RESEARCH ARTICLE

Editorial Process: Submission:01/01/2024 Acceptance:05/04/2024

Dosimetry and Biochemical Comparison of Early Radiation-Induced Lung Toxicity in Breast Cancer Patients Treated with 3D-CRT and IMRT: the Role of Serum Interleukin-6 and Pulmonary Surfactant Protein-D

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Abstract

Background: Radiation-induced lung disease is a potentially fatal, dose-limiting toxicity commonly seen after radiotherapy of thoracic malignancies, including breast cancer. **Aim:** To evaluate and compare the early lung toxicity induced by 3D-CRT and IMRT radiotherapy treatment modalities in breast cancer female patients using biochemical, dosimetry and clinical data. **Subjects and Methods:** this study included 15 normal healthy controls, 15 breast cancer patients treated with IMRT, and 15 breast cancer patients treated with 3D-CRT. One blood sample was obtained from the control group and 3 blood samples were withdrawn from cases before RT, after RT and after 3 months of RT. **Result:** IMRT delivered higher radiation dose to the breast tumor and lower doses to the lung as an organ at risk. There was a non-significant increase in the serum levels of *IL-6* before IMRT and 3D-CRT compared with its levels in the control group. There were significant increases in serum levels of *IL-6* after RT (IMRT and 3DCRT) compared with its levels before RT. There was a non-significant decrease in the serum levels of *IL-6* after 3 months of RT (IMRT and 3D-CRT) compared with its serum levels immediately after RT. There was a non-significant increase in the serum levels of SP-D before RT (IMRT and 3D-CRT) compared with its levels in the control group. There were significant-increases in serum levels of SP-D after RT (IMRT and 3D-CRT) compared with its levels before RT. There was a non-significant decrease in the serum levels of SP-D after 3 months of radiotherapy (IMRT and 3D-CRT) compared with its serum levels immediately after RT. **Conclusion:** serum of levels *IL-6* and SP-D can be used to diagnose the occurrence of early lung toxicity due to radiotherapy and the rate of recovery from radiation pneumonitis is apparent in case of IMRT than 3D-CRT.

Keywords: Breast- radiotherapy- *IL-6*

Asian Pac J Cancer Prev, **25 (5)**, 1707-1713

Introduction

Treatment options of breast cancer include: surgery, radiotherapy (RT), chemotherapy (CHT), hormonal(endocrine) therapy (HT), targeted therapy& immunotherapy [1], or a combination of these can increase therapeutic efficacy [2]. Radiotherapy has evolved from conventional external beam two- dimensional RT (2DRT) to three dimensional conformal RT (3DCRT). In a further advance, intensity modulated RT (IMRT) uses computed tomography- based planning and delivery of radiation, aided by computerized optimization of the intensities of multiple beams [3]. Radiation- induced lung disease is a disabling and potentially fatal dose- limiting toxicity commonly seen after radiotherapy in treatment of thoracic malignancies including esophageal cancer, lung cancer and breast cancer. Radiation- induced lung disease is either an early (acute) burst of an inflammatory response called radiation induced lung pneumonitis (RILP) or much delayed (chronic) response of pulmonary fibrosis [4]. Many studies have been made to identify clinical risk factors for the onset of radiation pneumonitis. These risk factors include total radiation dose, irradiated lung volume exceeding 20 Gy, mean lung dose, fractionation, pretreatment pulmonary function, low pretreatment blood oxygen and others [5, 6].

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Although breast treatment methods continuously improve with technological development, there is still not an accepted standard method [7]. Many studies reported that the peak incidence of radiation pneumonitis is within three months after completion of radiation treatment [8, 9]. Since lung tissues are not easily accessible, so measurement of blood biomarkers provides a potential noninvasive assessment as a substitute to tissue analysis [10]. The precise role of *IL-6* in predicting radiation pneumonitis and therefore its value as a biomarker have been debated. Chen et al considered *IL-6* to be an important and valuable biomarker in connection with radiation-induced pneumonitis [11]. Four specific surfactant proteins have been identified. One of them, surfactant protein-D (SP-D), acts as a pulmonary host defense and participates in the extracellular reorganization or turnover of pulmonary surfactant proteins [12].

Materials and Methods

Participants

There were 45 women included in this research, and they were split into two groups as follows:

Group I

It included 15 apparently normal healthy control females free from any lung disease with mean age 46±1.8 years.

Group II

It included 30 breast cancer female patients (clinical stages II and III) who already underwent surgery (modified radical mastectomy or conservative surgery). These patients were subdivided into two subgroups:

Group IIA

It consisted of 15 breast cancer patients that were treated with postoperative radiotherapy using 3D-CRT plan with mean age 48±2.7 years.

Group IIB

It consisted of 15 breast cancer patients that were treated with postoperative radiotherapy using IMRT plan with mean age 49±3.5 years.

Breast cancer patients were selected from those who admitted to Department of Cancer Management and Research, Medical Research Institute, University of Alexandria, Egypt. After approval of the study plane, all patients were treated with radiotherapy at Ayadi Al-Mostakbal Oncology hospital, Alexandria, Egypt. All patients were asked to freely volunteer to the study and informed written consents were gathered prior to their inclusion in the study according to the ethical guidelines of Medical Research Institute, Alexandria University, Egypt (Ethics code: IORG0008812).

Methods

The following steps were followed in the given sequence:

1. The patients were scanned separately using a simulation computed tomography (CT) with 5 mm slice thickness.

2. Both the target volume and organs at risk were contoured according to the radiation therapy oncology group (RTOG) using the focal system, then they were sent to the treatment planning system (TPS) for planning.

3. Fifteen breast cancer patients were treated using 3D-CRT and the other fifteen breast cancer patients were treated using IMRT.

Detection of radiation pneumonitis using high resolution computed tomography scan (HRCT-scan)

In the current study it was done pre-exposure to radiation therapy immediately after termination of radiation protocol and 3 months after termination of radiation therapy course to detect early occurrence of pulmonary toxicity to be correlated with the serum levels of *IL-6* and SP-D.

Laboratory investigations

Were carried out at Radiation Science Department, Medical Research Institute, University of Alexandria, Egypt. Three blood samples (5 ml each) were collected from cancer patients before RT, immediately after RT and 3 months after completion of RT course. One blood sample (5ml) was obtained from the control group. Blood samples were used to separate sera on which biochemical analysis were performed. Serum levels of *IL-6* and pulmonary surfactant D were measured in all studied groups using ready- for- use ELISA kits according to manufacturer's protocol.

Statistical analyses

The statistical analysis was carried out using the SPSS 21 software package. These numbers were summarized by making use of the median and range. We looked for normality in quantitative data distributions using the KolmogorovSmirnov and Shapiro-Wilk tests. The D'Agstino test was used if the findings from the first two tests disagreed. Non-parametric tests were used since the data had an atypical distribution. The Non-parametric Mann–Whitney U-test was performed to analyze the differences in serum *IL-6*, and SP-D between BC patients and a control group. The nonparametric Kruskal-Wallis test was used to examine changes in serum parameters before and after radiation. Non-Parametric Spearman's test was used to find a correlation between studied biomarkers and biochemical, dosimetry and clinical data.

Results

Clinicopathological characteristics of BC patients

According to Table 1 the statistical analysis of these results showed that there were non-significant differences regarding clinicopathological data characterizing the breast cancer patients group treated by 3D-CRT and IMRT radiotherapy modalities ($p>0.05$). The dosimetry data received by the target volume and lung in breast cancer patients treated with radiotherapy.

Table 2 showed that the planning target volume (breast tumor) received a dose of 3774.79±27.21 cGy in case of breast cancer patients treated by 3D-CRT; while

Table 1. Clinicopathological Data Characterizing the Breast Cancer Patients Group Treated by 3D-CRT and IMRT Radiotherapy Modalities

Clinicopathological Parameters		3D-CRT (n=15)		IMRT (n=15)		P-value
		Frequancy	Percent	Frequancy	Percent	
Clinical Stage	II	8	53.4	9	60	0.713
	III	7	46.6	6	40	
Pathological Grade	II	11	73.3	10	66.7	0.69
	III	4	26.7	5	33.3	
Tumor Size (cm)	< 5	6	40	7	46.6	0.713
	≥ 5	9	60	8	53.4	
Lymph node involvement	- ve	3	20	4	26.7	0.666
	+ ve	12	80	11	73.3	
ER status	- ve	3	20	3	20	0.785
	1	1	6.7	2	13.3	
	2	7	46.6	8	53.4	
	3	4	26.7	2	13.3	
PR status	- ve	2	13.3	2	13.3	0.475
	1	5	33.3	3	20	
	2	4	26.7	8	53.4	
	3	4	26.7	2	13.3	
Vascular Invasion	- ve	2	13.3	1	6.7	0.542
	+ ve	13	86.7	14	93.3	

ER, Estrogen receptor; PR, Progesterone receptor; Significance was considered at P-value<0.05

it received a dose of 3867±20.21 cGy in case of breast cancer patients treated by IMRT. The statistical analysis of these results showed that the radiation dose received by the planning target volume (breast tumor) in case of IMRT was significantly greater than that received in case of 3D-CRT (p=0.014).

Regarding the dosimetry data received by lung as one of the organs at risk for breast cancer treated with radiotherapy, Table 4 showed that the doses given to V_{20}% and V_{30}% of lung (V_{20} and V_{30}) were 22.18±1.72 Gy and 16.05±1.46 Gy ; respectively in case of 3D-CRT and they were 17.78±1.06 Gy and 13.41±0.94 Gy; respectively in case of IMRT. The statistical analysis of these results showed that V_{20} and V_{30} in case of 3D-CRT were significantly greater than that received in case of IMRT (p=0.039, 0.046; respectively).

The mean lung dose received in case of 3D-CRT was 10.71±0.72 Gy, while it was 8.58±0.51 Gy in case of IMRT. The statistical analysis of these results revealed that the mean lung dose received in case of 3D-CRT was significantly greater than that received in case of IMRT (p=0.036). Serum *IL-6* in the control group and breast cancer patient's subgroup treated with 3D-CRT plan.

According to Figure 1, the M±SD serum levels of IL.6 were 48.14±4.06 in the control group, 57.62±7.54 before radiotherapy, 75.73±10.03 after radiotherapy and 59.70±5.57 three months after completing radiotherapy course. The statistical analysis of these results showed a non-significant increase in the serum levels of *IL-6* before RT compared with its levels in the control group (p=0.401). However, there were significant increases in serum levels of *IL-6* after RT compared with its levels before RT (p=0.039) and compared with its levels in the control group (p=0.03*). There was a non-significant decrease in the serum levels of *IL-6* three months after radiotherapy compared with its serum levels immediately after RT (p=0.173) which was still within the same levels of the control group (p=0.434).

IL-6 levels in breast cancer patients treated with IMRT Plan

According to figure (2), the Mean±SD serum levels of *IL-6* were 48.14±4.06 in the control group, 55.37±6.5 before radiotherapy, 78.66±11.31 after radiotherapy and

Table 2. Mean±SD of Dosimetric Data Received by Tumor Target Volume and Lung as an Organ at Risk

Dosimetric Parameters (Mean±SD)	Breast cancer patients (n=30)		P-value
	3D-CRT (n=15)	IMRT (n=15)	
PTV95% (cGy)	3774.79±27.21	3867±20.21	0.014*
V_{20Gy} lung (%)	22.18±1.72	17.78±1.06	0.039*
V_{30Gy} lung (%)	16.05±1.46	13.41±0.94	0.046*
Mean lung dose (Dmean)	10.71±0.72	8.58±0.51	0.036*

*Significance was considered at P-value<0.05

Table 3. Correlations of Serum Levels of *IL-6* and SP-D with Dosimetric Data in Breast Cancer Patients Treated with 3D-CRT.

Dosimetric parameters		Breast cancer patients treated by 3D-CRT (n=15)			
		IL-6 immediately after radiotherapy	IL-6 after three months of radiotherapy	SP-D immediately after radiotherapy	SP-D after three months of radiotherapy
PTV	r	0.459	-0.476	-0.161	0.304
	p-value	0.057	0.085	0.308	0.29
V_{20}%	r	-0.454	0.244	-0.063	0.365
	p-value	0.06	0.4	0.423	0.199
V_{30}%	r	-0.366	0.313	0.2	0.196
	p-value	0.109	0.276	0.267	0.501
D_{mean}	r	-0.193	0.251	0.462	0.18
	p-value	0.264	0.387	0.065	0.539

r, Spearman's coefficient; Significance was considered at P-value<0.05

58.57±4.29 three months after completing radiotherapy course. The statistical analysis of these results showed a non-significant increase in the serum levels of *IL-6* before RT compared with its levels in the control group (p=0.505). However, there were significant increases in serum levels of *IL-6* after RT compared with its levels before RT (p=0.046#) and compared with its levels in the control group (p=0.04*). There was a non-significant decrease in the serum levels of *IL-6* three months after radiotherapy compared with its serum levels immediately after RT (p=0.013$) which was still within the same levels of the control group (p=0.369).

Serum SP-D in the control group and breast cancer patient's subgroup treated with 3D-CRT plan

Regarding the results shown figure (3), the M±SD serum levels of SP-D were 13.04±1.57 in the control group, 13.59±0.98 before radiotherapy, 18.22±1.12 after radiotherapy and 18.1±1.73 three months after completing radiotherapy course. The statistical analysis of these results showed anon significant increase in the serum levels of SP-D before RT compared with its levels in the control group (p=0.339). However, there were significant increases in serum levels of SP-D after RT compared with its levels before RT (p=0.028#) and compared with its levels in the control group (p=0.026*). There were non-significant decreases in the serum levels of SP-D three months after radiotherapy compared with its serum levels immediately after RT (p=0.07) and compared with its serum levels of the control group (p=0.046*).

SP-D levels in breast cancer patients treated with IMRT plan

According to the results shown figure (4), The

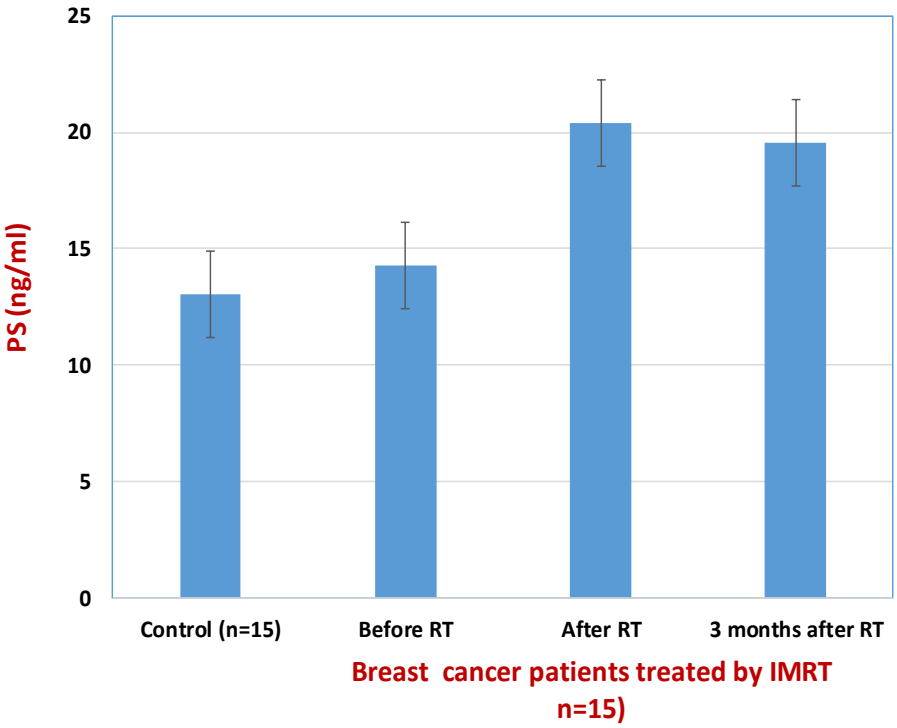

Figure 1. Bar Chart Showing Serum Levels of IMRT in the Control Group and Breast Cancer Patients Group Treated with IMRT before Radiotherapy, after Radiotherapy and Three Months after Radiotherapy.

Table 4. Correlations of Serum Levels of *IL-6* and SP-D with Dosimetric Data in Breast Cancer Patients Treated with IMRT.

Dosimetric parameters		Breast cancer patients treated by IMRT (n=15)			
		IL-6 immediately after radiotherapy	IL-6 after three months of radiotherapy	SP-D immediately after radiotherapy	SP-D after three months of radiotherapy
PTV	r	0.027	0.134	-0.027	0.508
	p-value	0.465	0.647	0.465	0.063
V_{20}%	r	0.758**	0.356	0.445	0.235
	p-value	0.001	0.212	0.064	0.418
V_{30}%	r	0.641**	0.213	0.08	0.224
	p-value	0.009	0.466	0.398	0.441
Dmean	r	0.737**	0.211	0.253	0.196
	p-value	0.002	0.468	0.202	0.502

r, Spearman's coefficient; Significance was considered at P-value<0.05

Mean±SD serum levels of SP-D were 13.04±1.57 in the control group, 14.29±1.10 before radiotherapy, 20.42±1.51 after radiotherapy and 19.54±1.47 three months after completing radiotherapy course. The statistical analysis of these results showed a non-significant increase in the serum levels of SP-D before RT compared with its levels in the control group (p=0.369). However, there was a significant increase in serum levels of SP-D after RT compared with its levels before RT (p=0.009#) and compared with its levels in the control group (p=0.004*). There was non-significant decrease in the serum levels of SP-D three months after radiotherapy compared with its serum levels immediately after RT (p=0.507) and, at the same time, its serum levels were significantly increased compared with the control group (p=0.008*).

Correlations between the studied serum biomarkers and dosimetry data

The results shown in Table 3 revealed that the serum levels of *IL-6* immediately after radiotherapy were directly and border-lined significantly correlated with the radiation dose received by the target breast tumor (PTV). The rest of the other correlations were non-significant.

The results shown in Table 4 revealed that the serum levels of *IL-6* immediately after radiotherapy was directly and significantly corelated with the radiation dose received by 20% of lung volume (V_{20}%), (r=0.758** , p=0.001), also directly correlated with the radiation dose received by 30% of lung volume (V_{30}%) , (r=0.641** , p=0.009), and also directly correlated with the mean lung dose (r=0.737**, p=0.002) in breast cancer patients treated with 3D-CRT plan. The rest of the other correlations were non-significant.

Discussion

Radiotherapy is one of the main methods for the treatment of thoracic tumors. However, radiation pneumonia (RP) is one of its common complications, leading to respiratory distress and even death in severe cases. [13]. Currently, risk assessment of RP typically depends on physical dosimetry parameters, such as mean lung dose (MLD) and percentage of lung volume exposed to doses exceeding a threshold. Multiple cytokines regulate RP through different pathways. However, at the present time, there are no reliable and validated predictive assays for the early prediction of RP in the clinical process [14].

According to the results of the current study, the planning target volume (breast tumor) received radiation dose that was significantly greater in case of IMRT than in case of 3D-CRT, at the same time, radiation doses received by the lung as an important organ at risk for breast cancer patients treated with radiotherapy were significantly lower in case of IMRT modality than in case of 3D-CRT modality; this means that the lungs are more protected from the damaging effects of ionizing radiation in case of IMRT plan than in case of 3D-CRT plan. These results were confirmed by the study of Verellen et al. [15] who reported that, for lung, IMRT in comparison to 3D-CRT significantly reduced the high-dose volumes (V_{20}, 24.52% vs. 29.62%; V49, 3.56% vs. 6.42%; $p < 0.001$) and the mean dose (10.21 Gy vs. 11.96 Gy, $p < 0.001$).

Regarding the levels of serum *IL-6* in the control group and breast cancer patients' subgroups treated with either 3D-CRT plan or IMRT plan, the statistical analysis of the results revealed anon-significant increase in the serum levels of *IL-6* before RT compared with its levels in the control group. This means that treatment of the breast cancer patients included in the current study with chemotherapy did not produce a toxic effect on their lungs. During the current study, we performed conventional CT-scan on breast cancer patients before radiotherapy to exclude those patients who developed lung toxicity due to chemotherapy, so all of the breast cancer patients included in the current study were free from any lung toxicity after completing their chemotherapeutic regimen.

Regarding the effect of radiotherapy (either 3D-CRT plan or IMRT plan) on the serum levels of *IL-6* in breast cancer patients, the results revealed that there was a significant increase in serum levels of *IL-6* after RT compared with its levels before RT and compared with its levels in the control group. The results of the current study were in accordance with the study performed by Arpin et al. [16] who found increased *IL-6* serum levels at three weeks from the beginning of radiotherapy. At the same time, the results of the current study confirmed those reported by Chen et al. [11] and Anscher et al. [17], Who found that the elevation of plasma *IL-6* levels were

positively correlated with the increase of radiation-related lung injury, thus they reported that *IL-6* could predict acute radiation-induced lung injury.

Regarding the serum levels of *IL-6* three months after radiotherapy using 3D-CRT plan, the results showed that there was a nonsignificant decrease in the serum levels of *IL-6* three months after radiotherapy compared with its serum levels immediately after RT. On the other hand, there was a significant decrease in the serum levels of the *IL-6* after three months of radiotherapy using IMRT plan compared with its values directly after finishing radiotherapy course which was still within the same levels of the control group. The results of the current study indicated that the radiation toxicity induced in the lungs immediately after terminating radiotherapy course was recovered in case of using IMRT plan.

With respect to the levels of serum SP-D in the control group and breast cancer patients' subgroups treated with either 3D-CRT plan or IMRT plan, the statistical analysis of the results showed a non-significant increase in the serum levels of SP-D before RT compared with its levels in the control group. This means that treatment of the breast cancer patients included in the current study with chemotherapy did not produce a toxic effect on their lungs. We performed conventional CT-scan on breast cancer patients before radiotherapy to exclude those patients who developed lung toxicity due to chemotherapy, so all of the breast cancer patients included in the current study were free from any lung toxicity after completing their chemotherapeutic regimen.

Regarding the effect of radiotherapy on the serum levels of SP-D in breast cancer patients subgroups treated with either 3D-CRT plan or IMRT plan, the results showed that, there was a significant increase in serum levels of SP-D after RT compared with its levels before RT and compared with its levels in the control group. The results of the current study confirmed those reported by the study performed by Takahashi et al. [18]. In their study, serum concentrations of SP-A and SP-D in 25 patients receiving radiotherapy for lung tumors were determined. Levels were measured before initiation of radiotherapy, 1 week and 3 weeks after the final irradiation. According to their findings, patients exhibited increases in SP-A and SP-D levels during therapy, irrespective of the development of radiation pneumonitis. Expression of the elevation rates of SP-A and SP-D as 1 week post/pre ratio, however, revealed that the ratio was significantly greater in patients with radiation pneumonitis than in patients without, for both markers. Mean serum SP-A and SP-D levels at completion of radiation therapy were higher in patients with radiation pneumonitis. Also the results of the current study were in accordance with another study which reported that the serum levels of SP-D in patients with radiation pneumonitis were significantly higher than in patients without radiation pneumonitis [19]. Regarding the serum levels of SP-D three months after radiotherapy using 3D-CRT plan, the results illustrated that there was a non-significant decrease in the serum levels of SP-D three months after radiotherapy compared with its serum levels immediately after RT. On the other hand, the results shown in there was significant decrease in the serum levels of SP-D three months after radiotherapy using IMRT plan compared with its serum levels directly after terminating radiotherapy course. The results of the current study indicated that the radiation toxicity induced in the lungs immediately after terminating radiotherapy course was recovered in case of using IMRT plan.

In conclusion, IMRT is more effective and accurate than 3D-CRT plan in terms of delivering maximum dose to the breast tumor and the minimum doses to the lung as an organ at risk.

Recommendations

Further studies using a greater sample size to confirm or disagree with the results reported in the current study are needed.

Author Contribution Statement

Taha I. Hewala: Designing & writing the manuscript. Sanaa A. El-Benhawy: Research proposal idea, literature review, writing the manuscript & practical lab part of the paper. Yasmine N. Elwany: Helped in sample collection, following up the cancer patient's radiotherapy participated in manuscript writing & paper submission. Sabbah I. Hammoury, PhD: Participated in samples collection. Mohamed A. Seada, MSc.: Contributed to data analysis, practical part, & participated in manuscript writing.

Acknowledgements

All authors have made significant contributions to this work. No funding to declare.

Approval

It is part of an approved student thesis

Ethical Declaration

Written informed consent was obtained from all study subjects. Also, approval of the ethics committee of the Medical Research institute (Ethics code IORG: 0008812) Alexandria University, Egypt, was obtained prior of the study. All procedures performed in our study were in accordance with ethical standards of our institution & with the 1975 Helsiniki declaration as revised in 2008.

Conflict of Interest

No conflict of interest is declared.

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