was only 36%. Quantitative PET accurately identifies low-risk patients, but a better selection of high-risk patients is warranted to submit them to intensive treatment, and further studies are needed. To increase the risk stratification obtained with quantitative PET, it has been proposed to combine the PET baseline data with the PET response data or other clinical/biologic parameters, a method called integrative PET. In HL, a combination of baseline MTV with interim PET (iPET) has improved risk stratification, and iPET-negative patients could be stratified according to different risk molecular profiles.[5] In this regard, Zucca et al[9] reported in the same series of PMBCL patients that the combination of baseline TLG with end treatment PET more accurately identified patients at risk, with a PPV reaching 47% without a detrimental effect on NPV.

Because early stratification is preferred before the end of first-line therapy, other approaches could be investigated to define new prognostic models: baseline PET data can be combined with other clinical data or with molecular data such as the presence of XPO1 mutations recently reported as a recurrent alteration, which could be a biomarker of prognostic impact[10]; they can also be combined with other PET data such as the heterogeneity of the SUV distribution in the tumor or with parameters obtained from other imaging techniques such as diffusion-weighted magnetic resonance imaging (MRI).

This stimulating study has opened an exciting field. It might be possible to use baseline quantitative FDG-PET to provide an earlier definition of a risk-adapted therapeutic strategy in PMBCL with this new imaging biomarker of tumor metabolism.

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● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Søgaard et al, page 957

Small clots with large impact

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In this issue of *Blood*, Kirstine Søgaard and colleagues report on the relevance of splanchnic vein thrombosis (SVT) as a marker of occult malignant disease.[1]

SVT is an uncommon but potentially life-threatening disease. It can affect the portal vein, mesenteric veins, splenic vein, or suprahepatic veins in Budd-Chiari syndrome, with symptoms varying from asymptomatic cases detected during imaging procedures to symptoms of acute abdomen or active gastrointestinal bleeding.[2-4] Many SVT events are caused by underlying clinical conditions such as liver cirrhosis, pancreatitis, inflammatory bowel disease, or abdominal surgery.[2,3,5]

However, SVT is also commonly associated with solid abdominal cancer, Philadelphia-negative myeloproliferative neoplasms, or JAK2V617F mutation. Although most SVT events occur during cancer therapy or are incidentally detected during restaging of malignancies, the diagnosis of SVT may also precede the diagnosis of these malignant conditions.[3] It was with this in mind that the authors set out to use large nationwide linked health care databases in Denmark to identify patients with a newly diagnosed SVT to study the prognostic relevance of SVT for later cancer occurrence and survival.

For us, this paper contributes outstandingly to our knowledge on the relevance of SVT for the following reasons:

- This study, which evaluated 1191 SVT cases, is the largest SVT study published so far.
- The applied methodology is rigorous, because it uses nationwide linked health care databases with unique patient identifiers. These databases cover not only diagnoses and hospitalizations but also comorbidities, treatments, and outcomes, including details on mortality. Such a database system has never been used to study the prognostic relevance of SVT. With this methodology, absolute risks and standardized incidence ratios for developing cancer in the years after SVT diagnosis could be calculated.
- The same methodology allowed a matched-pair comparison with cancer patients without SVT and, therefore, a detailed assessment of the contribution of SVT to short-term mortality in cancer patients.

The main findings of this paper were:

1. SVT is a marker of occult solid tumors, such as liver and pancreatic cancer, and not only of myeloproliferative neoplasms, as previously shown by a number of studies.[6]

2. SVT is a prognostic factor for short-term survival in patients diagnosed with liver and pancreatic cancer.

Readers may feel that these findings are hardly surprising, since it is known that patients with unprovoked venous thromboembolism (VTE) in general are at higher risk of occult malignant disease. Furthermore, it may be regarded as standard

knowledge that VTE contributes to cancer mortality. Although these considerations may be justified, the present study has the potential to put them into a better perspective.

Recent studies (many of which used extensive cancer screening) that evaluated the risk of being diagnosed with cancer after an episode of unprovoked VTE (classically leg vein thrombosis or pulmonary embolism) consistently established a 4% to 6% risk of receiving a cancer diagnosis within the next 12 months.[7-10] In contrast, the present study demonstrated that already within the first 3 months after SVT, the absolute risk of receiving a cancer diagnosis was as high as 8.0%. This translates into 33-fold increased short-term cancer probability compared with the standard population. Even after 12 months, the standardized incidence ratio (SIR) of cancer in SVT patients was 2.7. Therefore, SVT seems to be a much more potent predictor of occult cancer than unprovoked "classic" VTE.

The SIR for a 3-month cancer diagnosis was especially high for liver (SIR 1800), hematologic malignancies (SIR 765), pancreatic cancer (SIR 250), and "smoking-associated" cancer types such as lung, stomach, or bladder cancer (SIR 3-14), which indicates a high specificity of SVT to predict certain subtypes of cancer, because other cancer types such as colon, rectum, breast, uterus, or prostate cancer were not predicted by SVT. Such a specificity, to our knowledge, has not been demonstrated for unprovoked deep vein thrombosis of the lower limbs or pulmonary embolism.

Patients with liver and pancreatic cancer and SVT demonstrated a 1.5-fold increase of mortality compared with those with similar cancer types and stages without SVT, which was only statistically significant for the 3-month mortality rate ratio of liver cancer patients. In contrast, SVT did not have an impact on mortality in patients with myeloproliferative neoplasms. This may be explained by the longer patient survival in this latter group, suggesting that only a more extended period of follow-up would have detected any meaningful difference related to the occurrence of SVT and by a more favorable impact of disease-specific therapies after the diagnosis of occult myeloproliferative neoplasm as compared with liver or pancreatic cancer. Therefore, the prognostic value of VTE (and especially that of SVT) may vary considerably across different cancer types, which may also be relevant for SVT treatment decisions.

Thus, the contribution of the study by Kirstine Søgaard and coworkers in this issue of *Blood* improves our knowledge of a relatively rare disease and is hypothesis generating for further research.

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● ● ● IMMUNOBIOLOGY

Comment on Mamonkin et al, page 983

Engineered T cells can fight malignant T cells

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In this issue of *Blood*, Mamonkin and colleagues[1] report genetically engineered T cells with specificity for the lineage marker CD5 selectively kill T-lymphoma but not normal T cells, although both express the CD5 target antigen.

In the past few years, we have seen tremendous progress in the clinical application of T-cell therapy for the treatment of hematologic malignancies. Genetic-engineering technologies, based primarily on retro- and lentiviral vectors, have enabled the rapid and reliable production of therapeutic T cells with desired antigen specificity.[2,3] The most dramatic success was seen with therapeutic T cells engineered to express a chimeric antigen receptor (CAR) with specificity for CD19, a lineage marker expressed in B-cell malignancies and also in normal B cells.[4-6] Treatment of patients resulted in the effective elimination of malignant B cells, but required long-term antibody replacement therapy as the therapeutic T cells also killed normal B cells.

It was anticipated that a similar strategy would not work to target T-cell tumors. Redirecting T-cell specificity toward a T-cell marker may trigger mutual killing of the therapeutic T cells prior to infusion, and after infusion it may result in the elimination of endogenous T cells, leading to a severe form of immunodeficiency that, unlike B-cell deficiency, is not easily treatable.

However, in this issue of *Blood*, Mamonkin et al used retroviral gene transfer into primary human T cells to demonstrate that targeting the CD5 antigen enables therapeutic T cells to selectively kill human T-cell malignancies.[1] This is somewhat surprising, considering