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EPIDEMIOLOGY

Contrast-Enhanced Mammography (CEM) compared to Breast Magnetic Resonance (MRI) in the evaluation of breast lobular neoplasia

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Abstract

Purpose To compare the diagnostic performance (detection, assessment of correct disease extent and multifocality/centricity) of Contrast-Enhanced Mammography (CEM) Versus Breast Magnetic Resonance (MRI) in the study of lobular neoplasms.

Methods We retrospectively selected all the patients who underwent surgery for a lobular breast neoplasm, either an in situ or an invasive tumor, and had undergone both breast CEM and MRI examinations during the pre-surgical planning. Wilcoxon Signed Rank test was performed to assess the differences between size measurements using the different methods and the post-surgical pathological measurements, considered the gold standard. The agreement in identifying multifocality/multicentricity among the different methods and the pathology was assessed using the Kappa statistics.

Results We selected 19 patients, of which one presented a bilateral neoplasm. Then, the images of these 19 patients were analyzed, for a total of 52 malignant breast lesions. We found no significant differences between the post-surgical pathological size of the lesions and the calculated size with CEM and MRI (p-value of the difference respectively 0.71 and 0.47). In all 20 cases, neoplasm detection was possible both with CEM and MRI. CEM and MRI showed an excellent ability to identify multifocal and multicentric cases (K statistic equal to 0.93 for both the procedures), while K statistic was 0.11 and 0.59 for FFDM and US, respectively.

Conclusion The findings of this study suggest that CEM is a reliable imaging technique in the preoperative setting of patients with lobular neoplasm, with comparable results to breast MRI.

Keywords Contrast-Enhanced Mammography · Breast Magnetic Resonance · Lobular breast cancer

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Introduction

Breast neoplasm remains, to this day, the most common neoplasm in women, with more than 2.3 million new cases diagnosed globally each year [1]. Prompt and appropriate diagnosis is essential to properly manage patients with this condition, reducing mortality and comorbidities. Invasive lobular carcinoma (ILC) and lobular neoplasia (LN) are two different conditions in the large plethora of breast malignancies, whose diagnosis and management are still challenging [2, 3].

ILC is the second most common type of breast cancer (BC), accounting for 10–15% of all invasive breast tumors [4].

During the last two decades, an increase in ILC detection has been observed, mostly thanks to the improvements in BC diagnosis and due to the increasing use of hormone replacement therapy in post-menopausal women [5].

ILC is more frequently diagnosed in older women, with a higher incidence in Western countries [5] and, it may be associated with certain cancer-predisposing genetic alterations [6–8].

ILC typically presents as a large tumor, often multifocal or multicentric, with bilateral manifestation and with nodal involvement already at the time of diagnosis, having a high reintervention rate [9].

Furthermore, due to an insidious proliferative pattern with a lack of desmoplastic and fibrotic reactions [10], in many cases, lobular carcinoma remains clinically and radiologically elusive, with a high rate of tumor size underestimation and a high prevalence of missed synchronous lesions. For these reasons, detecting ILC with conventional imaging techniques, such as full field digital mammography or ultrasound, represents a real radiological challenge [11], eventually rendering the role of MRI essential.

Indeed, it is well known that Breast Magnetic Resonance Imaging (MRI) improves the management of patients diagnosed with breast lobular neoplasia: according to the most critical studies in literature, MRI imaging helps in the identification of new ipsilateral and contralateral lesions in up to 39% of cases and influences surgical management in about the 25% of cases investigated [12–14].

While the role of breast MRI in the study of lobular neoplasms is well established, there are very few published data, with few patients, on the diagnostic performance of Contrast Enhanced Spectral Mammography (CEM) in the evaluation of patients with lobular neoplasia [15, 16]: CEM is a relatively new method showing huge potential in the study of breast malignancies, although its role applied specifically to lobular neoplasms has been little investigated [17].

With this study, we aimed to compare the diagnostic performance of CEM versus Full Field Digital Mammography (FFDM), Breast Ultrasound (US), and Breast MRI in the study of lobular neoplasms. It is particularly intended to compare the ability of CEM and breast MRI in the assessment of correct disease extent and multifocality/centricity of the disease.

As CEM has been shown to be faster and cheaper than MRI and generally better tolerated by patients [18], demonstrating its utility in the study of lobular neoplasms, could provide a new personalized and effective approach in the assessment of those neoplasms without recurring to MRI.

Methods

This retrospective study was notified to the Ethics Committee and approved by the Institutional Review Board.

We retrospectively selected from our institution's datasets all operated patients with lobular breast neoplasm, either invasive or in situ, who underwent pre-surgical breast CEM and MRI. It was also assessed whether the same patients had performed breast ultrasounds and/or mammography.

Therefore, the inclusion criteria of the study were as follows:

- Patients diagnosed with lobular neoplasm of the breast.
- Patients underwent both CEM and MRI examinations before surgery.
- Patients treated in our institution.

The study exclusion criteria were:

- Patients with other type of breast malignancies (non-lobular neoplasms) or benign lesions.
- Patients who did not undergo both CEM and MRI before surgery (to be enrolled in the study, patients had to have performed both CEM and MRI before surgery.)
- Patients in whom the quality of the image stored in the PACS was not of sufficient quality for reevaluation. (Low-quality images that did not allow review by radiologists were excluded.)

The images were evaluated, retrospectively, by two expert radiologists with more than 5 years of experience in breast imaging: images were evaluated in consensus by the two radiologists included in the study. These radiologists first evaluated the low-energy CEM image, interpreting it as a conventional full field digital mammography. They then evaluated the recombined CEM image by assessing any additional information. This reevaluation of images also included evaluation of MRI, FFDM, and US performed in the same group of patients (in patients with images stored in institution PACs). In the re-evaluation, we assessed whether the lesion was visible with the method, the extent of the

Table 1 Surgery variables (N = 20)

Variable	Level	Overall (N = 20)
Year of surgery, N (%)	2013	11 (55)
	2014	4 (20)
	2015	5 (25)
Age at surgery (y), median (min–max)		49 (28–84)
Type of surgery, N (%)	Quadrantectomy	7 (35)
	Mastectomy	13 (65)
Side, N (%)	L	9 (45)
	R	11 (55)
Density (ACR), N (%)	B	3 (15)
	C	10 (50)
	D	7 (35)
Number of lesions, N (%)	1	9 (45)
	2	6 (30)
	5	1 (5)
	6	2 (10)
	7	2 (10)
Multifocality/multicentricity, N (%)	No	9 (45)
	Only multifocality	3 (15)
	Only multicentricity	3 (15)
	Both multifocality and multicentricity	5 (25)
Histologic subtype, N (%)	ILC	18 (90)
	LIN2	1 (5)
	LIN3	1 (5)
ER (%), N (%)	0	0 (0)
	> 0	19 (100)
	Missing	1
PgR (%), N (%)	0	1 (5)
	> 0	18 (95)
	Missing	1
Ki-67, N (%)	≤ 20%	13 (68)
	> 20%	6 (32)
	Missing	1
HER2, N (%)	0	11 (58)
	1+	6 (32)
	3+	2 (11)
	Missing	1
Grading, N (%)	G1	1 (5)
	G2	14 (74)
	G3	4 (21)
	Missing	1

lesion, and the presence of multifocality and multicentricity for each exam. We then compared, among the various methods (CEM; MRI; US, and FFDM), the ability to detect the lesion(s), identify multicentricity/multifocality, and define the extent of the lesion correctly. Images were analyzed following the latest version of BIRADS for MRI, CEM, US and FFDM [19–21].

The post-surgical pathological report was used as the gold standard to define the extent of the lesion(s) and to evaluate the multicentricity/multifocality. The term *"multifocality"* denoted the presence of multiple lesions in the same quadrant, while *"multicentricity"* the presence of multiple lesions in different quadrants.

Table 2 Differences between size measurements using MRI, CEM, FFDM, US, and size measurements at surgery (gold standard)

Tumor size measurements (mm)	N	Median (Q1–Q3)	P-value of the difference
Surgery—MRI	20	− 2 (− 3 to 2)	0.47
Surgery—CEM	20	− 2 (− 4 to 3)	0.71
Surgery—FFDM	10	21 (− 1 to 60)	0.041
Surgery—US	18	4 (0 to 26)	0.014

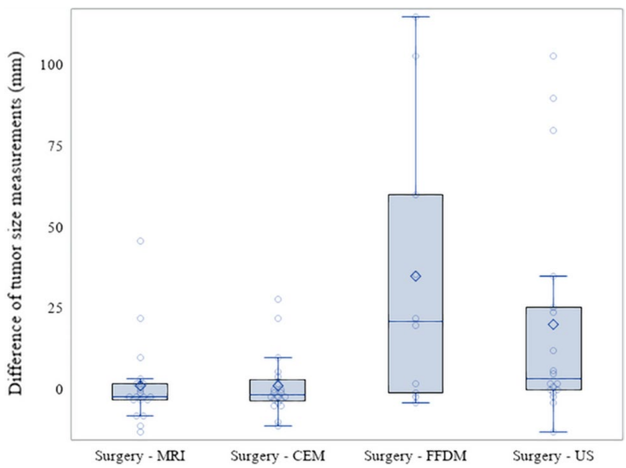

Fig. 1 Distribution of the differences between size measurements using MRI, CEM, FFDM, US, and size measurements at surgery (gold standard)

CEM protocol

We used GE® Healthcare, Senographe Pristina®, Chalfont St. Giles, UK, mammograph for CEM examination: after the intravenous injection of an iodinated contrast agent (Ioexolo) (300 mg/mL, 1.5 mL/kg, Omnipaque®, GE Healthcare, Chalfont St. Giles, UK) two bilateral Cranio Caudal (CC) and mediolateral oblique (MLO) projection views were acquired. Low-energy (26–32 kVp) and high-energy (45–49 kVp) exposures were acquired and then recombine to highlight the uptake of the contrast agent.

MRI protocol

All patients underwent breast MRI with a 1.5-Tesla scanner (Optima MR450w, General Electric Medical Systems, Milwaukee, WI, USA) equipped with a 34 mT/m gradient and a dedicated 8-channel breast coil. A standardized MRI protocol was performed consisting of an axial FSE T2-weighted image, axial DWI with the relative apparent diffusion coefficient (ADC) maps, and dynamic series performed once before and four times after intravenous administration of 0.1 mmol/kg of a gadolinium-chelate at 90 s, post-processing subtraction, and maximal intensity projection (MIP) images.

Statistical analysis

Continuous data were reported as median and ranges, or median and interquartile ranges (IQR). Categorical data were reported as counts and percentages.

Wilcoxon Signed Rank test was performed to assess the differences between size measurements using the different methods and the post-surgical pathological size of the lesion, considered as the gold standard.

The agreement in identifying multifocality/multicentricity among the different methods and the post-surgical pathology was assessed using the Kappa statistic, with 95% CI.

All reported p-values were two-sided, with a p-value less than 0.05 considered as statistically significant.

All analyses were performed with the statistical software SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

We selected 19 patients, of which one presented a bilateral neoplasm. Then, the images of these 19 patients were analysed for a total of 52 malignant breast lesions. The median age at surgery was 49 years (range 28–84). In 90% of the cases, the histology was that of an infiltrating lobular carcinoma. In the remaining cases, we had lobular carcinomas in situ. Table 1 summarizes the main descriptive characteristics of patients at surgery. Most patients (85%) had dense glandular breasts (ACR classification C or D). All patients were examined with CEM, MRI, and FFDM, while preoperative ultrasound was not performed in one case.

In 15% of cases, the neoplasm presented as multifocal; in 15% of cases as multicentric; in 25% of cases, both multifocal and multicentric. All cases were hormone-receptor-positive; Ki-67 was $\leq 20\%$ in 68% ($n = 13$) of cases, and Her-2 negative in 85% of cases.

We considered the diameter at surgery as the gold standard.

We found no statistically significant differences between the lesion diameter measured at surgery and the lesion diameter measured by CEM and MRI (p-value of the difference 0.71 and 0.47, respectively).

In contrast, we found statistically significant differences between the lesion diameter measured at surgery and the lesion diameter measured with FFDM and US (p-value of the difference 0.041 and 0.014, respectively).

These results are schematized in Table 2 and Fig. 1.

In all 20 cases, neoplasm detection was possible by CEM and MRI. Detection of neoplasia was possible in 18/20

Table 3 Comparison of detection and multifocality/multicentricity using MRI, CEM, FFDM, and US (N=20)

Variable	Level	Overall (N=20)
Detection with MRI, N (%)	No	0 (0)
	Yes	20 (100)
Multifocality/multicentricity with MRI, N (%)	No	8 (40)
	Only multifocality	4 (20)
	Only multicentricity	3 (15)
	Both multifocality and multicentricity	5 (25)
Detection with CEM, N (%)	No	0 (0)
	Yes	20 (100)
Multifocality/multicentricity with CEM, N (%)	No	9 (45)
	Only multifocality	4 (20)
	Only multicentricity	3 (15)
	Both multifocality and multicentricity	4 (20)
Detection with FFDM, N (%)	No	10 (50)
	Yes	10 (50)
Multifocality/multicentricity with FFDM, N (%)	No	19 (95)
	Only multifocality	0 (0)
	Only multicentricity	0 (0)
	Both multifocality and multicentricity	1 (5)
Detection with US, N (%)	No	1 (5)
	Yes	18 (95)
	Missing	1
Multifocality/multicentricity with US, N (%)	No	13 (68)
	Only multifocality	1 (5)
	Only multicentricity	2 (11)
	Both multifocality and multicentricity	3 (16)
	Missing	1

cases by ultrasound and in 10/20 cases by mammography (Table 3).

Considering post-surgical pathological report as the gold standard in multifocality/multicentricity assessment, we obtained: 9 cases (45%) without multifocality and multicentricity, 3 cases (15%) with only multifocality, and 3 cases (15%) with only multicentricity. In 5 cases (25%), we had both multifocality and multicentricity.

The agreement in identifying multifocality/multicentricity (considering surgery as the gold standard) was excellent for CEM and MRI [Kappa statistic 95% CI 0.93 (0.79–1.00)]; moderate for ultrasound [Kappa Statistic 95% CI 0.59 (0.30—0.88)] and very bad for mammography [Kappa statistic 95% CI 0.11 (− 0.09–0.30)]. (See Table 4).

In all cases, the lesions demonstrated enhancement in both CEM and MRI. In most cases (65% for CEM and 60% for MRI), the neoplasm showed non-mass enhancement (see Fig. 2).

Discussion

The diagnosis of lobular carcinoma of the breast represents a challenge both from the clinical and radiological standpoint, in particular with conventional imaging methods that may miss early signs of the neoplasm. In fact, lobular carcinomas have a peculiar growth pattern, with initial subtle changes involving the stroma, with only minor alterations of the surrounding architecture. This feature signifies that, in many cases, the diagnosis is delayed, occurring in more advanced stages, as the lesion becomes more evident [22].

Mammography has a low sensitivity in detecting this type of pathology: more than 30% of cases of lobular neoplasia can be missed by this method [23]. The sensitivity of breast ultrasound in detection seems to be better but still suboptimal and operator dependent [24, 25]. The sensitivity of breast MRI is superior in detecting lobular neoplasms, reaching a sensitivity of more than 90% [26].

Moreover, breast MRI allows us to cope with two additional aspects related to lobular neoplasms: the definition of the correct extent of pathology and the problem of multifocality/multicentricity, a tendency frequently displayed by lobular carcinoma, as also confirmed by our case series

Table 4 Agreement between multifocality/multicentricity using MRI (Panel A), CEM (Panel B), FFDM (Panel C), and the US (Panel D) with surgery (N = 20)

Panel A

Surgery	MRI				
	No	Multifoc	Multicent	Both	Total
No	8	1	0	0	9
Multifoc	0	3	0	0	3
Multicent	0	0	3	0	3
Both	0	0	0	5	5
Total	8	4	3	5	20

Agreement: 19 / 20 = 95%

Kappa Statistic (95% CI): 0.93 (0.79 - 1.00) [almost perfect agreement]

Panel B

Surgery	CEM				
	No	Multifoc	Multicent	Both	Total
No	9	0	0	0	9
Multifoc	0	3	0	0	3
Multicent	0	0	3	0	3
Both	0	1	0	4	5
Total	9	4	3	4	20

Agreement: 19 / 20 = 95%

Kappa Statistic (95% CI): 0.93 (0.79 - 1.00) [almost perfect agreement]

Panel C

Surgery	FFDM				
	No	Multifoc	Multicent	Both	Total
No	9	0	0	0	9
Multifoc	3	0	0	0	3
Multicent	3	0	0	0	3
Both	4	0	0	1	5
Total	19	0	0	1	20

Agreement: 10 / 20 = 50%

Kappa Statistic (95% CI): 0.11 (-0.09 - 0.30) [none to slight agreement]

Panel D

Surgery	US				
	No	Multifoc	Multicent	Both	Total
No	8	0	0	0	8
Multifoc	2	1	0	0	3
Multicent	1	0	2	0	3
Both	2	0	0	3	5
Total	13	1	2	3	19

Agreement: 14 / 19 = 74%

Kappa Statistic (95% CI): 0.59 (0.30 - 0.88) [moderate agreement]

[27, 28]. In turn, these features are essential to plan the best surgical approach.

While the role of MRI in the pre-surgical assessment of lobular neoplasms is well established, there are very few studies [15, 29, 30] that have evaluated the performance of CEM in the assessment of lobular neoplasms. In our work, we sought to compare the performance of CEM to MR in the detection, assessment of lesion extent, and identification of multifocality and/or pluricentric lobular neoplasms. The results, although preliminary and obtained on a limited set of patients, are highly encouraging: CEM is faster and generally better tolerated by patients [31, 32] and it might stand as a reliable alternative to MRI in the preoperative assessment of patients with lobular neoplasm [29, 30]. Some typical examples of CEM and MRI appearance of breast lobular neoplasm are shown in Figs. 2 and 3.

Based on these preliminary results, we think CEM could be proposed to patients at higher risk of developing lobular neoplasm. (e.g., patients with previous lobular neoplasm) in preventive and follow-up examinations. In study protocols, CEM could also be proposed as a replacement or complement to MRI in patients with a biopsy diagnosis of lobular neoplasm for proper preoperative assessment: our study presents auspicious results in this direction. In particular, CEM could be very promising in a setting where MRI may not be readily available or in cases where MRI is not tolerated or performable.

The main limitation of our work is the low number of patients involved and its retrospective nature. This work

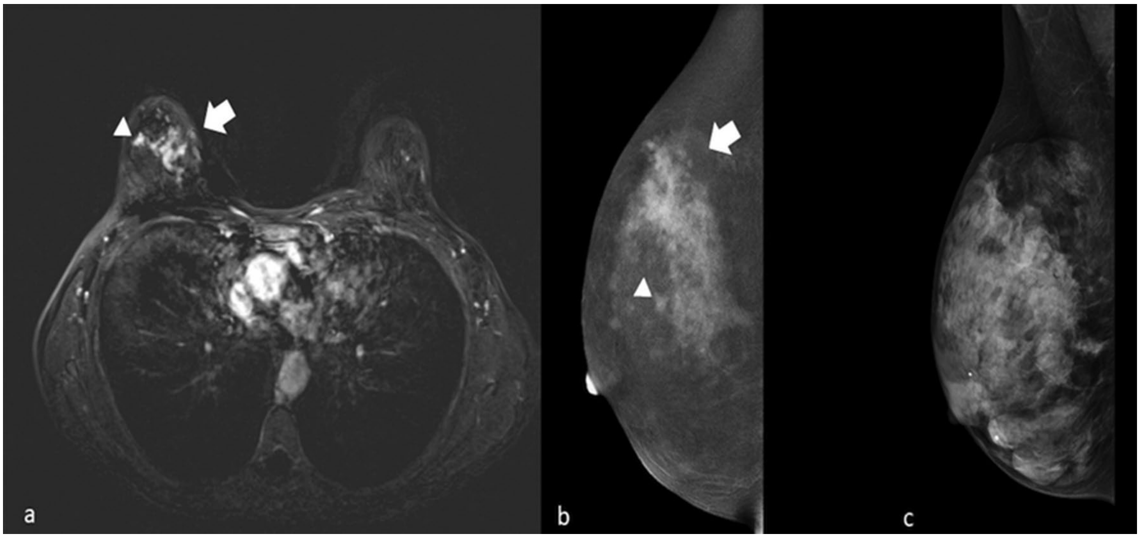

Fig. 2 Forty-six-year-old woman with bloody discharge from the nipple. The patient performs both MRI (**a**) and CEM (**b**). In the first post-contrast subtracted (**a**), we can appreciate a pathologic enhancement (arrow) consisting of multiple confluent nodules (multifocal and pluricentric pathology). One of the satellite pathological findings also shows up, separated from the central lesion (arrowhead). The exact appearance is appreciated in the recombined image of the CEM in the Mediolateral oblique projection. Again, the pathologic enhancement (arrow) is appreciated, with the satellite lesion evident (arrowhead). In this glandular breast, conventional mammography is not so clear in identifying the pathologic lesion. The histopathological examination of the surgical sample confirmed the presence of moderately differentiated invasive lobular carcinoma. The neoplastic cells exhibited expression of both estrogen (90%) and progesterone (60%) receptors, whereas there was no membrane immunoreactivity for Her-1/neu (score 0); the Ki-67 labeling index was determined to be 10%

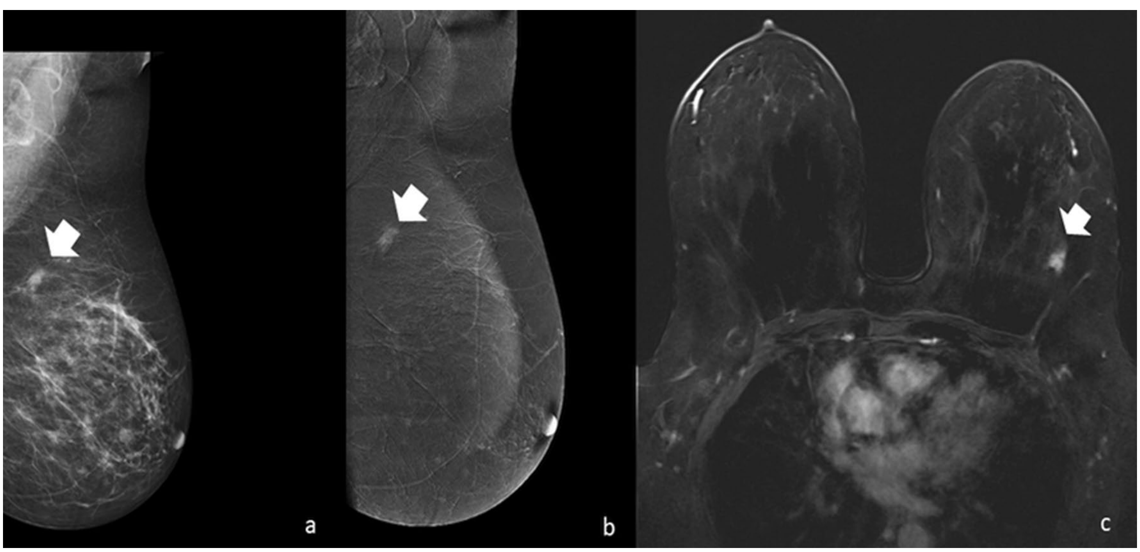

Fig. 3 Sixty-four-year-old patient with recent mammographic findings of newly appeared left breast lesion. An asymmetric mammographic thickening is appreciated in the mediolateral oblique projection of conventional mammography (**a**). At this thickening, a non-mass-like enhancement (arrow) with suspicious characters is appreciated in the recombined EMC image in mediolateral oblique projection (**b**). The focal non-mass enhancement (arrow) is also appreciated in the first post-contrast subtracted image (**c**). The histopathological examination of the surgical sample confirmed the presence of invasive lobular carcinoma. The neoplastic cells exhibited expression of both estrogen (95%) and progesterone (80%) receptors, whereas there was no membrane immunoreactivity for Her-1/neu (score 0); the Ki-67 labelling index was determined to be 13%

can be considered as a basis for prospective study protocols with a more significant number of patients that can evaluate the potential replacement role of CEM compared with MRI in the proper preoperative management of the patient with lobular neoplasia.

Conclusion

The findings of this study suggest that CEM is a reliable imaging technique in the preoperative setting of patients with lobular neoplasm, with comparable results to breast MRI for what concerns the lesion measurement and assessment of its extent and distribution (multicentric/multifocal).

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Author contributions Conceptualization: LN, OB; AR; methodology: FP and ACB; validation: ACB and GP; resources: NF; EC; writing—original draft preparation: LN and OB; writing—review and editing: all authors. Statystical analysis: SF; VB; data managment: CS; supervision, GC and EC. All authors read and approved the Final manuscript.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the local Institution (European Institute of Oncology, 20141, Milano).

Informed consent All patients have signed a written informed consent (Protocol number IEO 960).

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