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

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7 COST-EFFECTIVENESS OF COLORECTAL CANCER SURVEILLANCE IN HODGKIN LYMPHOMA SURVIVORS TREATED WITH PROCARBAZINE-BASED CHEMOTHERAPY AND/OR INFRADIAPHRAGMATIC RADIOTHERAPY

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ABSTRACT

Background

Hodgkin lymphoma (HL) survivors (HLS) treated with infradiaphragmatic radiotherapy (IRT) and/or procarbazine have an increased risk of developing colorectal cancer (CRC). We investigated the cost-effectiveness of CRC surveillance in Dutch HLS to determine the optimal surveillance strategy for different HL subgroups.

Methods

The Microsimulation Screening Analysis-Colon model was adjusted to reflect CRC and other-cause mortality risk in HLS. Ninety CRC surveillance strategies were evaluated varying in starting and stopping age, interval, and modality (colonoscopy, fecal immunochemical test [FIT, OC-Sensor; cut-offs: 10/20/47 μg Hb/g feces], and multi-target stool DNA test [Cologuard®]). Analyses were also stratified per primary treatment (IRT and procarbazine or procarbazine without IRT). CRC deaths averted (compared to no surveillance) and incremental cost-effectiveness ratios (ICERs) were primary outcomes.

The optimal surveillance strategy was identified assuming a willingness-to-pay threshold of €20,000 per life-year gained (LYG).

Results

Overall, the optimal surveillance strategy was annual FIT (47 μg) from age 45-70 years, which might avert 70% of CRC deaths in HLS (compared to no surveillance; ICER: €18,000/LYG). The optimal surveillance strategy in HLS treated with procarbazine without IRT was biennial FIT (47 μg) from age 45-70 years (CRC mortality averted 56%; ICER: €15,000/LYG), and when treated with IRT and procarbazine, annual FIT (47 μg) surveillance from age 40-70 was most cost-effective (CRC mortality averted 75%; ICER: €13,000/LYG).

Conclusions

CRC surveillance in HLS is cost-effective and should commence earlier than screening occurs in population screening programs. For all subgroups, FIT surveillance was the most cost-effective strategy.

Clinical trial registration number: Dutch Trial Registry (ID NTR4961)

INTRODUCTION

Hodgkin lymphoma (HL) survivors treated with infradiaphragmatic radiotherapy (IRT) and/or procarbazine-containing chemotherapy have a higher risk of developing CRC in comparison to the general population with a relative risk between 2 and 7.[1-6] Overtime, the treatment for HL changed resulting in a better survival and therefore these patients have a higher chance of developing late adverse events, among which the development of second primary malignancies.[7] CRC surveillance may be indicated as a higher prevalence of (advanced) adenomas and serrated polyps has been shown.[6] Colonoscopy surveillance has the possibility to remove benign precursor lesions and to detect CRC in an earlier stage. Therefore, CRC surveillance potentially could decrease CRC incidence and improve CRC related mortality in HL survivors. However, tailored recommendations are lacking for this population.

It is unknown whether surveillance could lead to a clinically meaningful reduction in CRC mortality for HL survivors diagnosed at an adult age. In the United States, colonoscopy surveillance is recommended for young adults who survived childhood cancer (including HL) diagnosed before the age of 21 years and were previously treated with IRT. However, so far patients treated with procarbazine-containing chemotherapy have not been included in the recommendations.[8] Moreover, despite surveillance being recommended, participation rates in colonoscopy surveillance have been low among cancer survivors. An alternative CRC surveillance modality would be a non-invasive stool test, like a fecal immunochemical test (FIT) or multi-target stool DNA test (mt-sDNA), which were found to identify advanced neoplasia among HL survivors diagnosed at an adult age.[9] However, it is still unclear from which age to start CRC surveillance and which surveillance modality – colonoscopy or stool test – would be optimal and if it should vary according to previous HL treatment.

In this study, we performed a cost-effectiveness analysis using a microsimulation modelling approach to determine the optimal CRC surveillance strategy for HL survivors in The Netherlands, including both colonoscopy and stool test surveillance.

MATERIALS AND METHODS

We adjusted well-established Microsimulation Screening Analysis-Colon (MISCAN-Colon)[8,10-13] model to reflect the HL survivor population. Subsequently the model was used to evaluate benefits, harms and costs of a range of potential surveillance strategies. An incremental cost-effectiveness analyses was performed to determine which strategy is optimal.

MISCAN-Colon model

We adjusted the existing Microsimulation Screening Analysis-Colon (MISCAN-Colon) model for the Dutch general population to reflect the CRC and the other-cause mortality risk observed among HL survivors. MISCAN-Colon is a validated microsimulation model described extensively in previous papers.[8,10-13]

Adaptions of the MISCAN-Colon model to HL survivors

The adjustments for the HL population were based on a large Dutch cohort study that aimed to prospectively assess the prevalence of colorectal neoplasia in HL survivors, selecting 5-year HL survivors with first treatment performed between 1965 and 1995. The treatment strategies of that study were in accordance with treatment protocols of the European Organisation for Research and Treatment of Cancer. However, treatments for recurrence were not standardized. The adjustments are described in Table 1.

In our analysis, we adjusted an existing version of the MISCAN-Colon model to reflect CRC risk and life-expectancy of HL survivors (Table 1). We adjusted our model parameters using the standardized incidence ratio (SIR) of CRC observed in a Dutch cohort of HL survivors. Those rates detected a 3.0-fold increased risk of developing CRC for HL survivors (regardless of the HL treatment strategy, but treatment included IRT and/or procarbazine-containing chemotherapy) compared to the general population.[1] The MISCAN-Colon model specifically simulates the adenoma-carcinoma sequence,[14,15] and does not directly simulate serrated lesions. In the current study, we assumed that the progression times from adenoma onset to CRC progression among HL survivors were comparable to the general population. However, adenomas were assumed to be more often located in the proximal colon as seen in the cohort of Dutch HL survivors. Our model assumptions (for the natural history of CRC) were tested replicating observed Dutch and worldwide data on HL survivors (Supplementary Figures S1 and S2).[6,16] In this modelling exercise (model validation), we tested both assumptions related to the causes of the higher CRC risk (as consequence of a higher onset of adenoma [base case analysis] versus as consequence of a combination of higher adenoma onset and faster progression from adenoma to carcinoma [sensitivity analysis]) as described in the Methods of our study. The results of the stool tests (fecal immunochemical test (FIT) and multi-target stool test (Mt-sDNA)) were based on a prospective study, which evaluated the diagnostic accuracy in HL survivors.[9]

Table 1 | Key modelling assumptions.

Input parameter	Model assumptions	One-way sensitivity analyses
Demography		
All-cause mortality	Dutch lifetables (2016),[17] adjusted assuming 5.2-fold increased all-cause mortality in HL survivors	**1.** Dutch lifetables (2016),[17] adjusted assuming the following increased risks in all-cause mortality according years since HL diagnosis:[18] 10-14 years: RR = 7.2 15-19 years: RR = 4.7 20-24 years: RR = 4.3 25-29 years: RR = 5.0 ≥30 years: RR = 6.9 **2.** Dutch lifetables (2016),[17] adjusted assuming 3.12-fold increased all-cause mortality in HL survivors[19]
Natural history		

Adenoma onset	Age-dependent (non-homogenous Poisson) with more frequent adenoma (assumed after diagnosis of HL, age 25 years) adjusted according to CRC risks observed in HL survivors: Entire cohort of HL survivors: RR = 3.4; [λ] HL survivors with IRT + Procarbazine: RR = 7.12; [λ] HL survivors treated with procarbazine without IRT: RR = 2.1 [λ].	**3.** Entire cohort of HL survivors combined: RR = 1.75; [λ] HL survivors with IRT + Procarbazine: RR = 3.65 ; [λ] HL survivors treated with procarbazine without IRT: RR = 1.1. [λ] Assuming a shorter adenoma state duration compared to the general population: Exp(λ=70)[λ] **4.** According to Rigter et al (2019), Supplementary Figure 2: Entire cohort of HL survivors: RR = 4.85; [λ] HL survivors with IRT + Procarbazine: RR = 7.16; [λ] HL survivors treated with procarbazine without IRT: RR = 3.1 [λ]
Adenoma localization	Rectum: 7.9%; Sigmoid: 11.45%; Descending:10.75%; Transverse: 31.85%; Ascending: 26.05%; and Cecum:12%.[6]	**5.** Rectum: 26.38%; Rectosigmoid: 9.12%; Sigmoid: 26.37%; Descending:6%; Transverse: 9.01%; Ascending: 8.85%; and Cecum:14.27%.[20]
Adenoma progression		
State transitions	Age-dependent	

State durations, years (total)	Exp(λ=140) [λ]				See 3.
Cancer progression (preclinical)					
Stage transitions	Age-dependent				
Stage durations, years	Exp(λ=2.5)				
Colorectal cancer survival	Age-/Stage-/Localization-dependent				**6.** 1.33-fold lower compared to Dutch general population with a CRC diagnosis[18]
FIT and sMT-DNA performance					
	FIT				
Sensitivity***, %	10 µg Hb/g feces	20µg Hb/g feces	47 µg Hb/g feces	MT-sDNA	**7.** Systematic FIT negative results were assumed[22] **8.** Sensitivity for adenomas (6-9mm, %)[20]: 10 µg Hb/g feces = 9.6; 20 µg Hb/g feces = 4.4; 47µg Hb/g feces = 2.5.
adenomas <10mm	0	0	0	0	
adenomas ≥10mm	26.5	18.5	12.6	31.1	
malignant neoplasia (early) §§[17]	65	52.5	50	97	
malignant neoplasia (late) §§[17]	90	83.5	82.5	86	
Specificity, %	91	95	96	62	
Colonoscopy performance					
Sensitivity†, %					
adenomas 0-5mm	75				
adenomas 6-9mm	85				
adenomas ≥10mm	95				
malignant neoplasia	95				
Specificity‡, %	86				

Complete colonoscopy examination, %	100[6]	**9.** 92[20]
Complication rates, % with polypectomy[§]	Age-dependent	
Fatal complications[‖]	0.000329	
without polypectomy	-	
Costs,[¶]		
FIT	15	
sMT-DNA	604*	
Colonoscopy		
with polypectomy	887	
without polypectomy	679	
Complications[#,**,††]	3,488	
Per life-year with cancer care		
Initial year, stage I-IV	15,222-30,444	**10-11.**
Ongoing, stage I-IV	414	50% higher and 100% higher
Terminal year (CRC death), stage I-IV	21,311-30,444	
Terminal year (other causes), stage I-IV	5,358-17,049	
Discounting rates (Cost-effectiveness analysis)		**12.**
Benefits	3%	1.5%
Costs	3%	4%

IRT = infradiaphragmatic radiation therapy; CRC = colorectal cancer; HL = Hodgkin Lymphoma; and RR = relative risk.

[λ] The combination of increased adenoma onset and short adenoma state duration resulted in a risk of CRC (compared to Dutch general population), respectively, of 3.0-fold higher in the entire cohort of HL survivors, 2.0-fold in HL survivors treated with

procarbazine without IRT, and 5.7-fold in HL survivors treated with IRT and procarbazine (Figure 1)[6];

† The sensitivity of colonoscopy for the detection of adenomas and CRC within the reach of the endoscope was obtained from a systematic review on miss rates seen in tandem colonoscopy studies[23];

‡ Specificity for colonoscopy is therefore based on an adenoma prevalence study of patients undergoing surveillance colonoscopy[24];

§ Age-specific risks for complications of colonoscopy requiring a hospital admission or emergency department visit were obtained from a study by Warren et al[25];

|| The mortality rate associated with colonoscopies with a polypectomy was derived by multiplying the risk for a perforation obtained from a study by Warren et al[25] by the risk for death given a perforation obtained from a study by Gatto et al [26].

¶ Costs are presented in Euro;

Serious GI complications included perforations, gastrointestinal bleeding, or transfusions;

** Other GI complications included paralytic ileus, nausea and vomiting, dehydration, or abdominal pain;

†† Cardiovascular complications included myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, or shock;

§§ FIT sensitivity for malignant neoplasia were informed using the study of Goede SL et al (2013). For FIT 47 µg Hb/g feces those sensitivity values were assumed equal to those provided for FIT 40 µg Hb/g feces;[20]

* maximum reimbursement cost in US as assumed in Lew et al. (2018) IJC[27];

*** Sensitivities were per-lesion.

Adjustments to reflect the Hodgkin lymphoma population: 3 cohorts

Briefly, we used the standardized incidence ratio (SIR) of CRC observed in a Dutch cohort of 5-year HL survivors to assume a 3.0-fold increased risk of CRC in HL survivors (for the entire cohort including all HL treatment strategies including IRT and/or procarbazine-containing chemotherapy) compared to the general population (Figure 1).[1] We did not assume changes in risk over calendar time. In our model, we assumed that the higher CRC risk was a consequence of a higher incidence of adenomas. We assumed the same adenoma incidence as the Dutch general population before HL diagnosis and treatment (from age 0 to 24 years), and increased adenoma incidence after that. Model validations are reported in Supplementary Document (Supplementary Figures S1 and S2). We also adjusted the model to consider the 5.2 times higher risk of death for all-causes (excluding anal and colorectal cancer mortality) observed among HL survivors (compared to the general population in same age, gender, and calendar period).[7]

The different treatment strategies for HL resulted in different SIRs for developing CRC.[1] Compared to the general population, HL survivors treated with procarbazine without IRT had a 2.0-fold higher SIR for CRC, whereas in those treated with IRT and procarbazine the risk was 5.7-fold higher.[1] We, therefore, also performed separate analyses considering differences in CRC risk based on HL treatment (increasing or decreasing the risk accordingly). In those analyses, we assumed no difference in all-cause mortality by HL treatment (i.e. 5.2-fold higher than the general population).[7] Validation of these two separate model versions was performed and reported in Figure 1.

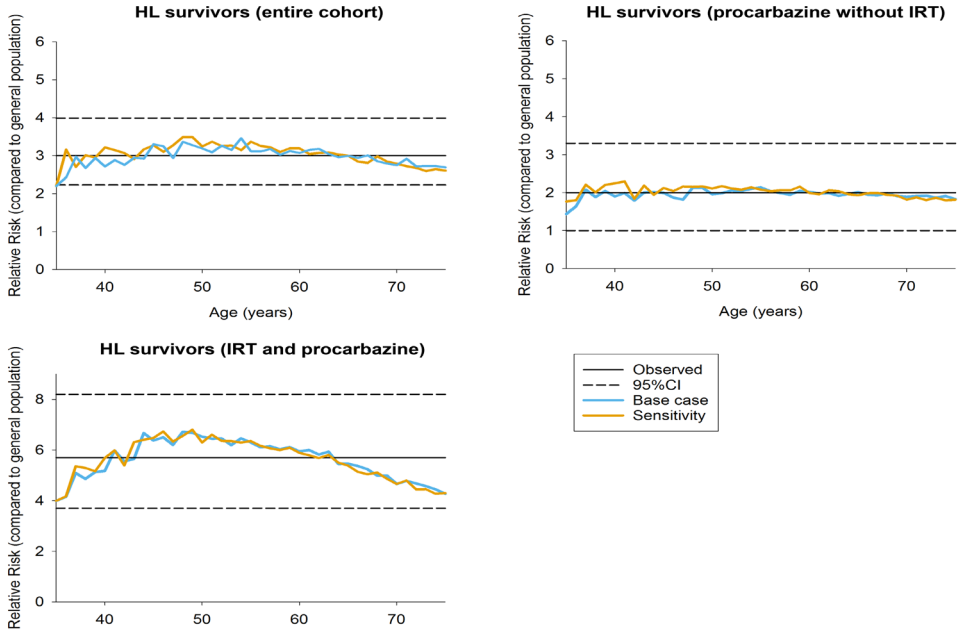

Figure 1 | Simulated and expected adenoma prevalence and relative risks for colorectal cancer (compared to average risk individuals) among Hodgkin Lymphoma survivors. Relative risks were also computed per primary cancer treatment (procarbazine-containing chemotherapy or combination of radiotherapy and procarbazine chemotherapy). Simulated outcomes were computed assuming no surveillance.

Surveillance strategies simulated

We performed a cost-effectiveness analysis for each HL survivor group to explore possible reasonable options to determine the most optimal surveillance strategy. We evaluated benefits and costs of 90 different surveillance strategies (including no surveillance) varying in test modality (colonoscopy, FIT with different positivity cut-offs, or mt-sDNA), age to start (35, 40, 45, 50 years), intervals (3, 5, and 10 years for colonoscopy, and 1 and 2 years

for stool tests), and age to end (70 or 75 years). These variations were evaluated to determine the most beneficial strategy for the different subgroups. Test characteristics of the stool tests for detecting advanced neoplasia were based on diagnostic analysis previously performed in HL survivors treated with IRT and/or procarbazine-containing chemotherapy who prospectively underwent a colonoscopy and performed stool tests prior to colonoscopy (Table 1).[9] For FIT (OC-Sensor, Eiken Chemical, Tokyo, Japan), three different pre-determined cut-offs were evaluated, specifically 10, 20, 47 µg Hb/g feces. The positivity at the mt-sDNA test (Cologuard®, Exact Sciences Corporation, Madison, United States) was classified as described in previous studies.[9,28] Participants with a positive stool test were simulated to undergo a colonoscopy.[6] We assumed that the completion rate of colonoscopy was 100% and the complication rate was similar to the general population. We assumed 100% participation in all surveillance and diagnostic follow-up.

Costs

We applied a modified societal perspective for the cost-effectiveness analysis, including patient time costs but no other indirect costs (i.e. traveling). Cost for colonoscopy and FIT surveillance has been informed from the monitoring report of the Dutch FIT organized screening programme.[29] As information on the cost for the mt-sDNA test are lacking in the Netherlands, we assumed the maximum out-of-pocket cost ($649, 2017) of Cologuard in U.S. market.[27,30] Costs for treatment and care of CRC have previously been published.[31] All costs were updated to the year 2019 using the cost price index from the Dutch Health Care Authority.[32]

Outcomes

We simulated three cohorts of 10 million HL survivors aged 35 years-old in 2019 (with HL diagnosed at age of 25 years) for the three treatment categories (entire cohort of HL survivors including all HL treatment strategies, HL survivors treated with procarbazine without IRT, and HL survivors treated with IRT and procarbazine). We simulated three cohorts of individuals all born in the same year. Although the actual number of HL survivors in the Netherlands evidently is not in that order of magnitude,[8,11] the large cohort sample size was chosen to guarantee stable model outcomes in our simulations. To endorse generalizability to HL survivor populations of different sizes all outcomes are reported per 1.000 survivors aged 35 years in 2019. Age 35 was chosen because the simulated increase in adenoma incidence from age 25 years onwards would require at least 10 years for these adenomas (caused by HL treatment) to result in an increase in CRC incidence. As the information used to inform the model was limited, the increase in the adenoma incidence

was assumed to not change according to period of HL diagnosis.
For each surveillance strategy, the surveillance effectiveness (i.e., number of CRC deaths prevented, relative CRC mortality reduction and life-years gained (LYG)) and resources (colonoscopies, FIT, mt-sDNA test and cost) were analysed, discounting the LYG and cost at the conventional 3% annual discount rate (Supplementary Tables S1-3). We calculated the number of colonoscopies needed to prevent a CRC death by dividing the total number of colonoscopies performed (per 1000) by the number of CRC deaths prevented per 1000 HL survivors screened, referred to as number needed to screen (NNS, Supplementary Tables S4-6). For each group of HL survivors, we also predicted CRC deaths and total costs simulating two existing surveillance recommendations indicated in the Netherlands: i) the screening strategy for the Dutch general population (biennial FIT, i.e, once every two years, from age 55 to 75 years, 47 µg Hb/g feces); and ii) the surveillance strategy for individuals with a family history of CRC (colonoscopy surveillance repeated every 5 years from age 45 to 75 years).

Cost-effectiveness analyses
The optimal CRC surveillance strategy in HL survivors was determined by first excluding strategies that were more expensive and less effective than (combinations of) other simulated strategies.[33] For the remaining strategies (defined as 'efficient strategies'), we calculated the incremental cost-effectiveness ratio (ICER) by comparing the ratio between additional costs and LYG to the next less expensive efficient strategy. The optimal strategy was defined as the most effective strategy with an ICER below the willingness-to-pay threshold of €20,000 per LYG.[31,34] Strategies with an ICER exceeding €20,000 were considered not cost-effective. A separate analysis was performed excluding the stool tests to evaluate which colonoscopy surveillance program was most cost-effective (results reported and discussed in the Supplementary Methods and Supplementary Tables S7-S9).

Senstivity analyses
Multiple one-way sensitivity analyses were performed to reinforce the results under a variety of assumptions (Table 1). Those assumptions included an adjustment in the lifetables including different relative risks for different intervals after HL treatment;[18] another adjustment in the lifetables based on Anderson et al;[19] higher CRC risk as shown in a prospective study in which HL survivors underwent a colonoscopy and a higher prevalence of advanced neoplasia was detected; Supplementary Figure S2;[6] different CRC localization (in line with the general Dutch population);[6] a 1.33 lower CRC relative survival;[21] systematic FIT negative results;[22] FIT sensitivity for medium ade-

nomas (6-9 mm) assumed as reported for the Dutch general population;[20] a different assumption for the pathway to higher CRC risk in HL survivors (CRC risk caused by a higher adenoma onset in combination with a twice-faster adenoma progression, Figure 1); a lower complete colonoscopy examination rate (92% instead of 100%); higher costs for CRC treatment and care (50% and 100% higher); and 4% discount rate for costs and 1.5% for benefits as recommended by the Dutch Ministry of Health.[35]

Data availability

The data generated in this study are available within the article and its supplementary data files. Detailed data generated in this study about the MISCAN model is available upon request from the corresponding author.

RESULTS

In the entire HL survivor cohort (not stratified by HL treatment), 26 CRC deaths per 1000 HL survivors (starting aged 35 years in 2019) were predicted over a lifetime in the absence of surveillance (Table 2). Up to 49% of those CRC deaths may be averted with the recommended screening strategy for the Dutch general population (Figure 2) with biennial FIT 47 µg Hb/g feces between 55-75 years of age at the total costs of € 1.1 million per 1000 HL survivors (NNS = 75, data not shown). The surveillance strategy indicated for individuals with family history of CRC being primary colonoscopy surveillance from age 45 years can prevent up to 80% of CRC mortality in HL survivors, however, at higher costs (total costs €2.4 million per 1000 HL survivors, NNS = 222). The most optimal cost-effective CRC surveillance strategy was annual FIT surveillance from age 45 to 70 years using a positivity cut-off threshold of 47 µg Hb/g feces, which prevented up to 70% of CRC mortality, however, at lower costs than the previous colonoscopy strategy (compared to no surveillance; total costs € 1.4 million per 1000 HL survivors; NNS = 75; ICER = €18,000 per LYG, Figure 3, Table 2, and Supplementary Table 7). For HL survivors treated with procarbazine without IRT, the model predicted 17 CRC deaths per 1000 HL survivors without surveillance. Up to 47% of those deaths could be prevented with the CRC screening strategy adopted for the Dutch general population (biennial FIT at cut-off 47 55 from age 75 years, total costs €0.8 million per 1000 HL survivors, NNS = 60, data not included); whereas 80% could be avoided by primary colonoscopy surveillance with a starting age of 45 years, however, at higher costs (total costs = €2.2 million per 1000 HL survivors, NNS = 336; Figure 2).

Table 2 | Efficient surveillance strategies among Hodgkin Lymphoma survivors per primary cancer treatment (base case analysis).

Surveillance strategies	Outcomes per 1,000 HL survivors free of CRC diagnosis and aged 35 years in 2019 (3%)*												Reductions:		ICER
	FITs	Scr. COLs	Diag. COLs	Surv. COLs	Total COLs	Com-pl.	CRCs†	CRC dea-ths†	CRC care	LYG ‡	Total costs	Net costs‡	Inci-dence (%)‡	Mortal-ity (%)‡	(*1,000)
Entire cohort of HL survivors															
No Surveillance	0	0	33	0	33	0	73	26	214	0	966	0	0	0	0
FIT47, 50-70, 2 years	3457	0	199	145	344	2	63	12	274	38	1161	196	13	54	5
FIT47, 45-70, 2 years	4936	0	254	198	452	2	60	11	273	46	1224	258	18	59	8
FIT20, 45-70, 2 years	4779	0	342	258	599	3	54	10	253	49	1271	306	26	63	13
FIT47, 45-70, 1 years	**8957**	**0**	**408**	**293**	**701**	**3**	**51**	**8**	**254**	**55**	**1373**	**407**	**30**	**70**	**18**
FIT47, 40-70, 1 years	12490	0	536	361	897	3	49	7	246	61	1537	571	33	72	29
FIT20, 40-70, 1 years	11975	0	740	447	1187	4	43	7	220	64	1681	716	41	75	53
FIT20, 35-70, 1 years	16252	0	976	510	1486	4	42	6	214	67	1943	978	42	76	75
FIT20, 35-75, 1 years	16611	0	997	511	1508	4	43	6	215	67	1967	1001	42	78	87
FIT10, 35-70, 1 years	15462	0	1491	634	2125	5	37	5	188	70	2339	1374	49	79	130
FIT10, 35-75, 1 years	15809	0	1523	634	2158	5	37	5	189	70	2370	1405	49	80	148
COL, 35-70, 3 years	0	4864	3	1956	6822	9	22	3	112	80	5337	4371	70	88	308
COL, 35-75, 3 years	0	5003	2	1956	6960	9	21	3	112	80	5437	4471	71	89	439
HL survivors treated with procarbazine without IRT															

No Surveillance	0	0	22	0	22	0	49	17	141	0	637	0	0	0	0
FIT47, 50-70, 2 years	3568	0	183	108	291	1	44	8	184	23	847	210	11	52	9
FIT47, 45-70, 2 years	**5075**	**0**	**240**	**147**	**387**	**2**	**42**	**8**	**183**	**28**	**916**	**279**	**15**	**56**	**15**
FIT20, 45-70, 2 years	4945	0	331	194	525	2	38	7	170	30	977	339	23	61	25
FIT47, 45-70, 1 years	9340	0	402	222	623	2	36	6	171	35	1091	453	27	68	28
FIT47, 40-70, 1 years	12963	0	535	273	808	2	34	5	167	38	1257	620	30	70	45
FIT47, 40-75, 1 years	13362	0	550	274	825	3	35	5	169	39	1279	642	29	72	71
FIT20, 40-70, 1 years	12528	0	753	343	1096	3	30	5	149	40	1418	781	39	74	88
FIT47, 35-75, 1 years	17784	0	713	314	1027	3	34	5	166	41	1479	842	31	74	91
FIT20, 35-75, 1 years	17273	0	1018	393	1411	3	29	4	146	43	1705	1068	40	77	115
FIT10, 35-70, 1 years	16223	0	1550	494	2043	4	25	4	127	45	2103	1465	49	79	182
FIT10, 35-75, 1 years	16597	0	1585	494	2079	4	25	3	127	45	2135	1498	49	80	191
COL, 35-70, 3 years	0	5209	2	1611	6822	7	14	2	73	52	5176	4539	72	88	461
COL, 35-75, 3 years	0	5359	1	1611	6972	8	14	2	73	52	5284	4647	72	90	623
HL survivors treated with IRT and procarbazine chemotherapy															
No Surveillance	0	0	59	0	59	1	127	47	392	0	1753	0	0	0	0
FIT20, 50-70, 2 years	3094	0	291	282	573	3	96	18	463	81	1867	113	24	61	1

FIT20, 45-70, 2 years	4465	0	367	387	754	4	90	16	451	100	1929	175	29	67	3
FIT10, 45-70, 2 years	4197	0	501	494	995	5	80	13	419	108	1998	244	37	72	8
FIT47, 45-70, 1 years	8255	0	426	434	860	4	85	13	451	109	2006	253	33	72	10
FIT47, 40-70, 1 years	**11623**	**0**	**545**	**540**	**1086**	**5**	**81**	**12**	**435**	**121**	**2156**	**403**	**36**	**75**	**13**
FIT20, 40-70, 1 years	10997	0	723	655	1378	5	72	11	391	125	2268	515	43	77	25
FIT20, 35-70, 1 years	15099	0	945	753	1698	6	70	10	377	132	2528	774	45	78	41
FIT20, 35-75, 1 years	15414	0	963	754	1717	6	70	10	378	132	2549	796	44	79	69
FIT10, 35-70, 1 years	14131	0	1393	916	2309	7	63	9	336	137	2877	1123	50	80	73
FIT10, 35-75, 1 years	14436	0	1422	916	2338	7	63	9	337	137	2904	1151	50	81	115
COL, 35-70, 3 years	0	4289	5	2516	6810	11	41	6	217	153	5700	3947	68	88	173
COL, 35-75, 3 years	0	4410	4	2516	6930	12	40	5	218	153	5787	4034	68	89	283

HL=Hodgkin Lymphoma; IRT = infradiaphragmatic radiation therapy; LYG= life years gained; COLs = colonoscopies; ICER = Incremental cost-effectiveness ratio (Δcosts/ΔLYs gained compared to the previous less costly efficient strategy); † CRC cases and CRC death were not discounted; ‡ Compared with no surveillance; * Full participation in surveillance and post-colonoscopy surveillance was assumed; Optimal surveillance strategies were reported in bold.

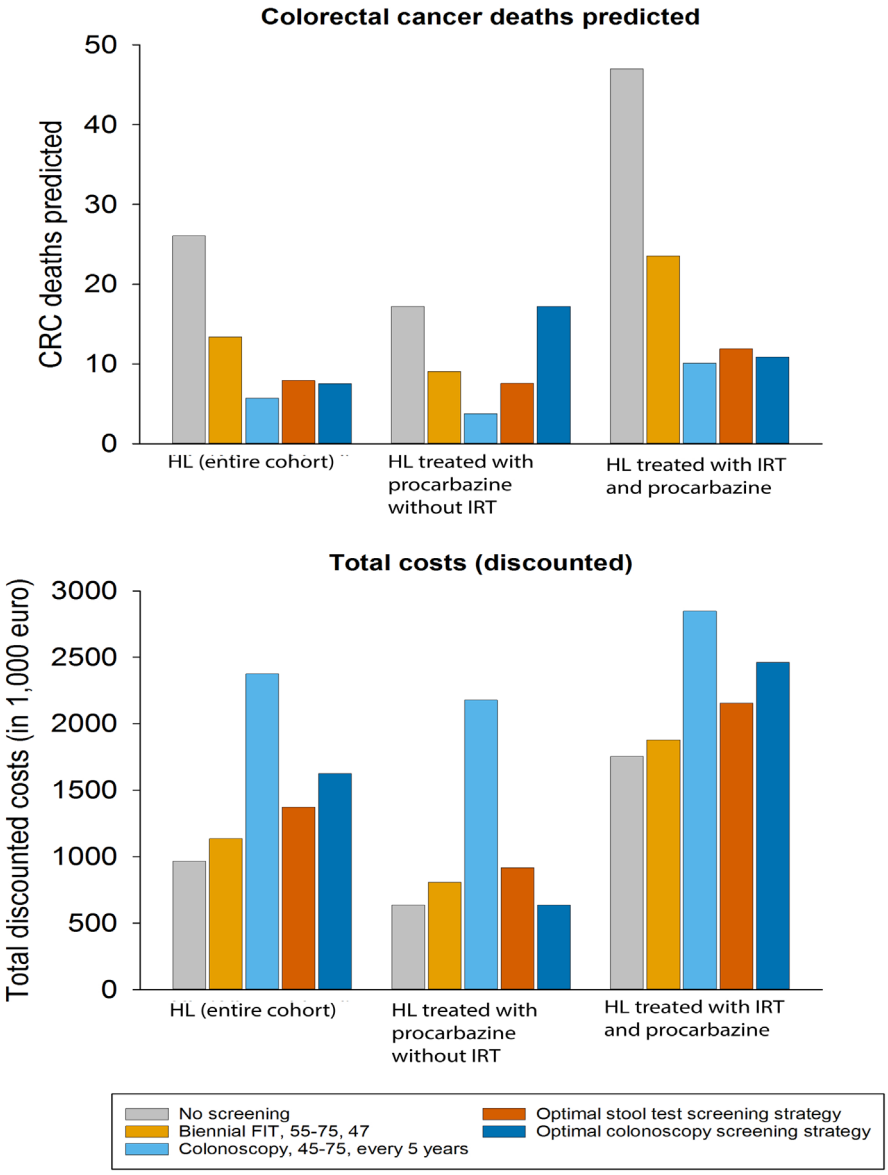

Figure 2 | Colorectal cancer deaths and total costs per 1,000 Hodgkin Lymphoma survivors aged 35-years old in 2019 under different surveillance scenarios. Optimal stool test surveillance strategies were determined in Table 2. Optimal colonoscopy surveillance strategies were determined in Supplementary Tables 4-6. A willingness-to-pay threshold of €20,000 per LYG was assumed in determining the optimal surveillance strategy in each group. CRC = Colorectal Cancer; HL = Hodgkin Lymphoma; COL = Colonoscopy; FIT = Fecal immunochemical test; IRT = infradiaphragmatic radiation therapy.

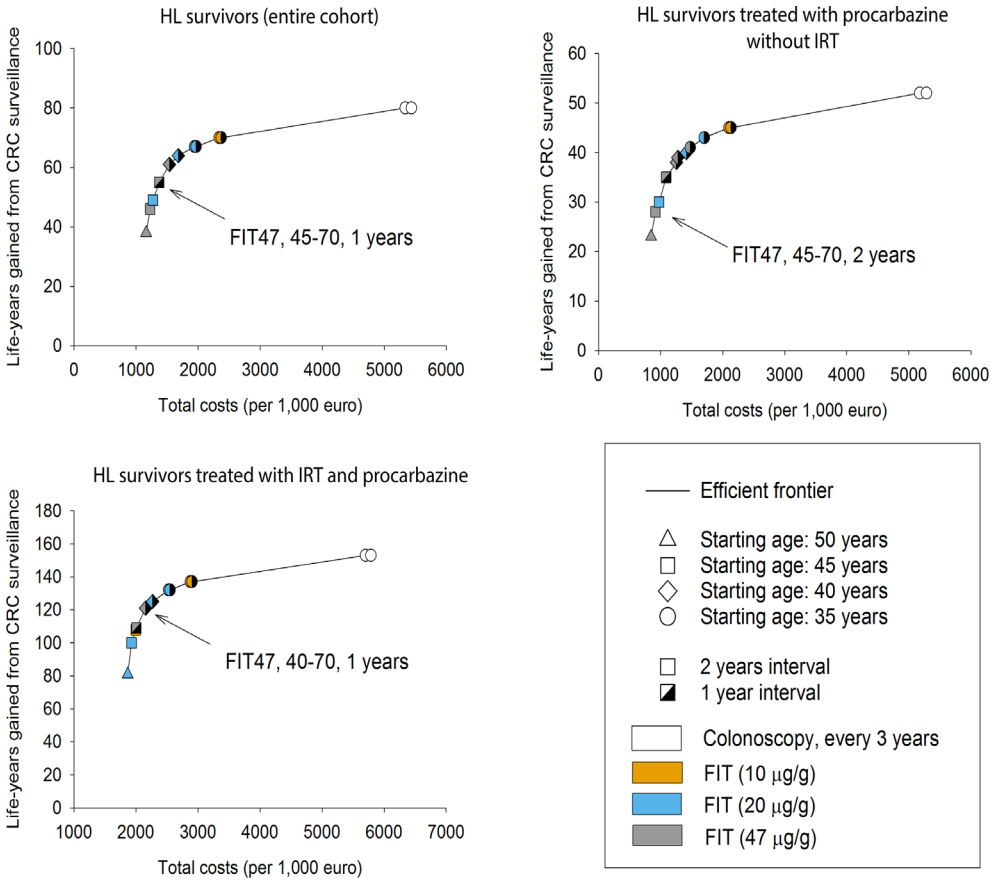

Figure 3 | Efficient frontier with efficient surveillance strategies for Hodgkin Lymphoma survivors (entire cohort), Hodgkin Lymphoma survivors treated with procarbazine chemotherapy, and Hodgkin Lymphoma survivors treated with infradiaphragmatic (IRT) and procarbazine chemotherapy. Total costs and life-years gained from surveillance were discounted (3% discounting rate) and 100% adherence was assumed for surveillance and diagnostic test. Optimal surveillance strategies are labelled and indicated by arrows.

However, we found that biennial FIT surveillance (47 µg Hb/g feces) from age 45 and 70 years was the optimal strategy, preventing 56% of CRC mortality (compared to no surveillance) at an acceptable cost of €15,000/LYG (total costs = € 0.9 million per 1000 HL survivors; NNS = 79; Figure 3, Table 2, and Supplementary Table 5 and 11).

In HL survivors treated with IRT and procarbazine, 47 CRC deaths (per 1000 HL) were predicted without surveillance. Screening as suggested for the Dutch general population may prevent up to 50% of those deaths (at the costs €1.9 million per 1000 HL survivors, NNS = 32, data not included); whereas surveillance recommended for individuals with family history of CRC prevented up to 81% of CRC (at the cost of €2.8 million per 1000 HL survivors, NNS = 124; Figure 2). Nevertheless, annual FIT surveillance (47 µg Hb/g feces) from age 40 and 70 years was optimal, averting 75% of CRC mortality (compared to no surveillance; total costs = € 2.2 million per 1000 HL survivors; ICER = €13,000 per LYG; NNS = 56; Figure 3, Table 2, and Supplementary Table 6 and 12).

For each group of HL survivors, colonoscopy surveillance was estimated not to be cost-effective in comparison to FIT (Supplementary Table 7-9). Separate analyses were performed excluding stool test surveillance and only including colonoscopy surveillance. This analysis is described in Supplementary Methods and Supplementary Tables 7-9.

Sensitivity analysis

In all sensitivity analyses, FIT surveillance was most cost-effective for all HL treatment strategies. The optimal cut-off for FIT was quite sensitive to model assumptions. The optimal cut-off changed to a lower cut-off in 31% of the sensitivity analyses. This included among others the analyses which assumed i) higher all-cause mortality in the entire HL cohort, ii) the same FIT sensitivity for medium adenomas as in the general population and iii) higher CRC treatment costs (Table 3). The age range was quite robust, and only changed in the two sensitivity analyses that assumed i) a higher CRC risk in HL survivors and ii) the Dutch discounting factors for the entire cohort. The most cost-effective interval changed in a few sensitivity analyses (Table 3).

Table 3 | Optimal surveillance strategies* under different sensitivity analyses.

	HL (Entire cohort)	HL (Procarbazine without IRT)	HL (IRT + Procarbazine)
Basecase analysis	FIT47, 45-70, 1 year	FIT47, 45-70, 2 years	FIT47, 40-70, 1 year
Sensitivity analyses:			
1. Adjustment lifetables including different relative risks for different intervals after HL treatment	FIT20, 45-70, 2 years	Unchanged	Unchanged
2. Adjustment in the lifetables based on other Anderson et al	Unchanged	FIT47, 45-70, 1 year	FIT20, 40-70, 1 year
3. Higher CRC risk caused by higher adenoma onset	FIT47, 40-70, 1 year	FIT47, 45-70, 1 year	Unchanged
4. Different adenoma localization	Unchanged	Unchanged	Unchanged
5. 1.33-fold Higher CRC relative survival	Unchanged	Unchanged	Unchanged
6. Systematic FIT negative results	Unchanged	Unchanged	Unchanged
7. FIT sensitivity for medium adenomas (6-9mm) as general population	Unchanged	Unchanged	FIT10, 40-70, 2 years
8. CRC risk caused directly by a combination of higher adenoma onset and faster adenoma progression	Unchanged	Unchanged	FIT20, 40-70, 1 year
9. Lower complete colonoscopy examination rate (92%)	Unchanged	Unchanged	Unchanged
10. Higher CRC treatment costs (+50%)	FIT10, 45-70, 2 years	FIT20, 45-70, 2 years	FIT10, 40-70, 2 years
11. Higher CRC treatment costs (+100%)	FIT10, 45-70, 2 years	FIT10, 45-70, 2 years	FIT20, 40-70, 1 year
12. Discounting factor (4% costs, 1.5% benefits)	FIT47, 40-70, 1 year	FIT47, 45-70, 1 year	FIT20, 40-70, 1 year

* assuming a willingness to pay threshold of €20,000 per life-year gained from surveillance.

DISCUSSION

Recent studies have suggested that HL survivors, who received IRT, procarbazine-containing chemotherapy or both, should undergo CRC surveillance at an earlier age than recommended in population screening programs due to their increased risk of developing CRC before age 55[1-4] and the high prevalence of colonic advanced neoplasia already at young ages.[6] Using an established micro-simulation model, we found that FIT is the most cost-effective CRC surveillance strategy in this population, regardless of the HL treatment associated CRC risk. Depending on the HL treatment, the optimal age of commencing surveillance ranged from 40 to 45 years, which is earlier than practised in most CRC screening programs. We showed that the optimal FIT positivity cut-off was 47 µg Hb/g feces when offering FIT annually to HL survivors in general (the entire cohort) or to those treated with IRT and procarbazine. This FIT positivity cut-off is also used in the Dutch CRC screening programme for the average-risk population where, however, FIT is offered biennially. For those HL survivors treated with procarbazine without IRT (patients at lower CRC risk than those with additional IRT) the same program as for the general population would be beneficial, only with a starting age at 45 (biennially and FIT positivity cut-off (47 µg Hb/g feces).

The earlier optimal age of surveillance invitation reflects the higher risk of CRC among HL survivors at a younger age[1,2,6,36] and is in line with the increased risk after 10 to over 30 years from HL treatment (at a median age of 27 years).[1] Moreover, our model shows that surveillance for HL survivors could stop at age 70 years, five years earlier than recommended in most (European) CRC screening programs (75 years). This can be related to the high all-cause mortality observed among HL survivors.[7,19] In HL survivors, performing surveillance at an older age might directly result in CRC overdiagnosis and overtreatment with no improvement of life-expectancy (no CRC death averted).

In line with previous studies on the cost-effectiveness of mt-sDNA in the asymptomatic population,[37-40] we found that mt-sDNA was not cost-effective compared to other modalities. Although mt-sDNA was estimated to reduce CRC incidence and mortality, it was an inefficient surveillance option (less effective and higher costs).[37]

This study has several limitations. Firstly, the MISCAN model assumes that all CRCs arise through a traditional adenoma-carcinoma sequence, and the pathway of development of serrated polyps is not (yet) included in MISCAN. To

avoid bias towards FIT surveillance, which is less sensitive for serrated lesions than mt-sDNA,[9,28,41] we have modelled advanced serrated lesions as large adenomas, assuming the same progression rate for both types of lesions. Previously, in the prospective colonoscopy study, we detected significantly more advanced serrated polyps and serrated polyposis syndrome in HL survivors compared with the general population,[6] which may have impact on our model adjustments even though the CRC risk was considered. As we could not disentangle those colonoscopy results to correctly inform our current model structure, we decided to consider the advanced serrated lesions as advanced adenomas. With this assumption, we could compute the adenoma prevalence in HL survivors in way which allow us to validate the model (Supplementary Figure S2). Furthermore, by applying FIT parameters computed from data which include both adenomas and serrated lesions in HL survivors, our model results were indirectly adjusted to account the potential presence of serrated lesions. A second limitation is that we cannot inform sensitivity of the FIT and mt-sDNA for CRC based on the prospective data in HL survivors, because no CRC was detected in this cohort, only precursor lesions.[6,9] Thus, CRC sensitivity model parameters were based on data from the average-risk population.[20] Furthermore even for precursor lesions, the sample size was small for evaluating the stool test sensitivity.[9] Moreover, the exact pathogenesis of CRC in HL survivors remains unknown. Previous research by our group detected a higher prevalence of microsatellite instability (MSI) CRC in HL survivors due to double somatic mutations in mismatch-repair genes,[42] suggesting a faster progression from precursor lesions to CRC.[43] Hence, we performed a specific sensitivity analysis assuming faster progression from adenoma to CRC in HL survivors. We found that the optimal surveillance strategy was not sensitive to this assumption. Furthermore, we assumed full adherence to follow-up and surveillance procedures because this provides unbiased estimates for optimal surveillance strategies. Results should therefore be used to guide policy, but not to take these results as the estimated impact of that policy. In practice, adherence to surveillance is usually lower, resulting in a lower impact of surveillance than suggested. When imperfect adherence is assumed, this would result in strategies with short intervals and larger age target to compensate for the suboptimal surveillance. This would result in HL survivors who adhere to surveillance to be over-screened. If only 41% of the population would participate, the costs, benefits and harms of the program would decrease proportionally. Considering the low uptake of colonoscopy screening observed among childhood cancer survivors in US (i.e. 11.5%),[44] our findings about the benefits of FIT surveillance in HL may have vital importance as stool tests are generally characterized by higher participation rates compared to colonoscopy (at least in the average-risk population).[45] To assess the robustness of our

modelling estimates, a full probabilistic sensitivity analysis was not performed as extremely resource-demanding. Thus, we focused our assessments carrying out several one-way sensitivity analyses on key specific model parameters. Finally, HL treatment regimens have changed over the past decades with a reduction of radiotherapy volumes and doses and changes in chemotherapy regimens, although procarbazine is still used in e.g. the BEACOPP regimen.[46] Hence, patients currently diagnosed with HL might have a lower CRC risk and a less intensive surveillance could be optimal.[2]

One of the strengths of this study is that this is the first cost-effectiveness analysis of stool testing performed for HL survivors. Our study suggests that FIT stool tests are cost-effective modalities for CRC surveillance in this known high-risk-group for developing CRC. FIT is easy to perform and non-invasive. Reducing the use of colonoscopy surveillance will reduce potential harms (i.e. colonoscopy burden and complications) and be beneficial for the national healthcare system limiting the demand of colonoscopy and the workload of gastroenterologists. This will not only impact HL survivors, but also other high-risk-groups. Currently, ongoing research is aiming to evaluate whether stool test surveillance might also be beneficial in other high-risk-groups.[47]

CONCLUSIONS

CRC surveillance in HL survivors at increased risk for CRC (treated with IRT and/or procarbazine-containing chemotherapy) is cost-effective and should commence earlier than in the general population. For all examined HL subgroups, FIT surveillance was the most cost-effective strategy. This implies introduction of surveillance with a modality that is currently not used for surveillance in high-risk groups but is extensively used in population-based CRC screening programs.

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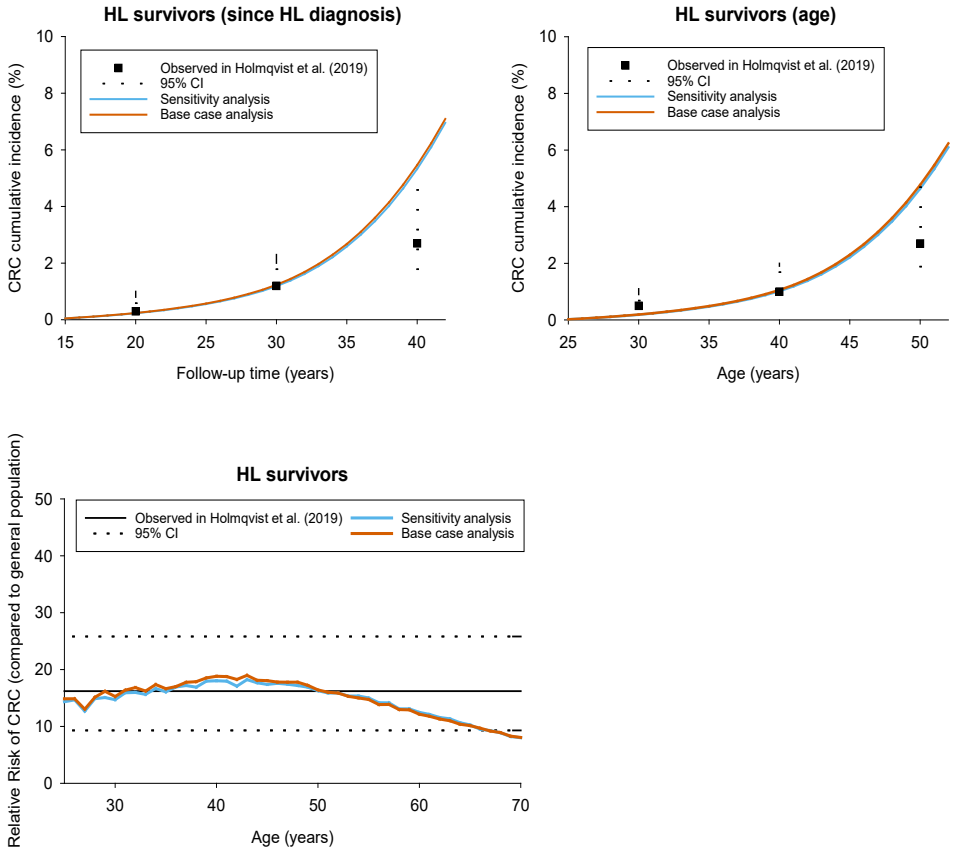
SUPPLEMENTARY DOCUMENT

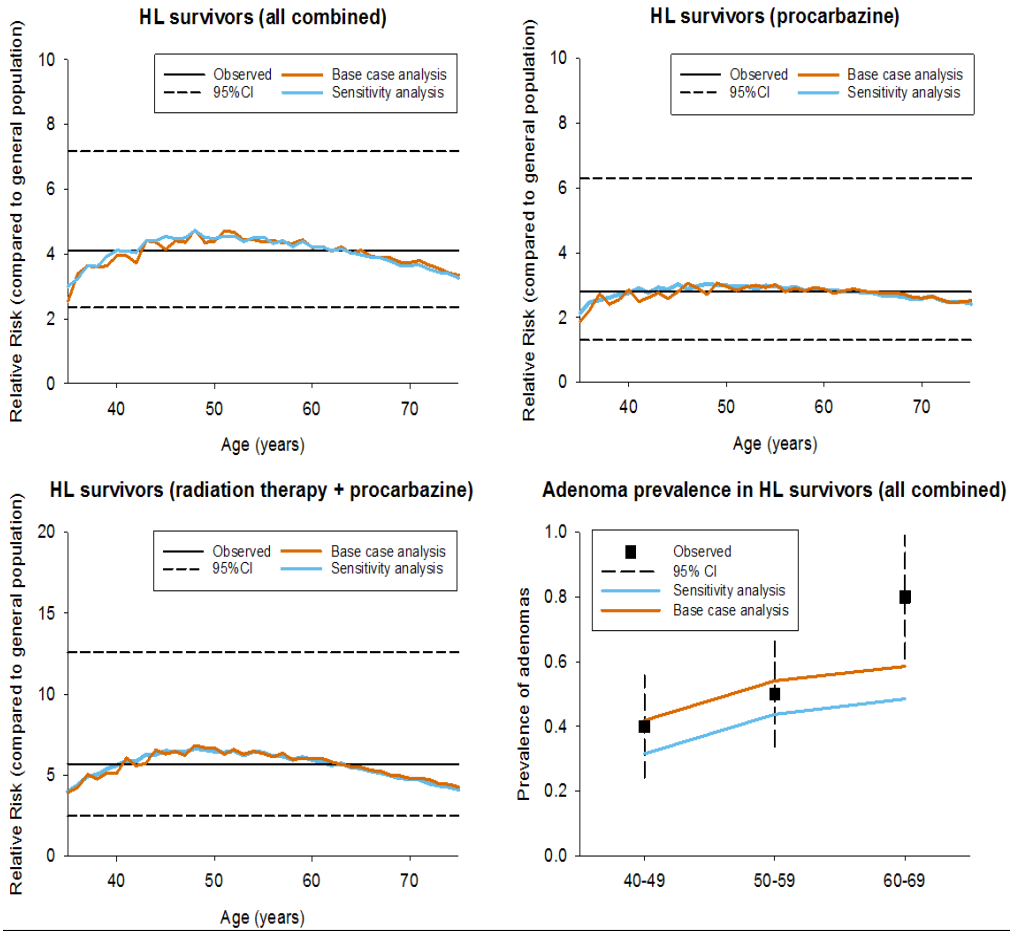
SUPPLEMENTARY METHODS

Model Validation

Our model was validated against published data (Figure 1 and Supplementary Figures S1 and S2) and it showed a good fit in replicating the observed data. However, there were two discrepancies between simulated and observed outcomes. First, our model overestimated long-term follow-up outcomes when replicating the results of the report from the Late Effects Study Group (Supplementary Figure S1). In that study, Holmqvist et al. estimated the cumulative incidence of CRC in a cohort of 1,136 HL survivors from United Kingdom (UK), Netherlands, and United States (US). After a follow-up of 40 years, it may be reasonable to assume that some of those HL survivors could have undergone colonoscopy surveillance as they met the criteria for being eligible (especially in the US).[1] We assumed no surveillance in our cohort, since information on uptake was not available, which could lead to a model overestimation of CRC cases after a long follow-up. Second, we validated our model using a Dutch prospective study in which HL survivors underwent a colonoscopy and performed stool tests,[2] where our model underestimated the proportion of adenomas in the older HL survivors (aged 60 to 69 years; Supplementary Figure S2).[2] As treatment changed substantially in the past three decades, older HL survivors were likely to be treated with high-dosage radiation therapy, which may result in a higher risk of developing adenomas. We could not inform our simulations with age- and treatment-specific inputs and, therefore, our model underestimated adenoma prevalence in that older age group.



Supplementary figure 1 | Simulated and observed relative risk for colorectal cancer (compared to average risk individuals) and cumulative colorectal cancer incidence rates among Hodgkin Lymphoma (HL) survivors per age and follow-up years since primary cancer diagnosis. Model assumptions were tested with external data from Holmqvist et al. (2019). Simulated outcomes were computed assuming no surveillance.



Supplementary figure 2 | Simulated and expected adenoma prevalence and relative risks for colorectal cancer (compared to average risk individuals) among the entire cohort of Hodgkin Lymphoma (HL) survivors. Relative risks were also computed per primary cancer treatment (procarbazine-containing chemotherapy without infradiaphragmatic radiotherapy (IRT) or combination of IRT and procarbazine chemotherapy). Simulated outcomes were computed assuming no surveillance. Observed results were collected from Rigter et al (2019).

SUPPLEMENTARY RESULTS

Multi-target stool DNA test

In line with previous studies on the cost-effectiveness of mt-sDNA in the asymptomatic population,[3-6] we found that mt-sDNA was not cost-effective compared to other modalities. Although mt-sDNA was estimated to reduce

CRC incidence and mortality, it was an inefficient surveillance option.[3]

Cost-effectiveness of only colonoscopy surveillance

In the entire cohort of HL survivors (not stratified by primary treatment), 26 CRC deaths per 1000 HL survivors (aged 35 years in 2019) were predicted in the absence of surveillance (Table 2). In our separate analysis without stool test surveillance, colonoscopy every 10 years from age 50 to 70 years was the optimal strategy, preventing 71% of CRC mortality compared to no surveillance (ICER = €13,000 per LYG; NNS = 143; Supplementary Tables S4 and S7). For HL survivors treated with procarbazine without IRT, the model predicted 17 CRC deaths per 1000 HL survivors without surveillance. Analysing only colonoscopy surveillance strategies, we found that colonoscopy surveillance should not be indicated in this group of survivors as surveillance benefits are not estimated to have a favourable balance with costs (Supplementary Tables S5 and S8). In HL survivors treated with IRT and procarbazine, 47 CRC deaths (per 1000 HL) were predicted without surveillance. In absence of stool test surveillance, colonoscopy repeated every 10 years from age 45 to 70 years was optimal, reducing CRC mortality up to 77% compared to no surveillance (at the acceptable costs of €13,000 per LYG; NNS = 96; Supplementary Tables S6 and S9).

These separate analyses (excluding stool tests) were performed because colonoscopy is the advised surveillance strategy for individuals found to be at high risk of developing CRC (as consequence of genetic predispositions, such as family history of CRC or Lynch Syndrome) in the Dutch guidelines.[7] In our separate analysis, we found that the optimal surveillance colonoscopy interval was 10 years in line with the results of previous modelling study for childhood cancer survivors (including HL survivors). However, colonoscopy surveillance for HL survivors treated with procarbazine without IRT was not considered cost-effective (ICER > €20,000). In addition, our findings highlighted a different age for commencing surveillance, i.e. 45 or 50 years (for HL survivors who received combination therapy or the entire cohort, respectively), while Gini et al found that the most optimal colonoscopy surveillance should start at age 40 years in the US for HL survivors.[8] We believe that this discrepancy might be related to the different model assumptions (i.e. different age for the diagnosis of the primary malignancy and willingness to pay threshold in determining the optimal surveillance strategy). Applying a similar willingness to pay threshold to our results (Supplementary Tables S7-S9), optimal surveillance strategies and the percentage of CRC mortality reductions were almost comparable.

SUPPLEMENTARY TABLES

Table S1 | All surveillance strategies among Hodgkin lymphoma survivors (Entire cohort of HL survivors, base case analysis).

	Outcomes per 1,000 HL survivors free of CRC diagnosis and aged 35 years in 2019 (3%)*												Reductions:	
Surveillance strategies	**FITs or MT-sDNA**	**Scr. COLs**	**Diag. COLs**	**Surv. COLs**	**Total COLs**	**Com-pl.**	**CRCs†**	**CRC deaths†**	**CRC care**	**LYG‡**	**Total costs**	**Net costs‡**	**Inc. (%)‡**	**Mortality (%)‡**
No Surveillance	0	0	33	0	33	0	73	26	214	0	966	0	0	0
COL, 35-70, 10 years	0	2063	6	797	2866	5	34	6	163	67	2637	1671	53	77
COL, 35-70, 3 years	0	4864	3	1956	6822	9	22	3	112	80	5337	4371	70	88
COL, 35-70, 5 years	0	3318	5	902	4225	6	32	5	152	71	3577	2612	56	80
COL, 35-75, 10 years	0	2122	6	797	2925	6	34	6	163	67	2682	1716	53	78
COL, 35-75, 3 years	0	5003	2	1956	6960	9	21	3	112	80	5437	4471	71	89
COL, 35-75, 5 years	0	3381	5	902	4288	7	32	5	152	71	3624	2659	57	81
COL, 40-70, 10 years	0	1591	6	716	2314	5	35	6	168	64	2252	1287	52	77
COL, 40-70, 3 years	0	3526	3	1696	5225	8	23	4	122	76	4215	3250	68	86
COL, 40-70, 5 years	0	2432	5	811	3249	6	33	5	157	68	2891	1926	55	79
COL, 40-75, 10 years	0	1591	6	716	2314	5	35	6	168	64	2252	1287	52	77
COL, 40-75, 3 years	0	3621	3	1696	5320	9	22	3	123	76	4284	3318	69	88

COL, 40-75, 5 years	0	2495	5	811	3311	6	32	5	158	68	2938	1972	56	80
COL, 45-70, 10 years	0	1153	7	641	1801	5	36	6	173	60	1897	932	51	75
COL, 45-70, 3 years	0	2448	4	1420	3872	8	25	4	140	69	3279	2314	66	85
COL, 45-70, 5 years	0	1739	6	694	2439	6	34	6	168	63	2334	1368	53	78
COL, 45-75, 10 years	0	1207	7	641	1854	5	36	6	174	60	1938	972	51	76
COL, 45-75, 3 years	0	2566	4	1420	3990	8	25	4	140	69	3365	2400	66	85
COL, 45-75, 5 years	0	1793	6	694	2493	6	34	6	168	63	2373	1408	54	78
COL, 50-70, 10 years	0	864	9	495	1368	5	39	8	188	52	1627	662	47	71
COL, 50-70, 3 years	0	1654	7	1025	2685	7	30	6	166	57	2494	1529	59	78
COL, 50-70, 5 years	0	1225	8	524	1758	5	37	7	185	53	1892	927	49	73
COL, 50-75, 10 years	0	864	9	495	1368	5	39	8	188	52	1627	662	47	71
COL, 50-75, 3 years	0	1791	6	1025	2822	7	30	5	166	57	2594	1628	59	79
COL, 50-75, 5 years	0	1295	8	524	1827	5	37	7	185	53	1944	978	49	73
FIT20, 35-70, 1 years	16252	0	976	510	1486	4	42	6	214	67	1943	978	42	76
FIT20, 35-70, 2 years	8868	0	568	358	927	3	51	9	243	57	1527	562	30	67

FIT20, 35-75, 1 years	16611	0	997	511	1508	4	43	6	215	67	1967	1001	42	78
FIT20, 35-75, 2 years	9091	0	582	359	942	3	52	8	245	58	1548	582	29	69
FIT20, 40-70, 1 years	11975	0	740	447	1187	4	43	7	220	64	1681	716	41	75
FIT20, 40-70, 2 years	6665	0	446	314	761	3	52	9	248	55	1390	424	28	66
FIT20, 40-75, 1 years	12337	0	761	447	1208	4	44	6	221	64	1705	739	40	76
FIT20, 40-75, 2 years	6817	0	456	315	771	3	53	8	249	55	1404	439	28	68
FIT20, 45-70, 1 years	8549	0	553	362	915	3	46	7	230	58	1468	502	37	72
FIT20, 45-70, 2 years	4779	0	342	258	599	3	54	10	253	49	1271	306	26	63
FIT20, 45-75, 1 years	8909	0	574	363	937	4	46	7	232	58	1492	526	37	74
FIT20, 45-75, 2 years	5003	0	356	258	615	3	55	9	256	50	1292	327	25	66
FIT20, 50-70, 1 years	5853	0	404	265	669	3	50	9	242	48	1306	340	31	67
FIT20, 50-70, 2 years	3343	0	261	189	451	2	58	11	259	41	1186	221	21	58
FIT20, 50-75, 1 years	6213	0	426	266	691	3	50	8	243	48	1330	364	31	68
FIT20, 50-75, 2 years	3497	0	271	190	461	2	58	10	260	41	1201	235	20	60
FIT47, 35-70, 1 years	16848	0	695	413	1108	3	48	7	241	64	1737	771	34	73
FIT47, 35-70, 2 years	9098	0	408	276	684	2	57	10	266	53	1417	452	22	62

FIT47, 35-75, 1 years	17218	0	710	413	1124	3	49	7	243	64	1758	792	33	75
FIT47, 35-75, 2 years	9330	0	419	277	696	3	59	9	270	54	1438	473	20	65
FIT47, 40-70, 1 years	12490	0	536	361	897	3	49	7	246	61	1537	571	33	72
FIT47, 40-70, 2 years	6866	0	326	242	568	2	58	10	269	50	1314	348	20	62
FIT47, 40-75, 1 years	12862	0	551	362	913	3	50	7	248	61	1558	592	32	74
FIT47, 40-75, 2 years	7023	0	334	243	576	2	59	10	272	51	1329	363	19	63
FIT47, 45-70, 1 years	8957	0	408	293	701	3	51	8	254	55	1373	407	30	70
FIT47, 45-70, 2 years	4936	0	254	198	452	2	60	11	273	46	1224	258	18	59
FIT47, 45-75, 1 years	9329	0	423	293	717	3	52	7	256	56	1395	429	29	71
FIT47, 45-75, 2 years	5169	0	266	199	464	2	61	10	276	46	1246	280	16	61
FIT47, 50-70, 1 years	6141	0	304	214	518	3	56	9	261	46	1251	285	24	64
FIT47, 50-70, 2 years	3457	0	199	145	344	2	63	12	274	38	1161	196	13	54
FIT47, 50-75, 1 years	6514	0	320	215	534	3	56	9	264	46	1273	307	23	66
FIT47, 50-75, 2 years	3615	0	206	146	352	2	64	11	277	38	1177	211	12	56
FIT10, 35-70, 1 years	15462	0	1491	634	2125	5	37	5	188	70	2339	1374	49	79
FIT10, 35-70, 2 years	8539	0	858	471	1329	4	45	7	220	63	1747	781	39	73

FIT10, 35-75, 1 years	15809	0	1523	634	2158	5	37	5	189	70	2370	1405	49	80
FIT10, 35-75, 2 years	8750	0	879	472	1351	4	45	7	222	64	1769	804	38	75
FIT10, 40-70, 1 years	11292	0	1108	555	1663	4	38	6	196	67	1963	997	48	78
FIT10, 40-70, 2 years	6376	0	660	413	1073	4	46	7	226	60	1546	581	37	72
FIT10, 40-75, 1 years	11642	0	1141	556	1697	5	38	5	196	67	1994	1028	48	79
FIT10, 40-75, 2 years	6523	0	675	413	1088	4	46	7	227	60	1562	597	37	73
FIT10, 45-70, 1 years	8008	0	809	451	1260	4	41	6	208	61	1657	692	45	76
FIT10, 45-70, 2 years	4555	0	494	338	832	3	48	8	235	55	1375	409	34	69
FIT10, 45-75, 1 years	8356	0	842	451	1293	4	41	6	209	61	1688	723	44	77
FIT10, 45-75, 2 years	4767	0	515	339	854	3	49	8	237	55	1398	432	34	71
FIT10, 50-70, 1 years	5469	0	579	329	908	4	45	8	224	50	1425	460	38	70
FIT10, 50-70, 2 years	3183	0	369	248	616	3	52	9	245	45	1250	284	29	64
FIT10, 50-75, 1 years	5815	0	612	330	942	4	45	7	225	51	1456	490	38	71
FIT10, 50-75, 2 years	3330	0	383	248	632	3	52	9	246	45	1266	301	28	65
MTDNA, 35-70, 1 years	13519	0	5112	924	6036	7	31	5	148	73	13019	12054	58	81
MTDNA, 35-70, 2 years	7448	0	2827	819	3646	6	33	5	163	71	7674	6708	54	80

MTDNA, 35-75, 1 years	13852	0	5237	924	6161	8	31	5	148	73	13310	12345	58	82
MTDNA, 35-75, 2 years	7635	0	2898	819	3716	6	33	5	164	71	7838	6873	55	81
MTDNA, 40-70, 1 years	9585	0	3632	811	4443	7	32	5	157	69	9522	8556	56	80
MTDNA, 40-70, 2 years	5419	0	2065	717	2783	6	34	5	171	67	5845	4880	53	79
MTDNA, 40-75, 1 years	9930	0	3762	811	4573	7	32	5	157	70	9824	8858	57	81
MTDNA, 40-75, 2 years	5557	0	2118	717	2835	6	34	5	172	68	5968	5002	53	80
MTDNA, 45-70, 1 years	6622	0	2521	663	3184	6	34	6	172	63	6861	5895	54	78
MTDNA, 45-70, 2 years	3796	0	1459	591	2050	5	36	6	186	62	4370	3404	50	77
MTDNA, 45-75, 1 years	6952	0	2645	663	3308	7	34	5	172	63	7150	6184	54	79
MTDNA, 45-75, 2 years	3977	0	1527	591	2118	5	36	6	186	62	4531	3565	50	77
MTDNA, 50-70, 1 years	4445	0	1708	490	2198	5	38	7	193	53	4896	3930	48	73
MTDNA, 50-70, 2 years	2632	0	1027	431	1458	5	41	7	205	51	3299	2333	44	71
MTDNA, 50-75, 1 years	4765	0	1828	490	2318	6	38	7	193	53	5176	4211	48	74
MTDNA, 50-75, 2 years	2767	0	1077	431	1509	5	41	7	205	51	3418	2452	44	72

HL=Hodgkin Lymphoma; Entire cohort= all HL survivors treated with infradiaphragmatic radiotherapy and/or procarbazine; LYG= life years gained; COLs = colonoscopies; † CRC cases and CRC death were not discounted; ‡ Compared with no surveillance.

* Full participation in surveillance and post-colonoscopy surveillance was assumed.

Table S2 | All surveillance strategies among HL Survivors (with procarbazine chemotherapy without infradiaphragmatic radiotherapy, base case analysis).

	Outcomes per 1,000 HL survivors free of CRC diagnosis and aged 35 years in 2019 (3%)*												Reductions:	
Surveillance strategies	**FITs or MT-sDNA**	**Scr. COLs**	**Diag. COLs**	**Surv. COLs**	**Total COLs**	**Compl.**	**CRCs†**	**CRC deaths†**	**CRC care**	**LYG‡**	**Total costs**	**Net costs‡**	**Ind. (%)‡**	**Mortality (%)‡**
No Surveillance	0	0	22	0	22	0	49	17	141	0	637	0	0	0
COL, 35-70, 10 years	0	2132	4	627	2763	4	23	4	109	42	2377	1739	53	76
COL, 35-70, 3 years	0	5209	2	1611	6822	7	14	2	73	52	5176	4539	72	88
COL, 35-70, 5 years	0	3507	3	717	4228	5	21	3	99	46	3394	2757	57	80
COL, 35-75, 10 years	0	2194	4	627	2825	5	23	4	109	42	2423	1786	53	77
COL, 35-75, 3 years	0	5359	1	1611	6972	8	14	2	73	52	5284	4647	72	90
COL, 35-75, 5 years	0	3573	3	717	4293	6	21	3	100	46	3442	2805	58	81
COL, 40-70, 10 years	0	1657	4	559	2221	4	24	4	112	40	1997	1360	52	75
COL, 40-70, 3 years	0	3827	2	1405	5234	7	15	2	79	49	4058	3421	70	87
COL, 40-70, 5 years	0	2598	4	644	3246	5	21	4	103	43	2703	2066	56	79
COL, 40-75, 10 years	0	1657	4	559	2221	4	24	4	112	40	1997	1360	52	75
COL, 40-75, 3 years	0	3925	2	1405	5332	7	14	2	79	49	4129	3492	71	88
COL, 40-75, 5 years	0	2663	3	644	3310	5	21	3	104	43	2751	2114	57	80

COL, 45-70, 10 years	0	1204	5	504	1712	4	24	4	116	38	1641	1004	51	74
COL, 45-70, 3 years	0	2679	3	1195	3876	6	16	3	90	44	3111	2474	67	85
COL, 45-70, 5 years	0	1870	4	555	2429	5	22	4	110	40	2135	1497	54	77
COL, 45-75, 10 years	0	1261	5	504	1770	4	24	4	116	38	1685	1047	51	75
COL, 45-75, 3 years	0	2807	2	1195	4005	7	16	2	90	45	3204	2567	68	86
COL, 45-75, 5 years	0	1928	4	555	2487	5	22	4	110	40	2177	1540	55	78
COL, 50-70, 10 years	0	903	6	394	1303	4	26	5	125	32	1374	737	47	70
COL, 50-70, 3 years	0	1809	4	876	2689	6	19	4	107	37	2306	1668	60	78
COL, 50-70, 5 years	0	1317	5	424	1746	4	25	5	121	34	1677	1039	50	73
COL, 50-75, 10 years	0	903	6	394	1303	4	26	5	125	32	1374	737	47	70
COL, 50-75, 3 years	0	1959	4	876	2839	6	19	4	108	37	2413	1776	61	80
COL, 50-75, 5 years	0	1388	5	424	1817	5	24	5	122	34	1729	1092	50	73
FIT20, 35-70, 1 years	16887	0	996	392	1388	3	29	4	145	43	1681	1043	41	75
FIT20, 35-70, 2 years	9097	0	563	271	834	2	35	6	164	36	1234	596	28	65
FIT20, 35-75, 1 years	17273	0	1018	393	1411	3	29	4	146	43	1705	1068	40	77
FIT20, 35-75, 2 years	9335	0	577	272	849	2	36	6	166	36	1254	616	26	67

FIT20, 40-70, 1 years	12528	0	753	343	1096	3	30	5	149	40	1418	781	39	74
FIT20, 40-70, 2 years	6871	0	439	236	675	2	36	6	167	34	1098	460	26	64
FIT20, 40-75, 1 years	12917	0	776	343	1119	3	30	4	150	40	1443	806	38	75
FIT20, 40-75, 2 years	7035	0	449	237	686	2	37	6	169	34	1112	474	25	66
FIT20, 45-70, 1 years	8992	0	558	278	836	3	31	5	155	36	1200	563	36	71
FIT20, 45-70, 2 years	4945	0	331	194	525	2	38	7	170	30	977	339	23	61
FIT20, 45-75, 1 years	9380	0	580	279	859	3	32	5	156	37	1225	587	35	73
FIT20, 45-75, 2 years	5184	0	346	195	540	2	38	6	173	31	997	360	22	64
FIT20, 50-70, 1 years	6177	0	402	204	606	2	34	6	162	30	1027	389	30	66
FIT20, 50-70, 2 years	3472	0	248	142	390	2	40	7	174	25	885	247	19	57
FIT20, 50-75, 1 years	6565	0	425	205	629	3	35	6	163	30	1052	414	30	68
FIT20, 50-75, 2 years	3636	0	259	143	402	2	40	7	175	26	899	262	18	58
FIT47, 35-70, 1 years	17387	0	697	314	1011	3	33	5	164	41	1457	820	32	72
FIT47, 35-70, 2 years	9286	0	396	206	602	2	40	7	179	33	1111	473	19	60
FIT47, 35-75, 1 years	17784	0	713	314	1027	3	34	5	166	41	1479	842	31	74
FIT47, 35-75, 2 years	9533	0	407	207	614	2	41	6	182	33	1130	493	17	63

FIT47, 40-70, 1 years	12963	0	535	273	808	2	34	5	167	38	1257	620	30	70
FIT47, 40-70, 2 years	7038	0	313	180	493	2	41	7	182	31	1009	371	17	59
FIT47, 40-75, 1 years	13362	0	550	274	825	3	35	5	169	39	1279	642	29	72
FIT47, 40-75, 2 years	7206	0	321	180	501	2	41	7	184	32	1022	385	16	61
FIT47, 45-70, 1 years	9340	0	402	222	623	2	36	6	171	35	1091	453	27	68
FIT47, 45-70, 2 years	5075	0	240	147	387	2	42	8	183	28	916	279	15	56
FIT47, 45-75, 1 years	9740	0	418	222	640	2	36	5	173	35	1112	475	26	70
FIT47, 45-75, 2 years	5324	0	251	148	399	2	43	7	186	28	937	299	13	59
FIT47, 50-70, 1 years	6427	0	294	162	456	2	38	6	176	29	957	320	22	63
FIT47, 50-70, 2 years	3568	0	183	108	291	1	44	8	184	23	847	210	11	52
FIT47, 50-75, 1 years	6828	0	310	163	473	2	39	6	177	29	980	342	21	65
FIT47, 50-75, 2 years	3737	0	190	109	299	2	44	8	186	24	861	224	9	54
FIT10, 35-70, 1 years	16223	0	1550	494	2043	4	25	4	127	45	2103	1465	49	79
FIT10, 35-70, 2 years	8823	0	869	361	1230	3	31	5	149	40	1470	832	37	71
FIT10, 35-75, 1 years	16597	0	1585	494	2079	4	25	3	127	45	2135	1498	49	80
FIT10, 35-75, 2 years	9050	0	891	362	1253	3	31	5	151	40	1492	855	36	73

FIT10, 40-70, 1 years	11947	0	1154	432	1586	4	26	4	132	43	1724	1087	47	77
FIT10, 40-70, 2 years	6630	0	667	315	982	3	32	5	153	38	1270	633	35	71
FIT10, 40-75, 1 years	12324	0	1190	432	1622	4	26	4	133	43	1757	1120	47	79
FIT10, 40-75, 2 years	6788	0	682	315	997	3	32	5	154	38	1287	649	35	72
FIT10, 45-70, 1 years	8522	0	840	352	1192	3	27	4	140	38	1412	775	44	75
FIT10, 45-70, 2 years	4755	0	494	259	753	3	33	6	158	34	1097	459	32	67
FIT10, 45-75, 1 years	8897	0	875	352	1227	3	28	4	140	39	1445	807	44	76
FIT10, 45-75, 2 years	4982	0	516	260	776	3	34	5	160	34	1120	483	32	69
FIT10, 50-70, 1 years	5837	0	594	258	853	3	30	5	149	32	1165	528	38	70
FIT10, 50-70, 2 years	3334	0	363	190	553	2	36	6	164	28	962	325	27	63
FIT10, 50-75, 1 years	6211	0	629	259	888	3	30	5	150	32	1198	561	38	71
FIT10, 50-75, 2 years	3492	0	378	190	569	2	36	6	165	29	979	342	26	64
MTDNA, 35-70, 1 years	14574	0	5507	738	6244	6	20	3	96	47	13621	12984	59	82
MTDNA, 35-70, 2 years	7907	0	2996	648	3644	5	22	3	108	46	7764	7126	55	80
MTDNA, 35-75, 1 years	14933	0	5642	738	6380	7	20	3	97	47	13936	13298	59	83
MTDNA, 35-75, 2 years	8108	0	3072	648	3720	5	22	3	109	46	7941	7304	55	81

MTDNA, 40-70, 1 years	10477	0	3964	649	4612	6	21	3	102	45	9996	9358	58	80
MTDNA, 40-70, 2 years	5814	0	2209	567	2776	5	23	4	114	43	5891	5253	54	79
MTDNA, 40-75, 1 years	10847	0	4103	649	4752	6	20	3	103	45	10320	9683	58	81
MTDNA, 40-75, 2 years	5963	0	2265	568	2832	5	23	4	114	43	6022	5385	54	80
MTDNA, 45-70, 1 years	7301	0	2770	534	3304	5	22	4	112	41	7164	6526	55	78
MTDNA, 45-70, 2 years	4094	0	1564	472	2036	4	24	4	123	39	4343	3705	51	76
MTDNA, 45-75, 1 years	7658	0	2905	534	3439	6	22	4	112	41	7476	6839	55	79
MTDNA, 45-75, 2 years	4293	0	1639	472	2110	5	24	4	123	39	4517	3879	51	77
MTDNA, 50-70, 1 years	4915	0	1875	399	2274	5	25	5	126	34	5023	4385	49	73
MTDNA, 50-70, 2 years	2844	0	1096	347	1443	4	27	5	135	33	3199	2562	45	71
MTDNA, 50-75, 1 years	5261	0	2006	399	2405	5	25	4	126	34	5327	4689	50	74
MTDNA, 50-75, 2 years	2988	0	1151	347	1498	4	27	5	135	33	3327	2689	45	72

HL=Hodgkin Lymphoma; LYG= life years gained; COLs = colonoscopies; † CRC cases and CRC death were not discounted;

‡ Compared with no surveillance. * Full participation in surveillance and post-colonoscopy surveillance was assumed.

Table S3: All surveillance strategies among HL Survivors (with a combination of infradiaphragmatic radiotherapy and procarbazine chemotherapy, base case analysis).

	Outcomes per 1,000 HL survivors free of CRC diagnosis and aged 35 years in 2019 (3%)*												Reductions:	
Surveillance strategies	**FITs or MT-sDNA**	**Scr. COLs**	**Diag. COLs**	**Surv. COLs**	**Total COLs**	**Compl.**	**CRCs** †	**CRC deaths** †	**CRC care**	**LYG** ‡	**Total costs**	**Net costs** ‡	**Inc. (%)**‡	**Mortality (%)**‡
No Surveillance	0	0	59	0	59	1	127	47	392	0	1753	0	0	0
COL, 35-70, 10 years	0	1937	9	1139	3086	7	59	10	294	133	3211	1458	53	79
COL, 35-70, 3 years	0	4289	5	2516	6810	11	41	6	217	153	5700	3947	68	88
COL, 35-70, 5 years	0	2995	8	1262	4266	8	56	9	280	138	4021	2268	56	81
COL, 35-75, 10 years	0	1992	9	1139	3141	8	59	9	294	133	3253	1499	54	80
COL, 35-75, 3 years	0	4410	4	2516	6930	12	40	5	218	153	5787	4034	68	89
COL, 35-75, 5 years	0	3056	8	1262	4326	9	56	9	280	138	4066	2313	56	82
COL, 40-70, 10 years	0	1477	10	1027	2514	7	60	10	303	128	2817	1064	53	78
COL, 40-70, 3 years	0	3050	6	2143	5198	10	43	6	237	145	4576	2822	66	86
COL, 40-70, 5 years	0	2163	9	1128	3300	8	57	9	291	132	3349	1595	55	80
COL, 40-75, 10 years	0	1477	10	1027	2514	7	60	10	303	128	2817	1064	53	78
COL, 40-75, 3 years	0	3139	5	2143	5287	11	42	6	237	146	4639	2886	67	87

COL, 40-75, 5 years	0	2223	9	1128	3359	8	57	9	292	133	3393	1640	55	81
COL, 45-70, 10 years	0	1070	11	893	1975	7	62	11	318	119	2460	707	51	77
COL, 45-70, 3 years	0	2103	8	1738	3848	10	47	8	272	131	3667	1914	63	84
COL, 45-70, 5 years	0	1538	11	944	2492	7	60	10	312	122	2811	1057	53	78
COL, 45-75, 10 years	0	1118	11	893	2022	7	62	11	319	120	2496	743	51	77
COL, 45-75, 3 years	0	2205	7	1738	3951	10	47	7	272	132	3742	1989	63	85
COL, 45-75, 5 years	0	1586	10	944	2540	8	60	10	313	122	2846	1093	53	79
COL, 50-70, 10 years	0	804	15	665	1484	6	68	13	351	100	2202	449	46	72
COL, 50-70, 3 years	0	1427	13	1219	2659	8	57	11	321	107	2946	1192	55	77
COL, 50-70, 5 years	0	1090	15	691	1795	6	67	13	348	101	2412	658	47	72
COL, 50-75, 10 years	0	804	15	665	1484	6	68	13	351	100	2202	449	46	72
COL, 50-75, 3 years	0	1547	12	1219	2778	9	56	11	322	107	3032	1278	56	78
COL, 50-75, 5 years	0	1156	14	691	1861	7	67	13	348	101	2461	708	47	73
FIT20, 35-70, 1 years	15099	0	945	753	1698	6	70	10	377	132	2528	774	45	78
FIT20, 35-70, 2 years	8428	0	582	545	1127	4	84	14	429	116	2173	419	34	71
FIT20, 35-75, 1 years	15414	0	963	754	1717	6	70	10	378	132	2549	796	44	79

FIT20, 35-75, 2 years	8625	0	595	546	1141	5	84	13	432	117	2192	439	33	72
FIT20, 40-70, 1 years	10997	0	723	655	1378	5	72	11	391	125	2268	515	43	77
FIT20, 40-70, 2 years	6273	0	465	477	942	4	86	14	439	110	2038	284	32	70
FIT20, 40-75, 1 years	11315	0	742	656	1398	6	73	10	392	126	2290	537	43	78
FIT20, 40-75, 2 years	6408	0	474	478	952	4	86	14	441	111	2051	298	32	71
FIT20, 45-70, 1 years	7775	0	551	525	1076	5	77	12	412	113	2068	314	39	74
FIT20, 45-70, 2 years	4465	0	367	387	754	4	90	16	451	100	1929	175	29	67
FIT20, 45-75, 1 years	8090	0	570	526	1096	5	77	12	414	114	2089	336	39	75
FIT20, 45-75, 2 years	4661	0	380	388	769	4	91	15	454	100	1948	195	29	68
FIT20, 50-70, 1 years	5275	0	416	379	795	4	85	15	434	93	1939	185	33	68
FIT20, 50-70, 2 years	3094	0	291	282	573	3	96	18	463	81	1867	113	24	61
FIT20, 50-75, 1 years	5589	0	435	380	815	4	85	15	436	93	1960	207	33	69
FIT20, 50-75, 2 years	3230	0	300	283	583	4	97	18	465	82	1881	127	24	62
FIT47, 35-70, 1 years	15842	0	696	621	1317	5	79	11	423	127	2354	600	38	76
FIT47, 35-70, 2 years	8724	0	434	427	862	4	93	16	470	109	2092	338	26	67
FIT47, 35-75, 1 years	16167	0	709	622	1331	5	79	11	425	128	2373	620	37	77

FIT47, 35-75, 2 years	8929	0	445	428	873	4	95	15	474	109	2113	359	25	68
FIT47, 40-70, 1 years	11623	0	545	540	1086	5	81	12	435	121	2156	403	36	75
FIT47, 40-70, 2 years	6527	0	356	374	730	4	96	16	478	103	1993	240	25	66
FIT47, 40-75, 1 years	11951	0	559	541	1100	5	82	11	437	121	2177	423	36	76
FIT47, 40-75, 2 years	6666	0	363	375	738	4	97	16	481	104	2008	254	24	67
FIT47, 45-70, 1 years	8255	0	426	434	860	4	85	13	451	109	2006	253	33	72
FIT47, 45-70, 2 years	4659	0	287	304	591	3	99	18	485	93	1912	159	22	63
FIT47, 45-75, 1 years	8581	0	439	435	874	4	86	13	454	110	2026	273	32	73
FIT47, 45-75, 2 years	4865	0	298	305	602	3	100	17	490	94	1934	180	21	64
FIT47, 50-70, 1 years	5607	0	329	313	642	4	93	16	466	89	1912	159	27	66
FIT47, 50-70, 2 years	3233	0	233	221	454	3	105	20	490	76	1871	118	17	58
FIT47, 50-75, 1 years	5933	0	343	314	657	4	93	16	469	90	1933	180	26	67
FIT47, 50-75, 2 years	3373	0	240	222	462	3	106	19	493	77	1886	133	16	59
FIT10, 35-70, 1 years	14131	0	1393	916	2309	7	63	9	336	137	2877	1123	50	80
FIT10, 35-70, 2 years	8013	0	842	700	1542	5	74	11	388	126	2357	604	42	76

FIT10, 35-75, 1 years	14436	0	1422	916	2338	7	63	9	337	137	2904	1151	50	81
FIT10, 35-75, 2 years	8199	0	861	701	1561	5	74	11	390	126	2378	625	41	77
FIT10, 40-70, 1 years	10186	0	1036	796	1832	6	65	10	352	131	2504	751	49	79
FIT10, 40-70, 2 years	5920	0	654	610	1265	5	76	12	401	120	2158	404	40	75
FIT10, 40-75, 1 years	10495	0	1065	796	1861	6	65	9	353	131	2532	779	49	80
FIT10, 40-75, 2 years	6050	0	667	611	1278	5	76	12	403	120	2172	419	40	75
FIT10, 45-70, 1 years	7154	0	767	636	1403	6	69	11	377	118	2216	463	45	77
FIT10, 45-70, 2 years	4197	0	501	494	995	5	80	13	419	108	1998	244	37	72
FIT10, 45-75, 1 years	7459	0	796	636	1433	6	70	11	378	118	2244	490	45	77
FIT10, 45-75, 2 years	4382	0	520	495	1014	5	81	13	422	109	2019	265	36	73
FIT10, 50-70, 1 years	4848	0	563	457	1020	5	78	14	407	97	2023	270	39	71
FIT10, 50-70, 2 years	2908	0	385	357	742	4	88	16	439	89	1899	145	31	66
FIT10, 50-75, 1 years	5150	0	592	458	1050	5	78	14	408	97	2051	297	39	71
FIT10, 50-75, 2 years	3038	0	398	358	756	4	88	16	441	89	1913	160	31	67
MTDNA, 35-70, 1 years	11781	0	4464	1278	5742	9	56	9	278	140	12175	10421	56	82

MTDNA, 35-70, 2 years	6676	0	2545	1149	3694	8	58	9	298	138	7659	5906	54	81
MTDNA, 35-75, 1 years	12072	0	4573	1278	5851	10	55	8	278	140	12430	10677	57	82
MTDNA, 35-75, 2 years	6840	0	2607	1149	3756	8	58	9	299	138	7805	6051	54	81
MTDNA, 40-70, 1 years	8192	0	3118	1111	4229	8	57	9	294	134	8948	7194	55	81
MTDNA, 40-70, 2 years	4785	0	1839	999	2838	7	60	9	315	132	5929	4175	53	80
MTDNA, 40-75, 1 years	8497	0	3233	1112	4344	9	56	9	294	134	9215	7462	55	81
MTDNA, 40-75, 2 years	4908	0	1885	999	2885	8	60	9	315	132	6038	4284	53	80
MTDNA, 45-70, 1 years	5603	0	2154	891	3045	8	61	10	323	122	6591	4838	52	78
MTDNA, 45-70, 2 years	3332	0	1302	805	2107	7	64	11	344	119	4587	2833	50	77
MTDNA, 45-75, 1 years	5890	0	2262	892	3153	8	60	10	323	122	6843	5090	52	79
MTDNA, 45-75, 2 years	3490	0	1362	805	2167	7	64	10	344	120	4727	2973	50	78
MTDNA, 50-70, 1 years	3755	0	1470	641	2111	7	68	13	362	101	4919	3166	46	73
MTDNA, 50-70, 2 years	2308	0	928	573	1501	6	72	13	381	98	3649	1896	43	71
MTDNA, 50-75, 1 years	4033	0	1575	642	2217	7	68	13	362	101	5163	3410	46	73
MTDNA, 50-75, 2 years	2427	0	973	574	1547	6	72	13	381	98	3754	2001	43	72

HL=Hodgkin Lymphoma; LYG= life years gained; COLs = colonoscopies; † CRC cases and CRC death were not discounted; ‡ Compared with no surveillance. * Full participation in surveillance and post-colonoscopy surveillance was assumed.

Table S4 | Number of colonoscopies needed to prevent a colorectal cancer death for each surveillance strategies among HL Survivors (entire cohort not stratified by treatment, base case analysis).

Surveillance strategy	Outcomes per 1,000 HL survivors free of CRC diagnosis and aged 35 years in 2019 (3%)*				
	CRC deaths predicted*,†	CRC mortality (reduction, %)*,‡	NNS†	COLs†	Total Costs ($1,000§)
No Surveillance	26.05	0.00	0.00	73.02	965.53
FIT10, 35-70, 1 years	5.46	79.03	164.35	3383.88	2339.48
FIT10, 35-75, 1 years	5.21	80.00	167.23	3485.07	2370.04
FIT10, 40-70, 1 years	5.74	77.96	141.99	2883.77	1962.79
FIT10, 40-75, 1 years	5.47	79.00	145.10	2986.24	1993.74
FIT10, 45-70, 1 years	6.36	75.58	120.68	2376.21	1657.40
FIT10, 45-75, 1 years	6.10	76.60	124.21	2478.05	1688.14
FIT10, 50-70, 1 years	7.77	70.17	101.88	1862.29	1425.14
FIT10, 50-75, 1 years	7.49	71.24	105.82	1963.93	1455.79
FIT10, 35-70, 2 years	7.03	73.01	115.07	2188.59	1746.81
FIT10, 35-75, 2 years	6.63	74.55	116.07	2254.01	1769.14
FIT10, 40-70, 2 years	7.30	71.99	101.94	1911.44	1546.32
FIT10, 40-75, 2 years	7.02	73.04	102.86	1957.47	1562.09
FIT10, 45-70, 2 years	7.99	69.32	88.55	1599.29	1374.86
FIT10, 45-75, 2 years	7.57	70.96	90.12	1665.39	1397.52
FIT10, 50-70, 2 years	9.37	64.02	76.71	1279.46	1249.98
FIT10, 50-75, 2 years	9.06	65.21	78.07	1326.46	1266.09
FIT20, 35-70, 1 years	6.18	76.27	122.78	2439.72	1943.12
FIT20, 35-75, 1 years	5.86	77.50	124.09	2505.44	1966.68
FIT20, 40-70, 1 years	6.52	74.97	107.97	2108.69	1681.30
FIT20, 40-75, 1 years	6.17	76.31	109.40	2174.95	1704.95
FIT20, 45-70, 1 years	7.18	72.45	93.21	1758.87	1467.73
FIT20, 45-75, 1 years	6.83	73.78	94.97	1825.40	1491.51
FIT20, 50-70, 1 years	8.60	66.98	79.70	1390.76	1305.60
FIT20, 50-75, 1 years	8.23	68.42	81.82	1458.02	1329.71
FIT20, 35-70, 2 years	8.57	67.09	89.90	1571.38	1527.39
FIT20, 35-75, 2 years	8.05	69.10	89.85	1617.25	1547.70
FIT20, 40-70, 2 years	8.78	66.29	80.36	1387.79	1389.96
FIT20, 40-75, 2 years	8.44	67.61	80.63	1419.82	1404.19
FIT20, 45-70, 2 years	9.52	63.47	70.95	1172.79	1271.31
FIT20, 45-75, 2 years	8.95	65.63	71.32	1219.65	1292.08
FIT20, 50-70, 2 years	10.81	58.49	62.21	948.09	1186.22

FIT20, 50-75, 2 years	10.43	59.98	62.82	981.18	1200.95
FIT47, 35-70, 1 years	6.94	73.38	97.54	1864.07	1736.64
FIT47, 35-75, 1 years	6.52	74.98	97.90	1911.92	1757.78
FIT47, 40-70, 1 years	7.28	72.04	86.66	1626.66	1536.67
FIT47, 40-75, 1 years	6.85	73.72	87.24	1674.92	1558.01
FIT47, 45-70, 1 years	7.93	69.56	75.46	1367.34	1372.94
FIT47, 45-75, 1 years	7.48	71.28	76.25	1415.96	1394.57
FIT47, 50-70, 1 years	9.37	64.05	65.25	1088.33	1250.59
FIT47, 50-75, 1 years	8.89	65.87	66.31	1137.95	1272.76
FIT47, 35-70, 2 years	9.82	62.30	73.08	1186.13	1417.45
FIT47, 35-75, 2 years	9.18	64.75	72.42	1221.67	1438.31
FIT47, 40-70, 2 years	10.00	61.63	65.80	1056.03	1313.93
FIT47, 40-75, 2 years	9.58	63.23	65.62	1080.74	1328.56
FIT47, 45-70, 2 years	10.72	58.84	58.53	897.26	1223.92
FIT47, 45-75, 2 years	10.04	61.45	58.32	933.78	1245.50
FIT47, 50-70, 2 years	11.92	54.26	51.73	731.00	1161.46
FIT47, 50-75, 2 years	11.46	56.02	51.87	756.73	1176.62
COL, 35-70, 3 years	3.11	88.07	443.34	10170.14	5336.68
COL, 35-75, 3 years	2.80	89.25	455.56	10591.84	5436.63
COL, 40-70, 3 years	3.52	86.48	379.76	8555.94	4215.14
COL, 40-75, 3 years	3.18	87.79	386.95	8849.50	4284.02
COL, 45-70, 3 years	4.04	84.51	316.91	6975.23	3279.24
COL, 45-75, 3 years	3.80	85.40	330.19	7346.64	3365.47
COL, 50-70, 3 years	5.72	78.06	258.88	5263.02	2494.03
COL, 50-75, 3 years	5.42	79.21	275.46	5682.77	2593.53
COL, 35-70, 5 years	5.16	80.21	298.77	6241.24	3577.31

COL, 35-75, 5 years	4.93	81.06	305.24	6446.76	3624.46
COL, 40-70, 5 years	5.39	79.31	254.83	5264.81	2891.22
COL, 40-75, 5 years	5.15	80.25	261.64	5468.25	2937.90
COL, 45-70, 5 years	5.84	77.59	214.93	4343.68	2333.61
COL, 45-75, 5 years	5.71	78.08	222.19	4519.44	2373.50
COL, 50-70, 5 years	7.12	72.67	181.08	3427.78	1892.12
COL, 50-75, 5 years	6.90	73.50	190.79	3653.55	1943.56
COL, 35-70, 10 years	5.89	77.40	210.21	4237.92	2636.91
COL, 35-75, 10 years	5.67	78.26	217.36	4429.72	2681.54
COL, 40-70, 10 years	6.11	76.56	188.43	3757.28	2252.49
COL, 40-75, 10 years	6.11	76.56	188.43	3757.28	2252.49
COL, 45-70, 10 years	6.44	75.28	161.45	3166.05	1897.15
COL, 45-75, 10 years	6.26	75.98	168.85	3341.50	1937.96
COL, 50-70, 10 years	7.52	71.14	143.09	2651.50	1627.44
COL, 50-75, 10 years	7.52	71.14	143.09	2651.50	1627.44
MTDNA, 35-70, 1 years	4.86	81.34	422.67	8956.34	13019.09
MTDNA, 35-75, 1 years	4.63	82.23	436.12	9341.64	13310.43
MTDNA, 40-70, 1 years	5.14	80.26	347.83	7273.04	9521.90
MTDNA, 40-75, 1 years	4.88	81.28	362.41	7672.24	9823.88
MTDNA, 45-70, 1 years	5.72	78.05	282.45	5742.12	6860.79
MTDNA, 45-75, 1 years	5.49	78.93	297.85	6123.73	7149.75
MTDNA, 50-70, 1 years	7.03	73.00	228.97	4355.05	4896.02
MTDNA, 50-75, 1 years	6.82	73.82	245.75	4725.72	5176.45
MTDNA, 35-70, 2 years	5.20	80.05	264.78	5520.70	7673.64
MTDNA, 35-75, 2 years	4.97	80.91	272.16	5737.22	7838.30
MTDNA, 40-70, 2 years	5.49	78.93	225.23	4630.76	5845.17
MTDNA, 40-75, 2 years	5.31	79.62	231.06	4792.09	5967.84
MTDNA, 45-70, 2 years	6.07	76.70	186.84	3733.16	4369.94
MTDNA, 45-75, 2 years	5.87	77.46	195.44	3943.97	4530.52
MTDNA, 50-70, 2 years	7.45	71.39	156.55	2911.75	3298.93
MTDNA, 50-75, 2 years	7.28	72.04	163.47	3068.33	3417.94

*Including deaths from complications of surveillance; CRC = colorectal cancer; NNS= number needed to screen to prevent one death from colorectal cancer; COLs = number of colonoscopies.

†outcomes not discounted.

‡compared with no surveillance.

§ currency is euro.

Table S5 | Number of colonoscopies needed to prevent a colorectal cancer death for each surveillance strategies among HL Survivors (with procarbazine chemotherapy without infradiaphragmatic radiotherapy, base case analysis).

Surveillance strategy	Outcomes per 1,000 HL survivors free of CRC diagnosis and aged 35 years in 2019 (3%)*				
	CRC deaths predicted*,†	CRC mortality (reduction, %)*,‡	NNS†	COLs†	Total Costs ($1,000§)
No Surveillance	17.21	0.00	0.00	49.03	637.38
FIT10, 35-70, 1 years	3.69	78.55	238.72	3227.48	2102.58
FIT10, 35-75, 1 years	3.48	79.76	242.98	3336.13	2134.91
FIT10, 40-70, 1 years	3.89	77.42	205.29	2734.47	1724.30
FIT10, 40-75, 1 years	3.67	78.69	210.07	2844.33	1757.12
FIT10, 45-70, 1 years	4.34	74.80	174.02	2239.65	1412.30
FIT10, 45-75, 1 years	4.12	76.06	179.43	2348.79	1444.88
FIT10, 50-70, 1 years	5.21	69.71	145.47	1745.68	1165.49
FIT10, 50-75, 1 years	4.98	71.04	151.65	1854.68	1198.10
FIT10, 35-70, 2 years	4.91	71.48	162.54	1999.26	1469.52
FIT10, 35-75, 2 years	4.58	73.38	163.77	2068.47	1492.37
FIT10, 40-70, 2 years	5.07	70.53	142.76	1733.06	1270.46
FIT10, 40-75, 2 years	4.84	71.87	144.02	1781.51	1286.55
FIT10, 45-70, 2 years	5.60	67.44	123.87	1438.17	1096.78
FIT10, 45-75, 2 years	5.25	69.47	126.08	1507.93	1120.04
FIT10, 50-70, 2 years	6.41	62.78	106.03	1145.15	962.47
FIT10, 50-75, 2 years	6.15	64.28	108.01	1194.54	978.93
FIT20, 35-70, 1 years	4.29	75.10	174.34	2252.49	1680.54
FIT20, 35-75, 1 years	4.02	76.64	176.07	2322.30	1704.99
FIT20, 40-70, 1 years	4.51	73.80	152.14	1932.19	1418.46
FIT20, 40-75, 1 years	4.22	75.45	154.16	2002.57	1443.12
FIT20, 45-70, 1 years	4.97	71.14	130.67	1599.38	1200.05
FIT20, 45-75, 1 years	4.68	72.80	133.27	1669.93	1224.76
FIT20, 50-70, 1 years	5.86	65.96	110.71	1256.57	1026.62
FIT20, 50-75, 1 years	5.55	67.73	113.88	1327.88	1051.66
FIT20, 35-70, 2 years	6.03	64.95	124.46	1391.42	1233.64
FIT20, 35-75, 2 years	5.62	67.36	124.15	1438.89	1253.53
FIT20, 40-70, 2 years	6.17	64.15	110.40	1218.77	1097.87
FIT20, 40-75, 2 years	5.89	65.80	110.58	1251.76	1111.84
FIT20, 45-70, 2 years	6.71	61.00	97.14	1020.02	976.66
FIT20, 45-75, 2 years	6.27	63.55	97.65	1068.27	997.07
FIT20, 50-70, 2 years	7.47	56.59	84.13	819.43	884.79

FIT20, 50-75, 2 years	7.16	58.40	84.91	853.36	899.17
FIT47, 35-70, 1 years	4.86	71.75	135.78	1676.92	1457.42
FIT47, 35-75, 1 years	4.53	73.68	136.21	1727.13	1479.07
FIT47, 40-70, 1 years	5.09	70.44	119.71	1450.86	1257.26
FIT47, 40-75, 1 years	4.73	72.50	120.30	1501.31	1279.06
FIT47, 45-70, 1 years	5.55	67.73	103.77	1209.94	1090.54
FIT47, 45-75, 1 years	5.19	69.83	104.90	1260.88	1112.37
FIT47, 50-70, 1 years	6.44	62.57	88.75	955.88	957.44
FIT47, 50-75, 1 years	6.05	64.83	90.29	1007.67	979.88
FIT47, 35-70, 2 years	6.93	59.76	99.83	1026.22	1110.71
FIT47, 35-75, 2 years	6.43	62.65	98.52	1062.07	1130.45
FIT47, 40-70, 2 years	7.01	59.26	88.75	905.26	1008.62
FIT47, 40-75, 2 years	6.68	61.20	88.33	930.10	1022.34
FIT47, 45-70, 2 years	7.57	56.03	79.02	761.72	916.32
FIT47, 45-75, 2 years	7.04	59.07	78.50	798.34	936.65
FIT47, 50-70, 2 years	8.25	52.05	68.73	615.81	847.06
FIT47, 50-75, 2 years	7.89	54.16	68.84	641.56	861.39
COL, 35-70, 3 years	2.03	88.21	669.33	10160.39	5176.05
COL, 35-75, 3 years	1.79	89.58	688.48	10616.32	5284.09
COL, 40-70, 3 years	2.30	86.63	575.04	8573.79	4058.11
COL, 40-75, 3 years	2.06	88.03	585.83	8875.40	4128.92
COL, 45-70, 3 years	2.64	84.65	478.84	6976.69	3111.26
COL, 45-75, 3 years	2.47	85.68	500.60	7378.89	3204.45
COL, 50-70, 3 years	3.74	78.28	390.91	5265.52	2305.70
COL, 50-75, 3 years	3.51	79.60	417.52	5719.98	2413.45
COL, 35-70, 5 years	3.41	80.16	452.15	6239.69	3393.95
COL, 35-75, 5 years	3.26	81.06	462.50	6451.91	3442.26
COL, 40-70, 5 years	3.61	79.05	386.61	5257.83	2703.04
COL, 40-75, 5 years	3.44	80.03	397.10	5468.11	2751.00
COL, 45-70, 5 years	3.88	77.43	324.51	4325.70	2134.75
COL, 45-75, 5 years	3.78	78.04	336.06	4513.31	2177.04
COL, 50-70, 5 years	4.73	72.53	273.10	3408.23	1676.75
COL, 50-75, 5 years	4.58	73.39	288.11	3638.83	1729.06
COL, 35-70, 10 years	4.11	76.12	309.44	4053.60	2376.52
COL, 35-75, 10 years	3.92	77.20	320.14	4254.68	2422.99
COL, 40-70, 10 years	4.27	75.19	277.66	3592.89	1997.47
COL, 40-75, 10 years	4.27	75.19	277.66	3592.89	1997.47
COL, 45-70, 10 years	4.45	74.17	234.95	2998.00	1641.37

COL, 45-75, 10 years	4.29	75.09	246.54	3185.25	1684.53
COL, 50-70, 10 years	5.15	70.11	209.29	2524.01	1374.20
COL, 50-75, 10 years	5.15	70.11	209.29	2524.01	1374.20
MTDNA, 35-70, 1 years	3.16	81.64	660.51	9280.19	13621.20
MTDNA, 35-75, 1 years	2.98	82.70	681.36	9695.79	13935.65
MTDNA, 40-70, 1 years	3.39	80.30	546.60	7554.06	9995.81
MTDNA, 40-75, 1 years	3.19	81.45	569.36	7982.39	10320.15
MTDNA, 45-70, 1 years	3.78	78.01	443.79	5960.15	7163.51
MTDNA, 45-75, 1 years	3.61	79.02	468.58	6372.71	7476.12
MTDNA, 50-70, 1 years	4.63	73.10	358.37	4508.34	5022.85
MTDNA, 50-75, 1 years	4.47	74.05	385.38	4909.72	5326.75
MTDNA, 35-70, 2 years	3.45	79.94	399.74	5500.42	7763.53
MTDNA, 35-75, 2 years	3.28	80.97	411.64	5734.10	7941.19
MTDNA, 40-70, 2 years	3.65	78.81	339.92	4609.31	5890.70
MTDNA, 40-75, 2 years	3.51	79.63	349.06	4782.15	6022.08
MTDNA, 45-70, 2 years	4.08	76.31	281.75	3699.35	4342.56
MTDNA, 45-75, 2 years	3.91	77.28	295.39	3928.63	4516.88
MTDNA, 50-70, 2 years	4.96	71.17	235.17	2880.85	3199.10
MTDNA, 50-75, 2 years	4.83	71.97	246.27	3048.77	3326.64

*Including deaths from complications of surveillance; CRC = colorectal cancer; NNS= number needed to screen to prevent one death from colorectal cancer; COLs = number of colonoscopies.

†outcomes not discounted.

‡compared with no surveillance.

§ currency is euro.

Table S6 | Number of colonoscopies needed to prevent a colorectal cancer death for each surveillance strategies among HL Survivors (with a combination of infradiaphragmatic radiotherapy and procarbazine chemotherapy, base case analysis).

Surveillance strategy	Outcomes per 1,000 HL survivors free of CRC diagnosis and aged 35 years in 2019 (3%)*				
	CRC deaths predicted*,†	CRC mortality (reduction, %)*,‡	NNS†	COLs†	Total Costs ($1,000§)
No Surveillance	47.01	0.00	0.00	126.75	1753.40
FIT10, 35-70, 1 years	9.30	80.22	98.49	3714.14	2876.79
FIT10, 35-75, 1 years	9.00	80.85	100.07	3803.63	2904.23
FIT10, 40-70, 1 years	9.74	79.29	85.69	3193.48	2504.44
FIT10, 40-75, 1 years	9.43	79.95	87.39	3284.20	2532.26
FIT10, 45-70, 1 years	11.00	76.61	73.58	2649.68	2216.43
FIT10, 45-75, 1 years	10.68	77.27	75.40	2739.39	2243.88
FIT10, 50-70, 1 years	13.85	70.55	62.94	2087.02	2023.32
FIT10, 50-75, 1 years	13.52	71.24	64.99	2176.53	2050.63
FIT10, 35-70, 2 years	11.43	75.68	72.38	2575.32	2357.39
FIT10, 35-75, 2 years	10.98	76.64	73.10	2633.87	2377.91
FIT10, 40-70, 2 years	11.93	74.62	64.68	2268.90	2157.65
FIT10, 40-75, 2 years	11.63	75.27	65.30	2310.27	2172.08
FIT10, 45-70, 2 years	13.33	71.65	56.86	1915.21	1997.79
FIT10, 45-75, 2 years	12.85	72.66	57.79	1974.18	2018.61
FIT10, 50-70, 2 years	16.09	65.77	49.70	1536.86	1898.59
FIT10, 50-75, 2 years	15.74	66.52	50.50	1579.27	1913.49
FIT20, 35-70, 1 years	10.27	78.15	76.82	2822.42	2527.69
FIT20, 35-75, 1 years	9.91	78.92	77.65	2880.98	2548.95
FIT20, 40-70, 1 years	10.80	77.04	68.07	2464.70	2268.32
FIT20, 40-75, 1 years	10.42	77.84	68.97	2523.77	2290.01
FIT20, 45-70, 1 years	12.10	74.27	59.31	2070.56	2067.78
FIT20, 45-75, 1 years	11.70	75.11	60.32	2129.88	2089.37
FIT20, 50-70, 1 years	15.00	68.10	51.45	1646.81	1938.69
FIT20, 50-75, 1 years	14.57	69.01	52.61	1706.70	1960.50
FIT20, 35-70, 2 years	13.70	70.86	58.29	1941.60	2172.61
FIT20, 35-75, 2 years	13.10	72.14	58.50	1983.70	2191.98
FIT20, 40-70, 2 years	14.16	69.87	52.74	1732.54	2037.73
FIT20, 40-75, 2 years	13.77	70.71	53.01	1761.96	2051.10
FIT20, 45-70, 2 years	15.59	66.83	47.04	1478.15	1928.56
FIT20, 45-75, 2 years	14.95	68.20	47.44	1521.00	1948.41
FIT20, 50-70, 2 years	18.23	61.23	41.69	1199.78	1866.76

FIT20, 50-75, 2 years	17.77	62.21	42.08	1230.34	1880.77
FIT47, 35-70, 1 years	11.34	75.88	62.97	2246.09	2353.82
FIT47, 35-75, 1 years	10.87	76.89	63.35	2289.32	2373.45
FIT47, 40-70, 1 years	11.89	74.71	56.40	1980.70	2156.44
FIT47, 40-75, 1 years	11.41	75.73	56.86	2024.32	2176.58
FIT47, 45-70, 1 years	13.21	71.91	49.66	1678.36	2005.97
FIT47, 45-75, 1 years	12.70	72.99	50.20	1722.50	2026.06
FIT47, 50-70, 1 years	16.07	65.81	43.44	1344.12	1912.37
FIT47, 50-75, 1 years	15.52	66.98	44.11	1389.12	1932.93
FIT47, 35-70, 2 years	15.65	66.72	48.47	1520.15	2091.86
FIT47, 35-75, 2 years	14.89	68.34	48.37	1553.70	2112.83
FIT47, 40-70, 2 years	16.07	65.82	44.20	1367.45	1993.44
FIT47, 40-75, 2 years	15.56	66.89	44.23	1390.88	2007.82
FIT47, 45-70, 2 years	17.52	62.74	39.81	1174.12	1912.17
FIT47, 45-75, 2 years	16.71	64.46	39.89	1208.59	1933.79
FIT47, 50-70, 2 years	19.98	57.51	35.54	960.59	1870.91
FIT47, 50-75, 2 years	19.40	58.73	35.68	985.08	1885.93
COL, 35-70, 3 years	5.72	87.84	246.02	10158.26	5700.33
COL, 35-75, 3 years	5.30	88.73	252.36	10525.97	5787.27
COL, 40-70, 3 years	6.50	86.18	209.97	8505.99	4575.85
COL, 40-75, 3 years	5.99	87.26	214.02	8779.29	4639.33
COL, 45-70, 3 years	7.54	83.96	175.76	6937.07	3667.19
COL, 45-75, 3 years	7.22	84.64	182.46	7260.08	3742.30
COL, 50-70, 3 years	10.91	76.79	144.54	5217.87	2945.63
COL, 50-75, 3 years	10.50	77.66	152.89	5582.19	3031.64
COL, 35-70, 5 years	8.92	81.03	165.85	6317.23	4020.98
COL, 35-75, 5 years	8.61	81.69	169.59	6512.38	4065.93
COL, 40-70, 5 years	9.40	80.00	142.28	5351.15	3348.62
COL, 40-75, 5 years	9.03	80.79	145.97	5544.06	3393.22
COL, 45-70, 5 years	10.28	78.13	120.76	4435.60	2810.78
COL, 45-75, 5 years	10.11	78.50	124.41	4590.69	2846.05
COL, 50-70, 5 years	12.96	72.43	102.63	3494.46	2411.72
COL, 50-75, 5 years	12.64	73.11	107.94	3709.73	2460.93
COL, 35-70, 10 years	9.74	79.28	123.73	4611.37	3211.13
COL, 35-75, 10 years	9.46	79.88	127.54	4789.01	3252.55
COL, 40-70, 10 years	10.18	78.35	111.21	4095.98	2816.99
COL, 40-75, 10 years	10.18	78.35	111.21	4095.98	2816.99
COL, 45-70, 10 years	10.86	76.91	96.42	3485.51	2460.25

COL, 45-75, 10 years	10.64	77.38	100.09	3640.37	2496.30
COL, 50-70, 10 years	13.33	71.64	85.40	2876.41	2202.15
COL, 50-75, 10 years	13.33	71.64	85.40	2876.41	2202.15
MTDNA, 35-70, 1 years	8.64	81.63	222.08	8521.07	12174.57
MTDNA, 35-75, 1 years	8.32	82.30	228.98	8859.25	12430.01
MTDNA, 40-70, 1 years	9.09	80.67	182.62	6925.00	8947.83
MTDNA, 40-75, 1 years	8.72	81.45	190.11	7279.31	9215.48
MTDNA, 45-70, 1 years	10.19	78.32	149.09	5489.42	6591.35
MTDNA, 45-75, 1 years	9.89	78.97	156.85	5822.28	6843.02
MTDNA, 50-70, 1 years	12.90	72.57	122.50	4178.37	4919.01
MTDNA, 50-75, 1 years	12.61	73.19	130.86	4501.74	5163.31
MTDNA, 35-70, 2 years	9.01	80.84	148.06	5626.11	7658.98
MTDNA, 35-75, 2 years	8.72	81.45	151.93	5817.30	7804.52
MTDNA, 40-70, 2 years	9.48	79.84	126.25	4738.25	5928.58
MTDNA, 40-75, 2 years	9.25	80.32	129.28	4881.55	6037.72
MTDNA, 45-70, 2 years	10.63	77.38	105.67	3844.33	4586.87
MTDNA, 45-75, 2 years	10.38	77.92	109.96	4027.80	4726.51
MTDNA, 50-70, 2 years	13.45	71.39	89.29	2996.47	3648.98
MTDNA, 50-75, 2 years	13.24	71.84	92.83	3134.82	3754.14

*Including deaths from complications of surveillance; CRC = colorectal cancer; NNS= number needed to screen to prevent one death from colorectal cancer; COLs = number of colonoscopies.

†outcomes not discounted.

‡compared with no surveillance.

§ currency is euro.

Table S7 | Efficient colonoscopy surveillance strategies among HL Survivors (entire cohort not stratified by treatment, base case analysis).

	Outcomes per 1,000 HL survivors free of CRC diagnosis and aged 35 years in 2019 (3%)*												Reductions:		
Surveillance strategies	**FITs**	**Scr. COLs**	**Diag. COLs**	**Surv. COLs**	**Total COLs**	**Compl.**	**CRCs †**	**CRC deaths †**	**CRC care**	**LYG ‡**	**Total costs**	**Net costs‡**	**Inc. (%)‡**	**Mortality (%)‡**	**ICER (*1,000)**
No Surveillance	0	0	33	0	33	0	73	26	214	0	966	0	0	0	0
COL, 50-70, 10 years	0	864	9	495	1368	5	39	8	188	52	1627	662	47	71	13
COL, 45-70, 10 years	0	1153	7	641	1801	5	36	6	173	60	1897	932	51	75	31
COL, 40-70, 10 years	0	1591	6	716	2314	5	35	6	168	64	2252	1287	52	77	90
COL, 35-70, 10 years	0	2063	6	797	2866	5	34	6	163	67	2637	1671	53	77	157
COL, 40-70, 3 years	0	3526	3	1696	5225	8	23	4	122	76	4215	3250	68	86	166
COL, 40-75, 3 years	0	3621	3	1696	5320	9	22	3	123	76	4284	3318	69	88	264
COL, 35-70, 3 years	0	4864	3	1956	6822	9	22	3	112	80	5337	4371	70	88	298
COL, 35-75, 3 years	0	5003	2	1956	6960	9	21	3	112	80	5437	4471	71	89	439

HL=Hodgkin Lymphoma; Entire cohort= all HL survivors treated with procarbazine-containing chemotherapy and/or infradiaphragmatic radiotherapy; LYG= life years gained; COLs = colonoscopies; Inc = incidence; ICER = Incremental cost-effectiveness ratio (Δcosts/ΔLYs gained compared to the previous less costly efficient strategy); † CRC cases and CRC death were not discounted; ‡ Compared with no surveillance. * Full participation in surveillance and post-colonoscopy surveillance was assumed.

Table S8 | Efficient colonoscopy surveillance strategies among HL Survivors (with procarbazine chemotherapy without infradiaphragmatic radiotherapy, base case analysis).

	Outcomes per 1,000 HL survivors free of CRC diagnosis and aged 35 years in 2019 (3%)*												Reductions:		
Surveillance strategies	**FITs**	**Scr. COLs**	**Diag. COLs**	**Surv. COLs**	**Total COLs**	**Com-pl.**	**CRCs †**	**CRC deaths †**	**CRC care**	**LYG ‡**	**Total costs**	**Net costs ‡**	**Inc. (%) ‡**	**Mor-tality (%) ‡**	**ICER (*1,000)**
No Surveil-lance	0	0	22	0	22	0	49	17	141	0	637	0	0	0	0
COL, 50-70, 10 years	0	903	6	394	1303	4	26	5	125	32	1374	737	47	70	23
COL, 45-70, 10 years	0	1204	5	504	1712	4	24	4	116	38	1641	1004	51	74	48
COL, 40-70, 10 years	0	1657	4	559	2221	4	24	4	112	40	1997	1360	52	75	162
COL, 35-70, 10 years	0	2132	4	627	2763	4	23	4	109	42	2377	1739	53	76	189
COL, 40-70, 3 years	0	3827	2	1405	5234	7	15	2	79	49	4058	3421	70	87	247
COL, 40-75, 3 years	0	3925	2	1405	5332	7	14	2	79	49	4129	3492	71	88	384
COL, 35-70, 3 years	0	5209	2	1611	6822	7	14	2	73	52	5176	4539	72	88	402
COL, 35-75, 3 years	0	5359	1	1611	6972	8	14	2	73	52	5284	4647	72	90	623

HL=Hodgkin Lymphoma; PRO=treated with procarbazine without infradiaphragmatic radiotherapy; LYG= life years gained; COLs = colonoscopies; Inc = Incidence; ICER = Incremental cost-effectiveness ratio (Δcosts/ΔLYs gained compared to the previous less costly efficient strategy); † CRC cases and CRC death were not discounted; ‡ Compared with no surveillance. * Full participation in surveillance and post-colonoscopy surveillance was assumed.

Table S9 | Efficient colonoscopy surveillance strategies among HL Survivors (with a combination of infradiaphragmatic radiotherapy and procarbazine chemotherapy, base case analysis).

	Outcomes per 1,000 HL survivors free of CRC diagnosis and aged 35 years in 2019 (3%)*											Reductions:		
Surveillance strategies	FITs	Scr. COLs	Diag. COLs	Surv. COLs	Total COLs	Compl.	CRCs †	CRC deaths †	CRC care	LYG ‡	Total costs	Net costs ‡	Inc. (%)‡	Mortality (%)‡	ICER (*1,000)
No Surveillance	0	0	59	0	59	1	127	47	392	0	1753	0	0	0	0
COL, 50-70, 10 years	0	804	15	665	1484	6	68	13	351	100	2202	449	46	72	5
COL, 45-70, 10 years	0	1070	11	893	1975	7	62	11	318	119	2460	707	51	77	13
COL, 40-70, 10 years	0	1477	10	1027	2514	7	60	10	303	128	2817	1064	53	78	42
COL, 35-70, 10 years	0	1937	9	1139	3086	7	59	10	294	133	3211	1458	53	79	86
COL, 40-70, 3 years	0	3050	6	2143	5198	10	43	6	237	145	4576	2822	66	86	107
COL, 35-70, 3 years	0	4289	5	2516	6810	11	41	6	217	153	5700	3947	68	88	148
COL, 35-75, 3 years	0	4410	4	2516	6930	12	40	5	218	153	5787	4034	68	89	283

HL=Hodgkin Lymphoma; IRT+PRO=treated with a combination of infradiaphragmatic radiation therapy and procarbazine chemotherapy; LYG= life years gained; COLs = colonoscopies; Inc = Incidence; ICER = Incremental cost-effectiveness ratio (Δcosts/ΔLYs gained compared to the previous less costly efficient strategy); † CRC cases and CRC death were not discounted; ‡ Compared with no surveillance. * Full participation in surveillance and post-colonoscopy surveillance was assumed.

Table S10 | Efficient surveillance strategies among HL Survivors (entire cohort not stratified by treatment, sensitivity analysis no. 8).

	Outcomes per 1,000 HL survivors free of CRC diagnosis and aged 35 years in 2019 (3%)*											Reductions:		
Surveillance strategies	**FITs**	**Scr. COLs**	**Diag. COLs**	**Surv. COLs**	**Total COLs**	**Com-pl.**	**CRCs** †	**CRC deaths**†	**CRC care**	**LYG** ‡	**Total costs**	**Net costs** ‡	**Inc. (%)**‡	**Mor-tality (%)**‡	**ICER (*1,000)**
No Surveil-lance	0	0	33	0	33	0	73	26	214	0	966	0	0	0	0
FIT47, 50-70, 2 years	3421	0	207	161	368	2	61	11	267	39	1156	190	17	56	5
FIT20, 50-70, 2 years	3293	0	272	211	483	3	55	10	249	42	1182	216	25	61	8
FIT47, 45-70, 2 years	4892	0	263	217	481	2	58	10	264	47	1220	255	21	61	8
FIT20, 45-70, 2 years	4719	0	353	283	636	3	51	9	243	51	1269	304	30	66	13
FIT47, 45-70, 1 years	8840	0	418	316	734	3	49	8	244	56	1371	406	33	71	20
FIT47, 40-70, 1 years	12361	0	547	386	932	3	47	7	236	62	1537	571	36	73	29
FIT20, 40-70, 1 years	11826	0	751	474	1225	4	41	6	209	65	1685	720	44	76	54
FIT20, 35-70, 1 years	16097	0	987	537	1524	4	40	6	203	68	1948	982	45	77	77
FIT20, 35-75, 1 years	16454	0	1008	538	1546	4	40	6	204	68	1971	1005	45	78	97
FIT10, 35-70, 1 years	15301	0	1501	661	2162	5	35	5	178	71	2346	1381	51	80	139
FIT10, 35-75, 1 years	15647	0	1534	661	2195	5	35	5	178	71	2377	1411	51	81	155
COL, 35-70, 3 years	0	4864	3	1956	6822	9	22	3	112	80	5337	4371	70	88	330

COL, 35-75, 3 years	0	5003	2	1956	6960	9	21	3	112	80	5437	4471	71	89	439

HL=Hodgkin Lymphoma; Entire cohort= all HL survivors treated with procarbazine-containing chemotherapy and/or infradiaphragmatic radiotherapy; LYG= life years gained; COLs = colonoscopies; ICER = Incremental cost-effectiveness ratio (Δcosts/ΔLYs gained compared to the previous less costly efficient strategy); † CRC cases and CRC death were not discounted; ‡ Compared with no surveillance. * Full participation in surveillance and post-colonoscopy surveillance was assumed.

Table S11 | Efficient surveillance strategies among HL Survivors (with procarbazine chemotherapy without infradiaphragmatic radiotherapy, sensitivity analysis no. 8).

	Outcomes per 1,000 HL survivors free of CRC diagnosis and aged 35 years in 2019 (3%)*												Reductions:		
Surveillance strategies	**FITs**	**Scr. COLs**	**Diag. COLs**	**Surv. COLs**	**Total COLs**	**Com-pl.**	**CRCs †**	**CRC deaths †**	**CRC care**	**LYG ‡**	**Total costs**	**Net costs ‡**	**Inc. (%)‡**	**Mor-tali-ty (%)‡**	**ICER (*1,000)**
No Surveil-lance	0	0	22	0	22	0	49	17	141	0	637	0	0	0	0
FIT47, 50-70, 2 years	3541	0	189	119	308	2	42	8	180	24	846	209	14	54	9
FIT47, 45-70, 2 years	5042	0	247	161	407	2	40	7	178	29	917	279	18	58	15
FIT20, 45-70, 2 years	4898	0	340	212	552	2	36	6	164	31	979	341	27	63	24
FIT47, 45-70, 1 years	9249	0	410	238	648	2	34	5	165	35	1092	455	31	69	30
FIT47, 40-70, 1 years	12861	0	543	291	835	3	33	5	160	39	1260	622	34	72	45
FIT47, 40-75, 1 years	13257	0	559	292	851	3	33	5	162	39	1281	644	33	74	77
FIT20, 40-70, 1 years	12408	0	763	363	1125	3	28	4	142	41	1423	786	42	75	88
FIT47, 35-75, 1 years	17671	0	722	333	1055	3	32	4	159	41	1482	845	34	75	94
FIT20, 35-70, 1 years	16762	0	1005	413	1418	3	28	4	138	43	1686	1049	44	76	116

FIT20, 35-75, 1 years	17146	0	1028	413	1441	3	28	4	139	43	1710	1073	43	78	116
FIT10, 35-70, 1 years	16090	0	1558	515	2073	4	24	4	120	46	2109	1472	51	79	190
FIT10, 35-75, 1 years	16463	0	1594	515	2109	4	24	3	120	46	2141	1504	51	80	199
COL, 35-70, 3 years	0	5209	2	1611	6822	7	14	2	73	52	5176	4539	72	88	500
COL, 35-75, 3 years	0	5359	1	1611	6972	8	14	2	73	52	5284	4647	72	90	623

HL=Hodgkin Lymphoma; PRO=treated with procarbazine without IRT; LYG= life years gained; COLs = colonoscopies; Inc = Incidence; ICER = Incremental cost-effectiveness ratio (Δcosts/ΔLYs gained compared to the previous less costly efficient strategy); † CRC cases and CRC death were not discounted; ‡ Compared with no surveillance. * Full participation in surveillance and post-colonoscopy surveillance was assumed.

Table S12 | Efficient surveillance strategies among HL Survivors (with a combination of radiotherapy and procarbazine chemotherapy, sensitivity analysis no. 8).

	Outcomes per 1,000 HL survivors free of CRC diagnosis and aged 35 years in 2019 (3%)*												Reductions:		
Surveillance strategies	**FITs**	**Scr. COLs**	**Diag. COLs**	**Surv. COLs**	**Total COLs**	**Compl.**	**CRCs †**	**CRC deaths †**	**CRC care**	**LYG ‡**	**Total costs**	**Net costs ‡**	**Inc. (%)‡**	**Mortality (%)‡**	**ICER (*1,000)**
No Surveillance	0	0	59	0	59	1	127	47	392	0	1753	0	0	0	0
FIT20, 50-70, 2 years	3025	0	304	315	620	4	91	17	445	84	1848	95	28	63	1
FIT20, 45-70, 2 years	4379	0	382	428	810	4	84	15	431	103	1914	161	33	69	4
FIT10, 45-70, 2 years	4078	0	519	548	1067	5	75	12	394	112	1988	235	41	73	8
FIT47, 40-70, 1 years	11443	0	558	580	1138	5	77	11	414	123	2148	394	39	76	14
FIT10, 40-70, 2 years	5791	0	672	667	1339	5	71	11	376	123	2153	400	44	76	17
FIT20, 40-70, 1 years	10793	0	736	698	1435	6	69	10	371	127	2267	514	46	78	29
FIT47, 35-70, 1 years	15654	0	709	661	1370	5	75	11	403	129	2349	595	41	77	42
FIT20, 35-70, 1 years	14891	0	958	795	1753	6	67	10	358	133	2530	776	47	79	43
FIT20, 35-75, 1 years	15204	0	977	795	1772	6	67	10	359	134	2550	797	47	80	75
FIT10, 35-70, 1 years	13917	0	1405	956	2362	7	61	9	318	138	2884	1131	52	81	80
FIT10, 35-75, 1 years	14220	0	1434	957	2391	7	61	9	319	138	2911	1158	52	81	118
COL, 35-70, 3 years	0	4289	5	2516	6810	11	41	6	217	153	5700	3947	68	88	186

COL, 35-75, 3 years	0	4410	4	2516	6930	12	40	5	218	153	5787	4034	68	89	283

HL=Hodgkin Lymphoma; IRT+PRO=treated with a combination of infradiaphragmatic radiation therapy and procarbazine chemotherapy; LYG= life years gained; COLs = colonoscopies; Inc. = Incidence; ICER = Incremental cost-effectiveness ratio (Δcosts/ΔLYs gained compared to the previous less costly efficient strategy); † CRC cases and CRC death were not discounted; ‡ Compared with no surveillance. * Full participation in surveillance and post-colonoscopy surveillance was assumed.

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