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Malignancies in patients with ANCA-associated vasculitis – A population based cohort study

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Malignancies in ANCA vasculitis

Abstract

Objectives: Patients with ANCA-associated vasculitides (AAV) exhibit higher rates of malignancy than the general population. In this study, we assessed whether the cancer risk is increased in a well-characterized population-based cohort of AAV in southern Sweden, followed for a median time of 8 years.

Methods: With case record review, the outcomes and malignancy development in a cohort of 195 patients with AAV (granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA), diagnosed between 1997 and 2010, were assessed. The patients were followed until death or December 31, 2015. The age- and sex-standardized incidence ratios (SIR) were estimated using the Swedish population data as a reference.

Results: During the approximately 1500 person-years observation period, we found 60 cancers in 52 of the 195 patients. SIR (95% CI) was 2.8 (2.1-3.6) for cancers at all sites, 1.8 (1.3-2.5) for all cancers excluding squamous cell carcinoma (SCC), 12.9 (8.4 -18.8) for SCC, 4.3 (1.4-10.0) for bladder cancer, and 7.0 (1.4-20.5) for pancreatic cancer. Cumulative doses of cyclophosphamide (CYC) less than 10g were not associated with higher incidence of cancers other than SCC (SIR 1.63 (95% CI: 0.8-2.9).

Conclusions: In contrast to recent publications assessing malignancy risk in patients with AAV, we show in this population-based cohort of patients, a persistent increased risk for overall malignancy, bladder cancer, and pancreatic cancer as well as a markedly increased risk for SCC. There was no increase in incidence of cancers other than SCC for those treated with less than 10 grams CYC.

Introduction

Systemic small vessel vasculitides, comprised of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) are in most cases associated with antibodies for proteinase 3 (PR3) and myeloperoxidase (MPO) in neutrophil granules(1). GPA, MPA and EGPA are grouped together under the name of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)(2). With the introduction of immunosuppressive agents such as glucocorticoids and cyclophosphamide, survival has improved substantially but is still decreased compared with the general population in the majority of patients(3). The standard treatment regimens today consist of high-dose corticosteroids combined with cyclophosphamide in the acute phase followed by lower doses of corticosteroids in combination with azathioprine or methotrexate(4). Rituximab is a drug that has been approved as an alternative to cyclophosphamide in the acute phase as well as an option for treating relapses(5-7). AAV often relapses, requiring repeated treatments with immunosuppression(8).

As survival of patients diagnosed with AAV has dramatically improved, the side effects of the immunosuppressive treatment have become a focus of interest and the development of malignancies is a major concern(9). Previously published observations suggested that the overall cancer incidence in patients treated for AAV is 1.6 to 2.4 times higher than in the general population and the relationship between malignancy and cumulative dose of cyclophosphamide has been highlighted in some of these studies(10-15). Interestingly, in a recent study, patients treated with rituximab did not show an increased malignancy risk compared with the general population(16).

Within the EUVAS-group we previously assessed the long-term malignancy risk in patients with AAV who had participated in one of four randomised clinical trials(12, 17-21). Even though the EUVAS studies included patients with variable clinical manifestations and disease severity, patients with EGPA and those who had a known previous malignancy were excluded.

In this study, we investigated long-term malignancy risk in a population-based cohort of 195 patients with AAV without any referral or exclusion bias, including all the diagnoses within the AAV spectrum, and these patients were followed for a median time of eight years.

Methods

Study design and participants

The occurrence of malignancy in a cohort of all incident cases with AAV in a defined geographical area of approximately 0.7 million inhabitants in southern Sweden was assessed. Potential cases of AAV, diagnosed between 1997 and 2010, were identified through healthcare registries using a previously described validated search algorithm(22) and were reviewed using case records. Patients were considered to have AAV if they had symptoms and signs compatible with small vessel vasculitis supported by histopathology, radiology, and/or serological findings, and if they had been classified as having GPA, MPA, or EGPA according to the European Medicine Agency 2007 algorithm(23). By review of each case record and pathology report for the 195 patients in the cohort, data of any malignancy occurring after the diagnosis of AAV were collected until December 31, 2015. If a patient developed several squamous cell carcinomas (SCC) only the first was reported. Likewise, if a patient developed several other cancers excluding SCC, only the first was reported. However, if a patient developed both SCC and any cancer excluding SCC, the first of both malignancies was reported, respectively. In the Swedish Cancer Registry, basal cell carcinoma

has only been reported since 2004; therefore the study did not include this diagnosis as no data on this disease is available for the general population throughout the period of investigation.

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethical Review Board in Lund (2010-517).

Baseline evaluation and treatment

Results from laboratory investigations collected at the diagnosis of AAV included plasma creatinine and ANCA serotype analysed with ELISA and capture ELISA. According to then-current guidelines used in southern Sweden, the majority of patients received cyclophosphamide and glucocorticoids as induction treatment. Cyclophosphamide was given orally, intravenously or, in many cases, both orally and intravenously at different time points. Patients with creatinine ≥500 μmol/l or those with rapidly progressive glomerulonephritis or pulmonary haemorrhage received plasma exchange and/or intravenous methylprednisolone in addition to cyclophosphamide as induction treatment. All patients who were treated with intravenous cyclophosphamide also received mesna to protect the urinary bladder. For those without systemic involvement, i.e. exclusively upper respiratory involvement, induction therapy was methotrexate together with

corticosteroids. After stable remission the treatment continued with azathioprine in the majority of patients. Thirty-one patients were treated with rituximab, of whom 4 did not receive any cyclophosphamide, 11 received 1-10g and 16 received >10g. For all included patients, medical charts were reviewed, and the cumulative doses of cyclophosphamide given throughout the entire follow-up period were calculated. In addition, information on immunosuppressive drugs other than cyclophosphamide was gathered.

Statistical analysis

Continuous variables are presented as medians and interquartile ranges (IQR). Categorical variables are expressed as counts and frequencies.

Estimation of cumulative cancer incidence and survival

Cumulative incidences of cancer, overall survival, and cancer-free survival were calculated using the Kaplan–Meier method. The calculations regarding cancer were performed both for all cancers and for SCC. Person-years of follow-up were calculated, starting from the date of diagnosis of AAV and ending at the earliest time of cancer of the selected kind, death or the end of follow-up on December 31, 2015. The person-years were calculated until the development of each specific cancer, regardless of a

diagnosis of other cancers. In order to enable comparisons with our previous study(12), as well as many others, in the calculation of cumulative incidence the occurrence of cancer was considered an event, whereas patients were followed until death or the end of the study period. For calculation of cancer-free survival, the occurrence of cancer or death was considered an event, and patients were followed through the end of the study period (24).

Calculation of standardized incidence ratios

For each patient, person-years of follow-up were calculated using the start and end dates described in the previous section; these calculations were made separately for each of the identified cancer endpoints. The person-years risk was calculated by sex and by age in 5-year groups. Standardized incidence ratios (SIRs) were calculated to compare the observed malignancies in the cohort with the expected numbers in the general population matched for gender, 5-year age groups and 1-year calendar time period, i.e. for each year the patients grow older and, when appropriate, the corresponding 5-year age groups in the general population were changed. A published SAS macro(25) was modified and expressed in the MATLAB language for these calculations. The expected numbers of cases of cancers of each kind were

calculated by multiplying the number of person-years for each sex and age group by the corresponding cancer incidence rates as provided by the Swedish Cancer Registry(26). Each healthcare provider in Sweden is obliged to send in a report to the Swedish Cancer Registry for every cancer case diagnosed at clinical, morphological and other laboratory examinations as well as cases diagnosed at autopsy. SIRs were calculated for cancers at all sites, for SCC and for each of the reported specific cancers in the cohort. SIRs were stratified by disease phenotype, ANCA serotype, sex and age group at entry (below vs. above 60 years), chronic kidney disease group (CKD) at entry (CKD 1-2 vs. CKD 3-5), previous malignancy (i.e. before diagnosis of AAV) and renal transplantation. We also performed a series of Poisson regressions to generate relative risks (RR) for cancer incidence in each subgroup.

Results

Patients

195 patients (98 female) with a median age of 69 years (IQR 55-77) at diagnosis of AAV fulfilled the inclusion criteria and were included in the study cohort. Among these patients, 94 (48%) were classified as GPA, 90

(46%) as MPA and 11 (6%) as EGPA. The follow-up time ranged between 0.3 and 18 years with a median follow-up time of 8 years (IQR 4.0-11.9). 98 (50%) of the patients died during follow-up. Further demographic data are summarized in Table 1. Of the patients included in this cohort, 7 had also participated in the EUVAS long-term follow-up and malignancy studies(12); of these 7 patients (21) one developed malignant melanoma and SCC and one developed lung cancer (both of whom participated in the MEPEX study).

Numbers and characteristics of observed cancers

52 of 195 patients developed 60 malignancies during the follow-up time of 1300 person-years. There were 26 SCC and 34 other types of cancers. The median time from the diagnosis of AAV to the first cancer diagnosis at any site was 5.13 years; to first SCC, 4.58 years; and to first malignancy of other types 5.50 years. Overall survival rate at 1, 2, 5 and 10 years was 87%, 82%, 70%, and 55%, respectively and the cancer-free survival rate for cancer at any site at 1, 2, 5 and 10 years was 84% (95% CI: 78-89), 77% (71-83), 61% (54-68) and 44% (37-52), respectively. The cancer-free survival at any site excluding SCC was 86% (95% CI: 81-91), 80% (75-86), 66% (60-73) and 49% (42-57), respectively (Figure 1). The cumulative 5- and 10-year incidence for cancers at all sites was 17% (95% CI: 11–23) and 30% (22–

38), respectively (Figure 2). The respective incidence for cancers of other types than SCC were 10% (95% CI: 5–15) and 20% (12–26) (Figure 2)

Among the 52 patients with cancer at any site, 29 died and among the 34 patients with non-SCC, 18 died; 15 of the total 98 deaths were attributed to cancer. Sixteen patients had had malignancies prior to the diagnosis of AAV; 8 of these were diagnosed with cancer during the follow-up period of this study, and another 8 had no new cancer detected (p=0.026). Seven patients underwent renal transplantation, and four of these were diagnosed with cancer.

Standardized incidence ratio of malignancies

The standardized incidence ratio (SIR) for all site cancers was 2.77 (95% CI: 2.07-3.64, p< 0.001) and for all sites excluding SCC was 1.81 (95% CI: 1.26-2.54, p = 0.001). Among the cancer site-specific analyses, incidences of SCC, bladder and pancreas cancers were significantly increased when compared with the general population. The SIR for SCC was 12.85 (95% CI: 8.40-18.83, p <0.001), the SIR for bladder cancer was 4.30 (95% CI 1.40-10.04, p=0.003) and the SIR for pancreas cancer was 7.00 (95% CI: 1.44-20.45, p= 0.002) (Table 2). During the first 5 years of follow-up, a total of 26 cancers were observed. The corresponding figures for SCC, for cancer at all sites

excluding SCC and bladder cancer were 14, 16, and 3, respectively. The cumulative follow-up time for the first 5 years was 735 person-years, and SIRs were 2.60 (95% CI: 1.70-3.80), for all sites, 14.9 (8.14-25.0) for SCC, 1.66 (0.95-2.69) for other types, and 5.36 (1.11-15.7) for bladder cancer.

Table 3 shows subgroup analyses for SIRs grouped by the predefined variables. The analysis indicates higher SIR for SCC in patients with EGPA, for those with negative ANCA, for patients younger than 60 years at diagnosis of AAV and for those with renal transplants. The results for overall cancer excluding SCC indicate higher SIR for patients with previous malignancies and those with renal transplant but a lower SIR for patients with EGPA and patients with negative ANCA.

Cumulative doses of cyclophosphamide less than 10g were not associated with higher incidence of cancers other than SCC (SIR 1.63 (95% CI: 0.8-2.9). Cumulative doses of cyclophosphamide higher than 36 g exhibited a SIR of 3.4 (95% CI: 1.5-6.4) for cancers other than SCC. The risk for SCC was markedly increased in patients not receiving cyclophosphamide (SIR 53.6 (95% CI: 21.6 -110.5). Among the 5 patients who developed bladder cancer, 3 were treated with cumulative cyclophosphamide doses higher than 10g (151, 31 and 17 g, respectively), and 2 patients were treated with doses

below 10g (7.5 and 8g, respectively). Table 4 shows risk ratios calculated using Poisson regression, showing, for example, that patients with previous malignancies had a risk ratio of 3.96 (1.73-7.96, $p<0.001$) compared with patients without previous malignancies.

Discussion

In this population-based cohort of patients, which includes all three diagnoses within the AAV spectrum, we show that risk for overall malignancy, bladder cancer, pancreatic cancer and SCC is still increased when compared with the general population.

A 2.77-fold increase in the risk for overall malignancy was seen in the AAV cohort compared with that in the general population. The highest risk was seen in SCC and was more than 12 times higher than that in the general population; the next highest risks were for pancreatic cancer with a 7-fold increase and bladder cancer with a 4.3-fold increased risk compared to the general population. There was no other significant increased risks for other reported malignancies.

Previous studies assessing malignancy risk in AAV have reported SIR for overall malignancy of different ranges. Earlier studies(27) have showed a 33-

fold increased risk for bladder cancer, and believed to be due to the use of higher doses of CYC for longer periods of time, but with current treatment protocols, these high risks are no longer seen. In more recent studies the SIR for overall cancers range from non-significant(28) to 3.76(11-13), the SIR for bladder cancer ranges from non-significant to a 3.6-fold increase, the SIR for the non-melanoma skin cancer (including SCC and basal cell carcinoma) ranges between a 2.8 and 4.7 increase, and the SIR for leukaemia ranges from non-significant to a 5.9-fold increase.

Two recent studies, one the EUVAS follow-up study of multicentre clinical trials(12) with a follow-up time of almost 5 years and the other a cohort of 138 patients identified through a pathology database(13) and followed for a median of 10 years both stress that the malignancy risk in patients with AAV treated according to current protocols is increased but that this increase is solely driven by the increased risk for SCC. However, in our study, the risk for SCC as well as the risk for both bladder and pancreatic cancer is significantly increased. The increased risk for bladder cancer is consistent with other previous studies from 2002 and 2006, but pancreatic cancer has not been shown to be increased in other studies. However, the patients who developed bladder cancer were treated with high cumulative doses of CYC, and the interpretation of the finding of increased risks for

pancreatic cancer must be made with caution, as the cohort is small. The treatment with cumulative doses of cyclophosphamide <10 g, corresponding to intravenous CYC for 3-6 months, was not associated with a higher risk for malignancies excluding SCC, indicating that the dosing of CYC with current treatment protocols is probably safe and not associated with an increased malignancy risk. However, cumulative doses of CYC of > 10 g were associated with higher incidence of cancers beyond SCC and an even higher risk was seen with doses > 36g. The cut-off of 36 g was chosen for comparison with a previous study from Faurschou et al., corresponding to treatment with 100 mg CYC/day for > 1 year (11).

The discrepancies, however small, between our findings and those in previous studies might have several explanations. The assessment of malignancies in Sweden is very thorough, and each health care provider is obliged to send in a report to the Swedish Cancer Registry for every cancer case diagnosed at clinical, morphological and other laboratory examinations as well as in cases diagnosed at autopsy. The assessment of malignancies both in our cohort as well as in the general population is reliable, and the probability that any cancer case is missed is very low. In the present study we included patients with previous malignancies, and in this group the risk for additional malignancies is known to be higher(29). In addition, the excess

risk of SCC might be explained to some extent by the high risk in patients with EGPA who have not been included in previous studies with the exception of the most recent one by van Daalen et al. (16). In our study 7 patients received a renal transplant, and in these patients the SIR was higher, especially for SCC, also adding to the higher risk in our previous study compared to others assessing malignancy risk in AAV. The risk for SCC among those patients receiving transplants has in several studies been shown to exceed that in the AAV population(30). The most probable explanation for the high risk for SCC that we see in patients not receiving cyclophosphamide is that these patients received other oral immunosuppressive drugs such as azathioprine, known to increase the risk for non-melanoma skin cancer including SCC(31).

The main limitation of this study is the relatively small number of patients. A larger number of patients would have strengthened the results, but the significant increased malignancy risk seen already in a smaller cohort shows that this still is an important factor to keep in mind in the follow-up of patients with AAV. Unfortunately, it is not possible to make a firm conclusion on the pathogenesis of the malignancies in our patients. In this study the main focus

was on the relationship between malignancies and immunosuppression as no data is available on other potential risk factors for cancer in AAV.

Our study has important strengths. We used a population-based cohort of patients with AAV in which the diagnoses of AAV are scrutinised by reviewing case records, and all patients are classified according to a defined algorithm using the EMA classification. Furthermore, all diagnoses of malignancies in the patients have been collected through case records, pathology, histology, and cytology databases without any missing data. In addition, the number of person-years of follow-up is approximately 1500 for a number of cancer diagnoses, and we were able to show important differences when comparing with the general population. Finally, the Swedish Cancer Registry enables comparison with the general population, which includes data from the entire Swedish population.

In conclusion, in this population-based cohort of patients, which includes all three diagnoses within the AAV spectrum, we show that the malignancy risk is still increased when compared with the general population, but in patients receiving CYC doses of less than 10 g, this is solely driven by the increased risk for SCC. In contrast to the most recent publications assessing malignancy risk in AAV patients, we show a persistent increased risk for

bladder cancer and pancreatic cancer in patients receiving CYC > 10 g, indicating that the risk for the development of solid tumours in patients treated for AAV should not be totally ignored.

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Conflict of interest

The authors have no financial or other conflicts of interest to report.

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Table 1. Baseline and follow-up demographics in 195 patients with incident ANCA-associated vasculitis.

	All (N=195)
Sex	
Male	50% (97)
Female	50% (98)
Age (years)	69 (55-77)
Age quartiles	
(0-55] years	25% (49)
(55-70] years	29% (57)
(70-80] years	27% (53)
(80-100] years	18% (36)
P-Creatinine (umol/l)	152 (75-319)
eGFR (ml/min)	40 (15-80)
CKD groups	
CKD 1-2	38% (74)
CKD 3	19% (38)
CKD 4	18% (36)
CKD 5	24% (47)
B-Haemoglobin (g/l)	110 (96-123)
Platelets (10^9/l)	366 (283-450)
CRP (mg/l)	87 (22-142)
ANCA	
PR3	51% (100)
MPO	43% (84)
Negative	6% (11)
Diagnosis	
GPA	48% (94)
MPA	46% (90)
EGPA	6% (11)
Renal transplantation	4% (7)
Previous malignancy	8% (16)
Follow-up (years)	8.0 (4.0-11.9)
Deaths	50% (98)
CYC < 1 g	15% (30)
CYC 1-10g	42% (82)
CYC >10 g	42% (83)
CYC > 36g	7% (14)

N, observations; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease (KDIGO 2013); CRP, C-reactive protein; ANCA, antineutrophil cytoplasmatic antibodies; PR3, proteinase 3; MPO, myeloperoxidase; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; CYC, cyclophosphamide. Data are presented in percentage (numbers) and median (interquartile range, IQR)

Table 2
Calculated age, sex and calendar year standardized incidence ratio (SIR) for observed cancers in 195 patients with ANCA associated vasculitis

Cancer site*	Person Year	Observed	Expected	SIR (95% CI)	p value
All sites	1300	52	18.7	2.77 (2.07-3.64)	<0.001
All sites excluding SCC	1399	34	18.7	1.81 (1.26-2.54)	0.001
SCC	1375	26	2.02	12.85 (8.40-18.83)	<0.001
Prostate	1468	7	4.21	1.66 (0.67-3.43)	0.129
Bladder	1485	5	1.16	4.30 (1.40-10.04)	0.003
Colorectal	1482	5	2.80	1.78 (0.58-4.17)	0.130
Lung	1502	3	1.70	1.77 (0.36-5.16)	0.186
Pancreas	1502	3	0.43	7.00 (1.44-20.45)	0.002
Breast	1491	2	2.51	0.80 (0.10-2.88)	0.919

*Ordered by decreasing numbers of observed cancer cases., SCC, squamous cell carcinoma.

Table 3 Standardized incidence ratios (SIR) for cancer at all sites. all sites excluding SCC and SCC according to selected subgroup variables.

	All sites					All sites excluding SCC					SCC				
Group	**PY**	**Obs**	**Exp**	**SIR (95% CI)**	**p**	**PY**	**Obs**	**Exp**	**SIR (95% CI)**	**p**	**PY**	**Obs**	**Exp**	**SIR (95% CI)**	**p**
Diagnosis															
-MPA	521	21	8.5	2.5 (1.5-3.8)	<0.001	555	13	8.1	1.61 (0.86-2.75)	0.0726	537	10	1.0	10.05 (4.82-18.48)	<0.001
-GPA	696	28	9.2	3.0 (2.0-4.4)	<0.001	778	20	9.9	2.02 (1.24-3.13)	0.0027	754	14	0.96	14.6 (7.98-24.50)	<0.001
-EGPA	83	3	1.1	2.7(0.6-8.0)	0.0513	86	1	1.1	0.92 (0.02-5.15)	0.5883	85	2	0.1	28.9 (3.50-104)	<0.001
ANCA serotype															
-MPO	534	21	8.5	2.5 (1.5-3.8)	<0.001	562	13	8.0	1.61 (0.86-2.76)	0.0723	552	10	1.0	10 (4.8-18.5)	<0.001
-PR3	690	26	9.5	2.7 (1.8-4.0)	<0.001	746	19	9.8	1.95 (1.17-3.04)	0.0053	747	12	1.0	12.2 (6.3-21.4)	<0.001
-neg	75	5	0.8	6.5 (2.1-15.1)	<0.001	91	2	0.9	2.17 (0.26-7.85)	0.1325	77	4	0.05	81.1 (22.1-207.6)	<0.001
Sex															
-Women	697	21	8.0	2.6 (1.6-4.0)	<0.001	743	14	8.0	1.8 (0.96-2.9)	0.034	726	10	0.68	14.8 (7.1-27.2)	<0.001
-Men	603	31	10.8	2.9 (2.0-4.1)	<0.001	657	20	10.8	1.9 (1.1-2.9)	0.007	650	16	1.3	11.9 (6.8-19.3)	<0.001
Age at entry															
< 60 ys	627	12	4.1	2.9 (1.5-5.1)	<0.001	657	9	4.3	2.09 (0.96-3.97)	0.0261	651	5	0.2	29.4 (9.6-68.7)	<0.001
> 60 ys	673	40	14.7	2.7 (1.9-3.7)	<0.001	742	25	14.4	1.73 (1.12-2.56)	0.0077	724	21	1.9	11.3 (7.0-17.3)	<0.001
CKD at entry															
1-2	645	19	7.8	2.4 (1.5-3.8)	<0.001	672	14	7.8	1.80 (0.98-3.02)	0.0277	677	9	0.67	13.4 (6.1-25.4)	<0.001
3-5	655	33	10.9	3.0 (2.1-4.2)	<0.001	726	20	11.0	1.82 (1.11-2.82)	0.009	699	17	1.35	12.6 (7.3-20.2)	<0.001
Previous malignancy															
- No	1243	44	17.6	2.5 (1.8-3.4)	<0.001	1327	28	17.6	1.59 (1.05-2.30)	0.0152	1309	23	1.9	12.4 (7.86-18.61)	<0.001
- Yes	57	8	1.1	7.1 (3.0-13.9)	<0.001	72	6	1.2	5.11 (1.87-11.13)	<0.001	66	3	0.17	17.73 (3.66-51.82)	<0.001
Renal transplantation															
- No	1238	48	18.3	2.6 (1.9-3.5)	<0.001	1321	30	18.0	1.67 (1.12-2.38)	0.0067	1308	24	2.0	12.0(7.69-17.86)	<0.001
- Yes	62	4	0.5	8.2 (2.2-21.0)	<0.001	78	4	0.7	5.52 (1.5-14.1)	0.0018	67	2	0.02	85.68(10.38-309)	<0.001
Immunosuppression															
CYC </= 1 g	152	8	1.8	4.3 (1.9 - 8.5)	<0.001	175	3	2.2	1.3 (0.3 - 3.9)	0.371	154	7	0.13	53.6 (21.6 - 110.5)	<0.001
CYC 1-36 g	1008	34	14.6	2.3 (1.6 - 3.2)	<0.001	1070	21	14.1	1.5 (0.9 - 2.3)	0.062	1049	18	1.7	10.8 (6.4 - 17.0)	<0.001

CYC > 36 g	152	9	2.7	3.4 (1.5 - 6.4)	<0.001	165	9	2.7	3.4 (1.5 - 6.4)	<0.001	186	1	0.35	2.9 (0.1 - 16.0)	0.096
AZA YES	414	14	6.11	2.3 (1.3-3.8)	0.003	439	8	6.1	1.3 (0.6-2.6)	0.319	426	9	0.7	12.6 (5.8-24.0)	<0.001
AZA NO	913	37	13.3	2.8 (2.0-3.8)	<0.001	986	25	13	1.9 (1.2-2.8)	0.002	977	17	1.5	11.6 (6.8-18.7)	<0.001
RTX YES	1081	47	17	2.8 (2.0-3.7)	<0.001	1175	31	17	0.8 (0.1-3.1)	0.803	1153	24	2	12.0 (7.7-17.9)	0
RTX NO	246	4	2.4	1.7 (0.5-4.3)	0.185	250	2	2.3	1.83 (1.2-2.6)	0.001	250	2	0.17	11.5 (1.4-41.7)	0.002
MMF YES	1047	41	15.5	2.6 (1.9-3.6)	<0.001	1122	24	15.3	1.6 (1.0-2.3)	0.027	1105	23	1.8	12.8 (8.1-19.2)	0
MMF NO	280	10	3.9	2.6 (1.2-4.7)	0.005	303	9	4	2.3 (1.0-4.3)	0.015	298	3	0.38	7.9 81.6-23.2)	0.001
MTX YES	939	41	14.3	2.9 (2.1-3.9)	<0.001	1005	27	14	1.9 (1.3-2.8)	0.001	997	19	1.7	11.2 (6.7-17.5)	<0.001
MTX NO	388	10	5.1	2.0 (0.9-3.6)	0.032	420	6	5.3	1.1 (0.4-2.5)	0.571	406	7	0.5	14.7 (5.9-30.3)	<0.001

SCC. Squamous cell carcinoma; MPA. microscopic polyangiitis; GPA. granulomatosis with polyangiitis; EGPA. eosinophilic granulomatosis with polyangiitis; ANCA. antineutrophil cytoplasmatic antibodies; MPO. myeloperoxidase; PR3. proteinase 3; CKD. chronic kidney disease (KDIGO 2013), CYC: Cyclophosphamide, AZA:Azathioprine, MMF: Mycophenolate mofetil, MTX: Methotrexate, RTX: Rituximab.

Table 4 . Relative risks, calculated by Poisson regression, according to selected subgroup variables.

	All sites					**All sites excluding SCC**					**SCC**				
Group	*PY*	*Obs*	*Exp*	*RR (95% CI)*	*p*	*PY*	*Obs*	*Exp*	*RR (95% CI)*	*p*	*PY*	*Obs*	*Exp*	*RR (95% CI)*	*p*
Diagnosis															
-MPA	521	21	8.5	1 (ref)		555	13	8.1	1 (ref)		537	10	1.0	1 (ref)	
-GPA	696	28	9.2	1.0 (0.57-1.78)	0.9	778	20	9.9	1.1 (0.55-2.3)	0.7	754	14	0.96	1.0 (0.45-2.3)	0.9
-EGPA	83	3	1.1	0.90 (0.21-2.6)	0.8	86	1	1.1	0.50 (0.03-2.5)	0.5	85	2	0.1	1.3 (0.19-4.8)	0.7
ANCA serotype															
-MPO	534	21	8.5	1 (ref)		562	13	8.0	1 (ref)		552	10	1.0	1 (ref)	
-PR3	690	26	9.5	0.96 (0.54-1.7)	0.8	746	19	9.8	1.1 (0.55-2.3)	0.7	747	12	1.0	0.89 (0.38-2.1)	0.7
-neg	75	5	0.8	1.7 (0.57-4.2)	0.2	91	2	0.9	0.95 (0.15-3.4)	0.9	77	4	0.05	2.9 (0.79-8.6)	0.07
Sex															
-Women	697	21	8.0	1 (ref)		743	14	8.0	1 (ref)		726	10	0.68	1 (ref)	
-Men	603	31	10.8	1.7 (0.99-3.0)	0.05	657	20	10.8	1.6 (0.82-3.3)	0.1	650	16	1.3	1.8 (0.82-4.1)	0.1
Age at entry															
< 60 ys	627	12	4.1	1 (ref)		657	9	4.3	1 (ref)		651	5	0.2	1 (ref)	
> 60 ys	673	40	14.7	3.1 (1.7-6.2)	<0.001	742	25	14.4	2.5 (1.2-5.6)	0.02	724	21	1.9	3.8 (1.5-11.3)	0.008
CKD at entry															
1-2	645	19	7.8	1 (ref)		672	14	7.8	1 (ref)		677	9	0.67	1 (ref)	
3-5	655	33	10.9	1.7 (0.98-3.1)	0.06	726	20	11.0	1.3 (0.67-2.7)	0.4	699	17	1.35	1.8 (0.83-4.3)	0.1
Previous malignancy															
- No	1243	44	17.6	1 (ref)		1327	28	17.6	1 (ref)		1309	23	1.9	1 (ref)	
- Yes	57	8	1.1	4.0 (1.7-8.0)	<0.001	72	6	1.2	3.9 (1.5-8.9)	0.002	66	3	0.17	2.6 (0.6-7.4)	0.1
Renal transplantation															
- No	1238	48	18.3	1 (ref)		1321	30	18.0	1 (ref)		1308	24	2.0	1 (ref)	
- Yes	62	4	0.5	1.7 (0.50-4.1)	0.3	78	4	0.7	2.3 (0.67-5.7)	0.1	67	2	0.02	1.6 (0.26-5.5)	0.5

SCC. Squamous cell carcinoma; MPA. microscopic polyangiitis; GPA. granulomatosis with polyangiitis; EGPA. eosinophilic granulomatosis with polyangiitis; ANCA. antineutrophil cytoplasmatic antibodies; MPO. myeloperoxidase; PR3. proteinase 3; CKD. chronic kidney disease (KDIGO 2013).

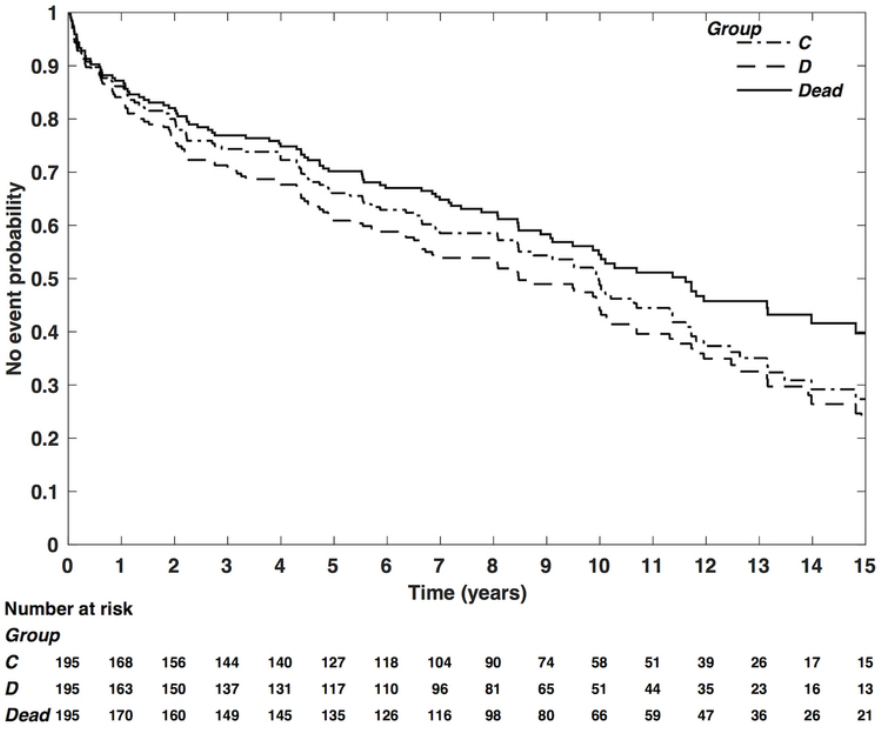

Figure 1 Overall survival (Dead), cancer free survival for cancer at any site (D), and cancer free survival for cancer at any site excluding squamous cell carcinoma (C).

71x57mm (300 x 300 DPI)

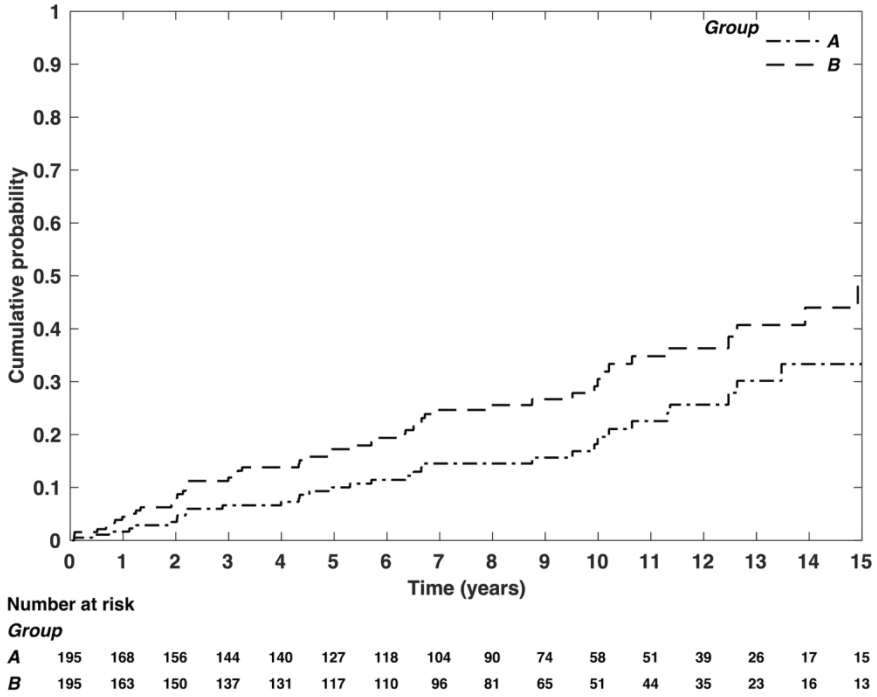

Figure 2 Cumulative incidence of cancer at any site (B), and cumulative incidence of cancer at any site excluding squamous cell carcinoma (A).

145x113mm (300 x 300 DPI)

Figure 1
Overall survival (Dead), cancer free survival for cancer at any site (D), and cancer free survival for cancer at any site excluding squamous cell carcinoma (C).

Figure 2
Cumulative incidence of cancer at any site (B), and cumulative incidence of cancer at any site excluding squamous cell carcinoma (A).