1. General introduction and outline of this thesis
SECOND PRIMARY CANCER DEVELOPMENT IN CANCER SURVIVORS

Cancer survival has greatly improved over the past decades for many cancer types. The growing population of cancer survivors has given the opportunity to study the late consequences of a prior cancer diagnosis and/or treatment. This research has shown that both radiotherapy and chemotherapy can induce late effects, for example the development of second primary cancers and cardiovascular disease. Second primary cancers are defined as a new primary cancer that occurs in a person who has had cancer in the past. The proportion of all new primary cancers that concerns a second primary cancer in cancer survivors is increasing and currently involves approximately 20% of all cancer diagnoses in the Western world (Figure 1).1,2

The development of second primary cancers is influenced by multiple factors, including genetic predisposition, lifestyle and environmental factors. Furthermore, certain cancer treatments have the (paradoxical) capability to cause cancer, due to mutagenic and genome destabilizing effects.

Figure 1. Occurrence of first and second primary cancers among adults during 1975-2009 in the United States of America.3

Data obtained from SEER (Surveillance, Epidemiology, and End Results). Reprinted with permission. © 2014 American Society of Clinical Oncology. All rights reserved.3
The recognition of long-term damaging effects of certain cancer treatments on healthy tissues and organs has led to an adaptation of the approach of cancer treatment over recent decades. Current decisions regarding cancer treatment involve a balance of disease control against the risk of long-term side effects of treatment.

Firstly, radiation volumes and doses are strongly associated with second primary cancer risk and have been reduced. In addition, radiation techniques have become more accurate. It is expected that these improvements will reduce the increased risk of second primary cancers. The potential risks and benefits of newer techniques, such as proton radiotherapy, are currently uncertain and can so far only be estimated from animal and cellular experiments. Secondly, chemotherapy regimens have been gradually adapted to (presumably) less toxic regimens with lower doses. Chemotherapy regimens that include alkylating agents have a dose-dependent association with increased risks of second primary cancers, including leukemia, lung cancer, stomach cancer, pancreatic cancer and colorectal cancer. Again, the late effects of recently developed agents, such as targeted agents and immunotherapy, are unknown.

Although morbidity and mortality from second primary cancers will hopefully reduce in future cancer survivors, a large population of survivors is currently at risk of developing second primary cancers.

This thesis will further focus on second primary cancer development in survivors of Hodgkin lymphoma, as second primary cancers contribute substantially to their excess morbidity and mortality.

**HODGKIN LYMPHOMA TREATMENT**

Hodgkin lymphoma is a malignant disease of the lymphatic system and occurs in approximately 3 cases per 100,000 persons. The incidence varies by age with a peak incidence in young adults in their twenties and a second peak in older adults, aged over 70 years.

Hodgkin lymphoma arises from germinal center or post-germinal center B cells. Reed/Sternberg cells are detected in classical Hodgkin lymphoma, in the
abundance of reactive bystander cells. Reed/Sternberg cells show deregulated activation of several signaling pathways. However, a key driver genomic alteration is unknown for Hodgkin lymphoma.

Up to the 1950s, Hodgkin lymphoma was incurable. Cure rates have increased to over 80% in current practice, due to the introduction of high-energy radiotherapy and multi-agent chemotherapy regimens. Both radiotherapy and chemotherapy regimens have changed substantially over time.\textsuperscript{16-19}

In the 1950s, local orthovoltage radiotherapy became available for the treatment of Hodgkin lymphoma, which provided the first chance of cure. Tissue infiltration beyond 6 cm became possible after the introduction of linear accelerators in the late 1960s. Common radiotherapy fields above the diaphragm included mantle field, whereas para-aortic, splenic and iliac fields were common fields below the diaphragm. (Figure 2) In the 1960s and 1970s, subdiaphragmatic radiotherapy in combination with supradiaphragmatic radiotherapy (total node or subtotal node radiotherapy) was also frequently given to patients without lymph node involvement below the diaphragm.

\textbf{Figure 2.} Common radiotherapy fields.\textsuperscript{20}
Since the late 1980s, sizes of radiation fields have been reduced to involved field, involved node or involved site radiotherapy. In addition, prescribed doses have decreased from approximately 40 Gray to 15-30 Gray. Currently, radiotherapy techniques are still evolving in order to provide an effective treatment with a limited dose to healthy tissues.

Advanced stages of Hodgkin lymphoma became curable after the introduction of MOPP chemotherapy (mechlorethamine, vincristine, procarbazine, prednisone) in the 1960s. In the 1980s, regimens evolved into hybrid MOPP-ABV and alternating MOPP/ABVD (mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, (dacarbazine)).

Additional multi-agent chemotherapy regimens have been developed, including ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). These regimens are still used to treat Hodgkin lymphoma patients, either alone or in combination with radiotherapy.

The efficacy of targeted agents and immunotherapy is being explored for HL treatment. Promising results have been achieved with agents such as brentuximab vedotin (an antibody drug that targets CD30), nivolumab and pembrolizumab (antibodies that block the interaction between PD-1 and its ligands, thereby activating T lymphocytes).

GASTROINTESTINAL CANCER RISK IN HODGKIN LYMPHOMA SURVIVORS

The risk of developing gastrointestinal cancer is increased in survivors of many primary cancers, including survivors of Hodgkin lymphoma, testicular cancer, Wilms tumor, central nervous system malignancies and bone cancer. These increased gastrointestinal cancer risks are associated with high doses of radiation and alkylating agents, especially procarbazine.

In Hodgkin lymphoma survivors, reported increased risks (relative risks or standardized incidence ratios) for site-specific gastrointestinal cancers range from 3-31 for esophageal cancer, 3-11 for gastric cancer, 12-16 for
small bowel cancer \cite{39,40} and 2-7 for colorectal cancer. \cite{5,35,39} However, not all studies report increased risks, which could be due to the lack of treatment stratification or insufficient follow-up time. Because of the strong association of these increased risks with prior cancer treatment, the tumors that developed in cancer survivors are further indicated as “therapy-related” tumors. However, it should be noted that a proportion of these tumors are not related to prior cancer treatment, but are sporadic tumors (estimated by subtracting the attributable risk from 1 (attributable risk=((relative risk-1)/relative risk). Currently, it is not possible to determine for individual patients whether a gastrointestinal cancer diagnosed in Hodgkin lymphoma survivors is due to treatment, or would have also occurred without prior treatment.

Dutch multicenter Hodgkin lymphoma survivor cohort
In this thesis, we have used the data of a large Dutch multicenter cohort of Hodgkin lymphoma survivors to get more insight into therapy-related gastrointestinal cancers. \cite{5} All patients were treated between 1965-2000 before the age of 51 years. Patients were identified through hospital-based cancer registries and data on Hodgkin lymphoma diagnosis and treatment were collected from medical records. Follow-up data, including second primary cancers and vital status, were obtained via general practitioners and linkage with the Netherlands Cancer Registry.
Several case-control studies reported on risks of second primary cancers based on data from this cohort. Results from these studies are important for this thesis, as they provide detailed information on risks of gastrointestinal cancer in Hodgkin lymphoma survivors.
In this cohort the risk of gastrointestinal cancer was 4.6-fold increased compared with the general population. The absolute excess risk of gastrointestinal cancer (which included stomach, pancreatic, and colorectal cancers) contributed to 20% of the overall absolute excess risk of second primary cancers in Hodgkin lymphoma survivors. \cite{5} Gastrointestinal cancer risk was increased from 10 years up to 40 years after treatment for Hodgkin lymphoma compared with the general population.
Patients who were treated with both infradiaphragmatic radiotherapy and procarbazine-containing chemotherapy, had a strongly increased risk of gastrointestinal cancer (standardized ratio 8.6 (95% confidence interval (CI) 6.4-11.4)). In addition, the risk of gastrointestinal cancers did not appear to have decreased – in spite of adapted treatment regimens – over the treatment period 1965-2000. (Figure 3)

**Figure 3.** Cumulative incidence of gastrointestinal cancer diagnosed in Hodgkin lymphoma survivors, according to period of diagnosis.

Competing risk analysis (death as competing risk), solid lines represent the observed incidence of gastric, pancreatic and colorectal cancer, dashed lines the expected incidence.


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For colorectal cancer specifically, multivariable Cox regression models (adjusted for age at Hodgkin lymphoma diagnosis and gender) demonstrated a hazard ratio of 3.3 (95% CI 1.8-6.1) for patients treated with high-dose procarbazine (>4.2 g/m²), and a hazard ratio of 2.8 (95% CI 1.6-4.9) for patients treated with infradiaphragmatic radiotherapy. In patients who received both these treatments, the hazard ratio for colorectal cancer was 6.8 (95% CI 3.0-15.6). 41

**Clinical consequences of the increased gastrointestinal cancer risk in Hodgkin lymphoma survivors**

The evidence for an increased risk of gastrointestinal cancer currently has very limited clinical consequences, mainly due to the lack of knowledge about clinical and histopathological tumor characteristics and molecular pathways of tumor development. 42 Although the general consensus is that radiotherapy and alkylating chemotherapeutics can cause second (gastrointestinal) cancers, the exact mechanism of action remains unclarified. Prior to this thesis, evidence of the pattern of development of gastrointestinal cancer in cancer survivors was mainly limited to cellular experiments, mouse models and case reports. 43-48 Due to the exposure to radiotherapy and/or chemotherapy, gastrointestinal cancer development may be different in Hodgkin lymphoma survivors than in the general population. This information, e.g. the presence of recognizable benign precursor lesions and knowledge of natural history of gastrointestinal cancer, is essential for surveillance recommendations.

Colorectal cancer is regarded as highly suitable for prevention, as precursor lesions such as conventional adenomas and serrated lesions are endoscopically removable, which results in reduced colorectal cancer incidence and improved colorectal-cancer-related survival. 49-53 However, the method of population screening for colorectal cancer in the Netherlands, a fecal immunochemical test (FIT)-based screening program, is considered insufficient for high-risk populations, as the detection rate of precursor lesions at risk for malignant development is low. 54, 55
Surveillance programs in high-risk populations for colorectal cancer such as patients with inflammatory bowel disease, familial or hereditary colorectal cancer (e.g. Lynch syndrome) and those with a history of polyps or cancer, have been implemented in the Netherlands. For colorectal cancer prevention in high-risk populations, colonoscopy surveillance results in reduced colorectal cancer incidence and improved colorectal-cancer-related survival rates. The preventive effect of colonoscopy surveillance is influenced by the development of a precursor lesion into cancer. The majority of colorectal cancers develop through a protrude polypoid neoplastic lesion that can easily be detected and resected endoscopically. Nevertheless, other precursor lesions are easily missed and/or difficult to resect, such as serrated lesions, or dysplastic foci that occur in inflammatory bowel disease. Furthermore, microsatellite instable tumors are likely to develop through an accelerated growth pattern that requires a higher frequency of surveillance. It is thus important to personalize CRC surveillance recommendations for different subgroups. Starting age and interval of surveillance colonoscopy depends on the clinical characteristics and population-specific risks of each high-risk population.

Currently, the Dutch follow-up guidelines for Hodgkin lymphoma survivors and childhood cancer survivors do not include colorectal cancer surveillance. This thesis will provide important information for the decision whether or not to implement colorectal cancer surveillance as standard of care.

AIMS AND OUTLINE OF THIS THESIS

This thesis provides insights into clinical perspectives and the pathogenesis of gastrointestinal neoplasia in Hodgkin lymphoma survivors. Clinical, histopathological and molecular characteristics of gastrointestinal neoplasia in Hodgkin lymphoma survivors will be evaluated to ascertain if they differ from sporadic gastrointestinal neoplasia.

A specific focus involves whether Hodgkin lymphoma survivors may or may not benefit from the implementation of a colorectal cancer surveillance program similar to other high-risk populations, and whether such a program should be
adapted because of a difference in carcinogenesis compared with the general population.

The clinical perspective on therapy-related gastrointestinal cancer is given in Part I. Chapter 2 describes the clinical issue of three cancer survivors with intestinal adenomatous polyposis, suggesting an association between abdominal radiotherapy and polyposis. Two of these cases also developed a gastrointestinal cancer, which underlines the malignant potential of polyps in these patients. Consequently, the benefits and harms of surveillance should be evaluated in cancer survivors who were treated with abdominal radiotherapy.

Important (long-term) aims for a colonoscopy surveillance program include reductions of both colorectal cancer incidence and colorectal-cancer-related mortality. It is unclear whether survival of cancer survivors diagnosed with second primary gastrointestinal cancer differs from sporadic gastrointestinal cancer patients. Reduced survival could for example be a consequence of poor gastrointestinal tumor characteristics, less treatment options or higher treatment-related mortality compared with gastrointestinal cancer in the general population. 61 The presence of a survival difference between gastrointestinal cancer in Hodgkin lymphoma survivors and first primary gastrointestinal cancer patients, and its potential causes, are investigated in Chapter 3.

For the implementation of a surveillance program in Hodgkin lymphoma survivors at increased risk of colorectal cancer, the benefit and the burden of such a program need to be evaluated. Therefore, the design of a first study on colonoscopy surveillance in Hodgkin lymphoma survivors is described in Chapter 4, of which the results are reported in Chapter 5. In Chapter 6, the psychological and physical burden of the first surveillance colonoscopy for the study participants is evaluated.

Part II involves research on histopathological and molecular characteristics of therapy-related gastrointestinal cancer, focusing on the question whether the pathogenesis of these tumors differs from sporadic gastrointestinal cancer. Histopathological and molecular characteristics of therapy-related colorectal cancer diagnosed in Hodgkin lymphoma survivors are described in Chapter 7.
Analyses include the mutation status of several oncogenes and extensive analyses on mismatch repair deficiency, which are compared with colorectal cancer diagnosed in a general population cohort.

**Chapter 8** evaluates histopathological and molecular characteristics of therapy-related gastric cancer diagnosed in survivors of Hodgkin lymphoma and testicular cancer. Similar to the analyses in therapy-related colorectal cancer, extensive analyses on mismatch repair deficiency are performed. Additional immunohistochemical characteristics are evaluated, leading to the distribution of these gastric cancers into molecular subtypes. These results are compared with data from the general population described in literature.

Finally, **Chapter 9** involves a summary of this thesis and a general discussion including future perspectives.
REFERENCES


