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Adjuvant hypofractionated radiotherapy with simultaneous integrated boost after breast-conserving surgery: A systematic literature review

Martin Schmitt [a], Inès Menoux [a], Isabelle Chambrelant [a], Carole Hild [b], Thierry Petit [c], Carole Mathelin [b], Georges Noël [a,*]

[a] Radiotherapy Department, Strasbourg Europe Cancer Institute, 17 Rue Albert Calmette, Strasbourg CEDEX 67200, France
[b] Breast Surgery Department, Strasbourg Europe Cancer Institute, 17 Rue Albert Calmette, Strasbourg CEDEX 67200, France
[c] Medical Oncology Department, Strasbourg Europe Cancer Institute, 17 Rue Albert Calmette, Strasbourg CEDEX 67200, France

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ABSTRACT

Purposes: Several studies have shown that simultaneous integrated boost provides better dose homogeneity, improves the biologically effective dose-volume histogram and reduces treatment time compared to sequential boost in breast cancer.
Patients and methods: We conducted a systematic review of published trials evaluating simultaneous integrated boost in hypofractionated radiotherapy to analyze the results in terms of overall survival, local control, early and late side effects, and radiotherapy techniques used.
Results: Upon 9 articles, the prescribed dose to the whole breast varied from 40 to 46.8 Gy. The number of fractions varies from 15 to 20 fractions. The prescribed dose per fraction to the boost varied from 2.4 Gy per fraction to 3.4 Gy per fraction for a total boost dose from 48 to 52.8 Gy.
Conclusions: Simultaneous integrated boost seems effective and safe when given hypofractionated whole-breast irradiation but needs to be validated in prospective trials.

Introduction

Breast cancer is the most common cancer in women worldwide, as it is also the leading cause of cancer death among women globally [1]. The use of radiotherapy in the adjuvant setting has improved both local control and overall survival in early-stage breast cancer patients [2].

Moderate hypofractionation is the standard of care for breast cancer requiring adjuvant radiotherapy. Several randomized controlled trials showed the equivalence of hypofractionated radiotherapy for local tumor control and the rates of late adverse effects in early breast cancer. In these trials, the boost to the tumor bed was performed sequentially with breast irradiation, thus prolonging the duration of treatment [3–5]. Simultaneous integrated boost (SIB) was introduced in combination with conventionally fractionated whole-breast irradiation (WBI) with advanced imaging techniques for accurate pretreatment staging and positioning and availability of daily image guidance before every radiotherapy session. Several studies have shown that SIB provides better dose homogeneity, improves the biologically effective dose-volume histogram and reduces treatment time compared to sequential boost [6–8]. Performing SIB with hypofractionated whole-breast irradiation would further reduce the overall treatment time.

In light of the literature, we conducted a systematic review of published trials evaluating SIB in hypofractionated radiotherapy for breast cancer to analyze the results in terms of overall survival (OS), local control, early and late side effects, and radiotherapy techniques used.

Materials and methods

For our article research, we followed the PRISMA guidelines [9]. A research protocol was published in the PROSPERO database (registration number: 297495). Articles corresponding to the Mesh terms “breast cancer” and “adjuvant radiotherapy” and the terms “hypofractionated” and “simultaneous integrated boost” were searched in the PubMed database. Articles corresponding to the terms “breast cancer”, “adjuvant radiotherapy”, “hypofractionated” and “simultaneous integrated boost” were searched in the Cochrane library. Studies published since 2015 reporting prospective trials published in English or French were

* Corresponding author.
E-mail address: ma.schmitt@icans.eu (M. Schmitt).

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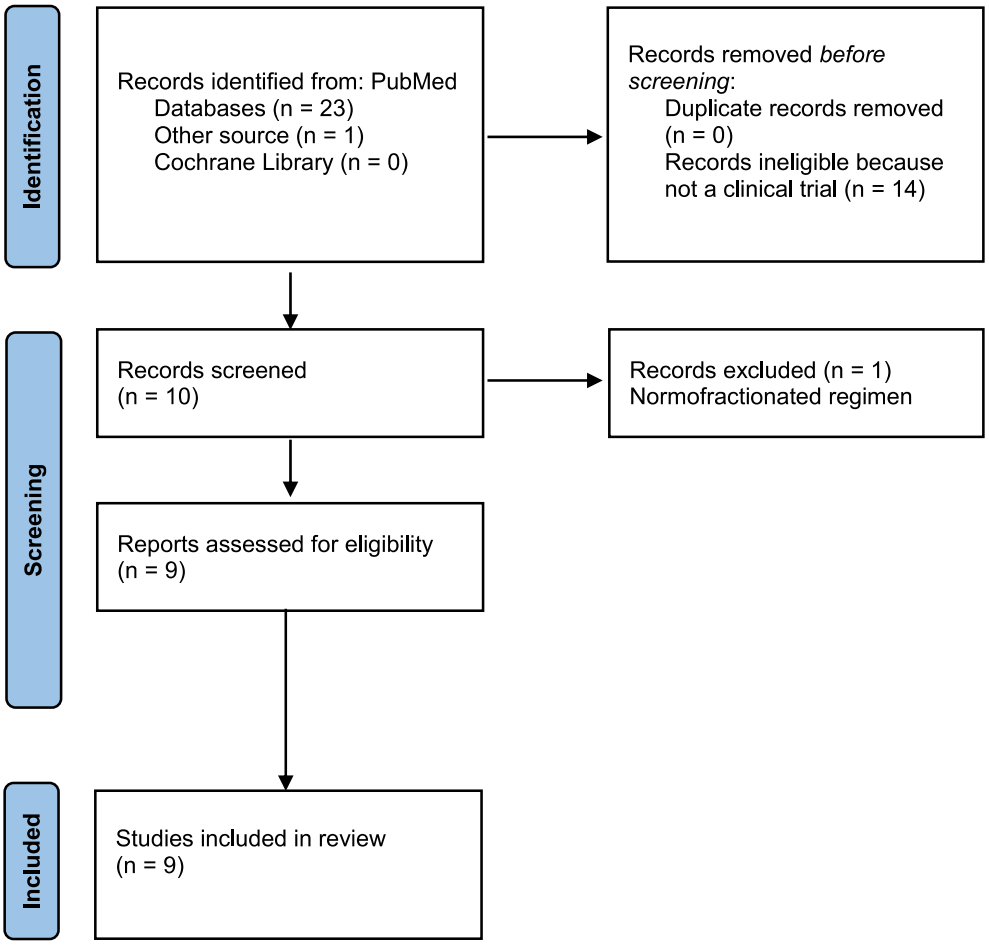

Fig. 1. PRISMA flowchart.

included. We closed the search on 31 December 2021. The flow diagram for our methods is shown in Fig. 1. Twenty-three articles were retrieved using PubMed. One article was retrieved through the references of another article. Fourteen articles were excluded because they did not meet the inclusion criteria. In each article, we collected the following data: the number of patients, the median age of patients, median follow-up, radiotherapy modalities, number of fractions, dose delivered to the breast, dose delivered to the boost, clinical outcomes and dosimetric outcomes.

Results

A total of 9 articles were reviewed. The characteristics of the studies are reported in Table 1. The articles were published from 2012 to 2021 [10–18]. Two trials were randomized and controlled [17,18]. One trial was multicentric [11]. The median follow-up ranged from 12 months to 86.4 months, with two trials without reported follow-up values.

Patient population

Patient and tumor characteristics are reported in Table 2. The number of patients ranged from 10 [15] to 151 [11]. The median age ranged from 47.9 years [15] to 68 years [16], and one trial did not report the median age of the included patients [12].

Tumor characteristics

All articles except two articles [14,17] reported study tumor characteristics. Concerning the pTNM stage, the authors mainly included patients with pT1 tumors, except for the series by Mondal et al. that included 80% of patients with pT2 tumors [15]. The proportion of pN1 varied, according to the articles, from 5% [13] to 40% [15]. The majority of patients had tumors expressing hormone receptors but not expressing HER2 receptors (Table 2). Only three articles reported the volume of the boost [10,15–17]. Mondal et al. reported a mean volume of PTV boost of 228.9 cc [15]. Van Hulle et al. reported respectively a mean volume of boost in SEB arm and SIB arm of 41.86 cc (SD 27.87) and 37.81 cc (SD 31.37) [17]. Scorsetti et al. reported a mean volume of PTV boost of 51.5 cc (±45.9) [16]. De Rose et al. reported the mean dose delivered at PTV boost according to the presence or absence of liponecrosis in patients, respectively, of 48 cc (±8) and 37 cc (±4) [10].

Irradiation technique

All studies except one [17] reported the irradiation technique. The irradiation techniques used were tridimensional radiotherapy (3DRT) [14], 3DRT or intensity-modulated radiotherapy (IMRT) in 59 and 41% for Krug et al. [13] and 30 and 70% for Dellas et al. [11], volumetric modulated arc therapy (VMAT) [10,15,16], tomotherapy [18] and tomotherapy with statics ports (TomoDirect) [12]. The authors of the three articles did not report the energy of the prescribed irradiation beams [12,17,18]. All the others treated their patients with 6 MV beams (Table 1).

Radiation therapy prescription

The prescribed dose to the whole breast varied from 40 to 46.8 Gy, with fraction numbers varying from 15 to 20 fractions. The total

Table 1
Characteristics of 9 studies.

Authors	Publication date	Randomization	Controlled trial	Primary objective	Number of patients	Follow-up time (months)	Median age (years)	Number of fractions	Whole breast dose per fraction (Gy)	Boost dose per fraction (Gy)	Technique	Energy (MV)
Versmessen et al. [18]	2012	1	1	Quality of life	121	26	55	15	2.8	3.4	Tomotherapy	NA
Scorsetti et al. [16]	2012	0	0	Feasibility	50	12	68	15	2.7	3.2	VMAT	6
Franco et al. [12]	2013	0	0	Acute skin toxicity	82	12	NA	20	2.25	2.5	Tomodirect	NA
Dellas et al. [11]	2014	0	0	Feasibility	151	NA	61	16	2.5	3	3DRT or IMRT	6
De Rose et al. [10]	2016	0	0	Cosmetic results at 2 years	144	24	62	15	2.7	3.2	VMAT	6
Mondal et al. [15]	2017	0	0	Feasibility	10	24	47.9	20	2.025	2.4	VMAT	6
Lertbutsayanukul et al. [14]	2020	0	0	Patient-rated cosmetic	114	86.4	50.8	16	2.7	3.3	3DRT	6
Krug et al. [13]	2021	0	0	Acute skin toxicity	149	NA	61	16	2.5	3	59% 3DRT and 41% IMRT	6
Van Hulle et al. [17]	2021	1	1	Cosmetic results at 2 years	150	24	55.5	15	3.12	3.33	NA	NA

3DRT: tridimensional radiotherapy; Gy: gray; IMRT: intensity-modulated radiation therapy; NA: not available; VMAT: volumetric-modulated arc therapy.

prescribed dose to the boost varied from 48 to 52.8 Gy. The prescribed dose per fraction to the boost varied from 2.4 Gy per fraction to 3.4 Gy per fraction for a total boost dose from 48 to 52.8 Gy (Table 1).

Dosimetric outcomes

Dosimetric and clinical outcomes are reported in Tables 3 and 4. Four articles reported dosimetric outcomes [12,13,15,[16]]. The mean $D_{2\%}$ (maximal dose covering 2% of the planned target volume) and $D_{98\%}$ (dose covering 98% of the planned target volume) varied to breast PTV from 105.1% to 118.5% and 91.8% to 95.1%, respectively. The mean $D_{2\%}$ and $D_{98\%}$ varied to boost the PTV from 101.8% to 107.4% and 95.1% to 96.2%, respectively [12,15,16].

Clinical outcomes

The majority of patients did not develop any acute skin reactions or grade 1 skin reactions to the radiotherapy. Acute skin reactions of grade 3 ranged from 0 to 2%. One trial did not report acute skin toxicity [18].

Four articles did not report an analysis of late skin toxicity [11,13,15, 18]. De Rose et al. reported a one-year grade 1 dermatitis rate of 14% [10]. Van Hulle et al. compared sequentially and simultaneously integrated boost arms and reported rates of breast retraction 28.6% and 25.7% ($p = 0.5$), edema 7.3% and 4.3% ($p = 0.5$), telangiectasia 7.3% and 5.8% ($p = 0.9$), fibrosis outside the tumor bed 12.7% and 13% ($p = 0.9$), fibrosis in the tumor bed 9.1% vs. 7.2% ($p = 0.7$) and pigmentation 17.6% and 22.1% ($p = 0.6$), respectively [17].

Regarding local control, 5 studies reported the number of local recurrences. No one reported local recurrence in patients treated with SIB [10,12,15–17]. The median follow-up was 12 months for two of these studies [12,16] and 24 months for the other three [10,15,17]. Van Hulle et al. reported one local recurrence in a group of 74 patients treated with sequential boost [17].

Discussion

The role of the boost to the surgical bed remains an object of debate, especially in the case of hypofractionated whole-breast irradiation. In the Canadian trial led by Whelan et al., patients did not receive any boosts. Still, the risk of local relapse at 10 years was only 7.5%, suggesting that the influence of the boost to the surgical bed could be limited [4]. In START A and B trials, 63% and 41% of patients received a boost, respectively [3,5]. None of the trials in this systematic review of the literature reported survival data. Recently, French national guidelines (RECORAD 2021) maintained the boost in patients under 50 years of age and did not provide conclusions regarding the benefit of SIB [19]. The European Society for Radiotherapy and Oncology (ESTRO) has unanimously retained the boost in the case of HF-WBI [20].

Concerning SIB in the case of HF-WBI, there are two large phase III prospective trials comparing sequential boost vs. SIB. The RTOG 1005 trial (NCT01349322) is a phase III prospective trial comparing conventional radiotherapy (50 Gy in 25 fractions or with hypofractionation option of 42.7 Gy in 16 fractions) followed by a sequential boost of 12–14 Gy in 6–7 fractions vs. a hypofractionated WBI schedule of 40.05 Gy in 15 fractions with an SIB to the tumor bed up to 48 Gy. No lymph node irradiation is planned in this trial [21]. The IMPORT HIGH trial (NCT00818051) assessed dose-escalated RT delivered with IMRT in early breast cancer patients. The standard arm comprises 40.5 Gy in 15 fractions and a sequential tumor bed boost of 16 Gy in 8 fractions. The two experimental arms are described as follows: patients in the first arm received 15 fractions of 2.4 Gy, 2.67 Gy and 3.2 Gy to the whole breast, the index quadrant and the tumor bed, respectively, while patients in the second arm received 15 fractions of 3.53 Gy to the tumor bed. The irradiation or absence of irradiation of lymph nodes is not specified in the trial protocol [22]. The 5-year results of IMPORT HIGH were presented in an abstract at ESTRO 2021. The estimated 5-year ipsilateral

Table 2
Patient and tumor characteristics.

Authors	pT1a (%)	pT1b (%)	pT1c (%)	pT2 (%)	pN0 (%)	pN1 (%)	grade SBR 1 (%)	grade SBR 2 (%)	grade SBR 3 (%)	HR status + (%)	HR status - (%)	HER2 + (%)	HER2 - (%)
Versmessen et al. [18]	63.6			36.3	77.4	30.6	27.2	44.6	23	84.2	15.8	10.7	89.3
Scorsetti et al. [16]	11	21	38	28	92	8	19	72	9	92	8	2	98
Franco et al. [12]	8	26	48	12	71	23	21	55	24	92	8	17	83
Dellas et al. [11]	5	24.8	47.5	19.2	92.2	7.8	NA	NA	NA	57.4	9.9	19.4	78.3
De Rose et al. [10]	2.8	25	53.5	16	84.7	11.8	11.1	70.8	15.3	93.8	4.2	13.2	79.2
Mondal et al. [15]	0	0	20	80	60	40	0	20	80	70	30	20	80
Lertbutsayanukul et al. [14]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Krug et al. [13]	32		48	19	95	5	NA	NA	NA	87	10	16	84
Van Hulle et al. [17]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

HER 2: Human epidermal growth factor receptor-2; HR: hormonal receptor; NA: not available; SBR: Scarff Bloom Richardson.

Table 3
Dosimetric and clinical outcomes.

Authors	Conformity index	Homogeneity index	Dosimetry	Cardiac side effect	Pulmonary side effect	Acute skin toxicity	Late skin toxicity	Cosmetic results	Ipsilateral breast tumor relapse
Versmessen et al. [18]	NA	NA	–	NA	NA	NA	NA	NA	NA
Scorsetti et al. [16]	NA	NA	PTVWB: $D_{98\%}$ = 37.2 Gy $D_{2\%}$ = 45 Gy PTVBOOST: $D_{98\%}$ = 45.8 Gy $D_{2\%}$ = 49.3 Gy	NA	NA	grade 0: 40% grade 1: 64% grade 2: 0% grade 3: 2% grade 4: 0%	comparable between treatment arms	excellent/good: 100%	0
Franco et al. [12]	NA	NA	PTVWB: $D_{98\%}$ = 42.8 Gy $D_{2\%}$ = 47.3 Gy PTVBOOST: $D_{98\%}$ = 48.1 Gy $D_{2\%}$= 50.9 Gy	NA	NA	grade 0: 41% grade 1: 53% grade 2: 6% grade 3 <1%	grade 1: 5% grade 2: 2% grade 3–4: 0%	excellent: 69% good: 22% fair: 5% poor: 4%	0
Dellas et al. [11]	NA	NA	–	NA	NA	grade 0: 49.7% grade 1: 41.8% grade 2: 8.5% grade 3: 0%	NA	NA	NA
De Rose et al. [10]	NA	NA	PTVWB: Standard dev. 0.9 PTVBOOST: Standard dev. 1.5	0	Pulmonary fibrosis G1: 36 patients (25%)	grade 2: 8% grade 3: 0.7% (1 pts)	grade 1: 14% grade 3–4: 0%	NA	0
Mondal et al. [15]	PTVWB: 0.97 PTVBOOST: 0.97	PTVWB: 1.2 PTVBOOST: 1.1	PTVWB: $D_{98\%}$= 93.3% $D_{2\%}$= 118.5% PTVBOOST: $D_{98\%}$= 95.1% $D_{2\%}$= 107.4%	NA	0	grade 1: 80% grade 2: 20% grade 3–4: 0%	NA	good-excellent: 100%	0
Lertbutsayanukul et al. [14]	NA	NA	NA	NA	NA	grade 1–2: 91.3% vs. 73.7% in C-SIB and H-SIB arms (p = 0.048)	grade 1–2: 100%	good/excellent: 80.7% (73.6% vs. 87.7% in C-SIB and H-SIB) satisfied/very satisfied: 93% (93% for both arms)	NA
Krug et al. [13]	NA	NA	PTVWB: 40.01 ± 0.12 Gy PTVBOOST: 48.01 ± 0.08 Gy	NA	NA	grade ≤1: 122 pts grade 2–3: 21 pts grade 4: 0 pts	NA	excellent: 34%–40% good: 51–57% fair: 6%–5% poor: 1%	NA
Van Hulle et al. [17]	NA	NA	NA	NA	NA	NA	grade 3–4: 0%	NA	1 pts in SEB arm

C-SIB: conventional simultaneous integrated boost; $D_{2\%}$: maximal dose covering 2% of the planning target volume; $D_{98\%}$: dose covering 98% of the planning target volume; Gy: Gray; H-SIB: hypofractionated simultaneous integrated boost; PTVBOOST: planning target volume boost; PTVWB: planning target volume whole breast; SEB: sequential boost.

Table 4
Dosimetric outcomes at organs at risk.

Authors	Heart	Ipsilateral lung	Controlateral lung	Controlateral breast
Versmessen et al. [18]	NA	NA	NA	NA
Scorsetti et al. [16]	Dmean = 5.4 Gy ± 2.0 D_{1cc} = 20.4 Gy ± 8.9	Dmean = 8.7 Gy ± 1.7 V_{5Gy} = 61.9% ± 15.9 V_{20Gy} = 8.6% ± 2.9 V_{25Gy} = 4.1% ± 1.9	Dmean = 2.5 Gy ± 0.9 V_{5Gy} = 8.9% ± 9.9	Dmean = 3.3 Gy ± 5.8 V_{5Gy} = 7.6% ± 15.0
Franco et al. [12]	* V_{5Gy} = 12.8% ± 8.6 V_{10Gy} = 2.7% ± 1.1 V_{20Gy} = 1.3% ± 0.5 V_{25Gy} = 1.1% ± 0.3 Dmean = 2.1 Gy ± 1.2 Dmax = 25.1 Gy ± 19.1	V_{5Gy} = 26.2% ± 4.5 V_{10Gy} = 15.6% ± 3.4 V_{20Gy} = 9.6% ± 3.1 Dmean = 6.4 Gy ± 1.5	Dmax = 2.1 Gy ± 1.1	Dmax = 2.9 Gy ± 1.3
Dellas et al. [11]	Dmedian = 1.4 Gy [0–4.6] Dmax = 28.4 Gy [0–43.5]	Dmedian = 2.5 Gy [0.0–7.9] Dmax = 45 Gy [0.0–48.8]	NA	Dmedian = 0.1 Gy [0.0–41]
De Rose et al. [10]	Dmean = 5.1 Gy ± 2.1 V_{18Gy} = 1.3% ± 1.7 V_{40Gy} = 0.0% ± 0.0	Dmean = 7.6 Gy ± 1.5 V20Gy = 7.6% ± 2.7 V5Gy = 50.9% ± 14.7	Dmean = 2.5 Gy ± 1.3	Dmean = 2.3 Gy ± 0.6
Mondal et al. [15]	Dmean = 6.22 Gy [4.17–8.4] V_{40Gy} = 0.17% [0.0–1.0] V_{25Gy} = 2.25% [0.0–11.83] V_{18Gy} = 4.24% [0.0–18.47]	Dmean = 13.92 Gy [7.39–21.61] V_{20Gy} = 21.53% [8.89–36.5] V_{5Gy} = 47.71% [38.34–54.29]	Dmean = 4.05 Gy [2.33–6.39] V_{20Gy} = 0.62% [0.0–3.33] V_{5Gy} = 12.66% [4.83–21.43]	Dmax = 35.51 Gy [23.9–45.12] Dmean = 6.35 Gy [4.59–8.67]
Lertbutsayanukul et al. [14]	NA	NA	NA	NA
Krug et al. [13]	NA	NA	NA	NA
Van Hulle et al. [17]	NA	NA	NA	NA

*: only left sided tumor; D_{1cc}: maximal dose covering 1 cubic centimeter of the planning target volume; Dmax: maximal dose; Dmean: mean dose; Dmedian: median dose; Gy: Gray; V_{xGy}: Volume expressed as a percentage receiving x Gray.
Krug et al. reported a mean dose to the breast planning target volume (PTV) and boosted PTV of 40.01 ± 0.12 Gy and 48.01 ± 0.08 Gy, respectively [13].
Mondal et al. reported conformity indices for the breast PTV and the boost PTV was equal to 0.97. The homogeneity indices reported for the breast PTV and boost PTV were equal to 1.2 and 1.1, respectively [15].

breast recurrence incidence was 1.9% (95% CI 1.2-3.1) for 40 + 16 Gy, 2.0% (95% CI 1.2-3.2) for 48 Gy, and 3.2% (95% CI 2.2–4.7) for 53 Gy. Five-year AE data were available for 1894 clinician assessments. The 5-year moderate/marked side effects rates were broadly similar between the groups and the control, with a higher risk of clinically assessed breast induration, breast distortion, and patient-assessed breast hardness/-firmness for 53 Gy versus 48 Gy. Both trials have been closed to accrual, and the results will provide evidence on this debated issue. While waiting for these results, it might be interesting to perform a meta-analysis on the subject for a quantitative and rigourous evaluation of these data.

Conclusion

The number of acute toxicities of grade >2 was low. The late cosmetic results are also encouraging, SIB with HF-WBI does not seem to increase late toxicities. Although follow-up was short, no local recurrence was described, except for one local recurrence in the sequential boost arm in a single trial. SIB was well tolerated when given with HF-WBI. The RTOG 1005 and IMPORT HIGH trials will probably confirm these results. However, trials considering lymph node irradiation with HF-WBI and SIB seem relevant.

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Martin Schmitt: Conceptualization, Methodology, Formal analysis, Investigation, Validation, Writing – original draft. **Inès Menoux:** Methodology, Validation, Writing – review & editing. **Isabelle Chambrelant:** Investigation, Validation, Writing – review & editing. **Carole Hild:** Validation, Writing – review & editing. **Thierry Petit:** Validation, Writing – review & editing. **Carole Mathelin:** Validation, Writing – review & editing. **Georges Noël:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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