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

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Discussion

11 SUMMARY

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An increased risk of developing second primary gastrointestinal (GI) malignancies has been described for several groups of cancer survivors, among whom Hodgkin lymphoma (HL) and testicular cancer (TC) survivors. For both HL and TC survivors, the relative risk of developing a second primary cancer is at least two-fold increased compared with the general population. This elevated risk does not manifest until 5-10 years after treatment and the relative risk remains increased for at least 30-40 years. This risk increase appears to be associated with the type and dose of anti-cancer treatment that was administered for the first malignancy and is considered a long-term effect of treatment. Little is known, however, about the molecular characteristics of these second primary GI cancers in cancer survivors. Due to the increased risk of developing colorectal cancer (CRC) in HL survivors treated with infradiaphragmatic radiotherapy and/or procarbazine-containing chemotherapy and in TC survivors treated with platinum-based chemotherapy, CRC surveillance has been advised.

In this thesis, we aimed to improve the knowledge about second primary gastrointestinal carcinomas in HL and TC survivors. We evaluated the carcinogenesis of several second primary GI malignancies and determined the effectiveness of CRC surveillance in these cancer survivors. The aim was to provide information to identify high-risk populations and come up with recommendations for CRC colonoscopy surveillance in these high-risk populations.

Additionally, we evaluated the adherence of pathologists to Dutch guidelines on Lynch syndrome screening among patients with ''early'' CRC. Also, in the context of Lynch syndrome, we assessed whether cutaneous squamous cell carcinoma (SCC) can also be considered as part of the Lynch syndrome spectrum.

Part I - Pathogenesis and molecular profile of second primary malignancies in cancer survivors

In **chapter 2,** we compared the gene expression profiles of esophageal squamous cell cancer (ESCC) in HL survivors with sporadic ESCC. We anticipated a different pathway, however, we found that the pathway expression, i.e. molecular characteristics at the RNA level, in ESCC in HL survivors and sporadic ESCC were for the most part similar using non-neoplastic tissue as a reference. Only the BRCA1 pathway was significantly upregulated at the RNA level in ESCC in HL survivors compared with corresponding non-neoplastic esophageal tissue of the HL survivor, suggesting a possible role of the tumor suppressor gene BRCA1 in the DNA damage response, since this pathway was upregulated in ESCC in HL survivors. Furthermore, we discovered a remarkable overlap between expression profiles of non-neoplastic (normal)

esophageal tissue and ESCC of HL survivors, suggesting early pre-cancerous changes in morphologically non-neoplastic esophageal mucosa, presumably induced by the treatment for HL. This insight into the disturbed gene expression profiles of morphologically normal esophageal mucosa is intriguing as it may offer the possibility of assessing the risk of developing second primary cancer among cancer survivors. As such, these findings serve as hypothesis-generating for future studies on surveillance strategies, earlier diagnosis and preventive measures.

In **chapter 3** we evaluated the copy number aberrations (CNAs) in second primary CRC and small bowel adenocarcinoma (SBA) in HL and TC survivors and compared these with primary CRC and SBA, respectively. In short, the overall pattern in CNAs in second primary bowel carcinomas and primary bowel carcinomas was similar. This contradicted our hypothesis and led us to conclude that – although some differences have been found – the majority of treatment-related second primary CRC and SBA may not be so different from primary CRC and SBA after all, at least not at the level of CNA.

In **chapter 4** we studied additional clinicopathological characteristics and risk factors for developing (advanced) colorectal neoplasia detected during a first colonoscopy surveillance in HL survivors treated with infradiaphragmatic radiotherapy and/or procarbazine-containing chemotherapy. This study represented a further analysis of data from a previous prospective study by Rigter et al. We demonstrated that polyp size of ≥ 10 mm was the main reason for classifying polyps as advanced, while dysplasia and a villous component for advanced adenoma occurred more frequently in advanced neoplasia in the general population. We found that MMR deficiency was not detectable in the advanced precursor lesions of CRC, while previously it had been demonstrated that MMR deficiency occurred more often in CRC in HL survivors. Risk factors for developing (advanced) colorectal neoplasia in HL survivors were a longer interval between HL diagnosis and colonoscopy, while gender, age at HL diagnosis, smoking, body mass index and family history of CRC did not significantly influence the prevalence of (advanced) neoplasia. This study extended the knowledge into the clinicopathological characteristics of large bowel precursor lesions among HL survivors, which can be of importance for endoscopists in order to recognize these lesions during the colonoscopy and emphasize the need for colonoscopy surveillance, especially when a long follow-up period between HL and diagnosis exists of more than 26 years.

In **chapter 5** we evaluated the pathogenesis of CRC in non-seminoma TC survivors. MMR deficiency did not occur more frequently in CRC in non-sem-

inoma survivors in comparison with CRC in the general population, however, biallelic and monoallelic somatic MMR gene inactivation is significantly more frequent in CRC in non-seminoma survivors in comparison with CRC in the general population. This finding is comparable to a previous finding of a higher frequency of biallelic and monoallelic somatic inactivation in HL survivors and thus our hypothesis is that an association exists between somatic MMR gene mutation or loss of heterozygosity with prior anti-cancer treatment.

Part II - Colorectal cancer surveillance in Hodgkin lymphoma and testicular cancer survivors

In **chapter 6** we evaluated the diagnostic accuracy of both fecal immunochemical test (FIT) and/or multi-target stool DNA test (mt-sDNA) in HL survivors treated with infradiaphragmatic radiotherapy and/or procarbazine-containing chemotherapy. The FIT had a higher specificity, while the mt-sDNA had a higher sensitivity for detecting advanced neoplasia using the colonoscopy as a reference. The diagnostic accuracy of these stool tests was used in a cost-effectiveness analysis to determine the optimal CRC surveillance strategy for HL survivors.

This cost-effectiveness analysis is reported in **chapter 7**, taking into account the standardized incidence ratio of CRC. The Microsimulation Screening Analysis-Colon model was adjusted to reflect CRC and other-cause mortality. The most optimal surveillance strategy was evaluated for i) the entire cohort, ii) HL survivors treated with only procarbazine-containing chemotherapy and iii) HL survivors treated with both infradiaphragmatic radiotherapy and procarbazine-containing chemotherapy. Different surveillance strategies were evaluated, including varying ages to start and stop surveillance, interval of surveillance and surveillance modality (colonoscopy, FIT at different positivity cut-offs (10, 20 or 47 µg Hb/g feces) or mt-sDNA). Using this simulation we found that FIT surveillance at a cut-off of 47 µg Hb/g feces was most cost-effective for all three HL treatment categories. The ages to start surveillance ranged from 40 to 45 years, and the age to stop was 70 years, performed either annually or biennially.

In **chapter 8** we described the study protocol of a currently ongoing prospective cross-sectional cohort study where the primary aim was to evaluate the yield of colonoscopy surveillance in TC survivors treated with (cis-)platinum-based chemotherapy. These TC survivors have a 3.8-increased risk for developing CRC. Therefore, participants are invited to undergo a colonoscopy. For secondary purposes, participants are asked to perform a FIT, obtain blood and urine sample, fill out questionnaires and consent to obtain additional bi-

opsies of normal colorectal mucosa during the colonoscopy. Thereby we can evaluate the diagnostic accuracy of FIT, determine the platinum level in blood and urine and determine the burden of colonoscopy and impact on quality of life of the participant. Furthermore, the normal colorectal tissue obtained during the colonoscopy can be used to expand the knowledge of the carcinogenesis of (the precursor lesions of) CRC among TC survivors. The colonoscopy and FIT results will be used to perform a cost-effectiveness analysis, which will provide recommendations for the follow-up of TC survivors.

Part III - Mismatch repair deficiency

In **chapter 9** we studied the frequency of MMR/microsatellite instability (MSI) testing in pT1 CRC diagnosed in the Dutch screening program for patients between 55 – 70 years old. In the Netherlands, MMR testing on all CRC under the age of 70 years is advised. We found that the MMR/MSI status had been assessed in only 83% of the pT1 CRC. The adherence to the guideline increased over time. Furthermore, MMR/MSI testing occurred significantly more often when the pT1 CRC was removed by oncological surgical resection compared with local excision. Moreover, in case pT1 CRC was removed by oncological surgical resection, the MMR/MSI status was known prior to surgery in 51% of the cases. MMR/MSI testing occurred significantly more frequently when pT1 CRC was diagnosed at a younger age or in an academic hospital. This study indicated that adherence to the guideline could be improved, as MMR/MSI testing should routinely be performed on the first tissue obtained, which is usually endoscopically, as already previously recommended by the Dutch CRC guideline.

In **chapter 10** we evaluated the frequency of MMR deficiency in cutaneous SCC diagnosed in individuals with Lynch syndrome. All cutaneous SCC were MMR deficient, and the lost MMR staining corresponded with the known germline mutation of Lynch syndrome. Cutaneous SCC were detected in individuals with a proven *MSH2* and *MLH1* germline mutation. We performed both MMR IHC and MSI PCR and showed that there was a low concordance between these two tests in this setting. Low concordance between these two tests has been described for various other tumor types, except for colorectal and endometrial cancer in which the concordance is high. We came to the conclusion that cutaneous SCC is indeed a part of the Lynch syndrome associated tumor spectrum. Therefore, these individuals – especially with a *MSH2* and *MLH1* germline mutation – may benefit from a single dermatological consultation in order to receive information about sun exposure and self-examination.