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Partial breast irradiation

Long-term risks of secondary cancer for various whole and partial breast irradiation techniques

Nienke Hoekstra [a], Emmanuelle Fleury [a], Tomas Rodrigo Merino Lara [b], Peter van der Baan [a], Andy Bahnerth [a], Gerson Struik [a], Mischa Hoogeman [a], Jean-Philippe Pignol [a,c,*]

[a] Erasmus MC Cancer Centre, Department of Radiation Oncology, Rotterdam, The Netherlands; [b] Pontificia Universidad Catolica de Chile, Santiago, Chile; [c] Dalhousie University, Department of Radiotherapy, Halifax, Canada

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ABSTRACT

Introduction: For early stage breast cancer patients, non-breast cancer mortality including secondary cancers and cardiac events can overshadow the benefit of adjuvant radiotherapy. This study evaluates the excess risk of secondary cancer for various breast radiotherapy techniques including accelerated partial breast irradiation (APBI).

Methods: Secondary cancers Lifetime Attributable Risks (LAR) were calculated using a modified BEIR-VII formalism to account for the specific survival of breast cancer patients. Those survivals were extracted from the SEER database. Doses scattered to various organs were measured into a Rando phantom with custom-made breast phantoms. Treatments delivered typical doses of brachytherapy APBI (34 Gy in 10 fractions), external beam APBI (38.5 Gy in 10 fractions) using 3D-conformal, Cyberknife stereotactic (CK), or VMAT, as well as whole breast irradiation (WBI) delivering 42.5 Gy in 16 fractions.

Results: WBI resulted in the highest total LAR, with 4.3% excess risk of secondary cancer for a patient treated at age 50 years. Lung cancers accounted for 75–97% of secondary malignancies. For a typical early stage patient irradiated at 50, the excess risks of secondary lung cancer were 1.1% for multicatheter HDR, between 2.2% and 2.5% for 3D-CRT or CK, 3.5% for VMAT APBI, and 3.8% for WBI.

Conclusions: APBI reduces the risk of secondary cancer 2–4 fold compared to WBI. These techniques are well suited for long-living early stage breast cancer patients. HDR brachytherapy and 3D-conformal APBI achieve mean lung doses between 1 and 1.5 Gy, which could serve as reference.

Today breast cancer is frequently diagnosed at an early stage and has an excellent prognosis. SEER data show that 60% of the patients are diagnosed at a localized stage, without extension to the regional nodes, and the 5-year cancer specific survival for those patients is 98.9% [1]. Standard treatment includes limited surgery followed by whole breast irradiation (WBI). Long-term follow-up of large randomized trials comparing lumpectomy with or without adjuvant radiotherapy has shown that the benefit of radiotherapy is eclipsed by non-breast cancer mortality [2,3]. The most common causes of non-breast cancer mortality include major cardiac events and secondary cancers [4–6]. To reduce cardiac toxicity, the radiation oncology community has massively adopted preventive measures like breath-hold [7,8]. The issue of secondary cancer has not yet led to changes regarding the breast irradiation technique.

Accelerated partial breast irradiation (APBI) has been recently proposed for selected patients with favorable characteristics, and results of the few randomized trials suggest non-inferiority in local control compared to WBI [9–12]. Introducing new irradiation techniques may result in differences in the amount of dose to the whole body and thus to differences in the risk of radiation-induced secondary cancer [6,13]. Scarce comparisons of secondary cancer risks for different techniques have been published [14–16]. They focused either exclusively on whole breast radiotherapy techniques or evaluated the scatter dose theoretically using Monte Carlo simulation. Currently there is no thorough comparison between whole breast radiotherapy and APBI.

The aim of this study is to evaluate the risk of secondary cancer of whole breast radiotherapy and several APBI techniques, using a modified BEIR VII formalism accounting for the specific survival of a breast cancer population, and experimentally measure the scatter dose to various organs for these breast radiotherapy techniques.

* Corresponding author at: Dalhousie University, Department of Radiotherapy, 5820 University Avenue, Halifax, NS B3H 1V7, Canada.
E-mail address: jean-philippe.pignol@dal.ca (J.-P. Pignol).

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Materials and methods

Calculation of lifetime attributable risks (LARs)

LARs were calculated using the BEIR VII formalism [17]. This model includes empirical and *in vitro* data to calculate secondary cancer risks for specific organs depending on sex, age at exposure and attained age. For the esophagus, we used the organ specific parameters from the study by Berrington de Gonzalez [18]. We selected age at exposure of 40 years and older, since this age corresponds to the lower threshold of the "cautionary group" of the ASTRO guidelines and the "intermediate-risk group" of the GEC-ESTRO guidelines [19–21]. We used the probability of survival for the general population from the U.S. Decennial Life Tables for 1999–2001 [22]. We corrected the probability of survival for breast cancer patients using the probability of survival after localized breast cancer from the SEER database [23]. The SEER database provides survival data up to 40 years after diagnosis. For the period after this, we extrapolated the linear trend in the survival probability. We used the baseline cancer risks for the general population from the SEER database [24]. To put the risks into perspective, we calculated the lifetime Relative Risk (RR) of secondary cancer per organ.

Radiotherapy planning and phantom treatments

Measurements of the scatter dose for various breast radiotherapy techniques were performed using a Rando-Alderson phantom (Radiology Support Devices, Inc., Long Beach, CA, USA) with custom-made tissue equivalent breast phantoms adapted from Ruschin et al. [25]. Five surgical clips were inserted in the upper outer quadrant of the right breast at typical places found on patients treated in our institutions, and creating a virtual seroma of about 3 cm in diameter.

Planning CT-scans of the realistic breast phantom were made according to our institutional protocol. The whole breast clinical target volume (CTV) was delineated up to the chest wall and excluded the first 5 mm below the surface. The whole breast CTV expanded by a 5 mm margin and limited 5 mm under the surface corresponded to the PTV for WBI. The tumor bed was delineated using the surgical clips. It was expanded with a margin of 15 mm to create the CTV for the APBI treatments following the NSABP B-39/RTOG 0413 protocol [26]. The planning target volume (PTV) margin was 10 mm for the external beam APBI techniques and zero mm for the HDR techniques [26].

Whole breast radiotherapy used a hypofractionated regimen of 42.5 Gy in 16 fractions mixing 6 and 10 MV tangent beams. Beam angles were optimized to limit the contralateral breast and lung dose. Dynamic wedges were used to improve the dose distribution and the treatment was delivered using an Elekta Synergy S linear accelerator.

The technique described by Baglan et al. was used to plan the 3D-conformal (3D-CRT) APBI treatment [27]. The prescribed dose was 38.5 Gy in 10 fractions. The plan fulfilled the dose constraints of the NSABP B-39/RTOG 0413 protocol [26]. VMAT APBI was delivered using a single 6 MV arc ranging from 190° to 20°. The plan was optimized for breast conformality, minimizing the heart and lung dose according to the NSABP B-39/RTOG 0413 constraints [26]. The prescribed dose was 38.5 Gy in 10 fractions. Cyberknife plans were created in Multiplan version 5.3.0 (Accuray Inc., Sunnyvale, USA) with an inverse plan optimization. Plans used either the Iris (CK-Iris) or the MLC (CK-MLC) collimators. Beams were not allowed to enter through the contralateral breast or heart. The prescribed dose, margins and dose constraints applied were identical to the other external beam APBI techniques.

For HDR multicatheter APBI, 8 catheters were inserted in the breast phantom in 2 planes using a free hand implantation technique. A post-implant CT-scan was acquired, and the images were transferred to the Oncentra brachytherapy dose planning system version 4.5.1 (Elekta). The prescribed dose was 34 Gy in 10 fractions. Dwell times were optimized to ensure that coverage and dose homogeneity were optimized following the constraints of the NSABP B-39 protocol [26]. To mimic a balloon for HDR balloon-based APBI, a single catheter was inserted in the breast phantom. On the planning CT-scan, a sphere of 3.5 cm diameter was delineated around the catheter to represent the balloon. A dose of 34 Gy in 10 fractions was delivered to a point 1 cm away from the balloon surface. The plan also satisfied the constraints from the NSABP B-39/RTOG 0413 protocol for balloon-based HDR [26]. Both HDR APBI techniques were delivered using a 192-Ir Flexitron Remote Afterloading system (Elekta).

Dose measurement

Dose was measured in the lungs, contralateral breast, thyroid, esophagus, colon, ovaries and the uterus. Those organs were chosen because of elevated risks of radiation-induced cancers reported in these organs [5,28–30]. Doses were measured using 34 ThermoLuminescent dosimeters (TLDs) distributed uniformly over the organs and Gafchromic film for the lungs (Ashland Advanced Materials, Bridgewater, USA). The LiF 700 powder TLDs were read out using the Pitman 654 TLD-reader and annealed with the Pitman 622/B annealing facility using a standard of 400 °C for 1.5 h and 80 °C for 16 h, with subsequent natural cooling down to room temperature. TLDs were calibrated for doses of 1 cGy to 10 Gy. Gafchromic EBT3 films were used next to TLDs to measure the scatter dose in the lungs in the presence of steep dose gradients. The films were analyzed after 24 h storage in the dark at room temperature using the dose-density curve for each batch of films.

For each technique a single dose of 10–12 Gy was delivered to the PTV, to ensure that the TLDs and films received a dose within its accuracy range. Measured doses were rescaled to the total dose that would be delivered per technique. Mean organ doses were calculated weighing the dose from each TLD or film for the percentage of the organ it represented. Each measurement was repeated 3 times.

Results

The mean organ doses per technique are shown in Table 1. The lungs had the highest mean doses, ranging from 50 to 200 cGy depending on the breast radiotherapy technique. The mean doses to the other organs varied a lot, but they generally remained well below 70 cGy. The only exception was the esophagus which received more than 100 cGy with the 3D-CRT APBI. The mean doses to the ovaries and uterus were very low, ranging from 1 to 8 cGy. Comparing the various techniques, whole breast radiotherapy delivered the highest doses overall. Conversely, all APBI techniques resulted in lower doses to the lungs and contralateral breast. The two Cyberknife techniques showed a slightly higher dose to the abdominal organs compared to other APBI techniques, which is due to the non-coplanar technique.

Table 2 shows the LARs for the individual organs and the total LARs per technique for ages at exposure of 40, 50, 60 and 80 years using the BEIR VII formalism. The results are presented graphically in Fig. 1 for age at exposure of 50 years, which corresponds to the ASTRO "suitable group" and the GEC-ESTRO "low-risk group" [19–21]. As the secondary cancer risks are proportional to the mean organ doses, the comparison of the various techniques in terms of LAR yields the same findings as the comparison of the various

Table 1
Mean dose per organ for the various breast radiotherapy techniques in cGy.

	WBI	3D-APBI	VMAT	Multicath HDR	Balloon HDR	CK-Iris	CK-MLC
Thyroid	17.6	10.4	1.6	15.5	20.6	9.0	14.3
Breast	45.5	6.6	14.9	17.4	24.2	18.8	30.2
Lung	202.1	114.6	182.1	58.4	93.7	129.5	132.6
Esophagus	33.0	116.3	48.4	41.8	63.5	40.5	25.8
Colon	21.8	3.7	0.5	12.4	19.6	59.0	32.7
Ovary	3.3	1.3	0.6	2.5	3.5	7.7	8.1
Uterus	2.6	1.1	0.5	1.8	2.4	5.6	6.0

WBI: Whole Breast Irradiation, 3D-APBI: 3D conformal Accelerated Partial Breast Irradiation, VMAT: Volumetric Modulated Arc partial breast radiotherapy, Multicath HDR: Multicatheter High Dose Rate brachytherapy, Balloon HDR: Balloon-based High Dose Rate brachytherapy, CK-Iris: Cyberknife stereotactic partial breast irradiation with Iris collimator, CK-MLC: Cyberknife stereotactic partial breast irradiation with multileaf collimator.

Table 2
Lifetime Attributable Risks for various breast radiotherapy techniques for a woman exposed at age 40, 50, 60 and 80 years, excess cases per 100,000 exposed persons.

		WBI	3D-APBI	VMAT	MulticathHDR	Balloon HDR	CK-Iris	CK-MLC
40	Thyroid	43	25	4	38	50	22	35
	Breast	521	76	171	199	277	215	346
	Lung	3687	2091	3322	1065	1709	2362	2419
	Esophagus	20	71	30	26	39	25	16
	Colon	148	25	3	84	133	402	223
	Ovary	7	3	1	5	7	16	17
	Uterus	3	1	1	2	3	6	6
	Total	4429	2292	3531	1419	2219	3048	3061
50	Thyroid	13	8	1	12	16	7	11
	Breast	283	41	93	108	151	117	188
	Lung	3847	2181	3466	1112	1784	2465	2524
	Esophagus	20	71	29	25	39	25	16
	Colon	142	24	3	81	127	383	212
	Ovary	6	2	1	5	7	14	15
	Uterus	3	1	0	2	2	5	6
	Total	4314	2328	3594	1344	2124	3016	2972
60	Thyroid	4	2	0	3	4	2	3
	Breast	132	19	43	51	70	55	88
	Lung	3668	2080	3305	1060	1700	2350	2406
	Esophagus	17	62	26	22	34	21	14
	Colon	124	21	3	71	112	336	186
	Ovary	5	2	1	4	5	11	12
	Uterus	2	1	0	1	2	4	4
	Total	3952	2186	3378	1211	1927	2779	2713
80	Thyroid	0	0	0	0	0	0	0
	Breast	16	2	5	6	9	7	11
	Lung	1580	896	1424	457	733	1012	1037
	Esophagus	6	21	9	8	12	7	5
	Colon	47	8	1	27	43	128	71
	Ovary	1	1	0	1	1	3	3
	Uterus	0	0	0	0	0	1	1
	Total	1652	928	1439	499	797	1159	1128

WBI Whole Breast Irradiation, 3D-APBI 3D conformal accelerated partial breast radiotherapy, VMAT Volumetric Modulated Arc partial breast radiotherapy, Multicath HDR Multicatheter High Dose rate brachytherapy, Balloon HDR Balloon-based High Dose Rate brachytherapy, CK-Iris Cyberknife with Iris collimator, CK-MLC Cyberknife with multileaf collimator.

techniques in terms of dose since the technique with the highest organ doses results in the highest LARs. The LAR values are highly variable between the organs. The lungs carry the highest LAR, with a 3.8% lifetime risk of a secondary lung malignancy for whole breast radiotherapy at age 50 years. In our calculations, lung tumors accounted for 75–97% of all secondary cancers. Conversely the LARs for the uterus were lower than 1/1000th of the LARs of the lungs.

We calculated the RRs for women exposed at age 40, 50, 60 and 80 years as compared to non-irradiated breast cancer patients of the same age (Table 3). Selecting a threshold of 50% RR increase as being clinically significant, only the WBI and the VMAT technique are significantly increasing the risk of secondary lung cancer, which remains dominant in absolute numbers. Selecting a threshold of 10% as being clinically significant, there was an increased risk of lung cancer for all techniques at all ages. At this 10% threshold, there was also an increased risk of esophagus cancers, but the absolute numbers remain small. The risks of secondary malignancies of the thyroid, contralateral breast, ovaries and uterus were close to the baseline risks and may not be detectable in population-based studies.

Discussion

Our study shows that all APBI techniques produce less scatter dose compared to whole breast radiotherapy, which translates into a lower secondary cancer risk. The use of APBI could eventually halve the lifetime secondary cancer risk. In our calculations, the lifetime risks are high, up to 4.3% for a woman treated at 50 years old. This strongly supports the generalization of partial breast irradiation as standard for early stage breast cancers or DCIS instead of whole breast radiotherapy.

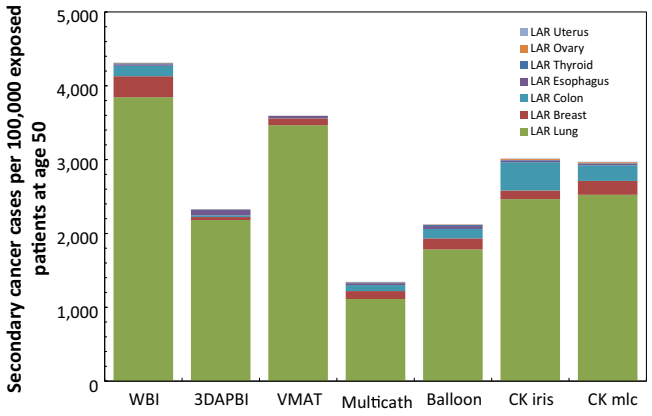

Fig. 1. Lifetime attributable risk of secondary cancer per organ for the various breast radiotherapy techniques. Number of cases per 100,000 persons receiving adjuvant breast radiotherapy at age 50 years.

Importantly our study also shows that the vast majority, between 75 and 97%, of the calculated secondary cancers involve the lungs. We calculated an absolute lifetime excess risk of lung cancer of 3.7% for patients treated with whole breast radiotherapy at age 60 years. The SEER database shows that the lifetime risk of lung cancer for a 60-year old female from the general population is 5.75% and the lifetime risk of dying from lung cancer is 4.66% [31]. This means that about 80% of lung cancer patients will die from their disease. Translated to our result, this means that whole breast radiotherapy could result in a 2.9% excess mortality due to secondary lung cancer.

One limitation of the present study is the use of a single phantom with average size breasts. Different patient geometries, for example larger breast volumes, may increase or decrease the mean lung dose for respectively brachytherapy or WBI [32]. However, those variations are relatively limited compared to the differences in techniques we tested. Also, the goal of this study was precisely to compare those techniques one with each other, which means we had to keep the patient's characteristics strictly identical between techniques, which is ideally performed using a phantom study.

Another limitation of the present study is the use of the BEIR-VII model for higher doses than intended in the report, where low doses were defined up to 0.1 Gy. Also, this model assumes a proportionality relationship that is not seen at doses above 3 or 4 Gy where a saturation effect has been demonstrated with a plateau between 10 and 20 Gy [33]. Also, our predictions for lung cancer compare well with other studies. We calculated a lung cancer RR of 1.68 for patients receiving whole breast radiotherapy at age 60 years. This number is in good agreement with a meta-analysis of patients treated with whole breast radiotherapy between 1935 and 2007 at a median age of 56 years where the standardized incidence ratio for lung cancer after 15 years was 1.91 [5]. The mean lung doses were not reported in this meta-analysis, but they were likely higher compared to our phantom study as modern radiation machines have a reduced scatter dose compared to older ones. For example, we used a virtual wedge technique while patients treated between 1935 and 2007 in the Grantzau cohort had probably much more often treatment with physical wedges which generate a much higher scatter dose [32]. Similarly, in the 2017 EBCTCG meta-analysis, which included 40,781 patients treated between 1972 and 1997 in randomized trials comparing the use of adjuvant radiotherapy or not, the RR of lung cancer at 10 years or more after irradiation was 2.1 [34]. This meta-analysis emphasized the large increased risk, about 10 times higher, for smokers versus non-smokers to develop secondary lung cancer applying the increased incidence probability to a population of non-smokers from the American Cancer Society Cancer Prevention Study II [35] and a

Table 3
Relative risks per organ for various breast radiotherapy techniques for a woman exposed at age 40, 50, 60 and 80 years, as compared to a non-irradiated localized breast cancer patient. Relative risks larger than 1.5 are shown in bold.

		WBI	3D-APBI	VMAT	Multicath HDR	Balloon HDR	CK-Iris	CK-MLC
40	Thyroid	1.046	1.027	1.004	1.040	1.054	1.023	1.037
	Breast	1.050	1.007	1.016	1.019	1.026	1.021	1.033
	Lung	**1.753**	1.427	**1.678**	1.217	1.349	1.482	1.494
	Esophagus	1.114	1.401	1.167	1.144	1.219	1.140	1.089
	Colon	1.040	1.007	1.001	1.023	1.036	1.108	1.060
	Ovary	1.007	1.003	1.001	1.005	1.007	1.015	1.016
	Uterus	1.001	1.001	1.000	1.001	1.001	1.003	1.003
50	Thyroid	1.018	1.011	1.002	1.016	1.021	1.009	1.015
	Breast	1.028	1.004	1.009	1.011	1.015	1.012	1.019
	Lung	**1.724**	1.410	**1.652**	1.209	1.336	1.464	1.475
	Esophagus	1.104	1.366	1.152	1.132	1.200	1.128	1.081
	Colon	1.036	1.006	1.001	1.020	1.032	1.097	1.054
	Ovary	1.006	1.002	1.001	1.004	1.006	1.014	1.014
	Uterus	1.001	1.000	1.000	1.001	1.001	1.003	1.003
60	Thyroid	1.007	1.004	1.001	1.006	1.008	1.004	1.006
	Breast	1.015	1.002	1.005	1.006	1.008	1.006	1.010
	Lung	**1.679**	1.385	**1.612**	1.196	1.315	1.435	1.446
	Esophagus	1.090	1.316	1.132	1.114	1.173	1.110	1.070
	Colon	1.032	1.005	1.001	1.018	1.029	1.086	1.048
	Ovary	1.005	1.002	1.001	1.004	1.005	1.012	1.013
	Uterus	1.001	1.000	1.000	1.001	1.001	1.002	1.002
80	Thyroid	1.000	1.000	1.000	1.000	1.001	1.000	1.000
	Breast	1.005	1.001	1.001	1.002	1.002	1.002	1.003
	Lung	**1.598**	1.339	**1.539**	1.173	1.277	1.383	1.392
	Esophagus	1.048	1.169	1.070	1.061	1.092	1.059	1.038
	Colon	1.017	1.003	1.000	1.010	1.015	1.046	1.025
	Ovary	1.003	1.001	1.001	1.002	1.003	1.007	1.007
	Uterus	1.001	1.000	1.000	1.000	1.001	1.001	1.001

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population of smokers from the Million Women Study in the United Kingdom [36].

The calculated lifetime risk of secondary lung cancer mortality is high and is in the same order of magnitude as the survival benefit of radiotherapy. In the 2011 EBCTCG meta-analysis node negative patients had a 3.3% reduction of breast cancer related mortality at 15 years [37]. On the other hand Darby et al. calculated that a 50-year old woman would have a risk of death from ischemic heart disease of 0.5% before the age of 80 for a patient without pre-existing cardiac risk factors, and of 0.7% in case of one or more additional risk factors [4]. Such excess in cardiac mortality has encouraged the widespread implementation of preventive techniques, including as deep inspiration breath-hold. Our calculations showed an absolute increase in lung cancer mortality before age 80 of 2.4% for a 50-year old woman treated with WBI, which is about 4 times as high as the reported cardiac mortality. The excess of lung cancer mortality has not yet encouraged clinicians to actively adopt measures reducing the mean lung dose. It is noteworthy that cardiac events occur much earlier than secondary cancers. In the Darby study 44% of cardiac events occurred in the first 10 years after treatment [4]. The risk of secondary lung cancer is increased after a latency period of at least 5 years, and continued to increase up to 15 years [5]. In our calculations, 93% of all secondary lung cancers occurred after 10 years (Fig. 2). This latency may explain why earlier meta-analysis including trails with limited follow-up primarily stressed the cardiac morbidity and did not fully capture the risk of lung cancer mortality.

With this in mind, and in the context of the improved outcomes of early stage breast cancer, it is important to select radiotherapy techniques generating the lowest scatter dose possible. In this study the lowest mean lung dose was obtained using brachytherapy or 3D-conformal radiotherapy, both leading to doses between 1 and 1.5 Gy. Following the ALARA (As Low As Reasonably Achievable) principle [37], it is reasonable to recommend keeping the mean lung dose below this achievable level. For patients with more aggressive disease requiring loco-regional radiotherapy and who have a poorer prognosis, a higher value for the constraint on the mean lung dose may be acceptable, especially when regional nodes must be treated.

In conclusion, the present study finds an excess of lung cancer mortality due to irradiation that appears larger than the excess of cardiac mortality for early stage breast cancer patients having a very long survival. This risk can be greatly reduced using partial breast irradiation techniques minimizing the mean dose to the lung in addition to smoking prevention.

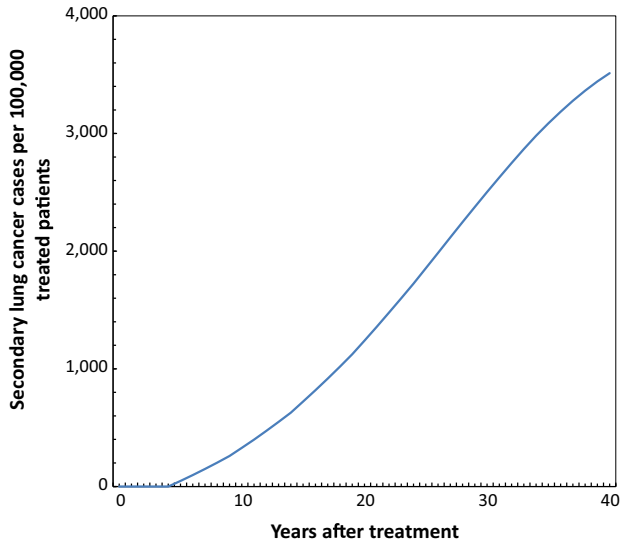

Fig. 2. Time occurrence of secondary lung cancers for a person exposed at age 50.

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