Received: 16 August 2023 | Revised: 24 October 2023 | Accepted: 25 October 2023

DOI: 10.1002/ijc.34810

RESEARCH ARTICLE

Cancer Therapy and Prevention

IJC INTERNATIONAL JOURNAL of CANCER

Prevalence of neoplasia at colonoscopy among testicular cancer survivors treated with platinum-based chemotherapy

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Funding information
Partly funded by the Dutch Digestive Foundation (Maag-Lever-Darm-Stichting), Grant/Award Number: WO 19-03

Abstract

Testicular cancer survivors (TCS) treated with platinum-based chemotherapy have an increased risk of colorectal cancer (CRC). We determined the yield of colonoscopy in TCS to assess its potential in reducing CRC incidence and mortality. We conducted a colonoscopy screening study among TCS in four Dutch hospitals to assess the yield of colorectal neoplasia. Neoplasia was defined as adenomas, serrated polyps (SPs), advanced adenomas (AAs: ≥10 mm diameter, high-grade dysplasia or ≥25% villous

component), advanced serrated polyps (ASPs: ≥10 mm diameter or dysplasia) or CRC. Advanced neoplasia (AN) was defined as AA, ASP or CRC. Colonoscopy yield was compared to average-risk American males who underwent screening colonoscopy ($n = 24{,}193$) using a propensity score matched analysis, adjusted for age, smoking status, alcohol consumption and body mass index. A total of 137 TCS underwent colonoscopy. Median age was 50 years among TCS (IQR 43–57) vs 55 years (IQR 51–62) among American controls. A total of 126 TCS were matched to 602 controls. The prevalence of AN was higher in TCS than in controls (8.7% vs 1.7%; $P = .0002$). Nonadvanced adenomas and SPs were detected in 45.2% of TCS vs 5.5% of controls ($P < .0001$). No lesions were detected in 46.0% of TCS vs 92.9% of controls ($P < .0001$). TCS treated with platinum-based chemotherapy have a higher prevalence of neoplasia and AN than matched controls. These results support our hypothesis that platinum-based chemotherapy increases the risk of colorectal neoplasia in TCS. Cost-effectiveness studies are warranted to ascertain the threshold of AN prevalence that justifies the recommendation of colonoscopy for TCS.

KEYWORDS
colonoscopy screening, colorectal cancer, platinum-based chemotherapy, testicular cancer survivors

What's new?

Colorectal cancer (CRC) risk is significantly elevated among testicular cancer survivors who receive platinum-based chemotherapy. The role of colonoscopy in CRC screening for these patients, however, remains uncertain. Here, the potential of colonoscopy for reducing CRC incidence and mortality was examined among testicular cancer survivors treated with platinum-based chemotherapy in the Netherlands. Neoplasia and advanced neoplasia (AN) prevalence was higher among platinum-treated survivors than matched controls. Non-advanced adenomas and serrated polyps were also significantly more common among testicular cancer survivors treated with platinum-based chemotherapy. The findings warrant additional investigation of cost-effectiveness and threshold of neoplasia prevalence necessary to support colonoscopy recommendation for testicular cancer survivors treated with platinum-based chemotherapy.

1 | INTRODUCTION

Over the past few decades, the proportion of second malignant neoplasms (SMNs) among all cancer diagnoses has increased substantially.[1] There are several known risk factors for SMNs, including environmental and lifestyle factors and aging, but also late side effects of prior cancer treatment. Due to the improved prognosis of cancer patients resulting in longer survival, the likelihood of developing an SMN increases. Especially among patients who received intensive (multimodality) treatment, the late side effects of the initial cancer treatment contribute to the development of these SMNs.[2]

Population-based CRC screening programs have been widely implemented for average-risk individuals, with the aim of reducing CRC incidence and mortality by removing precursor lesions and early detection.[3] A variety of screening modalities are used, including fecal immunochemical testing (FIT), multitarget stool DNA tests, sigmoidoscopy and colonoscopy.[3] For high-risk individuals, who may have at least two times the risk of developing CRC in their lifetime compared to those at average risk, surveillance programs are offered. Testicular cancer survivors (TCS) treated with platinum-based chemotherapy can be considered a high-risk group, as one study reported an almost four times higher CRC risk among platinum-treated TCS compared to TCS not treated with platinum-based chemotherapy[4] and several other studies also reported higher risk of gastrointestinal malignancies.[5,6] Treatment options for TC patients have improved over the past decades, resulting in very high 5-year overall survival rates of 73%–99%, depending on the presence and localization of metastases.[7] TC patients treated with chemotherapy usually receive bleomycin or ifosfamide, etoposide and cisplatin.[7] Cisplatin has been associated with numerous late side effects, including endothelial dysfunction, atherosclerosis, but also increased CRC risk.[8,9] This risk increased as higher platinum doses were administered.[4] The effectiveness of colonoscopy screening for TCS treated with (cis-)platinum-based chemotherapy has not yet been established.

In our study, we evaluated the yield of colonoscopy in TCS treated with platinum-based chemotherapy.

2 | MATERIALS AND METHODS

2.1 | Study design

The design of the CATCHER (Diagnostic Yield of Colonoscopy Surveillance in Testicular *Ca*ncer Survivors *T*reated With Platinum-based *Che*motherapy) study was described in detail previously.[10] In short, this prospective, cross-sectional study aimed to evaluate the yield of colonoscopy in detecting colorectal neoplasia, including advanced neoplasia (AN), in TCS treated with platinum-based chemotherapy.

2.2 | Population

The CATCHER study is nested in a well-defined Dutch multicenter cohort of 5,848 1-year TCS treated from 1976 to 2007 in 13 hospitals in the Netherlands.[4] TCS were eligible for inclusion in the CATCHER study if they met the following criteria: (a) First TC diagnosis <50 years of age, (b) TC treatment consisted of ≥3 cycles of platinum-based chemotherapy, (c) TC treatment was administered at least 8 years ago, (d) current survivors' age should be ≥35 and ≤75 years and (e) detection and treatment of colorectal neoplasia is considered beneficial when weighed against comorbidities. Individuals were excluded if undergoing surveillance colonoscopy for other indications (including hereditary CRC, familial CRC, inflammatory bowel disease and history of adenomas or CRC) or if they underwent colonoscopy in the past 3 years.[10] In total, 1,801 individuals treated in one of the four participating centers in the CATCHER study (Netherlands Cancer Institute, Radboud University Medical Center, University Medical Center Utrecht and Erasmus University Medical Center) met these eligibility criteria.[4]

2.3 | Control population

An effort was made to find an optimal cohort as a control population that included average-risk men who were offered a first colonoscopy screening with an age range overlapping with the CATCHER cohort. The only available Dutch colonoscopy screening cohort study included men aged 50–75. Due to the substantially older median age (61 years, $P < .0001$; data not shown), this Dutch cohort did not meet our comparison criteria.[10,11] Additionally, colonoscopies in our study were performed in 2009–2010.[11] Therefore, we searched for an international comparison cohort of men who were offered a first colonoscopy at young(er) ages. The New Hampshire Colonoscopy Registry (NHCR) cohort fulfilled all criteria for a valid comparison to our CATCHER cohort. This population-based, statewide registry collects colonoscopy data throughout the state of New Hampshire in the United States.[12] NHCR data selected included first screening colonoscopies in average-risk individuals from the recommended CRC screening age (50 years and older before 2021, now 45 years and older),[13] as well as colonoscopy data from young(er) individuals, who are defined as "average-risk screening equivalent" if they have a low risk of AN (ie, symptoms such as constipation or abdominal pain) and no family history of CRC in a first degree relative.[12] Data on colonoscopies were collected from October 2004 to November 2021. We excluded data from the NHCR on colonoscopies performed in men of non-white race, as the CATCHER population consisted solely of males of white race. Individuals with a prior colonoscopy or indication for surveillance were also excluded.

2.4 | Outcomes

The primary outcome was the yield of colorectal neoplasia by colonoscopy, defined as the most advanced lesion at colonoscopy and the number of neoplasia detected.

2.5 | Definitions

Colorectal neoplasia was defined as either an adenoma, a serrated polyp (SPs), advanced adenoma (AA), advanced serrated polyp (ASPs) or CRC. AA was defined as any adenoma with a size ≥10 mm and/or high-grade dysplasia and/or histologically confirmed villous component ≥25%. ASP was defined as at least one SP ≥10 mm, a sessile serrated lesion with dysplasia or a traditional serrated adenoma.[14] AN was defined as either AA, ASP or CRC. Each individual was categorized based on the most advanced lesion: (a) AN, (b) nonadvanced adenomas or nonadvanced SPs and (c) no relevant findings. Any neoplasia was defined as either nonadvanced adenomas, nonadvanced SPs or AN. Only complete colonoscopies (cecal intubation) with adequate bowel preparation (CATCHER cohort: Boston Bowel Preparation Scale ≥6, NHCR cohort: adequate (excellent, good or fair) bowel preparation[15]) were included.

2.6 | Methods—Study procedures

A total of 537 randomly selected individuals from the eligible CATCHER cohort were sent an invitation letter by mail (Figure 1). The invitation letter contained brief information about the risk of CRC and study procedures. If no response was received, two reminder letters were sent. Individuals could respond by mail or telephone and were contacted by the study coordinator or physician at one of the four participating centers for instructions on further study procedures. The usual colonoscopy procedures were followed in the event of relevant colonoscopy findings. Experienced gastrointestinal pathologists performed routine histologic evaluation of all resected lesions. Follow-up after colonoscopy was performed according to standard clinical care.

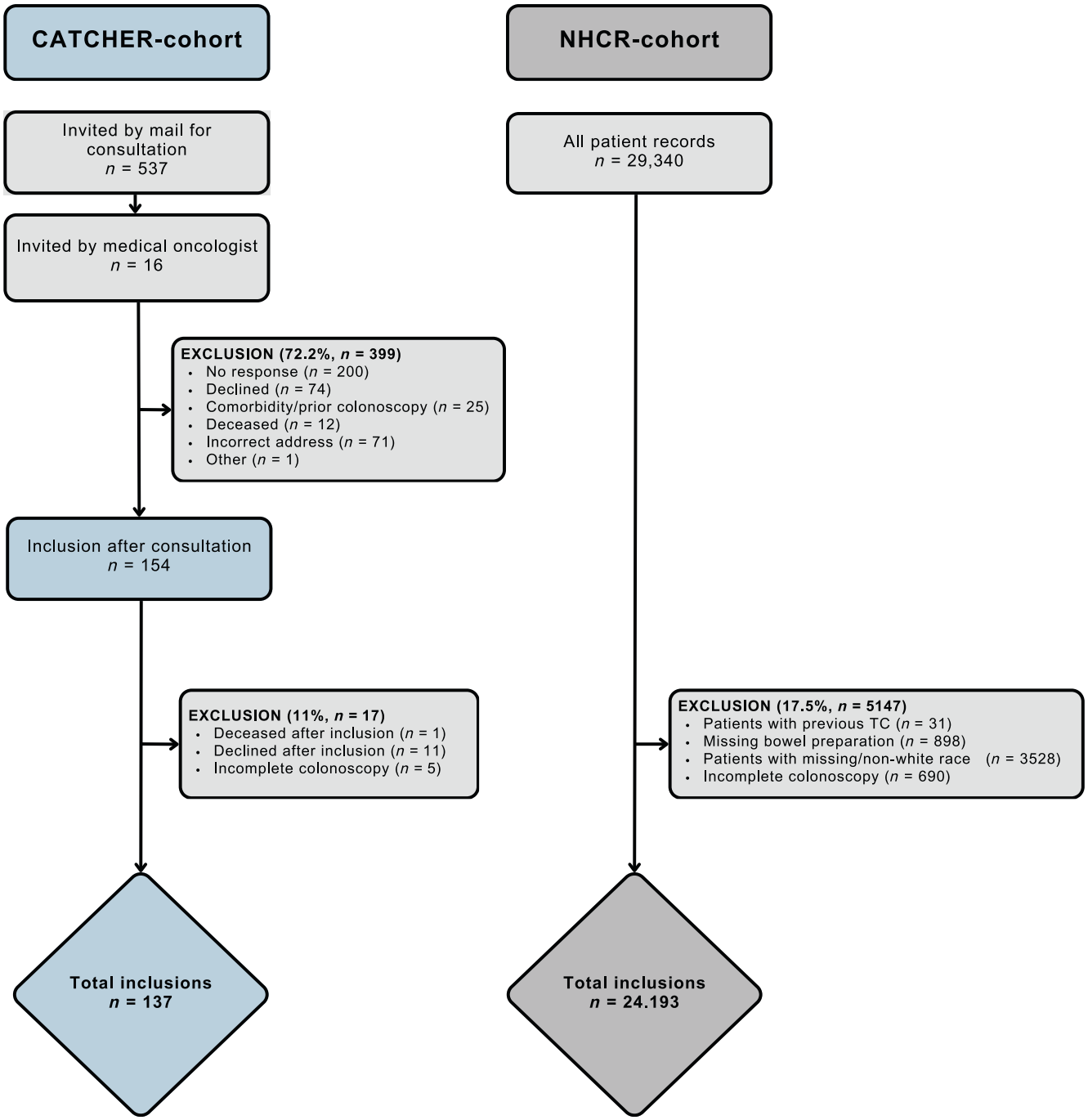

FIGURE 1 Flow diagram of study inclusions. NHCR, New Hampshire Colonoscopy Registry; TC, testicular cancer.

2.7 | Statistical analysis

Categorical data were compared using a χ^2 or Fisher's exact test; continuous data were compared using Mann–Whitney *U* tests. Two-sided *P*-values <.05 were considered statistically significant. We performed a propensity score matched analysis to balance the baseline characteristics of the CATCHER and NHCR cohort to reduce potential confounders using a logistic regression model, adjusting for age, smoking status, alcohol consumption and body mass index (BMI).[16] Each propensity score matching was performed using a 1:5 ratio and a "nearest-neighbor" algorithm. Covariate data (BMI, alcohol consumption or smoking status) were unavailable for 11 participants in the CATCHER cohort, who were therefore excluded in the propensity score matched analysis. Baseline covariates and distributions of standardized mean differences before and after matching are displayed in Figure S1 and Tables S1–S3. We compared colonoscopy outcomes between the CATCHER and the NHCR cohort. Data management and analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

Out of the 537 TCS who were invited to participate, 154 (28.7%) responded and were subsequently scheduled for a colonoscopy intake (Figure 1). We excluded 11 TCS, who declined participation after inclusion, one patient who died of COVID before colonoscopy and five participants due to incomplete colonoscopy, leaving 137 (89%) individuals, who underwent colonoscopy between February 20, 2020 and November 25, 2022, for analysis.

TABLE 1 Characteristics of the CATCHER study population.

Characteristic	
Age at TC treatment, median (IQR), y	27.5 (23–34)
Time since TC treatment, median (IQR), y	20.0 (16–26)
Histology of TC, *n* (%)	
Seminoma	21 (15.3)
Non-seminoma	108 (78.8)
Unknown	8 (5.8)
Stage of TC at initial diagnosis, *n* (%)	
I	28 (20.4)
II	37 (27.0)
III	10 (7.3)
IV	5 (3.6)
Unknown	57 (41.6)
Number of cycles of (cis)platin, *n* (%)	
3	43 (31.4)
4	76 (55.5)
≥5	15 (10.9)
Unknown	3 (2.2)
RT treatment for TC, *n* (%)	7 (5.1)
Age at colonoscopy, median (IQR), y	50 (43–58)
ASA-score at colonoscopy	
1	68 (49.6)
2	64 (46.7)
3+	4 (2.9)
Unknown	1 (0.7)
BMI, median (IQR), kg/m^2	26.0 (23.5–28.6)
Smoking status	
Current smoker	14 (10.2)
Former smoker	41 (29.9)
Never smoked	76 (55.5)
Unknown	6 (4.4)
Alcohol consumption	
≥15 units/week	9 (6.6)
<15 units/week	99 (72.3)
No alcohol	21 (15.3)
Unknown	8 (5.8)

Abbreviations: BMI, body mass index; IQR, interquartile range; RT, radiotherapy; TC, testicular cancer.

3.1 | Baseline characteristics

The median age of participants at TC diagnosis was 27.5 years (interquartile range [IQR]: 23–34; Table 1). TC histology was predominantly non-seminoma ($n = 108$, 78.8%), followed by 15.7% seminoma ($n = 21$). Forty-three (31.4%) participants received 3 cycles of platinum-based chemotherapy and 91 (66.4%) received ≥4 cycles. Seven participants (5.1%) received both radiotherapy and platinum-based chemotherapy.

3.2 | Findings CATCHER cohort

The median time between TC treatment (last cycle of platinum-based treatment) and colonoscopy was 20 years (IQR: 16–26). Median age at colonoscopy was 50 years (IQR 43–57 years). The ASA score at time of colonoscopy was 1 in 49.6% of individuals, 2 in 46.7% of individuals and 3 in 2.9% of individuals (Table 1). In total, 181 colorectal neoplasia were detected among 74 (54.0%) of 137 participants. The median number of neoplasia detected was 1 (IQR 0–2). The most advanced lesion was AN in 8.8% of participants, non-advanced adenomas/SPs in 45.3%, while no lesions were found in 46.0% (Table 2). No CRCs were detected in the CATCHER cohort. One participant was hospitalized for 1 day of observation for rectal bleeding after polypectomy; no other adverse events occurred.

3.3 | Findings NHCR cohort

Median age at colonoscopy in the NHCR cohort was 55 years (IQR 51–62 years). In total, 22,819 colorectal neoplasia were detected among 8578 (35.5%) of 24,193 men. The median number of neoplasia was 0 (IQR 0–1) in the NHCR cohort. The most advanced lesion was AN in 5.5% of participants, non-advanced adenomas/SPs in 30.0%, while no lesions were found in 64.5% (Table 2). A total of 37 (0.2%) CRCs were detected in the NHCR cohort.

3.4 | Comparison of colonoscopy findings in the CATCHER and NHCR cohorts

We compared the distribution of the most advanced lesions by age category, as the cohorts differed in age (Table 2, Figure 2). The prevalence of any neoplasia was significantly higher in the CATCHER cohort than in the NHCR cohort when combining all age groups (54.0% vs 35.5%, $P < .0001$); significant differences between the CATCHER cohort and the NHCR cohort were also observed in age categories 40–49, 50–59 and 60–69 years. The largest difference was observed in the 50–59 age category, where any neoplasia was found in 62.8% ($n = 27$) in the CATCHER cohort compared to 35.6% ($n = 4822$) in the NHCR cohort ($P = .0002$).

Based on propensity score matched analysis, 126 individuals (92%) from the CATCHER cohort were matched to 602 individuals from the NHCR cohort (Figure S1; Tables S1–S3). The propensity score matched analysis revealed an even more striking difference in

TABLE 2 Most advanced lesions in the CATCHER vs the NHCR cohort, stratified per age category.

Most advanced lesion, *n* (%)	CATCHER	NHCR	*P* value
Total	137	24,193	<.0001
No lesions	63 (46.0)	15,615 (64.5)	
Non-advanced adenomas and/or non-advanced SPs	62 (45.3)	7249 (30.0)	
Advanced neoplasia	12 (8.8)	1329 (5.5)[a]	
30–39 year olds			.36
No lesions	12 (70.6)	197 (81.1)	
Non-advanced adenomas and/or non-advanced SPs	4 (23.5)	39 (16.0)	
Advanced neoplasia	1 (5.9)	7 (2.9)	
40–49 year olds			.00091
No lesions	27 (51.9)	873 (74.7)	
Non-advanced adenomas and/or non-advanced SPs	22 (42.3)	238 (20.4)	
Advanced neoplasia	3 (5.8)	58 (5.0)	
50–59 year olds			.00098
No lesions	16 (37.2)	8713 (64.4)	
Non-advanced adenomas and/or non-advanced SPs	23 (53.5)	4101 (30.3)	
Advanced neoplasia	4 (9.3)	721 (5.3)	
60–69 year olds			.013
No lesions	8 (34.8)	4870 (63.4)	
Non-advanced adenomas and/or non-advanced SPs	13 (56.5)	2383 (31.0)	
Advanced neoplasia	2 (8.7)	434 (5.6)	
70–80 year olds			–
No lesions	0	962 (61.7)	
Non-advanced adenomas and/or non-advanced SPs	0	488 (31.3)	
Advanced neoplasia	2	109 (7.0)	

Abbreviations: CRC, colorectal cancer; SP, serrated polyp.
[a]AN included 37 (0.2%) CRCs in the NHCR cohort.

the distribution of most advanced lesions than the overall group analyses (Figure 3). In 45.2% ($n = 57$) of the CATCHER cohort, the most advanced lesion was a non-advanced adenoma/SP, compared to 5.5% ($n = 33$) of the NHCR cohort ($P < .0001$). AN was the most advanced lesion in 8.7% ($n = 11$) of the CATCHER cohort compared to 1.7% ($n = 10$) of the NHCR cohort ($P = .0002$). In the CATCHER cohort, 46.0% ($n = 58$) had no lesions compared to 92.9% ($n = 559$) in the NHCR cohort ($P < .0001$). The median number of any neoplasia was 1 (IQR 0–2) in the CATCHER cohort vs 0 (IQR 0–0) in the NHCR cohort ($P < .0001$).

4 | DISCUSSION

Our study demonstrates a higher prevalence of AN and any neoplasia (non-advanced adenomas/SPs and AN) in TCS treated with platinum-based chemotherapy compared to age-matched controls at average risk of CRC. These findings were supported by the propensity score matched analysis. No CRCs were detected in TCS treated with platinum-based chemotherapy.

The propensity score matched analysis shows that the prevalence of AN in TCS is much higher than in the NHCR cohort (8.7% vs 1.7%, $P = .0002$) after correction for baseline covariates associated with higher risk of neoplastic lesions. These findings are in line with the previously observed high risk of CRC.[4] As expected, the prevalence of any neoplasia and AN increases with age in both TCS and the comparison cohort. Although our study was initially powered on the yield of AN,[10] there is evidence that removal of non-high-risk polyps may also contribute to a reduction in CRC-related mortality.[17] Furthermore, the presence of non-advanced adenomas is associated with development of AN overtime[18] and with recurrence of (advanced) adenomas at follow-up colonoscopy.[19]

While the increased risk of AN is clear, additional evidence is needed to establish recommendations for CRC screening in TCS. Cost-effectiveness studies are warranted to determine whether or not the increase in prevalence of AN is high enough to merit a colonoscopy recommendation for TCS treated with platinum-based chemotherapy and how this recommendation may vary based on the patients' age and the number of years since treatment. FIT-screening may be a noninvasive alternative for colonoscopy and CRC screening recommendations for childhood cancer survivors (CCS), who are also at higher risk of developing (gastrointestinal) SMNs, may help guide CRC screening recommendations for TCS. However, the added value of alternative screening modalities has not been extensively investigated in CCS,[20]

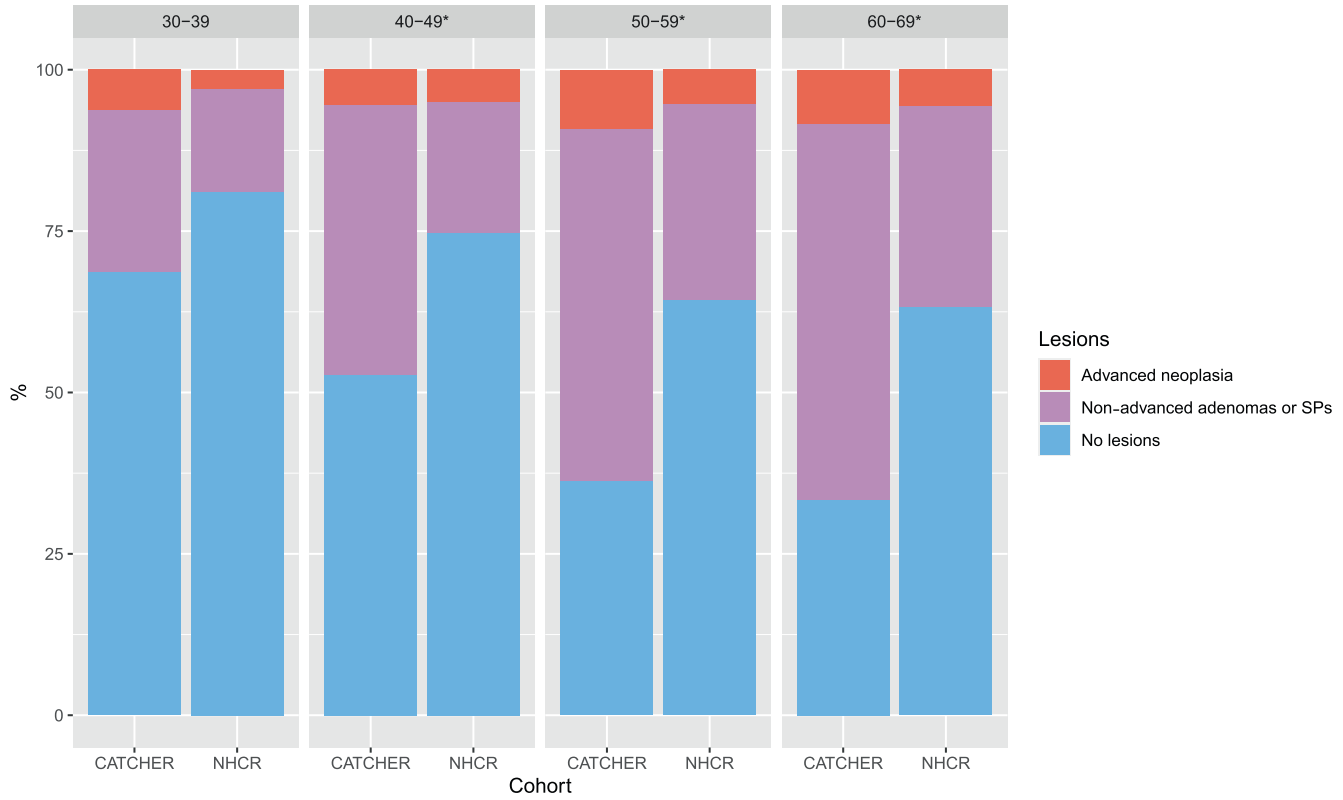

FIGURE 2 Distribution of most advanced lesions in the CATCHER and the NHCR cohort. SPs, serrated polyps. Asterisks denotes statistically significant difference.

and currently, colonoscopy screening repeated every 5 years, or multi-target stool DNA tests repeated every 3 years is only advised in the United States for CCS treated with radiotherapy, starting at age 30 or 5 years after radiation (whichever occurs last).[21] European guidelines on screening for gastrointestinal SMNs in CCS are more heterogeneous and do not provide clear recommendations on CRC screening,[21,22] and furthermore, it should be noted that background risk of gastrointestinal SMNs differs for different primary cancers, as well as the availability of healthcare resources in many countries. Notwithstanding, efforts are being made to harmonize recommendations to provide CCS and their healthcare providers with clear guidelines.[22–24] Defining the optimal strategy for each country will be aided by cost-effectiveness studies.

We hypothesize that the development of CRC in TCS may differ from that observed in the general population due to (epi)genetic changes caused by specific anticancer treatments.[8] Increasing evidence suggests that sporadic CRCs result from the stepwise accumulation of multiple somatic mutations, which is also observed in CRCs in TCS.[25] Kuijk et al showed that both capecitabine–oxaliplatin chemotherapy and radiotherapy are mutagenic in colorectal stem cells and that the mutational burden was significantly increased in normal noncancerous cells, in addition to the typical accumulation of mutations associated with aging, applying whole genome sequencing.[26] They found the pattern of single base substitutions (SBS) to be consistent with an SBS mutational signature from the Catalogue of Somatic Mutations in Cancer that has been ascribed to prior platinum-based treatment. However, our study was performed shortly after oxaliplatin treatment (several months) and the pharmacokinetics of oxaliplatin are different from those of cisplatin.[27] Further research on cisplatin accumulation in tissues of TCS, its relationship to colorectal neoplasia development and mutations in colonic mucosa is important to understand carcinogenesis and thus how best to prevent CRC in CCS.

A major strength of our study was the availability of detailed data on this well-defined cohort of TCS treated with platinum-based chemotherapy. Our results are applicable to a large population of TCS throughout the world, as TC patients are currently still treated with chemotherapy regimens similar to those in our cohort. Furthermore, our results may also be applicable to other cancer survivors treated with cisplatin for bladder, head and neck, lung and ovarian cancer. Finally, the availability of detailed data on the large NHCR comparison cohort allowed us to compare our results directly with those of average-risk individuals with similar patient characteristics. This showed that colonoscopy did indeed result in a higher yield of AN and any colorectal neoplasia in TCS treated with platinum-based chemotherapy.

Our study has some limitations; first, when weighing the screening colonoscopy detection rate of colorectal neoplasia and AN in a high-risk population, the choice of the comparison cohort will strongly impact conclusions drawn and clinical implications of the results. Despite the fact that the overall CRC incidence is higher in the Netherlands than in the United States, the CRC incidence in men aged 45–59 is slightly lower in the Netherlands than in the United States, which means that our results can be considered a conservative estimate.[28,29] In addition, the NHCR is one of the few registries to include

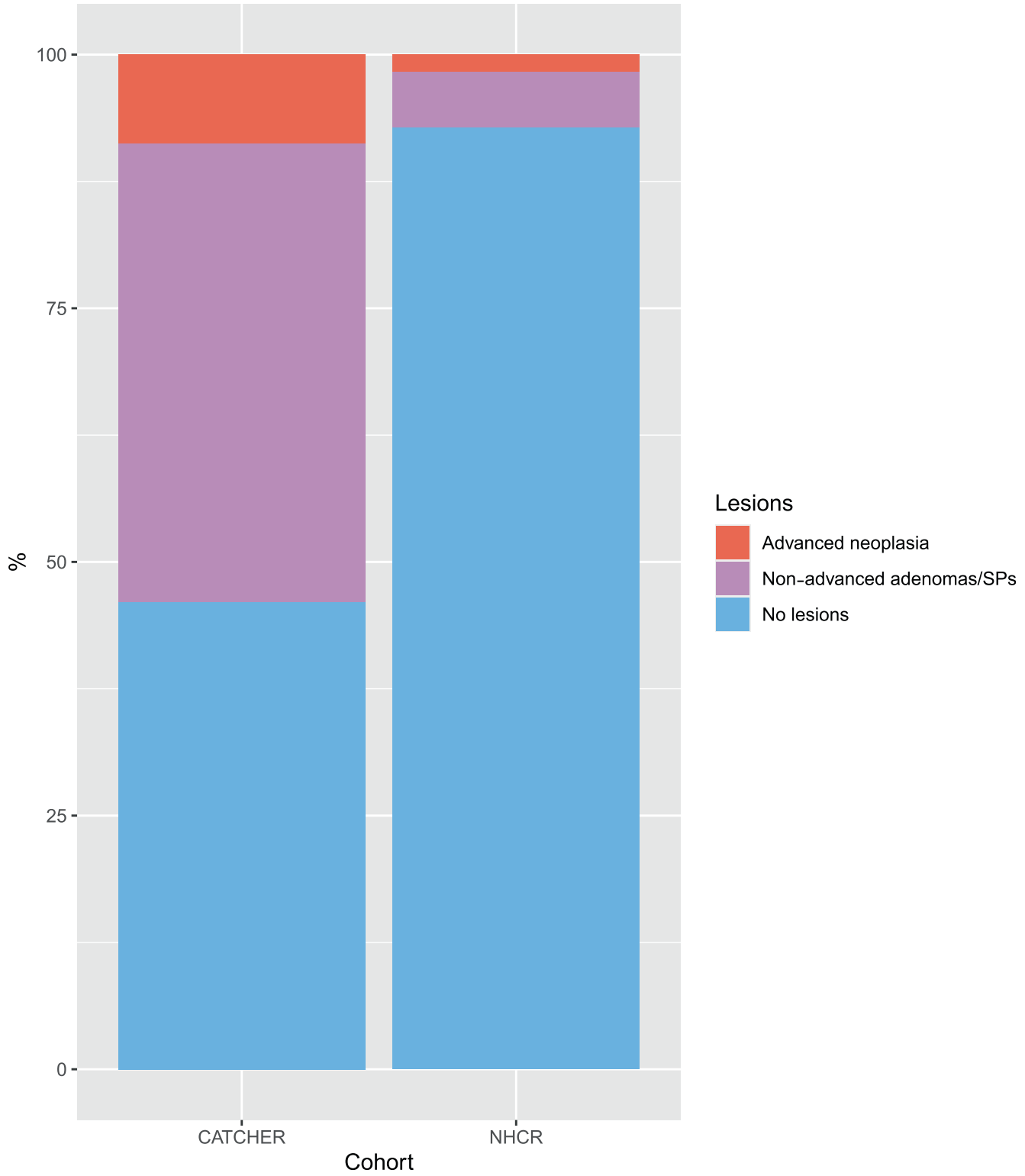

FIGURE 3 Most advanced lesions in the CATCHER vs the NHCR cohort after propensity score matched analysis. SPs, serrated polyps.

data on average-risk screening equivalents who are younger than the starting age of screening. Second, the colonoscopy participation rate of TC survivors was relatively low (28.7%). However, a lower participation rate of 22% was reported in a Dutch primary colonoscopy screening trial in the general population.[30] In a similar colonoscopy screening study in Hodgkin lymphoma (HL) survivors, the participation rate was somewhat higher (41%), which we hypothesize to be due to the fact that many HL survivors still received (follow-up) care when invited by their radiotherapist or medical oncologist to participate in colonoscopy.[31] Individuals in the CATCHER cohort were almost all

invited by mail, and we observed a higher participation rate in one of the participating centers where individuals were invited by their medical oncologist. This underscores the importance of clear risk communication at all levels of care, and ideally, TC survivors should be made aware of the increased risk of CRC, lifestyle recommendations and alarm symptoms, while still under the care of their medical oncologist, similar to how cardiovascular risks associated with cisplatin are communicated. TC survivors with bowel symptoms that may indicate CRC, or with additional CRC risk factors, should be referred for colonoscopy at a very low threshold. Last, individuals in the CATCHER cohort who had already developed CRC (at an early age) were excluded from the pool of eligible individuals. Unfortunately, data on CRC in these TCS were not available due to the enforcement of privacy laws in the Netherlands (no informed consent for retrieval of their data was given). However, based on this, the results of our study could only be an underestimate of the true risk of AN in TCS.

In conclusion, TCS treated with platinum-based chemotherapy have a higher prevalence of any colorectal neoplasia and AN compared to matched average-risk individuals. This increased risk already emerges at ages when population-based screening is not yet offered. These results support epidemiological observations showing that platinum-based chemotherapy increases the risk of colorectal neoplasia in TCS. Cost-effectiveness studies are warranted to determine the threshold of AN prevalence increase that would justify recommending colonoscopy for TCS as the test of choice for CRC screening and for TCS who are younger than the recommended age to begin CRC screening. Our results emphasize the importance of clear risk communication to TCS and their treating physicians. Insight into how platinum-based chemotherapy contributes to CRC carcinogenesis in TCS is of great importance and may also have implications for other cancer survivors treated with similar treatment regimens.

AUTHOR CONTRIBUTIONS

Emilie C. H. Breekveldt: Conceptualization, investigation, project administration, methodology and writing-review and editing; Accessed and verified the underlying data reported in the article; Wrote the original draft with supervision from Berbel L. M. Ykema, Michael Schaapveld, Flora E. van Leeuwen, Petur Snaebjornsson and Monique E. van Leerdam. **Berbel L. M. Ykema:** Conceptualization, investigation, project administration, methodology and writing-review and editing. **Michael Schaapveld:** Conceptualization, investigation, project administration, methodology and writing-review and editing; Accessed and verified the underlying data reported in the article. **Flora E. van Leeuwen:** Conceptualization, investigation, project administration, methodology and writing-review and editing. **Petur Snaebjornsson:** Conceptualization, investigation, project administration, methodology and writing-review and editing. **Monique E. van Leerdam:** Conceptualization, investigation, project administration, methodology and writing-review and editing. All authors contributed to interpretation of data, reviewing drafts of the article and approved the final article draft. All authors had full access to the data underlying the article and had final responsibility for the decision to submit for publication. The work reported in the article has been performed by the authors, unless clearly specified in the text.

ACKNOWLEDGEMENTS

We would like to thank all CATCHER study participants. We thank the New Hampshire Colonoscopy Registry (NHCR) for providing the de-identified data of the NHCR cohort.

FUNDING INFORMATION

The Dutch Digestive Foundation (Maag-Lever-Darm-Stichting) partly funded our study; grant number WO19-03. The funder had no role in the study design, the analyses, interpretation of the data, the writing of the report and the decision to submit the article for publication.

The NHCR receives support from the U.S. National Cancer Institute of the National Institutes of Health (Award R01CA243449). The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

NHCR data on cancer diagnoses is supported in part by the Centers for Disease Control and Prevention's National Program of Cancer Registries, cooperative agreement 5U58DP003930 awarded to the New Hampshire Department of Health and Human Services, Division of Public Health Services, Bureau of Public Health Statistics and Informatics. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or New Hampshire Department of Health and Human Services.

CONFLICT OF INTEREST STATEMENT

Manon C. W. Spaander has received research support from Sysmex, Sentinel and Norgine. All other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The CATCHER cohort data supporting our study are available on reasonable request from the last author (MvL).

ETHICS STATEMENT

All participants provided informed consent for participation in the study and use and publication of the data collected in our study. Our study was approved by the Medical Ethical Committee (study number M19CTR, clinical trial number: NCT04180033) of the Netherlands Cancer Institute.

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REFERENCES

1. Morton LM, Onel K, Curtis RE, Hungate EA, Armstrong GT. The rising incidence of second cancers: patterns of occurrence and identification of risk factors for children and adults. *Am Soc Clin Oncol Educ Book*. 2014; e57-e67. PMID: 24857148. doi:10.14694/EdBook_AM.2014.34.e57
2. Morton LM, Swerdlow AJ, Schaapveld M, et al. Current knowledge and future research directions in treatment-related second primary malignancies. *EJC Suppl*. 2014;12(1):5-17.

3. Pinsky P, Rabeneck L, Lauby-Secretan B. The IARC perspective on colorectal cancer screening. *N Engl J Med*. 2018;379(3):301-302.
4. Groot HJ, Lubberts S, de Wit R, et al. Risk of solid cancer after treatment of testicular germ cell cancer in the platinum era. *J Clin Oncol*. 2018;36(24):2504-2513.
5. Travis LB, Fossa SD, Schonfeld SJ, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst*. 2005;97:1354-1365.
6. Fung C, Fossa SD, Milano MT, Oldenburg J, Travis LB. Solid tumors after chemotherapy or surgery for testicular nonseminoma: a population-based study. *J Clin Oncol*. 2013;31:3807-3814.
7. Cheng L, Albers P, Berney DM, et al. Testicular cancer. *Nat Rev Dis Primers*. 2018;4(1):29.
8. Lubberts S, Meijer C, Demaria M, Gietema JA. Early ageing after cytotoxic treatment for testicular cancer and cellular senescence: time to act. *Crit Rev Oncol Hematol*. 2020;151:102963.
9. Gietema JA, Sleijfer DT, Willemse PH, et al. Long-term follow-up of cardiovascular risk factors in patients given chemotherapy for disseminated nonseminomatous testicular cancer. *Ann Intern Med*. 1992;116(9):709-715.
10. Ykema BLM, Bisseling TM, Spaander MCW, et al. Diagnostic yield of colonoscopy surveillance in testicular cancer survivors treated with platinum-based chemotherapy: study protocol of a prospective cross-sectional cohort study. *BMC Gastroenterol*. 2021;21(1):67.
11. de Wijkerslooth TR, de Haan MC, Stoop EM, et al. Study protocol: population screening for colorectal cancer by colonoscopy or CT colonography: a randomized controlled trial. *BMC Gastroenterol*. 2010;10:47.
12. Butterly LF, Siegel RL, Fedewa S, Robinson CM, Jemal A, Anderson JC. Colonoscopy outcomes in average-risk screening equivalent young adults: data from the New Hampshire colonoscopy registry. *Am J Gastroenterol*. 2021;116(1):171-179.
13. USPSTF, Davidson KW, Barry MJ, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2021;325(19):1965-1977.
14. Hassan C, Antonelli G, Dumonceau JM, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) guideline – update 2020. *Endoscopy*. 2020;52(8):687-700.
15. Anderson JC, Butterly LF, Robinson CM, Goodrich M, Weiss JE. Impact of fair bowel preparation quality on adenoma and serrated polyp detection: data from the New Hampshire colonoscopy registry by using a standardized preparation-quality rating. *Gastrointest Endosc*. 2014;80(3):463-470.
16. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46(3):399-424.
17. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med*. 2012;366(8):687-696.
18. Martínez ME, Baron JA, Lieberman DA, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. *Gastroenterology*. 2009;136(3):832-841.
19. de Jonge V, Sint Nicolaas J, van Leerdam ME, Kuipers E, Veldhuyzen Van Zanten S. Systematic literature review and pooled analyses of risk factors for finding adenomas at surveillance colonoscopy. *Endoscopy*. 2011;43(7):560-572.
20. Teepen JC, Ronckers CM, Kremer LCM. Colorectal cancer screening in childhood cancer survivors. *J Natl Cancer Inst*. 2019;111(11):1114-1115.
21. Children's Oncology Group. *Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*. Version 5.0. Children's Oncology Group; 2018.
22. Michel G, Mulder RL, van der Pal HJH, et al. Evidence-based recommendations for the organization of long-term follow-up care for childhood and adolescent cancer survivors: a report from the PanCareSurFup Guidelines Working Group. *J Cancer Surviv*. 2019;13(5):759-772.
23. Kremer LC, Mulder RL, Oeffinger KC, et al. A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Pediatr Blood Cancer*. 2013;60(4):543-549.
24. Brown MC, Levitt GA, Frey E, et al. The views of European clinicians on guidelines for long-term follow-up of childhood cancer survivors. *Pediatr Blood Cancer*. 2015;62(2):322-328.
25. Ykema BLM, Breekveldt ECH, Carvalho B, et al. Somatic hits in mismatch repair genes in colorectal cancer among non-seminoma testicular cancer survivors. *Br J Cancer*. 2022;127(11):1991-1996.
26. Kuijk E, Kranenburg O, Cuppen E, Van Hoeck A. Common anti-cancer therapies induce somatic mutations in stem cells of healthy tissue. *Nat Commun*. 2022;13(1):5915.
27. Bruno PM, Liu Y, Park GY, et al. A subset of platinum-containing chemotherapeutic agents kills cells by inducing ribosome biogenesis stress. *Nat Med*. 2017;23(4):461-471.
28. Surveillance, Epidemiology and End Results (SEER). Colon and Rectum SEER Incidence Rates by Age at Diagnosis [Internet]; 1969/2020.
29. Nederlandse Kankerregistratie (NKR). NKR Cijfers Incidentie per jaar, Dikkedarmkanker + Endeldarmkanker [Internet]. NKR Cijfers. 22AD.
30. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. *Lancet Oncol*. 2012;13(1):55-64. doi:10.1016/S1470-2045(11)70283-2
31. Rigter LS, Spaander MCW, Aleman BMP, et al. High prevalence of advanced colorectal neoplasia and serrated polyposis syndrome in Hodgkin lymphoma survivors. *Cancer*. 2019;125(6):990-999.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Breekveldt ECH, Ykema BLM, Bisseling TM, et al. Prevalence of neoplasia at colonoscopy among testicular cancer survivors treated with platinum-based chemotherapy. *Int J Cancer*. 2024;154(8):1474-1483. doi:10.1002/ijc.34810