequent among women with breast cancer proposed for surgery with or without (neo)adjuvant treatments: a quarter presented a declining trajectory of cognitive performance over five years after breast cancer diagnosis, and 18% had cognitive impairment at any time during the five years following cancer diagnosis, which remained or reverted to a normal cognitive score over time.

- Pre-treatment anxiety, depression and poor sleep quality were negatively associated with cognitive changes from a pre-treatment assessment to the five-year evaluation among women with breast cancer.
- The cognitive variation in MoCA scores during the first year after breast cancer diagnosis was essential to accurately predict long-term cognitive decline.
- The prevalence of cognitive impairment was similar among men with prostate cancer and men of the general population, and much lower than the reported in previous studies with other types of cancer and evaluating pre-chemotherapy cognitive performance.
- Cognitive decline, defined as a change in cognitive performance below 1.5 SD of the distribution of changes in the cohort, was more frequent one year after enrolment among men treated with ADT than among men who received other prostate cancer treatments. The one-year cumulative incidence of cognitive impairment (a MoCA score below the cut-off values from normative data) was nearly 7% among patients with prostate cancer and it was higher among those treated with ADT, an effect that may have been enhanced by changes imposed by the COVID-19 pandemic.

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