

MESTRADO INTEGRADO EM MEDICINA

Cerebrovascular Diseases and Cancer

Sofia de Castro Neves Padilha

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CEREBROVASCULAR DISEASES AND CANCER

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Estudante: Sofia de Castro Neves Padilha

Número de estudante: 201304859

Endereço de correio eletrónico: sofia.padilha@outlook.pt

Orientador: Luís Filipe Oliveira da Maia

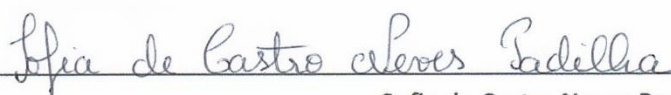
Professor Auxiliar Convidado do ICBAS

Assistente Hospitalar de Neurologia no CHUP

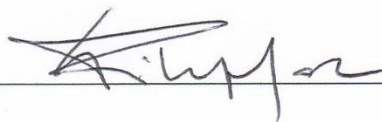
Co-Orientador: Rui Jorge Rocha Felgueiras

Assistente Hospitalar de Neurologia no CHUP

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Sofia de Castro Neves Padilha



Luís Filipe Oliveira da Maia



Rui Jorge Rocha Felgueiras

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RESUMO

Introdução: O cancro é uma doença complexa que pode provocar eventos cerebrovasculares. Foram já propostos vários mecanismos para explicar os acidentes vasculares cerebrais (AVC) de causa neoplásica, em particular a ocorrência de um estado de hipercoagulabilidade que favorece a trombose e a isquemia. É, portanto, plausível que mecanismos semelhantes possam provocar acidentes isquémicos transitórios (AITs). Nós pretendemos determinar a incidência de cancro após ataques neurológicos transitórios (ANTs) e avaliar se os AITs ou os ANTs não-isquémicos estariam associados com o desenvolvimento de cancro.

Métodos: Fizemos um estudo retrospectivo de todos os doentes com ANT incluídos no registo prospetivo ACIN 2, que foram admitidos no Hospital de Santo António (HSA), Porto, Portugal. Os participantes do estudo foram classificados em ANT não-isquémico ou AIT e caracterizados de acordo com dados sociodemográficos e fatores de risco vascular na altura do evento. Recorrendo ao processo clínico eletrónico e a entrevistas telefónicas, fizemos uma pesquisa sistemática pelos seguintes desfechos num período de 7 anos após o evento índice: óbito e causa de óbito, diagnóstico de cancro, localização e estadiamento, AVC, AIT e ANT.

Resultados: Entre 2009 e 2011, 594 doentes foram diagnosticados com o primeiro ANT. Na coorte final (510 doentes), 32% tiveram um evento índice AIT; 60.6% eram do sexo feminino e a idade média era de 63 anos. Foi encontrado cancro em 15.3%, e desses, 56.1% destes ocorreu após o evento índice. A incidência global de cancro (exceto pele) foi de 1064.4/100000/ano e de 1665.2/100000/ano nos doentes com AITs. O cancro foi mais prevalente nos doentes com AIT comparado com ANT não-isquémico (13.5% vs. 6.9%, $p=0.016$). O tipo mais frequente de cancro foi o gastrointestinal (28.3%). Foram encontradas metástases em 40.9% dos doentes com cancro diagnosticado após o AIT/ANT, mais frequentemente no grupo de AIT ($p=0.028$). A sobrevivência livre de cancro foi menor nos doentes com AIT do que ANT (log rank teste com $p=0.010$). Ainda assim, isto não foi confirmado na análise multivariada. AVC e AIT foram desfechos mais frequentes em doentes com AIT (25.8% vs. 3.7% para AVC; 13.5% vs. 1.4% para AIT; $p<0.001$). A mortalidade também foi mais elevada no grupo com AIT (22.7% vs. 9.2%, $p<0.001$).

Discussão: A taxa de incidência global de cancro e no grupo de doentes com AIT foi superior à taxa de incidência da população na região norte de Portugal. Ainda assim, a ocorrência de um AIT não foi um preditor independente de cancro. O baixo número de ocorrências de cancro pode ter limitado as nossas conclusões.

ABSTRACT

Introduction: Cancer is a complex disease that can lead to cerebrovascular events. Several mechanisms have been proposed to explain previously documented cancer-related strokes, in particular the occurrence of a hypercoagulable state that favours thrombosis and ischemia. Considering this, it is plausible that similar mechanisms could lead to transient ischemic attacks (TIAs). We aimed to determine the incidence of cancer after transient neurological attacks (TNAs) and evaluate if either TIAs or non-ischemic TNAs were associated with cancer.

Methods: We did a retrospective study of all the patients with TNA included in the ACIN 2 prospective registry, that were admitted to Hospital de Santo António (HSA), Porto, Portugal. Study participants were classified in non-ischemic TNA or TIA, characterized according to demographic data and vascular risk factors at the time of the event. Using e-medical records and telephone interviews, we did a systematic search for the following outcomes for a period of up to 7 years after the index event: death and cause of death, cancer diagnosis, location and staging, stroke, TIA and TNA.

Results: Between 2009 and 2011, 594 patients were diagnosed with the first TNA. In the final cohort (510 patients), 32% of patients had a TIA index event; 60.6% were female and mean age was 63 years. Cancer was found in 15.3% and 56.1% of them occurred after the index event. Global cancer incidence (excluding skin cancer) was 1064.4/100000/year and 1665.2/100000/year in TIA group. Cancer was more prevalent in TIA patients compared to non-ischemic TNA (13.5% vs. 6.9%, $p=0.016$). The most common type of cancer was gastrointestinal (28.3%). Metastasis were found in 40.9% of patients with cancer diagnosed after the TIA/TNA, most frequently in TIA group ($p=0.028$). Cancer-free survival time was shorter in TIA patients than non-ischemic TNA (log rank test with $p=0.010$), still this was not confirmed in a multivariate analysis. Stroke and TIA were more common outcomes in TIA patients (25.8% vs. 3.7% for stroke; 13.5% vs. 1.4% for TIA; $p<0.001$). Mortality was also higher in TIA group (22.7% vs. 9.2%, $p<0.001$).

Discussion: The global incidence rate of cancer and in TIA group was superior to the incidence rate of the population of the north region of Portugal. Still, occurrence of a TIA was not an independent predictor for cancer. The low number of cancer occurrences may have limited our conclusions.

Keywords: Transient Ischemic Attack, Stroke, Cancer, Incidence

LIST OF ABBREVIATIONS

TIA – Transient ischemic attack

TNA – Transient neurological attack

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INTRODUCTION

Cancer is a complex disease that manifests in the most diverse ways and various systems. One of the systems that is frequently affected by cancer is the nervous system, which can suffer a series of neurologic complications due to neoplastic disease. Neurologic complications of cancer have been divided in direct and indirect complications. Direct complications can implicate either central nervous system or peripheral nervous system, through brain, leptomeningeal, spine and peripheral nervous system metastasis or by the tumour itself (in the case of a nervous system neoplasm), which produce direct effects over nervous tissues and structures, such as compression, infiltration or oedema^[1]. Indirect effects of cancer over the nervous system include paraneoplastic neurologic disorders, cerebrovascular complications, infections and treatment effects^[1]. Some of the most studied indirect effects of cancer in the nervous system are paraneoplastic syndromes, that produce neurological symptoms through autoimmune mechanisms^[1-3]. These mechanisms are explained by the tumour production of an antigen usually expressed in the nervous system that leads to an anti-tumour response by the immune system that creates the neurologic symptoms^[2, 3]. Effects of cancer treatment result either for toxicity due to chemotherapy agents or from physical damage induced by radiation, and infections of the central nervous system are subsequent to the immunocompromised state of the cancer patient^[1, 3]. Cerebrovascular complications, like ischemic stroke, are another indirect effect of cancer over the nervous system and are due to a hypercoagulable state induced by neoplastic diseases^[1]. And, although haemorrhagic stroke is also a possible effect of cancer, this is less frequent and usually occurs in patients with bleeding tumours or metastasis^[1]. There are other ways by which a neoplasm can lead to ischemic stroke without involving coagulopathy, mainly through some of the effects mentioned above, such as cancer-therapy effects, infections and direct tumour effects, such as invasion or compression of blood vessels or embolization^[1, 4, 5].

In 1865, Trousseau noted that in the presence of cancer there was “a special condition of the blood predisposed to spontaneous coagulation”^[6] and, since that time, many authors have reported this association between cancer and hypercoagulable states. Although they are still not completely understood, potential mechanisms implicated in the prothrombotic effects of cancer, such as cancer-related stroke, are divided into two categories: the immune response to the neoplasm, which involves the production of acute phase reactants, abnormal protein metabolism and haemodynamic compromise, and the direct effects caused by the tumour cell^[7]. The tumour cell is able to secrete prothrombotic and fibrinolytic substances, as well as cytokines that promote an inflammatory procoagulant state^[5, 7]. In addition, the tumour-cell has the ability to interact with blood cells or vascular cells, such as endothelial cells, platelets and monocytes^[5, 7]. These

mechanisms can result either in localized thrombosis or in a series of coagulation disorders, such as disseminated intravascular coagulopathy and non-bacterial thrombotic endocarditis^[4, 8].

In about 50% of cancer patients, and up to 95% of those with metastasis, there is abnormal haemostasis^[8], which may reflect the importance of cancer-related pro-coagulant mechanisms in the development of ischemic stroke. And although the most frequent causes of stroke in cancer patients are the same as in the population – risk factors such as hypertension, diabetes mellitus, dyslipidaemia, tobacco use – cancer itself increases the risk of having a stroke^[9], which indicates a causal relationship between these two entities.

Therefore, it is plausible that similar mechanisms to those involved in stroke in cancer patients could lead to transient ischemic attacks (TIAs). TIAs are defined by the American Heart Association/American Stroke Association as brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction^[10] and are often described as focal subtype of transient neurological attacks (TNAs)^[11].

TNAs are attacks with neurological symptoms that last less than 24 hours, either focal, non-focal or both^[11]. TNAs can also be classified in ischemic TNAs, known as transient ischemic attacks (TIAs), and non-ischemic TNAs. Some examples of non-ischemic TNAs are migraine with aura, focal seizures, hypoglycaemic encephalopathy, hyperventilation syndromes, transient global amnesia, among other rare syndromes^[12]. It is unclear, however, if non-ischemic TNAs might have some relation with cancer, since this subject hasn't been sufficiently studied so far. Considering that the hypothesis of cancer-related TIA is based on its ischemic/prothrombotic underlying mechanism, it seems unlikely that the same mechanisms would be involved in a cancer-related non-ischemic TNA. However, as mentioned before, other mechanisms can be implicated in the development of neurological symptoms in cancer patients, such as paraneoplastic syndromes, that could be the origin of these non-ischemic TNAs. Additionally, many TNAs remain without a clear aetiology, sometimes difficult to distinguish from TIAs^[13], and therefore, these could eventually be associated with cancer.

Having this in mind, we will determine the incidence of cancer in patients after the first TNA and evaluate if TIAs or non-ischemic TNAs are associated with cancer. If this is the case, our study may lead to include the search for occult malignancies in the investigation protocol of patients with TIAs particularly in those with undetermined aetiology.

METHODS

We aimed to determine the incidence of cancer in the following years after a TIA or a non-ischemic TNA in (ACIN 2) study participants. *ACIN 2* is a prospective community-based registry of all neurological attacks (stroke, TIA and non-ischemic focal TNA) in the north of Portugal (including urban and rural areas) during the years and 2009-2011 (ACIN2)^[14].

Study Participants

In the present study we identified all the patients with TNA included in the ACIN 2 prospective registry. Such patients were evaluated by two study neurologists (Rui Felgueiras and Manuel Correia) to classify them into non-ischemic TNA or TIA. TIA was defined as a clinical syndrome characterized by acute loss of focal cerebral or monocular (*amaurosis fugax*) function lasting 24 hours and thought to be attributable to inadequate cerebral or ocular blood supply as a result of arterial thrombosis or embolism associated with arterial, cardiac, or haematological disease^[15]. TNA included all transitory abnormal symptoms or signs that presumably were the result of a focal structural or functional non-ischemic cerebral alteration, or in rare exceptions also global, with an acute onset and duration of less than 24h, including symptoms or signs affecting vision, speech, sensitive, motor system (including strength, coordination and balance), cognition or vertigo. Patients with vertigo with defined peripheral aetiology were not included in our study. The study was approved by local ethical committee and all the patients signed an informed consent to participate in the ACIN2 study.

Study Design

We did a retrospective study of all the patients with TNA included in the ACIN 2 prospective registry, that were admitted to the emergency department of Hospital de Santo António (HSA), Porto, Portugal. Study participants were classified in non-ischemic TNA or TIA, characterized according to demographic data, vascular risk factors at the time of the event: sex, age and vascular risk factors for stroke, such as arterial hypertension, diabetes mellitus, dyslipidemia, tobacco use, peripheral artery disease, ischemic heart disease, previous history of thrombotic events and atrial fibrillation. For that we considered previous diagnosis recorded in medical registries or, in the case of hypertension, diabetes or dyslipidemia, the use of the respective drug. Tobacco use considered both current and past smokers. Previous history of thrombotic events included superficial and deep venous thrombosis, pulmonary thromboembolism and previous stroke.

Using, e-medical records and a structured telephone interviews, we did a systematic search for the following outcomes for a period of up to 7 years (2560 days) after the index event: death and cause of death, cancer diagnosis, location and staging, stroke, TIA and non-ischemic TNA. All this data was collected by medical students and a neurology resident. Concerning the cerebrovascular event, which was the inclusion criteria in the ACIN study, we obtained the following parameters: date of hospital admission, definite diagnosis after adequate investigation (TIA or non-ischemic TNA) and the aetiology of the event, using the dichotomy “Known aetiology/Unknown aetiology”. We also collected information about relevant outcomes, namely death, stroke, TIA or non-ischemic TNA following the index event and related information. Occurrence of cancer was considered based on the patient’s physician previous diagnosis. We also collected the following parameters: date of diagnosis, primary location of cancer and cancer staging. Primary location of cancer was divided in 6 categories: gastrointestinal (which also included oral cavity cancer), genitourinary (which comprised bladder and urothelium, prostate, testicles, uterus, cervix, ovaries cancer), respiratory (including lung and respiratory epithelium cancer), skin, breast and others (thyroid, haematologic, central nervous system cancer, etc.). Cancer staging was divided in 3 categories: metastatic, non-metastatic or unknown (in cases where the staging wasn’t available or wasn’t conducted) and was based in consultations registries, as well as in results of complementary diagnostics.

Data collection started in December 2019 and ended in April 2019.

Statistical Analysis

We compared TIA and non-ischemic TNA patients according to their demographic characteristics, risk factors and possible outcomes (stroke, TIA, non-ischemic TNA, death and, our main outcome, cancer), using descriptive statistics and hypothesis tests. For comparing continuous variables, we performed independent samples t-test. For categorical variables, we conducted chi-square analysis. We also separated our groups into “Known aetiology” or “Unknown aetiology” and performed the same tests in these subgroups, to evaluate if there was a significant difference between these categories.

Regarding cancer outcome, the descriptive statistics and tests mentioned above were conducted in order to evaluate differences between the total of cancer patients, patients who had a previous diagnosis of cancer and patients with a cancer diagnosis after the main cerebrovascular event (TIA or non-ischemic TNA as criteria of inclusion in the ACIN study). We calculated 95% confidence intervals for cancer incidence using a Poisson distribution. Differences between cancer types and staging was assessed. Kaplan-Meier statistics and log-rank test were used to compare survival.

Univariate and multivariate cox regression analysis was conducted to assess the independent contribution of each parameter in cancer patients versus patients without cancer.

Kaplan-Meier and cox regression analysis were also performed for other endpoints, namely: cancer with metastasis, gastrointestinal cancer, stroke, TIA, TNA and death.

All statistical analysis was performed using IBM SPSS Statistics 25 software. A p value<0.05 was considered statistically significant.

RESULTS

Between 2009 and 2011, 594 patients had their first transient focal neurological symptoms and were included in the ACIN 2 registry. We excluded 84 patients (14.1%) that had vertigo of known peripheral aetiology. In the final cohort, 163 patients had a TIA (32.0%), and 347 patients had a non-ischemic TNA diagnosis (68.0%). In Figure 1 we depict the patients included in the study and the reasons for exclusion. Table I shows a comparison between these two groups.

Patients had a mean age of 63 ± 18 years, which was lower in the non-ischemic TNA group (59 ± 19) compared to the TIA group (71 ± 14). Most patients were female (60.6%), 81 within TIA group (49.7%) and 228 within non-ischemic TNA group (65.7%).

The most common risk factors were hypertension (51.4%), dyslipidemia (34.5%), diabetes mellitus (18.2%) and tobacco use (14.7%). Hypertension was more frequent in the TIA group (68.7% vs. 43.2%) than in the non-ischemic TNA group ($p < 0.001$). Dyslipidemia was found in 52.1% of TIA patients, whereas in TNA patients it accounted for only 26.2% ($p < 0.001$). Tobacco use was also more common in TIA patients (20.2% vs. 12.1%) than non-ischemic TNA ($p = 0.015$). The prevalence of other vascular risk factors (diabetes mellitus, peripheral artery disease, previous acute myocardial infarction, coronary artery disease, previous history of thrombotic events and previous diagnosis of atrial fibrillation) was not different in both groups.

The diagnosis of cancer was found in 78 patients (15.3%), during follow-up of 7 years. Forty-six patients (56.1% of cancer patients) were diagnosed after the index neurological event (TIA or non-ischemic TNA). Cancer wasn't significantly different between TIA and non-ischemic TNA groups ($p = 0.062$). However, when considered only diagnosis of cancer posterior to the neurological event (9% of all patients), cancer prevalence was higher in TIA patients compared to non-ischemic TNA patients (13.5% vs. 6.9%, $p = 0.016$), as shown in Table I. Global cancer incidence (excluding skin cancer) was 1064.4/100000/year (CI 95% 753.2-1461.1), accounting for 1665.2/100000/year in TIA patients and 782.2/100000/year in TNA patients, as shown in Table II. Mean age by the date of cancer diagnosis was 73.8 ± 12.1 years and wasn't significantly different in both groups.

The most common cancer diagnosed after the neurological event was originated from gastrointestinal system (28.3%), followed by genitourinary system (21.7%), skin (17.4%, none malignant melanoma), respiratory tract (13.0%), breast (6.5%) and others (13.0%). Gastrointestinal, genitourinary and respiratory tract cancers were more frequent among TIA patients (36.4% vs. 20.8%, 22.7% vs. 20.8% and 18.2% vs. 8.3%, respectively), whereas skin, breast and other type of cancers were more common in non-ischemic TNA patients (20.8% vs. 13.6%, 12.5% vs. 0% and 16.7% vs. 9.1%, respectively). There was one case of central nervous system cancer in the TIA group.

Regarding cancer staging, metastasis were found in 15 patients, 9 patients in TIA group and 6 in non-ischemic TNA group. From the 22 patients with cancer diagnosed posteriorly to the TIA, 40.9% had metastasis, which was more frequent than in cancer patients of the non-ischemic TNA group ($p=0.028$), that had a metastasis in 25% of the patients. From all patients, only one TIA patient had brain metastasis.

By the end of follow-up, estimated cumulative proportion of cancer-free patients in the TIA group was 82.1%, against 90.9% in the TNA group. Cancer-free survival time was shorter in TIA patients than TNA patients, with a Kaplan-Meier survival plot demonstrating different survival distribution (log rank test with $p=0.010$), as shown in Figure 2.

Increasing age, male sex, hypertension and current or past smoking habits were associated with cancer in univariate analysis (HR=1.04, $p<0.001$; HR=2.37, $p=0.004$; HR=1.96, $p=0.033$; HR=2.02, $p=0.036$; respectively), as shown in Table III. Other variables (diabetes mellitus, dyslipidemia, peripheral artery disease, ischemic heart disease, previous thrombotic events and previous atrial fibrillation) didn't demonstrate any statistically significant difference. In multivariate analysis, only age was an independent factor ($p<0.001$), but male sex and tobacco use showed tendency towards significance ($p=0.094$ and $p=0.090$, respectively). Other variables did not reach statistical significance in multivariate analysis. We found that there was a higher risk of cancer in TIA patients, only in univariate analysis (HR=2.11, $p=0.011$ in univariate analysis vs. HR=1.36, $p=0.329$ in multivariate analysis).

Kaplan-Meier analysis was also used to compare metastasis-free survival and gastrointestinal cancer-free survival. It showed that both metastasis-free survival and gastrointestinal cancer-free survival time was lower in the TIA group (log rank test with $p=0.012$ and $p=0.014$, respectively) (Figures 3 and 4). A cox regression analysis was not performed given the small number of patients. Concerning neurological outcomes, stroke and TIA occurred more frequently after a TIA as index event, with stroke occurring in 25.8% of TIA patients against 3.7% in non-ischemic TNA group ($p<0.001$) and TIA occurring in 13.5% TIA patients against 1.4% in non-ischemic TNA group ($p<0.001$). Of all strokes, 3 were haemorrhagic (5.5% of all strokes). There wasn't statistically significant difference in the incidence of non-ischemic TNA after the index event between both groups. To find if there was an independent relationship between neurological outcomes and our index event, a Kaplan-Meier analysis was performed, showing smaller survival time before stroke or TIA in TIA patients than TNA patients (log rank test with $p<0.001$ in both cases) (Figures 5 and 6). By the end of follow-up, estimated cumulative proportion of surviving patients for stroke endpoint in the TIA group was 68.8%, against 95.5% in the non-ischemic TNA group and 84.6% against 98.4% for TIA endpoint. When repeated for a non-ischemic TNA endpoint, this analysis didn't demonstrate significant difference in survival distribution in both groups (log rank test with $p=0.085$). Univariate

analysis and multivariate analysis confirmed TIA as an independent factor associated to stroke and TIA outcomes (HR=8.18, $p<0.001$ in univariate analysis and HR=5.21, $p<0.001$ in multivariate analysis) (Table IV and V). In univariate analysis, other variables showed an independent relationship with stroke: age (HR=1.05, $p<0.001$), hypertension (HR=5.60, $p<0.001$), dyslipidemia (HR=2.92, $p<0.001$), tobacco use (HR=1.91, $p=0.041$) and previous thrombotic events (HR=2.95, $p=0.003$). Previous atrial fibrillation showed tendency towards significance (HR=2.08, $p=0.092$). In multivariate analysis, some of these variables did not reach significance, except for age (HR=1.03, $p=0.006$), hypertension (HR=2.35, $p=0.038$) and previous thrombotic events (HR=2.94, $p=0.009$). Regarding the relationship between TIA outcome and variables other than the index event, age (HR=1.03, $p=0.043$), hypertension (HR=5.37, $p=0.002$), dyslipidemia (HR=2.36, $p=0.027$) and previous thrombotic events (HR=3.38, $p=0.014$) were demonstrated to be independent predictors for this outcome in univariate analysis. In multivariate analysis, only hypertension (HR=3.96, $p=0.022$) was confirmed as an independent factor for TIA. Other variables didn't show statistically significant difference for TIA events.

Mortality was higher in TIA group ($p<0.001$), with a total of 13.5% of deaths, 22.7% in TIA patients and 9.2% in non-ischemic TNA patients. The most common cause for death was infection (26.1%), followed by cancer (13%), cardiovascular events (4.3%), cerebrovascular events (4.3%) and other (5.8%). In 46.4% of patients we were not able to find the cause of death. Death by infection, cancer and cerebrovascular events was higher in TIA patients, unlike death by cardiovascular events and other causes, which were higher in non-ischemic TNA patients, as shown in Table I. Death of unknown cause was also more common in non-ischemic TNA patients. Kaplan-Meier analysis showed that survival time was lower in the TIA group (log rank test with $p<0.001$) (Figure 7). Considering these results, a cox regression analysis was performed, demonstrating TIA is an independent factor associated mortality both in univariate and multivariate analysis (HR=2.64, $p<0.001$ in univariate analysis and HR=1.78, $p=0.025$ in multivariate analysis), as shown in Table VI. Regarding other variables, only age and diabetes maintained as independent predictors for death in multivariate analysis.

DISCUSSION

We found that the global incidence rate of cancer (except for skin non-melanoma cancer) in our group of patients (1064.4/100000/year) was superior to the population incidence rate which was 502.1/100000/year in the year 2012 (Registo Oncológico Regional do Norte^[16]). Strikingly, TIA incidence rate (1665.2/100000 /year) was also superior to global incidence rate for the population of the north region of Portugal. In comparison, the non-ischemic TNA group incidence rate appears to be similar to the population. This is in line with our initial hypothesis, supporting a link between ischemic events and cancer. Consistently, we also found that, cancer occurring after the index event, was more frequent in TIA patients than TNA patients. To the best of our knowledge this is the first time such observation is documented, although several investigators considered the same goal regarding stroke and cancer^[17-23]. The similarity of the pathomechanisms underlying stroke and TIA, may justify this observation. Having said that, to complete our assessment, we showed that there was different cancer free-survival between TIA and non-ischemic TNAs. However, the association between TIA and cancer was not observed in the cox regression analysis. In fact, only age of the patient was confirmed as an independent risk factor for cancer development when comparing the 2 groups, which is also consistent with previous knowledge^[24]. Still the non-ischemic TNA group may not be the ideal control since it may enclose TIA patients wrongly diagnosed or non-ischemic TNAs may have also some relation to cancer through a different mechanism.

The most common cancers diagnosed after the neurological event were gastrointestinal tumours, as it has been described about the association of stroke and cancer^[17, 20]. Genitourinary system was also one of the most common type of tumour, which could be due to its diversity in possible primary locations (bladder, prostate, uterus, ovaries, cervix, testicles). The high incidence of skin cancer is probably explained by its high incidence in the population^[25], since none of the identified skin cancers was malignant melanoma. Some of the vascular risk factors mentioned above, particularly tobacco use, are also risk factors for several types of cancer^[26-29], which could explain a higher incidence of gastrointestinal, genitourinary and respiratory cancers in TIA patients, without necessarily being a direct relationship between TIA and each of these types of cancer. Besides, a few of those risk factors are also risk factors for breast cancer^[30], which we found was more common in TNA patients. Still these observations are limited by the low number of events.

Statistical significance was also found regarding the difference of metastasis incidence in TIA and non-ischemic TNA groups. Since only one patient had brain metastasis, we can assume that direct compression or infiltration of brain structures is unlikely to be the mechanism that lead to the index event. However, other mechanisms, such as metastasis emboli or vascular compression, have been

proposed to explain cerebral ischemia in cancer patients^[1, 5], which supports our hypothesis of an ischemic background in cancer patients' neurologic complications.

In our study, we found that mean age was higher in TIA patients, by a ten years difference, and that, while female patients were more common in non-ischemic TNAs, male sex was the most frequent gender in TIAs. This information is consistent with previous studies^[13, 31, 32], that confirm higher prevalence of TIA in men and older patients. As for non-ischemic TNA, the association with age and sex is less certain, which is explained its diverse aetiology, characterized by different demographic prevalence, but in general comprising a group of younger patients^[33-36].

Regarding risk factors, we found that hypertension, dyslipidemia and tobacco use were significantly different between these two groups, with a higher prevalence in TIA, as was expected. TIA has been consistently associated with cardiovascular risk factors in general^[13, 37, 38], in resemblance to stroke, due to its vasculo-thrombotic mechanisms^[39], therefore, it's predictable that these variables are associated with TIA events, rather than non-ischemic TNAs. Although other vascular risk factors (diabetes mellitus, peripheral artery disease, previous acute myocardial infarction, coronary artery disease, previous history of thrombotic events and previous diagnosis of atrial fibrillation) weren't significantly different between both groups, several of these factors have been previously associated with TIA, despite not always being found a significant association with the cerebrovascular event^[31, 37]. Systolic blood pressure, total cholesterol and angina pectoris have also been described as independent risk factors for focal TNA^[11], which could be an explanation for its high prevalence in TNA patients.

Concerning neurological outcomes, it has been previously described that there is a great risk of stroke after TIA^[40, 41], but recurrent TIA is also a frequent outcome^[42, 43]. That information is consistent with our findings, translated in a statistically significant difference between TIA and non-ischemic TNA patients' outcomes. The excessive difference in survival time estimates between TIA and non-ischemic TNA group regarding stroke or TIA endpoints, conveys exactly the same message, which is again demonstrated in univariate and multivariate analysis. It's interesting to see that, although TIA shares some risk factors with stroke and recurrent TIA, this event is for itself an independent predictor of stroke and recurrent TIA. Besides TIA, other variables were found to be independent predictors for these outcomes, namely hypertension (in both TIA and stroke outcomes), age and previous thrombotic events (solely considering stroke events), which is again consistent with risk factors previously described in literature^[13, 37].

Given that both cancer and stroke are more frequent outcomes in TIA patients, it would be expectable that mortality would be higher in this group. As such, not only mortality by these causes was superior in TIA patients, but also death by infection and global mortality accompanied this distribution. The fact that mortality by cardiovascular events, unlike the previously mentioned

causes, was higher in non-ischemic TNA patients is possibly due to the fact that all heart diseases in total account for more mortality than cerebrovascular disease in general population of Portugal^[44]. Death by cancer in total was high, as expected, not only because it is one of the main causes of death in Portugal^[44], but also because the incidence of cancer was found to be superior in TIA than in general population. However, death by cerebrovascular disease in all patients was low, considering its high incidence in Portuguese population^[44]. This might be explained by the great amount of cases in which the cause of death wasn't known (about 46.6% of death cases). Considering these facts, it was also expectable that survival time would be superior in non-ischemic TNA patients and that TIA would be an independent predictor for death, as we determined.

The retrospective design is the main limitation in our study: recording in electronic patient hospital records is not done systematic across all patients; the reliability of information given by patients during telephone interview; patient absenteeism. All these arguments might have undervalued the number of patients diagnosed with cancer and other possible outcomes. In addition, our initial purpose also included a comparison between two subgroups of known and unknown aetiology to see if there was a significant difference in outcomes between these categories. However, we found that, in our group of patients, the distribution of Known and Unknown aetiology patients didn't match previous descriptions in literature. In a study about aetiology, duration and prognosis of TIAs in Germany, the frequency of TIAs of unknown aetiology was 43.2%, not very different from stroke of unknown aetiology (29.5%)^[45], which is similar to what has been previously described by the American Heart Association/American Stroke Association^[46]. These values are very different from what we found in our TIA patients, in which the frequency of unknown aetiology was 82.8%. This was due to the fact that aetiology was determined only based on the first assessment of the patient at the emergency department. For this reason, we decided not to compare these groups. Still, this issue needs to be addressed and future studies should clarify if there is a difference in the incidence of cancer between TIAs of different aetiologies and TIAs of unknown aetiology, as a way to shorten the eligible group of TIA patients for occult cancer screening.

CONCLUSION

Cancer incidence is higher in our group of patients compared to the general population of the same geographical origin. This is particularly striking for the TIA group that presents a higher incidence of cancer, namely GI tract and metastasized cancers.

Our study suggests that there might be a link between cancer and TIA. However, our results don't allow us to state with certainty that occult cancer is the cause for the index cerebrovascular event, since multivariate analysis didn't confirm the difference between TIA and non-ischemic TNA group found in previous tests. Future studies could deepen this discussion and help to clarify if there is in fact a causal relationship between cancer and TIAs.

If this cause-effect relationship is proven, healthcare professionals should consider screening for occult malignancies in patients with TIAs, particularly those with unknown aetiology, as well as in stroke patients, since an early diagnosis of cancer has a great impact on patients' survival ^[47].

APPENDICES

APPENDIX A – TABLE I

Table I – Study population baseline characterization and outcomes

	TIA (N=163)	Non-ischemic TNA (N=347)	Total (N=510)	p value
Female, n (%)	81 (49.7)	228 (65.7)	309 (60.6)	0,001
Age, mean ± SD	70,8 ± 14.1	58,9 ± 18.6	62,7 ± 18.1	<0,001
Vascular risk factors, n (%)				
Hypertension	112 (68.7)	150 (43.2)	262 (51.4)	<0,001
Diabetes Mellitus	36 (22.1)	57 (16.4)	93 (18.2)	0,123
Dyslipidemia	85 (52.1)	91 (26.2)	176 (34.5)	<0,001
Tobacco use	33 (20.2)	42 (12.1)	75 (14.7)	0,015
Peripheral artery disease	4 (2.5)	11 (3.2)	15 (2.9)	0,655
Previous acute myocardial infarction	6 (3.7)	11 (2.9)	16 (3.1)	0,629
Coronary artery disease	10 (6.1)	14 (4)	24 (4.7)	0,296
Previous thrombotic events	13 (8)	24 (6.9)	37 (7.3)	0,667
Previous diagnosis of atrial fibrillation	14 (8.6)	17 (4.9)	31 (6.1)	0,104
With known aetiology, n (%)	28 (17.2)	94 (27.1)	122 (23.9)	0,014
Neurological outcomes, n (%)				
Stroke	42 (25.8)	13 (3.7)	55 (10.8)	<0,001
TIA	22 (13.5)	5 (1.4)	27 (5.3)	<0,001
Non-ischemic TNA	7 (4.3)	29 (8.4)	36 (7.1)	0,095
Cancer, n (%)	32 (19.6)	46 (13.3%)	78 (15.3)	0,062
Previous to the event	10 (6.1)	22 (6.3)	32 (6.3)	0,929
Posterior to the event	22 (13.5)	24 (6.9)	46 (9)	0,016
All types except for skin	19 (11.7)	19 (5.5)	38 (7.5)	
Gastrointestinal tract	8 (4.9)	5 (1.4)	13 (2.5)	
Genitourinary system	5 (3.1)	5 (1.4)	10 (2)	
Skin	3 (1.8)	5 (1.4)	8 (1.6)	
Respiratory tract	4 (2.5)	2 (0.6)	6 (1.2)	
Breast	0 (0)	3 (0.9)	3 (0.6)	
Others	2 (1.2)	4 (1.2)	6 (1.2)	
With metastasis	9 (5.5)	6 (1.7)	15 (2.9)	0,028
Mortality, n (%)	37 (22.7)	32 (9.2)	69 (13.5)	<0,001
Infection	13 (8)	5 (1.4)	18 (3.5)	
Cancer	6 (3.7)	3 (0.9)	9 (1.8)	
Cardiovascular disease	1 (0.6)	2 (0.6)	3 (0.6)	
Cerebrovascular disease	2 (1.2)	1 (0.3)	3 (0.6)	
Other causes	2 (1.2)	2 (0.6)	4 (0.8)	
Unknown cause	13 (8)	19 (5.5)	32 (6.3)	

APPENDIX B – TABLE II

Table II – Cancer Incidence rates in the study population

	Incidence rate /100000 per year	95% CI /100000 per year
Total	1064.4	753.2 - 1461.1
TIA patients	1665.2	1002.6 - 2600.4
Non-ischemic TNA patients	782.2	471.0 - 1221.5

APPENDIX C – TABLE III

Table III – Univariate and multivariate Cox regression analysis of variables associated with increased cancer occurrence

	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
TIA vs. Non-ischemic TNA	2.11	1.19-3.77	0.011	1.36	0.74-2.49	0.329
Age	1.04	1.02-1.06	<0.001	1.04	0.91-3.23	0.094
Sex (Male vs. Female)	2.37	1.31-4.25	0.004	1.72	1.02-1.06	<0.001
Hypertension	1.96	1.06-3.63	0.033	1.26	0.63-2.55	0.517
Diabetes mellitus	1.46	0.74-2.87	0.278	1.12	0.54-2.30	0.764
Dyslipidemia	1.35	0.75-2.42	0.323	0.82	0.43-1.56	0.547
Tobacco use	2.02	1.05-3.90	0.036	1.91	0.90-1.03	0.090
Peripheral artery disease	1.00	0.14-7.24	0.998	0.59	0.07-4.70	0.620
Ischemic heart disease	1.52	0.47-4.89	0.485	1.07	0.30-3.81	0.913
Previous thrombotic events	1.30	0.47-3.63	0.613	1.22	0.40-3.69	0.728
Previous atrial fibrillation	0.74	0.18-3.05	0.675	0.48	0.11-2.01	0.314

APPENDIX D – TABLE IV

Table IV – Univariate and multivariate Cox regression analysis of variables associated with increased stroke occurrence

	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
TIA vs. Non-ischemic TNA	8.18	4.39-15.25	<0.001	5.21	2.72-9.98	<0.001
Age	1.05	1.03-1.07	<0.001	1.03	1.01-1.06	0.006
Sex (Male vs. Female)	1.52	0.90-2.59	0.119	1.11	0.62-2.00	0.733
Hypertension	5.60	2.64-11.84	<0.001	2.35	1.05-5.26	0.038
Diabetes mellitus	1.46	0.79-2.72	0.231	1.08	0.57-2.07	0.807
Dyslipidemia	2.92	1.70-5.01	<0.001	1.49	0.85-2.61	0.169
Tobacco use	1.91	1.03-3.56	0.041	1.58	0.76-3.28	0.225
Peripheral artery disease	1.60	0.39-6.56	0.516	0.83	0.18-3.76	0.806
Ischemic heart disease	1.68	0.61-4.64	0.320	0.67	0.22-2.08	0.487
Previous thrombotic events	2.95	1.44-6.03	0.003	2.94	1.32-6.55	0.009
Previous atrial fibrillation	2.08	0.89-4.84	0.092	1.22	0.51-2.94	0.653

APPENDIX E – TABLE V

Table V – Univariate and multivariate Cox regression analysis of variables associated with increased TIA occurrence

	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
TIA vs. Non-ischemic TNA	10.17	3.85-26.87	<0.001	10.15	3.48-29.61	<0.001
Age	1.03	1.00-1.05	0.043	0.98	0.95-1.02	0.324
Sex (Male vs. Female)	1.98	0.93-4.24	0.077	1.83	0.81-4.17	0.148
Hypertension	5.37	1.86-15.52	0.002	3.96	1.22-12.83	0.022
Diabetes mellitus	1.32	0.53-3.27	0.549	0.95	0.37-2.44	0.910
Dyslipidemia	2.36	1.10-5.03	0.027	1.14	0.50-2.59	0.749
Tobacco use	0.45	0.11-1.91	0.280	0.16	0.03-0.73	0.019
Peripheral artery disease	1.52	0.21-11.21	0.681	1.85	0.21-16.45	0.582
Ischemic heart disease	2.72	0.82-9.02	0.103	0.85	0.19-3.89	0.832
Previous thrombotic events	3.38	1.28-8.93	0.014	2.98	0.92-9.70	0.069
Previous atrial fibrillation	2.20	0.66-7.31	0.198	1.30	0.37-4.61	0.684

APPENDIX F – TABLE VI

Table VI – Univariate and multivariate Cox regression analysis of variables associated with increased mortality

	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
TIA vs. Non-ischemic TNA	2.64	1.65-4.24	<0.001	1.78	1.08-2.94	0.025
Age	1.08	1.06-1.10	<0.001	1.07	1.05-1.10	<0.001
Sex (Male vs. Female)	1.36	0.85-2.19	0.203	1.23	0.74-2.07	0.425
Hypertension	2.96	1.69-5.18	<0.001	1.38	0.74-2.56	0.310
Diabetes mellitus	2.64	1.61-4.31	<0.001	2.31	1.36-3.92	0.002
Dyslipidemia	1.48	0.92-2.38	0.107	0.81	0.48-1.36	0.427
Tobacco use	0.74	0.36-1.55	0.426	0.71	0.31-1.67	0.437
Peripheral artery disease	4.40	1.90-10.16	0.001	2.96	1.00-8.80	0.050
Ischemic heart disease	2.03	0.88-4.68	0.098	1.04	0.39-2.75	0.943
Previous thrombotic events	1.95	0.93-4.07	0.076	1.67	0.64-4.35	0.295
Previous atrial fibrillation	2.27	1.09-4.75	0.029	1.04	0.47-2.30	0.917

APPENDIX G – FIGURE 1

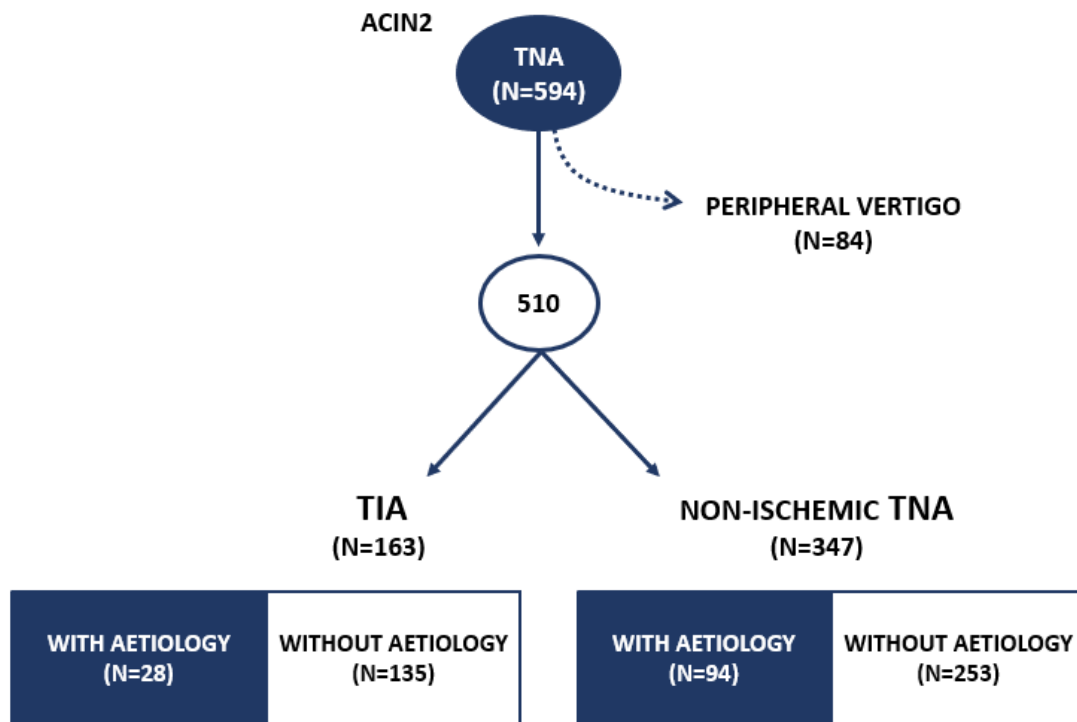


Figure 1 – ACIN 2 study population selection diagram

APPENDIX H – FIGURE 2

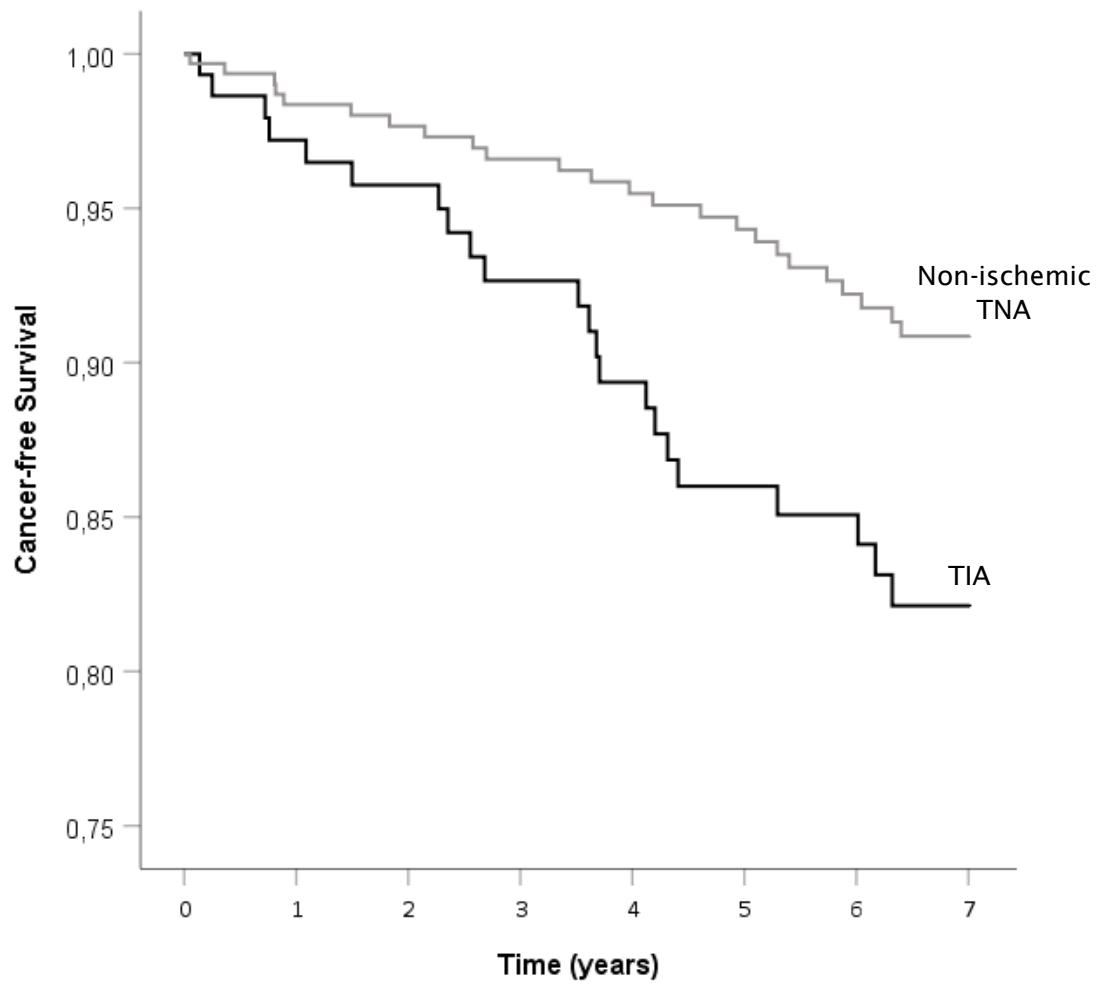


Figure 2 – Kaplan-Meier curve for cancer-free survival

APPENDIX I – FIGURE 3

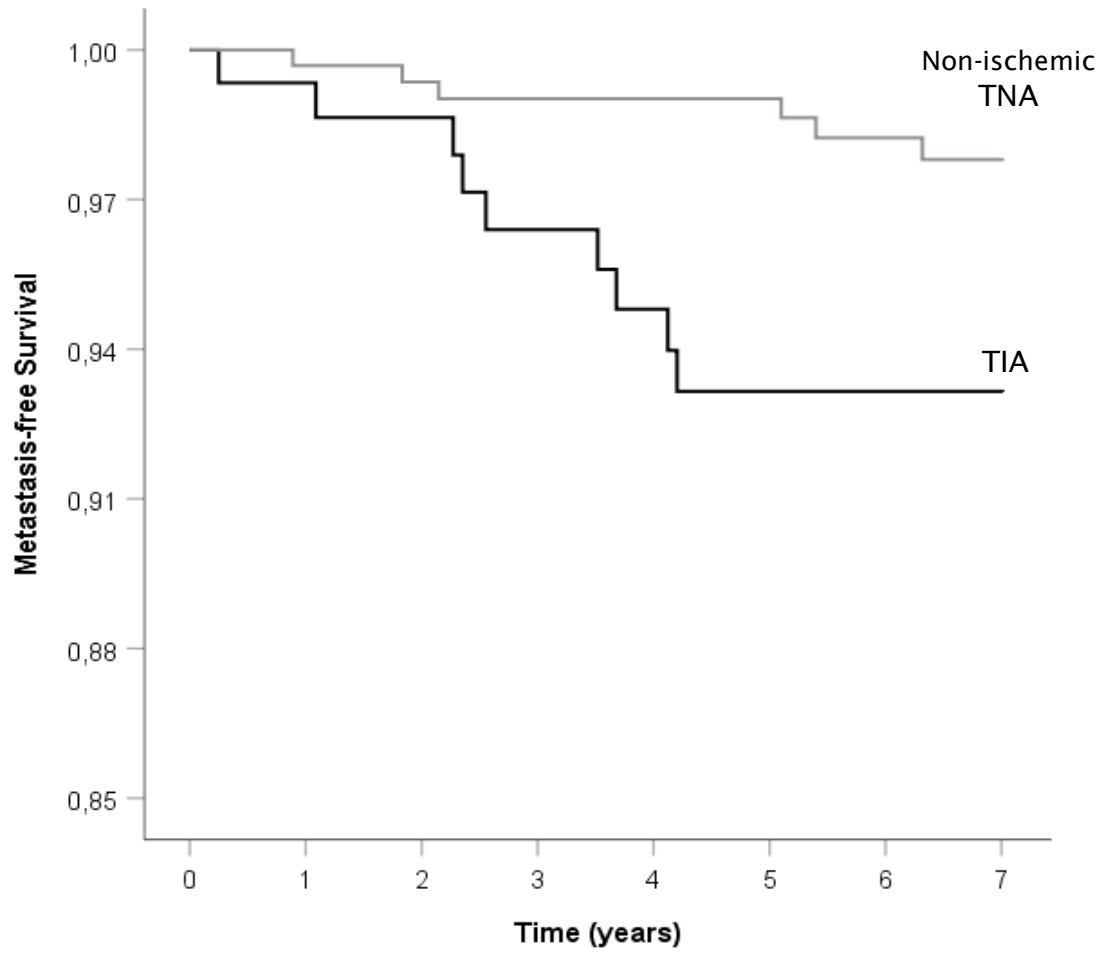


Figure 3 – Kaplan-Meier curve for metastasis-free survival

APPENDIX J – FIGURE 4

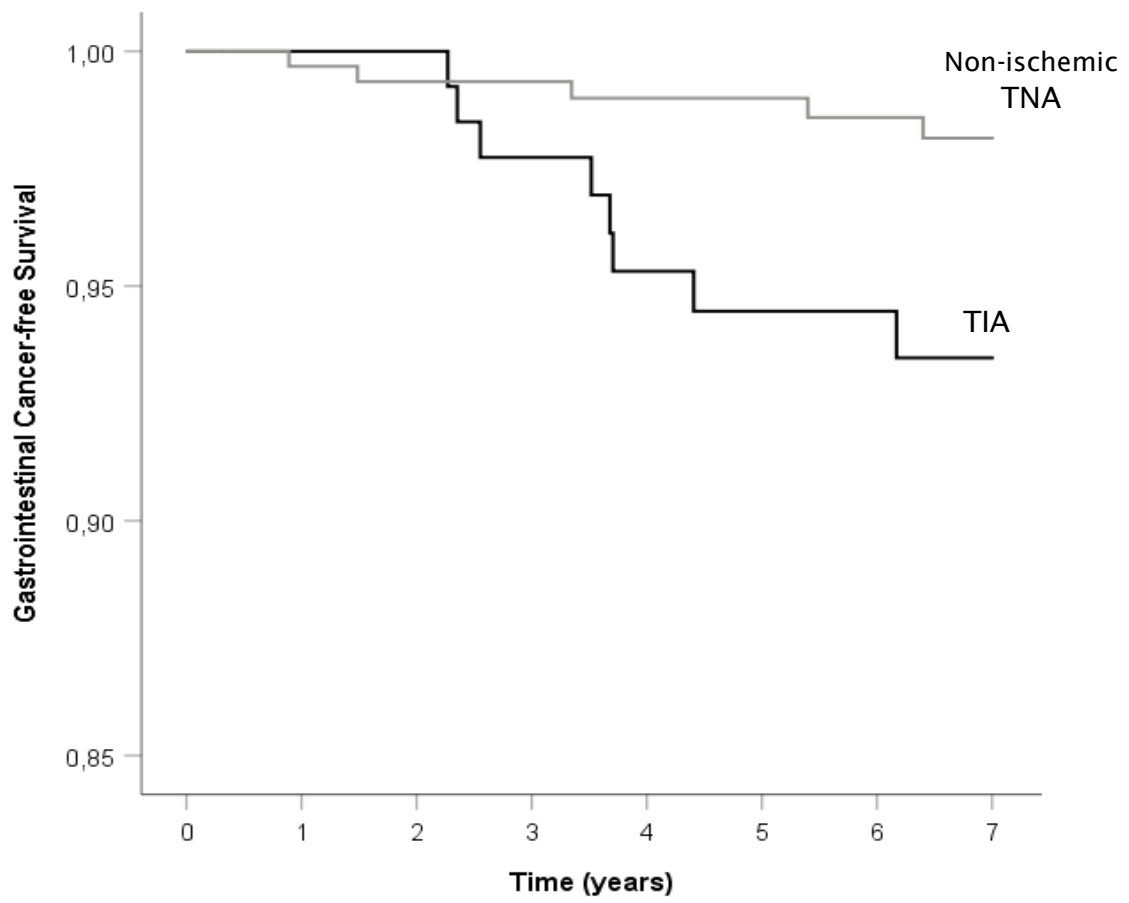


Figure 4 – Kaplan-Meier curve for gastrointestinal cancer-free survival

APPENDIX K – FIGURE 5

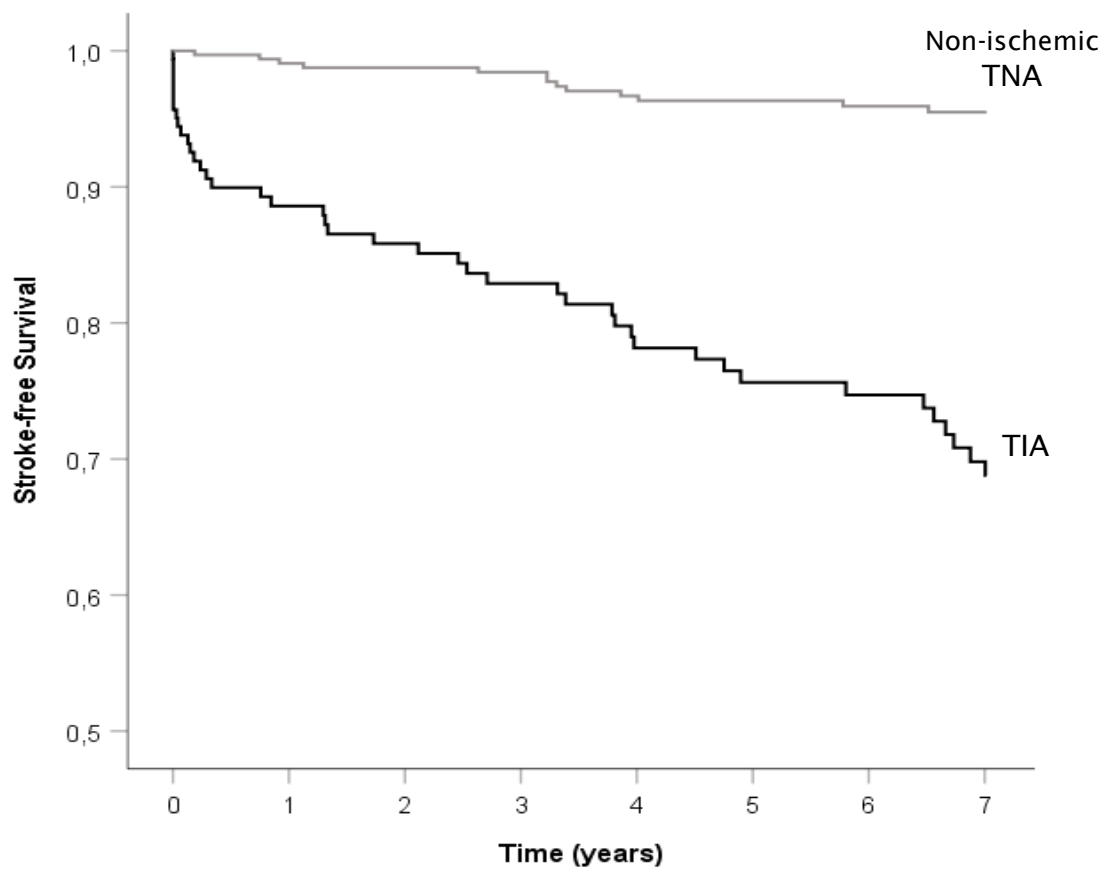


Figure 5 – Kaplan-Meier curve for stroke-free survival

APPENDIX L – FIGURE 6

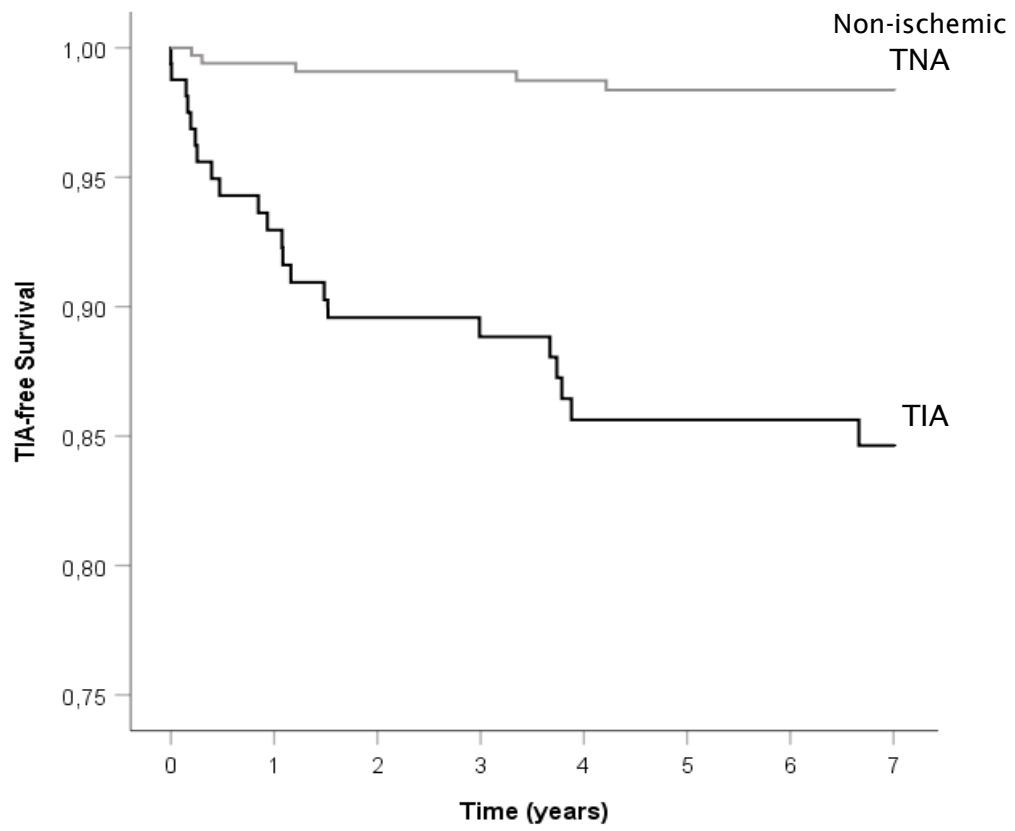


Figure 6 – Kaplan-Meier curve for TIA-free survival

APPENDIX M – FIGURE 7

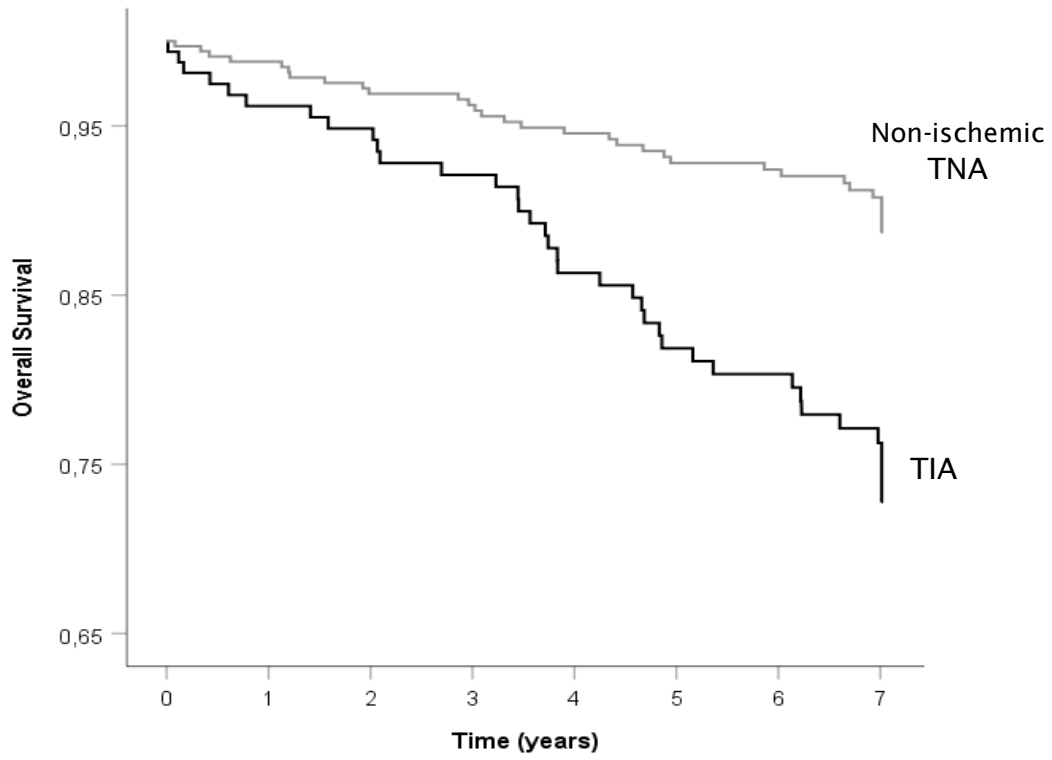


Figure 7 – Kaplan-Meier curve for overall survival

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