Original Research

Cost-effectiveness of lung cancer screening with low-dose computed tomography in heavy smokers: a microsimulation modelling study

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Abstract *Background:* Lung cancer screening with low-dose computed tomography (LDCT) reduces lung cancer mortality. The aim of this study was to evaluate the cost-effectiveness of lung cancer screening with LDCT in a high-risk population.
Methods: The study used an adapted microsimulation model in a cohort of Dutch heavy smokers for a lifetime horizon from a health insurance perspective. The main outcomes included average cost-effectiveness ratio (ACER), incremental cost-effectiveness ratio (ICER) and lung cancer mortality reduction. The comparator was no screening. Scenarios with different screening intervals and starting and stopping ages were evaluated for 100,000 male heavy smokers and 100,000 female heavy smokers. A cost-effectiveness threshold of 60 k€ per life year gained (LYG) was assumed acceptable.
Results: The evaluated screening scenarios yielded ACERs ranging from 17.7 to 32.4 k€/LYG for men and from 17.8 to 32.1 k€/LYG for women. The lung cancer mortality reduction ranged from 9.3% to 16.8% for men and from 7.8% to 13.7% for women. The optimal screening scenario was annual screening from 55 to 80 years for men and biennial screening from 50 to 80 years for women, with an ICER of 51.6 and 45.8 k€ per LYG compared with its previous efficient alternative, respectively. Compared with no screening, the optimal screening scenario yielded an ICER of 27.6 k€/LYG for men and 21.1 k€/LYG for women. The mortality reduction of lung cancer was 15.9% for men and 10.6% for women.

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Conclusions: Lung cancer LDCT screening is cost-effective in a high-risk population. The optimal screening scenario is dependent on sex.

1. Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death in the Netherlands [1]. The life expectancy is estimated to be 13 years shorter for heavy smokers than for non-smokers [2]. Screening for lung cancer by low-dose computed tomography (LDCT) of the chest has been shown to prevent premature death by detection of developing cancers at an early stage [3]. The National Lung Screening Trial (NLST) found that three annual screenings with LDCT in (ex-)smokers aged 55−74 years reduced lung cancer mortality by 20% six years after baseline compared with three annual screenings with chest radiography [4]. The Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) confirmed the benefits of LDCT screening for lung cancer, showing that lung cancer mortality reduced by 24% for men and 33% for women in the LDCT screening group as compared with the no-screening group at 10 years of follow-up [5]. The European position statement on lung cancer screening recommended that Europe should prepare for the implementation of LDCT screening [3].

However, there is still debate on the optimal screening strategy [3]. Given that the Multicentric Italian Lung Detection trial found no difference in mortality comparing annual and biennial screening intervals at 5-year follow-up [6], the benefits and harms of biennial screening need to be further investigated, and the optimal screening strategy requires further investigation.

A model-based economic evaluation of different lung cancer screening strategies could provide a reference for policymakers to facilitate selecting an optimal strategy for lung cancer screening. Previous modeling studies that estimated the cost-effectiveness in Europe concluded that lung cancer screening can be cost-effective [7−9]. However, these studies yielded inconclusive results on the average cost-effectiveness ratio (ACER) relative to no screening, ranging from 16.8 to 48.4 k€ per life year gained (LYG) [7−9]. In addition, these studies were limited to studying only a single (annual) screening interval, or they excluded possible harms from screening (such as false positives and radiation risk) [7−9] or did not consider the cost of immunotherapy [8,9]. The aim of this study was therefore to assess the cost-effectiveness of various LDCT lung cancer screening strategies in a high-risk population, overcoming the limitations of previous studies.

2. Methods

2.1. Microsimulation model

The microsimulation model Simulation Model on Radiation Risk and cancer Screening (SiMRiSc) was used and adapted for the purpose of lung cancer LDCT screening. This model has previously successfully been used to investigate the cost-effectiveness of breast cancer screening programs. The structure of the model and its underlying assumptions have been extensively described [10,11]. The basic principle of the model was that lung cancers were detected at an earlier stage when screening was implemented compared with no screening. Consequently, participants with lung cancer have a longer survival owing to the smaller tumour size and lower probability of positive lymph nodes and metastasis at detection. Thus, the life expectancy of the population in a screening setting is higher than that in a no-screening setting. The microsimulation model simulates the life history of each individual in the considered population from 20 years old until death in the presence and in the absence of LDCT screening. Several modules are incorporated in the model. The model allows for the simulation of various screening intervals. Remarkably, the sensitivity of LDCT was a function of tumour size instead of a fixed value independent of tumour size. The sensitivity was 0% for tumours of size less than 3 mm, 100% for tumours of size larger than 5 mm and a continuous function for tumours of size between 3 and 5 mm. Furthermore, the model included a module for radiation-induced tumour risk based on the model in the BEIR VII report [12]. A detailed description of the model is presented in Supplementary.

2.2. Simulated population

The model simulated two cohorts of 100,000 male and 100,000 female heavy smokers in the Netherlands from 20 years old until death. All simulations were repeated 10 times to assure that the standard error of the simulated outcomes was always less than 5% of point estimate. The average value of the 10 simulated results was derived and presented. A heavy smoker was defined as a current smoker who smokes at least 20

cigarettes per day according to the Dutch Central Bureau of Statistics [13].

2.3. Parameters of the model

In the simulation, every individual was assumed to die at a predetermined natural death age, which was sampled from the cumulative mortality distribution [14] (Table S1). Lifetime risk for developing lung cancer and the mean age (and spread) at the time of lung cancer diagnosis was derived from the estimated lung cancer incidence for male and female heavy smokers. The incidence of lung cancer among heavy smokers was based on the lung cancer incidence in the general population [15] and the population attributable fraction for lung cancer due to tobacco smoking [16] (Table S2). In the 'tumor growth module', the volume doubling time of lung cancers was based on the publication of Henschke *et al.* [17]. The self-detection size in the 'self-detection module' was based on the article of Rami-Porta et al [18]. The lung cancer survival parameters were derived from the literature on survival by stage of lung cancer (Table S3 and Table S4) [19]. The function that described the sensitivity of LDCT as a function of tumour diameter [20] and the specificity of LDCT was based on the published data [21]. The 'tumor induction module' consisted of the average dose per LDCT scan [22] and the risk of lung cancer induction from ionising radiation [12]. We used a health insurance perspective. Costs related to screening, diagnosis and treatment of lung cancer were considered and valued in euro [23−25]. Details of cost are presented in Supplementary. Discounting of 4% for costs and 1.5% for health effects (LYG) was applied according to Dutch guidelines [26]. To allow for international comparison, we also applied a discount rate of 3% for both costs and effects [27]. Values of all input parameters were independently taken from the literature and are summarised in Table 1.

2.4. Validation of the model

The population used for the validation of the model consisted of Dutch heavy smokers aged 50−75 years, similar to the population of the NELSON study [28].

Table 1
Input parameters of the SiMRiSc model.

Input parameter	Value		Reference
Life expectancy of Dutch heavy smokers (years)	74.4		[14], details in Table S1
Cumulative incidence rate	Men	Women	[15], details in Table S2
Lifetime risk, mean ± SD	0.22 ± 0.05	0.20 ± 0.04	
Mean age (years), mean ± SD	72.48 ± 1.08	69.62 ± 1.49	
Spread (years), mean ± SD	9.28 ± 1.62	9.73 ± 1.83	
Lung cancer growth			[17]
VDT (days), geometric mean	98		
VDT, log-transformed geometric mean, mean ± SD	4.59 ± 0.21		
Spread	0.74		
Self-detection module			[18]
Self-detected diameter (mm), geometric mean	20.84		
Self-detected diameter, log-transformed geometric mean, mean ± SD	3.037 ± 0.014		
Spread	0.61		
Lung cancer survival	Table S3 and Table S4, Fig. S1		[19]
LDCT sensitivity and specificity			
LDCT sensitivity	0%; diameter < 3 mm (0.5*diameter-1.5)* 100%; 3 mm ≤ diameter < 5 mm 100%; diameter ≥ 5 mm		[20]
LDCT specificity, mean ± SD	99.2% ± 0.076%		[21]
Lung cancer induction	Men	Women	
Dose per LDCT scan (mSv), on average	1.0	1.4	[22]
Excess relative risk of lung cancer per Sv exposure, mean ± SD	0.32 ± 0.28	1.40 ± 0.58	[12]
Cost			
LDCT screening per scan	€ 176		[23]
Diagnosis per patient	€ 1908		[24]
Treatment for stage I−III per patient	€ 37,909		[24]
Treatment for stage IV per patient	€ 56,556		[24,25]

VDT = volume doubling time; LDCT = low-dose computed tomography; SD = standard deviation; mSv = millisievert; SiMRiSc = Simulation Model on Radiation Risk and cancer Screening.

The model was validated by comparing the simulated outcomes (number of screen-detected lung cancers and interval lung cancers per 1000 screened individuals, and size distribution of screen-detected lung cancers) with the observed data from the first and second screening rounds of the NELSON lung cancer screening trial [28], as shown in Table S5 and Table S6.

2.5. Screening scenarios

The evaluated screening scenarios combined different key characteristics of LDCT screening strategies: screening interval and start and stop age of screening. Annual and biennial screening intervals were considered. The considered values for the screening start age were 50, 55 and 60 years and for the screening stop age were 75, 80 and 85 years, which covers all of the current recommendations regarding screening age. Overall, 18 scenarios were modelled for men and women separately. Perfect attendance of screening was assumed for all the base-case scenarios.

2.6. Outcomes and cost-effectiveness

The primary outcomes of the model assessed for each scenario were ACER, incremental cost-effectiveness ratio (ICER) and lung cancer mortality reduction. The ACER was estimated as the ratio of the difference in costs to the difference in health effects of the investigated screening scenario compared with no screening. The secondary outcomes were LYG, number of lung cancer deaths averted, interval lung cancers, false positives, radiation-induced lung cancers and additional costs relative to no screening. The LYG was the difference in death age of the simulated population between a screening and no-screening setting.

The efficient scenarios were selected based on the cost per LYG and per averted lung cancer death in male and female heavy smokers. Scenarios that were more costly and less effective (fewer LYG or less lung cancer deaths prevented) than other scenarios or a combination of other scenarios were ruled out. The remaining screening scenarios were considered efficient and constituted the efficient frontier. For each efficient screening scenario, the ICER was estimated as the ratio of incremental costs to incremental health effects (LYG or averted lung cancer deaths) of a screening strategy relative to the previous efficient scenario. The Dutch National Health Care Institute uses a threshold of 80 k€ per quality-adjusted life year (QALY) gained for high-burden diseases [29]. Given that the cost per LYG is usually lower than the cost per QALY gained [30] and the mean utility score was 0.74 for lung cancer survivors based on a Dutch investigation [31], a conservative estimation of the cost-effectiveness threshold of 60 k€/LYG was used in this study. The scenario with the highest ICER below the threshold was considered optimal.

2.7. Sensitivity analysis

One-way sensitivity analyses were carried out to explore parameter uncertainty of the most cost-effective scenario at the assumed threshold. We varied the baseline values of the input parameters by an increase or decrease of two standard deviations for the base case analysis. Cost values were increased or decreased by 50% of the value of the base case analysis. Imperfect attendance was evaluated by assuming 50% attendance rates. The values of the input parameters in the sensitivity analyses are presented in Table S7. Tornado plots were constructed to visualise the impact of parameter uncertainty on the ACER.

3. Results

The LYG across all the screening scenarios compared with no screening ranged from 4991 to 8641 for men and from 4854 to 8741 for women (Table 2). The ACERs ranged from 17.7 to 32.4 k€/LYG for men and from 17.8 to 32.1 k€/LYG for women compared with no screening (Table S8). The lung cancer mortality reduction ranged from 9.3% to 16.8% for men and from 7.8% to 13.7% for women (Table 2). The scenario representing the screening scenario of the NELSON study (A-50-75) had a cost of 31.4 k€/LYG for men and 30.9 k€/LYG for women, with 14.9% and 12.4% mortality reduction, respectively, compared with no screening. Of the evaluated scenarios, six were judged to be efficient for men and seven were efficient for women based on the cost per LYG (Fig. 1). The efficient frontier consisted of a mix of annual and biennial scenarios. The estimated ICER ranged from 17.7 to 188.0 k€/LYG for men and from 17.8 to 191.1 k€/LYG for women compared with its previous efficient scenario (Table 3). The outcomes of all scenarios in which a discount rate of 3% for both costs and effects was applied are presented in Table S9.

Assuming a cost-effectiveness threshold of 60 k€/LYG as acceptable for the Dutch healthcare system, the optimal screening strategy was annual screening from 55 to 80 years old (A-55-80) for male heavy smokers, yielding an ICER of 51.6 k€/LYG compared with its previous efficient scenario. The optimal screening strategy for female heavy smokers was biennial screening from 50 to 80 years old (B-50-80), with an ICER of 45.8 k€/LYG compared with its previous efficient scenario. Compared with no screening, the optimal screening scenario yielded a cost of 27.6 k€/LYG and 15.9% mortality reduction of lung cancer for men and a cost of 21.1 k€/LYG and 10.6% mortality reduction of lung cancer for women (Table 3).

Table 2
Outcomes of the scenarios per 100,000 male and per 100,000 female heavy smokers.

Scenario[a]	Discounted LYG relative to no screening		Number of lung cancer deaths averted		LC mortality reduction compared with no screening		Number of interval lung cancers		Number of false positives		Number of radiation-induced LC cases		Discounted additional cost vs no screening (in million €)	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
A-50-75	8279	8479	1091	950	14.9%	12.4%	890	958	15,336	15,137	86	464	260.3	262.2
A-55-75	8026	7935	1048	921	14.3%	12.0%	835	868	11,627	11,475	58	305	215.5	215.4
A-60-75	6689	6311	921	792	12.6%	10.3%	720	692	8166	8053	37	177	166.7	164.8
A-50-80	8594	8708	1204	1031	16.5%	13.4%	1052	1081	16,760	16,566	88	473	273.2	274.7
A-55-80	8370	8187	1163	1001	15.9%	13.0%	993	992	13,069	12,921	60	314	231.1	230.6
A-60-80	7047	6578	1033	869	14.1%	11.3%	880	811	9595	9492	39	189	185.7	183.3
A-50-85	8641	8741	1231	1050	16.8%	13.7%	1121	1127	17,636	17,452	89	476	279.6	281.0
A-55-85	8424	8218	1190	1018	16.3%	13.3%	1063	1037	13,934	13,800	61	317	238.9	238.2
A-60-85	7099	6615	1057	886	14.5%	11.5%	949	858	10,475	10,385	39	191	195.2	192.6
B-50-75	6143	6570	808	744	11.1%	9.7%	2288	2483	7758	7663	45	239	135.4	135.5
B-55-75	6027	6134	802	730	11.0%	9.5%	2285	2317	6077	5999	31	156	115.0	113.9
B-60-75	4991	4854	683	601	9.3%	7.8%	1843	1794	4150	4091	18	95	88.2	86.3
B-50-80	6423	6776	908	812	12.4%	10.6%	2829	2878	8622	8532	46	244	143.4	143.2
B-55-80	6245	6272	871	774	11.9%	10.1%	2640	2574	6656	6581	33	159	121.5	120.1
B-60-80	5315	5081	781	668	10.7%	8.7%	2384	2181	5003	4950	19	100	100.1	97.6
B-50-85	6453	6795	923	824	12.6%	10.7%	2976	2973	8961	8877	46	244	146.1	145.7
B-55-85	6291	6308	895	792	12.2%	10.3%	2873	2724	7184	7118	33	161	126.5	124.8
B-60-85	5347	5102	796	679	10.9%	8.8%	2531	2281	5360	5314	19	100	104.0	101.4

LC = lung cancer; LYG = life year gained.
The lifetime number of lung cancer deaths without screening was estimated to be 7308 per 100,000 male heavy smokers and 7679 per 100,000 female heavy smokers.
Costs were discounted by 4% annually, and LYG was discounted by 1.5% annually.
  [a] Screening interval (A = annual, B = biennial)-screening start age-screening start age.

Fig. 1. The cost-effectiveness in cost per life year gained (top) and cost per lung cancer death averted (bottom) of all evaluated scenarios for men (left) and women (right). Annual screening intervals are shown in round shape, and biennial screening intervals are shown in triangle shape. The scenarios that constitute an efficient frontier are labelled (A = annual, B = biennial-screening start age-screening stop age).

Table 3
Cost-effectiveness of screening scenarios on the efficient frontier for 100,000 male and 100,000 female heavy smokers.

Scenario[a]	Discounted additional cost vs no screening (in million €)		ACER vs no screening (in k€/LYG)		ACER vs no screening (in k€/one averted lung cancer death)		ICER vs the previous efficient scenario (in k€/LYG or k€/one lung cancer death averted)	
	Men	Women	Men	Women	Men	Women	Men	Women
Efficient scenarios based on the cost per LYG								
B-60-75	88.2	86.3	17.7	17.8	129.2	143.6	17.7	17.8
B-55-75	115.0	113.9	19.1	18.6	143.5	156.1	25.9	21.6
B-55-80	121.5	120.1	19.5	19.1	139.5	155.2	30.0	44.7
B-50-80[c]	NE	143.2	NE	21.1	NE	176.3	NE	45.8
A-55-80[b]	231.1	230.6	27.6	28.2	198.7	230.4	51.6	61.9
A-50-80	NE	274.7	NE	31.6	NE	266.5	NE	84.8
A-55-85	238.9	NE	28.4	NE	200.8	NE	144.8	NE
A-50-85	279.6	281.0	32.4	32.1	227.1	267.6	188.0	191.1
Efficient scenarios based on the cost per lung cancer death averted								
B-60-75	NE	86.3	NE	17.8	NE	143.6	NE	143.6
B-60-80	100.1	97.6	18.8	19.2	128.1	146.1	128.1	169.2
B-55-80	NE	120.1	NE	19.1	NE	155.2	NE	212.4
B-55-85	126.5	124.8	20.1	19.8	141.3	157.6	231.2	263.2
A-55-85	238.9	238.2	28.4	29.0	200.8	230.4	381.5	506.5
A-50-85	279.6	281.0	32.4	32.1	227.1	267.6	982.9	1016.4

ACER = average cost-effectiveness ratio; ICER = incremental cost-effectiveness ratio; k€ = 1000 euro. NE, not efficient; LYG = life year gained.

Costs were discounted by 4% annually, and LYG was discounted by 1.5% annually.

  [a] Screening interval (A = annual, B = biennial)-screening start age-screening stop age.
  [b] Optimal strategy for men at the cost-effectiveness threshold of 60 k€/LYG.
  [c] Optimal strategy for women at the cost-effectiveness threshold of 60 k€/LYG.

3.1. Sensitivity analysis

The most influential factors on the ACER were lifetime risk of lung cancer and screening cost. An increase in the lifetime risk by 2 standard deviations in the optimal screening scenarios resulted in a 33% and 28% decrease of the base ACER, for male and female heavy smokers, respectively. The ACER changed by more than 40% after a 50% variation of screening cost. Detailed results of sensitivity analyses are available in Fig. S2 and Fig. S3.

4. Discussion

A previously published simulation model was applied and validated for the purpose of the analysis presented here. The model reproduced the observed data of the first and second screening rounds of the NELSON study to a high accuracy. The simulations indicated that lung cancer screening with LDCT is cost-effective in a high-risk population. At a cost-effectiveness threshold of 60 k€/LYG, the most promising scenario was annual screening from the age of 55 to 80 years for male heavy smokers and biennial screening from the age of 50 to 80 years for female heavy smokers, yielding a cost of 27.6 k€/LYG and 21.1 k€/LYG relative to no screening, respectively.

The model-based cost-effectiveness analyses on lung cancer screening with LDCT in other European countries applied a discount rate of 3% for both costs and effects. When the same discounting rate was applied in our study, the ACER ranged from 23.3 to 51.9 k€/LYG for men and 23.3 to 50.2 k€/LYG for women. Our results are comparable with the results of model-based cost-effectiveness analyses on lung cancer screening with LDCT conducted in Switzerland but higher than those of analyses conducted in Germany. The cost-effectiveness analysis conducted in Switzerland indicated that annual or biennial screening for the high-risk population with various smoking history may be cost-effective at a cost of 25.6–48.4 k€/LYG compared with no screening [7]. The simulation analysis conducted in Germany showed that annual screening may be cost-effective at a cost of 19.3 k€/LYG and 30.3 k€/QALY in heavy smokers aged 55–75 years compared with the standard clinical care [9]. The lower treatment cost applied in that study could contribute to the difference in ACER in the present study.

Several studies evaluated the cost-effectiveness of lung cancer screening with LDCT outside Europe, especially in the United States, Canada and Australia. The US Preventive Services Task Force recommended annual screening for a population aged 55–80 years with 30 or more pack-years after balancing the benefits and harms of 576 scenarios [32]. A cost-effectiveness analysis in a Canadian population indicated that annual screening for individuals aged 55–80 years required 43.0 to 50.0 k$/LYG compared with no screening [33]. However, in a simulation analysis of an

Australian population using NLST criteria, lung cancer screening with LDCT was not likely to be cost-effective owing to the high cost of 138.0 kAU$/LYG (approximately 104.7 k$/LYG) [34].

Our analysis indicated different optimal scenarios for men and women and lung cancer screening was more cost-effective in women than in men (an ACER of 21.1 k€/LYG for women vs 27.6 k€/LYG for men), which is in line with the previous findings [35,36]. The optimal screening scenario for women indicated that screening should be started at an earlier age than for men and a biennial screening should be adopted. This is in line with the previous studies, showing that women diagnosed with lung cancer were significantly younger than men [37,38]. In addition, given that women are more vulnerable to radiation-induced tumours than men [22], biennial screening is warranted.

Remarkably, the scenario of the NELSON study (A-50-75) was not included in the efficient frontiers. However, this scenario was very close to the efficient frontier based on the cost per LYG, which is consistent with a previous study conducted in Germany [8]. The selection criteria of the NELSON population were made based on a statistical power analysis for mortality reduction [39], and cost-effectiveness was not the main aim, which might explain the efficiency difference compared with other scenarios.

Our model has some limitations. First, not all the values of the input parameters were derived from the Dutch setting, which might have an impact on the effectiveness of screening. However, we incorporated this uncertainty by applying (normal and lognormal) distributions on the input parameters and evaluated the impact using a sensitivity analysis. In addition, because the external validation of the model to the observed data from a lung cancer screening program in the Dutch population showed good results, the evaluation of cost-effectiveness is considered valid. Second, we could not evaluate the ICER of lung cancer screening in populations with different smoking histories in terms of pack-years owing to a lack of data. However, we evaluated the ICER by varying the lung cancer lifetime risk in the sensitivity analyses, indicating that lung cancer screening in a more high-risk population will be more cost-effective, as expected. Third, a single-treatment cost was used for stage I to stage III tumours owing to the lack of data for each histological stage, which might lead to an overestimation of the cost per LYG because of the shift to an earlier stage (lower treatment cost) from screening. Fourth, our analysis focused only on quantitative outcomes. The quality of life of patients with lung cancer and the disutility associated with LDCT screening were not incorporated in our model. However, the NELSON study indicated that the impact of LDCT screening itself on the quality of life was negligible in the long term [40]. Fifth, assuming that all tumours are spherical is a limitation. In the NELSON study, more than half of the malignant nodules were polygonal and irregular [41]. A spiculated, non-spherical growth might yield a smaller self-detection size owing to the larger probability of being symptomatic, which implies an overestimation of the cost-effectiveness. However, from the sensitivity analyses, it follows that the influence of self-detection size on cost-effectiveness is only minor. Therefore, we estimate that this limitation will not change the major outcomes of our simulations.

In conclusion, the results from a microsimulation model show that lung cancer screening with LDCT is cost-effective in a high-risk population. At a cost-effectiveness threshold of 60 k€/LYG, the optimal screening scenario for male heavy smokers is annual screening from 55 to 80 years old, yielding a cost of 27.6 k€/LYG and 15.9% mortality reduction of lung cancer relative to no screening. The optimal screening scenario for female heavy smokers is biennial screening from 50 to 80 years old, yielding a cost of 21.1 k€/LYG and 10.6% mortality reduction of lung cancer relative to no screening.

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.05.004.

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