Gastrointestinal malignancies in high-risk populations = Gastro-intestinale maligniteiten in hoog-risico populaties

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General Introduction

1 GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Second primary malignancies in cancer survivors

Cancer treatment has improved over the past decades, resulting in a better survival of cancer survivors.[1,2] With improved survival, however, it has become clear that long-term cancer survivors have an increased risk of several adverse events, especially when treated for a malignancy at a young age. Different late events can develop after chemotherapy and/or radiotherapy, among which cardiovascular disease, nephrotoxicity, diabetes, psychosocial disorders and the development of second primary malignancies.[3-5] Second primary malignancies account for 20% of cancer diagnosis in the Western world.[3] The occurrence of second primary malignancies has increased over time due to the improved prognosis of cancer patients and increased life expectancy in general (Figure 1).[6]

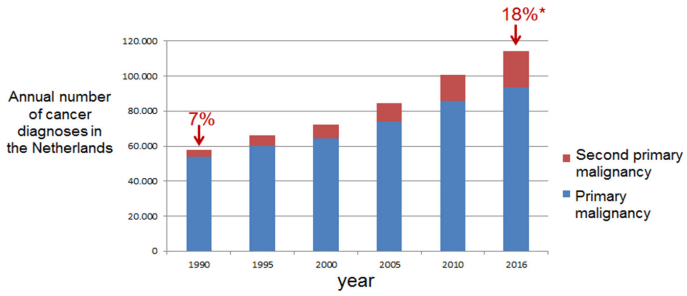

Figure 1 | Occurrence of primary malignancies and second primary malignancies among adults in the Netherlands between 1990 and 2016 (unpublished data of Netherlands Cancer Registry). In the United States, a percentage of 19% of second primary malignancies has been reported.[6]

The development of cancer treatment strategies has already led to an adaption of treatment, taking into account the long-term effects of treatment. Both chemotherapy and radiotherapy have been changed to more accurate and less toxic treatments, with adjustments of the dosage and for radiotherapy also to the size of the radiation field.[7,8] These alterations will result in more precise treatments and also will cause less damage on non-neoplastic (surrounding) tissue.[9] However, the long-term effects of new therapies are not known yet. The development of second primary malignancies is partly due to the late effects of cancer treatment as dose-dependent relationships have been described, but also germline variants, lifestyle factors and environmental factors can be involved.[10] The development of second primary malignancies has been described early after treatment, but also after 10 years up to 40 years after treatment.[3,11]

Further evaluation of the characteristics of second primary malignancies is of importance. If the carcinogenesis of these second primary malignancies differs from that of sporadic malignancies, this could affect preventive options. For certain second primary malignancies, surveillance can be offered in order to reduce the incidence of that malignancy, resulting in a better survival of the cancer survivor. Secondly, differences in pathogenesis could affect treatment options for those malignancies necessitating more personalized treatment.

The increased risk of developing second primary (gastrointestinal) malignancies has been reported for different types of cancer survivors, among which childhood cancer.[12-14] This thesis focusses on second primary gastrointestinal malignancies in Hodgkin lymphoma and testicular cancer survivors, as both malignancies are diagnosed at a relatively young age and data of two large Dutch cohorts were available.[11,15]

Second primary gastrointestinal malignancies in Hodgkin lymphoma survivors

The increased survival for Hodgkin lymphoma survivors has been the result of the introduction of combination chemotherapy and high-energy radiotherapy. However, even though the treatment regimens for Hodgkin lymphoma have changed over time,[16-20] the cumulative incidence of gastrointestinal malignancies did not appear to differ significantly among the different treatment periods of Hodgkin lymphoma treatment, ranging from 1965 through 2000.[11] High doses of (supra- or infradiaphragmatic) radiotherapy, chemotherapy containing alkylating agents (predominately procarbazine-containing chemotherapy) and especially the combination of chemotherapy and radiotherapy have been associated with an increased risk of developing a second primary (gastrointestinal) malignancy in Hodgkin lymphoma survivors.[11,21,22] The increased risk of developing a second primary malignancy is elevated 10 years after the treatment, and remains elevated up to 40 years after treatment.[11]

The risk of developing a gastrointestinal malignancy is about 5-fold higher in Hodgkin lymphoma survivors compared with the general population.[11,21,23,24] A strongly increased risk of gastrointestinal cancer has been shown for patients who were treated with both infradiaphragmatic radiotherapy and procarbazine-containing chemotherapy.[11] Furthermore, younger age at Hodgkin lymphoma diagnosis has been associated with an increased risk of developing a second gastrointestinal malignancy (Figure 2).[21]

A higher relative risk for developing esophageal cancer (4 to 9-fold), gastric cancer (3 to 11-fold) and small bowel cancer (11 to 16-fold) in Hodgkin lym-

phoma survivors has been reported.[25,26] Compared with the general population, Hodgkin lymphoma survivors have a 2 to 7-fold higher risk of developing colorectal cancer.[11-14,21,23,27] The 30 year cumulative incidence of esophageal and stomach cancer was 1.5% and 1.6%, respectively. The cumulative risk for developing colorectal cancer in Hodgkin lymphoma survivors was 0.6% at 20 years and 2.1% at 30 years of follow-up.[21]

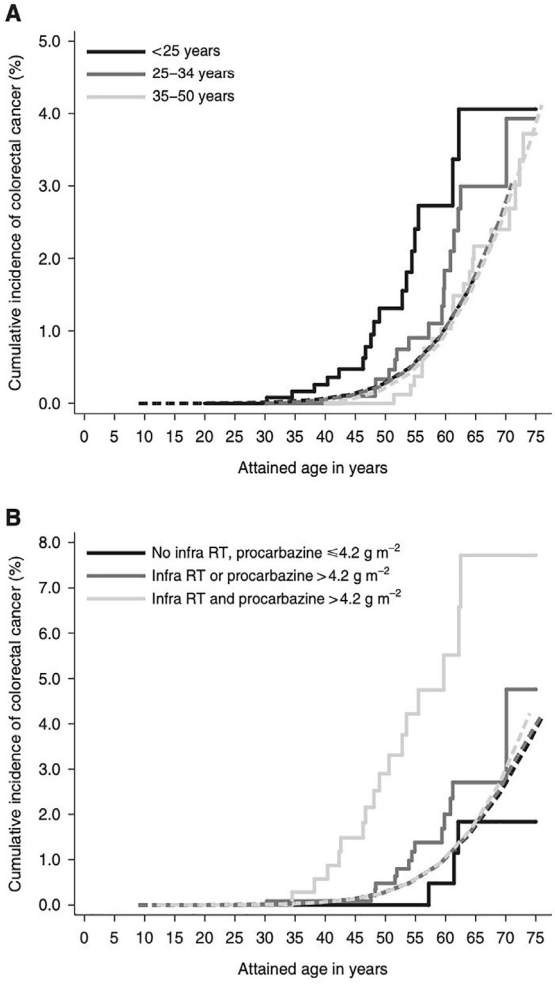

Figure 2 | A. Cumulative incidence of colorectal cancer by age at diagnosis according to age at Hodgkin lymphoma treatment.[21]

B. Cumulative incidence of colorectal cancer by age at diagnosis according to infradiaphragmatic (infra) radiation therapy (RT) and procarbazine dose for Hodgkin lymphoma patients treated before the age of 35 years.[21]

In the Netherlands, we have assembled a large cohort of Hodgkin lymphoma survivors who were alive at least five years after the initiation of the treatment for Hodgkin lymphoma.[11] These Hodgkin lymphoma survivors were retrieved from seven Dutch hospitals. This cohort was used for the retrieval of cases of second primary gastrointestinal malignancies in Hodgkin lymphoma survivors.

Second primary gastrointestinal malignancies in testicular cancer survivors

The introduction of cisplatin-containing chemotherapy has led to improved prognosis of patients with testicular cancer.[28,29] The 10-year survival of patients diagnosed with testicular cancer is currently higher than 95%.[28] The incidence of testicular cancer is increasing and accounts for about 1% of all cancers in men. The main histological types include seminoma and non-seminoma. The treatment strategies differ between these two histological subtypes and stages of the malignancy, but nearly always include orchiectomy. For non-seminoma, treatment can consist of chemotherapy (frequently consisting of cisplatin, etoposide and bleomycin (BEP)) and/or retroperitoneal lymph node dissection as first-line therapy, and sometimes radiotherapy. The treatment for seminoma more frequently consists of radiotherapy, targeting the para-aortic and/or iliac fields but could also consist of platinum-based chemotherapy.

Testicular cancer survivors have an increased risk of developing various second primary malignancies.[15,30-40] Especially (cis)platinum-based chemotherapy has been associated with increased risk of second primary malignancies, including an increased risk for gastrointestinal malignancies.[15,34,40] This increased risk of second gastrointestinal malignancies has also been reported in childhood cancer survivors who received platinum-based chemotherapy with a hazard ratio of 7.9.[13] Moreover, a cisplatin-dose-dependent relationship has been shown for the risk of gastrointestinal second malignancies in testicular cancer survivors, with the hazard ratio increasing by 53% per 100 mg/m^2 increase of platinum-containing chemotherapy (Figure 3).[15] Furthermore, an association between administered infradiaphragmatic radiotherapy dose and the risk for second primary gastrointestinal malignancies was shown, as the hazard ratio increased by 9% per Gray.[15]

The risk for developing a solid malignancy is especially increased from 10 years after treatment and remains significantly elevated for at least 35 years.[30,34] A standardized incidence ratio of 4 to 5 has been reported for developing small bowel cancer among testicular cancer survivors.[15,41] For colorectal cancer, a

hazard ratio of 3.9 has been described in testicular cancer survivors treated with platinum-based chemotherapy.[15]

To study the risk of second primary malignancies in testicular cancer survivors, a large Dutch cohort study was assembled. One year testicular cancer survivors from a multicenter cohort were evaluated to determine the risk of second primary malignancies and identify treatment-related risk factors.[15]

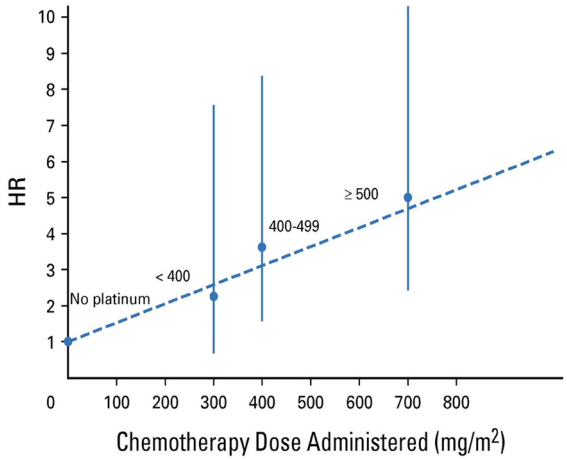

Figure 3 | Risk of second gastrointestinal malignancy in testicular cancer survivors treated with platinum-based chemotherapy increased with a higher dosage of platinum-containing chemotherapy (hazard ratio increased by 0.53 for each additional dosage of 100 mg/m^2 of body surface area of platinum-containing chemotherapy.[15]

Pathogenesis and molecular profile of second primary (gastrointestinal) malignancies

Even though an increased risk for developing second primary gastrointestinal malignancies has been reported, this has not resulted in an alternative clinical approach for these high-risk individuals. This could be the effect of limited knowledge on the pathogenesis and molecular profile of these second primary malignancies. Survival data indicate that second primary colorectal cancers may be different from first primary colorectal cancers.[42] Also, studies have suggested that the carcinogenesis and the subsequent molecular tumor profile of second primary malignancies in cancer survivors may differ from sporadic malignancies,[43-45] as chemotherapy and radiotherapy have been associated with the increased risk of second primary malignancies. In mouse models it has been shown that chemotherapy and radiotherapy can induce tumorigenesis in mismatch repair deficient mice[46-48] and that radiotherapy

can induce a mutational signature in radiation-induced malignancies.[49] A small exploratory study detected a genetic diversity in esophageal cancer in both Hodgkin lymphoma and breast cancer survivors compared with sporadic esophageal cancer.[44] Furthermore, a mutational signatures has previously been described for different cancer therapies in metastatic tumors originating from different tumors.[50]

Besides affecting the tumor tissue of the primary malignancy, anti-cancer treatment has also been shown to induce changes in non-neoplastic tissue. This includes changes within the radiation field,[8,51-56] as well as chemotherapy and radiation therapy induced field cancerization in the body. Various changes on both genetic and epigenetic level have been reported.[57]

Our group has previously reported that mismatch repair deficiency occurred more often in colorectal cancers of patients with a history of Hodgkin lymphoma (24%) compared with colorectal cancer in the general population (11%). This increased frequency was due to biallelic somatic inactivation in the mismatch repair genes, which occurs more frequently in colorectal cancer diagnosed in Hodgkin lymphoma survivors (7/10, 70%) in comparison with colorectal cancer in the general population (8/36, 22%).[58] Based on these findings, we hypothesized that increased frequency of mismatch repair deficiency might also be found in second primary colorectal cancer in testicular cancer survivors. However, whether we can expect higher frequency of mismatch repair deficiency in various types of second primary gastrointestinal cancers is not straight forward, as it has already been shown that mismatch repair deficiency did not occur more frequent in second primary gastric adenocarcinomas compared with primary gastric adenocarcinomas.[59]

Mismatch repair deficiency testing

Evaluating the mismatch repair status is of great importance in sporadic malignancies and second primary malignancies in order to identify Lynch syndrome and because of potential treatment with immune checkpoint inhibitors.[60]

Patients with Lynch syndrome have an increased risk of developing colorectal cancer, but also other malignancies among which endometrial cancer and ovarian cancer, as well as stomach, hepatobiliary, urinary, brain and skin malignancies. Lynch syndrome is caused by mutations in one of four mismatch repair genes (*MLH1, MSH2, MSH6, PMS2* or deletions in 3' region of *EPCAM* gene) and these tumors display microsatellite instability.[61] For individuals diagnosed with Lynch syndrome, recommendations for surveillance of col-

orectal cancer and endometrial cancer have been developed. For colorectal cancer, surveillance has been shown to reduce the incidence and mortality in individuals affected with Lynch syndrome.[62,63] For some malignancies such as cutaneous squamous cell carcinoma, an association with Lynch syndrome has been suggested, but these malignancies are not included yet in the spectrum of tumors associated with Lynch syndrome.[64,65]

Colorectal cancer surveillance in Hodgkin lymphoma and testicular cancer survivors

For individuals with an average-risk of colorectal cancer, fecal immunochemical testing is offered every two years in the Dutch population-based screening program to asymptomatic individuals aged 55 to 75 years old.[66] In high-risk populations for developing colorectal cancer, colonoscopy surveillance is advised, which has been shown to be cost-effective.[62,63,67] In patients with a familial risk for colorectal cancer, the European guideline recommends a colonoscopy every five years in order to reduce colorectal cancer incidence and/or mortality by detecting colorectal cancer at an early stage and/or direct removal precursor lesions of colorectal cancer.[68,69]

Both Hodgkin lymphoma survivors treated with infradiaphragmatic radiotherapy and/or procarbazine-containing chemotherapy and testicular cancer survivors treated with platinum-based chemotherapy have an increased risk of developing colorectal cancer compared with the general population.[15,21] Based on the magnitude of the risk increase, these cancer survivors can be considered a high-risk-group for developing colorectal cancer as the risk of developing colorectal cancer is 2.5–fold higher compared with the general population. Comparable to individuals with familial risk of colorectal cancer, the life-time risk for colorectal cancer is >10% in these cancer survivors. Therefore, a similar surveillance program can be advised to these cancer survivors as for patients with a familial risk of colorectal cancer.[68,69]

Currently, colonoscopy surveillance is not yet implemented in the Dutch follow-up guideline for Hodgkin lymphoma and testicular cancer survivors. Our group previously evaluated the diagnostic yield of colonoscopy surveillance a prospective study of in Hodgkin lymphoma survivors treated with abdominal radiotherapy and/or procarbazine-containing chemotherapy. The participants were offered a colonoscopy, in order to determine whether these Hodgkin lymphoma survivors would benefit from colorectal cancer surveillance.[70] The results were compared with the colonoscopies performed in Dutch asymptomatic individuals who underwent a screening colonoscopy, at a significant higher age (median age 60 years) compared with Hodgkin lymphoma survivors (me-

dian age at colonoscopy 51 years).[71] This prospective study detected a significantly higher prevalence of neoplasia and advanced neoplasia (advanced adenoma (defined as high-grade dysplasia, ≥25% villous component, or ≥10 mm diameter), advanced serrated lesion (defined as dysplasia or ≥10-mm diameter) or colorectal cancer) in Hodgkin lymphoma survivors compared with the control group. The higher prevalence included adenomas and advanced adenoma, but especially more serrated lesions and advanced serrated lesions were detected. Furthermore, serrated polyposis syndrome occurred significantly more frequently in Hodgkin lymphoma survivors.[71,72] Colorectal cancer was not detected in the Hodgkin lymphoma survivors. Based on the significantly higher prevalence of (advanced) neoplasia, colonoscopy surveillance was recommended in Hodgkin lymphoma survivors who were treated with abdominal radiotherapy and/or procarbazine-containing chemotherapy.[72] For testicular cancer survivors treated with platinum-based chemotherapy, the diagnostic yield of colonoscopy surveillance is not yet known.

However, colonoscopy surveillance is quite burdensome. A different, less invasive surveillance strategy could be a stool test – fecal immunochemical test or multi-target stool DNA test – to determine whether occult fecal blood is detectable, and subsequently offer a colonoscopy to these individuals with a positive fecal test or at a positive outcome of the multi-target stool DNA test. In the average-risk population, multi-target stool DNA test has a higher sensitivity for detecting advanced neoplasia in comparison with fecal immunochemical test.[73-75] At this time the diagnostic accuracy of stool tests in high-risk-groups is unknown. A possible advantage of stool test surveillance would be that the participation rate could increase. To determine the most optimal surveillance strategy for colorectal cancer, a cost-effectiveness analysis[76,77] can provide guidance for recommendations in the follow-up guideline of Hodgkin lymphoma and testicular cancer survivors (being colonoscopy or stool test surveillance).

OUTLINE OF THIS THESIS

General outline

This thesis provides insight into the pathogenesis and molecular profile of second primary gastrointestinal malignancies diagnosed in Hodgkin lymphoma and/or testicular cancer survivors. Furthermore, for Hodgkin lymphoma survivors, the stool tests as an alternative surveillance strategy are evaluated. We will determine what the most cost-effective strategy is for colorectal cancer surveillance in this group. This will give guidance to the implementation of surveillance in the follow-up guideline of Hodgkin lymphoma survivors.

Recently, it has been observed that testicular cancer survivors treated with platinum-based chemotherapy also have an increased risk of developing colorectal cancer. A prospective study has been developed to determine the yield of colorectal cancer surveillance in that population and is currently ongoing. Additionally, this thesis will focus on mismatch repair deficiency, as identification of Lynch syndrome could have implications for the patients and implications for treatment choice.

Outline per part/chapter

Part I evaluates the pathogenesis of second primary gastrointestinal malignancies in Hodgkin lymphoma and testicular cancer survivors. **Chapter 2** investigates the gene expression profiles of esophageal squamous cell cancer in Hodgkin lymphoma survivors in comparison with expression profiles of sporadic esophageal squamous cell cancer. **Chapter 3** involves the copy number aberrations (gains or losses on chromosomes) of small bowel adenocarcinoma in Hodgkin lymphoma and testicular cancer survivors. These copy number aberrations are compared with copy number aberrations of sporadic forms of small bowel adenocarcinoma. Furthermore, copy number aberrations of colorectal cancers in Hodgkin lymphoma survivors and sporadic colorectal cancers are evaluated in order to examine whether there exists a possible 'therapy-induced' pattern in copy number aberrations. The clinicopathological features of advanced neoplasia and risk factors for developing (advanced) neoplasia in Hodgkin lymphoma survivors are shown in **chapter 4**. The last chapter of this part, **chapter 5**, evaluates the histopathological and molecular characteristics of colorectal cancer diagnosed in non-seminoma testicular cancer survivors.

Part II gives insight into colorectal cancer surveillance in Hodgkin lymphoma and testicular cancer survivors. Previously it has been shown that Hodgkin lymphoma survivors have a higher prevalence of neoplasia and advanced neoplasia as detected in a prospective multi-center study of Rigter et al.[72]. **Chapter 6** and **chapter 7** will elaborate on this previously performed prospective study. **Chapter 6** evaluates the diagnostic accuracy of different stool tests in detecting advanced neoplasia in Hodgkin lymphoma survivors in order to evaluate whether stool tests could be an effective method for colorectal cancer surveillance. A cost-effectiveness analysis is performed in **chapter 7**, which includes both colonoscopy and stool test surveillance. This analysis determines the most optimal surveillance strategy for Hodgkin lymphoma survivors who received different treatment strategies. **Chapter 8** describes the study protocol for a prospective study of the diagnostic yield of colonoscopy surveillance in testicular cancer survivors treated with platinum-based che-

motherapy. This study will also evaluate the burden of colonoscopy, accuracy of fecal immunochemical test, analysis of platinum in the plasma in order to correlate this with the colonoscopy result and determine the most cost-effective surveillance strategy for this population. These data will be used for recommendations for the follow-up guideline of testicular cancer survivors.

Data on mismatch repair testing is provided in **part III**, including adherence to MMR testing in pT1 colorectal cancer and widening the Lynch syndrome associated tumor spectrum. **Chapter 9** describes the adherence to guidelines regarding mismatch repair deficiency testing in early invasive colorectal cancer (pT1) diagnosed before the age of 70 years in the Dutch population-based screening program. As mismatch repair testing is recommended in all newly diagnosed colorectal cancer, we wanted to evaluate whether differences occurred between locally excised pT1 colorectal cancer and pT1 colorectal cancer removed by oncological resection. **Chapter 10** evaluates whether cutaneous squamous cell carcinomas can be included into the spectrum of Lynch syndrome associated tumors, since an association has been suggested. For other types of skin malignancies an association has already been described with Lynch syndrome.

Finally, **chapter 11** and **chapter 12** includes the general discussion, summary and future perspectives.

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