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Can we treat with radiation breast cancer patients with covid-19 infection?

Results from a prospective study

Pouvons-nous irradier les patientes atteintes d'un cancer du sein et de la covid-19 ?

Résultats d'une étude prospective

Sofiane ALLALI¹, Vincent SERVOIS², Arnaud BEDDOK¹, Alain FOURQUET¹, Youlia KIROVA^{1*,3}

¹Department of Radiation Oncology, institut Curie, 26, rue d'Ulm, 75005 Paris, France

² Department of Radiology, institut Curie, 26, rue d'Ulm, 75005 Paris, France

³ Université Versailles-Saint-Quentin-en Yvelines, 55, avenue de Paris, 78035 Versailles cedex, France

*Corresponding author: Youlia M. Kirova, M.D.; Tel. : 33144324000; E-mail: youlia.kirova@curie.fr

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Conflict of interests

The authors declare that there is no conflict of interests.

Research data

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Keywords

Cancer, covid-19, treatments, radiation therapy, prognosis, Sars-CoV-19, breast cancer, adverse effects.

Mots clés

Cancer, covid-19, traitements, radiothérapie, pronostic, Sars-CoV-19, cancer du sein, effets indésirables

Abstract

Purpose.- The coronavirus disease 2019 (covid-19) caused by the severe acute respiratory syndrome coronavirus 2 (Sars-Cov-2) is at the origin of a global pandemic. This pandemic has prompted the

current health system to reorganize and rethink the care offered by health establishments. We report the early and late toxicity in patients infected with covid-19 treated at the same time for early-stage breast cancer.

Material and methods.- This is a monocentric prospective study of patients treated in our hospital between March and June 2020 who were diagnosed with covid-19 infection. The inclusion criteria were to be irradiated for early stage breast cancer and to have a positive covid diagnosis on a polymerase chain reaction (PCR) test and / or a lung computed tomography (CT) scan and / or suggestive clinical symptoms. All of them needed 6 months follow-up clinic after the end of the radiotherapy with clinical examination, mammogram, as well as CT scan to evaluate the lung status. Radiotherapy consisted of breast or chest wall irradiation with or without lymph node irradiation, with protocols adapted to pandemic situation. The treatment-related toxicity was graded according to the Common Toxicology Criteria for Adverse Events (version 4.03).

Results.- All 350 patients treated for early stage breast cancer were studied. Of them, 16 presented clinical symptoms of covid-19 infection, and of them 12 had clinical, CT scan and PCR confirmation. This entire cohort of 12 patients with median age of 56 years (range: 42-72 years) underwent their radiotherapy. During the radiotherapy, nine patients presented radiodermatitis: eight grade 1 (66%) and one grade 2 (8%). Two patients with lymph nodes irradiation presented grade 2 oesophagitis. Late toxicity was evaluated 6 months after the end of the radiotherapy, and there was no radiation or covid lung sequel on the CT scans. One patient presented covid-related dyspnoea, and two had fibrosis.

Conclusion.- The half-year follow-up of prospective covid-19 cohort, treated for early stage breast cancer demonstrated an acceptable toxicity profile with few low-grade adverse events. It seems that the covid-19 infection does not appear to increase the side effects of radiotherapy. Therefore radiotherapy should not be delayed.

Résumé

Objectif de l'étude.- La *coronavirus disease* (covid-19) causée par le *severe acute respiratory syndrome coronavirus 2* (Sars-Cov-2) est à l'origine d'une pandémie mondiale. Cette pandémie a incité le système de santé actuel à se réorganiser et à repenser les soins offerts par les établissements de santé. Nous rapportons la toxicité précoce et tardive chez les patientes atteintes par la covid-19 prises en charge en même temps pour un cancer du sein de stade précoce.

Matériel et méthodes.- Il s'agissait d'une étude prospective monocentrique portant sur des patientes prises en charge dans notre hôpital entre mars et juin 2020, avec un diagnostic de covid-19. Les critères d'inclusion étaient patientes irradiées pour un cancer du sein de stade précoce avec un diagnostic de covid selon un test par *polymerase chain reaction* (PCR) et/ou une tomographie pulmonaire et/ou des symptômes cliniques évocateurs. Toutes les patientes ont eu un contrôle de suivi

à 6 mois de la fin de la radiothérapie avec un examen clinique, une mammographie, ainsi qu'une tomodensitométrie pour évaluer l'état pulmonaire. La radiothérapie consistait en une irradiation du sein ou de la paroi thoracique avec ou sans irradiation des ganglions lymphatiques, avec des protocoles adaptés à la situation pandémique. La toxicité liée au traitement a été classée selon les Common Terminology Criteria for Adverse Events version 4.03.

Résultats.- Toutes les 350 patientes prises en charge pour un stade précoce d'un cancer du sein ont été prises en compte. Parmi elles, 16 ont souffert de symptômes cliniques de covid-19 et parmi ces dernières, 12 ont eu une confirmation clinique, tomodensitométrie et PCR. Toute cette cohorte de 12 patientes d'un âge médian de 56 ans (intervalle : 42-72 ans) a été irradiée. Au cours de la radiothérapie, neuf patientes ont eu une radiodermite : de grade 1 dans huit cas (soit 66 %), et de grade 2 chez une (soit 8%). Deux patientes recevant une irradiation ganglionnaire ont souffert d'une œsophagite de grade 2. La toxicité tardive évaluée 6 mois après la fin de la radiothérapie n'a pas retrouvé de séquelles pulmonaires liées à la radiothérapie ou à la covid-19 sur les tomodensitométries. Cliniquement, une patiente souffrait d'une dyspnée, et deux d'une fibrose liée à la covid-19.

Conclusion.- Avec un suivi minimum de 6 mois de la cohorte prospective atteinte de covid-19, prise en charge pour un stade précoce d'un cancer du sein, a démontré un profil de toxicité acceptable avec peu d'événements indésirables de bas grade. La covid-19 ne semble pas augmenter les effets secondaires de la radiothérapie. En conséquence, la radiothérapie ne doit pas être retardée.

1. Introduction

Coronavirus disease 2019 (covid-19), caused by the severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2), is responsible for a global pandemic [1]. It was first detected on 17 November 2019 in the city of Wuhan, China, and then spread around the world via the flow of people, especially tourists [2–4]. The World Health Organization (WHO) declared a state of public health emergency in France on 30 January 2020.

Sars-CoV-2 is an RNA virus that mainly infects the respiratory tract [5]. It is usually asymptomatic, but can cause fever (77.4-98.6%), cough (59.4-81.8%), asthenia (38.1-69.6%) and dyspnoea (3.2-55%) [6,7]. The mean age of patients hospitalised for covid-19 is 47 years, comprising 42% of females and 58% of males, and the mortality rate varies between 1 and 3% depending on the country [8,9].

This pandemic has required reorganization of the current health system and a new approach to the management provided by healthcare facilities. New guidelines have therefore emerged to limit spread of the virus. Learned societies have issued guidelines for hygiene and barrier measures (covid-19 arrowed pathways in healthcare facilities, use of masks, rubbing hands with sanitizer gel, etc.), as well as new practices in each medical or surgical, radiation oncology specialty [10–17]. New guidelines for the management of cancer patients have emerged, with a preference for oral versus intravenous

chemotherapy, 3-week versus weekly regimens, home chemotherapy injections, postponement of non-urgent care [18-23]. Surgery for carcinoma in situ can therefore be delayed for 3 to 6 months and surgery for invasive ductal carcinoma can be delayed for up to 6 weeks [22,23]. Reorganization of radiotherapy has required temporary suspension of time-consuming irradiation techniques (isocentric lateral decubitus irradiation, respiratory gating, etc.), the use of hypofractionated treatment regimens, or of dedicated machines for covid-19 patients [17, 24-29].

Many authors have questioned whether cancer is a risk factor for a severe form of covid-19 [30-37]. Data in the literature on this subject remain discordant at the present time due to an underrepresentation of cancer patients in published series, preventing identification of cancer as an independent risk factor[34]. However, the literature tends to agree on a non-statistically significant association between cancer and severe forms of covid-19, but the comorbidities of these patients are generally considered to account for the more severe forms of covid-19 in this population[34,35].

To date, no publication has evaluated the short-term and long-term effects of radiotherapy in Sars-CoV-2-infected patients treated for non-metastatic breast cancer during the first wave of the pandemic. In this study, we therefore tried to assess the effects of radiotherapy in a prospective cohort of Sars-CoV-2-infected patients treated for breast cancer in our institution.

2. Material and methods

This study, conducted on a prospective, single-centre cohort, evaluated all patients treated by radiation for breast cancer between March 2020 and June 2020 at the institut Curie (Paris, France) radiotherapy department.

Starting in March 2020, in agreement with the institut Curie (Paris) institutional review board, all confirmed or suspected cases of covid-19 were prospectively registered in an institutional database. Notification of all confirmed or suspected cases of covid-19 was made compulsory by the director of the institut Curie. All notified patients were included in the registry on the day of notification. We consecutively registered all patients presenting symptoms suggestive of covid-19 and/or covid-19 confirmed by reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swabs and/or chest CT images suggestive of covid-19. The multidisciplinary covid-19 patient registration group was set up to centralize and coordinate all decisions and strategies related to the covid-19 pandemic. This study was submitted to the covid-19 Group and was approved as a prospective study to be conducted on this database. This study was also proposed to and approved by Copil19. All patients provided their oral consent for inclusion in this study.

Study inclusion criteria were patients treated for non-metastatic breast cancer at the institut Curie (Paris) with a positive diagnosis of covid-19 on RT-PCR test and/or chest CT and/or suggestive clinical symptoms (fever, dyspnoea, ageusia, anosmia, etc.) [7, 35,36].

The study, designed to assess radiation-related toxicity in a population of breast cancer patients treated by locoregional radiation with a concomitant diagnosis of covid-19, diagnosed during the radiotherapy was proposed to and approved by the institut Curie covid-19 group scientific and ethics committee. We used dedicated machine with special measures for the protection of the medical and paramedical staff.

Patient characteristics are shown in Table 1.

Routine screening including a questionnaire and systematic body temperature measurement was implemented at the entrance to the institut Curie at the beginning of the epidemic. According to French national guidelines, the Sars-CoV-2 RNA test on nasopharyngeal swabs was initially limited to healthcare workers and critically ill patients [37]. Subsequently, RT-PCR tests became more widely available for patients with symptoms of covid-19 and were performed whenever possible. Most of the patients included in this study presenting symptoms suggestive of covid-19 were therefore screened by RT-PCR or diagnostic chest computed tomography (CT). Weekly review in the outpatients department or by teleconsultation was set up to monitor the course of the infection and covid-19 symptoms and to assess any acute adverse effects of radiotherapy.

A 6-month evaluation of covid-19 after completion of radiotherapy was planned from the time of inclusion of the patients in the study, and consisted of a 6-month follow-up visit comprising clinical examination assessing the initial symptoms associated with Sars-CoV-2 infection, and late toxicity of radiotherapy. A 6-month follow-up chest CT scan was also planned at the time of inclusion with centralized review by the same expert radiologist who interpreted the initial chest CT scans.

3. Chest CT protocol and image interpretation

Chest CT scans were acquired with the patient in the supine position with breath-holding following inspiration. Examinations were performed on a Somatom multislice CT scanner from Siemens Healthineers, Erlangen, Germany. The following technical parameters were used: detector collimation width: 0.625, tube current modulation: 100-250 mAs, and tube voltage: 120 kV. Image reconstruction parameters were as follows: slice thickness: 1-1.25 mm, iterative reconstruction Br40 (mediastinal) and BI57 (lung) kernels (Siemens Healthineers). Images were obtained with both mediastinal (width 400 HU; level 40 HU) and parenchymal (width 1500 HU; level -700 HU) window settings.

Qualitative assessment was performed by a senior radiologist in accordance with previous reports of covid-19 imaging [38,39]. The following features were recorded for each examination: ground-glass opacity, crazy paving, focal or linear consolidation. The predominant CT signs were recorded for each examination. A severity score (five classes) was implemented according to the extent of lung parenchyma involvement as follows: absent/minimal (0-<10%); moderate (10-25%); extensive (26-50%); severe (51-75%); critical (75%) [39]. The study chest CT scan (covid-19) was also compared

with a previous chest CT scan available on the PACS system. The follow-up CT scan performed at 6 months was classified as normal or abnormal (presence of parenchymal abnormalities, regardless of their appearance). CT scans were analysed centrally by an expert radiologist.

In accordance with new guidelines issued during the pandemic, concerning the pathway and treatment in the radiotherapy department, the majority of patients with covid-19 were treated on a dedicated machine, Halcyon, which is a new generation accelerator from Varian [17,29,40]. Whenever possible, patients were treated by hypofractionation modalities with a dose of 40 Gy in 15 fractions or according to conventional fractionation with a dose of 50 Gy in 25 fractions, by intensity-modulated radiation using a volumetric intensity-modulated radiation technique (VMAT) by ArcTherapy, which consists of imaging-guided irradiation, allowing modulation of radiation beams on a complete arc of 360° [28,41-45]. This latter technique is especially used for patients treated for breast cancer with lymph node irradiation. A minority of patients were treated by three-dimensional (3D) radiation using an isocentric lateral decubitus technique that requires special expertise and trained radiotherapy technicians [24,46]. This technique consists of 3D irradiation delivering a homogeneous dose to a target volume, while preserving organs at risk and constitutes an alternative to intensity modulation for the treatment of large breasts. An electron beam technique was also used for superficial lesions with an energy ranging from about 4 to 25 MeV (however, electron beams are used less and less commonly) and is particularly suitable for chest wall irradiation [47]. The main types of radiation used were 6 MeV photons and electron beams, in some cases.

4. Results

This prospective single-centre study evaluated 350 patients treated for early-stage breast cancer in our department between March 2020 and June 2020 (Figure 1). A very detailed analysis was performed on 12 patients to address a previously unanswered question: "Does radiation used in the treatment of breast cancer increase the risk of side effects, including lung sequelae, in patients irradiated during the course of covid-19?".

4.1. Primary outcome

Sars-CoV-2 RT-PCR and/or chest CT were performed in 12 of these patients. Six patients had a positive PCR test, and four patients had chest CT signs compatible with covid-19.

Six of the 12 patients had images indicating initial lung involvement. Chest CT scan to screen for covid-19 was performed in 50% of this population and, in four out of six patients, chest CT demonstrated minimal to moderate signs of covid-19. Two patients presented signs of lung involvement considered to be minimal (<10%) and two other patients presented moderate involvement (10-25%). Eleven of the 12 patients were reviewed at a 6-month follow-up visit with follow-up CT scan in ten cases to demonstrate late toxicity and lung disease 6 months after covid-19. All chest CT

scans performed at 6 months showed no signs of covid-19 sequelae or radiation-induced lung lesions. Examples of patients CT scan images are given in Figure 2.

4.2. Toxicity

Adverse effects experienced by patients during treatment were assessed at treatment visits by the Common Toxicity Criteria for Adverse Events (CTCAE; version 4.03). Analysis of acute toxicity according to the CTCAE criteria found: 66% of grade 1 radiation dermatitis, 8% of grade 2 radiodermatitis, 25% of grade 1 oesophagitis/dysphagia and 17% of grade 1 asthenia (Table 2). These results are in line with the toxicity classically reported in the literature on this subject.

Adverse effects experienced by patients at 6 months were assessed according to the CTCAE criteria at a 6-month follow-up visit after completion of radiotherapy. Analysis of late toxicity according to the CTCAE criteria found: 25% of grade 1 breast fibrosis, 17% of grade 1 skin hyperpigmentation, 8% of grade 2 lymphoedema and 8% (one patient) of grade 2 dyspnoea (Table 3). Further investigations (particularly cardiological) are underway to characterise persistence of grade 2 dyspnoea in one of these patients (a patient who underwent adjuvant paclitaxel chemotherapy in association with trastuzumab). This patient was treated in lateral position only to the breast without lymph node irradiation (minimal dose to organs at risk).

4.3. Dosimetric analysis

In this study population, 36% of patients were treated by hypofractionation with a dose of 40 Gy in 15 fractions and 63% were treated according to conventional fractionation with a dose of 50 Gy in 25 fractions. The following techniques were used: nine patients were treated by VMAT IMRT, two patients were treated by 3D isocentric lateral decubitus technique and one patient received electron beam radiotherapy to the chest wall.

Dosimetric analysis of organs at risk, especially the doses received, is consistent with data published in the literature. Dosimetric data are presented in Table 4.

One patient, who did not receive a standard irradiation protocol, was not included in the dosimetric analysis. This patient received a total dose of 50 Gy in 25 fractions to the left breast, level II to IV lymph nodes and Rotter nodes using a 6 MV photon beam according to a VMAT technique. A total dose of 30 Gy in 15 fractions was also delivered to the right chest wall and level II to IV and interpectoral (IP) nodes. Treatment was discontinued for 1 month due to a right chest wall abscess requiring drainage and antibiotics, followed by staphylococcal surgical site infection.

One of the two patients treated by isocentric lateral decubitus technique to the breast alone discontinued radiotherapy two fractions before the end because the appearance of symptomatic covid-19 requiring hospitalization and oxygen therapy.

5. Discussion

This is the first prospective study and currently the largest series evaluating the long-term lung toxicity by CT scan in covid-19 patients irradiated for breast cancer.

The current literature on covid-19 in cancer patients mainly adopts the various management guidelines for these patients during the epidemic, as well as new guidelines [12-16,18,20-23,29,48]. Some studies have tried to analyse risk factors for severe forms of covid-19 in cancer patients, and tend to suggest that cancer is not an independent risk factor for excess mortality in Sars-CoV-2-infected patients [33-35]. However, in the field of oncology, and particularly radiotherapy, no publication has analysed the late adverse effects of radiotherapy in covid-19 patients. This study, based on a prospective, single-centre cohort in the institut Curie (Paris) department of radiotherapy assessed the early and late (6 months) adverse effects of radiotherapy in breast cancer patients with concomitant covid-19. Of the 350 patients treated for breast cancer during the inclusion period, only 12 had confirmed covid-19. Baseline and 6-month follow-up chest CT scans were reviewed centrally by an expert radiologist to assess the course of covid-19-related lung lesions prior to and 6 months after radiotherapy. This CT analysis did not reveal any sequelae of covid-19 or radiation-induced lesions in the patients studied. Analysis of acute and late toxicity at the end-of-treatment and 6-month follow-up visits did not reveal any increase in clinical adverse effects (respiratory, skin, etc.) compared to data of the literature.

The patient who presented grade 2 dyspnoea was treated to the breast alone in lateral position with doses to heart and lung close to 0 Gy, therefore this symptom was probably associated with covid-19 and/or the systemic treatment by taxans and trastuzumab.

Covid-19 therefore does not appear to increase the adverse effects of radiotherapy, and radiotherapy does not appear to accentuate or prolong the initial lung damage caused by Sars-CoV-2 infection in patients irradiated for breast cancer. Radiotherapy should therefore not be delayed in patients requiring this type of therapy, despite concomitant covid-19.

However, these results need to be confirmed by studies based on larger patient cohorts, as the small number of patients included in this study and the small number of patients assessed by baseline and 6-month follow-up chest CT scan did not allow comparison of CT signs, which must be evaluated in larger series. All these patients were diagnosed during the radiotherapy and it was difficult to stop their treatment especially in patients without symptoms because the risk of recurrence.

This study highlights the value of treating each patient with a technique adapted to anatomy and comorbidity. Hypofractionation protocols must also be adapted to the volumes irradiated.

These results therefore tends to show that the initial lesions or lung sequelae associated with covid-19 are not more severe or more prolonged after radiotherapy, in patients treated for breast cancer with

proven covid-19. Radiotherapy should therefore not be delayed in patients requiring radiation, despite the presence of covid-19.

6. Conclusion

Radiotherapy for breast cancer patients with covid-19 is feasible and well tolerated in minimally symptomatic patients treated by techniques adapted to their anatomy. No lung sequelae were detected 6 months after radiotherapy. These data need to be confirmed by larger series.

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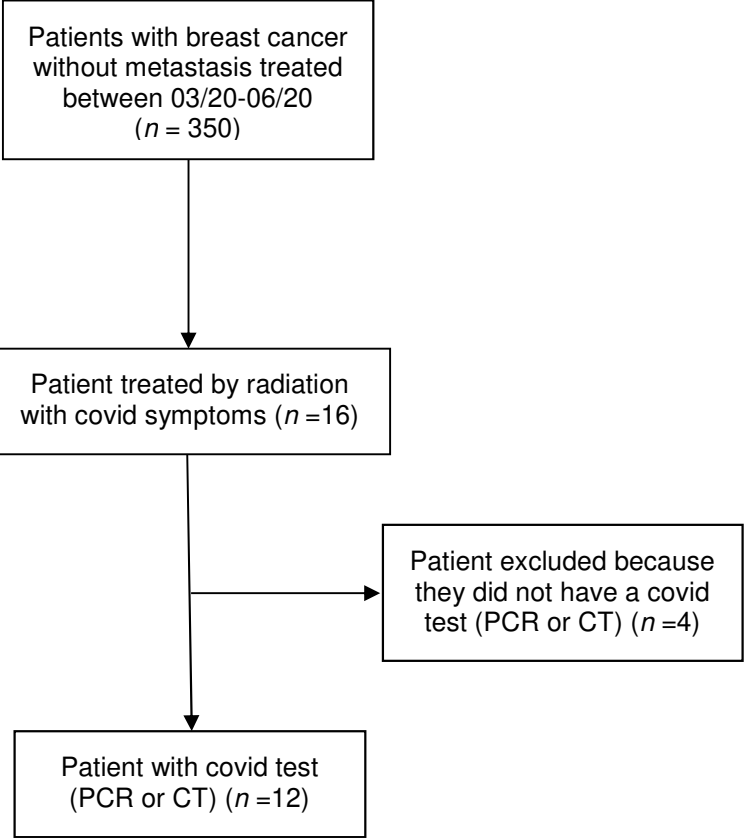
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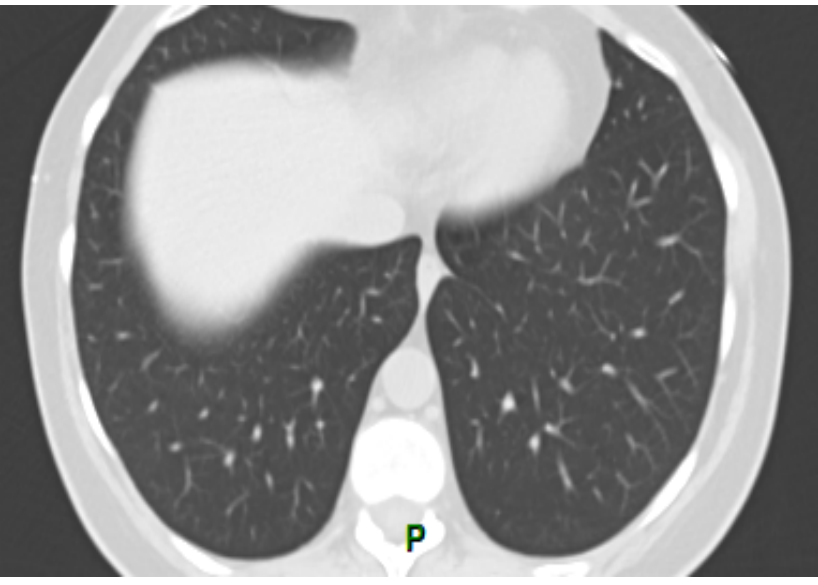
Figure 1. Prospective study on patients diagnosed with severe acute respiratory syndrome coronavirus 2 infection treated for early-stage breast cancer: flow chart of the study. Covid: coronavirus disease; PCR: polymerase chain reaction; CT: computed tomography.

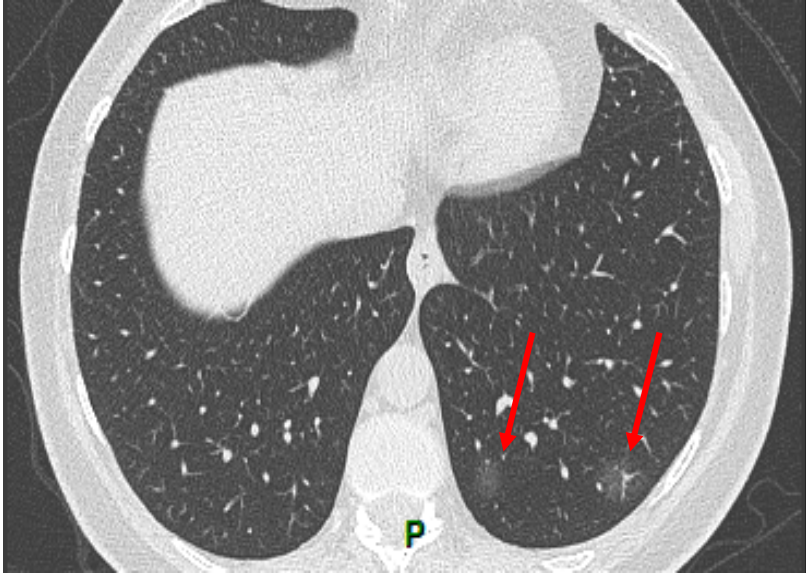
Organigramme de l'étude.

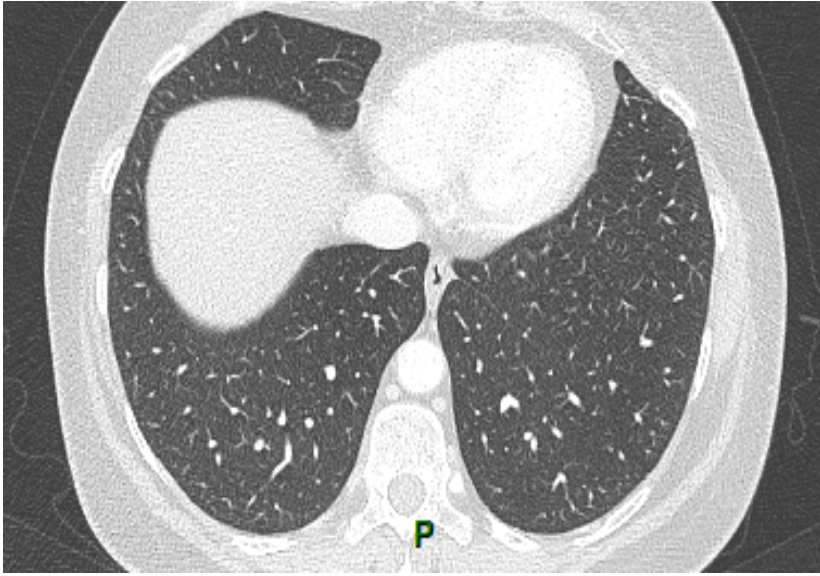
Figure 2. a–l: Lung CT evaluation of the severe acute respiratory syndrome coronavirus 2 infection (coronavirus disease 2019 [covid-19]) in patients with breast cancer treated by radiation; a,d,g,j: before covid-19 infection, normal CT images (g: frontal reconstruction); b,e,h,k: images at baseline of covid; b: discrete peripheral ground glass opacities areas predominant in the left lower lobe (arrows); e: predominantly peripheral ground glass opacities areas in the left upper lobe (arrows); h: frontal reconstruction showing areas associating ground glass opacities, reticulations and peribronchial thickenings in the left lower lobe (arrows); k: central and peripheral ground glass opacities areas predominant in the two upper lobes (arrows); c,f,i,l: images 6 months after covid showing no sequellar lesion (i: frontal reconstruction).

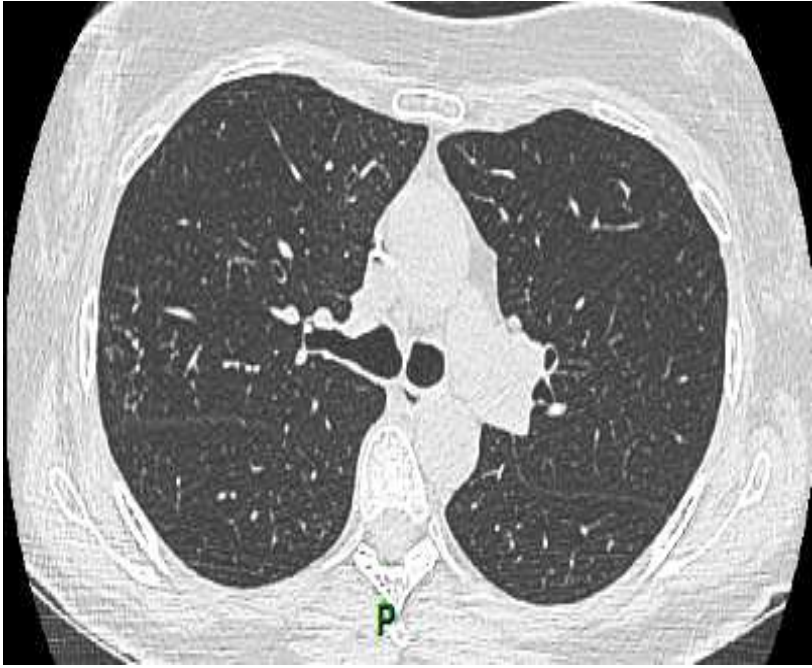
Évaluation pulmonaire de la covid-19 par scanographie. a,d,g,j : avant la covid-19 ; b,e,h,k : au début de l'infection ; c,f,i,l : 6 mois après.

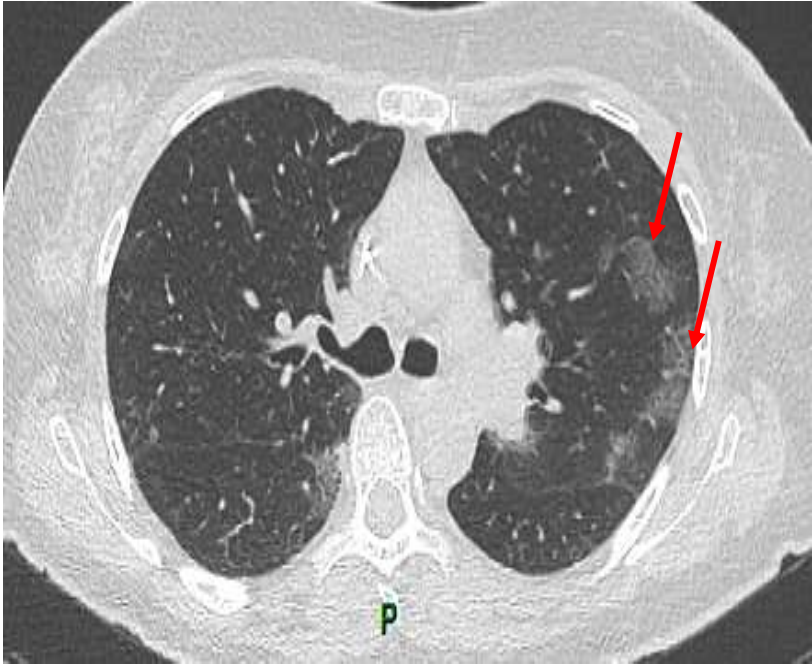


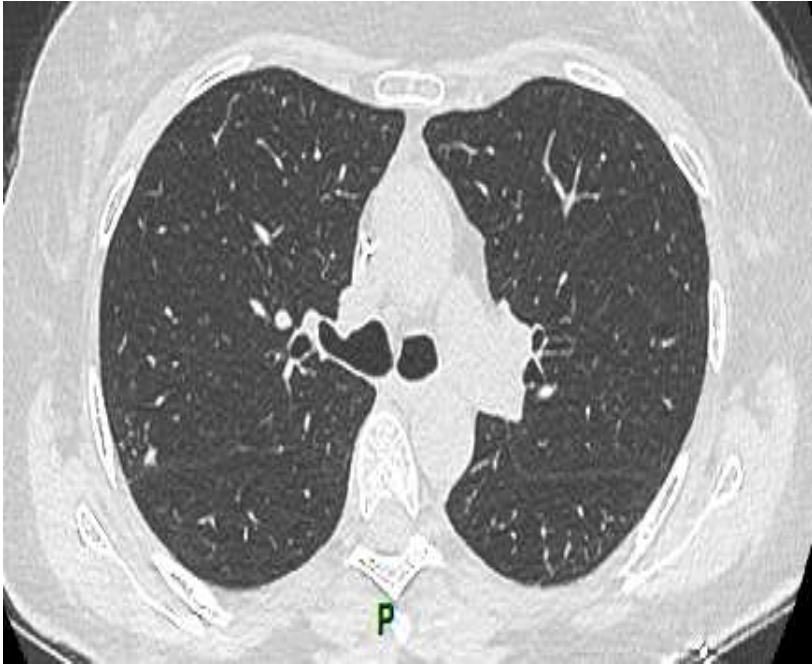


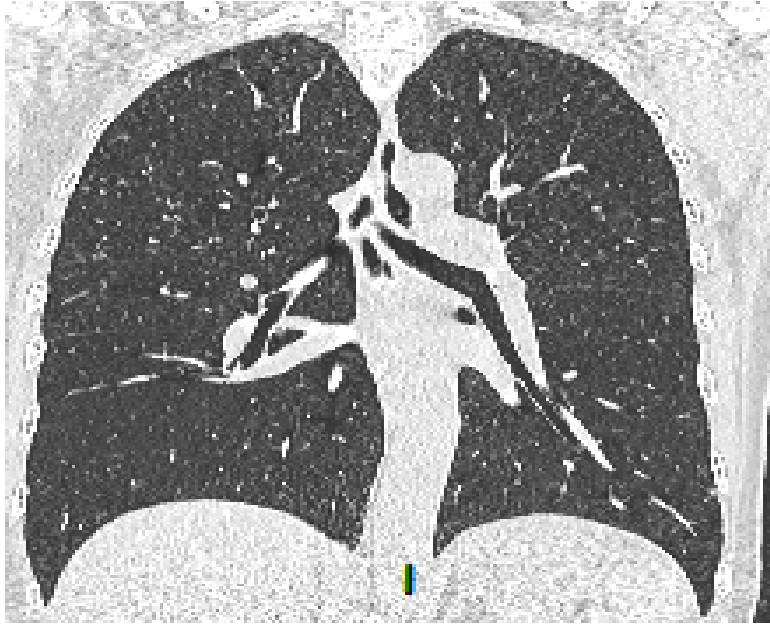


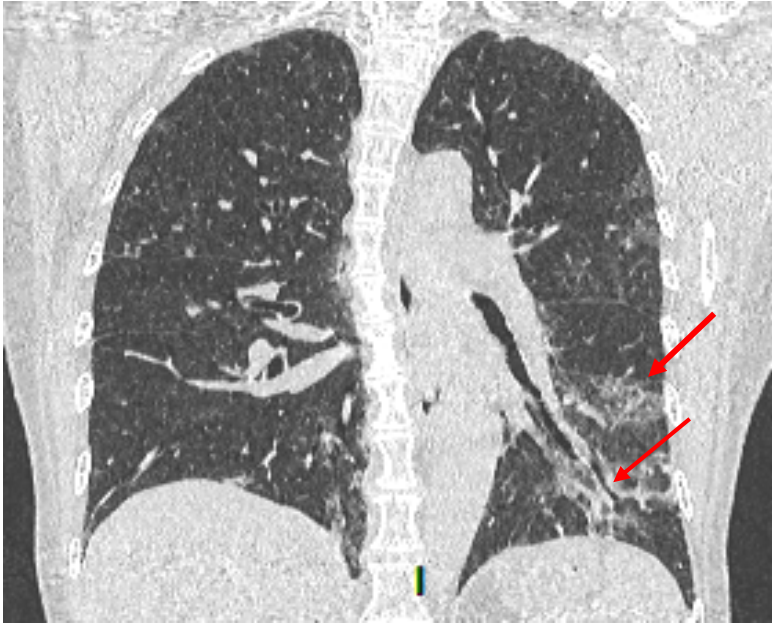




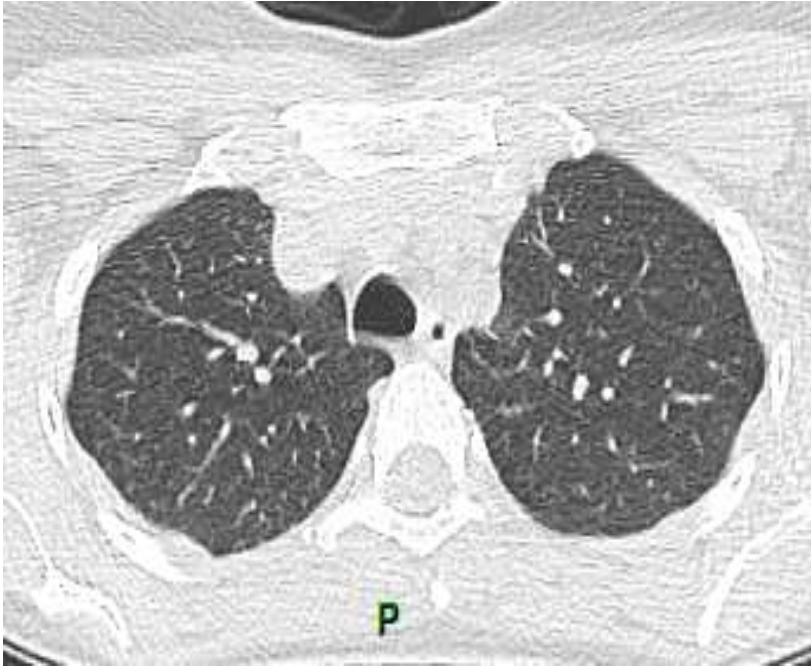


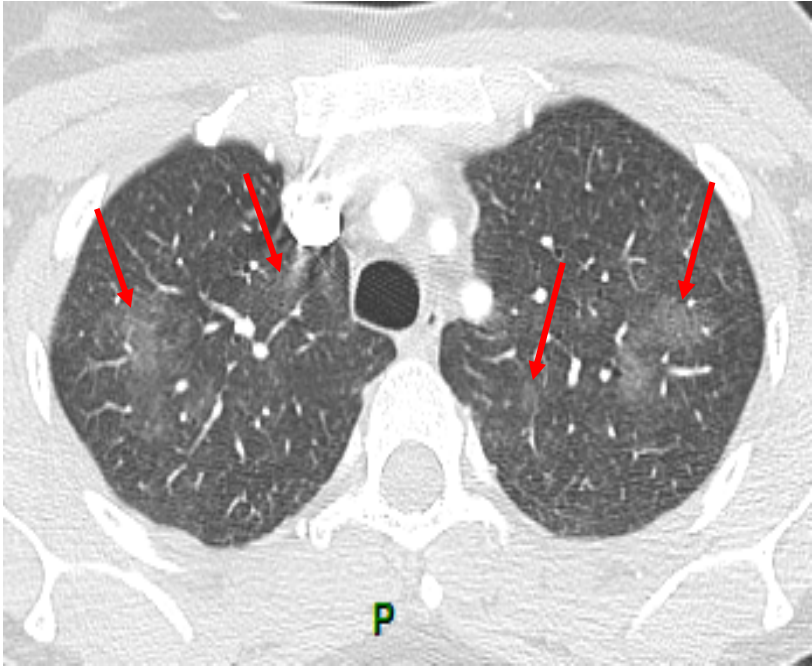












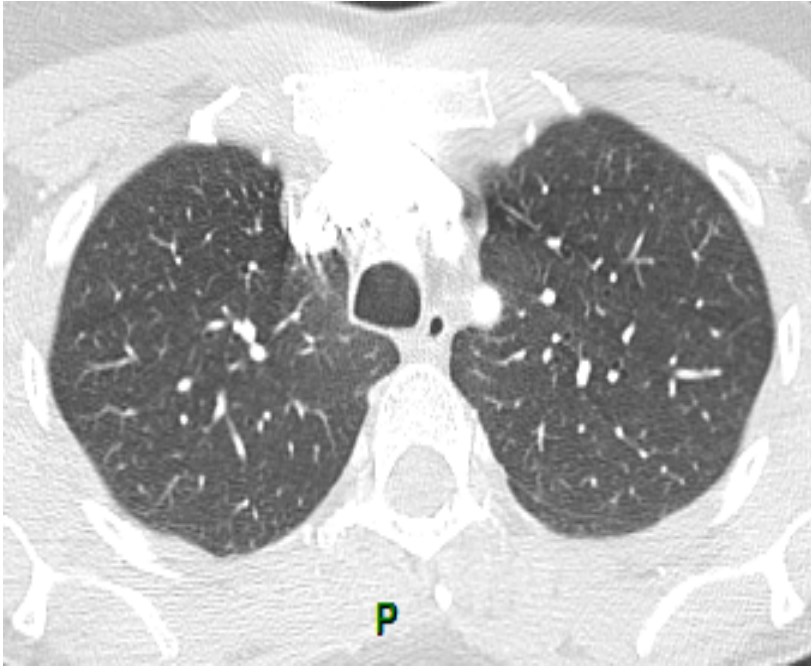


Table 1. Prospective study on patients diagnosed with severe acute respiratory syndrome coronavirus 2 infection (coronavirus disease 2019 [covid-19]) treated for early-stage breast cancer by radiation: characteristics of the patients at baseline.

Patient no.	Age (years)	Tumour stage	Histology	Grade	HR	Her2	Ki	Comorbidity				BMI (kg/m ²)	ASA	Chemotherapy ^b	Tumorectomy	Surgeries		Covid diagnosis		
								HBP	Obesity ^a	Alcohol	Tobacco					Mastectomy	LND	Lung CT scan	PCR	Clinical symptoms
1	71	ypT2N1a	IDC	2	+	-	4%	1	1	0	0	41,6	2	3 C100 + 2 C75	Right		RAC	0	1	1
2	46	pTis	DCis	Intermediate				1	0	0	0	25	2		Right			1	1	1
3	65	pT1bN0	TC	2	+	-	2%	0	1	1	1	27,5	2		Left		LAC	0	1	1
4	43	pT3N1	IDC	2	-	+	25%	0	0	0	0	23,3	2	3 C 3 D–trastuzumab		Right	RAC	1	1	1
5	72	pT2N0	IDC	3	+	-	50%	1	0	0	0	22,6	2	4 DC		Right	RAC	0	1	1
6	62	pT1bN0	IDC	3	-	+	60%	1	0	0	1	22	ns	12 P–trastuzumab	Left			1	1	1
7	51	pT1cN1	ILC	2	+	-	2%	0	1	0	1	25,5	1	3 C + 3D	Left			0	0	1
8	60	pT1aN0	DCis	High	-		10%	1	1	1	0	32,5	2		Left		LAC	0	1	1
9	48	pT1cN0	IDC	2	+	-	5%	0	0	0	0	27,8	2		Left			1	0	1
10	43	cT4dN1	ILC	3	-	-	30%	0	0	0	0	22,6	2	6 AC–capecitabine		Left	LAC	1	1	1
11	52	cT2N1	IDC	3	+	+	40%	0	1	0	1	31,2	2	4 C + 4 D–trastuzumab	Right		RAC	0	0	1
12	73	pT1cN1	IDC	2	+	-	5%	0	1	0	0	32,4	2	Letrozole	Left	Right	LAC	1	1	1
		ypT2N0	ILC	2																

IDC: invasive ductal carcinoma; DCis: ductal carcinoma in situ; TC: tubular carcinoma; ILC: invasive lobular carcinoma; LND: lymph node dissection; RAC: right axillary dissection; LAC: left axillary, dissection; HR: expression of hormone receptors ; Her2: expression of epidermal growth factor receptor; Ki: proliferation index; HBP : high blood pressure; BMI: body mass index; ASA: ?; PCR: polymerase chain reaction; C: cyclophosphamide; P: paclitaxel; AC: adriamycin and cyclophosphamide; D: docetaxel; DC: docetaxel and cyclophosphamide.

^a BMI > 25 kg/m².

^b Neoadjuvant chemotherapy.

Table 2. Prospective study on patients diagnosed with severe acute respiratory syndrome coronavirus 2 infection (coronavirus disease 2019 [covid-19]) treated for early-stage breast cancer by radiation: acute toxicity of radiotherapy according to the Common Toxicity Criteria for Adverse Events.

Patient no. and radiotherapy	Radiodermatitis	Oesophagitis/dysphagia	Asthenia	Pneumonia
Patient 1: right breast +lymph nodes	2	1	0	0
Patient 2: right breast	1	0	1	0
Patient 3: left breast	0	0	0	0
Patient 4: right chest wall + lymph nodes	0	0	0	0
Patient 5: right chest wall	1	0	0	0
Patient 6: left breast	0	0	0	0
Patient 7: left breast + boost + lymph nodes	1	0	0	0
Patient 8: left breast + boost	1	0	1	0
Patient 9: left breast + boost	1	0	0	0
Patient 10: left breast + lymph nodes	1	1	0	0
Patient 11: right breast + lymph nodes	1	0	0	0
Patient 12: bilateral	1	1	0	0

Table 3. Prospective study on patients diagnosed with severe acute respiratory syndrome coronavirus 2 infection (coronavirus disease 2019 [covid-19]) treated for early-stage breast cancer by radiation: late toxicity of radiotherapy according to the Common Toxicity Criteria for Adverse Events.

Patient no. and radiotherapy	Fibrosis	Hyperpigmentation	Dyspnoea	Lymphoedema
Patient 1: right breast + lymph nodes	0	0	0	0
Patient 2: right breast	0	0	0	0
Patient 3: left breast	1	1	0	0
Patient 4: right chest wall + lymph nodes	1	0	0	0
Patient 5: right chest wall	0	0	0	0
Patient 6: left breast	0	0	2	0
Patient 7: left breast + boost + lymph nodes	0	0	0	0
Patient 8: left breast + boost	NA	NA	NA	0
Patient 9: left breast + boost	0	1	0	0
Patient 10: left breast + lymph nodes	0	0	0	0
Patient 11: right breast + lymph nodes	1	0	0	0
Patient 12: bilateral	0	0	0	2

Table 4. Prospective study on patients diagnosed with severe acute respiratory syndrome coronavirus 2 infection (coronavirus disease 2019 [covid-19]) treated for early stage breast cancer by radiation: dosimetric analysis.

Patient	Volume	Dose (Gy)	Number of fractions	Technique	Radiation	Spinal cord (D2%)	Lung (Dmean, V20, V30)	Heart (D2%, Dmean)	Coronary (D2%)	Oesophagus (D2%)
Patient 1	Right breast + lymph nodes II-IV	50	25	VMAT	Photons 6 MeV	10.8 Gy	10Gy 12Gy 5.5Gy	4.3Gy 1.1Gy	1.9	6.3Gy
Patient 2	Right breast	45.5	18	VMAT	Photons 6 MeV	0.7Gy	8 Gy 14.8 Gy 9 Gy	2.3 Gy 0.6 Gy	0.48 Gy	0.7 Gy
Patient 3	Left breast	40	15	VMAT	Photons 6 MeV	0.4 Gy	5.6 Gy 9.8 Gy 2.7 Gy	17.4 Gy 2 Gy	16.2 Gy	6.8 Gy
Patient 4	Right chest wall + lymph node II-IV	50	25	VMAT	Photons 6 MeV	8.9 Gy	12.5 Gy 24.4 Gy 12.9 Gy	11 Gy 2.3 Gy	1.6 Gy	9.6 Gy
Patient 5	Right chest wall	40.05	15	3D conformal	Electrons	0 Gy	6 Gy 12 Gy 10 Gy	1.1 Gy 0.3 Gy	0 Gy	0 Gy
Patient 6	Left breast	32.04	12	3D-lateral	Photons 6 MeV	0 Gy	0.7 Gy 0 Gy 0 Gy	2.3 Gy 0.7 Gy	0 Gy	0 Gy
Patient 7	Left breast + boost + lymph nodes I-IV	64.4	28	VMAT	Photons 6 MeV	13 Gy	11.6 Gy 16.1 Gy 16.6 Gy	14.9 Gy 4.3 Gy	6.9 Gy	29.4 Gy
Patient 8	Left breast + boost	64.4	28	VMAT	Photons 6 MeV	0.2 Gy	4.1 Gy 5.8 Gy 3.9 Gy	4.7 Gy 1 Gy	4 Gy	0.3 Gy
Patient 9	Left breast + boost	62.1	27	VMAT	Photons 6 MeV	4.1 Gy	6.7 Gy 10 Gy 8 Gy	3.9 Gy 1.2 Gy	12 Gy	4.5 Gy
Patient 10	Left breast + lymph nodes I-IV	50	25	VMAT	Photons 6 MeV	28 Gy	14.1 Gy 25 Gy 15 Gy	30 Gy 6.8 Gy	35 Gy	43 Gy
Patient 11	Right breast + lymph nodes II-IV	50	25	VMAT	Photons 6 MeV	12 Gy	13.4 Gy 22 Gy 12 Gy	19 Gy 4.8 Gy	7.9 Gy	20 Gy
Patient 12	Bilateral	50	25	IMRT	Photon 6 MeV	12 Gy	14.4 Gy 24 Gy 14 Gy	19 Gy 4.4 Gy	6.9 Gy	22 Gy

VMAT: volumetric archtherapy; D2%: dose in 2% of the volume; Dmean: mean dose; Vx: ??; 3D: three-dimensional; IMRT: intensity-modulated radiation therapy.