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Original Article

Survival impact of primary site surgery on metastatic breast cancer patients at diagnosis

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ABSTRACT

Background. – Stage IV breast cancer was considered to be an incurable disease. Primary site surgery used to be reserved to control local complications. In the present study, we compared the survival of women who received therapeutic breast surgery for stage IV breast cancer at initial diagnosis to the survival of those who did not.

Methods. – Two French hospitals databases were retrospectively screened from 2005 to 2012. We identified all women with metastatic breast cancer at diagnosis. Patients' data were obtained by a review of their medical history. Data were analyzed according the four breast cancer subtypes (luminal A, luminal B, her 2 and triple negative).

Results. – One hundred thirty nine women were included, of whom 69 had primary site surgery. TNM stage and phenotypes of breast cancer were comparable in the two groups but operated women were younger than women who did not ($p < 0.0001$). Average follow-up was 31 ± 23.3 months [1–97]. Through logistic regression, we observed that tumor resection decreased death hazard ratio vs no surgery: HR 0.33, 95% CI [0.16–0.66] $p = 0.001$. In the surgery group, there was no survival difference if women received chemotherapy ($p = 0.23$). There were more patients with only one metastatic site in the surgery group ($p = 0.002$) and they had been more treated with systemic therapy. When we compared tumor phenotypes individually, surgery increased survival on luminal A breast cancer patients ($p < .0001$).

Conclusion. – Women with luminal A breast cancer and synchronous metastasis seemed to benefit from surgery. The development of a national reporting system or registers for outcomes would facilitate the investigation of the disease across a multitude of aspects of stage IV breast cancer.

Introduction

Breast cancer is the first cancer-affecting women in developed countries. Among the women affected, 3–10% has distant metastases at initial presentation. The survival of breast cancer patients presenting with metastases at diagnosis has improved [1]. It is still considered as an incurable disease without any consensual standard treatment. Primary site surgery has been reserved for symptomatic wound complications to prevent or control local complications. It is generally admitted in this case that tumor excision does not increase survival. Palliative systemic therapy (hormonal, chemotherapy or targeted therapy) is started according to age, comorbidities and symptoms. Therapeutic strategy is then adapted to disease response.

Khan et al. [2] were the first who asked: "Does aggressive local therapy improve survival in metastatic breast cancer?". They retrospectively included 16,023 patients and concluded that women treated with primary cancer surgical resection with free margins had superior survival with a hazard ratio of 0.61 (95%CI 0.58–0.65). The available literature regarding this subject comprises retrospective observational studies. In 2006, two studies [3,4] with respectively 317 and 224 patients showed contradictory results. In 2007, Fields et al. [5] reported the data of 409 patients from 1988 to 2003. They concluded that patients who underwent surgical resection had longer median survival when compared to patients who did not undergo surgery (HR 0.53, 95%CI [0.42–0.67]). The largest study was reported by Gnerlich et al. [6] (16,023 patients), Their results showed that extirpation of the primary

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breast cancer tumor in patients with stage IV disease was associated with a marked reduction in risk of dying (HR 0.63, 95% CI [0.60–0.66]) but location of metastatic sites and use of chemotherapy or hormonal therapy were not recorded in the database. In 2008, Shien et al. [7] in a study including 344 patients managed from 1962 to 2007, showed an increase of survival in the surgery group when patients were young (under 50 years old). In 2009, three studies [8–10] did not find any positive effect of surgery on overall survival in patients with primary metastatic breast cancer whereas Ruiterkamp et al. [11] found in their cohort (728 patients managed from 1993 to 2004) that surgery appeared to be an independent prognosis factor.

Nowadays, in the era of molecular signature, we know that there are several phenotypes of breast cancer. Their prognoses are different. The treatment proposed must be adapted to each subtype. Neuman et al. [12] in 2010 was the first who searched for a relationship between surgery in stage IV breast cancer patients and tumor molecular subtype.

In our study, we aimed to assess differences in characteristics and outcomes of patients who received therapeutic breast surgery for stage IV breast cancer at initial diagnosis (surgery group) compared to patients who did not (no surgery group). The major issue of our study was to target which patient could take advantage of primary site surgery.

Material and methods

Study population

In our descriptive study, two French hospitals databases (university teaching hospital of Tours and regional hospital of Orléans) were retrospectively screened to identify all women with metastatic breast cancer at diagnosis. Women were included from January 1st, 2005 to December 31st, 2012. Patients' data were obtained by a review of their medical history. We chose not to select patients diagnosed before 2005 to have a uniform cohort. Indeed, all patients could have her2 status testing and if needed, benefit from treatment with targeted therapy (Trastuzumab). Patients with personal history of breast cancer or another primary cancer were not included because of the impossibility to affirm which primary tumor led to the metastatic disease.

Data collected

Medical records were reviewed for menopausal status, body mass index (BMI) and date of diagnosis. Tumor characteristics were also recorded. Clinical stage was established following the TNM stage system [13] (T1 < 2 cm, T2 2–5 cm, T3 >5 cm, T4 inflammatory or skin/thoracic wall involvement; N1 axillary lymph node N2 fixed axillary lymph node N3 supraclavicular or controlateral node involvement). We recorded also if there were several tumors in the same breast or on the two sides. Thanks to hormonal receptor presence and her2 status, we grouped tumors in subtypes [14–17]. Four phenotypes were determined: luminal A (hormonal receptor positive, her status negative), luminal B (oestrogene or progestogen receptor positive, her2 status positive), her2 overexpression (hormonal receptor negative and her 2 status positive) and triple negative (hormonal receptor and her2 status negative). In case of herceptest ++, a FISH amplification technique was performed.

Metastases were classified in three different major sites: bone metastases, visceral metastases and brain metastases. Visceral metastases included lung, pleura, mediastinal and liver metastases. We choose to separate the brain metastases because of their own bad prognosis. Treatments received were compared: primary cancer surgery, chemotherapy (before and/or after surgery), hormonal therapy, Trastuzumab and radiation to primary site. Surgery was classified in time of surgery (before systemic therapy if metastatic was unknown), conservative or not, free or positive margins and axillary lymph node exploration.

Follow up was performed according to consultations or hospitalisations. In the cases when we did not have any recent data, we called general practitioner.

Statistical analysis

Data were analyzed using R2.13.1 (http://www.cran.r-project.org/). For numerical data, results are reported as mean and median values ± standard deviation (SD). The Fischer exact and χ^2 chi-square tests were used to compare categorical values. Student tests were used for continuous values. We considered $p < 0.05$ to be statistically significant. For the survival analysis, data on surviving patients without disease recurrence or progression were censored on the date of their last follow-up examination. Survival curves were generated (in months) using the method of Kaplan–Meier, based on the interval from the date of diagnosis to the date of last contact or death from any cause. The log-rank test was used to compare differences between survival curves.

Results

Population characteristics (Table 1)

139 patients with stage IV breast cancer at initial presentation were included in our study, of them, 70 were recorded in the university hospital center of Tours and 69 in the Orléans Hospital. This amounts to 2.6% of breast cancers diagnosed in the study period in these hospitals. The study population characteristics are provided in Table 1.

In our cohort, 69 patients (49.6%) had primary site surgery, of whom 22 (31.9%) had unknown metastatic disease at the time of surgery. They were found to have stage IV breast cancer by imaging procedures performed in the post-operative period.

Operated patients were younger ($p < .0001$) than patients of the no surgery group but had comparable BMI ($p = 0.38$). There were more patients who were under 40 years old in the surgery group ($p = .0006$), and more patients who were over 75 years old in the no

Table 1
Population characteristics.

	All patients ($n = 139$)	With surgery ($n = 69$)	Without surgery ($n = 70$)
Mean age (year ± SD, range)	62.7 ± 15.4 [25–94]	56 ± 15.4 [25–93]	67.9 ± 13.7 [41–94]
<40 years	10 (7.1%)	10 (14.5%)	0
≥75 years	37 (26.6%)	12 (17.4%)	25 (35.7%)
Mean body mass index (kg/m^2)	26.9 ± 5.9 [16–56.2]	26.5 ± 4.8 [19.6–40.2]	27.4 ± 7.2 [16–56.2]
During pregnancy	1	1	0
Menopausal status			
Postmenopausal	105 (75.5%)	44 (63.8%)	61 (87.1%)
Premenopausal	34 (24.4%)	25 (36.2%)	9 (12.8%)

Table 2
Cancer characteristics.

	All patients ($n = 139$)	Patients with surgery ($n = 69$)	Without surgery ($n = 70$)
Multifocal	26 (18.7%)	20 (28.9%)	6 (8.6%)
Inflammatory	35 (25.2%)	18 (26.1%)	17 (24.3%)
Bilateral breast cancer	6 (4.3%)	2 (2.9%)	4 (5.7%)
Clinical size (mm)	73.1 ± 50.7 [0–300]	74.5 ± 44.1 [0–180]	71.4 ± 56.4 [0–300]
Radiological size (mm)	60.6 ± 47.7 [0–300]	57.8 ± 38.3 [8–180]	63.6 ± 56.3 [0–300]
T status			
T0	2 (1.4%)	0 (0%)	2 (2.8%)
T1	7 (5%)	5 (7.2%)	2 (2.8%)
T2	43 (30.9%)	22 (31.8%)	21 (30%)
T3	23 (16.5%)	13 (18.8%)	10 (14.3%)
T4	64 (46%)	29 (42%)	35 (50%)
N status			
N0	48 (34.5%)	35 (50.7%)	13 (18.6%)
pN0		5 (19.2%)	
N1	53 (38.1%)	29 (29%)	24 (34.3%)
N2	20 (14.4%)	2 (2.9%)	18 (25.7%)
N3	7 (5%)	2 (2.9%)	5 (7.1%)
Invasive ductal carcinoma	86 (61.9%)	47 (68.1%)	39 (55.7%)
Invasive lobular carcinoma	18 (12.9%)	9 (13%)	9 (12.8%)
Mixed	19 (13.7%)	6 (8.7%)	13 (18.6%)
Poorly differentiated	16 (11.5%)	7 (7.2%)	9 (12.8%)
ER status positive	108 (77.7%)	56 (81.1%)	52 (74.3%)
PR status positive	91 (65.5%)	56 (81.1%)	35 (50%)
Her2neu status positive	28 (20.1%)	15 (21.7%)	13 (18.6%)
Phenotype			
Luminal A	94 (67.6%)	50 (72.4%)	44 (62.8%)
Luminal B	17 (12.2%)	7 (10.1%)	10 (14.3%)
Triple negative	17 (12.2%)	4 (5.8%)	13 (18.6%)
Her	11 (7.9%)	8 (11.6%)	3 (4.3%)
Number of sites			
1	78 (56.1%)	48 (69.5%)	30 (42.8%)
2	43 (30.9%)	17 (24.3%)	26 (37.1%)
3	16 (11.5%)	4 (5.7%)	12 (17.1%)
4	1 (0.7%)	0	1 (1.4%)
5	1 (0.7%)	0	1 (1.4%)
Bone metastasis	99 (71.2%)	49 (51.1%)	50 (71.4%)
Visceral metastasis	80 (57.6%)	30 (43.5%)	50 (71.4%)
Brain metastasis	8 (5.8%)	3 (4.3%)	5 (7.1%)
Chemotherapy	91 (65.5%)	53 (76.8%)	38 (54.2%)
Hormonal therapy	97 (69.8%)	56 (81.1%)	41 (58.6%)
Trastuzumab	19 (13.7%)	10 (14.5%)	9 (12.8%)
Radiation to primary	61 (43.9%)	55 (79.7%)	6 (8.6%)

surgery group ($p = .003$). There were more postmenopausal patients in the no surgery group ($p = .001$).

Disease characteristics (Table 2)

The histological types were invasive ductal carcinoma, invasive lobular carcinoma, mixed or poorly differentiated. Their repartition was equivalent between the two groups ($p = 0.13$). There were as many inflammatory tumors ($p = 0.8$) and bilateral tumors ($p = 0.7$) in the surgery group as in the non surgery group. Concerning the tumor's size, clinical ($p = 0.72$) and radiological mensurations ($p = 0.48$) were comparable between the two groups. Estrogen receptor expression ($p = 0.33$), her2 neu status ($p = 0.64$) and cancer phenotype type ($p = 0.22$) were also comparable in the two groups. There were more multifocal tumor in the surgery group ($p = .002$) and more progestogen receptor expression ($p < .0001$) as compared to there were in non operated on patients.

Metastases characteristics are described in Table 2. For overall population, 54 (38.8%) patients had only bone metastasis, 23 (16.5%) only visceral metastasis and one patient (0.7%) had only one cerebral metastasis. In the surgery group, 34 patients (49.3%) had only bone metastasis, 13 (18.8%) only visceral metastasis and one patient (1.4%) only one cerebral metastasis. There were more patients with one metastatic site in the surgery group ($p = 0.002$).

Treatments

Primary site surgery concerned 69 patients (49.6%) 22 of whom (29%) had breast conservative surgery. The margins were positive for 7 patients (31.8%). Fifty five women (79.7%) had an associated axillary surgery (axillary lymph node dissection total, partial lymph node resection or sentinel lymph node biopsy) with a mean number of lymph nodes resected of 11 ± 6 [1–25] and a mean number of positive axillary lymph nodes of 4 ± 5 [0–20]. Systemic treatments are described in Table 2.

In the surgery group, 26% ($n = 18$) had chemotherapy before surgery, 33% ($n = 23$) after surgery and 17% ($n = 12$) had both. For Luminal A patients, women who had surgery to primary received more chemotherapy (70% for the surgery group vs 48% for the non surgery group) and more hormonotherapy than non operated patients ($p = 0.03$, $p = 0.01$ respectively) but radiation to primary was equivalent $p = 0.45$.

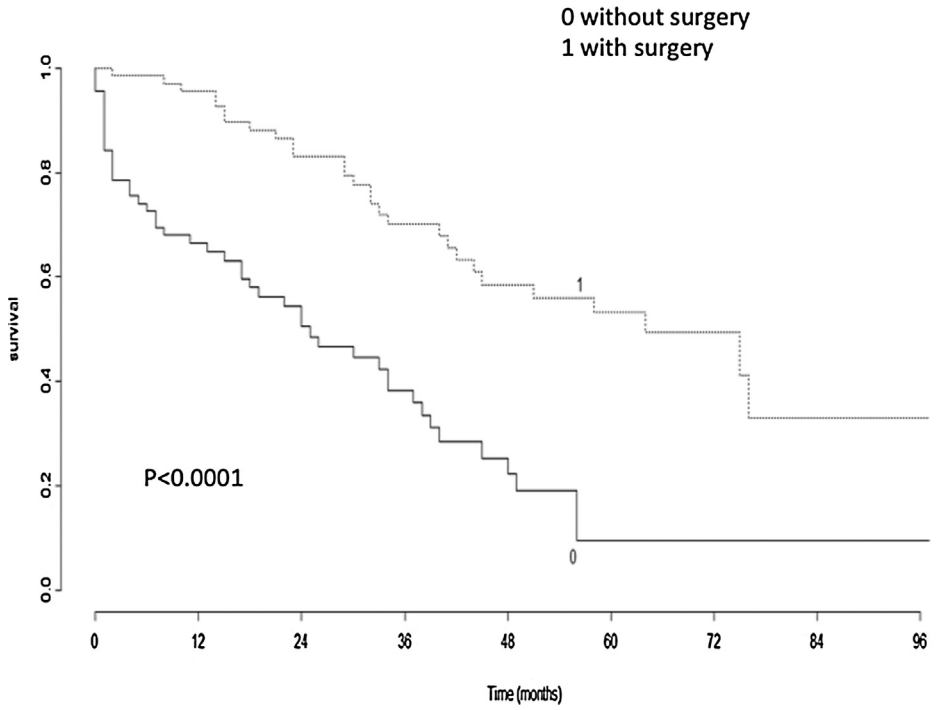

Fig. 1. Kaplan–Meier survival curves of all patients comparing surgery to no surgery.

Survival

Overall survival was 46.1% for all patients. Average follow-up was 31 ± 23.3 months [1–97] for all patients, 40.7 ± 22.6 months [2–97] for the surgery group and 21.3 ± 19.8 months [0–97] for the non surgery group. 75 patients (53.9%) died among whom 28 (37.3%) had primary site surgery. Overall survival was 59.4% in the surgery group versus 32.8% for the no surgery group ($p < .0001$). Fig. 1 shows the Kaplan–Meier survival curves of all patients comparing surgery to no surgery. Through logistic regression, we observed that tumor resection decreases death hazard ratio vs no surgery: HR 0.33, 95% CI [0.16–0.66] $p = .001$.

For overall population, survival was statistically different depending on tumor phenotype (Fig. 2) $p < .0001$. The mortality rate was 52% for luminal A phenotype (49/94), 35% for luminal B phenotype (6/17), 55% for her2 phenotype (6/11) and 82% for triple negative phenotype (14/17).

In the surgery group, survival difference did not statistically vary with age for patients (under 40 years old $p = 0.76$ or over 75 years old $p = 0.72$), menopausal status ($p = 0.12$), cancer characteristics (T stage $p = 0.3$, N stage $p = 0.32$, inflammatory $p = 0.68$, multifocality $p = 0.84$, eostrogen receptor $p = 0.08$, progestogen $p = 0.24$, her2neu status $p = 0.16$, lymphovascular invasion $p = 0.44$ or tumor phenotype $p = 0.22$). Mortality rate was 36% for luminal A subtype (18/50), 28.5% for luminal B subtype (2/7), 75% for her2 subtype (6/8) and 50% for triple negative subtype (2/4).

Concerning the surgical procedure, survival did not depend on breast conservative surgery or mastectomy ($p = 0.64$), free margins

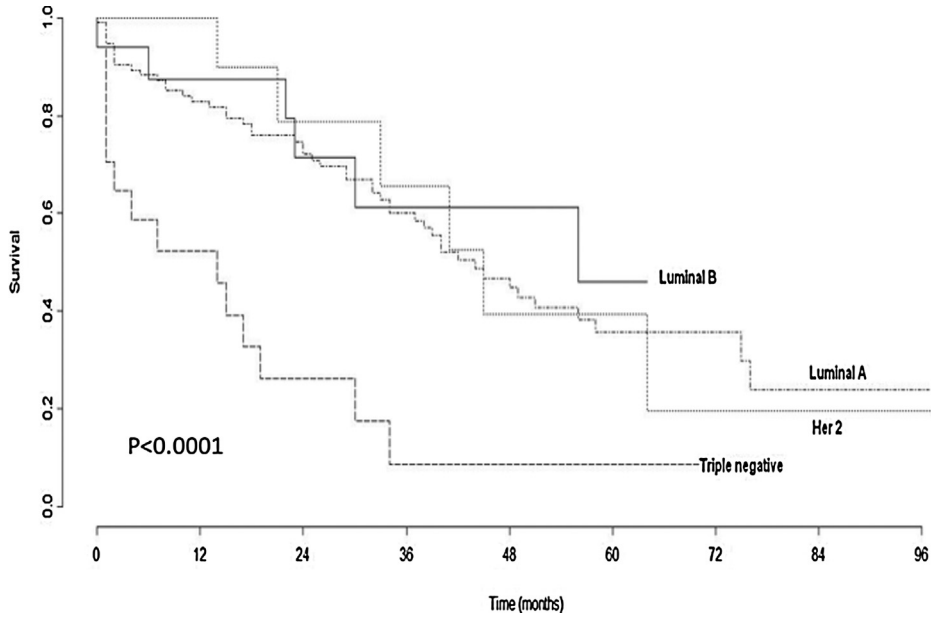

Fig. 2. Overall survival according to breast cancer phenotype.

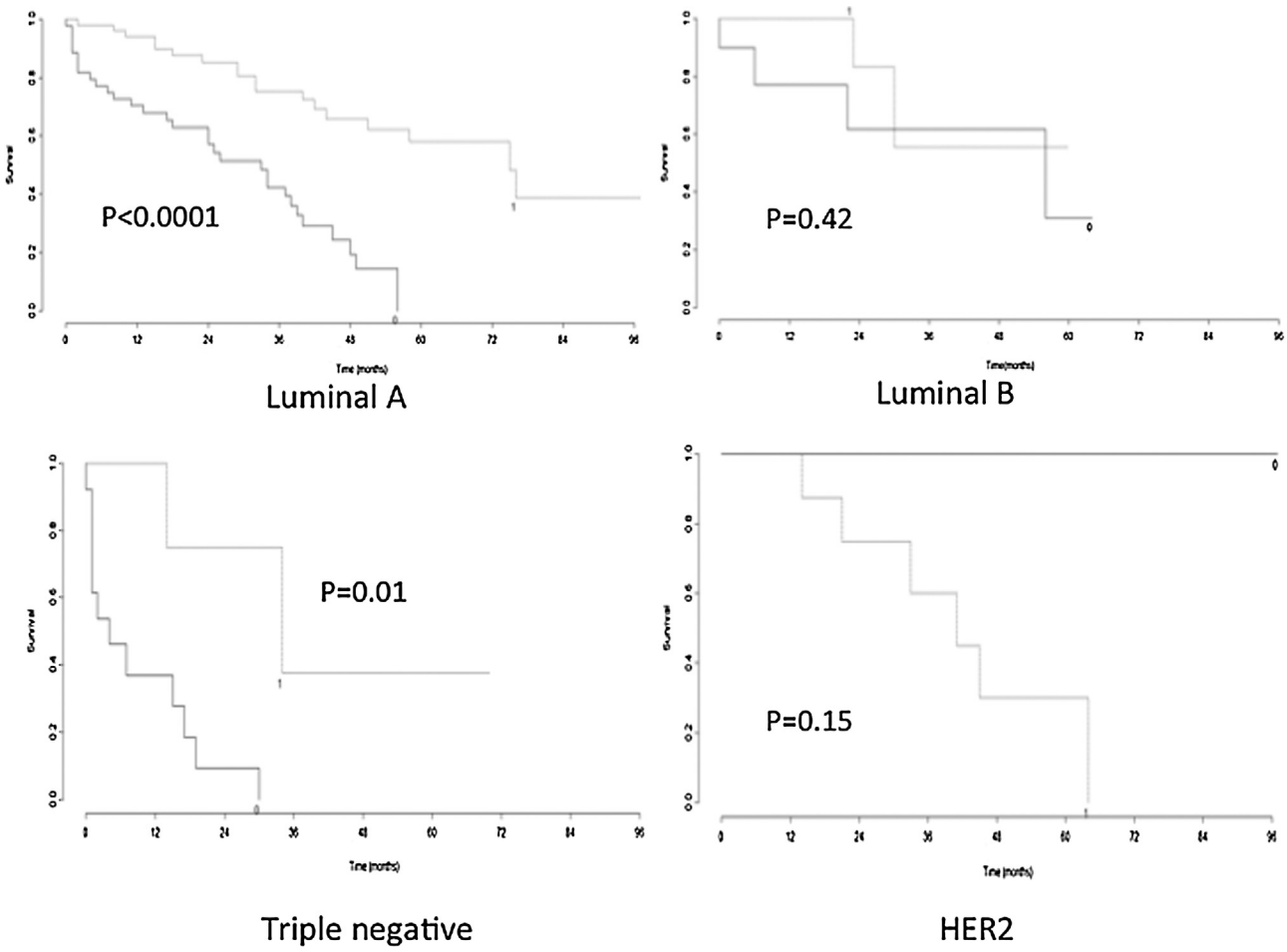

Fig. 3. Kaplan–Meier survival curves of all patients comparing surgery to no surgery.

($p = 0.43$), axillary lymph node resection ($p = 0.23$). There was no survival difference if chemotherapy was before surgery ($p = 0.27$) or chemotherapy before or after surgery ($p = 0.23$).

When we compared tumor phenotypes individually (Fig. 3a and b), survival was statistically different between the two groups for luminal A breast cancer patients $p < .0001$ (18 deaths for 50 patients in the surgery group and 33 deaths for 44 patients in the no surgery group) and for triple negative breast cancer patients $p = .01$ (2 deaths for 4 patients in the surgery group and 12 death for 13 patients). For other phenotypes (Fig. 3c and d) there

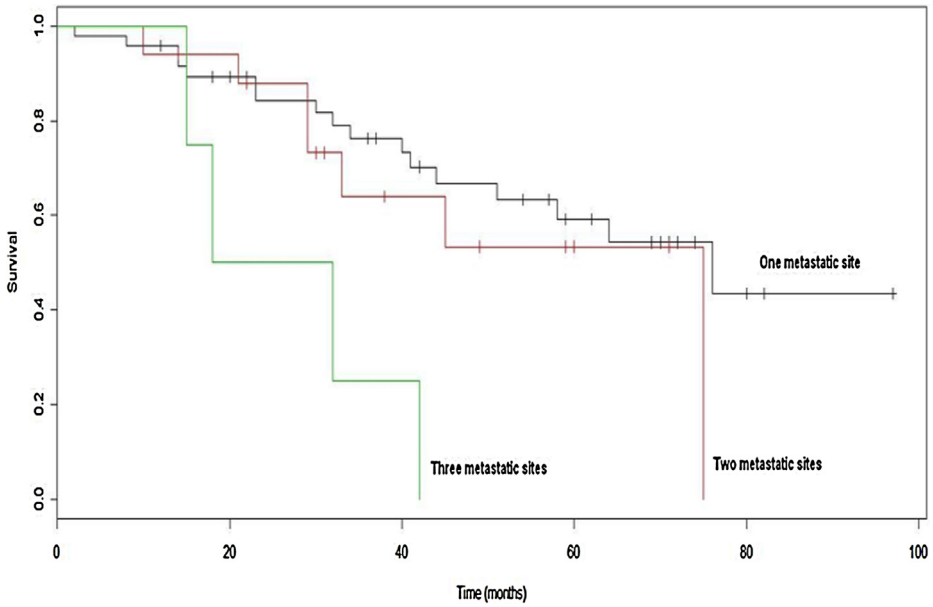

Fig. 4. Survival and metastatic site number in the surgery group.

was no statistical difference between surgery vs no surgery (luminal B: 2 deaths for 7 patients in the surgery group and 4 deaths for 10 patients in the no surgery group $p = 0.42$; her2: 6 deaths for 8 patients in the surgery group and 0 death for 3 patients in the no surgery group $p = 0.15$).

In the surgery group, we observed that through logistic regression, patients treated with radiotherapy to primary site decreased their death rate: HR = 0.14, 95% CI [0.03–0.54] $p = 0.007$. There was a statistical survival difference depending on metastatic site number $p = 0.005$ (Fig. 4). The mortality rate of patients who had one metastatic site was 35% versus 41% for patients who had two metastatic sites. All patients with three or more sites of metastases died during the follow up. A patient with three metastatic sites vs only one site has a death hazard ratio (HR) estimated at 2.3, 95% CI [1.1–5.8], $p = 0.05$. Survival did not vary with bone or visceral site ($p = 0.67$ vs $p = 0.52$) but varied with cerebral site $p < 0.0001$ (25 deaths/66 patients without cerebral site vs 3 deaths/3 patients with cerebral site).

Discussion

We observed that for breast cancer patients with stage IV at initial diagnosis, tumor resection increases survival compared to no surgery: HR 0.33 [0.16–0.66] $p = .001$. This is concordant with the systematic review of literature by Ruiterkamp et al. [18] who concluded that "surgery of the primary tumor appeared to be an independent factor for an improved survival" with a pool hazard ratio for overall mortality at 0.65 (95% CI [0.59–0.72]). In seven years we have diagnosed 139 breast cancers with synchronous metastasis which represents 2.6% of the breast cancers identified and is comparable with literature (3–10% [19]). In our overall population, we had more patients with luminal A subtype. This is indeed the most frequently subtype described and the one with a better prognosis [20,21]. As we already know [22], patients with triple negative subtype and patients with three or more metastatic sites have had the worst prognosis.

On one side, many studies, including two databases, have found an increase in survival by performing surgery on metastatic breast cancer patients [23–25].

A meta-analysis showed also a gain in survival at three years for patients who underwent surgery with an HR = 2.32, IC95% = [2.08; 2.6], $p < 0.01$ [17]. However, in this study patients operated on differ from patients who did not benefit from surgery concerning tumor size, number of metastasis and comorbidities [26].

When we compared phenotypes individually, surgery increases survival for luminal A breast cancer patients $p < .0001$ and for triple negative breast cancer patients $p = .01$. There was no survival difference between surgery and non surgery groups for all patients with her2 tumors whatever their hormonal status. In the Cancer journal, Neuman et al. [12] in their study from 2000 to 2004 concluded that no survival benefit was observed in patients with triple negative disease ($p = .001$). Their patient number was 186 and they had 35 triple negative breast cancer patients.

Concerning the surgical procedure, survival does not depend on the type of surgery (conservative surgery or mastectomy). Like Ruiterkamp et al. [18] in their review of the literature, we did not find a significant contribution of nodal dissection to the prognosis. For lymph node surgical resection, there are neither consensual standard nor homogeneous results in literature. This is also the case for free margins. Two studies [2,27] demonstrated that when the resection margins were tumor free, survival was increased but we observed, like Rapiti et al. [3] did, no difference.

In our study, we notice that surgery was more proposed in the university center. So as recommendations are relatively hazy, treatment depends on work team in each center. In France, we search systematically secondary localisations from T3 or T4. As there is metastatic disease with T1 or T2 without symptoms, there are patients in the surgery group who were operated on before the diagnosis of stage IV disease. According to Pedez-Fidalgo et al. [28], carrying out surgery before or after systemic therapy does not affect survival ($p = 0.996$).

Retrospectively, we saw that patients in the group with surgery resection of primary tumor were younger. All patients under 40 years old were operated on. So there were more non menopausal patients in this group. This fact can be explained because young patients have a low anesthesia risk. Moreover their life expectancy is longer and they are exposed to local complication or local recidive.

Our two groups differed in age and metastatic number of sites. This selection bias was due to retrospective observation. Most studies in literature were retrospective. Thanks to his stratified analysis, Rapiti et al. [3] found that survival increases only in the bone metastasis group. For Fields there is an advantage if patients have only bone metastasis and if margins are free. Shien et al. [7] and Rashan et al. [29] demonstrate that younger patients had an increased survival. In our study, the low number of luminal B, her 2 and triple negative subtypes does not allow us to extrapolate our results for these ones. We observed more chemotherapy treatments in the surgery group and more particularly in the luminal A subtype. We cannot exclude a confusion bias. Cady et al. [8] in their matched pair analysis suggest that bias could be responsible for the impression of survival increase but their charts seems to show the contrary [18]. In the light of literature, surgery seems unavoidable for young patients and complete responses after neo-adjuvant treatments.

In 2004, Bernard et al. [30] affirm that her2-overexpressing breast cancer could well be a distinct disease entity requiring a separate approach in terms of treatment. Our study is the first who included an homogeneous population since we started using trastuzumab treatment in 2004. We are among the first ones to evaluate surgery benefit separating the different subtypes of breast cancer with synchronous metastasis.

More recently, Tosello et al., published a review including two trials enrolling 624 women, they concluded that it is uncertain whether breast surgery improves overall survival as the quality of the evidence has been assessed as very low (HR 0.83, 95% CI 0.53 to 1.31). Breast surgery may improve local progression-free survival (HR 0.22, 95% CI 0.08 to 0.57; while it probably worsened distant progression-free survival (HR 1.42, 95% CI 1.08 to 1.86) [31].

New technologies such as molecular signature and approximate classification in subtype by hormonal and her2 receptors could allow us to adapt the standard of care for breast cancer with synchronous metastasis to the own development of each cancer and operate on only patients who could benefit from it.

In our study, patients with luminal A breast cancer phenotypes and synchronous metastasis seem to benefit from surgery. For these patients, tumor resection could not only prevent them from having local complications but also increase their survival.

There are still concerns about primary site surgery benefits for patients with stage IV breast cancer due to the influence of case selection on reported outcomes. Because of the multitude of stage IV breast cancer aspects, we need larger scale studies. The development of a national reporting system or registers for outcomes would facilitate the investigation of this disease.

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