


ORIGINAL ARTICLE

Treatment time interval in breast cancer: A population-based study on the impact of type and number of cancer centres attended

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Abstract

Objectives: We studied both the independent and combined effects of the places of biopsy and treatment on the treatment time interval based on a population-based study.

Methods: We analysed the proportion of patients having a treatment time interval higher than the EUSOMA recommendation of 6 weeks, as a function of the number and the type of care centres the patients attended, from a French population-based regional cohort of women treated in 2015 for an incident invasive non-metastatic cancer ($n = 505$).

Results: About 33% [95% CI: 27; 38] of patients had a treatment time interval higher than 6 weeks. About 48% of the patients underwent their biopsy and their initial treatment in the different centres. Results from multivariable analyses supported the impact of the type and number of centres attended on the proportion of time intervals over 6 weeks. This proportion was higher among patients with biopsy and treatment in different centres and among patients treated in a university hospital.

Conclusion: We pointed out the independent impact of the type and the number of care centres the patients attended, from biopsy to first treatment, on the treatment time interval, which is a well-known prognosis factor.

KEYWORDS

breast cancer, place of care, place of diagnosis, population-based study, treatment time interval

1 | INTRODUCTION

In breast cancer, as in other localisation, treatment delay is associated with decreased survival (Hanna et al., 2020; Richards et al., 1999). The treatment time interval (Weller et al., 2012), that is, the time from diagnosis to treatment, is considered as a quality-

of-care indicator. Indeed, the European Society of Breast Cancer Specialists (i.e., the EUSOMA working group) have set the standard of having at least 80% of patients with treatment time interval less than 6 weeks for quality accreditation (Biganzoli et al., 2017). In practice, treatment time interval may depend on the patients' sociodemographic characteristics (Ayrault-Piault et al., 2016; Nouws

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et al., 2019; Padilla-Ruiz et al., 2021; Redaniel et al., 2013; Reeder-Hayes et al., 2019; Robertson et al., 2004; Smith et al., 2013), the patients (Molinié et al., 2013; Padilla-Ruiz et al., 2021) and the cancer clinical characteristics (Dong et al., 2020; Nouws et al., 2019; Quillet et al., 2016), as well as the cancer treatment (Bleicher, 2018; Prakash et al., 2021). Besides the patients and cancer features, studies addressing the influence of healthcare provider on the treatment time interval have shown disparities related to the type of the treatment facility (Ayrault-Piault et al., 2016; Molinié et al., 2013; Quillet et al., 2016; Revaux et al., 2014; Robertson et al., 2004). However, although breast cancer management may rely on several healthcare providers, on possible different places, very few authors have gone beyond the first treatment centres or surgery centre to characterise the places where patients were treated. Yet studies have supported the influence of the type of the centre of origin among patients referred to a university hospital (Alves Soares Ferreira et al., 2017; Li et al., 2019). We found only two population-based studies addressing the potential effect of patients transfer between centres during the care trajectory showing longer delay in multicentric trajectory in two different care organisation settings, in the USA (Bleicher et al., 2019), more liberal with high financial constraints, and in the Netherlands (Heeg et al., 2019), where patients only access a specialist on the recommendation of their GP but with lower financial constraints. In the French context, characterised by a National Health Insurance covering most of the healthcare costs while leaving patients free in the choice of their practitioner with mild financial constraints, we found no data on the effect of changing centre during the healthcare trajectory on treatment time intervals. Yet regional data suggest that at least 25% of patients had a multicentric referral pattern for the surgery/chemotherapy sequence (Boinot et al., 2007). Thus, this study aims at testing whether the treatment time interval was influenced by both the places of diagnosis and first treatment among patients with an incident locally infiltrating breast cancer.

2 | METHODS

2.1 | Study design

Data came from the regional observational study EvaSein, which initially aimed at assessing the quality of care of breast cancer patients treated in the Midi-Pyrénées region (2.9 million of inhabitants), in the south-west of France. The database was built accordingly to French regulations (CNIL no. DR-2014-495 and CCTIRS no. 14.192). The EvaSein study has been described in detail elsewhere (Pons-Tostivint et al., 2019). Briefly, this study included all female patients cared for an incident breast cancer in the region. Patients were identified from the first discussion of their therapeutic strategy in a multidisciplinary team meeting (MTM) between 1 January and 30 April 2015. Patients with sarcoma or lymphoma histological types, or with ipsilateral or contralateral breast cancer recurrence, with bilateral breast cancer, or

with in situ cancer, or metastases were excluded. Inclusion in EvaSein was stratified according to the centre activity to allow for representativeness regarding the MTM activity. All eligible patients were included from the centres with an activity comprised between 10 and 100 patients treated over the inclusion period. Only one fourth of the eligible patients were included from the centres whose activity was higher than 100. Centres that treated less than 10 patients over the period were excluded, representing 20 patients excluded. In overall, 652 patients were included in the EvaSein study. In this work, we focused on the patients who had a locally infiltrating breast cancer with a histological confirmation, representing 519 women. Sampling weights were used in the analyses to ensure the representativeness of the analysed sample regarding the eligible patients.

2.2 | Data collected

Data were collected from medical files by trained investigators. The histological diagnosis and treatment dates were documented as well as the corresponding centres. The treatment time interval, in days, was defined from the date of the diagnosis biopsy to the date of the first treatment and categorised as up to 6 weeks or higher than 6 weeks, accordingly to EUSOMA guidelines (Biganzoli et al., 2017). In the rest of the manuscript, we will refer to treatment intervals higher than 6 weeks as 'long treatment time intervals'. From the exact places of biopsy and first treatment, the type of centre was categorised as follows: (1) university hospitals (UH) that include both comprehensive cancer centres and university centres in the region, (2) public local hospitals (PUH) that encompass all public non-university hospital in the region, (3) private local hospitals (PRH) that include all private non-university hospitals in the region, (4) other centres encompassing private radiology or gynaecology medical practices (PMP) whatever their location and (5) all centres outside the region (COR). Indeed, although the EvaSein study only included patients treated in the region, no restriction existed regarding the place of diagnosis. In addition, from the places of diagnosis and first treatment, we defined patients' management as multicentric when the patient's biopsy and first treatment centres were different and as monocentric otherwise. In addition, the patients' characteristics included age (less than 50 years [ref.], 50 to 74 years and higher than 75 years), personal history of ovarian cancer (yes and no [ref.]) and familial history of breast or ovarian cancer (yes and no [ref.]). The characteristics of the disease included the cancer clinical stage cTNM (in category of sufficient sample size where code 9 indicated missing value: cT0-1N0 [ref.], cT2-4N0-1 and cT9N0/N9), the Scarff-Bloom-Richardson (SBR) grade (I [ref.], II and III) and the tumour molecular profile (triple-negative breast cancer [PR-, ER- and HER2-], hormone-sensitive tumour [PR+/ER+/HER2+] and undefined) (Wolff et al., 2014). The patients' management characteristics included the discussion in pre-therapeutic MTM (yes and no [ref.]), having a magnetic resonance imaging (MRI) (yes and no [ref.]) and the treatment received (neoadjuvant treatment [ref.], initial surgery and non-surgery-based treatment).

2.3 | Statistical analyses

To ensure the representativeness regarding the patients with locally advanced breast cancer treated in the region, we use sample rate-based weights: All the patients from centre with an activity lower than 100 patients during the including period were included, their weight

was then 1; only one on four was included for the centre with a higher activity, their weight was then 4. The studied population characteristics were described on the weighted sample (Table 1), as well as the proportion of patients with a long treatment time interval through an origin–destination matrix based on the types of centres, by first treatment and separately for monocentric and multicentric management

TABLE 1 Population characteristics (weighted sample and %)

		Up to 6 weeks		Higher than 6 weeks		Total	
		n	Row %	n	Row %	n	Col %
Age at diagnosis	20–49 years	113	73.9	40	26.1	153	21.3
	50–74 years	295	65.6	155	34.4	450	62.7
	75 years or more	76	66.1	39	33.9	115	16.0
Personal history of ovarian cancer	No	452	67.6	217	32.4	669	93.2
	Yes	4	100.0	0	0.0	4	0.6
	Unknown	28	62.2	17	37.8	45	6.3
Family history of ovarian or breast cancer	No	261	68.9	118	31.1	379	52.8
	Yes	184	66.4	93	33.6	277	38.6
	Unknown	39	62.9	23	37.1	62	8.6
Multidisciplinary team meeting (MTM)	No	214	85.6	36	14.4	250	34.8
	Yes	270	57.7	198	42.3	468	65.2
Magnetic resonance imaging (MRI)	No	279	68.2	130	31.8	409	57.0
	Yes	133	62.7	79	37.3	212	29.5
	Unknown	72	74.2	25	25.8	97	13.5
Cancer clinical TNM stage at diagnosis	cT0-1N0	222	66.3	113	33.7	335	46.7
	cT2-4N0/N1	186	68.6	85	31.4	271	37.7
	cT9/N9	76	67.9	36	32.1	112	15.6
Tumour SBR grade	I	123	65.4	65	34.6	188	26.2
	II	249	64.7	136	35.3	385	53.6
	III	102	76.1	32	23.9	134	18.7
	Unknown	10	90.9	1	9.1	11	1.5
Molecular profile	Triple-negative	54	57.5	40	42.6	94	13.1
	Hormone-sensitive	251	69.2	112	30.9	363	50.6
	Other profile	62	72.1	24	27.9	86	12.0
	Unknown	117	66.9	58	33.1	175	24.4
Initial treatment	Neoadjuvant treatment	43	75.4	14	24.6	57	7.9
	Initial surgery	427	66.2	218	33.8	645	89.8
	Non-surgery-based treatment	14	87.5	2	12.5	16	2.2
Centre of biopsy	Private hospital (PRH)	302	74.0	106	26.0	408	56.8
	Public hospital (PUH)	71	71.7	28	28.3	99	13.8
	University hospital (UH)	40	62.5	24	37.5	64	8.9
	Private medical practice (PMP)	57	50.0	57	50.0	114	15.9
	Centre outside the region (COR)	14	42.4	19	57.6	33	4.6
Centre of initial treatment	Private hospital (PRH)	270	86.0	44	14.0	314	43.7
	Public hospital (PUH)	84	73.7	30	26.3	114	15.9
	University hospital (UH)	130	44.8	160	55.2	290	40.4
Patients' management	Multicentric	180	52.6	162	47.4	342	47.6
	Monocentric	304	80.9	72	19.2	376	52.4

(Tables 2 and 3). Both bivariate (Table 4) and multivariable (Table 5) analyses were implemented on the unweighted sample, as the university centre-specific sampling rate was already accounted for in the random intercept of the mixed models. Indeed, patients were distributed over dyads consisting in the centre of biopsy and the centre of the first treatment. Consequently, the probability of having a long treatment time interval may vary both between patients in the same dyad and between dyads. Thus, we generalised linear model with logit link function that accounted for dyads as random intercept for modelling the association between the probability of being treated with a long treatment time interval and the number and the types of centres attended. Potential confounders for adjusting the multivariable models were identified from bivariate analyses. In the multivariable analyses, we tested the influence of the places of biopsy and initial treatment, and the type of cancer management, that is, whether it was monocentric or multicentric, on the outcome, separately first (models 2, 3 and 4, respectively), then two by two (models 5 to 7) and

finally simultaneously (model 8). Regarding the risk of over-adjustment and collinearity deriving from the dependence between the place of biopsy and treatment, several adjustment strategies were tested, and we retained those with the lowest AIC between models 5 and 8. Global p values are provided for categorical variables from Wald tests. All missing data on the final sample were coded (code 9) to avoid excluding the corresponding patients. We considered 0.2 and 0.05 as statistical significance thresholds in respectively bivariate and multivariable analyses. The model selection was based on the AIC criterion. All analyses were done using STATA software (StataCorp LP, College Station, TX, version 15.1).

3 | RESULTS

From the 519 eligible patients, we excluded two patients with missing date of biopsy, nine with missing place of biopsy and three without any data regarding the treatment and consequently the place of treatment. This resulted in a sample used for the analyses of 505 patients whose characteristics are presented in Table 1 after accounting for the sampling design. The patients were mainly aged between 50 and 74 years, without personal history of ovarian cancer nor family history or either ovarian or breast cancer. They had more frequently less advanced cancer (cT0-1N0), SBR grade II. Regarding their care trajectory, most patients had no MRI but have been discussed in pretherapeutic MTM. They were mainly initially treated by surgery. The most frequent place of biopsy and initial treatment was PRH. More than one in two patients had a monocentric trajectory. In overall, we estimated a weighted proportion (% [95% CI]) of the patients having a long treatment time interval of about 33 [27; 38] %.

The origin-destination matrixes of the weighted number and proportion of patients having a long treatment time interval for each type

TABLE 2 Proportion of patients (with 95%CI) with a treatment time interval higher than 6 weeks by first treatment, among the patients with monocentric management

Centre of cancer biopsy and treatment (n = 374)		
	Surgery	Non-surgical treatment
Private hospital (PRH)	13.9 [10.0; 19.0] (n = 223)	6.7 [0.8; 38.6] (n = 15)
Public hospital (PUH)	21.9 [13.4; 33.7] (n = 64)	25.0 [5.7; 64.9] (n = 8)
University hospital (UH)	46.1 [21.5; 72.8] (n = 52)	0 [NA] (n = 12)

Note: (weighted sample).

TABLE 3 Proportion of patients (with 95%CI) with a treatment time interval higher than 6 weeks by first treatment and type of centre dyads, among the patients with multicentric management

		Centre of initial treatment		
		Private hospital (PRH)	Public hospital (PUH)	University hospital (UH)
First treatment surgery (weighted n = 306)				
Centre of biopsy	Private hospital (PRH)	10.8 [4.1; 25.7] (n = 37)	14.3 [3.5; 43.1] (n = 14)	59.2 [40.1; 76.0] (n = 108)
	Public hospital (PUH)	16.7 [2.2; 63.7] (n = 6)	66.7 [15.0; 95.8] (n = 3)	50.0 [12.1; 87.9] (n = 16)
	University hospital (UH)	No observation		NA
	Private medical practice (PMP)	31.2 [13.5; 57.0] (n = 16)	38.1 [20.2; 60.0] (n = 21)	64.3 [37.3; 84.5] (n = 56)
	Centre outside the region (COR)	25.0 [6.2; 62.7] (n = 8)	100 [NA] (n = 1)	80.0 [30.4; 97.3] (n = 20)
Non-surgical first treatment (weighted n = 38)				
Centre of biopsy	Private hospital (PRH)	0 [NA] (n = 6)	No observation	80.0 [16.6; 98.8] (n = 5)
	Public hospital (PUH)	0 [NA] (n = 1)	No observation	0 [NA] (n = 1)
	University hospital (UH)	No observation	No observation	NA
	Private medical practice (PMP)	0 [NA] (n = 2)	33.3 [3.6; 87.0] (n = 3)	43.7 [10.5; 83.7] (n = 16)
	Centre outside the region (COR)	No observation	No observation	0 [NA] (n = 1)

Note: (weighted sample).

TABLE 4 Bivariate analyses of the factors associated with being treated in a time interval higher than 6 weeks

Bivariate analyses		OR	[95% CI]	
Age at diagnosis	20–49 years	Ref.		0.040
	50–74 years	2.35	[1.19; 4.67]	0.014
	75 years or more	2.46	[1.09; 5.56]	0.031
Personal history of ovarian cancer	No	Ref.		
	Yes		Not estimable	
	Unknown	1.30	[0.50; 3.37]	0.590
Family history of ovarian or breast cancer	No	Ref.		0.321
	Yes	0.72	[0.41; 1.27]	0.257
	Unknown	1.32	[0.60; 2.92]	0.492
Multidisciplinary team meeting (MTM)	No	Ref.		
	Yes	2.72	[1.53; 4.86]	0.001
Magnetic resonance imaging (MRI)	No	Ref.		0.982
	Yes	1.04	[0.60; 1.81]	0.881
	Unknown	1.06	[0.47; 2.41]	0.881
Cancer clinical TNM stage at diagnosis	cT0–1N0	Ref.		0.304
	cT2–4N0/N1	0.78	[0.44; 1.36]	0.376
	cT9/N9	1.35	[0.70; 2.64]	0.373
Tumour SBR grade	I	Ref.		0.172
	II	0.87	[0.51; 1.49]	0.616
	III	0.43	[0.20; 0.94]	0.035
	Unknown	0.47	[0.04; 5.18]	0.535
Molecular profile	Triple-negative	Ref.		0.398
	Hormone-sensitive	0.69	[0.33; 1.43]	0.324
	Other profile	0.40	[0.14; 1.14]	0.087
	Unknown	0.72	[0.32; 1.61]	0.424
Initial treatment	Neoadjuvant treatment	Ref.		0.331
	Initial surgery	1.76	[0.67; 4.61]	0.248
	Non-surgery-based treatment	0.73	[0.11; 5.03]	0.753
Centre of biopsy	Private hospital (PRH)	Ref.		0.082
	Public hospital (PUH)	1.58	[0.63; 3.99]	0.332
	University hospital (UH)	3.04	[0.33; 27.62]	0.324
	Private medical practice (PMP)	3.11	[1.18; 8.25]	0.022
	Centre outside the region (COR)	5.06	[1.02; 25.08]	0.047
Centre of initial treatment	Private hospital (PRH)	Ref.		0.000
	Public hospital (PUH)	2.45	[1.26; 4.78]	0.009
	University hospital (UH)	9.03	[4.35; 18.74]	0.000
Patients' management	Multicentric	Ref.		
	Monocentric	0.34	[0.17; 0.69]	0.003

of dyad of biopsy and treatment centres are presented in Tables 2 and 3 for respectively monocentric and multicentric management. In overall, the most frequent type of dyads was observed among patients initially treated with surgery with monocentric patients in PRH/PRH dyads (31%) and with multicentric dyads in PRH/UH dyads (15%). Among patients with monocentric management (Table 2), we

observed lower proportions of long treatment time intervals in PRH for those receiving surgery as first treatment and in PRH a UH for those receiving first non-surgical treatment. Among patients with multicentric management (Table 3), the proportion of long treatment time intervals was in average the lowest in dyads involving PHR for biopsy and treatment for patients receiving first surgery. For those receiving

TABLE 5 Multivariable analyses of the association between being treated in a time interval higher than 6 weeks and the types and number of centres attended during the care trajectory

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8	
	OR	[95% CI]	OR	[95% CI]	OR	[95% CI]	OR	[95% CI]	OR	[95% CI]	OR	[95% CI]	OR	[95% CI]	OR	[95% CI]
Centre of biopsy																
Private hospital (PRH)	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Public hospital (PUH)	1.61	[0.68; 3.81]	1.61	[0.68; 3.81]	1.12	[0.42; 2.97]	1.12	[0.42; 2.97]	1.12	[0.42; 2.97]	1.99	[0.89; 4.46]	1.99	[0.89; 4.46]	1.19	[0.44; 3.19]
University hospital (UH)	1.71	[0.25; 11.97]	1.71	[0.25; 11.97]	0.38	[0.08; 1.71]	0.38	[0.08; 1.71]	0.38	[0.08; 1.71]	2.81	[0.48; 16.41]	2.81	[0.48; 16.41]	0.46	[0.09; 2.40]
Private medical practice (PMP)	3.50	[1.39; 8.79]	3.50	[1.39; 8.79]	2.26	[0.95; 5.39]	2.26	[0.95; 5.39]	2.26	[0.95; 5.39]	2.07	[0.82; 5.20]	2.07	[0.82; 5.20]	2.02	[0.80; 5.14]
Centre outside the region (COR)	3.55	[0.78; 16.03]	3.55	[0.78; 16.03]	2.33	[0.59; 9.17]	2.33	[0.59; 9.17]	2.33	[0.59; 9.17]	2.07	[0.49; 8.82]	2.07	[0.49; 8.82]	2.08	[0.51; 8.50]
Centre of initial treatment																
Private hospital (PRH)	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Public hospital (PUH)	2.62	[1.32; 5.19]	2.62	[1.32; 5.19]	2.14	[0.86; 5.33]	2.14	[0.86; 5.33]	2.14	[0.86; 5.33]	2.45	[1.26; 4.77]	2.45	[1.26; 4.77]	2.06	[0.83; 5.10]
University hospital (UH)	7.47	[3.44; 16.21]	7.47	[3.44; 16.21]	7.62	[3.39; 17.12]	7.62	[3.39; 17.12]	7.62	[3.39; 17.12]	5.49	[2.50; 12.04]	5.49	[2.50; 12.04]	6.69	[2.70; 16.57]
Patients' management																
Multicentric	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Monocentric	0.34	[0.17; 0.66]	0.34	[0.17; 0.66]	0.37	[0.17; 0.78]	0.37	[0.17; 0.78]	0.37	[0.17; 0.78]	0.52	[0.28; 0.95]	0.52	[0.28; 0.95]	0.79	[0.36; 1.73]
Patient-level intercept	0.08	[0.03; 0.20]	0.06	[0.02; 0.16]	0.05	[0.02; 0.13]	0.13	[0.05; 0.34]	0.05	[0.02; 0.13]	0.10	[0.04; 0.28]	0.08	[0.03; 0.21]	0.06	[0.02; 0.17]
Random component																
Between-cluster variance	1.01	[0.63; 1.62]	0.79	[0.42; 1.48]	0.51	[0.22; 1.18]	0.77	[0.43; 1.36]	0.41	[0.14; 1.15]	0.64	[0.32; 1.29]	0.45	[0.18; 1.11]	0.41	[0.15; 1.13]
Intra-class correlation coefficient	0.24	[0.11; 0.44]	0.16	[0.05; 0.40]	0.07	[0.01; 0.30]	0.15	[0.05; 0.36]	0.05	[0.01; 0.29]	0.11	[0.03; 0.34]	0.06	[0.01; 0.27]	0.05	[0.01; 0.28]
Akaike's information criterion	505.12		505.37		485.41		498.15		485.68		500.88		482.90		487.33	

Note: Models adjusted for age, grade and having been discussed in MTM prior treatment.

first non-surgical treatment, it corresponds to the type of centres dyad where treatment occurred in PRH. In overall, results from Tables 2 and 3 show that for a given type of dyads, the average proportion of long treatment time intervals is almost always lower in monocentric than in multicentric management. But, and although it is likely not statistically significant, a lower proportion of long treatment intervals have been observed among patients with multicentric management in PRH centres than among their counterparts with monocentric management. At the exception of patients initially treated by non-surgical treatment with monocentric management, patients from dyads involving UH as centre of treatment had in average the highest proportion of long treatment time intervals.

From Table 4, the results from bivariate analyses show that having a long treatment time interval was associated with patients' age at diagnosis, the discussion of patient case in MTM, the tumour SBR grade, whether patients had a multicentric management and the type of the centres of biopsy and of first treatment. Table 5 presents the results of the multivariable analyses, all adjusted for the covariates identified from the previous step. From model 1, we observed that there was a statistically significant variation in the probability of having a long treatment time interval between biopsy and treatment centres dyads, representing almost one fourth of the whole variability of the outcome (ICC [95% CI] = 0.24 [0.11; 0.44]), not explained by the characteristics of patients and their cancer (model 1). The results from models 2 to 4 confirm the association between the probability for treatment interval to be higher than 6 weeks and the centres of biopsy and treatment, and the type of management, separately. Models 5 to 8 test several combinations of simultaneous adjustments for biopsy and treatment centres and type of management, showing the lowest AIC for model 7. According to this model, the treatment interval length was independently affected by both the place of treatment and whether the patient underwent biopsy and treatment in the same place or not. In comparison with model 1 ICC (0.24 [0.11; 0.44]), these centres-level characteristics explain most of the inter-dyad variations in outcome (ICC = 0.06 [0.01; 0.27]).

4 | DISCUSSION

In this study, we estimated that about 33% [27; 38] of women treated for locally infiltrating breast cancer in the region had a long treatment time interval, that is, treatment time interval higher than 6 weeks. About 48% of the patients underwent their biopsy and their initial treatment in the different centres. The most frequently observed dyad corresponded to patients having both their biopsy and their treatment in the same private hospital (PRH/PRH). In average, dyads with PRH as treatment centre had, in average, the lowest proportion of long treatment time interval. In average, the highest proportion of long treatment time intervals was observed in dyads with UH as treatment. However, these poor results in UH may likely translate the large weight of patients referred to UH from other centres, representing about 78% of the patients treated in UH. Results from multivariate models support the impact of both the number and the type of

centres attended by patients for their biopsy and treatment on treatment time interval that is not explained by differences in case mix. Time intervals higher than 6 weeks were more frequent among patients with multicentric management and among those treated elsewhere than in private hospitals.

The main strength of our study is to provide an inclusive approach of the first care trajectory steps by addressing the influence of both places of biopsy and treatment, as well as of changing location between these steps. Up to this study, there were no data in France describing the centre of treatment and the centre of biopsy to investigate their influence of patients' treatment time interval. This was done thanks to the nature of the EvaSein study, which was designed to assess the quality of care of patients treated for a primary breast cancer in the region. The retrospective data collection from medical files induced a dependence regarding the quality of the medical record keeping. In the whole EvaSein population study, only 8% of had missing data on clinical or pathological stage or on the histological confirmation. The analysed sample represented more than 97% of the 519 patients with a histological confirmed non-metastatic and non-in situ invasive breast cancer. The inclusion of the only patients whose management was discussed in MTM beyond an activity threshold higher than 10 patients during the inclusion period may have hampered the representativeness of our sample regarding the locally infiltrating breast cancer patients treated in the region. However, the small number of concerned cases ($n = 20$) limits this bias. In this study, we focused on a regional sample covering the French former region of Midi-Pyrénées (about 2 million of inhabitants in 2014), in the south-west of the mainland territory. However, it is unlikely that the health-care organisation differed from what would be observed at the national level. Indeed, since 2003, the implementation of the successive national cancer plans has provided efforts for improving the harmonisation of clinical practices and reducing both social and territorial inequalities in cancer management. Since 2009, an official authorisation must be obtained by centre for managing cancer patients, notably based on a minimal level of activity for some specific treatments, or cancer localisations. Thus, the organisation of cancer care provision is centralised and relayed at the regional level by the Regional Health Agencies.

At the international level, a monocentric Mexican study gives a value between 18% and 42% for respectively treatment time interval higher than 45 days and 30 days among patients diagnosed between 2005 and 2012 (Flores-Balcázar et al., 2020). In a study over patients from the Portuguese Institute of Oncology of Porto diagnosed in 2012, the authors estimated a median [IQR] treatment time interval of 44 [31; 57] days, which means that between 50% and 75% of the patients have treatment time intervals longer than 6 weeks (Nouws et al., 2019). From a monocentric US study, about 78% of the patients newly diagnosed and initiating surgery between 2009 and 2015 had a time interval lower than 45 days (Dong et al., 2020). More recent data from the Netherlands Cancer Registry concerning patients diagnosed in 2014–2016 found median [IQR] time intervals between diagnosis and surgery varying between 22 [17; 29] and 43 [33; 58] depending on the type of surgery and the occurrence of a transfer of hospital

between diagnosis and treatment (Heeg et al., 2019). In this study, our results provide an estimate of about one third of the sample having a treatment time interval higher than 6 weeks, which is beyond the EUSOMA objective of 20% (Biganzoli et al., 2017). The worst results were observed for dyads with UH as treatment centres which had in average, whatever the patients' management, the highest proportion of long treatment time intervals. However, these poor results in UH translate at least partially the large weight of patients referred to UH from other centres, representing about 78% of the patients treated in UH. Considering that EUSOMA time interval is computed from the first diagnosis exam whereas we use the biopsy as starting point—occurring later in the care trajectory, our results may underestimate the true proportion of patients managed over the EUSOMA guidelines by reflecting only the more deviant patients' trajectories. Despite this limitation, our results are consistent with previous French observations on breast cancer patients' treatment time intervals. Previous results from a population-based cancer registry study over French women diagnosed in 2003 estimated that 19.4% had a time interval higher than 2 months between the first radiological detection and the start of the treatment France (Molinié et al., 2013). Among women diagnosed in 2007, another French population-based registry estimated a median [IQR] treatment time interval of 31 [23; 42] days, which was 1 day shorter when the biopsy occurred in the same time than the first imaging procedure (Ayrault-Piault et al., 2016). Similar estimates were provided by the French National Cancer Institute among patients diagnosed in 2010 (Ledésert et al., 2012). In overall, the dyads with UH as centre of treatment had, in average, higher proportions of long treatment time intervals.

Regarding of the impact of places of care on the treatment time intervals, our results are in line with those recently described in the Netherlands (Heeg et al., 2019) and in the USA (Bleicher et al., 2019), supporting that patients who are diagnosed and treated in different centres may have increased treatment time interval. The first study included patients diagnosed between 2014 and 2016 among which 8.5% transferred hospital between diagnosis and first treatment. Transferred patients had a median treatment time interval 9 days longer than non-transferred patients regarding the time from diagnosis to surgery (Heeg et al., 2019). The second study included patients initiating treatment between 2004 and 2015 with an increasing proportion of transfer between diagnosis and first treatment from 29% in 2004 to almost 40% in 2015. Transferred patients had longer treatment time intervals than their non-transferred counterparts, with and increased median times to surgery, chemotherapy, radiotherapy and endocrine therapy of respectively 6, 7, 9 and 10 days (Bleicher et al., 2019). To our knowledge, these are the only studies to address both the impact of the places of diagnosis and treatment on the time to treatment initiation. These studies were done in two different contexts of healthcare organisation: more liberal with high financial constraints in the USA and with lower financial constraints and more constraints on patients as they only access a specialist on the recommendation of their GP but with lower financial constraints. In the French context, characterised by a National Health Insurance covering most of the healthcare costs while leaving patients free in the choice

of their practitioner with mild financial constraints, we found no data on the effect of changing centre during the healthcare trajectory on treatment time intervals. Indeed, our results showed that this delay may be independently affected by the places of diagnosis and first treatment initiation. In our study, almost 48% of our sample moved between diagnosis to first treatment. Compared with these patients, those who stayed in the same centres were half as likely to have a treatment interval longer than 6 weeks. This may be due to higher proportion of long treatment time interval, that is, longer than 6 weeks, among patients treated in UH in combination with the fact that most of the patients with a multicentre management were treated in UH.

5 | CONCLUSION

Finally, our study supports the influence of both the locations of biopsy and initial treatment on the treatment time interval among non-metastatic and non-in situ invasive breast cancer patients. Our results pointed out shorter time intervals when both biopsy and initial treatment were done in the same place and thus the relevance of taking into account the characteristics of all centres wherein patients are treated while studying their health care trajectories. As our analyses were adjusted for the characteristics of the patients' care trajectory up to the treatment initiation, the centres-related disparities in treatment time intervals are unlikely to translate centres-related differences in the compliance to guidelines. Each stage of the care process takes time, and the real challenge is probably to differentiate time and delay, the latter negatively affecting survival. Further studies are needed to better understand the determinants of the patients' care trajectory, especially the role of the healthcare providers, and how to deal with trajectory that may be at risk of suboptimal quality of care and the cancer outcome.

HUMAN STUDIES AND SUBJECTS

The EVASEIN project was declared to the Commission Nationale de l'Informatique et des Libertés (no. DR-2014-495) and approved by national ethics committee (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé). This article does not contain any studies with human participants or animals performed by any of the authors. The study is based on data collected from medical files. For this type of study, formal consent is not required.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

DATA AVAILABILITY STATEMENT

Data are available upon request. Please contact the EvaSein project coordinators at bauvin@onco-occitanie.fr, pascale.grosclaude@inserm.fr and laetitia.daubisse-marliac@inserm.fr.

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