Prognostic Factors for Breast Cancer Recurrence after Conservative Treatment

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ABSTRACT
Breast cancer is nowadays a real public health problem all over the world. Conservative therapy has been one of the approved treatment options for several years. The objective of this work was to describe the prognostic factors of breast cancer recurrence in our context after conservative treatment.

We performed a retrospective study with analysis of clinical, pathological, and therapeutic parameters in patients with breast cancer recurrence after conservative treatment over a period of 2 years. During the study period, a total of 17 patients were selected. The mean age at diagnosis of the primary tumor was 54.56 years.

The occurrence of recurrence was correlated with advanced tumor size with a rate of 64.7% for stage 2, lymph node invasion in 11 patients or 41.18%, and the presence of metastasis which was present in 2 patients. On the other hand, invasive ductal carcinoma was the most frequent histological type with 13 cases (76.47%) with predominantly intermediate or high SBR histopronostic grades (II and III: 47.05% each), vascular emboli and Comedonecrosis was present in 3 patients (17.64%), and the resection margins were healthy in all patients. As for estrogen receptors, they were positive in 9 patients, i.e., 52.94% of cases and those of a progesterone type were present in 8 patients (47.05%), HER-2 receptors were overexpressed in 3 patients (17.64%) and Ag Ki67 was greater than 20 in 76.47% of cases. Thus, 8.33% of the tumors were classified Luminal A, 47.06% were Luminal B, 11.76% were of the HER-2 type, and 35.29% were triple negative. All our patients had benefited from conservative treatment of the primary tumor made by conservative surgery followed by radiotherapy, with a delay between surgery and radiotherapy ranging from 8 to 23 months in patients who received chemotherapy and an average of 11 months, and from 4 to 8 months in patients who received radiotherapy directly after surgery, for an average of 5.25 months, on the other hand, adjuvant chemotherapy was administered in 11 patients (64.70%), hormone therapy was prescribed for 9 patients (52.94%) and only one patient had benefited from targeted therapy such as HERCEPTIN.

In conclusion, conservative treatment is currently indicated in most T1 and T2 mammary carcinomas given that it constitutes a therapeutic alternative combining carcinological and aesthetic benefits, however much remains to be done to be able to optimize its results and thus minimize the risk of recurrence.

Keywords
Prognostic Factors, Breast cancer recurrence, Conservative Therapy.

Introduction
Breast cancer in women is one of the main cancers in the world in terms of new cases/year. In Morocco, its frequency is constantly increasing and it is currently the most frequent cancer in women, and
Infiltrating ductal carcinoma (IDC) was found in 13 patients, had metastases, i.e., 11.77%. Regarding the histological type, node involvement of the 17 patients diagnosed, only 2 patients More than 40% of the patients had histologically confirmed lymph vascular emboli, lumpectomy margins, immunohistochemically classification, different therapeutic methods, time between surgery and radiotherapy.

Methods
This retrospective study, interested all patients admitted for a recurrence of breast cancer after conservative treatment, relates to a period of two years, which spread from January 1, 2018 to December 31, 2019. It was conducted at the Mohamed 6 Center for Cancer Treatment of Casablanca. The data were collected from the ENOVA software and the paper archives of the service. All patients hospitalized in the department during the study period for recurrence of breast cancer after conservative treatment were included in our study. Patients admitted for a first breast cancer as well as patients admitted for a recurrence of breast cancer but after radical treatment were excluded from our study, as well as patients with metastatic or distant recurrence. The prognostic factors studied were: Patient's age, duration of evolution, tumor size according to TNM classification, lymph node status, presence or absence of metastases, histological type, SBR grade, vascular emboli, lumpectomy margins, immunohistochemically classification, different therapeutic methods, time between surgery and radiotherapy.

Results
During our study period, 717 patients were operated on for breast cancer in our facility, we recorded 17 cases of breast cancer recurrence after conservative treatment. The recurrence rate represents 2.37% of all breast cancers admitted and operated. The average age at the time of discovery of recurrence was 54.56 years with extremes ranging from 25 to 78 years. The study of tumor size showed that 5 patients had a tumor smaller than 2 cm (29.41%), 11 patients had a tumor with a major axis between 2 and 5 cm (64.7%), and 1 patient was classified as T4b (skin ulceration). More than 40% of the patients had histologically confirmed lymph node involvement of the 17 patients diagnosed, only 2 patients had metastases, i.e., 11.77%. Regarding the histological type, infiltrating ductal carcinoma (IDC) was found in 13 patients, i.e., 76.47%, and only 1 patient had ductal carcinoma in situ, i.e. 5.88%. On the other hand, we found only one case of infiltrating lobular carcinoma (ILC) or 5.88%. The study of the histopronostic grade showed the predominance of grades 2 and 3 with 47.05% for each of the two stages followed by stage 1 with 5.89% of cases. The search for vascular emboli was positive in only 1 patient, i.e., 5.88%, while 2 patients had comedonecrosis, i.e., 11.76%. The resection margins were healthy in 100% of the cases, with 4 cases of tumor recurrence due to incomplete resection, flush resection, or economic margins of 1 mm. Estrogen receptor assay was positive in 52.94% of cases. Progesterone receptor assay was positive in 47.05% of cases. HER2 overexpression was present in 3 patients (17.64% of cases). Tumors with a high proliferation index > 20% represented 76.47% or 13 cases in total.

In the 17 tumors analyzed, 8.33% were classified as Luminal A, 41.66% as Luminal B HER 2 negatives, 12.5% as Luminal B HER 2 positives, 4.16% as HER 2 and 33.33% as triple negative. In our series, all patients had undergone conservative surgery. All of them had undergone radiotherapy. In addition to irradiation of the affected breast + boost on the tumor bed, 8 patients had received irradiation of the supraclavicular lymph nodes (47.05%), and the internal mammary chain (IMC) was irradiated in 4 patients (23.52%). For patients who received chemotherapy, we take into account the period during which the patients received chemotherapy, which can vary between 4 and 6 months, and which is automatically included in this period. The time from surgery to the start of radiotherapy for these patients ranged from 8 to 23 months (patients lost to follow-up), with an average of 11 months. For those who did not receive chemotherapy, the time from surgery to the start of radiotherapy for these patients ranged from 4 to 8 months with a mean of 5.25 months. The mean time to recurrence was 6 years with extremes ranging from 8 months to 15 years.

Recurrences were mostly local (82.35), with 3 cases of axillary (regional) recurrence (17.64%). Invasive ductal adenocarcinoma was the most frequent with a rate of 70.58%, followed by invasive lobular carcinoma with a frequency of 11.76%. On the other hand, 3 recurrences or 17.64% were undifferentiated invasive breast carcinomas. According to the molecular classification, the recurrences were divided into 2 Luminal A tumors, i.e. 11.76%, 8 Luminal B tumors, 3 of which were Luminal B HER-2 negative, i.e. 17.64%, 5 Luminal B HER-2 positive, i.e. 29.41%, 1 HER-2 positive tumor, i.e. 5.88% and finally 6 triple negative tumors, i.e. 35.29% of the cases. There was a slight change in the molecular profiles, notably an increase in Luminal A profile and a decrease in HER-2 positives. Having initially received conservative treatment, most patients had undergone radical surgery for recurrence with a rate of 88.23% or 15 patients. 76.47% of the patients had received chemotherapy (13 patients in total), on the other hand 11 patients had received radiotherapy (64.70%) and only 6 patients had received hormone therapy again (23.52%).

Discussion
In Morocco, the incidence of breast cancer is increasing, making it currently the most common cancer in women. It represents therefore constitutes a real public health problem. The prognosis of breast cancer is now good, especially if it is diagnosed and treated early. Net survival at 5 years has improved. Consideration of the heavy therapeutic, functional, and aesthetic sequelae, the introduction of new cancer and plastic surgery techniques, as well as new approaches to systemic treatment have led to an extension of the indications for conservative treatment.

The indications for conservative treatment are limited and concern only early stage tumors. Currently, the combination of adjuvant treatments has made it possible to operate on larger tumors with preservation of the breast, however, the indications must be considered and the carcinological result must be emphasized to guarantee a better survival without recurrence. However, prognostic factors should not be neglected as they play an essential role in the therapeutic decision. Thus, the objective of our study is to highlight the different prognostic factors of loco regional recurrence of breast cancer diagnosed in the onco-gynecology department of the Mohamed 6 Center after conservative treatment over a period of 2 years, spanning from January 1, 2018 to December 31, 2019.
35.8% of all incident female cancers during the period 2008-2012. Many risk factors, clinical and anatomical-pathological, have been analyzed to try to predict the risk of recurrence after radiosurgery. Age is the most important risk factor for local recurrence in young patients, whereas older age is associated with a lower risk of local recurrence. In our study, 96% of the cases studied were older than 41 years with an average age of 54 years, which is in agreement with the Dutch study which consisted of a 28-year follow-up of patients treated for breast cancer by conservative treatment and which concluded that young age (<40 years) is an independent risk factor for locoregional and distant recurrence after conservative treatment [1].

On the other hand, the determining factor is age<35 years and for some it is biological factors age would be rather than a factor influencing the therapeutic choice [2]. Tumor size is a risk factor for recurrence found in several studies. In a study of 802 conservative treatments with a median follow-up of 8 years, tumor size was separated into several categories. The rate of local recurrence increased with tumor size. It was 1.48% for tumors smaller than 1 cm, 2.62% for tumors smaller than 2 cm, 4.78% for tumors smaller than 3 cm and 15.74% for tumors larger than 3 cm. Thus, in our study, tumors measuring less than 5cm were the most dominant with a rate of 94.11%. Node invasion is considered an important parameter to specify, especially for its impact on the management of the tumor. Indeed, lymph node status: lymph node involvement, the number, the percentage of invasion, and finally the presence of capsular invasion are all factors of recurrence [3]. According to Elasayed et al., patients with advanced lymph node status had a 2.46-fold higher risk of developing loco regional recurrence after conservative treatment compared with those with low nodal status. As well as that, the 5-year survival was 75% for N3 patients and 95.7% for N1 patients [4].

However, in our study, we had patients with node status ranging from N0 to N2, and where N0 status predominated with a rate of 58.82%, followed by N1 which reached 29.41%. The occurrence of metastasis is a fairly frequent event in the evolution of breast cancer. In the literature, it is considered that the occurrence of local recurrence is predictive of distant metastasis, thus increasing breast cancer mortality, especially when the interval of their occurrence is short enough after the initial diagnosis [5].

The SBR grade of the tumor is another risk factor for recurrence found in some series. Kümmel et al. showed in their study that a high tumor grade (G3) was associated with a significantly higher risk of local and metastatic recurrence [6]. Histological grade is part of the multifactorial Nottingham prognostic index, along with tumor size and lymph node stage, which is used to stratify patients for appropriate treatment. The multifocal nature of invasive breast tumors is a risk factor for local recurrence after conservative treatment found in several studies, including the meta-analysis by Fang et al. whose aim was to compare the risk of recurrence of multifocal tumors after conservative versus radical treatment, and which concluded that the local recurrence of multifocal breast cancer after conservative treatment was higher than that of patients with unifocal tumors who received the same treatment [7].

The presence of vascular emboli in the primary tumor site is associated with a higher risk of regional lymph node metastasis at diagnosis and subsequent distant recurrence in early breast cancer [8]. The status of the excisional margins is a well-established prognostic predictor for patients undergoing breast cancer conservative surgery [9]. The rate of breast recurrence is at least 2-fold higher with incomplete resection in the majority of studies [10].

According to Fragomeni et al., ER and PR are indeed among the most important prognostic biomarkers in breast cancer. Thus, the status of these receptors is predictive of the response to targeted therapy, but also has an important prognostic role in terms of locoregional recurrence after conservative treatment [11]. Hormone receptor positivity is a protective factor against local recurrence. This is particularly true for estrogen receptors [12].

Most patients with documented locoregional recurrence will do so within 5 years of their surgery, with the highest risk of recurrence in the second year after diagnosis. Recurrences after breast-conserving treatment are usually identified on surveillance imaging and can be categorized as true recurrences or a second primary tumor, the distinction being made when the observed lesion occurs within 3 cm of the primary tumor bed and is histologically similar to the primary tumor. True recurrences represent the majority of early recurrences and tend to be more aggressive than primary tumors [13].

The landmark National Surgical Adjuvant Breast and Bowel Project (NSABP) -B06 study accelerated the adoption of conservative treatment. Local recurrence rates at 20 years were nearly 40% with lumpectomy alone versus 15% when combined with radiation therapy, and survival rates were equivalent to those after mastectomy. Recalling that the goal of breast cancer treatment is threefold: optimal local and regional control and reduction of the risk of recurrence. Conservative surgery followed by radiation therapy is considered both appropriate and the most adequate treatment for most women with early breast cancer. Conservative treatment optimally provides a high rate of local control and more acceptable cosmetic results with low morbidity.

The combination of radiation therapy with breast-conserving surgery or mastectomy has been shown to not only reduce recurrence, but also decrease distant metastases and improve long-term survival [14]. Several randomized trials have established the equivalence of breast-conserving treatment and mastectomy on overall survival in patients with early breast cancer after 20 years of follow-up. The addition of radiation therapy reduces the risk of local recurrence at 10 years by 16%, which translates into a 4% reduction in the risk of breast cancer death [15]. Olivotto's team conducted a study to determine the interval between conservative surgery and adjuvant radiotherapy that can impact local control and survival, and their results were statistically similar for intervals up to 20 weeks, but were lower for intervals beyond 20 weeks. Thus,
it is reasonable to allow time for the breast to heal and for patients to consider all their treatment options, but radiation therapy should begin within 20 weeks of conservative surgery to minimize the risk of local recurrence [16].

Adjuvant chemotherapy has been shown to be effective in locoregional recurrence of breast cancer with improved outcomes and overall survival, particularly in hormone receptor-negative recurrences [17]. In our series, chemotherapy was administered in 64.70% of patients. Hormone therapy decreases the risk of disease recurrence by 41% and the risk of death by 34% by breast cancer when treated in an early stage with positive hormone receptors. Hormone therapy also has the added benefit of preventing cancer, not only of the contralateral breast but also elsewhere [18].

Several teams have studied prognostic factors for survival after isolated local recurrence. One prognostic factor is unanimously agreed upon: the time to onset of recurrence after the initial treatment. Early breast recurrence reduces survival [19]. If the time to recurrence is a prognostic factor while the time to recurrence is a significant prognostic factor in most studies, the cut-off time differs in the literature. Patients with isolated locoregional recurrence of breast cancer represent a complex clinical challenge, as their management must take into account the previous treatment received before considering the best course of action. Total mastectomy is still the usual treatment for breast recurrence after conservative management. It is performed in more than 80% of cases. The axillary cavity is only approached if curage has not been previously performed or if it has been incomplete (less than 1 cm). The axillary fossa is only approached if a previous curage has not been performed or if it was incomplete (less than 8 to 10 nodes removed during the initial curage), or if there is palpable adenopathy. The question is not clear after the initial sentinel node [20].

The possibility of performing a second conservative treatment at the time of local recurrence is still controversial today. It is rarely performed. Although several teams in Europe and worldwide perform limited excision of local recurrence, the results available with this type of treatment are based on a few retrospective series with a small number of patients [21]. Additional medical treatment is justified only if it improves patient survival after surgical treatment of the recurrence. The selection of these women were decided on a case-by-case basis by PCR. There are no standards; anatomopathology, hormone receptor positivity or not, age, and previous medical treatments are taken into account [22]. Locoregional recurrence as the first event after conservative treatment of breast cancer is an independent risk factor for poor long-term prognosis. Even after a long interval, recurrence is strongly associated with poor outcome and even subsequent distant relapse [23]. Thus, the prognostic factors for recurrence of breast cancer after conservative treatment can be gathered in the following table:

<table>
<thead>
<tr>
<th>Prognostic factors for recurrence of breast cancer after conservative treatment:</th>
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<tbody>
<tr>
<td>- Age less than 40 years</td>
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<td>- Increased initial tumor size</td>
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<tr>
<td>- Lymph node involvement</td>
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<tr>
<td>- Metastasis</td>
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<tr>
<td>- Histological type: CLI - prognosis more or less poor</td>
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<tr>
<td>- Presence of ductal carcinoma in situ</td>
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<tr>
<td>- Advanced SBR grade</td>
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<tr>
<td>- Multifocal character of the tumor</td>
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<td>- Presence of vascular emboli</td>
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<td>- Impacted resection margin</td>
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<tr>
<td>- Hormone receptor negative</td>
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<tr>
<td>- HER-2 overexpression</td>
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<tr>
<td>- Ki67 ag amplification</td>
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<tr>
<td>- Molecular profiles: triple negative and HER-2 positive</td>
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<td>- Delayed access to adjuvant radiotherapy</td>
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<td>- Omission of systemic treatments indicated</td>
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**Conclusion**

The management of breast cancer has undergone great progress over the years, including today the conservative treatment which holds a great place in the treatment of breast tumors, especially those diagnosed at early stages. However, the risk of recurrence is always present with any breast cancer regardless of the treatment chosen, hence the interest in studying and highlighting the factors that must be taken into consideration in the context of conservative treatment to improve the survival rate of patients with this disease. Our work has allowed us to clarify these prognostic factors of recurrence through our results and by consulting the literature and what it reports in this sense. Thus, we were able to study all parameters that could be involved, including the histological characteristics on the one hand, through the initial tumor size, lymph node invasion, metastatic status, histological type, presence of carcinoma in situ, SBR grade, multifocal character of the tumor, presence of vascular emboli, and the status of the excision margins, and on the other hand the immuno-histochemical characteristics that include the status of hormone receptors, HER-2 receptors and Ki67 antigen that allow to classify breast tumors into subtypes according to their molecular profiles where triple negative and HER-2 positive subtypes have shown poor prognosis in terms of loco-regional recurrence, and finally the adjuvant treatment with all these options that also plays an important role in preventing recurrence.

Finally, conservative treatment remains a good management option, even the first choice when the indication is well established in the framework of a collaboration between the gynecologist, the anatomopathologist, the oncologist and the radiotherapist. A conclusion that was the result of several studies conducted and that showed no difference in terms of loco-regional recurrence or overall survival between conservative and radical treatment.

**References**