Cancer and thrombosis
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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE
Chapter 1

PREFACE

“In 20 years, cancer will be a chronic and well-treatable disease for 90% of patients.”
Prof. René Bernards, Dutch cancer researcher, 2013

If René Bernards is proven right, most patients will no longer die from cancer in the near future, but rather live with it as a chronic disease. Continuous advances in our understanding of cancer genetics and interactions between tumor cells and the immune system have led to the development of targeted drugs and immunotherapies that are associated with significant improvements in cancer survival. Consequently, a profound increase in cancer prevalence is to be expected, and this trend is already dawning. Over the past 3 decades, cancer-related mortality has steadily decreased, while cancer incidence has increased in parallel. The 10-year cancer prevalence in The Netherlands has almost doubled since 1999, with about 600,000 registered cancer cases today (Figure 1).

Figure 1. 10-year cancer prevalence, incidence, and mortality for all types of cancer in The Netherlands from 1999 to 2015
The red line represents cancer-related mortality, defined as the number of cancer deaths per 100,000 persons per year, age-adjusted for the European population (European Standardized Rate; right y-axis). The blue line represents cancer incidence, defined as the number of newly diagnosed cancers per year (left y-axis). The black line represents the 10-year cancer prevalence, defined as the number the number of cancer patients still alive with cancer diagnosed in the 10 preceding years (left y-axis).
Source: www.cijfersoverkanker.nl
BACKGROUND
A frequent and burdensome complication of cancer is venous thromboembolism, which encompasses deep vein thrombosis and pulmonary embolism. Nowadays, one in five venous thromboembolism events is related to cancer and it has been estimated that about 10% of cancer patients will develop venous thromboembolism during the course of their disease (Timp et al., Blood, 2013). These figures will continue to rise, as the cancer population grows and ages, and also because of the introduction of novel, thrombogenic anti-cancer therapies. This implies that a broad spectrum of clinicians, including general practitioners, pulmonologists, oncologists, and thrombosis specialists, will have to make an increasing number of decisions about prevention, diagnosis, and treatment of cancer-associated venous thromboembolism in their practices.

AIM AND OUTLINE OF THESIS
Chapter 2 provides a comprehensive overview of the diagnostic and therapeutic management of venous thromboembolism, with a special focus on patients with cancer.

Part I. Prevention
Venous thromboembolism in cancer patients is associated with significant morbidity, mortality, and can delay or interrupt cancer treatment. Keeping in mind that prevention is better than cure, much attention in the last two decades has been directed to evaluating thromboprophylaxis in ambulatory cancer patients. However, this intervention has traditionally been evaluated in unselected groups of cancer patients – regarding cancer as a single entity – while the risk of a first episode of venous thromboembolism varies widely across different tumor types and stages, and is influenced by various patient- and treatment-related factors (Figure 2). For example, the estimated overall venous thromboembolism incidence rate in cancer patients is 4 per 100 person-years, while the risk in patients with metastatic pancreatic cancer is approximately 20-fold higher than in patients with localized prostate cancer. Universal thromboprophylaxis is therefore currently not recommended, because the substantial number needed to treat in the whole cancer population does not outweigh the potential risk of bleeding and the burden of daily subcutaneous injections. There is clearly a need to identify ambulatory cancer patients at high risk of venous thromboembolism in whom thromboprophylaxis would be justified, and to shift to risk stratification, based on clinical prediction scores.
Evaluations of prediction scores for venous thromboembolism in cancer patients are reported in Chapters 3 to 5, in which we particularly focus on the Khorana score, which incorporates tumor type, blood counts, and body mass index. We conducted a multinational prospective cohort study of patients with advanced cancer receiving chemotherapy (Chapter 3), a retrospective cohort study of pancreatic cancer patients (Chapter 4), and an individual patient data meta-analysis of seven randomized controlled trials in which the effect of low-molecular-weight heparin on survival was evaluated (Chapter 5). In Chapter 6, we continue by exploring the potential of the procoagulant activity of extracellular vesicles exposing tissue factor to predict venous thromboembolism in cancer patients. Chapter 7 describes a derivation and validation study of a novel clinical prediction model to identify ambulatory cancer patients at high risk of venous thromboembolism.

**Figure 2. Risk factors for venous thromboembolism in cancer patients**

A schematic overview of the various risk factors for venous thromboembolism in cancer patients roughly ordered by the strength of their association. All factors need to be taken into account to estimate an individual’s absolute risk of venous thromboembolism. For example, a young woman recently curatively treated for local breast cancer and not receiving therapy anymore is at very low risk of developing venous thromboembolism (<1% per year), whereas the risk is very high in an elderly patient in poor condition who receives palliative chemotherapy for metastasized pancreatic adenocarcinoma (~20% per year).
Part II. Diagnosis of venous thromboembolism in cancer patients and cancer in venous thromboembolism patients

In the diagnostic management of cancer-associated venous thromboembolism, clinicians are best not to mirror the approaches that are recommended for venous thromboembolism in patients without cancer. For example, diagnostic algorithms to rule out deep vein thrombosis or pulmonary embolism, which are based on clinical decision rules and D-dimer testing, can perform differently in patients with cancer than in those without cancer. These algorithms may be less efficient in cancer patients (i.e. rule out venous thromboembolism without imaging in a lower proportion of patients) and less safe (i.e. are associated with a higher proportion of false negatives). Whether modifications of the clinical decision rules and D-dimer thresholds can improve efficiency and safety, is as yet unknown.

In the study reported in Chapter 8, the efficiency and safety of a fixed and an age-adjusted D-dimer threshold were evaluated in patients with clinically suspected pulmonary embolism classified as ‘pulmonary embolism unlikely’ by the Wells rule. In Chapter 9, the performance of a simplified version of the Wells rule is compared to the original Wells rule in ruling out pulmonary embolism. In Chapter 10, we reverse the relationship between cancer and venous thromboembolism, by investigating the risk of occult cancer in patients with unprovoked venous thromboembolism and the potential benefit of screening strategies.

Part III. Treatment of venous thromboembolism in cancer patients

Differences between patients with and without cancer matter in the treatment of venous thromboembolism. Vitamin K antagonists are not recommended in patients with cancer, because of the notoriously difficult anticoagulation control in this population, due to interactions with chemotherapy, reduced intake in case of anorexia and nausea, and gastrointestinal malabsorption following chemotherapy-induced mucosal defects and diarrhea. Subcutaneous low-molecular-weight heparin is therefore the preferred treatment for acute venous thromboembolism in cancer patients, after the seminal CLOT trial demonstrated its superior efficacy over vitamin K antagonists. Yet, in many parts of the world, low-molecular-weight heparin is still not widely adopted, for two main reasons: it is expensive and it is burdensome, since it requires daily subcutaneous injections with inherent side effects as bruising and infiltrates. An attractive alternative are direct oral anticoagulants, which, like low-molecular-weight heparin, offer stable pharmacokinetics and pharmacodynamics allowing for fixed dosing. However, their efficacy and safety profile needs to be evaluated in cancer patients before they can be used in clinical practice.
Chapter 11 summarizes the evidence of phase 3 trials that have compared vitamin K antagonists with direct oral anticoagulant for the treatment of acute deep vein thrombosis or pulmonary embolism, with a specific focus on subgroups including cancer patients. In Chapter 12, we provide an in-depth analysis of the subgroup of cancer patients who were enrolled in the Hokusai-VTE study, which evaluated the efficacy and safety of edoxaban in the treatment of acute venous thromboembolism. Finally, in Chapter 13 we describe the rationale and design of the recently completed Hokusai VTE-cancer trial, in which edoxaban was compared to dalteparin for the treatment of cancer-associated venous thromboembolism. The results of this landmark study may lead to a simpler and less burdensome treatment.

Venous thromboembolism can have a profound impact on patients with cancer. This became crystal clear during my first ever night shift as internal medicine resident, when a 59-year old lady recently diagnosed with pancreatic cancer with severe dyspnea and in hemodynamic shock was brought to the emergency department, where she died from a pulmonary embolism. To me, this illustrated the dramatic consequences of cancer-associated venous thromboembolism and made it clearer than ever that this common complication needs to acknowledged, safely prevented, and adequately treated whenever possible.