RESEARCH ARTICLE
DOI: 10.4274/tjh.galenos.2024.2024.0199

Secondary Solid Cancers Among Patients with Philadelphia Chromosome-Negative Myeloproliferative Neoplasms: A Multicenter Study

Philadelphia-Negatif Kronik Miyeloproliferatif Neoplazili Hastalarda Sekonder Solid Kanser Gelişimi: Çok Merkezli Çalışma

Hindilerden F. et al.: Secondary Solid Cancer in Ph- MPNs Patients

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May 30, 2024
August 7, 2024

Abstract
Objective: We investigated the occurrence and characteristics of secondary solid cancers (SSC) in Philadelphia chromosome-negative myeloproliferative neoplasm (Ph- MPN) patients from Türkiye. We identified the potential risk factors for SSC development including the impact of cytoreductive therapies and assess the influence of SSC on patient survival.
Material and Methods: 1013 Ph- MPN patients diagnosed between 1995 and 2022 was retrospectively analyzed. Data related to demographics, clinical and laboratory parameters, SSC development, cytoreductive therapy exposure and survival outcomes were collected. Statistical analyses were performed using SPSS 26.0 software.
Results: Of the Ph- MPN patients, 6.6% developed SSC, with carcinoma being the most common type. Older age at Ph- MPN diagnosis and male gender were associated with SSC occurrence. Ph- MPN patients diagnosed with SSC and patients with no diagnosis of SSC showed no significant difference for complete blood count, spleen size, Ph- MPN diagnostic groups and driver mutation frequencies. However, SSC patients showed a higher frequency of arterial thrombosis and tendency towards increased rate for total thrombosis (p=0.030, p=0.069; respectively). In multivariate analysis, arterial thrombosis was the sole independent risk factor and interferon (IFN)-based therapy the sole protective factor for SSC development. Median overall survival (OS) did not differ between patients with and without SSC except for polycythemia vera (PV) patients with SSC, who had shorter OS (175±15 and 321±26 months, respectively; p = 0.005).
Conclusion: Our study highlights the prevalence and characteristics of SSC in Turkish patients diagnosed with Ph- MPN. Arterial thrombosis was associated with increased SSC risk while IFN-based therapy offered potential protection from SSC. Screening for SSC in Ph- MPN patients with arterial thrombosis may be relevant**.** These findings emphasize the importance of malignancy screening in Ph- MPN patients, especially in high-risk subgroups and call for further research to elucidate the underlying mechanisms and optimize treatment strategies.
Keywords: Philadelphia chromosome-negative myeloproliferative neoplasm, secondary solid cancers, cytoreductive treatment, interferon
Öz:

Amaç: Türk popülasyonunda Philadelphia-negatif miyeloproliferatif neoplazi (Ph-MPN) hastalarında sekonder solid kanserlerin (SSK) sıklığının ve özelliklerinin araştırılması amaçlanmıştır. Sitoredüktif tedavinin etkisi de dahil olmak üzere SSK gelişiminde risk faktörlerinin tanımlaması ve SSK'nın hastanın sağkalımı üzerindeki etkisinin değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntem: 1995- 2022 yılları arasında tanı alan 1013 Ph-MPN hastası retrospektif olarak analiz edilmiştir. Demografik özellikler, klinik ve laboratuvar parametreleri, SSK gelişimi, sitoredüktif tedaviye maruz kalma ve sağkalım ile ilgili veriler toplanmıştır. İstatistiksel analizler SPSS 26.0 yazılımı kullanılarak yapılmıştır.

Bulgular: Ph-MPN hastalarının %6,6'sında SSK gelişmiştir ve en sık görülen tip karsinomdur. Ph-MPN tanısında ileri yaş ve erkek cinsiyet SSK gelişimiyle ilişkili bulunmuştur. SSK olan ve olmayan hastalarda kan sayımı, dalak boyutu, Ph-MPN tanı grupları ve somatik mutasyon sıklığı açısından anlamlı farklılık görülmemiştir. SSK gelişen hastalarda arteriyel tromboz sıklığı daha yüksek olmakla beraber total tromboz sıklığında artış eğilimi bulunmuştur (sırasıyla p=0.030, p=0.069). Çok değişkenli analizde, SSK gelişimi için arteriyel tromboz tek bağımsız risk faktörü ve interferon (IFN) bazlı tedavi tek koruyucu faktör olarak bulunmuştur. SSK gelişen ve gelişmeyen hastalar arasında ortanca sağkalım (OS) benzer bulunmuştur. PV'de SSK gelişen hastalarda gelişmeyenlere göre OS daha kısa bulunmuştur (sırasıyla 175±15 ve 321±26 ay; p=0.005).
Sonuç: Çalışmamız Ph-MPN tanısı alan Türk hastalarda SSK'nın prevalansını ve özelliklerini yansıtmaktadır. Arteriyel tromboz artmış SSK riski ile ilişkili bulunmakla beraber IFN bazlı tedavi SSK'ya potansiyel koruyucu etki göstermiştir. Arteriyel trombozu olan Ph- MPN hastalarında SSK taraması yapılması uygun olabilir Bu bulgular Ph-MPN hastalarında, özellikle de yüksek riskli grupta malignite taramasının önemini ve altta yatan mekanizmaların aydınlatılması ve tedavi stratejilerinin optimize edilmesi için daha fazla araştırma yapılmasının önemini vurgulamaktadır
Anahtar Kelimeler: Philadelphia-Negatif Kronik Miyeloproliferatif Neoplazi, sekonder solid kanser, sitoredüktif tedavi, interferon

Introduction:
Philadelphia chromosome-negative myeloproliferative neoplasms (Ph- MPN) are characterized by overproduction of differentiated cells, clonal myeloproliferation, and somatic mutations in JAK2, CALR, MPL or other subclones (1–3). Polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) are classified as Ph- MPNs (4). Major complications of Ph-MPNs are thrombosis, bleeding, transformation to myelofibrosis, acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) (5). One important concern in the course of Ph-MPNs is the risk of development of solid cancers. Some studies have reported increased risk of secondary solid cancer (SSC) in Ph- MPNs while others have found no relationship between Ph- MPN and SSC when compared to population-based cohorts (6–10). The proposed mechanisms accountable for the increased SSC risk include the presence of shared genetic risk factors, an inherent tendency to develop cancer, the impact of antineoplastic agents and a possible link with chronic inflammation or immune dysfunction (11–14).
In a large cohort of Turkish Ph-MPN patients, we aimed to determine the types and frequencies of SSC, identify the risk factors for SSC including the role of cytoreductive therapies and also study the impact of SSC on survival in Ph-MPNs.

Material and Methods:
Patients:
A cohort of 1013 patients diagnosed with Ph- MPNs from 1995 and 2022 under follow up at adult hematology sections of University of Health Sciences Istanbul Bakırköy Dr Sadi Konuk Training and Research Hospital and Istanbul University Medical Faculty were included. All Ph- MPN patients selected fulfilled the 2016 WHO diagnostic criteria. In this retrospective descriptive study, data related to demographic characteristics, laboratory and clinical parameters at the time of diagnosis, JAK2V617F, MPL, CALR mutation status, SSC development status during follow-up, date of diagnosis of SSC, death, presence of history of thrombosis regardless of Ph-MPN diagnosis**,** overall survival (OS) and malignancy-free survival (MFS) were collected from patient reports and electronic medical records. Triple-negative MPN patients were defined as ET or PMF patients, who did not display the JAK2, MPL or CALR driver mutations.
Ethical approval was obtained from the Local Ethics Committee of University of Health Sciences Istanbul Bakırköy Dr Sadi Konuk Training and Research Hospital (study number 2021-18-14).

Statistical Analysis:

Statistical analysis was performed using SPSS 26.0 software. Kolmogorov-Smirnov and Shapiro-Wilk Tests were used to confirm that our data were normally distributed. Median minimum-maximum values were given for data not normally distributed and mean±standard deviation values were given for data with normal distribution. Categorical variables were expressed as number of cases and percentages. Cross-table statistics with Pearson Chi Square Test and Fisher's Exact Test were used to compare categorical variables between the groups. Quantitative data not normally distributed were evaluated with Mann Whitney U and Kruskal Wallis tests. Multivariate analysis was performed using the Cox proportional hazards regression model. Estimations of OS and MFS in PV, ET, and PMF were performed by Kaplan-Meier analysis. For all hypotheses tested, two tailed p-values<0.05 were considered statistically significant.

Results:

Characteristics of Ph- MPN Patients

Our study group comprised of a total of 1013 Ph- MPN patients with a mean follow-up period of 91.5 months (SD 65.1 months). Patient clinical features are outlined in Table 1. The frequencies of diagnosis of ET, PV and PMF were 41.4%, 37.5% and 21.1%, respectively. The median age at Ph- MPN diagnosis was 54 (range 12-88). The median age of ET patients was lower than PV and PMF patients (51, 55 and 57.5 years, respectively; p<0.001).

Sixty-seven patients (6.6%) developed SSC. Among the 67 patients diagnosed with SSC, there were 43 patients with carcinoma (64.2%), 16 with non-melanoma skin cancer (NMSC) (23.9%), 3 with sarcoma (4.5%), 2 with melanoma (3%). In 9 patients, different types of SSC were diagnosed both prior to and after the diagnosis of Ph- MPN. Table 2 summarizes the occurrence of SSCs in our study group.

Comparative analysis of Ph- MPN patients with secondary solid cancer

The mean time to SSC occurrence was 80.03 ± 60.5 months. PV, ET and PMF patients showed no significant difference in the median time to SSC occurrence (p >0.05). The median age at Ph- MPN diagnosis was significantly higher for patients diagnosed with SSC compared to patients with no diagnosis of SSC. (63 (37-78), 54 (12-88), respectively; p<0.001). The frequency of patients aged ≥ 65 years in the patients diagnosed with SSC was higher than patients with no diagnosis of SSC. (44.8% and 26.1%, respectively; p=0.001). Males comprised 64.2% (n=43) and 50% (n=473) of patients diagnosed with SCC and patients with no diagnosis of SCC, respectively. The frequency of males was significantly higher in patients with SSC (p=0.025). Ph- MPN patients diagnosed with SSC and patients with no diagnosis of SSC showed no significant difference in leukocyte count, hemoglobin and hematocrit level, platelet count, spleen size, Ph- MPN diagnostic subgroups, frequencies of driver mutations and follow-up period (p >0.05) (Table 3). There was a trend for increased incidence of total thrombosis in Ph- MPN patients diagnosed with SSC compared to those patients with no diagnosis of SSC (44.8% and 34.5%, respectively; p=0.069). The frequency of arterial thrombosis in Ph- MPN patients diagnosed with SSC was statistically significantly higher compared to patients with no diagnosis of SSC (37.3% and 25.3%, respectively; p=0.030).

Clinical characteristics of Ph- MPN patients with SSCs stratified by the diagnostic subgroups are summarized in Table 4.

Cytoreductive therapy exposure

Eight out of 141 (5.7%) Ph- MPN patients not exposed to cytoreductive treatment developed SSC while 8 out of 67 Ph- MPN patients diagnosed with SSC had no history of cytoreductive treatment. Regardless of whether hydroxyurea (HU) exposure was as a single line of cytoreductive treatment or as a part of multiple lines of cytoreductive treatment, the rate of SSC among patients exposed to hydroxyurea (HU) was 7%. The rates of SSC for Ph- MPN patients exposed to ruxolitinib (RUX), anagrelide and interferon (IFN)-based therapy were 5.3, 4%, 2.1%, respectively. A trend towards a decrease in SSC development was observed with IFN treatment compared to the non-IFN group (3% and 97%, respectively; p = 0.066) (Table 3).

For Ph- MPN patients under cytoreductive treatment, the impact of first and second-line treatments on the development of SSC was examined. The rate of SSC was significantly higher in patients with exposure to HU as first-line monotherapy compared to patients with exposure to HU as a part of multiple lines of cytoreductive treatment and patients without exposure to HU (7.8% and 4.6%, respectively, p = 0.046) (Table 3).

The impact of cytoreductive treatment options on the subtype of SSC diagnosed was examined. It was determined that 63.8% of SSCs diagnosed in patients exposed to HU were carcinomas, 25.9% were NMSC and 3.4% were concomitant carcinoma and NMSC. The difference in the rates of aforementioned SSC subtypes diagnosed was not significant (p >0.05). There was no significant difference across SSC subtypes diagnosed in patients exposed to anagrelide or IFN-based therapy. Five patients with RUX exposure developed SSC, all of which were NMSC while 11 of 62 (17.7%) Ph- MPN patients without exposure to RUX developed SSC (p=0.009). All the 5 patients, who were exposed to RUX and developed SSC, had previous history of HU exposure and 1 of those 5 patients had previous history of exposure to anagrelide. Of the 18 Ph- MPN patients who developed NMSC, 17 had been exposed to HU.

Multivariate Analysis:
We performed cox regression analysis to investigate the impact of patient age ≥ 65, male gender, arterial thrombosis, HU as first-line monotherapy and IFN-based therapy on the time to development of SSC. After adjustment for confounding variables, occurrence of arterial thrombosis remained independently associated with risk of SSC (odds (OR) ratio 2.024; 95% CI 1.100 to 3.724; p=0.023). SSC was independently prevented by IFN-based therapy (OR 0.101; 95% CI 0.11 to 0.967; p=0.047 (Figure 1). In multivariate analysis, patient age ≥ 65, male gender and HU as first-line monotherapy lost their significance on the time to development of SSC.

Median survival and Malignancy-free survival
Median OS in patients diagnosed with SSC and in patients with no diagnosis of SSC were 273 months and 195 months, respectively (p>0.05). PV patients diagnosed with SSC had significantly worse median OS compared to PV patients with no diagnosis of SSC (175±15 months 95% CI: 144-206 and 321±26 months 95% CI: 144-206 270-372, respectively; p=0.005). ET and PMF patients stratified by the status of SSC development showed no significant difference in OS. Mean MFS was 359.7 months (95% CI: 339-380) in the total cohort (Figure 2). There was no difference in MFS between PV and ET, PMF patients and median MFS has yet not been reached.

Discussion:
The most common types of cancer detected in our study population after exclusion of basal cell carcinoma were breast cancer, prostate cancer and lung cancer Our finding is in accordance with the 2020 Global Cancer Observation Data (GLOBOCAN) database, which reports the aforementioned cancers as the three most common type of cancer in the general population, but the distribution frequencies and order are different for our Ph-MPN patients (15).

In the study of Khanal et al., which included PV patients, the frequency of SSC was higher in patients aged ≥60 years(16). Similarly, Brunner et al. reported an increased risk of secondary cancer in Ph- MPN patients with advanced age (17). Consistent with previous data, the median age at Ph- MPN diagnosis in our cohort was older and the frequency of patients aged ≥65 years at diagnosis was higher in our patients diagnosed with SSC compared to our patients with no diagnosis of SSC. Yet on our multivariate analysis, patient age ≥65 showed no independent impact on SSC diagnosis. Our observation was contrary to the findings by Zhang et al., who had identified patient age ≥65 as a risk factor for developing secondary cancer in MPN patients on their multivariate analysis (18) .

Among Ph-MPN patients, a higher male frequency for SSC diagnosis was reported in some studies while others reported no difference in sex frequency (18,19). In our study, the frequency of males was higher in patients diagnosed with SSC. However, no impact of gender on SSC development was observed on multivariate analysis. Zhang et al. found no relationship with JAK2V617F mutation and development of SSC (18). Similarly in our study, Ph-MPN patients diagnosed with SSC and patients with no diagnosis of SSC showed no difference for the frequency of triple negative mutated, JAK2V617F, CALR, MPL mutated Ph-MPN patients. In line with our findings, Barbui et al. reported no relationship with the aforementioned mutations and diagnosis of SSC(20). Moreover, the incidence of PV, PMF and ET were similar between our patients diagnosed with SSC and patients with no diagnosis of SSC.

There is conflicting data about the relationship between secondary cancers and arterial thrombosis (18,20). In the study by Barbui et al., which included 647 Ph- MPN patients diagnosed with cancer and 1234 matched Ph- MPN patients without cancer diagnosis, the frequency of secondary cancers was higher in Ph- MPN patients with arterial thrombosis (20). Yet, the secondary cancers diagnosed in that study included both solid and hematological cancers. Zhang et al. had reported that arterial thrombosis after MPN diagnosis did not increase the risk of secondary solid or hematological cancers (18). Our study reported a higher frequency of arterial thrombosis for patients diagnosed with SSC than patients with no diagnosis of SSC. On our multivariate analysis, arterial thrombosis emerged as a predictor of SSC. Chronic inflammation may be a common pathogenic mechanism between arterial thrombosis and secondary cancer in MPN patients (21,22). In agreement with previous studies, the frequency of venous thrombosis was not different between our Ph-MPN patients diagnosed with SSC and patients with no diagnosis of SSC (18,20).

The impact of HU therapy on secondary cancers in Ph-negative MPNs is still a matter of debate. Kissova et al. reported higher risk of SSC in patients treated with HU than patients treated with other cytoreductive therapies(23). In other studies which included Ph- MPN patients diagnosed with solid or hematologic cancers, a significant relationship between HU and SSC had not been demonstrated (18,20,24). In our study, the frequency of SSC tended to be higher in patients on HU monotherapy compared to patients not exposed to HU. However on multivariate analysis, we did not demonstrate HU monotherapy as an independent risk factor for SSC. Our patients exposed to HU showed no significant difference for the subtypes of solid cancers diagnosed. In the cancer-specific multivariate analysis of the study by Barbui et al., HU exposure was associated with a two-fold higher risk of NMSC regardless of exposure to multiple lines of therapy or monotherapy(20). The contradictory result obtained in the study by Barbui et al. may be attributed to the larger number of enrolled patients diagnosed with cancer.

Hansen et al. demonstrated that the risk of developing solid cancer on HU monotherapy was significantly higher than on IFN (25). In the study by Hansen et al., it was demonstrated that patients treated with HU had a tendency to show a higher risk of developing skin cancer while skin cancer developed only in 1 patient exposed to IFN (25). In our study, NMSC and malign melanoma did not develop in patients exposed to IFN. However, some other studies showed no association between IFN therapy and SSC risk (18,20). The frequency of SSC diagnosis showed a tendency to be lower in our patients exposed to IFN-based therapy compared to non-exposed patients. Furthernore, a protective effect of IFN-based therapy against development of SSC was demonstrated on Cox multivariate analysis.

Several previous studies have demonstrated that induction of molecular remission by early initiation of IFN, a drug with potential to reduce chronic inflammation and prohibit clonal expansion, reduces thrombohemorrhagic complications, myelofibrotic or leukemic transformation and the rate of development of secondary cancers (13,26).

Barbui et al. reported that the risk of secondary cancer in Ph-MPN patients exposed to RUX was almost four-fold higher than those not exposed to RUX and that the increased risk was limited to NMSC (20). We observed a significant relationship between RUX exposure and NMSC development. In our study, the 5 patients, who developed solid cancer under RUX, were diagnosed with NMSC. Yet, all of the 5 patients were exposed to HU and 1 patient was exposed to anagrelide. Therefore, in our study, the relationship between RUX and the risk of NMSC is disputable.

To our knowledge, this is the first study focusing on the relationship between SSC and OS in Ph- MPN. In our study, there was no difference in OS between Ph- MPN patients diagnosed with SSC and patients with no diagnosis of SSC. However, analysis across Ph- MPN subcategories demonstrated that PV patients diagnosed with SSC had significantly shorter OS. Some previous studies had reported poor OS in Ph- MPN patients developing secondary cancers (18,27,28). Yet in contrast to our study population, the secondary cancers reported were not limited to SSC, but also included hematological malignancies. Differences in the Ph- MPN subgroup analysis should be confirmed by studies including higher number of patients.

In conclusion, our results imply that in a large series of Ph- MPN patients, the most common type of SSC diagnosed was carcinoma and that patients diagnosed with SSC are older at diagnosis of Ph-MPN and are more frequently males. HU exposure as first-line monotherapy was associated with increased risk of SSC. However, on multivariate analysis including IFN-based therapy and arterial thrombosis was performed, there was no significant impact of age ≥65, male gender and exposure to HU as first-line monotherapy on SSC risk. In patients diagnosed with SSC, there was a trend for increased incidence of total thrombosis and a significant increase in incidence of arterial thrombosis. The protective effect of INF-based therapy against SSC was of borderline significance but became significant when multivariate analysis was performed. RUX exposure was associated with a higher risk of NMSC compared to patients not exposed to RUX. In the entire cohort, there was no significant OS difference between Ph- MPN patients diagnosed with SSC and patients with no diagnosis of SSC. PV patients diagnosed with SSC had a significantly worse median OS compared to PV patients with no diagnosis of SSC.

Study Limitations:

The limitations of our study are its retrospective design and the lack of a cancer database providing the cumulative incidence with which we can compare our cohort. Our Ph- MPN study population consists of patients, who referred to the two centers between 1995 and 2022. Thus, it is not possible to compare our data with the cumulative cancer incidence in our country. The other limitation is the lack of information regarding the duration and cumulative dose of cytoreductive therapy exposed. Thus, our findings may be insufficient to demonstrate a clear relationship between SSC and cytoreductive therapy. The strengths of our study are the recruitment of a larger Ph- MPN population than some previous studies, inclusion of PV, ET and PMF patient subgroups enabling separate analysis of SSC development in Ph- MPN subcategories, long follow-up period and multicenter study design.

Our study contributes to the literature by providing the first analysis of the relationship between Ph-MPN and malignancies limited to solid cancers in a relatively large patient population. For Ph- MPN, malignancy screening seems to gain more importance in patients with arterial thrombosis. Further studies are needed to determine whether MPN patients are predisposed to SSC regardless of the use of cytoreductive therapy, to determine whether the duration and cumulative dose of cytoreductive therapy exposed have an impact on SSC occurrence, to elucidate the role of HU or RUX for increased risk of SSC in MPNs, to confirm the potential protective effect of IFN from SSC and to figure out other factors that may lead to the emergence of SSC. Our data need to be confirmed with further studies enrolling more patients.

Ethics:

Ethics Committee Approval: Ethical approval was obtained from the Local Ethics Committee of University of Health Sciences Istanbul Bakırköy Dr Sadi Konuk Training and Research Hospital (study number 2021-18-14).

Informed Consent: Retrospective study.

Authorship Contributions: Concept F.H.; Design: F.H., İ.Y.H.; Data Collection or Processing: Ö.N.A., E.A.; Analysis or Interpretation: Ö.N.A., E.G.; Literature Search: Ö.N.A, A.D.A, E.G., M.N. Writing: F.H., İ.H.Y., E.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References:

1. Lundberg P, Karow A, Nienhold R, Looser R, Hao-Shen H, Nissen I, et al. Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms. Blood. 2014 Apr 3;123(14):2220–8.
2. Tefferi A, Pardanani A. Myeloproliferative Neoplasms. JAMA Oncol. 2015 Apr 1;1(1):97.
3. Grinfeld J, Nangalia J, Baxter EJ, Wedge DC, Angelopoulos N, Cantrill R, et al. Classification and Personalized Prognosis in Myeloproliferative Neoplasms. New England Journal of Medicine. 2018 Oct 11;379(15):1416–30.
4. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391–405.
5. Barbui T, Finazzi G, Falanga A. Myeloproliferative neoplasms and thrombosis. Blood. 2013 Sep 26;122(13):2176–84.
6. Stempel JM, Wang R, Shallis RM, Huntington SF, Zeidan AM, Neparidze N, et al. Second Malignancies Among Older Patients with Classical Myeloproliferative Neoplasms Treated with Ruxolitinib. Blood. 2022 Nov 15;140(Supplement 1):11004–6.
7. Frederiksen H, Farkas DK, Christiansen CF, Hasselbalch HC, Sørensen HT. Chronic myeloproliferative neoplasms and subsequent cancer risk: a Danish population-based cohort study. Blood. 2011 Dec 15;118(25):6515–20.
8. Marchetti M, Ghirardi A, Masciulli A, Carobbio A, Palandri F, Vianelli N, et al. Second cancers in MPN: Survival analysis from an international study. Am J Hematol. 2020 Mar 22;95(3):295–301.
9. Susini MC, Masala G, Antonioli E, Pieri L, Guglielmelli P, Palli D, et al. Risk of second cancers in chronic myeloproliferative neoplasms. Blood. 2012 Apr 19;119(16):3861–2.
10. Landtblom AR, Bower H, Andersson TML, Dickman PW, Samuelsson J, Björkholm M, et al. Second malignancies in patients with myeloproliferative neoplasms: a population-based cohort study of 9379 patients. Leukemia. 2018 Oct 30;32(10):2203–10.
11. Finazzi G, Ruggeri M, Rodeghiero F, Barbui T. Second malignancies in patients with essential thrombocythaemia treated with busulphan and hydroxyurea: long-term follow-up of a randomized clinical trial. Br J Haematol. 2000 Sep 24;110(3):577–83.
12. Hasselbalch HC. Chronic inflammation as a promotor of mutagenesis in essential thrombocythemia, polycythemia vera and myelofibrosis. A human inflammation model for cancer development? Leuk Res. 2013 Feb;37(2):214–20.
13. Hasselbalch HC. Perspectives on the increased risk of second cancer in patients with essential thrombocythemia, polycythemia vera and myelofibrosis. Eur J Haematol. 2015 Feb 16;94(2):96–8.
14. Cumbo C, Anelli L, Zagaria A, Coccaro N, Tarantini F, Specchia G, et al. Second Cancer Onset in Myeloproliferative Neoplasms: What, When, Why? Int J Mol Sci. 2022 Mar 15;23(6):3177.
15. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May 4;71(3):209–49.
16. Khanal N, Giri S, Upadhyay S, Shostrom VK, Pathak R, Bhatt VR. Risk of second primary malignancies and survival of adult patients with polycythemia vera: A United States population-based retrospective study. Leuk Lymphoma. 2016 Jan 2;57(1):129–33.
17. Brunner AM, Hobbs G, Jalbut MM, Neuberg DS, Fathi AT. A population-based analysis of second malignancies among patients with myeloproliferative neoplasms in the SEER database. Leuk Lymphoma. 2015 Jul 9;1–4.
18. Zhang Y, Han Y, Teng G, Du C, Gao S, Yuan W, et al. Incidence and risk factors for second malignancies among patients with myeloproliferative neoplasms. Cancer Med. 2023 Apr 2;12(8):9236–46.
19. Pettersson H, Knutsen H, Holmberg E, Andréasson B. Increased incidence of another cancer in myeloproliferative neoplasms patients at the time of diagnosis. Eur J Haematol. 2015 Feb 1;94(2):152–6.
20. Barbui T, Ghirardi A, Masciulli A, Carobbio A, Palandri F, Vianelli N, et al. Second cancer in Philadelphia negative myeloproliferative neoplasms (MPN-K). A nested case-control study. Leukemia. 2019 Aug 29;33(8):1996–2005.

21. Hasselbalch HC. Perspectives on chronic inflammation in essential thrombocythemia, polycythemia vera, and myelofibrosis: is chronic inflammation a trigger and driver of clonal evolution and development of accelerated atherosclerosis and second cancer? Blood. 2012 Apr 5;119(14):3219–25.
22. Bhuria V, Baldauf CK, Schraven B, Fischer T. Thromboinflammation in Myeloproliferative Neoplasms (MPN)—A Puzzle Still to Be Solved. Int J Mol Sci. 2022 Mar 16;23(6):3206.
23. Kissova J, Ovesna P, Penka M, Bulikova A, Kiss I. Second malignancies in philadelphia-negative myeloproliferative neoplasms-single-center experience. Anticancer Res. 2014 May;34(5):2489–96.
24. Wang R, Shallis RM, Stempel JM, Huntington SF, Zeidan AM, Gore SD, et al. Second malignancies among older patients with classical myeloproliferative neoplasms treated with hydroxyurea. Blood Adv. 2023 Mar 14;7(5):734–43.
25. Hansen IO, Sørensen AL, Hasselbalch HC. Second malignancies in hydroxyurea and interferon-treated Philadelphia-negative myeloproliferative neoplasms. Eur J Haematol. 2017 Jan 1;98(1):75–84.
26. Hasselbalch HC. Perspectives on chronic inflammation in essential thrombocythemia, polycythemia vera, and myelofibrosis: is chronic inflammation a trigger and driver of clonal evolution and development of accelerated atherosclerosis and second cancer? Blood. 2012 Apr 5;119(14):3219–25.
27. Hong J, Lee JH, Byun JM, Lee JY, Koh Y, Shin DY, et al. Risk of disease transformation and second primary solid tumors in patients with myeloproliferative neoplasms. Blood Adv. 2019 Nov 26;3(22):3700–8.
28. Marchetti M, Ghirardi A, Masciulli A, Carobbio A, Palandri F, Vianelli N, et al. Second cancers in MPN: Survival analysis from an international study. Am J Hematol. 2020 Mar 22;95(3):295–301.

Table 1

	MPN (n=1013)	**PV (n=380)**	**ET(n=419)**	**PMF(n=214)**	**p****	**PV vs ET***	**PV vs PMF***	**ET vs PMF***
Gender **Female. n (%)** **Male. n (%)**	497 (49.1%) 516 (50.9%)	122 (32.1%) 258 (67.9%)	266 (63.5%) 153 (36.5%)	109 (50.9%) 105 (49.1%)	**<0.001**	**<0.001**	**<0.001**	**0.002**
Age at MPN diagnosis, median (range) **<65, n (%)** **≥65, n (%)**	54 (12-88) 736 (72.7%) 277 (27.3%)	55 (17-84) 284 (74.7%) 96 (25.3%)	51 (12-88) 312 (74.5%) 107 (25.5%)	57.5 (21-84) 140 (65.4%) 74 (34.6%)	**<0.001** **0.028**	**0.029** 0.926	**0.008** **0.016**	**<0.001** **0.017**
JAK2V617F n (%)	730 (72.1%)	305 (80.3%)	269 (64.2%)	156 (72.9%)	<0.001	<0.001	0.039	0.019
CALR n (%)	71 (7%)	.	58 (13.8%)	13 (6.1%)	.	.	.	0.003
MPL n (%)	4 (0.4%)	.	3 (0.7%)	1 (0.4%)	.	.	.	1.000
Triple negative n (%)	136 (13.4%)	.	90 (21.5%)	46 (21.5%)	.	.	.	0.996
WBC at MPN diagnosis, median (range)	10400 (2300-94000)	10795 (2510-34300)	9900 (4200-51400)	11350 (2300-94000)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
HB at MPN diagnosis, median (range)	14.7 (5.5-24.5)	17.8 (11.4-24.5)	13.6 (6.7-17.1)	11.4 (5.5-19.5)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
HCT at MPN diagnosis, median (range)	44.5 (14-85)	54 (36-85)	41 (21-55.5)	35.4 (14-62.7)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
PLT at MPN diagnosis, median (range)	636000 (28000-2786000)	(40600-1818000)	853000 (110000-2786000)	425500 (28000-230	**<0.001**	**<0.001**	0.204	**<0.001**
Spleen size at MPN diagnosis, median (range)	120 (70-340)	120 (87-260)	120 (75-301)	178 (70-340)	**<0.001**	0.113	**<0.001**	**<0.001**
CV Risk n(%)	716(70.7%)	300(78.9%)	278(66.3%)	138(64.5%)	**<0.001**	**<0.001**	**<0.001**	**0.640**

Thrombosis, n (%) **Arterial, n (%)** **Venous, n (%)**	356 (35.1%) 264(25.1%) 92(12.3%)	144(37.9%) 110(28.9%) 42(11.1%)	138(32.9%) 107(25.2%) 48(11.5%)	74(34.6%) 47(22%) 34(15.9%)	0.335 0.168 0.184	0.143 0.279 0.857	0.421 0.064 0.090	0.678 0.321 0.116
Cytoreductive Therapy, n (%) **Hydroxyurea, n (%)** **IFN, n (%)** **RUX,n (%)**	871(86%) 831(82%) 94(9.3%) 95(9.4%)	314(82.6%) 311(81.8%) 16(4.2%) 15(3.9%)	355(84.7%) 327(78%) 59(14.1%) 5(1.2%)	202(94.4%) 193(90.2%) 19(8.9%) 75(35%)	**<0.001** **<0.001** **<0.001** **<0.001**	0.425 0.181 **<0.001**	**<0.001** **0.006** **0.02** **<0.001**	**<0.001** **<0.001** 0.06 **<0.001**
Secondary Solid Cancer n (%)	67 (6.6%)	31 (8.4%)	26 (6.2%)	10 (4.7%)	0.236	0.284	0.108	0.431

Table 2

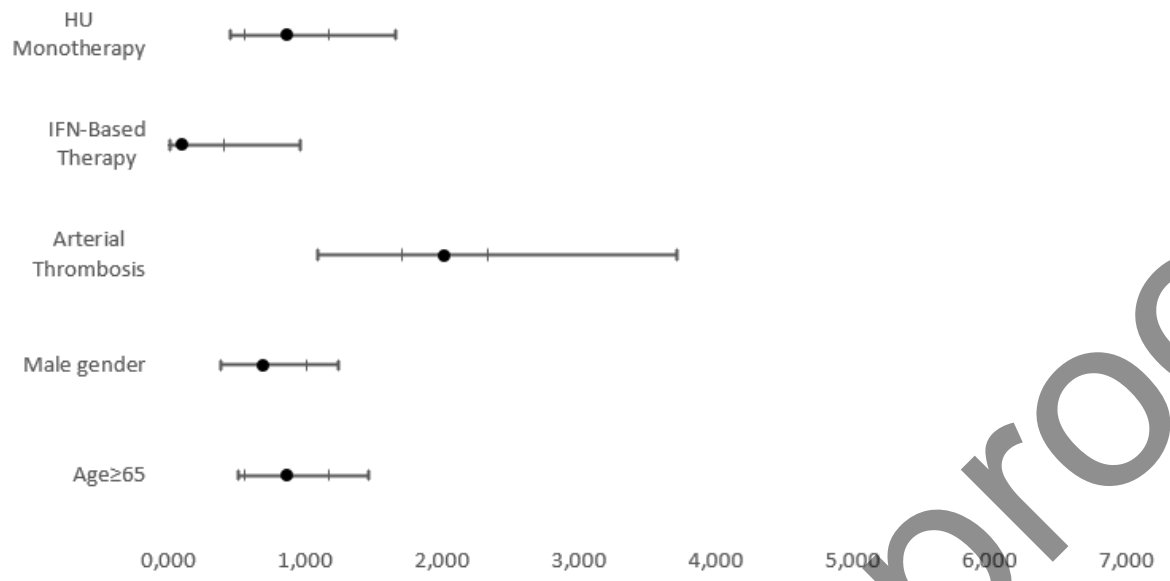
Solid Cancer Subtype After Mpn Diagnosis	**n (%)**
Basal Cell Carcinoma	**11 (16.4%)**
Breast	**8 (11.9%)**
Prostate	**8 (11.9%)**
Lung	**6 (9.0%)**
Blader	5 (7.5%)
Endocrine	4 (6%)
Colorectal	4 (6.0%)
Kidney	3 (4.5%)
Stomach	3 (4.5%)
Squamous Cell Carcinoma	3 (4.5%)
BCC and SCC	2 (3.0%)
Melanoma	2 (3.0%)
Liver	1 (1.5%)
Mesothelioma	1 (1.5%)
Liposarcoma	1 (1.5%)
Over	1 (1.5%)
Head-Neck	1 (1.5%)
BCC and Lung	1 (1.5%)
BCC and Kidney	1 (1.5%)
Lung and Bladder	1 (1.5%)
Total	**67 (100%)**

Table 3

	SSC (n=67)	Non-SSC (n=946)	p
Gender			
Female n (%)	24 (35.8%)	473 (50.0%)	**0.025**
Male n (%)	43 (64.2%)	473 (50.0%)	
Age at MPN diagnosis. median (range)	63 (37-78)	54 (12-88)	**<0.001**
<65 n (%)	24 (35.8%)	24 (35.8%)	**0.001**
≥65 n (%)	43 (64.2%)	43 (64.2%)	
WBC at MPN diagnosis, median (range)	10160 (3900-57260)	10400 (2300-94000)	0.457
HB at MPN diagnosis, median (range)	15.6 (5.8-21)	14.6 (5.5-24.5)	0.734
HCT at MPN diagnosis, median (range)	45.12 (19-69.5)	44.40 (14-85)	0.882
PLT at MPN diagnosis, median (range)	621000 (80000-2786000)	645500 (28000-2631000)	0.803
Spleen size at MPN diagnosis, median (range)	120 (102-320)	120 (70-340)	0.658
Diagnostic Group			
PV n (%)	31 (46.2%)	349 (36.9%)	0.236
ET n (%)	26 (38.8%)	393 (41.5%)	
PMF n (%)	10 (14.9%)	204 (21.6%)	
Driver mutation			
JAK n (%)	49 (73.1%)	681 (84.9%)	
CALR n (%)	7 (10.4%)	65 (8.1%)	0.201
MPL n (%)	1 (1.6%)	3 (0.4%)	
Triple Negative n (%)	10 (14.9%)	53 (6.6%)	
Thrombosis n (%)	30 (44.8%)	326(34.5%)	0.069
Arterial n (%)	25 (37.3%)	239 (25.3%)	0.03
Venous n (%)	6 (9.0%)	118 (12.5%)	0.396
Cytoreductive Therapy			
None Cytoreductive Therapy			
Hydroxyurea (HU)			
Single drug- HU exposure (first-line monotherapy)	8(11.9%)	133 (14%)	0.628
Interferon (IFN)Therapy	58(86.6%)	773 (81.7%)	0.317
Single drug- IFN exposure (first-line monotherapy)	49 (**73.1** %)	576 (60.8%)	**0.046**
Ruxolitinib (RUX)	2 (2.9%)	92 (9.7%)	**0.066**
Single drug- RUX exposure (first-line monotherapy)	1 (**1.45** %)	21 (2.2%)	1.000
Anagrelide	5 (7.5%)	90 (9.5%)	0.578
Single drug- anagrelide exposure (first-line monotherapy)	0 (**0.0** %)	7 (0.73%)	1.000
	4 (5.9%)	96 (10.1%)	0.268
	0 (**0.0** %)	4 (0.4%)	1.000

Table 4

	PV (n=31)	ET(n=26)	PMF(n=10)	p**	PV vs ET*	PV vs PMF*	ET vs PMF*
Gender **Female n (%)** **Male n (%)**	 9 %29.0 22 %71.0	 9 %34.6 17 %65.4	 6 %60.0 4 %40.0	0.204	0.652	0.130	0.260
Age at MPN diagnosis. median (range) **<65 n (%)** **≥65 n (%)**	 62 (43-78) 18 %58.1 13 %41.9	 64.5 (37-78) 13 %50.0 13 %50.0	 59 (49-77) 6 %60.0 4 %40.0	 0.932 0.786	 0.724 0.543	 0.952 1.000	 0.804 0.717
WBC at MPN diagnosis, median (range)	9600 (3900-24800)	9745 (5600-24500)	14100 (4200-57260)	0.188	0.496	0.076	0.174
HB at MPN diagnosis, median (range)	17.2 (13.5-21)	13.75 (6.7-16.5)	10.85 (5.8-16.1)	**<0.001**	**<0.001**	**<0.001**	**0.039**
HCT at MPN diagnosis, median (range)	51.6 (38.4-9.5)	40.7 (22-47)	32.3 (19-49)	**<0.001**	**<0.001**	**<0.001**	0.077
PLT at MPN diagnosis, median (range)	375000 (93000-1246000)	848000 (453000-2786000)	331500 (80000-1267000)	**<0.001**	**<0.001**	0.671	**0.005**
Spleen Size (mm) at MPN diagnosis. median (range)	120 (110-200)	120 (114-180)	195 (102-320)	**<0.001**	0.306	**<0.001**	**<0.001**
Driver mutation **JAK n (%)** **CALR n (%)** **MPL n (%)** **Triple Negative n (%)**	 24 %77.4 . . .	 17 %65.4 5 1 3	 8 %80.0 1 0 1	 0.516	 0.314	 1.000	 0.688
Thrombosis n (%) **Arterial n (%)** **Venous n (%)**	12 10 %32.3 3 %9.7	13 11 %42.3 2 %7.7	5(4 (%40.0) 1(%10.0)	0.436 0.252 0.176	0.156 0.285 0.754	0.455 0.166 0.265	0.652 0.321 0.565
Cytoreductive Therapy **None Cytoreductive Therapy** **Hydroxyurea** **Interferon Therapy** **Ruxolitinib** **Anagrelide**	 5(16.1%) 25(80.6%) 1(3.2%) 0(0.0%) 0(0.0%)	 3(11.5%) 23(88.4%) 1(3.8%) 0(0.0%) 1(3.8%)	 0 (0.0%) 10(100.0%) 0(0.0%) 5(50.0%) 3(30.0%)	 0.464 0.277 0.827 **0.001** **0.002**	 0.715 0.422 1.000 1.000 0.271	 0.310 0.307 1.000 **0.009** **0.011**	 0.545 0.262 1.000 **<0.001** 0.057



	Odds Ratio (95% CI)	p value
HU Monotherapy	0.868 (0.453-1.662)	0.668
IFN-Based Therapy	0.101 (0.011-0.967)	0.047
Arterial Thrombosis	2.024 (1.1-3.724)	0.023
Male Gender	0.698 (0.392-1.243)	0.222
Age≥65	0.869 (0.513-1.472)	0.601

Figure 1. Multivariate Cox regression analysis of factors contributing to SSC development

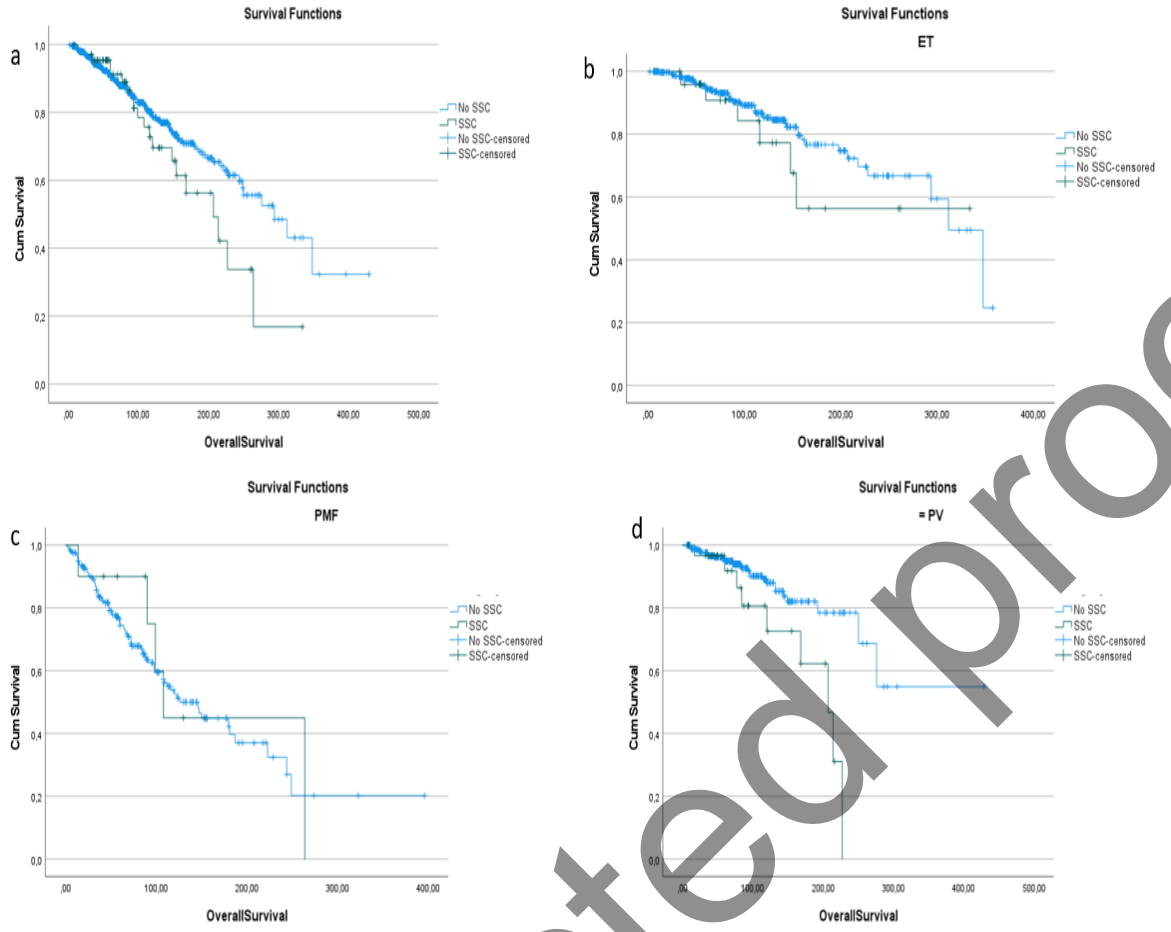


Figure 2. Median OS stratified by development of SSC. a. Entire patient cohort b. ET patients c. PMF patients d. PV patients